

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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MIM SOFTWARE INC.  
Petitioner

v.

EXINI Diagnostics AB.  
Patent Owner

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U.S. PATENT NO. 11,941,817  
Filing Date: March 29, 2023  
Issue Date: March 26, 2024  
Title: SYSTEMS AND METHODS FOR PLATFORM AGNOSTIC WHOLE  
BODY IMAGE SEGMENTATION

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*Inter Partes* Review No.: IPR2025-00827

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**DECLARATION OF DR. BRUCE ROSEN**

**Mail Stop: Patent Board**  
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U.S. Patent and Trademark Office  
P.O. Box 1450  
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## EXHIBIT LIST

No.	Description
Ex1001	U.S. Patent No. 11,941,817 (“the Patent”)
Ex1002	Declaration of Dr. Bruce Rosen
Ex1003	Dr. Rosen Curriculum Vitae
Ex1004	Prosecution History File of the Patent (Application No. 18/127,991)
Ex1005	U.S. Patent Application Publication No. 2012/0123253 (“Renisch”)
Ex1006	U.S. Patent Application Publication No. 2011/0007954 (“Suehling”)
Ex1007	U.S. Patent No. 10,140,544 (“Zhao”)
Ex1008	U.S. Patent Application Publication No. 2018/0144828 (“Baker”)
Ex1009	Eiber, “Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): Proposed miTNM Classification for the Interpretation of PSMA-Ligand PET/CT,” <i>The Journal of Nuclear Medicine</i> 59(3):469-478 (March 2018) (“Eiber”)
Ex1010	U.S. Patent Application Publication No. 2010/0032575 (“Iagaru”)
Ex1011	U.S. Patent Application Publication No. 2015/0287188 (“Gazit”)
Ex1012	RESERVED
Ex1013	Second Amended Complaint, <i>Progenics Pharmaceuticals, Inc. v. MIM Software Inc.</i> , Case No. 1:24-cv-10437-PBS, Dkt. 25, April 5, 2024.
Ex1014	U.S. Patent No. 8,855,387 (“Hamadeh”)
Ex1015	Kaur, “Various Image Segmentation Techniques: A Review,” <i>International Journal of Computer Science and Mobile Computing</i> 3(5):809-814 (May 5, 2014) (“Kaur”)
Ex1016	Sharma, “Automated medical image segmentation techniques,” <i>Journal of Medical Physics</i> 35(1):3-14 (2010) (“Sharma”)
Ex1017	Greenspan, “Deep Learning in Medical Imaging: Overview and Future Promise of an Exciting New Technique,” <i>IEEE Transactions on Medical Imaging</i> 35(5):1153-1159 (May 2016) (“Greenspan”)
Ex1018	Litjens, “A Survey on Deep Learning in Medical Image Analysis,” <i>Medical Image Analysis</i> 42:60-88 (Dec. 2017) (“Litjens”)
Ex1019	Shen, “Deep Learning in Medical Image Analysis,” <i>Annual Review of Biomedical Engineering</i> 19:221-248 (2017) (“Shen”)
Ex1020	Gandaglia, “Distribution of metastatic sites in patients with

prostate cancer: A population-based analysis,” <i>The Prostate</i> 74(2):210-216 (2014) (“Gandaglia”)
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## I. INTRODUCTION

1. I have been retained by GE HealthCare Technologies Inc. (“GEHC”) and its wholly owned subsidiary, MIM Software Inc. (“MIM”), to provide a declaration in support of MIM’s Petition for *Inter Partes* Review of U.S. Patent No. 11,941,817 (“the Patent”) (Ex1001). The opinions presented here are my own and are based on my own personal knowledge.

2. The Patent contains claims that recite systems and methods for automatically processing 3D images to automatically identify cancerous lesions within a subject.

3. I have been asked to prepare this declaration explaining the reasons and bases for my opinions that claims 1-5, 7-14, 16-19, 22-26, and 28-32 of the Patent are unpatentable. As discussed below, I have concluded that these claims are anticipated and/or would have been obvious to the person of ordinary skill in the art at the time of the alleged invention in light of prior art publications including: U.S. Patent Application Publication No. 2012/0123253 (“Renisch”) (Ex1005); U.S. Patent Application Publication No. 2011/0007954 (“Suehling”) (Ex1006); U.S. Patent No. 10,140,544 (“Zhao”) (Ex1007); U.S. Patent Application Publication No. 2018/0144828 (“Baker”) (Ex1008); and *Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE)*, The Journal Of Nuclear Medicine (March 2018) (“Eiber”) (Ex1009).

4. In reaching my opinions, I relied on the documents cited herein and on my decades of knowledge and experience in the fields of radiology and nuclear medicine (outlined in Section II).

5. This report is based on information currently available to me. I reserve the right to supplement my opinions in response to arguments raised by the Patent owner, EXINI Diagnostics AB (“EXINI”), or in response to any additional information that becomes available to me.

## **II. QUALIFICATIONS AND EXPERIENCE**

6. My qualifications for forming the opinions set forth in this declaration are summarized in the following paragraphs and listed in more detail in my curriculum vitae (“CV”), which is attached as Ex1003.

7. I am a M.D. Radiologist and Ph.D. Medical Physicist, employed for the last 42 years at the Massachusetts General Hospital (“MGH”).

8. I received an undergraduate degree in Astronomy and Astrophysics from Harvard University in 1977, a Masters Degree in Physics from the Massachusetts Institute of Technology in 1980, an M.D. degree from Hahnemann Medical College in 1982, and a Ph.D. in Medical Physics/Medical Engineering from the combined Harvard/MIT Health Sciences and Technology Program in 1984.

9. I received my Radiology Residency training from the MGH, which I

completed in 1987, and which included training in nuclear medicine. I was subsequently Board Certified in Diagnostic Radiology from the American College of Radiology that same year. I received and have held my medical license from the state of Massachusetts since that time. After completing my residency training, I served as the Director of the Clinical MRI Service at the MGH and, in 2001, became Director of the Athinoula A. Martinos Center for Biomedical Imaging at the MGH, one of the world's largest medical imaging laboratories.

10. In 2019, I became the Vice-Chairman for Research in the Department of Radiology at the MGH and, in 2023, I became the Vice-Chairman of the MGH Executive Committee on Research.

11. In 1985, I created the graduate level course in Magnetic Resonance Imaging at MIT and Harvard, and I've been teaching that course for over 20 years.

12. I have published over 470 publications relating to magnetic resonance imaging (MRI), positron emission tomography (PET), tumor and stroke imaging, functional imaging, radiologic image analysis, and similar medical imaging topics.

13. The Martinos Center, which I currently direct, is a program with over 300 scientists and engineers and more than 100 faculty working in the field of advanced medical imaging and medical image analysis.

14. I have been elected as a member of the National Academy of Inventors and the US National Academy of Medicine of the National Academies of

Science. I have also been elected as a Fellow of the American Academy of Arts and Sciences.

15. I am a Fellow of the International Society of Magnetic Resonance in Medicine and the American Institute of Medical and Biological Engineering. I am also a member of the Council of Distinguished Investigators of the Academy of Radiology Research, and was the recipient of the Distinguished Researcher award from the Radiological Society of North America, and the Gold Medal from the International Society of Magnetic Resonance in Medicine.

16. During my medical imaging and radiology training, and during the subsequent 35+ years as a faculty member (now Full Professor) within the Department of Radiology at the Massachusetts General Hospital and the Harvard/MIT Division of Health Sciences and Technology, I have had opportunity to learn about and investigate many aspects of medical imaging, both clinical and technical in nature. My radiologic training included all facets of modern diagnostic radiology, including the use of PET, SPECT, CT, MRI, Ultrasound, and conventional X-rays for medical diagnoses of all disorders. Nuclear medicine is one essential element of radiology training, board certification, and Radiology Department practice here in the USA. I have extensively published on the use of radiologic imaging to diagnose and follow treatment of cancers, strokes, neurodegenerative diseases such as Alzheimer's, and other clinical conditions. In

these studies, I have acquired and analyzed images from multiple modalities, including positron emission tomography (PET), magnetic resonance imaging (MRI), computed tomography (CT), and hybrid imaging technologies such as PET/CT and PET/MRI scanners. I have also published work in advanced computational analysis of medical images for improved medical diagnosis and for the fundamental study of human diseases, including cancer, stroke and others. This work includes methods for image segmentation, registration, visualization, and physiological modeling, using both conventional and machine learning methods including artificial intelligence (“AI”) methods. My work has also included the use of both common and novel radiotracers for radionuclide imaging, and in the application of these tracers to the study of diseases such as cancer. My Gold Medal was in the field of Functional Imaging, where I was amongst the first to invent and apply these tools to study the brain and brain diseases. I am familiar with the design of distributed networks of imaging scanners and computational analysis computers through my role of Director of the Martinos Center for Biomedical Imaging, where we have over 15 imaging instruments, including PET, CT and MRI scanners, and hundreds of computers on a distributed network, including remote PACS systems and Cloud storage and computing clusters.

### **III. COMPENSATION AND PRIOR TESTIMONY**

17. With respect to this matter, I am working as an independent

consultant. I am being compensated at an hourly rate of \$850 USD, plus expenses, for the time I spend working on this matter. Prior to my engagement in the present case, I never worked as a consultant for MIM, and I have never been adverse to EXINI in any proceeding. I own no stock in MIM and am aware of no other financial interest I have relating to MIM or EXINI. My compensation is not contingent upon the outcome of this matter.

18. During the past four years, I was also retained by the General Electric Company in *Steady State Imaging, LLC v. General Electric Company*, U.S. District Court for the District of Minnesota, Case No. 17-cv-01048-JRT-KMM, where I was deposed and gave testimony in court. I have not testified in any other matters in the last four years.

#### **IV. LEGAL STANDARDS**

19. Although I am not an attorney and do not expect to offer any opinions regarding the law, I have been informed of certain legal principles that I relied on in forming the opinions set forth in this report.

##### **A. Priority Date**

20. I have been asked to assume that the priority date of the Patent is January 7, 2019.

##### **B. Claim Construction**

21. I understand that in an *inter partes* review proceeding the claims of a patent are construed using the same claim construction standard that would be used to construe the claims in a civil action. I understand that under this standard the words of a claim are generally given their ordinary and customary meaning. I understand the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention. I understand the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but also in the context of the entire patent, including the specification.

22. I understand claim construction focuses on the “intrinsic evidence,” which consists of the claims themselves, the specification, and the prosecution history. I understand the surrounding claim language can provide helpful context for how to interpret a claim term. I also understand the specification is highly relevant to the claim construction analysis and usually dispositive concerning the meaning of a claim term.

23. I understand that “extrinsic evidence” may also be considered when determining the meaning of a claim term. I understand there are different sources of extrinsic evidence, including dictionaries, inventor testimony, expert testimony, and learned treatises. I understand that intrinsic evidence is generally favored over

extrinsic evidence, and that extrinsic evidence may not be used to contradict the meaning of the claim term when read in light of the intrinsic evidence.

24. I understand there are two primary exceptions to the general rule that claim terms are given their ordinary and customary meaning as understood by a person of ordinary skill in the art: (1) when the claim terms are expressly defined in the patent (i.e., “lexicography”); and (2) disavowal. I understand that in order for a patentee to act as its own lexicographer, the patentee must clearly set forth a definition of the claim term that is different than its plain and ordinary meaning, and clearly express an intent to redefine the term. I understand that disavowal requires a clear and unmistakable disclaimer of claim scope, such as the specification or prosecution history making clear that the invention does not include a particular feature, or that it is limited to a particular embodiment of the invention.

### **C. Anticipation**

25. I understand that a prior art reference “anticipates” an asserted claim, and thus renders the claim unpatentable, if all elements of the claim are disclosed in that prior art reference, either explicitly or inherently.

26. I understand that an element is inherently disclosed in a reference if it necessarily is present in that which is described in the reference. Thus, a prior art reference, even without expressly referring to a claim limitation, may nonetheless

anticipate by inherency.

27. I understand that, once the claims of a patent have been properly construed, the second step in determining anticipation of a patent claim requires a comparison of the properly construed claim language to the prior art on a limitation-by-limitation basis.

#### **D. Obviousness**

28. I understand that even if a patent claim is not anticipated, it is still invalid if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the pertinent art.

29. I understand that a person of ordinary skill in the art provides a reference point from which the prior art and claimed invention should be viewed. This reference point prevents one from using his or her own insight or hindsight in deciding whether a claim is obvious.

30. I also understand that an obviousness determination includes the consideration of various factors such as (1) the scope and content of the prior art, (2) the differences between the prior art and the asserted claims, (3) the level of ordinary skill in the pertinent art, and (4) the existence of secondary considerations of obviousness or non-obviousness.

31. I understand that an obviousness determination can be based on a

single prior art reference, a combination of multiple prior art references, or a combination of prior art references and the patentee's admissions regarding the scope and content of the prior art.

32. I understand that the prior art itself may provide a suggestion, motivation, or reason to combine or modify the teachings of the prior art, or that such a reason may come from other sources, such as the knowledge of a person having ordinary skill in the art, common sense, and market forces. I understand that the following rationales may support a finding of obviousness:

- Combining prior art elements according to known methods to yield predictable results;
- Simple substitution of one known element for another to obtain predictable results;
- Use of a known technique to improve similar devices, methods, or products in the same way;
- Applying a known technique to a known device, method, or product ready for improvement to yield predictable results;
- “Obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design

incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

- Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

33. I understand that a patentee's admissions, for example in the specification of the patent, are permissible evidence for establishing the background knowledge possessed by a person of ordinary skill in the art and provide a factual foundation as to what a skilled artisan would have known at the time of invention.

34. I understand that a patentee's admissions regarding the scope and content of the prior art can be used to: (1) supply missing claim limitations that were generally known in the art prior to the effective filing date of the claimed invention; (2) support a motivation to combine particular disclosures; or (3) demonstrate the knowledge of the ordinarily skilled artisan at the time of the effective filing date of the claimed invention.

35. I understand that an obviousness determination when combining or modifying prior art elements requires a reasonable expectation of success in achieving the claimed invention.

36. I understand that secondary considerations of non-obviousness may include (1) a long felt but unmet need in the prior art that was satisfied by the invention of the patent; (2) commercial success or lack of commercial success of processes covered by the patent; (3) unexpected results achieved by the invention; (4) praise of the invention by others skilled in the art; (5) the taking of licenses under the patent by others; (6) deliberate copying of the invention; (7) teaching away; and, *contra*, (8) the simultaneous invention of the claimed subject matter. I understand that contemporaneous and independent invention by others is a secondary consideration supporting an obviousness determination.

37. I understand that any secondary consideration must bear a nexus to the claimed invention. Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention. For example, when commercial success is due to marketing rather than the patented features of a product, the commercial success is not an indication of non-obviousness. I further understand that the patentee bears the burden of demonstrating that the relevant commercial success is attributable to the claimed invention, as opposed to other economic and commercial factors unrelated to the technical quality of the patented subject matter.

**E. Person of Ordinary Skill in the Art (“POSITA”)**

38. I have been informed that a person of ordinary skill in the art is a

hypothetical person who is presumed to have known all the relevant art at the time of the invention. I have been informed that the person of ordinary skill in the art may possess the education, skills, and experience of multiple actual people who would work together as a team to solve a problem in the field. I have been informed that factors that may be considered in determining the level of ordinary skill in the art may include: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) the sophistication of the technology; and (6) the educational level of active workers in the field.

39. Based on my consideration of these factors and my experience in the field of radiology, including my familiarity with medical radiography systems generally, I have been asked to opine as to the level of skill of the hypothetical person of ordinary skill in the art to which the Patent is directed. In my opinion, the hypothetical person of ordinary skill in the art would include a person who, at the time of the invention, had a medical (MD) degree and/or an advanced degree in Computer Engineering, Computer Science, Physics, or other field related to computer imaging, and at least 3 years of field experience with medical imaging devices, such as PET/CT or SPECT/CT systems.

40. I have undertaken to consider the knowledge the POSITA would have had as of January 7, 2019, which is the date I have been asked to assume is the

priority filing date for the Patent. When I refer to the POSITA in this declaration in my discussion of the Patent, I am referring to a person of ordinary skill in the art as of that date.

## **V. TECHNOLOGICAL BACKGROUND**

41. I have been asked to provide a brief background discussion relating to the technologies and terminology at issue. Except where otherwise noted, this background is based on my personal knowledge and experience.

### **A. Medical Imaging**

42. Medical imaging is a non-invasive technology for visualizing and quantifying the structure inside the human body – as well as its function – thus aiding clinicians in the diagnosis and treatment of various medical conditions and diseases.

#### **1. Anatomical Imaging**

43. Some medical imaging techniques and technologies are designed to visualize anatomical structures within the human body. Examples of structural imaging techniques that produce “anatomical images” include standard 2D X-ray Radiography, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI). Each of these technologies is valuable for visualizing, in high resolution, the shape, size, and position of different anatomical structures including organs,

tissues, and anomalies.

## **2. Functional Imaging**

44. Other medical imaging techniques capture physiological processes within the body to produce what are often referred to as “functional images.” These functional imaging techniques provide information, including quantitative data, on how scanned organs or tissues currently function. Examples of functional imaging techniques include Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), and Functional Magnetic Resonance Imaging (fMRI). These techniques visualize the physiological state of organs or tissues, such as blood flow, metabolism, and drug uptake. Additionally, certain functional imaging techniques, such as PET and SPECT scans, fall under the umbrella of “nuclear medicine” imaging, because they employ radioactive isotopes (sometimes referred to as radiotracers, radiopharmaceuticals, radionuclides, etc.) and detect radiation emitted from the patient to reconstruct 3D medical images.

45. To perform nuclear medicine imaging, radionuclides are purposefully introduced into a patient’s body in the form of a radiopharmaceutical (or radiotracer). Radiopharmaceuticals are compounds that include a biologically active delivery molecule labeled with a radiation emitting radionuclide. The delivery molecule is selected to target a cell or tissue associated with a particular disease or metabolic activity of interest. The molecules are chosen based on their

ability to accumulate preferentially in certain tissues or organs, and many delivery molecules targeting different organs or disease states have been created. Thus, the delivery molecule that is selected will determine how the radiopharmaceutical behaves inside the human body and will direct the radiation emitting radionuclide toward specific organs or tissues in the body.

46. Many delivery molecules have been developed to target various types of cancer tissue including various forms of cancer. As new and better delivery molecules are developed, they are implemented with existing nuclear medicine PET and SPECT scanners.

47. As radionuclides decay, they emit radiation that is detected by the PET or SPECT scanner, which will collect and compile, from multiple views around the patient's body, many 2D projections of all detected radiation emitted from the patient. Using powerful computer algorithms that account for the precise direction from which the radiation was detected, the PET and SPECT scanners will then generate a reconstructed 3D image in which areas of high emission due to high radionuclide accumulation are depicted as high intensity "hot spots." This allows PET and SPECT cameras to achieve visualization and quantification of specific physiological processes and diseases within the body.

### **3. Registered/Hybrid/Composite Images**

48. Anatomical images provide clear structural information regarding the

location, shape, and size of organs and other tissues. Nuclear medicine functional images provide complementary information regarding physiological activity but often lack the clarity necessary to provide important structural context, such as the location of hot spots relative to other tissues. Complex diseases, such as many types of cancer, often require both structural and functional imaging to properly inform healthcare professionals with respect to diagnosis, dosimetry, and other clinical decisions. Therefore, it has long since been known to register, overlay, fuse or otherwise combine anatomical and functional images together for concurrent display in a composite/hybrid image. *See, e.g.,* Ex1010 (“Iagaru”), [0048] (“The medical images provided by the PET scanner and CT scanner are complementary, and it is advantageous to have images from both types of scans. To be most useful, the PET and CT images need to be overlaid or co-registered such that the functional features in the PET images can be correlated with the structural features, such as bones, tumors, and lung tissue, in the CT images.”).

49. Image registration is the process of aligning two or more images so that corresponding points in each image match. Although many advanced registration techniques have been developed, they can be summarized using the broad categories of rigid registration and non-rigid registration.

50. Rigid registration is most effectively employed when registering multi-modality images (e.g., CT and SPECT) that were obtained at approximately

the same time such that the patient remains in essentially the same position (e.g., when the images are obtained using a hybrid imaging system). Rigid registration is accomplished by adjusting one complete image in six degrees of freedom relative to the other image before overlaying them – for example by translating or rotating one image relative to the other.

51. Non-rigid registration permits deformation of one image or parts of the image by, for example, stretching, shearing, or bending. Thus, if the patient's head is in a slightly different position in PET and CT images taken at different times, non-rigid registration can apply a different technique to the head portion of the image than is applied to the rest of the image to obtain the most accurate alignment of the whole body. Similarly, when registering pre- and post-treatment images of a tumor, non-rigid registration can accurately align the images despite changes in the tumor's shape and size.

## **B. Image Segmentation**

52. Image segmentation is the partition of an image – anatomical or functional – into meaningful regions or objects based on some physical criteria of the image itself, such as intensity, color, texture, shape, or motion. *See generally* Ex1015, Ex1016. Image segmentation is essential for many medical image analysis tasks, such as detecting lesions or tumors, classifying tissues, contouring the overall shape or volume of organs, and localizing anatomical landmarks. In the

past, radiologists manually segmented 3D volumes, 2D slice-by-slice, which was a laborious task that made comprehensive, whole-body analyses impractical. Eventually, numerous automated segmentation techniques were developed that greatly improved medical image analysis. *See generally* Ex1015, Ex1016. Although there are many types of image segmentation techniques, I will focus on some of the most common, including methods that use machine learning algorithms.

## **1. Thresholding**

53. Thresholding is a simple technique that separates the pixels or voxels into foreground and background by comparing their intensity values with a threshold value. Ex1015 at 811. The threshold value can be predetermined based on medical teachings or adapted depending on the characteristics of the image and the object being segmented from the image. Classic examples of segmenting by thresholding include: (i) identification of hot spots (i.e., potential lesions) in functional images; and (ii) identification of bone in CT images.

## **2. Clustering**

54. Clustering methods use machine learning to group pixels or voxels into homogenous clusters based on their similarity or proximity in a feature space, such as intensity, color, texture, and/or location. Ex1016 at 10-11. The object of clustering is to find natural groupings of pixels or voxels based on their

characteristics such that members of one cluster are more similar to each other than to members of other clusters. The most common form of clustering divides the pixels or voxels of an image into a predetermined number of clusters and then iteratively reassigns each pixel or voxel to a different cluster until an optimization function is minimized – meaning that further reassignment among the clusters would not produce more homogenous clusters.

### **3. Artificial Neural Networks**

55. Artificial Intelligence (AI) is a broad concept that generally refers to any technique that enables computers to mimic human intelligence. Applications for AI include complex tasks such as object identification in images, which is the basis of medical image segmentation.

56. Machine learning is a subset of AI that focuses on the development of algorithms that allow computers to learn from, and make predictions based on, data. Instead of being explicitly programmed to perform a task, machine learning algorithms are trained on large datasets and use statistical techniques to identify patterns and make decisions based on predictions.

57. Deep learning is a specialized subset of machine learning that uses artificial neural networks with many layers (hence “deep”) to analyze and iteratively learn from data such as images. An artificial neural network is a computational model inspired by the highly interconnected structure of neurons in

the human brain. It consists of interconnected nodes (like neurons) organized in layers. Each connection between neurons in adjacent layers has an associated weight, and the selected weight for each connection of the cumulative network determines the ability of the network to accurately predict outcomes (e.g., whether an image contains the number “8”).

58. Artificial neural networks often use supervised learning, meaning that the model is trained with labeled data (e.g., labeled pictures of cats and dogs) to make a prediction about how new data should be labeled (e.g., cat or dog). Specifically, the process of supervised training adjusts the weights between each interconnected node of the network to minimize the error in predicted outputs.

59. Most pertinent to medical image segmentation, Convolutional Neural Networks (CNNs) are artificial neural networks specially adapted for analyzing images. *See generally* Ex1017, Ex1018, Ex1019. At a high level, CNNs are constructed of convolutional layers of nodes that apply filters to the input image, looking for hierarchical patterns (e.g., edges, curves, circles), and creating feature maps that depict detected patterns. Eventually, fully connected layers of the CNN evaluate the features extracted by the convolutional layers to make final predictions including, for example, whether a particular pixel of an image is part of a particular organ that the neural network has been trained to look for. In this way, artificial neural networks can segment organs or bones in a medical image by

accurately predicting which pixels/voxels in the image correspond to a particular organ or bone.

#### **4. Digital Segmentation Masks**

60. Whereas anatomical structures, such as particular organs and bones, can be clearly identified and segmented in anatomical images, such as CT images, identifying these structures in functional images may be much more difficult, if not impossible. Likewise, whereas regions of high radiotracer uptake corresponding to likely lesion candidates can be clearly identified and segmented in functional images, such as PET and SPECT images, identifying cancerous lesions in anatomical images may be much more difficult, if not impossible. Therefore, it is important, as discussed above, to be able to digitally register anatomical and functional images in a manner such that segmented structures in one image can be digitally transferred to the co-registered image for further evaluation and quantification. Additionally, because the segmented structures within a digital image are often the only portions of the image for which further processing or evaluation is required, it is desirable to be able to digitally separate the segmented structures from the rest of the image. These functions are typically accomplished using digital masks – also referred to as segmentation masks.

61. In my experience, it is standard practice within the field of digital image segmentation to represent and track segmented regions-of-interest (“ROIs”)

using a digital mask. *See, e.g.,* Ex1007, 5:11-6:11, Ex1011, [0042]. Each mask generated for a segmented image may be, for example, a digital space containing the same number of pixels/voxels as the digital image, where each pixel/voxel of the mask contains a value to denote whether a corresponding pixel/voxel of the digital image (i.e., in the same position) is located within a segmented region-of-interest. For example, for a digital image that contains only a single segmented ROI, a binary mask can be generated in which each pixel/voxel of the mask is either zero or non-zero depending on whether the pixel/voxel is located within the segmented ROI. *See e.g.,* Ex1010, [0064] (describing the generation of a binary bone mask). In other words, the digital mask may be, at least initially, an empty digital space into which the segmented region of interest is inserted by assigning a non-zero value to each pixel/voxel corresponding to the location of the ROI in the digital image. These masks, once generated, can then be applied as a digital filter to remove unwanted image data or transfer the ROIs to other co-registered digital images. *See, e.g.* Ex1010, [0064] (“To facilitate localization of lesions within a subject’s skeletal structure, the PET image can be masked by the generated digital bone mask.”)

62. When segmented images contain multiple, distinct ROIs, each ROI can be associated with a unique value and each pixel/voxel of the digital mask can be assigned the value associated with the particular ROI in which the pixel/voxel is

located. For example, a segmented image of the chest might produce a corresponding mask in which voxels located within the region of the lungs are labeled with one value and voxels located within the region of the heart a labeled with a different value. The mask can then be filtered or sorted by pixel value to generate a plurality of binary masks, each representing a single ROI.

## **VI. THE PATENT AND PROSECUTION HISTORY**

### **A. The Patent**

63. The Patent, which is entitled “SYSTEMS AND METHODS FOR PLATFORM AGNOSTIC WHOLE BODY IMAGE SEGMENTATION,” was filed on March 29, 2023, and issued on March 26, 2024. Ex1001, cover. I have been instructed by counsel to conservatively treat January 7, 2019, as the priority date of the Patent, which is the filing date of priority Provisional Application No. 62/789,155. The assignee identified on the cover of the Patent is EXINI Diagnostics AB (Sweden).

64. The Patent is generally directed to systems and methods for automated analysis of three-dimensional (3D) medical images of a subject in order to “automatically identify specific 3D volumes within the 3D images that correspond to specific anatomical regions e.g., organs and/or tissue.” Ex1001, 3:3-7. The *claims* of the Patent are specifically directed to systems and methods for “automatically processing 3D images to automatically identify cancerous lesions

with a subject.” *Id.* at claims 1 and 10.

65. The Patent emphasizes – in comparison to EXINI’s prior U.S. Patent No. 8,855,387 (“Hamadeh”) (Ex1014) – that:

The capability of the approaches described herein to handle 3D images is an important advantage over certain other image analysis that only identify 2D regions in 2D images. For example, one approach relevant for cancer detection, EXINI Diagnostics AB's Bone Scan Index (BSI) software, detects regions of suspected bone cancer (see also U.S. Pat. No. 8,855,387, issued Oct. 7, 2014). However, the BSI analysis is carried out on two-dimensional scintigraphy images, as opposed to on three dimensional images.

*Id.* at 3:21-29. I note that EXINI’s Hamadeh patent states that it “relates to automated processing and interpretation of two-dimensional bone scan images produced via isotope imaging.” Ex1014, 1:16-20 (emphasis added).

66. The Patent explains that “[f]unctional images such as SPECT and PET provide detailed and specific information on biological processes in the body, but their potential is only realized when combined with a detailed anatomical map so that function can be localized to individual organs and structures.” *Id.* at 3:34-39. Accordingly, the Patent describes automatically segmenting, using machine learning algorithms, 3D anatomical images, such as CT and MR images, into specific tissue regions corresponding to organs and bones (*id.* at 5:12-27, 10:45-12:16) and mapping the segmented tissue regions from the anatomical image to the

functional image to identify the corresponding volumes in the functional image (*id.* at 32:65-33:8, 37:15-48). For example, the Patent states:

[T]he full body segmentation approaches described herein allow for automated analysis of combinations of anatomical and functional images in order to accurately identify and grade cancerous lesions within a subject. In particular, a PET/CT composite image can be acquired for a subject following administration of a radiopharmaceutical, such as a PSMA binding agent like PyL™. The automated, machine learning-based segmentation approaches described herein are used to identify, within the CT image of the PET/CT composite, target volumes of interest (VOIs) representing target tissue regions where cancerous lesions may be found. For example, a skeletal VOI corresponding to a graphical representation of one or more bones of the subject may be identified. Once the skeletal VOI is identified in the anatomical, CT, image, it can be mapped to the PET image to identify a corresponding skeletal volume therein. The corresponding skeletal volume in the PET image is then analyzed to detect one or more localized regions of relatively high intensity, referred to as hotspots. These hotspots correspond, physically, to local regions of increased radiopharmaceutical accumulation and, accordingly, prospective cancerous lesions.

*Id.* at 3:49-4:3.

67. With respect to the segmentation process, the Patent explains:

The AI-based segmentation technologies described herein utilize machine learning techniques, such as Convolutional Neural Networks

(CNNs) to automatically to identify a plurality of target 3D volumes of interest (VOIs) each corresponding to a specific target tissue region, such as one or more organs, portions of organs, particular bone(s), a skeletal region etc. Each identified 3D VOI may be represented via a segmentation mask. The multiple segmentation masks, identifying multiple target tissue regions across a patient's body, can be stitched together to form a segmentation map. The segmentation map, and/or various segmentation masks that it comprises, may be used compute various quantities from medical images, such as useful indices that serve as measures and/or predictions of cancer status, progression, and response to treatment. Segmentation maps and masks may also be displayed, for example as a graphical representation overlaid on a medical image to guide physicians and other medical practitioners.

*Id.* at 32:3-21 (emphasis added).

68. I note that the Patent appears to assume that the reader knows what a segmentation mask is because the Patent makes no attempt to define segmentation masks. With respect the creation of a segmentation map from segmentation masks, the Patent explains that “[i]n certain embodiments”:

[A processor may] digitally stitch together the plurality of 3D segmentation masks to form the 3D segmentation map {e.g., by creating an initially empty image volume (e.g., initializing all voxel values to zero) and then inserting labels from each segmentation mask into the image volume [e.g., by mapping labeled (e.g., as representing a particular target tissue region as determined by a machine learning

module) voxels of input images to one or machine learning modules to voxels of the image volume (e.g., so as to match voxels of the image volume to voxels of the input images that represent a same physical location, thereby labeling voxels of the image volume correctly)]}.

*Id.* at 16:18-29. Additionally, the Patent states:

Segmentation maps generated by automated AI-based analysis of anatomical images can be transferred to 3D functional images in order to identify, within the 3D functional image, 3D volumes corresponding to the target VOIs identified in the anatomical image. In particular, in certain embodiments, the individual segmentation masks (of the segmentation map) are mapped from the 3D anatomical image to the 3D functional image.

*Id.* at 37:15-22 (emphasis added).

69. With respect to the detection of hotspots that may be cancerous lesions, the Patent explains:

[H]otspots are detected via a thresholding approach—by comparing intensities of voxels within the functional image to one or more thresholds values. Groupings of voxels with intensities above a threshold may be detected as hotspots. A single, global, threshold value may be used, or, in certain embodiments, multiple region specific thresholds may also be used. For example, segmentation of the co-registered anatomical image can be used to set different thresholds for different tissue regions used for hotspot detection.

*Id.* at 40:25-34.

70. With respect to the detection of cancerous lesions, that Patent states that “[h]otspots may ... be classified following their initial detection, e.g., as cancerous or not,” and the “classification may be performed by extracting hotspot features (e.g., metrics that describe characteristics of a particular hotspot) and using the extracted features as a basis for classification.” *Id.* at 41:27-34. For example, hotspots may be determined to represent lesions “based on intensities of voxels within the 3D functional image [e.g., based on a comparison of intensities within the 3D functional image with a threshold value (e.g., wherein the 3D functional image is a 3D PET image and the threshold is a particular standard uptake value (SUV) level)].” *Id.* at 8:3-10.

## **B. The Patent’s Prosecution History**

71. I have reviewed the prosecution history of the Patent as it is available from the USPTO website. Ex1004.

72. The Patent was filed on March 29, 2023, with 116 original claims. Ex1004, pp.153-185. On June 26, 2023, the Applicant filed a Preliminary Amendment cancelling most of the original claims, and adding new claims that correspond to claims 19-32 of the issued Patent. *Id.* at pp.231-242. The Applicant also filed, on June 26, 2023, an Information Disclosure Statement disclosing over 140 patent references and over 110 non-patent publications. Ex1004, pp.245-256.

73. By October 13, 2023, the Examiner – without having made any claim rejections – issued a first Notice of Allowance, allowing all pending claims. *Id.* at pp.317-326. In his Reasons for Allowance, the Examiner stated: “**The closes[t] prior art** is [EXINI’s] **Hamadeh et al. (US 8,855,387)**.” *Id.* at p.323 (emphasis in original). The Examiner also stated:

However [Hamadeh] **fails to teach** a cancerous lesion automatically identification method for (d) receiving, by the processor, a 3D functional image of the subject obtained using a functional imaging modality; (e) identifying, within the 3D functional image, one or more 3D volume(s), each corresponding to an identified target VOI, using the 3D segmentation map; and(f) automatically detecting, by the processor, within at least a portion of the one or more 3D volumes identified within the 3D functional image, one or more hotspots determined to represent lesions based on intensities of voxels within the 3D functional image.

*Id.* at p.324 (emphasis in original). As I explained before, and as is directly relevant to the Examiner’s stated reasons for allowance, Hamadeh is expressly directed to “automated processing and interpretation of two-dimensional bone scan images.” Ex1014, 1:18-20 (emphasis added). Additionally, although not mentioned by the Examiner, Hamadeh does not appear to receive a 3D anatomical image obtained by an anatomical image modality (e.g., CT or MR) as claimed. Nor does Hamadeh automatically identify, using a machine learning module, target

volumes-of-interest with the 3D anatomical image as claimed. Instead, Hamadeh appears to be limited to identifying skeletal regions in a 2D functional bone scintigraphy image using a “segmentation-by-registration method” comprising: (i) comparing a (functional) bone scan image with an atlas image; (ii) adjusting the atlas image, which has anatomical regions marked in it, to the bone scan image, and (iii) superimposing the marked anatomical regions of the atlas image (i.e., skeleton) on the bone scan image. Ex1014, 3:6-15.

74. On October 30, 2023, the Applicant submitted a Request for Continued Examination to correct informalities in the specification (e.g., referring to application paragraph numbers) and disclose additional prior art. Ex1004, pp..330-351.

75. On November 21, 2023, the Examiner issued a second Notice of Allowance providing the same reasons for allowance as in the first Notice of Allowance. *Id.* at pp.421-431.

76. As far as I can tell, the Examiner did not give any material consideration to the prior art references I rely on here – at least because he did not realize that they are more pertinent than Hamadeh. Additionally, the prosecution history of the Patent does not include any substantive discussion or analysis of any of the prior art references on which my analysis is based.

### **C. The Claims of the Patent**

77. I address below claims 1-5, 7-14, 16-19, 22-32 of the Patent.

**1. Claim 1**

78. Independent claim 1 of the Patent reads:

A method for automatically processing 3D images to automatically identify cancerous lesions within a subject, the method comprising:

- (a) receiving, by a processor of a computing device, a 3D anatomical image of a subject obtained using an anatomical imaging modality, wherein the 3D anatomical image comprises a graphical representation of tissue within the subject;
- (b) automatically identifying, by the processor, using one or more machine learning modules, for each of a plurality of target tissue regions, a corresponding target volume of interest (VOI) within the 3D anatomical image;
- (c) determining, by the processor, a 3D segmentation map representing a plurality of 3D segmentation masks, each 3D segmentation mask representing a particular identified target VOI;
- (d) receiving, by the processor, a 3D functional image of the subject obtained using a functional imaging modality;
- (e) identifying, within the 3D functional image, one or more 3D volume(s), each corresponding to an identified target VOI, using the 3D segmentation

map; and

(f) automatically detecting, by the processor, within at least a portion of the one or more 3D volumes identified within the 3D functional image, one or more hotspots determined to represent lesions based on intensities of voxels within the 3D functional image.

Ex1001, 79:5-33.

## **2. Claim 2**

79. Claim 2 depends from claim 1 and further states “comprising using, by the processor, the one or more detected hotspots to determine a cancer status for the subject.” Ex1001, 79:34-36.

## **3. Claim 3**

80. Claim 3 depends from claim 1 and further states “wherein the target tissue regions comprise one or more reference tissue regions and wherein the method comprises:

using the 3D segmentation map to identify, by the processor, within the 3D functional image, one or more 3D reference volume(s), each corresponding to a particular reference tissue region;

determining, by the processor, one or more reference intensity values, each associated with a particular 3D reference volume of the one or more 3D reference volume(s) and corresponding to a measure of intensity within the

particular 3D reference volume;

determining, by the processor, one or more individual hotspot intensity values, each associated with a particular hotspot of at least a portion of the detected one or more hotspots and corresponding to a measure of intensity of the particular hotspot; and

determining, by the processor, one or more individual hotspot index values using the one or more individual hotspot intensity values and the one or more reference intensity values.

Ex1001, 79:37-57.

#### **4. Claim 4**

81. Claim 4 depends from claim 3 and further states “wherein the reference tissue regions comprise one or more members selected from the group consisting of: a liver, an aorta, and a parotid gland.” Ex1001, 79:58-60.

#### **5. Claim 5**

82. Claim 5 depends from claim 2 and further states “comprising, determining, by the processor, an overall index value indicative of a cancer status of the subject using at least a portion of the one or more hotspot index values.”

Ex1001, 79:61-64.

#### **6. Claim 7**

83. Claim 7 depends from claim 1 and further states “wherein:  
the anatomical 3D image is an x-ray computed tomography (CT) image, and  
the 3D functional image is a 3D positron emission tomography (PET) image.  
Ex1001, 80:1-5.

**7. Claim 8**

84. Claim 8 depends from claim 7 and further states “wherein the 3D PET  
image of the subject is obtained following administration to the subject of a  
radiopharmaceutical comprising a prostate-specific membrane antigen (PSMA)  
binding agent.” Ex1001, 80:6-9.

**8. Claim 9**

85. Claim 9 depends from claim 8 and further states “wherein the  
radiopharmaceutical comprises [<sup>18</sup>F]DCFPyL.” Ex1001, 80:10-11.

**9. Claim 10**

86. Independent claim 10 reads:  
A system for automatically processing 3D images to automatically identify  
cancerous lesions within a subject, the system comprising:  
a processor of a computing device; and  
a memory having instructions stored thereon, wherein the instructions, when  
executed by the processor, cause the processor to:

(a) receive a 3D anatomical image of a subject obtained using an anatomical imaging modality, wherein the 3D anatomical image comprises a graphical representation of tissue within the subject;

(b) automatically identify, using one or more machine learning modules, for each of a plurality of target tissue regions, a corresponding target volume of interest (VOI) within the 3D anatomical image;

(c) determine a 3D segmentation map representing a plurality of 3D segmentation masks, each 3D segmentation mask representing a particular identified target VOI;

(d) receive a 3D functional image of the subject obtained using a functional imaging modality;

(e) identify, within the 3D functional image, one or more 3D volume(s), each corresponding to an identified target VOI, using the 3D segmentation map; and

(f) automatically detect, within at least a portion of the one or more 3D volumes identified within the 3D functional image, one or more hotspots determined to represent lesions based on intensities of voxels within the 3D functional image.

Ex1001, 80:12-41.

## **10. Claim 11**

87. Claim 11 depends from claim 10 and further states “wherein the instructions cause the processor to use the one or more detected hotspots to determine a cancer status for the subject.” Ex1001, 80:42-44.

### **11. Claim 12**

88. Claim 12 depends from claim 10 and further states “wherein the target tissue regions comprise one or more reference tissue regions and wherein the instructions cause the processor to:

use the 3D segmentation map to identify, within the 3D functional image, one or more 3D reference volume(s), each corresponding to a particular reference tissue region;

determine one or more reference intensity values, each associated with a particular 3D reference volume of the one or more 3D reference volume(s) and corresponding to a measure of intensity within the particular 3D reference volume;

determine one or more individual hotspot intensity values, each associated with a particular hotspot of at least a portion of the detected one or more hotspots and corresponding to a measure of intensity of the particular hotspot; and

determine one or more individual hotspot index values using the one or more individual hotspot intensity values and the one or more reference intensity

values.”

Ex1001, 80:45-64.

### **12. Claim 13**

89. Claim 13 depends from claim 12 and further states “wherein the reference tissue regions comprise one or more members selected from the group consisting of: a liver, an aorta, and a parotid gland.” Ex1001, 80:65-67.

### **13. Claim 14**

90. Claim 14 depends from claim 11 and further states “wherein the instructions cause the processor to determine an overall index value indicative of a cancer status of the subject using at least a portion of the one or more hotspot index values.” Ex1001, 81:1-4.

### **14. Claim 16**

91. Claim 16 depends from claim 10 and further states “wherein:  
the anatomical 3D image is an x-ray computed tomography (CT) image; and  
the 3D functional image is a 3D positron emission tomography (PET)  
image.”

Ex1001, 81:8-12.

### **15. Claim 17**

92. Claim 17 depends from claim 16 and further states “wherein the 3D

PET image of the subject is obtained following administration to the subject of a radiopharmaceutical comprising a prostate-specific membrane antigen (PSMA) binding agent.” Ex1001, 81:13-16.

**16. Claim 18**

93. Claim 18 depends from claim 17 and further states “wherein the radiopharmaceutical comprises [<sup>18</sup>F]DCFPyL.” Ex1001, 81:17-18.

**17. Claim 19**

94. Claim 19 depends from claim 1 and further states “wherein the target tissue regions comprise one or more background tissue regions and wherein the method comprises:

at step (e), using the 3D segmentation map to identify, within the 3D functional image, as at least a portion of the one or more 3D volumes, one or more 3D background tissue volume(s), each corresponding a particular background tissue region; and

excluding voxels of the 3D within the 3D background tissue from the voxels used to automatically detect the one or more hotspots at step (f).”

Ex1001, 81:19-29.

**18. Claim 22**

95. Claim 22 depends from claim 8 and further states “wherein the

radiopharmaceutical comprises  $^{68}\text{Ga}$ -PSMA-11.” Ex1001, 82:1-2.

**19. Claim 23**

96. Claim 23 depends from claim 8 and further states “wherein the radiopharmaceutical comprises  $^{68}\text{Ga}$ -PSMA-617.” Ex1001, 82:3-4.

**20. Claim 24**

97. Claim 24 depends from claim 8 and further states “wherein the radiopharmaceutical comprises  $^{68}\text{Ga}$ -PSMA-I&T.” Ex1001, 82:5-6.

**21. Claim 25**

98. Claim 25 depends from claim 8 and further states “wherein the radiopharmaceutical comprises  $^{18}\text{F}$ -PSMA-1007.” Ex1001, 82:7-8.

**22. Claim 26**

99. Claim 26 depends from claim 10 and further states “wherein the target tissue regions comprise one or more background tissue regions and wherein the instructions cause the processor to:

at step (e), using the 3D segmentation map to identify, within the 3D functional image, as at least a portion of the one or more 3D volumes, one or more 3D background tissue volume(s), each corresponding a particular background tissue region; and

exclude voxels of the 3D within the 3D background tissue from the voxels

used to automatically detect the one or more hotspots at step (f).”

Ex1001, 82:9-20.

**23. Claim 27**

100. Claim 27 depends from claim 14 and further states “wherein:  
the overall index value is associated with a particular target tissue region corresponding to a particular target VOI identified within the anatomical image; and  
the overall index value is determined using hotspot index values of a subset of hotspots located within a particular 3D volume in the 3D functional image that corresponds to the particular identified target VOI.”

Ex1001, 82:21-28.

**24. Claim 28**

101. Claim 28 depends from claim 26 and further states “wherein the particular target tissue region is selected from the group consisting of: a skeletal region comprising one or more bones of the subject, a lymph region, and a prostate region.” Ex1001, 82:29-32.

**25. Claim 29**

102. Claim 29 depends from claim 17 and further states “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-11.” Ex1001, 82:33-34.

**26. Claim 30**

103. Claim 30 depends from claim 17 and further states “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-617.” Ex1001, 82:35-36.

**27. Claim 31**

104. Claim 31 depends from claim 17 and further states “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-I&T.” Ex1001, 82:37-38.

**28. Claim 32**

105. Claim 32 depends from claim 17 and further states “wherein the radiopharmaceutical comprises <sup>18</sup>F-PSMA-1007.” Ex1001, 82:39-40.

**VII. OPINIONS REGARDING CLAIM CONSTRUCTION**

**A. Ordinary and Customary Meaning**

106. Unless otherwise stated herein, I interpret the terms of the Patent’s claims as having their ordinary and customary meaning.<sup>1</sup> After having reviewed the Patent specification and prosecution history, I do not see any need to deviate from the plain and ordinary meaning of the claim language based on, for example,

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<sup>1</sup> I reserve the right, in the district court litigation brought by Patent Owner against Petitioner, to identify other claim terms and phrases that might require construction. Such additional terms – not addressed here – might be material to the determination of infringement of the accused instrumentalities, even if they are not relevant based on the features of the prior art cited in this Petition.

disclaimer, disavowal, or unique lexicography.

107. I do not interpret any terms of the Patent's claims to be means-plus-function terms.

**B. 3D Segmentation Map (Claims 1, 3, 10, 12, 19, 26)**

108. The claim term "3D segmentation map" does not have a well-established ordinary and customary meaning. Accordingly, I look to the intrinsic evidence, including the Patent claim language and specification, to determine how the term is used in Patent.

109. The Patent claims internally define a 3D segmentation map as "representing a plurality of 3D segmentation masks, each 3D segmentation mask representing a particular identified target VOI." Ex1001, 79:19-22, 80:27-30. This description is consistent with the Patent specification, which explains that each 3D VOI corresponding to a specific target tissue region, such as one or more organs, may be represented via a segmentation mask, and "[t]he multiple segmentation masks, identifying multiple target tissue regions across a patient's body, can be stitched together to form a segmentation map." Ex1001, 32:6-13. Based on this intrinsic evidence, I interpret the term "3D segmentation map" as simply "a plurality of 3D segmentation masks distinguishing a plurality of regions within a 3D image."

110. Although I do not rely on it for my interpretation, I note that the

Patent Owner has asserted that Petitioner infringes claim 1 of the Patent, Ex1013, ¶¶110-117, and that Petitioner’s accused product satisfies the limitation “determining, by the processor, a 3D segmentation map representing a plurality of 3D segmentation masks ...” simply “because ... [the accused product’s] physiological uptake removal technique involves creating 3D organ contours that represent and delineate particular organs, for example, in order to transfer them to 3D nuclear medicine (e.g., SPECT and/or PET) images.” Ex1013, ¶114 (emphasis added). From this, I understand that the Patent Owner is not ascribing any special definition to the term “3D segmentation map” and is using it in a manner consistent with the scope of my interpretation.

## **VIII. SUMMARY OF THE PRIOR ART**

### **A. US2012/0123253 (“Renisch”)**

111. Renisch is a United States patent application that published on May 17, 2012. Ex1005, cover. I understand, therefore, that Renisch is prior art to the Patent, even if I assume that the Patent’s priority date is January 7, 2019.

112. Renisch teaches that, as of its filing date, nuclear medicine imaging was being increasingly used in cancer imaging due to the success of tracers such as FDG. *Id.* at [0003]. FDG, when injected into a patient, accumulates in regions of high metabolic activity, including cancerous tumors. *Id.* When FDG accumulates in high amounts, it can be seen in nuclear medicine (functional) images as regions

of high intensity, also known as hot spots. *Id.*

113. Renisch also teaches that, as of its filing date, the current clinical practice was for a clinician to manually identify and segment hot spots as potential lesions, which was time consuming and prone to error, particularly for metastatic cancer that involves many separate lesions throughout the body. *Id.* at [0004]. Additionally, because uptake of the FDG tracer is also high in normally functioning organs with high metabolic activity, such as the brain and liver, lesions can be obscured by regions of high FDG uptake that are not related to cancer. *Id.* Accordingly, Renisch discloses an improved hot spot identification system that automatically segments lesions while suppressing regions where high physiological uptake is expected. *Id.* at [0006].

114. Renisch discloses a hot spot detection system for automatically segmenting and quantifying hot spots in functional images, such as PET or SPECT images. *Id.* The hot spot detection system includes: (i) a segmentation unit to segment anatomical images (e.g., CT or MR images) into regions corresponding to anatomical structures; (ii) a classification unit to classify the identified hot spots according to their location relative to the segmented anatomical structures; (iii) a suppression unit to suppress detected hot spots based on the results of the classification unit (e.g., if the hot spots are classified as being located within a normal functioning organ that is expected to have high physiological uptake); and

(iv) an identification unit that identifies unsuppressed hot spots as either a potential cancerous lesion or not a lesion. *Id.*

115. With reference to Fig. 1, which is reproduced below, Renisch discloses that the hot spot detection system 70 receives 3D anatomical images from a first diagnostic scanner 12, such as a CT scanner, and 3D functional images from a second diagnostic scanner 40, such as a PET scanner, through a workstation 62. *Id.* at [0020]-[0023].

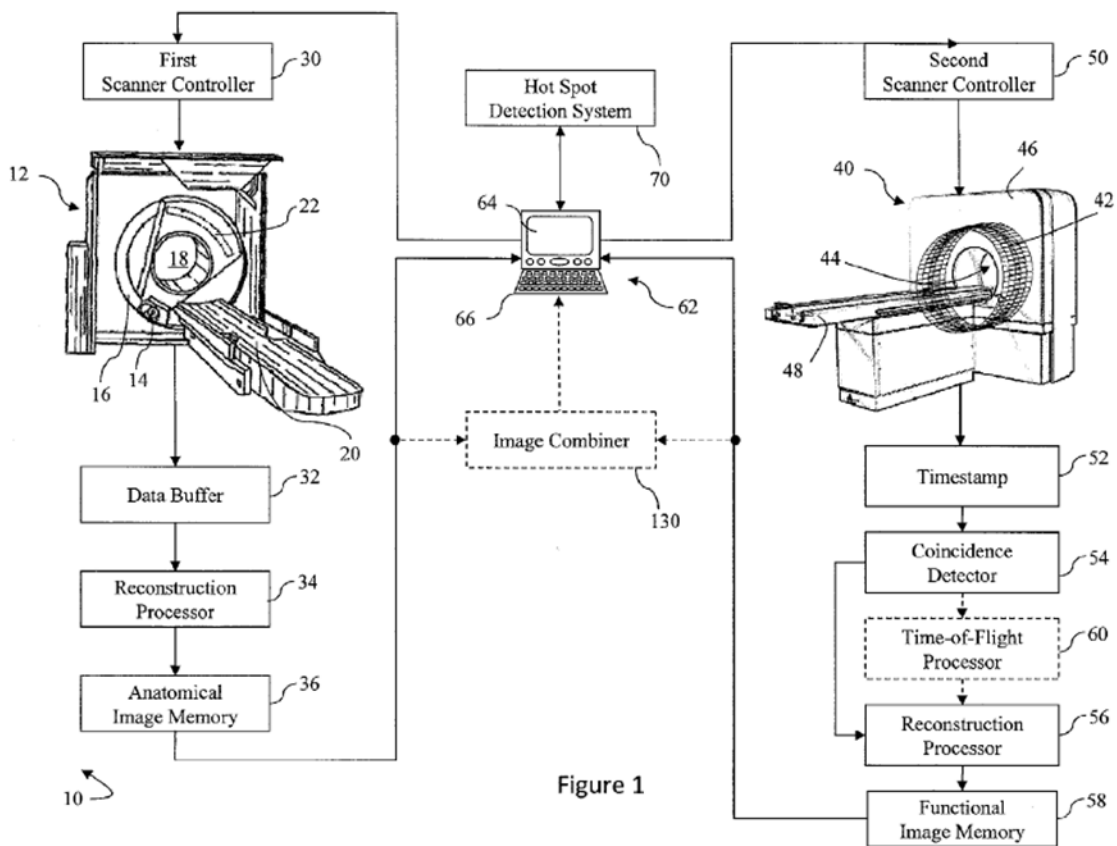


Figure 1

116. Referring now to Fig. 2, which is reproduced below, a segmentation unit 76 of the hot spot detection system 70 automatically segments the received

anatomical images into regions that correspond to anatomical structures such as the brain, heart, bladder, liver, and kidneys. *Id.* at [0025]. The segmentation can be model-based, using atlas images, or can be accomplished using machine learning algorithms such as clustering or artificial neural networks. *Id.* at [0027].

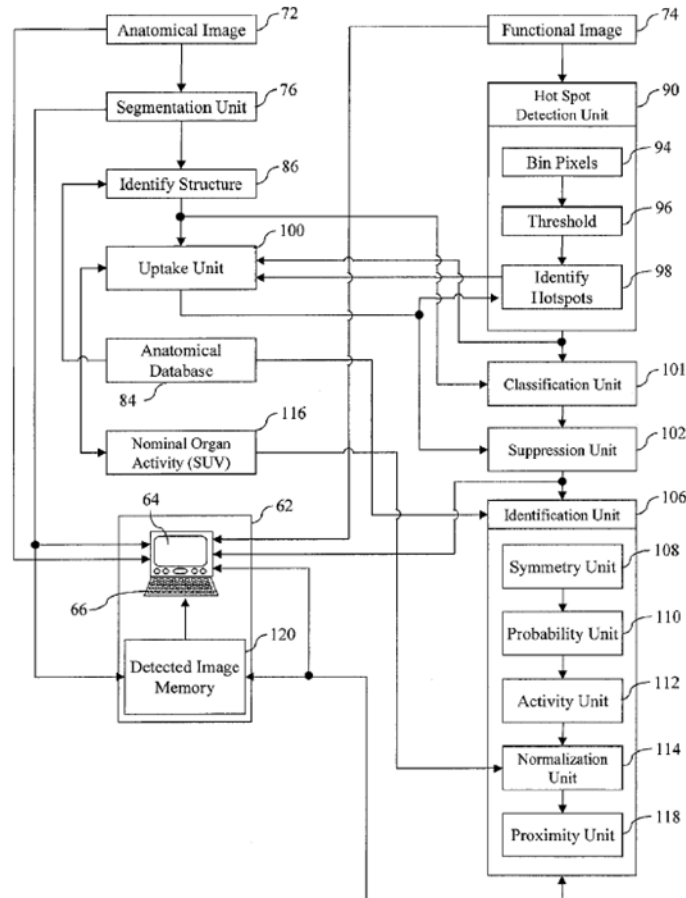


Figure 2

117. Renisch teaches that “[s]egmentation can ... be helpful for accurately determining a location of the hot spots relative to the patient’s anatomy” and “anatomical regions identified in the anatomical first image representation [] can be carried over to the functional second image representation [] in order to

delineate anatomical structures in the second image representation.” *Id.* at [0025], [0034].

118. With reference to Figs. 3A-3C, Renisch produces images in which regions of high radioactive tracer uptake are segmented as hot spots in a functional image (Fig. 3A), images in which segmented organ tissue regions (e.g., brain, heart, bladder) are geographically identified as graphical overlays on the functional image containing segmented hot spots (Fig. 3B), and images in which segmented hot spots located within normal functioning organs with high physiological uptake are suppressed, leaving only hot spots that are suspected to be potential cancerous lesions. (Fig. 3C). *Id.* at [0015]-[0017], [0025], [0029], [0031].

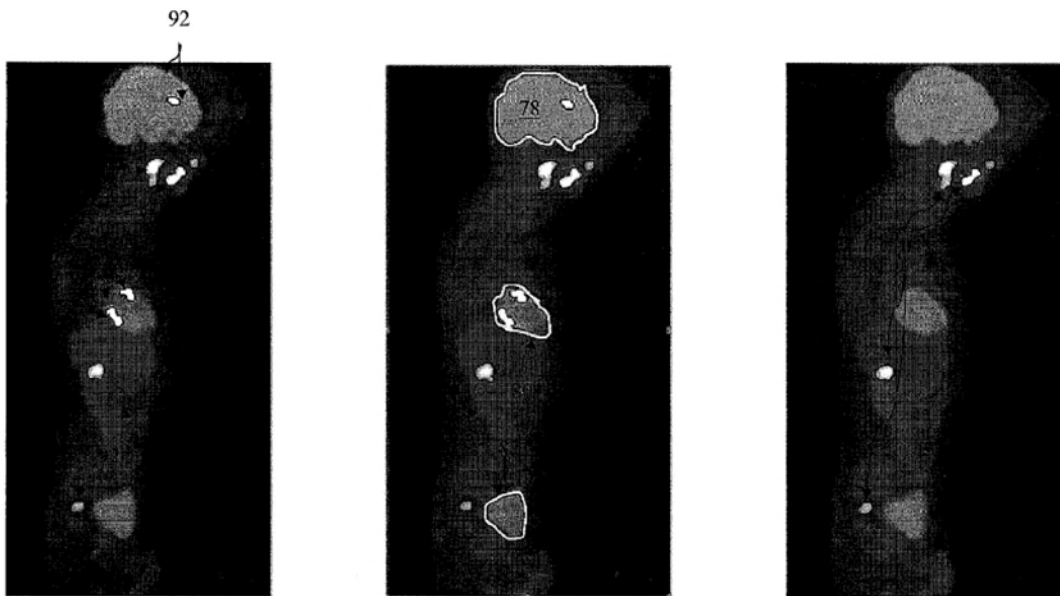


Figure 3A

Figure 3B

Figure 3C

119. Additionally, Renisch expressly states that the segmented anatomical and functional images can be combined for concurrent display on a graphical user interface. *Id.* at [0036]-[0037]. For example, Renisch explains that “the images can be superimposed in different colors, the outline of the functional second image representation hotspots can be superimposed on the first image representation, the outline of the segmented anatomical structures of the anatomical first image representation can be superimposed on the functional second image representation, ... or the like.” *Id.* at [0037]. Likewise, Renisch states that “[t]he segmented and unsegmented anatomical images, the function [sic] images, the functional image with high uptake organs suppressed, in image or map of quantified hot spots, and superimposed combinations thereof are stored.” *Id.* at [0036] (emphasis added).

**B. US10,140,544 (“Zhao”)**

120. Zhao is a U.S. patent issued on November 27, 2018. Ex1007, cover. I understand, therefore, that Zhao is prior art to the Patent, even if I assume that the Patent is entitled to a priority date of January 7, 2019.

121. Zhao relates, generally, to “digital image segmentation and region of interest identification.” *Id.*, Abstract. Zhao states that “[a] digital image may contain one or more regions of interests (ROIs)” and “recognition of ROIs in a digital image and identification of boundaries for these ROIs using computer vision often constitute a critical first step before further image processing is

performed.” *Id.* at 5:11-17. Zhao further states that “[i]dentification of ROIs in a digital image is often alternatively referred to as image segmentation,” (*id.* at 5:21-22) and that “[s]egmentation of images may be performed by a computer using a model developed using deep neural network-based machine learning algorithms” (*id.* at 6:31-33).

122. While explaining the state of the art, rather than a new invention, Zhao states that “ROIs, once determined, may be represented by a digital mask containing a same number of pixels as the digital image or down-sized number of pixels from the digital image.” *Id.* at 5:25-28. Additionally, Zhao states that “[a] digital mask may be alternatively referred to as a mask or segmentation mask.” *Id.* at 5:28-29.

123. Zhao explains:

Each pixel of the mask may contain a value used to denote whether a particular corresponding pixel of the digital image is among any ROI, and if it is, which type of ROI among multiple types of ROIs does it fall. For example, if there is only a single type of ROI, a binary mask is sufficient to represent all ROIs. In particular, each pixel of the ROI mask may be either zero or one, representing whether the pixel is or is not among the ROIs. For a mask capable of representing multiple types of ROI, each pixel may be at one of a number of values each corresponding to one type of ROIs. A multi-value mask, however, may be decomposed into a combination [sic] the more fundamental binary masks each for one type of ROI.

*Id.* at 5:30-42.

124. Additionally, Zhao explains:

ROI masks are particularly useful for further processing of the digital image. For example, an ROI mask can be used as a filter to determine a subset of image data that are among particular types of ROIs and that need be further analyzed and processed. Image data outside of these particular types of ROIs may be removed from further analysis.

125. Zhao further discloses that “ROI identification and segmentation may be implemented in medical image processing” including processing of “Computed Tomography (CT) images.” *Id.* at 5:60-64. Zhao states: “For example, an ROI may be an entire organ. As such, a corresponding binary ROI mask may be used to mark the location of the organ tissue and the regions outside of the ROI and that are not part of the organ.” *Id.* at 6:4-7.

### **C. US2018/0144828 (“Baker”)**

126. Baker is a U.S. patent application published on May 24, 2018. Ex1008, cover. It was filed on October 26, 2017, claiming priority to a provisional application filed on October 27, 2016. *Id.* The sole named inventor is Mark R. Baker, and the Applicant/Assignee is Progenics Pharmaceuticals, Inc. *Id.* I understand, therefore, that Baker is prior art to the Patent, even if I assume that the Patent is entitled to a priority date of January 7, 2019.

127. Baker discloses that “commonly available nuclear medicine cameras, known as single-photon emission computerized tomography (SPECT) or positron emission tomography (PET) cameras, found in most hospitals throughout the world” are used by physicians “to determine the presence and the extent of disease in a patient.” *Id.* at 1:30-47. For example, “[a]n oncologist may use images from a targeted PET or SPECT study of a patient as input in her assessment of whether the patient has a particular disease, e.g., prostate cancer, what stage of the disease is evident, what the recommended course of treatment (if any) would be, whether surgical intervention is indicated, and likely prognosis.” *Id.* at 2:4-10. Additionally, the Baker explains that “[t]here are also a number of radiopharmaceuticals available for imaging particular kinds of cancer” including “the small molecule diagnostic 1404” which can be used for “the detection of primary and metastatic prostate cancer.” *Id.* at 1:51-61.

128. Baker discloses “a software tool ... featuring a graphical user interface (GUI) element ... for ... presentation of a 3D risk image corresponding to a patient organ (and/or other tissue) for comparison with reference images (e.g., for use in communication of results to [a] patient as a decision-making support).” *Id.* at 3:15-20. “For example, a patient for whom a risk of cancer is detected can display a map indicating areas and/or degrees of risk and can compare this risk map with those of others for whom a given course of treatment is recommended.”

*Id.* at 3:26-30.

129. In pertinent part, Baker describes a “decision support system” (and method) comprising a processor and a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to: (i) access one or more medical images associated with a patient from a database (e.g., PET/SPECT/CT/MRI/US and composites thereof); (ii) “automatically analyze one or more of the medical images [e.g., to generate a risk index ... and/or a risk map, e.g., a visual representation (e.g., 3D representation) of tissue (e.g., an organ or other part of the body) with graphical denotations (e.g., texture- or color-coding) marking regions of risk of current disease or risk of recurrence of disease, e.g., cancer];” and (iii) display the risk map via a graphical user interface (GUI) “e.g., wherein the risk map is displayed as an overlay of the PET/SPECT/CT/MRI/US/combined/derived/fused image of the tissue, or is in place of the image of the tissue.” *Id.* at 3:43-4:12.

130. Baker states that its “automatic analysis” of the one or more medical images can be carried out using machine learning algorithms, including artificial neural networks, to perform tasks such as: (i) segmentation of tissue regions in CT scans (*id.* at 26:50-55); (ii) classification of hot spots in nuclear medicine images (e.g., PET or SPECT) as cancerous lesions (*id.* at 25:41-45); and (iii) predicting a risk index value (*id.* at 25:64-26:3).

131. In some embodiments described by Baker, a nuclear medicine image, such as a PET scan, and an anatomical image, such as a CT scan, are combined as a composite image by overlaying the anatomical image with the nuclear medicine image. *Id.* at 26:34-36. Baker explains that “overlaying one image (e.g., a CT scan) with another (e.g., a PET scan) refers to establishing a mapping between coordinates and/or pixels or voxels of the two images that that [sic] represent the same physical locations (e.g., within the patient).” *Id.* at 26:36-40.

132. Baker states:

CT scans provide accurate anatomical information in the form of detailed three-dimensional (3D) images of internal organs, bones, soft tissue, and blood vessels. Accordingly, 3D boundaries of specific regions of imaged tissue can be accurately identified by analysis of CT scans. For example, automated segmentation of CT scans can be performed to identify 3D boundaries of specific organs (e.g., a prostate, lymph nodes, a lung or lungs), sub-organs, organ regions, as well as other regions of imaged tissue, such as particular bones and an overall skeletal region of the patient.

*Id.* at 26:40-50 (emphasis added). Baker further explains that:

Once the 3D boundaries of various regions are identified within a CT scan of a composite image, by virtue of the mapping between the CT scan and PET scan of the composite image, the identified 3D boundaries can be transferred to the PET image. Accordingly, regions of the PET image falling within and/or outside of the identified 3D

boundaries can be accurately identified.

*Id.* at 26:61-66.

133. Baker discloses using the 3D boundaries of specific tissue regions that have been transferred to nuclear medicine images, such as PET images, to calculate risk indices and produce a risk map. For example, Baker explains that a bone scan index (“BSI”) value is “a risk index that is a numeric value that quantifies the fraction of the total skeleton of the patient that is involved by cancerous tissue (e.g., tumors), based on [] detected hotspots.” *Id.* at 26:4-7. According to Baker, BSI is computed by segmenting a whole-body scan of the patient “to geographically identify boundaries of regions ... that correspond to ... the patient’s skeleton.” *Id.* at 25:21-25. “Hotspots corresponding to cancerous tissue lesions within the patient’s skeleton, once detected, can be used to determine a risk index that provides a measure of disease state for the patient.” *Id.* at 25:46-49.

134. Similarly, Baker states:

[O]nce the 3D boundaries of the various regions are identified within the PET scan, one or more risk indices can be computed in a similar fashion to that described above with regard to BSI. In particular, in certain embodiments, intensity values of the PET scan in relation to (e.g., within and/or outside of) the 3D boundaries of the identified regions can be used to determine levels of cancerous tissue within the

identified regions, e.g., based on features of detected hotspots (e.g., detected hotspots corresponding to metastases). Risk indices can then be computed based on the determined cancerous tissue levels. For example, hotspots within the PET scan can be identified, and, based on features such as their size, number, and distribution with respect to the identified regions, used to compute one or more risk indices.

*Id.* at 27:11-25.

#### **D. The PROMISE Criteria (“Eiber”)**

135. Eiber (Ex1009) is a scientific journal article published in March 2018. I understand, therefore, that it is prior art to the Patent even if I assume that the Patent is entitled to a priority date of January 7, 2019. Eiber was disclosed during examination of the Patent in an information disclosure statement filed on June 26, 2023. Ex1004, p.784.

136. Following the advent of prostate-cancer-specific radiotracers, such as the PSMAAs described in Baker above, efforts were made to standardize reporting of prostate cancer nuclear medicine imaging results. Eiber explains: “Prostate-specific membrane antigen (PSMA)-ligand PET/CT or PET/MRI provides high sensitivity and specificity for prostate cancer staging. The accuracy of PSMA-ligand hybrid imaging is superior to that of conventional imaging and tracers.” Ex1009, p.469. Eiber also states: “We anticipate increased adoption of PSMA-ligand PET/CT fueled by upcoming evidence and inclusion into guidelines. Thus,

reporting standards must be created now to aid reproducibility, enhance communication, and ultimately support acceptance of this technology.” *Id.* Accordingly, Eiber introduces the “Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria.” *Id.*

137. Eiber states:

[W]e propose a molecular imaging TNM (miTNM) [(molecular imaging tumor/node/metastases)] framework for PSMA-ligand PET/CT prostate cancer staging. This framework may also be applied for PSMA-ligand PET/MRI, SPECT/CT, or similar approaches. miTNM serves to provide standardized reporting of the presence, location, and extent of local prostate cancer and its pelvic spread; the presence, location, extent, and distribution pattern of extrapelvic metastases; the PSMA expression level of tumor lesions; and diagnostic confidence about reported findings.

*Id.* at 2 (emphasis added). With reference to Table 1, which is reproduced below,

Eiber states:

We propose a miPSMA score that enables standardized reporting of PSMA expression as detected with PSMA-ligand PET. Expression categories are defined in relation to mean uptake in the blood pool, liver, and parotid gland (Table 1; Fig. 1). Results are reported as 0, 1, 2, or 3 for no, low, intermediate, or high PSMA expression, respectively.

*Id.* at 3.

**TABLE 1**  
miPSMA Expression Score

Score	Reported PSMA expression	Uptake
0	No	Below blood pool
1	Low	Equal to or above blood pool and lower than liver*
2	Intermediate	Equal to or above liver* and lower than parotid gland
3	High	Equal to or above parotid gland

\*For PSMA ligands with liver-dominant excretion (e.g., <sup>18</sup>F-PSMA1007) spleen is recommended as reference organ instead of liver.

Eiber also states: “[W]e advise comparison of the mean SUVs [(standard uptake values)] of the respective lesions and the reference organ.” *Id.* Thus, Eiber discloses a standardized method of scoring individual lesions (i.e., hotspots) detected using PSMA PET by: (i) measuring the uptake (intensity) of a lesion; (ii) measuring the uptake in reference organs such as the liver; and (iii) comparing the uptake in the lesion to the uptake in the reference organs to place the lesion on a scale relative to the reference organs, e.g., more or less uptake than the liver.

**E. US2011/0007954 (“Suehling”)**

138. Suehling is a United States patent application that published on January 13, 2011. Ex1006, cover. I understand, therefore, that Suehling is prior art to the Patent, even if I assume that the Patent is entitled to a priority date of

January 7, 2019.

139. Suehling discloses a system for automatically detecting, segmenting, and displaying lesions in 3D medical images such as CT images or hybrid PET/CT images. *Id.* at Abstract, Fig. 1, [0006], [0025]. With reference to Figs. 1 and 2, which are reproduced below, Suehling receives a 3D medical image and automatically segments the image into lesion search regions corresponding to particular organs and bones, as well as search regions outside the organs and bones. *Id.* at [0007], [0026]-[0031].

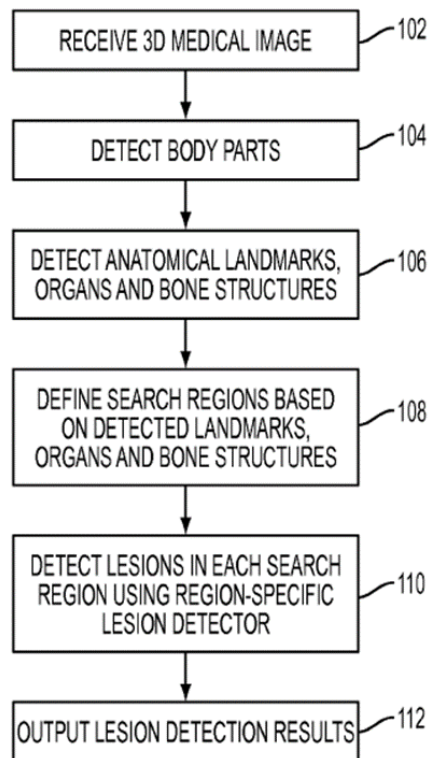


FIG. 1

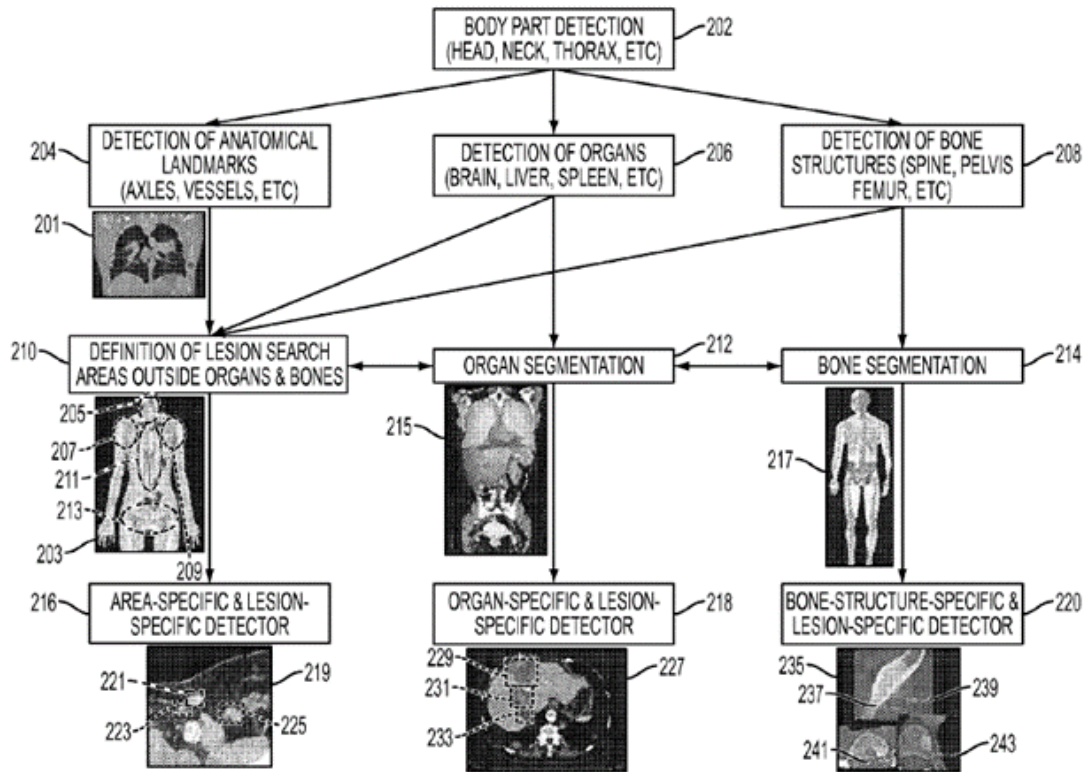


FIG. 2

140. Anatomical segmentation of organs and bones (e.g., brain, liver, spleen, kidneys, lungs, heart, spine, pelvis, femur) to define search regions is accomplished using “well known organ segmentation techniques” including machine learning algorithms such as “Marginal Space Learning.” *Id.* at [0027], [0030]. The search regions for lesions outside the organs and bones are defined using the segmentation results “to exclude the detected organs and bones from these search regions.” *Id.* at [0029], Fig. 2 (210) (“Definition Of Lesion Search Areas Outside Organs And Bones”).

141. Suehling teaches that “[a] general lesion detection algorithm for the whole body is ... unlikely to yield reliable results.” *Id.* at [0024]. Accordingly,

Suehling detects lesions in each of the search regions, separately, using respective region-specific lesion detectors. *Id.* at [0032]-[0033]. The region-specific lesion detectors likewise use trained machine learning algorithms including marginal space learning (MSL). *Id.*

142. It is apparent that Suehling determines a segmentation map comprising a plurality of segmentation masks because after detecting lesions throughout the body, Suehling automatically labels lesions by location so that lesion detection results can be navigated on a region-by-region basis (e.g., displaying only liver lesions or only lung lesions). *Id.* at [0042]-[0043]. Additionally, after the organs and bones are segmented, they are excluded or masked from rest of the body to define the search regions outside the organs and bones. *Id.* at [0029].

## **IX. DETAILED OPINIONS REGARDING INVALIDITY**

143. As detailed below, claims 1-5, 7-14, 16-19, 22-26, and 28-32 of the Patent are unpatentable as anticipated and/or obvious in view of the prior art. I rely principally on two alternative primary references, Renisch (Ex1005) and Baker (Ex1008).

144. The following table sets forth the prior art that anticipates and/or the combination of prior art that renders obvious each of claims 1-5, 7-14, 16-19, 22-26, and 28-32:

<b>Ground</b>	<b>Prior Art</b>	<b>Basis</b>	<b>Claims Challenged</b>
A	Renisch	Anticipation	1-5, 7, 10-14, 16, 19, 26
B	Renisch in view of Zhao	Obviousness	1-5, 7, 10-14, 16, 19, 26
C	Renisch, or Renisch in view of Zhao, each in view of Baker	Obviousness	8-9, 17-18, 22-25, 29-32
D	Renisch, or Renisch in view of Zhao, each in view of Eiber	Obviousness	8-9, 17-18, 22, 24-25, 29, 31-32
E	Baker in view of Zhao	Obviousness	1-2, 7-11, 16-18, 22-25, 29-32
F	Baker in view of Zhao and Eiber	Obviousness	3-5, 12-14
G	Baker in view of Zhao and Suehling	Obviousness	19, 26, 28

**A. Grounds A and B: Anticipation by Renisch or Obviousness Over Renisch in view of Zhao**

**1. Independent Claim 1**

- a) **Preamble: “A method for automatically processing 3D images to automatically identify cancerous lesions within a subject, the method comprising:”**

145. I understand that the preamble of a claim is typically just a statement of intended use that does not limit the scope of the claim. For the purposes of providing a thorough analysis, however, I will assume that the preamble of claim 1 is limiting and I will address it like any other claim limitation. It is my opinion that Renisch discloses “[a] method for automatically processing 3D images to automatically identify cancerous lesions within a subject.”

146. Renisch teaches that regions of high radiotracer uptake in nuclear medicine images are known as “hot spots,” and that hot spots indicate regions of

high metabolic activity, which may be cancerous lesions caused by tumor growth. Ex1005 at [0003], [0029].

147. Renisch discloses: “A hot spot detection system for automatically segmenting and quantifying hot spots in functional images” where “regions of high uptake are identified ... as one of potential lesions and non-potential lesions.” *Id.* at Abstract, [0032] (“perform various checks ... to determine if they are lesions”).

148. The images that Renisch automatically analyzes are 3D anatomical images, such as CT scans (*id.* at [0020]-[0021]), and 3D functional images, such as PET and SPECT scans (*id.* at [0022]-[0023]).

149. With reference to Fig. 3A below, Renisch depicts the automatic segmentation of high intensity voxels (i.e., hot spots) in a 3D functional image highlighted with color overlays to identify the locations of potential lesions. *Id.* at [0015], [0029].

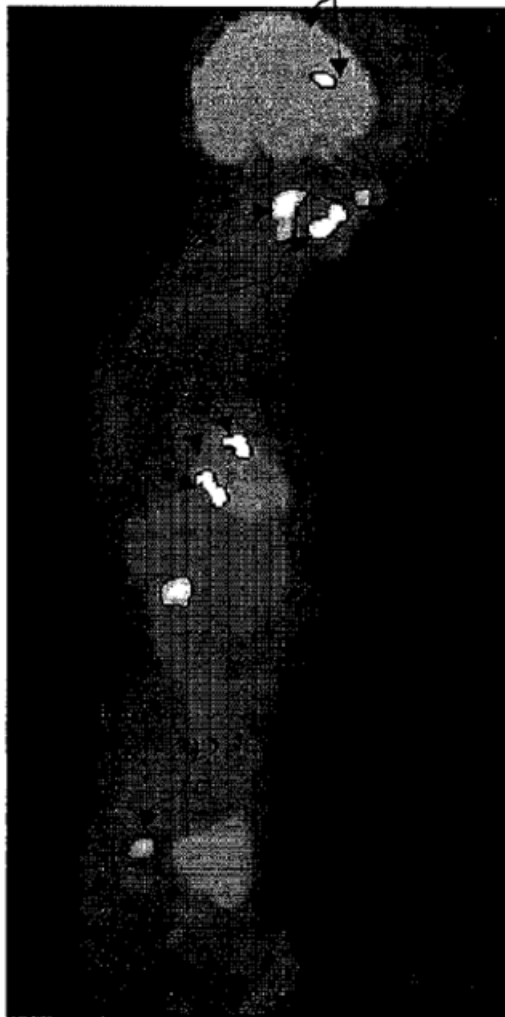


Figure 3A

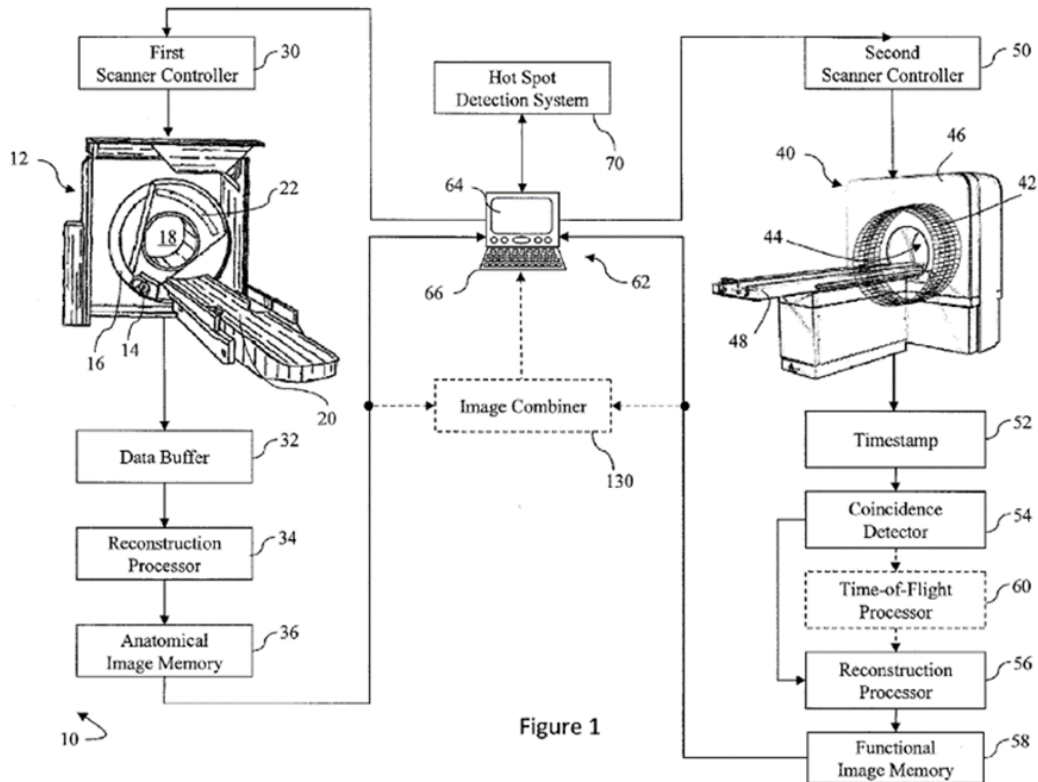
150. Accordingly, Renisch discloses the preamble of claim 1.

- b) **Limitation 1(a): “receiving, by a processor of a computing device, a 3D anatomical image of a subject obtained using an anatomical imaging modality, wherein the 3D anatomical image comprises a graphical representation of tissue within the subject;”**

151. It is my opinion that Renisch discloses Limitation 1(a) of claim 1. *Id.*

at Figs. 1 and 2, [0021], [0025].

152. Referring to Fig. 1 below, Renisch discloses a computer implemented diagnostic system 10 comprising a first anatomical imaging scanner 12, a second functional imaging scanner 40, such as a PET scanner, a workstation/GUI 62, and an automatic hot spot detection system 70. *Id.* at [0020], [0022]. The anatomical imaging scanner 12, which is an x-ray CT scanner, produces 3D anatomical images that constitute a graphical representation of tissue within the patient/subject. *Id.* at [0020]-[0021].



153. With reference to Fig. 2, which is reproduced below, the hot spot

detection system 70 comprises functional units (e.g., segmentation unit 76) that Renisch alternatively describes as “processors” or “algorithms”. *Id.* at [0014], [0030] (“uptake unit, processor, or algorithm”), [0031] (“classification unit, processor, or algorithm”), [0032] (“identification unit, processor, or algorithm”), [0034] (“quantification unit also includes a probability unit, processor, or algorithm”).

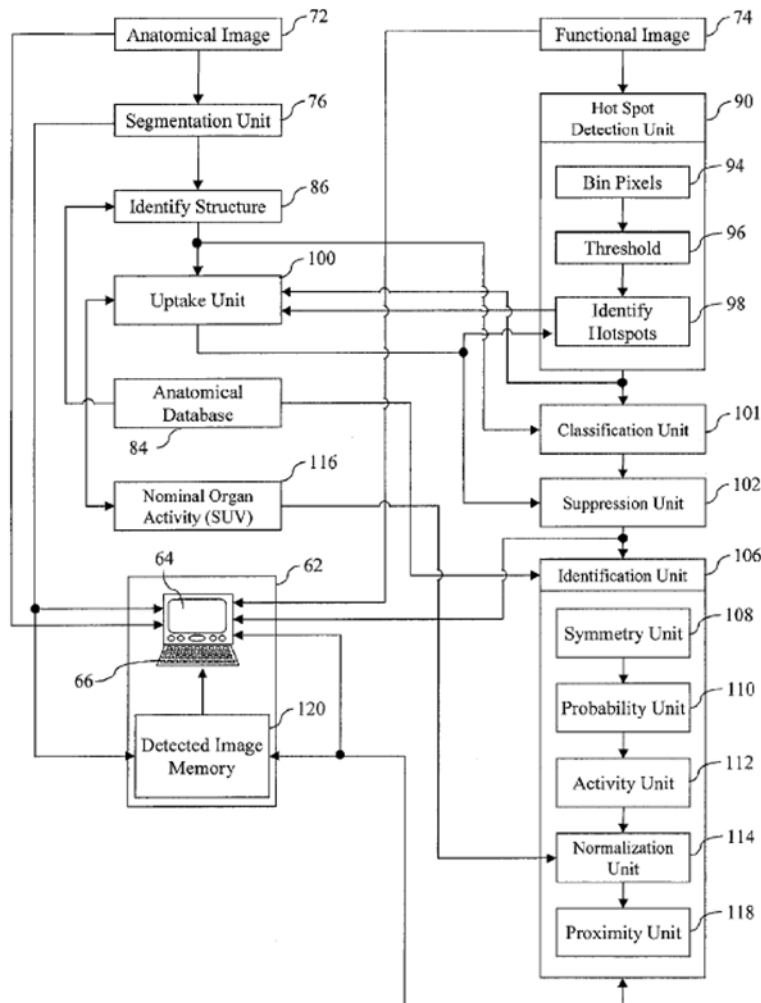


Figure 2

154. Renisch states that “the diagnostic system 10 includes a hot spot

detection system 70 for automatic detection of ... a lesion ... based on anatomical images 72 from the anatomical image memory 36 and functional images 74 from the functional image memory 58.” *Id.* at [0025]. As depicted in Fig. 2 above, the segmentation unit 76 (i.e., processor) receives the anatomical image 72, which is a reconstructed 3D image. *Id.* at [0021].

155. Accordingly, it is my opinion that Renisch discloses Limitation 1(a).

**c) Limitation 1(b): “automatically identifying, by the processor, using one or more machine learning modules, for each of a plurality of target tissue regions, a corresponding target volume of interest (VOI) within the 3D anatomical image;”**

156. It is my opinion that Renisch discloses Limitation 1(b). *Id.* at [0008] (“anatomical regions identified in the anatomical first image representation”), [0016] (“FIG. 3B illustrates anatomical structures segmented in an anatomical image representation”), [0025], [0027], [0038].

157. Renisch states:

A segmentation unit 76 segments the anatomical first image representation 72 into regions which correspond to anatomical structures, particularly anatomical structures with high radiopharmaceutical tracer uptake which may obscure potential lesions of interest. In the case of FDG-PET, the brain 78, the heart 80, and the bladder 82 are organs of FIG. 3B which, when functioning normally, are examples of anatomical structures which often show high uptake unrelated to cancer. Other organs with high uptake

include the kidneys and liver which are also contemplated for segmented anatomical structures.

*Id.* at [0025]. Thus, Renisch automatically segments, into volumes-of-interest, a plurality of predefined target tissue regions that correspond to organs that are expected to have high physiological uptake. Renisch further states:

The segmentation unit 76 is capable of employing different types of segmentation methods. For example, the segmentation unit 76 can employ a model-based segmentation in which the central assumption is that the anatomical structures of interest have, to some extent, relatively consistent forms of geometry and position across patients. A library of three-dimensional anatomical structure models explaining the shape, geometrical location, size, and variations thereof are defined in an anatomical database 84 prior to the segmentation. During segmentation, the models act as templates to identify 86 and define the boundary of the structure of interest. It is to be appreciated, however, that other segmentation methods such as clustering, edge detection, region growing, principle components analysis, neural network, and the like are also contemplated.

*Id.* at [0027] (emphasis added). Both clustering and artificial neural networks are known machine learning algorithms used for medical image segmentation task. *See, e.g.*, Ex1016 (“Sharma”) at pp.10-11.

158. Accordingly, it is my opinion that Renisch discloses Limitation 1(b).

**d) Limitation 1(c): “determining, by the processor, a 3D**

**segmentation map representing a plurality of 3D segmentation masks, each 3D segmentation mask representing a particular identified target VOI;”**

159. It is my opinion that Renisch discloses Limitation 1(c). Ex1005, [0025], [0027], [0030]-[0031], [0034], [0037], Figs. 3B and 3C. Alternatively, it is my opinion that Zhao discloses Limitation 1(c) – more explicitly than Renisch does – and that it would have been obvious to implement image segmentation as disclosed in Renisch using the segmentation masks expressly described in Zhao. Ex1007, 5:11-6:11.

160. As I previously explained in Section V.B.4 above, generating a segmentation mask is a standard operation in digital image segmentation. Typically, to effectuate segmentation, each pixel or voxel within an image (or corresponding digital space) is labeled to indicate whether the pixel or voxel is located within a segmented region-of-interest (“ROI”) or outside the ROI. *See, e.g.,* Ex1010 (“Iagaru”), [0064]; Ex1011 (“Gazit”), [0033] (“each mask defines which pixels (or voxels) belong to it”), [0038] (“the image may feature an organ and a background to that organ”), [0042] (explaining that mask boundaries or locations may be determined by segmentation); Ex1007 (“Zhao”), 5:21-48 (“Each pixel of the mask may contain a value used to denote whether a particular corresponding pixel of the digital image is among any ROI.”) (emphasis added), 6:4-7. For example, if the brain is to be segmented in an image, then all voxels in

the region of the brain might be labeled with the same non-zero value and all other voxels are labeled zero – thus creating a binary mask of the brain. This permits further computer operations to be carried out on the brain and non-brain volumes, respectively, by sorting the image voxels according to their mask labels. Ex1007 (“Zhao”), 5:43-48.

161. A segmentation map is merely the combination of a plurality of segmentation masks when a plurality of distinct regions have been segmented within the same image. *See, e.g.*, Ex1007 (“Zhao”), 5:37-42 (“For a mask capable of representing multiple types of ROI, each pixel may be at one of a number of values each corresponding to one type of ROIs. A multi-value mask, however, may be decomposed into a combination [of] the more fundamental binary masks each for one type of ROI.”) (emphasis added). Indeed, the claim language itself defines a segmentation map this way by stating: “determining, by the processor a 3D segmentation map representing a plurality of 3D segmentation masks.” Ex1001, 79:19-22 (emphasis added).

162. To be clear, the Patent does not purport to have invented segmentation masks or segmentation maps. These are, in my experience, routine computer-implemented techniques for performing image segmentation and the principle means by which distinctly segmented regions within an image are tracked and operated on separately. *See, e.g.*, Ex1007, 5:11-6:11. Accordingly, it is my

opinion that a POSITA would understand that Limitation 1(c) is merely reciting a routine detail that is the natural result of segmenting multiple regions-of-interest in a digital image as recited in preceding Limitation 1(b).

163. It is also my opinion that Renisch discloses a segmentation map representing a plurality of segmentation masks – even if Renisch does not use the same terminology. As I already explained, Renisch discloses a segmentation unit that segments a 3D anatomical image into *multiple* regions corresponding to different anatomical structures, such as the brain, heart, liver, and bladder. Ex1005, [0025], Fig. 3B. Each segmented region within the 3D image space is its own segmentation mask, as evidenced by the fact that each region, once segmented, can be separately suppressed from the image as explained below. *Id.* at [0030]-[0031].

164. Renisch explains that it analyzes each segmented organ to evaluate whether the organ is operating normally. For example, Renisch states:

[A]n uptake unit ... examines the segmented regions ... of the first image representation to determine whether the anatomical structure is functioning normally or abnormally based on, for example, at least one of homogeneity and uptake. The uptake unit ... correlates metabolic activity from the functional image representation 74 corresponding to the segmented regions of the anatomical image representation 72 to determine an uptake value, particularly a standardized uptake value (SUV), a measure of the concentration of the radiopharmaceutical tracer. A segmented region with a consistent

uptake value throughout the segmented region and an average uptake value consistent with a predefined level is considered normal.

*Id.* at [0030]. If an organ that is expected to have high metabolic activity (e.g., the liver) is determined to be operating normally, then the uptake in the normally functioning organ can be suppressed from the functional image and excluded from the search for potential lesions. For example, Renisch states that “normally functioning anatomical structures are suppressed from the functional second image representation while unsuppressed regions ... of high intensity are further analyzed to determine if they are plausible lesions.” *Id.* at [0031]. Thus, depending on the results of Renisch’s organ-specific evaluations, some segmented organs might be suppressed while others are kept for further analyses.

165. Because each segmented organ is evaluated separately, and because each organ can be separately suppressed, it is apparent that each segmented organ comprises its own segmentation mask – even if they are not referred to as such.

166. Collectively, the image segmentation results produced by Renisch are a segmentation map representing a plurality of 3D segmentation masks, each mask representing a 3D segmented organ volume. The relative size and location of the segmented organs is maintained in a common coordinate system as evidenced by the fact that each separately segmented region can be transferred from the anatomical image to the functional image. For example, Renisch states that “[t]he

anatomical regions identified in the anatomical first image representation 72 can be carried over to the functional second image representation 74 in order to delineate anatomical structures in the second image representation 74.” *Id.* at [0034]. Additionally, Renisch states that “the outline of the segmented anatomical structures of the anatomical first image representation can be superimposed on the functional second image representation.” *Id.* at [0037]. These descriptions are essentially identical to the Patent, which states “segmentation performed on an anatomical image, such as CT image, is transferred (e.g., mapped) to a co-registered functional image, such as a PET or SPECT image, allowing for specific tissue volumes of interest within the functional image that correspond to particular tissue regions of interest to be identified.” Ex1001, 37:58-64.

167. Accordingly, it is my opinion that Renisch discloses Limitation 1(c).

168. Additionally, Zhao, which is in the same field of art, *expressly describes* the use of segmentation masks to implement 3D medical image segmentation like that discussed in Renisch. Ex1007, 5:11-6:51 (“ROI identification and segmentation may be implemented in medical image processing. Such medical images may include ... Computed Tomography (CT) images, Magnetic Resonance Imaging (MRI) images, ... and the like.”) (“[A]n ROI may be an entire organ.”) (emphasis added). Zhao teaches that the identification of ROIs in a digital image is often referred to as “image segmentation” (*id.* at 5:21-24) and

that segmentation of images may be performed by network-based machine learning algorithms such as deep convolutional neural networks (*id.* at 6:31-35). Zhao states that “ROIs, once determined, may be represented by a digital mask containing a same number of pixels as the digital image” and “[a] digital mask may be alternatively referred [to] as a mask or a segmentation mask.” *Id.* at 5:25-29. Thus, Zhao discloses the use of segmentation masks representing particular volumes-of-interest within 3D medical images, such as entire organs within CT images.

169. Additionally, Zhao discloses the determination of a segmentation map representing a plurality of segmentation masks. For example, Zhao states:

Each pixel of the mask may contain a value used to denote whether a particular corresponding pixel of the digital image is among any ROI, and if it is, which type of ROI among multiple types of ROIs does it fall. For example, if there is only a single type of ROI, a binary mask is sufficient to represent all ROIs. In particular, each pixel of the ROI mask may be either zero or one, representing whether the pixel is or is not among the ROIs. For a mask capable of representing multiple types of ROI, each pixel may be at one of a number of values each corresponding to one type of ROIs. A multi-value mask, however, may be decomposed into a combination the more fundamental binary masks each for one type of ROI.

*Id.* at 5:30-42 (emphasis added). Accordingly, it is my opinion that Zhao discloses Limitation 1(c).

170. It is my opinion that a POSITA would have found it obvious to implement the medical image segmentation described in Renisch using the segmentation mask techniques described in Zhao based on the express motivations and teachings provided in Zhao. Both Renisch and Zhao are directed to segmentation of 3D medical images, such as CT images, using neural networks. Renisch explains that “[s]egmentation can ... be helpful for accurately determining a location of ... hot spots relative to the patient’s anatomy.” Ex1005, [0025]. Zhao teaches that medical image segmentation may produce “[o]ne or more ROI masks, alternatively referred to as segmentation masks” and that an “ROI mask may be used to mark the location of ... organ tissues and the regions outside of the ROI ... that are not part of the organ.” Ex1007, 6:1-7. Zhao further states that “ROI masks are particularly useful for further processing of [] digital images” because “an ROI mask can be used as a filter to determine a subset of image data that ... need be further analyzed....” Ex1007, 5:43-46. Furthermore, “[i]mage data outside of these particular types of ROIs may be removed from further analysis.” Ex1007, 5:47-48. Accordingly, a POSITA would have been motivated to use a segmentation mask, as described in Zhao, to better differentiate between regions located inside and outside of a segmented organ so as to better determine the location of hot spots relative to a patient’s anatomy, as described in Renisch. Moreover, a POSITA would have had a reasonable expectation of success

combining Renisch and Zhao in this manner since both are directed to 3D medical image segmentation and because the generation of segmentation masks was a well-established image processing technique long before the priority filing date of the Patent. Indeed, Renisch already describes the same functionality – but without using the term segmentation mask – by describing the segmentation of multiple ROIs, which can then be separately analyzed and/or transferred to another image.

171. Alternatively, improving Renisch with the teachings of Zhao would merely have amounted to applying a known technique (segmentation masks) to a known device (Renisch) ready for improvement to yield predictable results. As set forth herein, Renisch discloses every element of claim 1 of the Patent even though it does not *explicitly* use the term “segmentation mask.” If, for the sake of argument, Renisch did not use segmentation masks, as claimed, then Renisch constitutes a prior art device ready for improvement. Renisch describes segmenting anatomical medical images into a plurality of anatomical regions—specifically, a plurality of ROIs corresponding to organs—followed by transferring those anatomical regions to functional medical images. Zhao’s technique for determining a 3D segmentation map representing a plurality of 3D segmentation masks – each corresponding to a segmented ROI – was known prior to the Patent’s priority date and is applicable to Renisch. Furthermore, Zhao discloses that the use of segmentation masks are particularly useful when processing a digital image

because “an ROI mask can be used as a filter to determine a subset of image data that ... need be further analyzed” while “[i]mage data outside these ... ROIs may be removed from further analysis.” Ex1007, 5:43-48. Thus, in my opinion, a POSITA would have recognized that applying Zhao’s technique to Renisch was predictable and would result in an improved system. Additionally, this improvement would not, in my opinion, produce an unexpected result since: (i) segmentation masks are a standard implementation detail of image segmentation; (ii) Renisch already describes the same functionality performed by segmentation masks; and (iii) the Patent does not describe any unexpected result or improvement that is achieved by the use of segmentation masks.

172. Accordingly, it is my opinion that a POSITA would have been motivated to combine Renisch and Zhao as proposed here and would have had a reasonable expectation of success in doing so.

e) **Limitation 1(d): “receiving, by the processor, a 3D functional image of the subject obtained using a functional imaging modality;”**

173. It is my opinion that Renisch discloses Limitation 1(d). Ex1005, Fig. 2 (functional image 74); Fig. 1 (functional image memory 58 connected to hot spot detection system 70 through workstation 62), [0022], [0025], [0029] (“a hot spot detection unit 90 detects from the functional second image representation 74 regions of high intensity 92, depicted in FIG. 3A”).

174. As already explained, Renisch includes a “functional imaging scanner 40” that produces “three-dimensional imaging data.” *Id.* at [0020]. Additionally, Renisch states that its automatic hot spot detection system, which includes a processor, detects lesions “based on anatomical images 72 from the anatomical image memory 36 and functional images 74 from the functional image memory 58.” *Id.* at [0025].

175. Accordingly, it is my opinion that Renisch discloses Limitation 1(d).

**f) Limitation 1(e): “identifying, within the 3D functional image, one or more 3D volume(s), each corresponding to an identified target VOI, using the 3D segmentation map; and”**

176. It is my opinion that Renisch discloses Limitation 1(e) or Renisch in view of Zhao teaches Limitation 1(e) for the same reasons set forth in Section IX.A.1.d) above. *Id.* at [0008], [0025], [0031], [0034], [0037], Figs. 3A-3C.

177. The Patent states:

Segmentation maps generated by automated AI-based analysis of anatomical images can be transferred to 3D functional images in order to identify, within the 3D functional image, 3D volumes corresponding to the target VOIs identified in the anatomical image. In particular, in certain embodiments, the individual segmentation masks (of the segmentation map) are mapped from the 3D anatomical image to the 3D functional image.

Ex1001, 37:15-22 (emphasis added).

178. Renisch, nearly identically to the Patent, describes segmenting 3D anatomical images into specific organ volumes (Ex1005, [0025]) and transferring those segmented volumes to a 3D functional nuclear medicine image so that regions of high radiotracer uptake in the functional image (i.e., hot spots) can be compared to the organ locations to evaluate if those hot spots are cancerous lesions or just normal physiological uptake (*id.* at [0025], [0031]). Renisch states that “anatomical regions identified in the anatomical first image representation could be carried over to the functional second image representation in order to delineate anatomical structures there.” Ex1005, [0008], [0034]. Additionally, Renisch states that “the outline of the segmented anatomical structures of the anatomical first image representation can be superimposed on the functional second image representation.” *Id.* at [0037].

179. For the reasons already explained in Section IX.A.1.d), the plurality of segmented organs identified by Renisch constitute a segmentation map or, alternatively, Renisch in view of Zhao teaches a segmentation map. Thus, it is my opinion that Renisch, or Renisch in view of Zhao, also discloses Limitation 1(e): “identifying, within the 3D functional image, one or more 3D volume(s), each corresponding to an identified target VOI, using the 3D segmentation map.”

- g) Limitation 1(f): “automatically detecting, by the processor, within at least a portion of the one or more 3D volumes identified within the 3D functional image,**

**one or more hotspots determined to represent lesions based on intensities of voxels within the 3D functional image.”**

180. It is my opinion that Renisch discloses Limitation 1(f). Ex1005, [0025] (“automatic detection of a region of interest (ROI) pertaining to a lesion”), [0029]-[0032], Figs. 3A-3C.

181. As I previously explained, Renisch automatically detects hot spots in 3D functional images based on the intensity values of voxels within the image. *Id.* at [0029]. Renisch then compares the locations of the identified hot spots with the locations of segmented organs that have been transferred from an anatomical image to determine if the hot spots are lesions or just normal physiological uptake. *Id.* at [0030]-[0031].

182. Renisch states:

[A] hot spot detection unit 90 detects from the functional second image representation 74 regions of high intensity 92, depicted in FIG. 3A. The regions of high intensity 92, generally referred to as hot spots, are regions in the functional second image representation that indicate high metabolic activity, which potentially can be caused by tumor growth or by other malignant processes. These regions of high intensity also include normal functioning structures/organs such as the heart, bladder, kidney, liver, and brain. The regions of high intensity 92 are detected, for example, by a watershed algorithm. A bin sorting unit, processor, or algorithm 94 sorts all the voxels of the second image representation 74 according to grayscale values.

*Id.* at [0029]. Renisch also states that:

[An] uptake unit 100 correlates metabolic activity from the functional image representation 74 corresponding to the segmented regions of the anatomical image representation 72 to determine an uptake value, particularly a standardized uptake value (SUV), a measure of the concentration of the radiopharmaceutical tracer. A segmented region with a consistent uptake value throughout the segmented region and an average uptake value consistent with a predefined level is considered normal.

*Id.* at [0030] (emphasis added). “To improve detection of potential lesions, normally functioning anatomical structures are suppressed from the functional second image representation while unsuppressed regions ... of high intensity are further analyzed to determine if they are plausible lesions. *Id.* at [0031] (emphasis added). Thus, a segmented organ that cannot be confirmed to be functioning normally, will be further examined to determine if the hot spots within the segmented organ are cancerous lesions. For example, Renisch explains:

[A] quantification unit includes a number of modules that perform various checks on the unsuppressed regions 104 to determine if they are lesions. For example, a symmetry unit, processor, or algorithm 108 determines symmetric pairs of the high intensity regions of the second and/or first image representation that correspond to paired anatomical structures. For example, if a high intensity region is identified, by the identification unit 98, as a salivary gland, the

symmetry unit searches for the corresponding salivary gland on the other side of the patient. Activity patterns between the symmetric pairs are determined by an activity unit, processor, or algorithm 110. If an asymmetry of metabolic activity exists between the symmetric pair, the unsuppressed high intensity region 104 is identified as a potential lesion.

*Id.* at [0032].

183. Accordingly, Renisch also discloses Limitation 1(f). Renisch describes automatically detecting high intensity hot spots within segmented organ volumes and determining that those hot spots represent lesions based on a variety of criteria, including the intensity of the hot spots within a 3D functional image.

184. Because Renisch discloses every limitation of claim 1, it is my opinion that Renisch anticipates claim 1 and renders it unpatentable. Alternatively, if, for some reason, Renisch is not found to sufficiently disclose the recited feature of determining a segmentation map representing a plurality of 3D segmentation masks (Limitation 1(c)), then it is also my opinion that Renisch in view of Zhao teaches every limitation of claim 1 and renders it unpatentable as obvious.

**2. Dependent Claim 2: “The method of claim 1, comprising using, by the processor, the one or more detected hotspots to determine a cancer status for the subject.”**

185. Claim 2 depends from claim 1, which I explained above in Section IX.A.1 is anticipated by Renisch and/or rendered obvious by the combination of

Renisch in view of Zhao. Claim 2 states: “The method of claim 1, comprising using, by the processor, the one or more detected hotspots to determine a cancer status for the subject.” It is my opinion that Renisch discloses the limitations of claim 2.

186. Renisch states:

An identification unit, processor, or algorithm 106 is configured to calculate metrics corresponding to the unsuppressed regions. The metrics include, but are not limited to, total tumor burden, glycolytic volume, SUV, average activity, maximum activity, minimum activity, homogeneity, and the like. In addition to calculating metrics, the quantification unit includes a number of modules that perform various checks on the unsuppressed regions 104 to determine if they are lesions. For example, a symmetry unit, processor, or algorithm 108 determines symmetric pairs of the high intensity regions of the second and/or first image representation that correspond to paired anatomical structures. For example, if a high intensity region is identified, by the identification unit 98, as a salivary gland, the symmetry unit searches for the corresponding salivary gland on the other side of the patient. Activity patterns between the symmetric pairs are determined by an activity unit, processor, or algorithm 110. If an asymmetry of metabolic activity exists between the symmetric pair, the unsuppressed high intensity region 104 is identified as a potential lesion.

Ex1005, [0032] (emphasis added). Thus, Renisch evaluates hotspots to determine

if they are cancer and quantifies the hotspots (e.g., total tumor burden) to determine the severity of cancer. Renisch also describes a “quantification unit” that includes a “processor” which determines the likelihood that a lymph node is present in a high intensity region (hotspot) of the functional image, which Renisch states “is a critical component in determining whether a tumor is likely to have metastasized, which dictates the therapeutic options for cancer patients.” Ex1005, [0034]. Thus, Renisch also discloses determining from a hotspot whether cancer has metastasized.

187. Because Renisch discloses every limitation of claim 2, including the limitations of claim 1 from which claim 2 depends, it is my opinion that claim 2 is anticipated by Renisch. Alternatively, it is also my opinion that Renisch in view of Zhao, as applied to claim 1 in Section IX.A.1, renders claim 2 obvious.

### **3. Dependent Claim 3**

188. Dependent claim 3 depends from claim 1, which I explained above in Section IX.A.1 is anticipated by Renisch and/or rendered obvious by the combination of Renisch in view of Zhao. It is also my opinion that Renisch discloses all the limitations of claim 3.

- a) **Preamble: “The method of claim 1, wherein the target tissue regions comprise one or more reference tissue regions and wherein the method comprises:”**

189. Renisch discloses the additional limitations recited in the preamble of

claim 3: “wherein the target tissue regions comprise one or more reference tissue regions.”

190. As I already explained in Section IX.A.1.c) above, Renisch automatically segments a plurality of predefined target tissue regions corresponding to organs – such as the liver. Ex1005, [0025]. Renisch also states: “The metabolic activity of the liver can be used as a reference for comparison. Since the liver is segmented and indentified [sic] by the segmentation unit 76, an unsuppressed high intensity region can easily be compared to the uptake in the liver.” *Id.* at [0034].

191. Accordingly, it is my opinion that Renisch discloses the preamble of claim 3.

**b) Limitation 3(a): “using the 3D segmentation map to identify, by the processor, within the 3D functional image, one or more 3D reference volume(s), each corresponding to a particular reference tissue region;”**

192. Renisch discloses Limitation 3(a): “using the 3D segmentation map to identify, by the processor, within the 3D functional image, one or more 3D reference volume(s), each corresponding to a particular reference tissue region.”

193. As I explained in Section IX.A.1.d) above, it is my opinion that Renisch discloses a 3D segmentation map comprised of a plurality of organ segmentation masks all mapped to a common coordinate system that can be

transferred to or co-registered with a 3D functional image. Alternatively, it is my opinion that Renisch in view of Zhao teaches the claimed 3D segmentation map.

194. Additionally, Renisch discloses using such segmentation map to identify, within the 3D functional image, one or more 3D reference volumes corresponding to a particular tissue region (i.e., the liver). Renisch states:

Since the liver is segmented and indentified [sic] by the segmentation unit 76, an unsuppressed high intensity region can easily be compared to the uptake in the liver. Previously, a clinician had to manually delineate a region of the liver on a workstation which is time consuming and highly subjective. The anatomical regions identified in the anatomical first image representation 72 can be carried over to the functional second image representation 74 in order to delineate anatomical structures in the second image representation 74. The tracer uptake in these structures could be used as a reference for the quantification of the hot spots.

Ex1005, [0034].

195. Accordingly, it is my opinion that Renisch discloses Limitation 3(a).

- c) **Limitation 3(b): “determining, by the processor, one or more reference intensity values, each associated with a particular 3D reference volume of the one or more 3D reference volume(s) and corresponding to a measure of intensity within the particular 3D reference volume;”**

196. Renisch discloses Limitation 3(b): “determining, by the processor, one or more reference intensity values, each associated with a particular 3D reference

volume of the one or more 3D reference volume(s) and corresponding to a measure of intensity within the particular 3D reference volume.”

197. Renisch identifies regions of high intensity in a 3D functional image by sorting the voxels of the image according to their grayscale values. Ex1005, [0029]. Renisch explains that these regions “can be caused by tumor growth” but “[t]hese regions of high intensity also include normal functioning structures/organs such as the ... liver.”). *Id.*

198. Renisch states:

The metabolic activity of the liver can be used as a reference for comparison. Since the liver is segmented and indentified [sic] by the segmentation unit 76, an unsuppressed high intensity region can easily be compared to the uptake in the liver. Previously, a clinician had to manually delineate a region of the liver on a workstation which is time consuming and highly subjective. The anatomical regions identified in the anatomical first image representation 72 can be carried over to the functional second image representation 74 in order to delineate anatomical structures in the second image representation 74. The tracer uptake in these structures could be used as a reference for the quantification of the hot spots, e.g. the relative activity of a hot spot compared with that of normal liver tissue could be computed.

*Id.* at [0034] (emphasis added). Accordingly, it is my opinion that Renisch discloses Limitation 3(b).

- d) **Limitation 3(c): “determining, by the processor, one or more individual hotspot intensity values, each associated with a particular hotspot of at least a portion of the detected one or more hotspots and corresponding to a measure of intensity of the particular hotspot; and**

199. It is my opinion that Renisch discloses Limitation 3(c): “determining, by the processor, one or more individual hotspot intensity values, each associated with a particular hotspot of at least a portion of the detected one or more hotspots and corresponding to a measure of intensity of the particular hotspot.”

200. Renisch explains that regions of high intensity in functional images are generally referred to as “hot spots.” Ex1005, [0029]. Hot spots are identified in functional images by sorting the voxels of the image according to their grayscale values (i.e., intensity). *Id.* Renisch calculates metrics for identified hot spots including “SUV [standard uptake value], average activity, maximum activity, minimum activity, homogeneity, and the like.” *Id.* at [0032]. Renisch also explains that individual hot spots can be quantified by comparison to normal organs, stating “the relative activity of a hot spot compared with that of normal liver tissue could be computed.” *Id.* at [0034] (emphasis added).

201. Accordingly, it is my opinion that Renisch discloses Limitation 3(c).

- e) **Limitation 3(d): “determining, by the processor, one or more individual hotspot index values using the one or more individual hotspot intensity values and the one or more reference intensity values.”**

202. It is my opinion that Renisch discloses limitation 3(d): “determining, by the processor, one or more individual hotspot index values using the one or more individual hotspot intensity values and the one or more reference intensity values.”

203. The Patent describes the determination of an individual hotspot index value as including the comparison of an individual hotspot intensity value to the intensity value of a reference region. Ex1001, 55:1-20.

204. Renisch states:

A normalization unit, processor, or algorithm 114 compares the metabolic activity of an unsuppressed high intensity region with normally functioning structures, e.g. those identified by the uptake unit 100. For example, metabolic activity of a potential lesion is commonly compared to a standard uptake value determined by a nominal activity unit, processor, or algorithm 116.... The metabolic activity of the liver can be used as a reference for comparison. Since the liver is segmented and identified by the segmentation unit 76, an unsuppressed high intensity region can easily be compared to the uptake in the liver. Previously, a clinician had to manually delineate a region of the liver on a workstation which is time consuming and highly subjective. The anatomical regions identified in the anatomical first image representation 72 can be carried over to the functional second image representation 74 in order to delineate anatomical structures in the second image representation 74. The tracer uptake in these structures could be used as a reference for the quantification of

the hot spots, e.g. the relative activity of a hot spot compared with that of normal liver tissue could be computed.

Ex1005, [0034] (emphasis added).

205. Accordingly, it is my opinion that Renisch discloses Limitation 3(d).

206. Because Renisch discloses every limitation of claim 3, including every limitation of claim 1 from which claim 3 depends, it is my opinion that claim 3 is anticipated by Renisch. Alternatively, it is also my opinion that claim 3 is rendered unpatentable as obvious based on the combination of Renisch and Zhao, as applied to claim 1 in Section IX.A.1 above.

**4. Dependent Claim 4: “The method of claim 3, wherein the reference tissue regions comprise one or more members selected from the group consisting of: a liver, an aorta, and a parotid gland.”**

207. Claim 4 depends from claim 3 and is anticipated by Renisch and/or rendered obvious by the combination of Renisch in view of Zhao for the same reasons already provided in Section IX.A.3 above. Renisch teaches that “[t]he metabolic activity of the liver can be used as a reference for comparison.” Ex1005, [0034].

208. Because Renisch discloses every limitation of claim 4, including every limitation of claims 1 and 3 from which claim 4 depends, it is my opinion that claim 4 is anticipated by Renisch. Additionally, it is my opinion that Renisch in view of Zhao renders claim 4 unpatentable as obvious in the same manner that

Renisch and Zhao have been applied to claim 1 in Section IX.A.1 above.

**5. Dependent Claim 5: “The method of claim 2, comprising, determining, by the processor, an overall index value indicative of a cancer status of the subject using at least a portion of the one or more hotspot index values.”**

209. Claim 5 depends from claim 2 and is anticipated by Renisch and/or rendered obvious by the combination of Renisch in view of Zhao for the same reasons already provided in Section IX.A.2 above. In my opinion, Renisch discloses the additional limitations of claim 5.

210. As a preliminary matter, it is my opinion that claim 5 contains a typographical error and should properly be read to depend from claim 3. The structure and content of the claims supports my opinion. Specifically, claim 5 describes “using at least a portion of the one or more hotspot index values.” Ex1001, 79:63-64 (emphasis added). Neither claim 2 (from which claim 5 purports to depend) nor independent claim 1 (from which claim 2 depends) references a “hotspot index value.” *See* Ex1001, 79:5-36. Claim 3 determines, for the first time in the claims, “one or more individual hotspot index values.” Ex1001, 79:54-55. Therefore, because claim 5 appears to lack proper antecedent basis as written, it is my opinion that a POSITA reading the claims would recognize that claim 5 properly depends from claim 3.

211. Regardless, claim 5 is in my opinion invalid as written. The claim

states that the “overall index value indicative of a cancer status” can be determined using “at least a portion of the one or more hotspot index values.” Ex1001, 79:62-64. In my opinion, the phrase “at least a portion of the one or more” provides for determining the overall index value using a single hotspot index value. *See also* Ex1001, 38:1-9. As I explained in Section IX.A.3.e) above, Renisch determines individual hotspot index values by comparing their respective intensities to the intensity of a reference, such as the liver. Therefore, in my opinion, at least for the embodiment in which an overall index value is determined using a single hotspot index value, Renisch discloses the additional limitations of claim 5. Thus, in my opinion Renisch anticipates, or Renisch in view of Zhao renders obvious, claim 5.

**6. Dependent Claim 7: “The method of claim 1, wherein: the 3D anatomical image is an x-ray computed tomography (CT) image, and the 3D functional image is a 3D positron emission tomography (PET) image.”**

212. Claim 7 depends from independent claim 1, which I explained above in Section IX.A.1 is anticipated by Renisch and/or rendered obvious by Renisch in view of Zhao. Renisch also discloses the additional limitations of claim 7: “wherein: the 3D anatomical image is an x-ray computed tomography (CT) image, and the 3D functional image is a 3D positron emission tomography (PET) image.”

213. Renisch discloses a diagnostic system 10 that includes a first imaging scanner 12 and a second imaging scanner 40. Ex1005, Fig. 1, [0020]-[0022]. The

first imaging scanner may be “a computed tomography (CT) imaging scanner ... for obtaining anatomical diagnostic images” using an x-ray source. *Id.* at [0020]. Although unnecessary, Renisch explains that the CT scanner includes a processor that “reconstructs 3D image representations from the acquired imaging data.” *Id.* at [0021]. The second imaging system 40 may be a “PET scanner ... for obtaining functional images” (*id.* at [0022]) and likewise acquires “three-dimensional imaging data” (*id.*).

214. Because Renisch discloses every limitation of claim 7, including the limitations of claim 1 from which claim 7 depends, it is my opinion that claim 7 is anticipated by Renisch. In addition, it is my opinion that Renisch in view of Zhao renders claim 7 unpatentable as obvious in the same manner as applied to claim 1 in Section IX.A.1 above.

## **7. Independent Claim 10**

215. Independent claim 10 of the Patent is nearly identical to independent claim 1, which I explained in Section IX.A.1 above is anticipated by Renisch and/or rendered obvious by Renisch in view of Zhao. Whereas claim 1 is directed to a method, claim 10 is directed to a system that essentially performs the method recited in claim 1. Whereas claim 1 (the method claim) recites a series of steps, each performed “by a processor,” claim 10 (the system claim) recites a “processor” and “memory” having stored instructions that, when executed by the processor,

perform the same steps recited in claim 1. Accordingly, it is my opinion that claim 10 is anticipated by Renisch and/or rendered obvious by Renisch in view of Zhao for the same reasons I explained in Section IX.A.1 above.

a) **Preamble: “A system for automatically processing 3D images to automatically identify cancerous lesions within a subject, the system comprising:”**

216. The preamble of claim 10 is essentially the same as the preamble of claim 1 except that claim 10 recites a system whereas claim 1 recites a method. Assuming the preamble is considered a limitation on the scope of the claim, it is my opinion that Renisch discloses the limitations of the preamble for the same reasons provided in Section IX.A.1.a) above.

b) **Limitation 10(i): “a processor of a computing device; and a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to:”**

217. It is my opinion that Renisch discloses Limitation 10(i), which is nothing more than a generic recitation of standard structure found in any computer implemented system: “a processor of a computing device; and a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to...”

218. Renisch discloses a computing device including a workstation 62 and an automatic hot spot detection system 70 – both of which necessarily contain a

processor and stored instructions for performed their described functions. Ex1005, Fig. 1. With reference to Fig. 2, which is reproduced below, Renisch describes the hot spot detection system as comprising various functional units (e.g., segmentation unit 76) that Renisch alternatively describes as “processors” or “algorithms”. *Id.* at [0014], [0030] (“uptake unit, processor, or algorithm”), [0031] (“classification unit, processor, or algorithm”), [0032] (“identification unit, processor, or algorithm”), [0034] “quantification unit also includes a probability unit, processor, or algorithm”). A POSITA would understand from this description that the described functional units could be different algorithms (i.e., stored instructions) that are carried out on a single processor, or multiple processors that carry out respective stored instructions to perform the respective described functions.

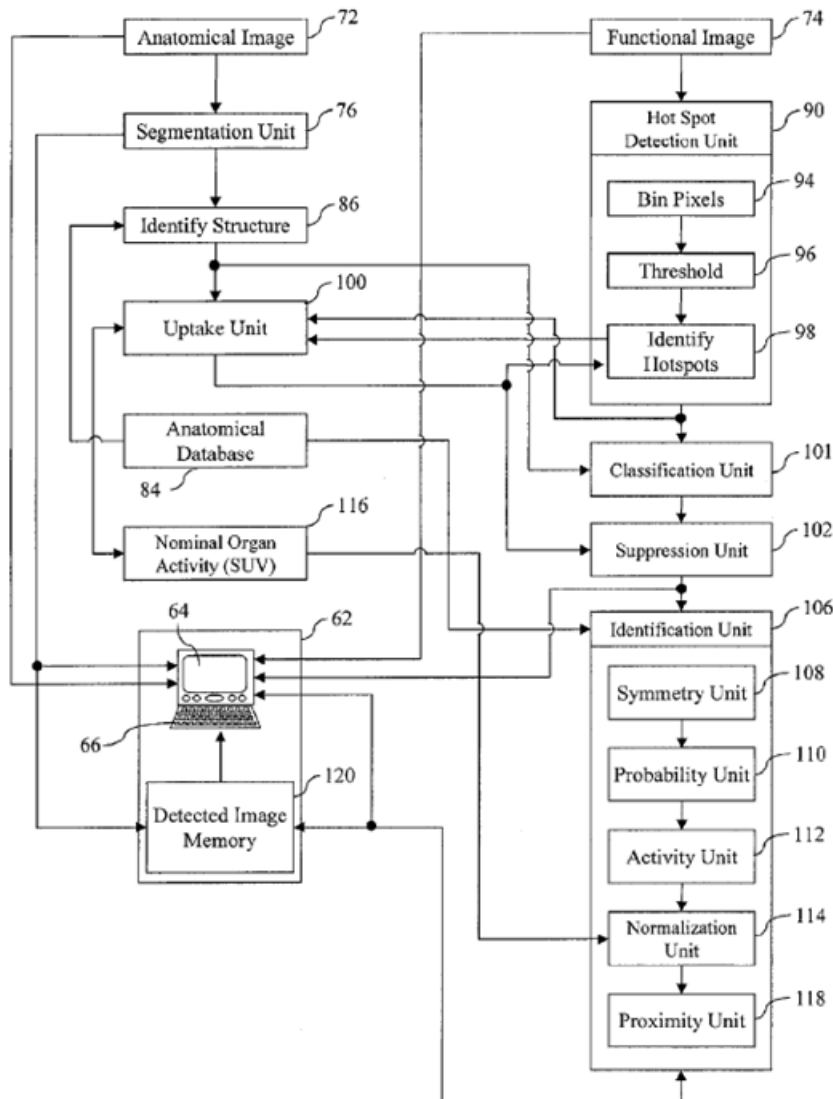


Figure 2

219. Accordingly, it is my opinion that Renisch discloses Limitation 10(i).

- c) **Limitation 10(ii): “(a) receive a 3D anatomical image of a subject obtained using an anatomical imaging modality, wherein the 3D anatomical image comprises a graphical representation of tissue within the subject;”**

220. Limitation 10(ii) is essentially identical to Limitation 1(a), which is addressed in Section IX.A.1.b) above. The only difference is that, whereas

Limitation 1(a) recites “receiving, by a processor of a computing device, a 3D anatomical image ...,” Limitation 10(ii) relates to instructions that cause a processor to “receive a 3D anatomical image ....” Accordingly, it is my opinion that Renisch discloses Limitation 10(ii) for the same reasons explained in Section IX.A.1.b) above.

- d) **Limitation 10(iii): “(b) automatically identify, using one or more machine learning modules, for each of a plurality of target tissue regions, a corresponding target volume of interest (VOI) within the 3D anatomical image;”**

221. Limitation 10(iii) is essentially identical to Limitation 1(b), which is addressed in Section IX.A.1.c) above. The only difference is that, whereas Limitation 1(b) recites “automatically identifying, by the processor ...,” Limitation 10(iii) relates to instructions that cause a processor to “automatically identify ....” Accordingly, it is my opinion that Renisch discloses Limitation 10(iii) for the same reasons explained in Section IX.A.1.c) above.

- e) **Limitation 10(iv): “(c) determine a 3D segmentation map representing a plurality of 3D segmentation masks, each 3D segmentation mask representing a particular identified target VOI;”**

222. Limitation 10(iv) is essentially identical to Limitation 1(c), which is addressed in Section IX.A.1.d) above. The only difference is that, whereas Limitation 1(c) recites “determining, by the processor, a 3D segmentation map

...,” Limitation 10(iv) relates to instructions that cause a processor to “determine a 3D segmentation map ....” Accordingly, it is my opinion that Renisch discloses Limitation 10(iv), or Renisch in view of Zhao teaches limitation 10(iv), for the same reasons explained in Section IX.A.1.d) above.

**f) Limitation 10(v): “(d) receive a 3D functional image of the subject obtained using a functional imaging modality;”**

223. Limitation 10(v) is essentially identical to Limitation 1(d), which is addressed in Section IX.A.1.e) above. The only difference is that, whereas Limitation 1(d) recites “receiving, by the processor, a 3D functional image ...,” Limitation 10(v) relates to instructions that cause a processor to “receive a 3D functional image ....” Accordingly, it is my opinion that Renisch discloses Limitation 10(v) for the same reasons explained in Section IX.A.1.e) above.

**g) Limitation 10(vi): “(e) identify, within the 3D functional image, one or more 3D volume(s), each corresponding to an identified target VOI, using the 3D segmentation map; and**

224. Limitation 10(vi) is essentially identical to Limitation 1(e), which is addressed in Section IX.A.1.f) above. Accordingly, it is my opinion that Renisch discloses Limitation 10(vi) for the same reasons explained in Section IX.A.1.f) above.

**h) Limitation 10(vii): “(f) automatically detect, within at**

**least a portion of the one or more 3D volumes identified within the 3D functional image, one or more hotspots determined to represent lesions based on intensities of voxels within the 3D functional image.”**

225. Limitation 10(vii) is essentially identical to Limitation 1(f), which is addressed in Section IX.A.1.g) above. The only difference is that, whereas Limitation 1(f) recites “automatically detecting, by the processor, ...,” Limitation 10(vii) relates to instructions that cause a processor to “automatically detect ....” Accordingly, it is my opinion that Renisch discloses Limitation 10(vii) for the same reasons explained in Section IX.A.1.g) above.

**8. Dependent Claim 11: “The system of claim 10, wherein the instructions cause the processor to use the one or more detected hotspots to determine a cancer status for the subject.”**

226. Claim 11 depends from claim 10 (system claim) and is essentially the same as dependent claim 2, which depends from claim 1 (method claim). For the same reasons I explained in Sections IX.A.2 (claim 2) and IX.A.7 (claim 10) above, it is my opinion that claim 11 is anticipated by Renisch and/or rendered obvious by Renisch in view of Zhao.

**9. Dependent Claim 12: Wherein the Target Tissue Regions Comprise One or More Reference Tissue Regions**

227. Dependent claim 12 depends from claim 10 (system claim) and is essentially the same as dependent claim 3, which depends from claim 1 (method

claim). Whereas claim 3 is a method claim that recites a series of steps performed “by the processor,” claim 12 is a system claim that recites “wherein the instructions cause the processor to” perform the same steps recited in claim 3. For the same reasons I explained in Sections IX.A.3 (claim 3) and IX.A.7 (claim 10) above, it is my opinion that claim 12 is anticipated by Renisch and/or rendered obvious by Renisch in view of Zhao.

**10. Dependent Claim 13: “The system of claim 12, wherein the reference tissue regions comprise one or more members selected from the group consisting of: a liver, an aorta, and a parotid gland.”**

228. Except for depending from claim 12 (system claim), claim 13 is the same as claim 4, which depends from claim 3 (method claim). For the same reasons I explained in Sections IX.A.4 (claim 4) and IX.A.7 (claim 10) above, it is my opinion that claim 13 is anticipated by Renisch and/or rendered obvious by Renisch in view of Zhao.

**11. Dependent Claim 14: “The system of claim 11, wherein the instructions cause the processor to determine an overall index value indicative of a cancer status of the subject using at least a portion of the one or more hotspot index values.”**

229. Except for depending from claim 11 (system claim), claim 14 is the

same as claim 5, which depends (as written) from claim 2 (method claim).<sup>2</sup> For the same reasons I explained above in Sections IX.A.5 (claim 5) and IX.A.7 (claim 10) above, it is my opinion that claim 14 is anticipated by Renisch and/or rendered obvious by Renisch in view of Zhao.

**12. Dependent Claim 16: “The system of claim 10, wherein: the 3D anatomical image is an x-ray computed tomography (CT) image, and the 3D functional image is a 3D positron emission tomography (PET) image.”**

230. Except for depending from claim 10 (system claim), claim 16 is the same as claim 7, which depends from claim 1 (method claim). For the same reasons I explained in Sections IX.A.6 (claim 7) and IX.A.7 (claim 10) above, it is my opinion that claim 12 is anticipated by Renisch and/or rendered obvious by Renisch in view of Zhao.

**13. Dependent Claim 19**

231. Claim 19 depends from claim 1, which I explained above in Section IX.A.1 is anticipated by Renisch and/or rendered obvious by the combination of Renisch in view of Zhao. Renisch also discloses all the limitations of claim 19.

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<sup>2</sup> As discussed above, it is my opinion that claim 5 should properly depend from claim 3. However, my analysis with respect to claim 14 is the same regardless of claim 5’s dependency, as both claims 2 and 3 are method claims.

Accordingly, it is also my opinion that claim 19 is anticipated by Renisch and/or rendered obvious by the combination of Renisch in view of Zhao.

a) **Preamble: “The method of claim 1, wherein the target tissue regions comprise one or more background tissue regions and wherein the method comprises:”**

232. With reference to Limitation 1(b) in Section IX.A.1.c) above, the “target tissue regions” of claim 1 are regions of an anatomical image that are automatically segmented by a machine learning algorithm, such as a convolutional neural network, into target VOIs corresponding to specific tissue regions such as organs and particular bones. The Patent describes the “background tissue regions” as being “e.g., a background tissue region in which significant radiopharmaceutical uptake occurs under normal circumstances and is not necessarily indicative of presence of cancerous lesions.” Ex1001, 8:57-65. Examples of background tissue regions, according to the Patent, include “a bladder (e.g., a urinary bladder), a kidney, a duodenum, a small intestine, a spleen, a liver, a pancreas, a stomach, an adrenal gland, a rectum, and testes.” *Id.* at 18:48-52.

233. Rensich discloses these same features, stating:

A segmentation unit 76 segments the anatomical first image representation 72 into regions which correspond to anatomical structures, particularly anatomical structures with high radiopharmaceutical tracer uptake which may obscure potential lesions of interest. In the case of FDG-PET, the brain 78, the heart 80,

and the bladder 82 are organs of FIG. 3B which, when functioning normally, are examples of anatomical structures which often show high uptake unrelated to cancer. Other organs with high uptake include the kidneys and liver which are also contemplated for segmented anatomical structures.

Ex1005, [0025]. Accordingly, it is my opinion that Renisch discloses the preamble of claim 19.

**b) Limitation 19(a): “at step (e), using the 3D segmentation map to identify, within the 3D functional image, as at least a portion of the one or more 3D volumes, one or more 3D background tissue volume(s), each corresponding a particular background tissue region; and”**

234. Step (e) of claim 1 (*i.e.*, Limitation 1(e)) recites: “identifying, within the 3D functional image, one or more 3D volume(s), each corresponding to an identified target VOI, using the 3D segmentation map.” As I explained in Section IX.A.1.f) above, Renisch discloses Limitation 1(e) or Renisch in view of Zhao teaches Limitation 1(e). Renisch also discloses the additional limitations of Limitation 19(a) for the same reasons already stated above in Section IX.A.13.a) above.

235. Renisch describes segmenting anatomical images into regions that correspond to anatomical structures, particularly anatomical structures with high radiopharmaceutical tracer uptake that is likely unrelated to cancer (e.g., the

bladder and liver). Ex1005, [0025]. Renisch further discloses that “[t]he anatomical regions identified in the anatomical first image representation 72 can be carried over to the functional second image representation 74 in order to delineate anatomical structures in the second image representation 74.” *Id.* at [0034]. Accordingly, it is my opinion that Renisch discloses Limitation 19(a) and/or Renisch in view of Zhao teaches Limitation 19(a), including the use of a segmentation map.

- c) **Limitation 19(b): “excluding voxels of the 3D [sic] within the 3D background tissue from the voxels used to automatically detect the one or more hotspots at step (f).”**

236. Limitation 19(b) appears to include a typographical error. For my analysis, I assume that Limitation 19(b) should read: “excluding voxels of the 3D [functional image] within the 3D background tissue from the voxels used to automatically detect the one nor more hotspots at step (f).” It is my opinion that Renisch discloses this limitation. Ex1005, [0031]-[0032].

237. Step (f) of claim 1 (*i.e.*, Limitation 1(f)) recites, in pertinent part, and with emphasis added, “automatically detecting ... one or more hotspots determined to represent lesions based on intensities of voxels with the 3D functional image.” As I already explained in Section IX.A.1.g) above, Renisch discloses Limitation 1(f). As I explain here, Renisch also discloses the additional features of Limitation 19(b): “excluding voxels of the 3D [functional image] within the 3D background

tissue from the voxels used to automatically detect the one or more hotspots at step (f).”

238. Renisch automatically detects hotspots determined to represent lesions based on intensities of voxels in the functional image after suppressing from the functional image normally functioning organs that are expected to have high physiological uptake unrelated to cancer. *Id.* at [0025], [0031]-[0032]. For example, Renisch states:

[R]egions of high intensity that correspond to normally functioning anatomical structures may obscure potentially hazardous lesions. To improve detection of potential lesions, normally functioning anatomical structures are suppressed from the functional second image representation while unsuppressed regions 104, shown in FIG. 3C, of high intensity are further analyzed to determine if they are plausible lesions.

*Id.* at [0031] (emphasis added). In addition, Renisch explains that a “quantification unit ... perform[s] various checks on the unsuppressed regions 104 to determine if they are lesions.” *Id.* at [0032] (emphasis added). For example, Renisch states:

[A] symmetry unit, processor, or algorithm 108 determines symmetric pairs of the high intensity regions of the second and/or first image representation that correspond to paired anatomical structures. For example, if a high intensity region is identified, by the identification unit 98, as a salivary gland, the symmetry unit searches for the corresponding salivary gland on the other side of the patient. Activity

patterns between the symmetric pairs are determined by an activity unit, processor, or algorithm 110. If an asymmetry of metabolic activity exists between the symmetric pair, the unsuppressed high intensity region 104 is identified as a potential lesion.

*Id.* at [0032] (emphasis added). Accordingly, Renisch automatically detects hot spots determined to be lesions based on intensities of voxel within the 3D functional image (Limitation 1(f)) after first excluding voxels from the functional image corresponding to normally functioning high uptake organs (Limitation 19(b)).

239. It is my opinion, therefore, that Renisch discloses Limitation 19(b).

240. Because Renisch discloses all the limitations of claim 9, including all the limitations of claim 1 from which claim 19 depends, it is my opinion that Renisch anticipates claim 19. Alternatively, it is my opinion that Renisch in combination in view of Zhao, as applied to claim 1 in Section IX.A.1 above, renders claim 19 unpatentable as obvious.

#### **14. Dependent Claim 26: Wherein the Target Tissue Regions Comprise One Or More Background Tissue Regions**

241. Dependent claim 26 depends from claim 10 (system claim) and is essentially the same as dependent claim 19, which depends from claim 1 (method claim). Even the typographical error in claim 19 has been carried over to claim 26. Whereas claim 19 is a method claim that recites a series of steps, claim 26 is a

system claim that recites “wherein the instructions cause the processor to” perform the same steps recited in claim 19. For the same reasons I explained in Sections IX.A.7 (claim 10) and IX.A.13 (claim 19) above, it is my opinion that claim 26 is anticipated by Renisch and/or rendered obvious by Renisch in view of Zhao.

**B. Ground C and D, Obviousness over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber**

**1. Dependent Claim 8: “The method of claim 7, wherein the 3D PET image of the subject is obtained following administration to the subject of a radiopharmaceutical comprising a prostate-specific membrane antigen (PSMA) binding agent.”**

242. Claim 8 depends from claim 7, which I explained in Section IX.A.6 above is anticipated by Renisch and/or rendered obvious by Renisch in view of Zhao, where Zhao is only relied on to provide a more explicit description of a segmentation map representing a plurality of organ segmentation masks. Although Renisch does not expressly state, as recited in claim 8, that its 3D PET image of the subject is “obtained following administration to the subject of a radiopharmaceutical comprising a prostate-specific membrane antigen (PSMA) binding agent,” that additional limitation is obvious in view of the teachings in Baker or Eiber.

243. Renisch discloses a system for imaging and analyzing cancerous lesions throughout the body and is not limited to any particular type of cancer or radiopharmaceutical. Renisch explains: “Typically, an object or patient to be

imaged is injected with one or more radiopharmaceutical or radioisotope tracers and placed in the examination region” of a PET scanner. Ex1005, [0023]. “Examples of such tracers are 18F FDG, C-11, Tc-99m, Ga67, and In-111.” *Id.* (emphasis added).

244. A POSITA would immediately recognize that Renisch could be useful for evaluating prostate cancer. Indeed, a POSITA would know that 18F FDG, which is identified in Rensich, could be used to image many types of cancer, including prostate cancer. Ex1010 (“Iagaru”), [0004] (“(<sup>18</sup>F-FDG) positron emission tomography and computed tomography (PET/CT) is established as a powerful imaging tool for cancer detection.”), [0006]-[0008], [0024] (describing the result of imaging prostate cancer using <sup>18</sup>F-FDG PET), [0056] (“<sup>18</sup>F-FDG PET has limited ability to detect osseous metastatic lesions, but can still be useful in the detection of metastatic nodal and soft tissue disease.”), Table 1. Furthermore, in my opinion, it was general knowledge in the art at the time of the Patent that prostate cancer is one of the most common forms of cancer among men. Ex1020, p.211.

245. Baker discloses that “[t]here are also a number of radiopharmaceuticals available for imaging particular kinds of cancer” including PSMAAs for prostate cancer. Ex1008, [0004], [0019], [0090], [0092] (“A variety of radionuclide labelled PSMA binding agents may be used a radiopharmaceutical

imaging agents for nuclear medicine imaging to detect and evaluate prostate cancer.”). For example, Baker states:

For example, the small molecule diagnostic 1404 targets the extracellular domain of prostate specific membrane antigen (PSMA), a protein amplified on the surface of >95% of prostate cancer cells and a validated target for the detection of primary and metastatic prostate cancer. 1404 is labeled with technetium-99m, a gamma emitter isotope that is widely available, relatively inexpensive, facilitates efficient preparation, and has spectrum characteristics attractive for nuclear medicine imaging applications.

*Id.* (emphasis added). Baker also discloses:

Another example radiopharmaceutical is PyL™ (also known as [<sup>18</sup>F]DCFPyL, and 18F-PyL), which is a clinical-stage, fluorinated PSMA-targeted PET imaging agent for prostate cancer. A proof-of-concept study published in the April 2015 issue of the Journal of Molecular Imaging and Biology demonstrated that PET imaging with PyL™ showed high levels of PyL™ uptake in sites of putative metastatic disease and primary tumors, suggesting the potential for high sensitivity and specificity in detecting prostate cancer.

*Id.* at [0005] (emphasis added). Accordingly, in my opinion a POSITA would have known, prior to the priority date of the Patent, that PSMA binding agents existed for PET imaging of prostate cancer, as evidence by Baker.

246. It is my opinion that a POSITA would have been motivated to use a

PSMA targeting molecule to perform PET imaging with Renisch and would have had a reasonable expectation of success doing so based on the express teachings in Baker and the general knowledge of a POSITA. The proposed combination would merely involve a straightforward substitution of one radiopharmaceutical, 18F FDG, with a PSMA-based radiopharmaceutical – and using it for its intended purpose. Therefore, it is my opinion that claim 8 is obvious based on Renisch, or Renisch in view of Zhao, each in view of Baker.

247. Alternatively, Eiber discloses, before the priority date of the Patent, that “[p]rostate-specific membrane antigen (PSMA)-ligand PET/CT ... provides high sensitivity and specificity for prostate cancer staging” and “[t]he accuracy of PSMA-ligand hybrid imaging is superior to that of conventional imaging and tracers.” Ex1009, p.469.

248. It is also my opinion, therefore, that a POSITA would have been motivated to use a PSMA targeting molecule to perform PET imaging with Renisch and would have had a reasonable expectation of success doing so based on the express teachings in Eiber and the general knowledge of a POSITA. Indeed, Eiber states that prostate cancer imaging with PSMA-PET has already been successful.

249. Accordingly, it is my opinion that claim 8 is obvious based on Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber.

**2. Dependent Claim 9: “The method of claim 8, wherein the radiopharmaceutical comprises [<sup>18</sup>F]DCFPyL.”**

250. Claim 9 depends from claim 8, which I explained in the preceding Section is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber. Claim 9 adds “wherein the radiopharmaceutical comprises [<sup>18</sup>F]DCFPyL,” which is also disclosed by both Baker (Ex1008, [0005], [0017], [0036], [0045], [0095]-[0096]) and Eiber (Ex1009, p, 472 (Fig. 1)). Accordingly, it is my opinion that claim 9 is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber or the same reasons previously stated in Section IX.B.1 above.

**3. Dependent Claim 17: “The system of claim 16, wherein the 3D PET image of the subject is obtained following administration to the subject of a radiopharmaceutical comprising a prostate-specific membrane antigen (PSMA) binding agent.”**

251. Claim 17 depends from claim 16, which I explained in Section IX.A.12 above is anticipated by Renisch and/or obvious over Renisch in view of Zhao. The additional limitations in claim 17 (system claim) are identical to those in dependent claim 8 (method claim), which I already explained in Section IX.B.1 above are obvious in view of the teachings in Baker or Eiber. It is my opinion that claim 17 is unpatentable for the same reasons already expressed in Sections IX.A.12 (claim 16) and IX.B.1 (claim 8) above. A POSITA would have known, prior to the priority date of the Patent, that PSMA binding agents existed for PET

imaging of prostate cancer, as evidence by Baker or Eiber. Additionally, a POSITA would have been motivated to use a PSMA targeting molecule to perform PET imaging with Renisch and would have had a reasonable expectation of success doing so using known PSMA tracers identified in Baker or Eiber. Accordingly, it is my opinion that claim 17 is unpatentable as obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber.

**4. Dependent Claim 18: “The system of claim 17, wherein the radiopharmaceutical comprises [18F]DCFPyL.”**

252. Dependent claim 18 depends from claim 17, which I explained in the preceding Section is obvious over Renisch, or Renisch with Zhao, each in view of Baker or Eiber. The additional limitations in claim 18 (system claim) are identical to those in dependent claim 9 (method claim), which I already explained in Section IX.B.2 above are disclosed in both Baker and Eiber. It is my opinion, therefore, that claim 18 is unpatentable for the same reasons already expressed in Sections IX.B.3 (claim 17) and IX.B.2 (claim 9) above. Both Baker and Eiber disclose that <sup>18</sup>F-DCFPyL is one of the known PSMA for PET imaging of prostate cancer before the priority date of the Patent. Ex1008, [0005], [0017], [0036], [0045], [0095]-[0096]; Ex1009, p.472 (Fig. 1).

**5. Dependent claim 22: “The method of claim 8, wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-11.”**

253. Claim 22 depends from claim 8, which I explained in the Section

IX.B.1 above is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber. Claim 22 adds “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-11,” which is also disclosed by both Baker (Ex1008, [0099]-[0100]) and Eiber (Ex1009, p.472 (Fig. 1)). Accordingly, it is my opinion that claim 22 is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber for the same reasons previously stated in Section IX.B.1 above.

**6. Dependent Claim 23: “The method of claim 8, wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-617.”**

254. Claim 23 depends from claim 8, which I explained in the Section IX.B.1 above is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker. Claim 23 adds “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-617,” which is also disclosed by Baker. Ex1008, [0101]-[0102]. Accordingly, it is my opinion that claim 23 is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker for the same reasons previously stated in Section IX.B.1 above.

**7. Dependent Claim 24: “The method of claim 8, wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-I&T.”**

255. Claim 24 depends from claim 8, which I explained in the Section IX.B.1 above is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber. Claim 24 adds “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-I&T,” which is also disclosed by both Baker (Ex1008, [0103]-[0104]) and

Eiber (Ex1009, p.472 (Fig. 1)). Accordingly, it is my opinion that claim 24 is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber for the same reasons previously stated in Section IX.B.1 above.

**8. Dependent Claim 25: “The method of claim 8, wherein the radiopharmaceutical comprises <sup>18</sup>F-PSMA-1007.”**

256. Claim 25 depends from claim 8, which I explained in the Section IX.B.1 above is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber. Claim 25 adds “wherein the radiopharmaceutical comprises <sup>18</sup>F-PSMA-1007,” which is also disclosed by both Baker (Ex1008, [0105]-[0106]) and Eiber (Ex1009, p.472 (Fig. 1)). Accordingly, it is my opinion that claim 25 is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber for the same reasons previously stated in Section IX.B.1 above.

**9. Dependent Claim 29: “The system of claim 17, wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-11.”**

257. Claim 29 depends from claim 17, which I explained in the Section IX.B.3 above is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber. Claim 29 adds “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-11,” which is also disclosed by both Baker (Ex1008, [0099]-[0100]) and Eiber (Ex1009, p.472 (Fig. 1)). Accordingly, it is my opinion that claim 29 is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber for the same reasons previously stated in Section IX.B.3 above.

**10. Dependent Claim 30: “The method of claim 17, wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-617.”**

258. Claim 30 depends from claim 17, which I explained in the Section IX.B.3 above is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker. Claim 29 adds “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-617,” which is also disclosed by Baker. Ex1008, [0101]-[0102]. Accordingly, it is my opinion that claim 30 is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker for the same reasons previously stated in Section IX.B.3 above.

**11. Dependent Claim 31: “The method of claim 17, wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-I&T.”**

259. Claim 31 depends from claim 17, which I explained in the Section IX.B.3 above is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber. Claim 31 adds “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-I&T,” which is also disclosed by both Baker (Ex1008, [0103]-[0104]) and Eiber (Ex1009, p.472 (Fig. 1)). Accordingly, it is my opinion that claim 31 is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber for the same reasons previously stated in Section IX.B.3 above.

**12. Dependent Claim 32: “The method of claim 17, wherein the radiopharmaceutical comprises <sup>18</sup>F-PSMA-1007.”**

260. Claim 32 depends from claim 17, which I explained in the Section

IX.B.3 above is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber. Claim 32 adds “wherein the radiopharmaceutical comprises <sup>18</sup>F-PSMA-1007,” which is also disclosed by both Baker (Ex1008, [0105]-[0106]) and Eiber (Ex1009, p.472 (Fig. 1)). Accordingly, it is my opinion that claim 32 is obvious over Renisch, or Renisch in view of Zhao, each in view of Baker or Eiber for the same reasons previously stated in Section IX.B.3 above.

### C. Ground E, Obviousness Over Baker in view of Zhao

#### 1. Independent Claim 1

- a) **Preamble: “A method for automatically processing 3D images to automatically identify cancerous lesions within a subject, the method comprising:”**

261. Assuming that the preamble is a limitation on the scope of claim 1, Baker discloses: “A method for automatically processing 3D images to automatically identify cancerous lesions within a subject.”

262. Baker describes a method of “automatically analyzing ... one or more ... medical images[,] e.g., ... computed tomography (CT) images, ... to generate a risk map, e.g., a visual representation (e.g., 3D representation) of tissue ... with graphical denotations ... marking regions of risk of current disease ..., e.g., cancer.” *Id.* at [0032] (emphasis added). The CT images analyzed by Baker are 3D medical images. *Id.* at [0137] (“CT scans provide accurate anatomical information in the form of detailed three-dimensional (3D) images.”). Baker also states that

hotspots within the medical images are “automatically identified” (*id.* at [0152]) and that “[h]otspots may be ... classified as corresponding to cancerous lesions (e.g., metastases) using a variety of approaches (*id.* at [0131]).

263. Accordingly, it is my opinion that Baker discloses the features of the preamble of claim 1 to the extent they are limitations.

**b) Limitation 1(a): “receiving, by a processor of a computing device, a 3D anatomical image of a subject obtained using an anatomical imaging modality, wherein the 3D anatomical image comprises a graphical representation of tissue within the subject;”**

264. In my opinion, Baker discloses limitation 1(a). Ex1008, [0032], [0036], [0137].

265. For context, the Patent states:

In one aspect, the invention is directed to a method for automatically processing a 3D image ..., the method comprising: (a) receiving, by a processor of a computing device, a 3D anatomical image of a subject obtained using an anatomical imaging modality [e.g., x-ray computed tomography (CT); e.g., magnetic resonance imaging (MRI); e.g., ultra-sound], wherein the 3D anatomical image comprises a graphical representation of tissue (e.g., soft-tissue and/or bone) within the subject.

Ex1001, 5:12-21 (emphasis added).

266. Baker likewise discloses:

[T]he invention is directed to a method comprising ... receiving and

storing, by a processor of a server computing device (e.g., received over a network from a client computing device) medical images [e.g., comprising one or more of the following: ... computed tomography (CT) images, magnetic resonance (MR) images, [or] ultrasound (US) images.”

Ex1008, [0032], [0036] (“the medical images comprise ... a CT scan of the ... patient”). Additionally, Baker explains: “CT scans provide accurate anatomical information in the form of detailed three-dimensional (3D) images of internal organs, bones, soft tissue, and blood vessels.” *Id.* at [0137] (emphasis added).

267. Accordingly, it is my opinion that Baker discloses Limitation 1(a).

- c) **Limitation 1(b): “automatically identifying, by the processor, using one or more machine learning modules, for each of a plurality of target tissue regions, a corresponding target volume of interest (VOI) within the 3D anatomical image;”**

268. In my opinion, Baker discloses this limitation. Ex1008, [0032], [0132], [0137].

269. For context, the Patent explains:

The automated, machine learning-based segmentation approaches described herein are used to identify, within the CT image of the PET/CT composite, target volumes of interest (VOIs) representing target tissue regions where cancerous lesions may be found. For example, a skeletal VOI corresponding to a graphical representation of one or more bones of the subject may be identified. Once the

skeletal VOI is identified in the anatomical, CT, image, it can be mapped to the PET image to identify a corresponding skeletal volume therein. The corresponding skeletal volume in the PET image is then analyzed to detect one or more localized regions of relatively high intensity, referred to as hotspots. These hotspots correspond, physically, to local regions of increased radiopharmaceutical accumulation and, accordingly, prospective cancerous lesions.

Ex1001, 3:55-4:3, 10:45-12:16 (listing target tissue regions as specific bones or organs), 15:40-56 (“target tissue regions (e.g., one or more specific bones, e.g., one or more specific organs)”).

270. Baker likewise discloses:

[A]utomated segmentation of CT scans can be performed to identify 3D boundaries of specific organs (e.g., a prostate, lymph nodes, a lung or lungs) ... as well as other regions of imaged tissue, such as particular bones and an overall skeletal region of the patient. Automated segmentation of CT scans can be accomplished via a variety of approaches, include [sic] machine learning techniques [e.g., ANN-based approaches (including, e.g., convolutional neural networks (CNNs))].

*Id.* at [0137] (emphasis added). Baker also makes clear that its automatic analysis of medical images comprises “geographically identifying one or more organs ... and/or other regions of the imaged tissue” (*id.* at [0032](emphasis added)) and that the “[p]roperties of the one or more regions, such as their area or volume may ...

be used” (*id.* at [0132](emphasis added)).

271. Accordingly, it is my opinion that Baker discloses Limitation 1(b).

- d) **Limitation 1(c): “determining, by the processor, a 3D segmentation map representing a plurality of 3D segmentation masks, each 3D segmentation mask representing a particular identified target VOI;”**

272. For context, the Patent explains:

The AI-based segmentation technologies described herein utilize machine learning techniques, such as Convolutional Neural Networks (CNNs) to automatically to identify a plurality of target 3D volumes of interest (VOIs) each corresponding to a specific target tissue region, such as one or more organs, portions of organs, particular bone(s), a skeletal region etc. Each identified 3D VOI may be represented via a segmentation mask. The multiple segmentation masks, identifying multiple target tissue regions across a patient's body, can be stitched together to form a segmentation map.... Segmentation maps and masks may ... be displayed, for example as a graphical representation overlaid on a medical image to guide physicians and other medical practitioners.

Ex1001, 32:3-21 (emphasis added). Additionally, the Patent states

Segmentation maps generated by automated AI-based analysis of anatomical images can be transferred to 3D functional images in order to identify, within the 3D functional image, 3D volumes corresponding to the target VOIs identified in the anatomical image. In particular, in certain embodiments, the individual segmentation

masks (of the segmentation map) are mapped from the 3D anatomical image to the 3D functional image.

*Id.* at 37:15-22 (emphasis added).

273. As I explained in the preceding Section IX.C.1.c), Baker describes automatically segmenting an anatomical CT image into specific organ volumes. Once the 3D boundaries of various regions are identified within a CT scan, the identified 3D boundaries can be transferred to a PET image by virtue of “mapping between the CT scan and PET scan.” Ex1008, [0138]. Baker also states that it’s “automatic analysis” includes “geographically identifying one or more organs ... of the patient and production of a 3D image of the geographically identified tissue with PET, SPECT, CT, [or] MRI ... data overlaid.” Ex1008, [0032]. This description is nearly identical to the Patent’s description of a segmentation map being displayed as a graphical representation overlaid on a medical image. *See* Ex1001, 32:3-21.

274. Baker does not use the term “segmentation mask.” But Zhao, which is in the same field of art as Baker, *expressly describes* the use of segmentation masks to implement 3D medical image segmentation like that discussed in Baker. Ex1007, 5:11-6:51 (“ROI identification and segmentation may be implemented in medical image processing. Such medical images may include ... Computed Tomography (CT) images, Magnetic Resonance Imaging (MRI) images, ... and

the like.”) (“[A]n ROI may be an entire organ.”) (emphasis added). Zhao, like Baker, describes “image segmentation” (*id.* at 5:21-24) using machine learning algorithms such as deep convolutional neural networks (*id.* at 6:31-35). Zhao states that “ROIs, once determined, may be represented by a digital mask containing a same number of pixels as the digital image” and “[a] digital mask may be alternatively referred [to] as a mask or a segmentation mask.” *Id.* at 5:25-29 (emphasis added). Thus, Zhao discloses the use of segmentation masks representing particular volumes-of-interest within 3D medical images, such as entire organs within CT images.

275. Additionally, Zhao discloses the determination of a segmentation map representing a plurality of segmentation masks. Zhao states:

Each pixel of the mask may contain a value used to denote whether a particular corresponding pixel of the digital image is among any ROI, and if it is, which type of ROI among multiple types of ROIs does it fall. For example, if there is only a single type of ROI, a binary mask is sufficient to represent all ROIs. In particular, each pixel of the ROI mask may be either zero or one, representing whether the pixel is or is not among the ROIs. For a mask capable of representing multiple types of ROI, each pixel may be at one of a number of values each corresponding to one type of ROIs. A multi-value mask, however, may be decomposed into a combination [sic] the more fundamental binary masks each for one type of ROI.

*Id.* at 5:30-42 (emphasis added). Thus, instead of the term “segmentation map,” Zhao uses the term “multi-value mask” to refer to a plurality of (binary) segmentation masks that are combined. Accordingly, in my opinion Zhao discloses Limitation 1(c).

276. It is my opinion that a POSITA would have found it obvious to implement the medical image segmentation described in Baker using the segmentation mask techniques described in Zhao based on the express motivations and teachings provided in Baker and Zhao. Both Baker and Zhao are directed to segmentation of 3D medical images, such as CT images, using neural networks. Baker explains the value of mapping the 3D boundaries of specific tissue regions from segmented anatomical scans (e.g., CT) to functional scans (e.g., PET) – so that risk indices can be accurately calculated based on the level of cancerous tissue (i.e. hotspots) within the 3D boundaries. Ex1008, [0138], [0140]. Zhao teaches the use of image segmentation to produce “[o]ne or more ROI masks, alternatively referred to as segmentation masks” that “may be used to mark the location of ... organ tissues and the regions outside of the ROI ... that are not part of the organ.” Ex1007, 6:1-7. Additionally, Zhao teaches that segmentation masks are particularly useful when processing a digital image because “an ROI mask can be used as a filter to determine a subset of image data that ... need be further analyzed” while “[i]mage data outside these ... ROIs may be removed from further

analysis.” Ex1007, 5:43-48. Since Baker is concerned with the accurate mapping of 3D organ boundaries to functional images, a POSITA would have been motivated to use a segmentation mask, as described in Zhao, to better differentiate between regions located inside and outside of a segmented organ. Moreover, in my opinion a POSITA would have had a reasonable expectation of success combining Baker and Zhao in this manner since both are directed to 3D medical image segmentation and because the generation of segmentation masks is a standard technique in the field of image segmentation as described in Zhao.

277. Alternatively, improving Baker with the teachings of Zhao would merely have amounted to combining prior art elements—specifically, segmenting 3D medical images and generating digital masks of segmented ROIs—according to known methods (as described in Zhao) to yield predictable results. Baker, like the Patent, describes the segmentation of medical CT images into a plurality of ROIs corresponding to organs. Ex1008, [0137]. Baker does not, however, expressly describe the determination of a segmentation map. Zhao, describing basic implementations of image segmentation, teaches a technique for producing a 3D segmentation map from a plurality of 3D segmentation masks – each corresponding to a segmented ROI. Ex1007, 5:25-42, 5:60-6:4. Zhao also discloses that segmentation masks are particularly useful when processing a digital image because “an ROI mask can be used as a filter to determine a subset of image data

that ... need be further analyzed” while “[i]mage data outside these ... ROIs may be removed from further analysis.” Ex1007, 5:43-48. In my opinion, because Baker and Zhao are in the same field of image segmentation, a POSITA could thus have predictably combined Baker and Zhao, using Zhao’s segmentation mask technique, without altering the functionality of either Baker or Zhao. Additionally, this improvement would not, in my opinion, produce an unexpected result since: (i) segmentation masks are a standard implementation detail of image segmentation; and (ii) the Patent does not describe any unexpected result or improvement that is achieved based on the use of segmentation masks.

278. Accordingly, it is my opinion that a POSITA would have been motivated to combine Baker and Zhao as proposed here and would have had a reasonable expectation of success in doing so.

**e) Limitation 1(d): “receiving, by the processor, a 3D functional image of the subject obtained using a functional imaging modality;”**

279. It is my opinion that Baker discloses this limitation. Ex1008, [0032], [0036]. For example, Baker states:

[T]he invention is directed to a method comprising ... receiving and storing, by a processor of a server computing device (e.g., received over a network from a client computing device) medical images [] e.g., comprising one or more of the following: ... targeted PET images [or] targeted SPECT images ..., each medical image

associated with a particular patient.”

*Id.* at [0032]. A POSITA would understand that PET and SPECT images are reconstructed 3D images obtained using a functional (nuclear medicine) imaging modality. Ex1008, [0038] (“nuclear medicine image (e.g., a SPECT scan; e.g., a PET scan)”) (“geographically identify a 3D boundary ... within the nuclear medicine image”).

280. Accordingly, it is my opinion that Baker discloses Limitation 1(d).

**f) Limitation 1(e): “identifying, within the 3D functional image, one or more 3D volume(s), each corresponding to an identified target VOI, using the 3D segmentation map; and”**

281. For context, the Patent states:

Segmentation maps generated by automated AI-based analysis of anatomical images can be transferred to 3D functional images in order to identify, within the 3D functional image, 3D volumes corresponding to the target VOIs identified in the anatomical image. In particular, in certain embodiments, the individual segmentation masks (of the segmentation map) are mapped from the 3D anatomical image to the 3D functional image.

Ex1001, 37:15-22. Baker describes the same process.

282. As I explained in Section IX.C.1.d) above, Baker in view of Zhao teaches automatic segmentation of an anatomical image to determine a segmentation map representing a plurality of segmentation masks as recited in

Limitation 1(c). Additionally, Baker describes identifying, within a 3D functional image, one or more 3D volume(s), each corresponding to an identified target VOI in the anatomical image, as recited in Limitation 1(e). For example, Baker states: “Once the 3D boundaries of various regions are identified within a CT scan of a composite image, by virtue of the mapping between the CT scan and PET scan of the composite image, the identified 3D boundaries can be transferred to the PET image. Accordingly, regions of the PET image falling within and/or outside of the identified 3D boundaries can be accurately identified.” Ex1008, [0138], [0038] (“geographically identify a 3D boundary for each of one or more regions of imaged tissue [e.g., organs...] within the nuclear medicine image (e.g., such that portions of the nuclear medicine image falling within and/or outside of the 3D boundaries can be differentiated from each other”).

283. Accordingly, it is my opinion that Baker discloses Limitation 1(e).

**g) Limitation 1(f): “automatically detecting, by the processor, within at least a portion of the one or more 3D volumes identified within the 3D functional image, one or more hotspots determined to represent lesions based on intensities of voxels within the 3D functional image.”**

284. It is my opinion that Baker discloses these limitations. Ex1008, [0032], [0038], [0039], [0129]-[0132], [0138], [0140], [0152] (“the automatically identified hotspots may be adjusted by the radiologist”).

285. Baker describes automatically analyzing 3D medical images, including functional PET images and anatomical CT images, to generate a risk map comprising a visual representation of tissue overlaid with graphical denotations marking regions of risk of cancer. *Id.* at [0032]. Baker also describes automatically computing risk indices based on the amount of cancerous tissue measured within particular 3D volumes (e.g., the skeleton) identified in the functional images. *Id.* at [0038], [0131]-[0132]. Both the automatically generated risk map and the automatically calculated risk indices are based on the automatic detection of hotspots determined to be lesions.

286. Hotspots are localized regions of high intensity within functional images. Ex1008, [0131]. Baker expressly states that hotspots are “automatically identified.” *Id.* at [0152]. Baker also states: “Hotspots may be detected and/or classified as corresponding to cancerous lesions (e.g., metastases) using a variety of approaches, including, as described in U.S. Pat. No. 8,855,387,” which Baker incorporates by reference in its entirety. *Id.* at [0131], [0129] (“U.S. Pat. No. 8,855,387 ... is incorporated herein by reference in its entirety.”) U.S. Patent No. 8,855,387 (Ex1014) describes detection of hotspots by thresholding images to identify pixels/voxels above a certain threshold intensity. Ex1014, 5:27-38.

287. With respect to the identification of one or more 3D volumes within a functional image, Baker states:

Once the 3D boundaries of various regions are identified within a CT scan of a composite image, by virtue of the mapping between the CT scan and PET scan of the composite image, the identified 3D boundaries can be transferred to the PET image. Accordingly, regions of the PET image falling within and/or outside of the identified 3D boundaries can be accurately identified.

Ex1008, [0138].

288. With respect to detecting hotspots determined to be lesions within the one or more identified 3D volumes, Baker states:

[O]nce the 3D boundaries of the various regions are identified within the PET scan, one or more risk indices can be computed.... In particular, in certain embodiments, intensity values of the PET scan in relation to (e.g., within and/or outside of) the 3D boundaries of the identified regions can be used to determine levels of cancerous tissue within the identified regions, e.g., based on features of detected hotspots (e.g., detected hotspots corresponding to metastases).

*Id.* at [0140] (emphasis added). Accordingly, Baker automatically detects hotspots determined to represent cancerous lesions based on the intensities of voxels within a 3D functional image. Additionally, Baker discloses detecting these hotspots within 3D volumes identified within the 3D functional image (e.g., the skeleton).

289. Therefore, it is my opinion that Baker discloses Limitation 1(f).

290. Thus, because Baker in view of Zhao teaches all the limitations of claim 1, it is my opinion that Baker in view of Zhao renders claim 1 obvious.

**2. Dependent Claim 2: “The method of claim 1, comprising using, by the processor, the one or more detected hotspots to determine a cancer status for the subject.”**

291. Claim 2 depends from claim 1, which I explained in Section IX.C.1 above is obvious over Baker in view of Zhao. Claim 2 further states “using, by the processor, the one or more detected hotspots to determine a cancer status for the subject.” It is my opinion that Baker discloses this limitation. Ex1008, [0039], [0053], [0131], [0152].

292. As I explained in the immediately preceding Section, Baker discloses a method for automatically detecting hotspots and classifying those hotspots as corresponding to cancerous lesions. *Id.* at [0152] (“automatically identified hotspots”), [0131] (“Hotspots may be ... classified as corresponding to cancerous lesions.”). Baker also discloses automatically computing one or more risk indices based on the number or volume of hotspots within one or more tissue regions (*id.* at [0039]) and tracking cancer progression using the risk indices, where the values of the risk indices correspond to “numeric values identifying a particular cancer stage” (*id.* at 0053).

293. Because Baker discloses every limitation of claim 2, it is my opinion that Baker in view of Zhao renders claim 2 obvious under the same rationale expressed in Section IX.C.1 above.

**3. Dependent Claim 7: “The method of claim 1, wherein: the**

**3D anatomical image is an x-ray computed tomography (CT) image, and the 3D functional image is a 3D positron emission tomography (PET) image.”**

294. Claim 7 depends from claim 1, which I explained above in Section IX.C.1 is rendered obvious by Baker in view of Zhao. It is my opinion that Baker also discloses the additional limitations recited in claim 7. Ex1008, [0032], [0036], [0038], [0136]-[0140]. For example, Baker states:

In certain embodiments, the medical images comprises a positron emission tomography (PET) scan of a first patient obtained following administration to the first patient of an imaging agent comprising [18F]DCFPyL (DCFPyL labeled with <sup>18</sup>F), and a CT scan of the first patient, wherein the method comprises overlaying the PET scan with the CT scan to create a composite image (PET-CT) of the first patient.

Ex1008, [0036]. Although Baker does not appear to explicitly refer to “x-ray” computed tomography, a POSITA would understand, based on their general level of knowledge, that a generic reference to “CT scans,” as in Baker, includes, most notably, x-ray computed tomography.

295. Because Baker discloses all the limitations of claim 7, it is my opinion that Baker in view of Zhao renders claim 7 obvious for under the same rationale provided in Section IX.C.1 with respect to claim 1.

4. **Dependent Claim 8: “The method of claim 7, wherein the 3D PET image of the subject is obtained following administration to the subject of a radiopharmaceutical comprising a prostate-specific membrane antigen (PSMA)**

**binding agent.”**

296. Claim 8 depends from claim 7, which I explained in the immediately preceding Section IX.C.3 is rendered obvious by Baker in view of Zhao. It is my opinion that claim 8 is unpatentable for the same reason as claim 7.

297. The Patent states that “[<sup>18</sup>F]DCFPyl ... is a clinical-stage, fluorinated PSMA-targeted PET imaging agent for prostate cancer.” Ex1001, 2:1-4. As stated in Section IX.C.3, Baker discloses obtaining a PET scan following administration of “[<sup>18</sup>F]DCFPyL.” Ex1008, [0036]. Accordingly, Baker discloses the limitations of claim 8, and it is my opinion that Baker in view of Zhao renders claim 8 obvious under the same rationale previously expressed with respect to claim 1 in Section IX.C.1 above.

**5. Dependent Claim 9: “The method of claim 8, wherein the radiopharmaceutical comprises [<sup>18</sup>F]DCFPyL.”**

298. Claim 9 depends from claim 8, which I explained in the immediately preceding Section IX.C.4 is obvious over Baker in view of Zhao. As stated in Section IX.C.3, Baker discloses obtaining a PET scan following administration of “[<sup>18</sup>F]DCFPyL.” Ex1008, [0036]. Therefore, it is also my opinion that Baker in view of Zhao renders claim 9 obvious for the same reasons expressed in Section IX.C.4.

**6. Independent Claim 10**

299. Independent claim 10 of the Patent is nearly identical to independent claim 1, which I explained in Section IX.C.1 above is rendered obvious by Baker in view of Zhao. Whereas claim 1 is directed to a method, claim 10 is directed to a system that essentially performs the method recited in claim 1. Whereas claim 1 (the method claim) recites a series of steps, each performed “by a processor,” claim 10 (the system claim) recites a “processor” and “memory” having stored instructions that, when executed by the processor, perform the same steps recited in claim 1. Accordingly, it is my opinion that claim 10 is rendered obvious by Baker in view of Zhao for the same reasons I explained in Section IX.C.1 above.

- a) **Preamble: “A system for automatically processing 3D images to automatically identify cancerous lesions within a subject, the system comprising:”**

300. The preamble of claim 10 is essentially the same as the preamble of claim 1 except that claim 10 recites a system whereas claim 1 recites a method. Assuming the preamble is considered a limitation on the scope of the claim, it is my opinion that Baker discloses the limitations of the preamble for the same reasons provided in Section IX.C.1.a) above.

- b) **Limitation 10(i): “a processor of a computing device; and a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to:”**

301. It is my opinion that Baker discloses Limitation 10(i), which is

nothing more than a generic recitation of standard structure found in any computer implemented system. Ex1008, [0164]-[0165], Fig. 8.

302. With reference to Fig. 8, reproduced below, Baker states “FIG. 8 shows an example of computing device 800 ... that can be used in the methods and systems described in this disclosure.” *Id.* at [0164]. Baker also states that the computing device 800 includes a processor 802 and a memory 804 and “[t]he processor 802 can process instructions for execution within the computing device 800, including instructions stored in memory 804.” *Id.* at [0165].

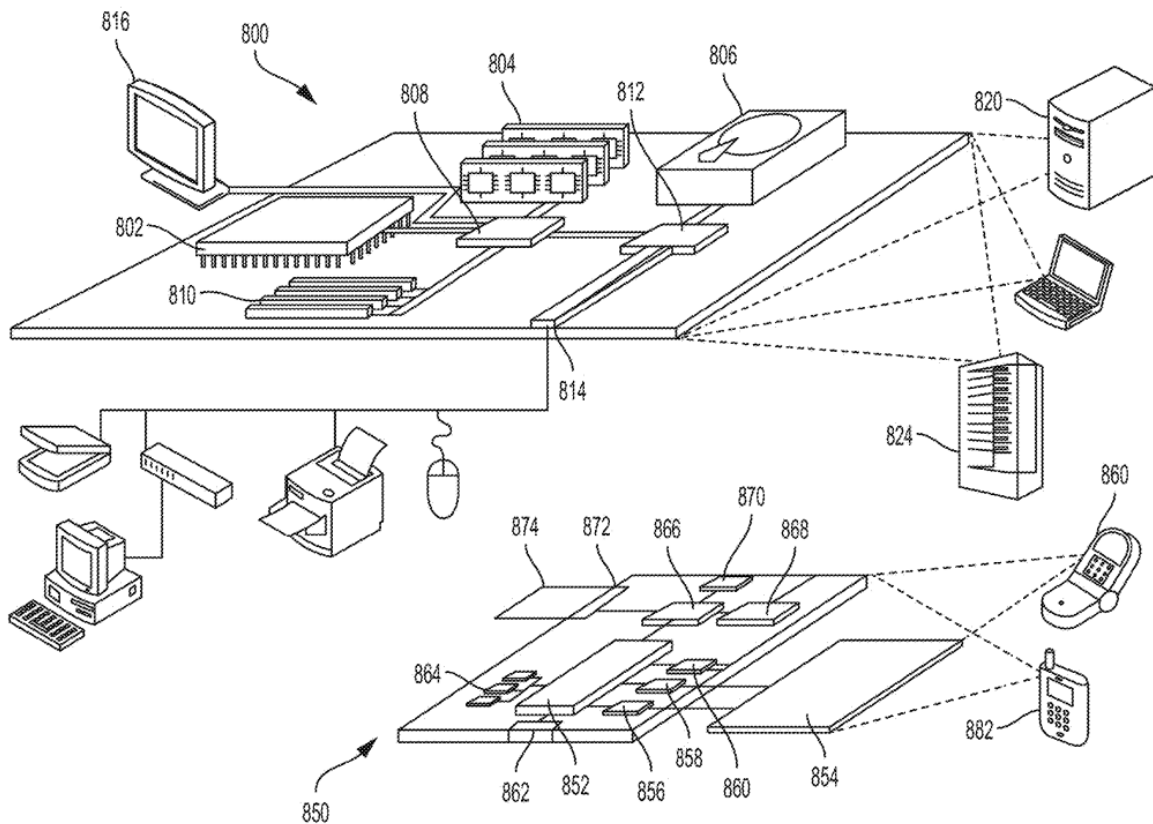


FIG. 8

303. Accordingly, it is my opinion that Baker discloses Limitation 10(i).

- c) **Limitation 10(ii): “(a) receive a 3D anatomical image of a subject obtained using an anatomical imaging modality, wherein the 3D anatomical image comprises a graphical representation of tissue within the subject;”**

304. Limitation 10(ii) is essentially identical to Limitation 1(a), which is addressed in Section IX.C.1.b) above. The only difference is that, whereas Limitation 1(a) recites “receiving, by a processor of a computing device, a 3D anatomical image ...,” Limitation 10(ii) relates to instructions that cause a processor to “receive a 3D anatomical image ....” Accordingly, it is my opinion that Baker discloses Limitation 10(ii) for the same reasons explained in Section IX.C.1.b) above.

- d) **Limitation 10(iii): “(b) automatically identify, using one or more machine learning modules, for each of a plurality of target tissue regions, a corresponding target volume of interest (VOI) within the 3D anatomical image;”**

305. Limitation 10(iii) is essentially identical to Limitation 1(b), which is addressed in Section IX.C.1.c) above. The only difference is that, whereas Limitation 1(b) recites “automatically identifying, by the processor ...,” Limitation 10(iii) relates to instructions that cause a processor to “automatically identify ....” Accordingly, it is my opinion that Baker discloses Limitation 10(iii) for the same reasons explained in Section IX.C.1.c) above.

- e) **Limitation 10(iv): “(c) determine a 3D segmentation**

**map representing a plurality of 3D segmentation masks, each 3D segmentation mask representing a particular identified target VOI;”**

306. Limitation 10(iv) is essentially identical to Limitation 1(c), which is addressed in Section IX.C.1.d) above. The only difference is that, whereas Limitation 1(c) recites “determining, by the processor, a 3D segmentation map ...,” Limitation 10(iv) relates to instructions that cause a processor to “determine a 3D segmentation map ....” Accordingly, it is my opinion that Baker in view of Zhao teaches limitation 10(iv) for the same reasons explained in Section IX.C.1.d) above.

**f) Limitation 10(v): “(d) receive a 3D functional image of the subject obtained using a functional imaging modality;”**

307. Limitation 10(v) is essentially identical to Limitation 1(d), which is addressed in Section IX.C.1.e) above. The only difference is that, whereas Limitation 1(d) recites “receiving, by the processor, a 3D functional image ...,” Limitation 10(v) relates to instructions that cause a processor to “receive a 3D functional image ....” Accordingly, it is my opinion that Baker discloses Limitation 10(v) for the same reasons explained in Section IX.C.1.e)above.

**g) Limitation 10(vi): “(e) identify, within the 3D functional image, one or more 3D volume(s), each corresponding to an identified target VOI, using the 3D segmentation map; and**

308. Limitation 10(vi) is essentially identical to Limitation 1(e), which is addressed in Section IX.C.1.f) above. Accordingly, it is my opinion that Baker discloses Limitation 10(vi) for the same reasons explained in Section IX.C.1.f) above.

**h) Limitation 10(vii): “(f) automatically detect, within at least a portion of the one or more 3D volumes identified within the 3D functional image, one or more hotspots determined to represent lesions based on intensities of voxels within the 3D functional image.”**

309. Limitation 10(vii) is essentially identical to Limitation 1(f), which is addressed in Section IX.C.1.g) above. The only difference is that, whereas Limitation 1(f) recites “automatically detecting, by the processor, ...,” Limitation 10(vii) relates to instructions that cause a processor to “automatically detect ....” Accordingly, it is my opinion that Baker discloses Limitation 10(vii) for the same reasons explained in Section IX.C.1.g) above.

**7. Dependent Claim 11: “The system of claim 10, wherein the instructions cause the processor to use the one or more detected hotspots to determine a cancer status for the subject.”**

310. Claim 11 depends from claim 10 (system claim) and is essentially the same as dependent claim 2, which depends from claim 1 (method claim). For the same reasons I explained in Sections IX.C.2 (claim 2) and IX.C.6 (claim 10) above, it is my opinion that claim 11 is rendered obvious by Baker in view of

Zhao.

- 8. Dependent Claim 16: “The system of claim 10, wherein: the 3D anatomical image is an x-ray computed tomography (CT) image, and the 3D functional image is a 3D positron emission tomography (PET) image.”**

311. Except for depending from claim 10 (system claim), claim 16 is the same as claim 7, which depends from claim 1 (method claim). For the same reasons I explained in Sections IX.C.3 (claim 7) and IX.C.6 (claim 10) above, it is my opinion that claim 12 is rendered obvious by Baker in view of Zhao.

- 9. Dependent Claim 17: “The system of claim 16, wherein the 3D PET image of the subject is obtained following administration to the subject of a radiopharmaceutical comprising a prostate-specific membrane antigen (PSMA) binding agent.”**

312. Dependent claim 17 depends from claim 16, which I explained in the immediately preceding Section IX.C.8 obvious over Baker in view of Zhao. The additional limitations in claim 17 (system claim) are identical to those in dependent claim 8 (method claim), which I already explained in Section IX.C.4 above is also obvious over Baker in view of Zhao. It is my opinion that claim 17 is unpatentable for the same reasons already expressed in Sections IX.C.8 (claim 16) and IX.C.4 (claim 8) above.

- 10. Dependent Claim 18: “The system of claim 17, wherein the**

**radiopharmaceutical comprises [18F]DCFPyL.”**

313. Dependent claim 18 depends from claim 17, which I explained in the preceding Section IX.C.9 is obvious over Baker in view of Zhao. The additional limitations in claim 18 (system claim) are identical to those in dependent claim 9 (method claim), which I already explained in Section IX.C.5 disclosed by Baker. It is my opinion that claim 18 is unpatentable for the same reasons already expressed in Sections IX.C.9 (claim 17) and IX.C.5 (claim 9) above.

**11. Dependent claim 22: “The method of claim 8, wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-11.”**

314. Claim 22 depends from claim 8, which I explained in the Section IX.C.4 above is obvious over Baker in view of Zhao. Claim 22 adds “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-11,” which is also disclosed by Baker. Ex1008, [0099]-[0100]. Accordingly, it is my opinion that claim 22 is obvious over Baker in view of Zhao for the same reasons previously stated in Section IX.C.4 above.

**12. Dependent Claim 23: “The method of claim 8, wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-617.”**

315. Claim 23 depends from claim 8, which I explained in the Section IX.C.4 above is obvious over Baker in view of Zhao. Claim 23 adds “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-617,” which is also disclosed by Baker. Ex1008, [0101]-[0102]. Accordingly, it is my opinion that claim 23 is

obvious over Baker in view of Zhao for the same reasons previously stated in Section IX.C.4 above.

**13. Dependent Claim 24: “The method of claim 8, wherein the radiopharmaceutical comprises  $^{68}\text{Ga}$ -PSMA-I&T.”**

316. Claim 24 depends from claim 8, which I explained in the Section IX.C.4 above is obvious over Baker in view of Zhao. Claim 24 adds “wherein the radiopharmaceutical comprises  $^{68}\text{Ga}$ -PSMA-I&T,” which is also disclosed by Baker. Ex1008, [0103]-[0104]. Accordingly, it is my opinion that claim 24 is obvious over Baker in view of Zhao for the same reasons previously stated in Section IX.C.4 above.

**14. Dependent Claim 25: “The method of claim 8, wherein the radiopharmaceutical comprises  $^{18}\text{F}$ -PSMA-1007.”**

317. Claim 25 depends from claim 8, which I explained in the Section IX.C.4 above is obvious over Baker in view of Zhao. Claim 25 adds “wherein the radiopharmaceutical comprises  $^{18}\text{F}$ -PSMA-1007,” which is also disclosed by Baker. Ex1008, [0105]-[0106]. Accordingly, it is my opinion that claim 25 is obvious over Baker in view of Zhao for the same reasons previously stated in Section IX.C.4 above.

**15. Dependent Claim 29: “The system of claim 17, wherein the radiopharmaceutical comprises  $^{68}\text{Ga}$ -PSMA-11.”**

318. Claim 29 depends from claim 17, which I explained in the Section

IX.C.9 above is obvious over Baker in view of Zhao. Claim 29 adds “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-11,” which is also disclosed by Baker. Ex1008, [0099]-[0100]. Accordingly, it is my opinion that claim 29 is obvious over Baker in view of Zhao for the same reasons previously stated in Section IX.C.9 above.

**16. Dependent Claim 30: “The method of claim 17, wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-617.”**

319. Claim 30 depends from claim 17, which I explained in the Section IX.C.9 above is obvious over Baker in view of Zhao. Claim 29 adds “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-617,” which is also disclosed by Baker. Ex1008, [0101]-[0102]. Accordingly, it is my opinion that claim 30 is obvious over Baker in view of Zhao for the same reasons previously stated in Section IX.C.9 above.

**17. Dependent Claim 31: “The method of claim 17, wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-I&T.”**

320. Claim 31 depends from claim 17, which I explained in the Section IX.C.9 above is obvious over Baker in view of Zhao. Claim 31 adds “wherein the radiopharmaceutical comprises <sup>68</sup>Ga-PSMA-I&T,” which is also disclosed by Baker. Ex1008, [0103]-[0104]. Accordingly, it is my opinion that claim 31 is obvious over Baker in view of Zhao for the same reasons previously stated in Section IX.C.9 above.

**18. Dependent Claim 32: “The method of claim 17, wherein the radiopharmaceutical comprises <sup>18</sup>F-PSMA-1007.”**

321. Claim 32 depends from claim 17, which I explained in the Section IX.C.9 above is obvious over Baker in view of Zhao. Claim 32 adds “wherein the radiopharmaceutical comprises <sup>18</sup>F-PSMA-1007,” which is also disclosed by Baker. Ex1008, [0105]-[0106]. Accordingly, it is my opinion that claim 32 is obvious over Baker in view of Zhao for the same reasons previously stated in Section IX.C.9 above.

**D. Ground F, Obviousness over Baker in view of Zhao and in further view of Eiber**

**1. Dependent Claim 3**

322. Dependent claim 3 depends from claim 1, which I explained in Section IX.C.1 above is rendered obvious by Baker in view of Zhao. Baker, as I explained, discloses a method for automatically segmenting and processing 3D images to automatically identify cancerous lesions within a subject. Zhao, as I explained, teaches the determination of a segmentation map from the results of image segmentation like the automatic image segmentation performed by Baker.

323. Independent claim 1 recites detecting hotspots determined to represent lesions based on their intensities. Claim 3 adds determining hot spot index values based on the detected hotspot’s intensity and the intensity of a reference volume. This additional feature is recommended by the PROMISE criteria disclosed by

Eiber (Ex1009). Accordingly, as set forth more fully below, it is my opinion that claim 3 is rendered obvious by Baker in view of Zhao and in further view of Eiber.

324. As is pertinent to dependent claim 3, the Patent states:

In certain embodiments, the ability to accurately and rapidly perform full body segmentation via the approaches described herein is leveraged to provide a useful and uniform scale on which to evaluate and/or measure radiopharmaceutical uptake levels in physical lesions corresponding to detected hotspots (e.g., to thereby grade expression levels of particular biomolecules, such as PSMA). In particular, in addition to detecting target VOIs corresponding to specific target tissue regions in which cancerous lesions may occur, additional target VOIs corresponding to reference tissue regions are also detected. These reference VOIs are also mapped to the PET image, to identify corresponding reference volumes therein. Measures of intensity, such as a mean, peak, maximum, etc., within these reference volumes are then computed and used as reference points against which to evaluate intensities of individual detected hotspots and convert them to index values on the scale.

For example, in certain embodiments, an aorta and a liver VOI, corresponding to a representation of a portion of an aorta and liver, respectively, are identified within the anatomical image and mapped to the functional image to identify corresponding reference volumes therein. Intensity levels of each of these reference volumes are determined (e.g., as a mean, median, peak, etc. of intensities of voxels within each reference volume), and assigned corresponding index

levels on a scale. Then, for each particular individual hotspot, a hotspot intensity level is determined (e.g., similarly, as a mean, median, peak, etc. of voxel intensities within the detected hotspot). A corresponding individual hotspot index value is then determined based on individual hotspot intensity level, the aorta reference intensity level, and the liver reference intensity level. This approach provides a standardized scale on which to evaluate and measure uptake associated with hotspots across different images. This allows, for example, for comparison of multiple images obtained for a single subject at different time points, as well as comparison between images of different subjects.

Ex1001, 4:4-40, 58:31-59.

325. The above description in the Patent is essentially a restatement of the prior art PROMISE criteria – without mentioning the PROMISE criteria. As I explained in Section VIII.D above, Eiber introduced the PROMISE criteria in 2018 stating:

We propose a miPSMA score that enables standardized reporting of PSMA expression as detected with PSMA-ligand PET. Expression categories are defined in relation to mean uptake in the blood pool, liver, and parotid gland (Table 1; Fig. 1). Results are reported as 0, 1, 2, or 3 for no, low, intermediate, or high PSMA expression, respectively.

Ex1009, p.471. Eiber further states, “we advise comparison of the mean SUVs of the respective lesions and the reference organ” though “further validation and

investigation [is required] to clarify whether SUV<sub>mean</sub>, SUV<sub>max</sub>, or SUV<sub>peak</sub> is the most appropriate parameter.” *Id.* Thus, Eiber discloses and recommends standardized reporting of detected lesions using an index value (0-3) determined by comparing the lesion uptake to a reference uptake, including uptake in the liver. Lesion uptake lower than the liver uptake is scored as a “1” for example. Lesion uptake equal to or above the liver uptake is scored as a “2” for example. *Id.* at 2.

326. In my opinion, it would have been obvious to a POSITA to practice the PROMISE method for standardized reporting using the system and method disclosed by the combination of Baker and Zhao based on the express motivation, teaching, and suggestion provided in Eiber. Baker discloses a system and method for automatically identifying cancerous lesions in a subject, including lesions representing prostate cancer detected using PSMA-ligand PET. Ex1008, [0092], [0136]-[0140]. Eiber provides the express teaching to report lesions detected with PSMA PET in a standardized manner to “aid reproducibility” and “enhance communication” because “[p]recise description and organized classification of PSMA-ligand PET/CT findings re needed to serve both clinical reporting (to help with defining tumor extent, tailoring therapy, assessing prognosis, and facilitating exchange of information between center) and research (to help with validating findings, pooling data ..., and performing metaanalyses for published data).” Ex1009, p.469. Accordingly, in my opinion it would have been obvious to a

POSITA to combine the teachings of Baker (with Zhao) and Eiber and to characterize detected lesions based on a comparison to uptake in a reference organ.

327. Additionally, in my opinion a POSITA would have had a reasonable expectation of success combining Baker (in view of Zhao) with Eiber as proposed here. To determine a lesion index value (i.e., expression category), Eiber must identify the uptake in reference organs such as the liver and lymph nodes. Baker already expressly teaches the automatic segmentation of one or more anatomical regions including the liver and lymph nodes, which are then transferred to a functional image so that the uptake within the 3D boundaries of the segmented regions can be evaluated. Ex1008, [0137]-[0140]. Thus, in my opinion it would have been straightforward for a POSITA to segment the liver, as described in Baker, and use the liver uptake as a reference value, as suggested by Eiber.

328. As more fully set forth below, in my opinion the combination of Baker in view of Zhao and in further view of Eiber teaches every limitation of claim 3.

- a) **Preamble: “The method of claim 1, wherein the target tissue regions comprise one or more reference tissue regions and wherein the method comprises:”**

329. As I already explained in Section IX.C.1.c) above, Baker automatically segments anatomical images to identify 3D boundaries for target tissue regions corresponding to organs – such as the liver. Ex1008, [0038].

330. Eiber teaches a method for “standardized reporting of PSMA expression as detected with PSMA-ligand PET” using “[e]xpression categories” that are defined in relation to measured uptake in reference organs, such as the liver. Ex1009, p.471.

331. As I already explained in the immediately preceding Section, it is my opinion that it would have been obvious to a POSITA to use one of Baker’s segmented regions as a reference region based on the express motivation supplied by Eiber – thus satisfying the preamble.

**b) Limitation 3(a): “using the 3D segmentation map to identify, by the processor, within the 3D functional image, one or more 3D reference volume(s), each corresponding to a particular reference tissue region;”**

332. As I explained in Section IX.C.1.d) above, it would be obvious to a POSITA to use Baker’s image segmentation results to determine a segmentation map representing a plurality of segmentation masks as described in Zhao. Thus, Baker in view of Zhao teaches the use of a 3D segmentation map. Additionally, Baker already discloses identifying one or more tissue regions in a 3D functional image by using its segmentation results. Ex1008, [0138] (“Once the 3D boundaries of various regions are identified within a CT scan ... the identified 3D boundaries can be transferred to the PET image.”). Thus, in my opinion, Baker in view of Zhao renders obvious: “using the 3D segmentation map to identify, by the

processor, within the 3D functional image, one or more 3D ... volume(s).”

333. As I explained in the immediately preceding Section, it would be obvious to use one or more of the segmented tissue regions identified by Baker (e.g. liver and lymph nodes) as a reference tissue region, as expressly suggested by Eiber. Accordingly, in my opinion, Baker in view of Zhao – as modified based on the teachings of Eiber – discloses Limitation 3(a).

- c) **Limitation 3(b): “determining, by the processor, one or more reference intensity values, each associated with a particular 3D reference volume of the one or more 3D reference volume(s) and corresponding to a measure of intensity within the particular 3D reference volume;”**

334. It is my opinion that Baker in combination with Eiber teaches this limitation. Baker discloses automatically computing one or more risk indices based on the intensity values of a 3D functional image within one or more identified 3D boundaries. Ex1008, [0140]. Thus, Baker is already measuring the intensity values within 3D segmented volumes. Eiber, as I have already explained, teaches determining reference intensity values corresponding to the measured intensity within particular reference volumes of a functional image, including the heart, liver, and parotid gland. Ex1009, p.471. Furthermore, as I explained in the immediately preceding Section, it would have been obvious to use one of Baker’s segmented volumes as a reference volume based on the express motivations disclosed in Eiber. Thus, in my opinion, Baker, as modified by the teachings of

Eiber – i.e., by using one of Baker’s segmented 3D volumes as a “reference 3D volume” – teaches Limitation 3(b).

- d) **Limitation 3(c): “determining, by the processor, one or more individual hotspot intensity values, each associated with a particular hotspot of at least a portion of the detected one or more hotspots and corresponding to a measure of intensity of the particular hotspot; and**

335. It is my opinion that Baker and Eiber both disclose Limitation 3(c). Baker states: “[C]ancerous tissue levels within one or more regions ... can be determined based on features of detected hotspots.... For example, a cancerous tissue level within a region ... may be determined based on ... an average intensity of detected hotspots, a maximal intensity of detected hotspots, and the like.” Ex1008, [0132]. Eiber states: “[W]e advise comparison of the mean SUVs of the respective lesions and the reference organ.” For context, the Patent uses “intensity” and “SUV” synonymously. *See, e.g.*, Ex1001, 58:31-59 (“intensity (SUV)”) (“blood and liver reference intensities (SUVs)”).

336. Accordingly, it is my opinion that Baker in view of Zhao in further view of Eiber renders obvious limitation 3(c).

- e) **Limitation 3(d): “determining, by the processor, one or more individual hotspot index values using the one or more individual hotspot intensity values and the one or more reference intensity values.”**

337. It is my opinion that Baker in combination with Eiber teaches

Limitation 1(d). Baker discloses automatically calculating one or more risk index values using a processor. Ex1008, [0038] (automatically analyzing an image by computing risk indices), [0132], [0140], [0164] (“computing device 800 ... can be used in the methods and systems described in this disclosure”), [0165] (“computing device 800 includes a processor 802”) (“processor 802 can process instructions for execution within the computing device 800”). Baker does not, however, expressly describe determining individual hotspot index values using individual hotspot intensity values and reference intensity values. Eiber teaches these limitations.

338. As I already explained above, Eiber discloses PSMA “expression categories” for individual lesions that are defined in relation to the measured uptake in the blood pool, liver, and parotid gland. Ex1009, p.471. As I also explained above, Eiber discloses “comparison of the mean SUVs of the respective lesions and the reference organ” to determine an index value, e.g., “0, 1, 2, or 3 for no, low, intermediate, or high PSMA expression.” *Id.* at 3, 2 (Table 1).

339. It is my opinion that it would have been obvious to determine individual hotspot index values, as recited in Limitation 3(d), using Baker’s processor based on the express motivation, teaching, and suggestion in Eiber. Moreover, a POSITA would have had a reasonable expectation of success in doing so since Baker already automatically segments tissue regions, such as the liver and

lymph nodes, already automatically measures the intensity of detected hotspots within the segmented regions, and automatically calculate one or more risk index values based on hotspot intensity values within segmented regions. The additional task of calculating, with the processor, individual hotspot index values using hotspot intensities that have already been measured and a reference intensity selected from a segmented region, such as the liver, would be routine for a POSITA.

340. Because Baker in view of Zhao and in further view of Eiber teaches every limitation of claim 3, including every limitation of claim 1 from which claim 3 depends, it is my opinion that claim 3 is rendered obvious by the combination of Baker, Zhao, and Eiber.

**2. Dependent Claim 4: “The method of claim 3, wherein the reference tissue regions comprise one or more members selected from the group consisting of: a liver, an aorta, and a parotid gland.”**

341. Claim 4 depends from claim 3 and is, in my opinion, rendered obvious by Baker in view of Zhao and in further view of Eiber for the same reasons already provided in Section IX.D.1 above. Eiber discloses every element of claim 4 because, as I already explained, Eiber teaches the use of the liver, a blood pool located in the aorta, and the parotid gland as reference tissue regions. Ex1009, p.471. My impression is that the Patent attempts to claim an automated

implementation of the prior art PROMISE criteria. Accordingly, it is my opinion that Baker in view of Zhao and in further view of Eiber renders claim 4 obvious in the same manner that Baker, Zhao, and Eiber have been applied to claim 3 in Section IX.D.1 above.

**3. Dependent Claim 5: “The method of claim 2, comprising, determining, by the processor, an overall index value indicative of a cancer status of the subject using at least a portion of the one or more hotspot index values.”**

342. Claim 5 depends from claim 2 and is, in my opinion, rendered obvious by Baker in view of Zhao and in further view of Eiber for the same reasons already provided in Section IX.C.2 above. In my opinion, Eiber discloses every additional limitation of claim 5. As explained above in Section IX.D.1, Eiber determines individual hotspot index values called “PSMA scores.” Ex1009, pp.470-471. Eiber further teaches using one or more of the PSMA scores to determine cancer status, i.e., as positive or negative. Ex1009, pp.472-473 (Figure 2). In my opinion, this constitutes determining an “overall index value indicative of cancer status.”

343. Alternatively, to the extent Eiber’s determination of cancer status does not directly constitute an “overall index value,” in my opinion it renders this limitation obvious. Eiber’s cancer status (positive or negative) could be alternatively expressed as an “overall index value” by assigning values to the cancer status, e.g., assigning “0” for a negative cancer status and a “1” for a

positive cancer status. In my opinion, this representation of Eiber's cancer status would be an obvious modification to a POSITA. Furthermore, to the extent that Eiber's determination of cancer status is not automated, it would have been within the general level of skill in the art to automate such process to be performed by a processor as claimed. For example, Baker's processor, which already calculates risk indices, could be further programmed to calculate hotspot index values and determine cancer status as taught by Eiber.

**4. Dependent Claim 12: Wherein the Target Tissue Regions Comprise One or More Reference Tissue Regions**

344. Dependent claim 12 depends from claim 10 (system claim) and is essentially the same as dependent claim 3, which depends from claim 1 (method claim). Whereas claim 3 is a method claim that recites a series of steps performed "by the processor," claim 12 is a system claim that recites "wherein the instructions cause the processor to" perform the same steps recited in claim 3. For the same reasons I explained in Sections IX.C.6 (claim 10) and IX.D.1 (claim 3) above, it is my opinion that claim 12 is rendered obvious by Baker in view of Zhao and in further view of Eiber.

**5. Dependent Claim 13: "The system of claim 12, wherein the reference tissue regions comprise one or more members selected from the group consisting of: a liver, an aorta, and a parotid gland."**

345. Claim 13 is the same as claim 4, except that claim 13 depends from

claim 12, which is a system claim, whereas claim 4 depends from claim 3, which is a method claim. For the same reasons I explained in Sections IX.C.6 (claim 10) and IX.D.2 (claim 4) above, it is my opinion that claim 13 is rendered obvious by Baker in view of Zhao and in further view of Eiber.

**6. Dependent Claim 14: Overall Index Value Indicative of Cancer Status**

346. Claim 14 is the same as claim 5, except that claim 14 depends from claim 11, which is a system claim, whereas claim 5, as written, depends from claim 2, which is a method claim. For the same reasons I explained in Sections IX.C.6 (claim 10) and IX.D.3 (claim 5) above, it is my opinion that claim 14 is rendered obvious by Baker in view of Zhao in further view of Eiber.

**E. Ground G, Obviousness over Baker in view of Zhao and in further view of Suehling**

**1. Dependent Claim 19**

347. Claim 19 depends from claim 1, which I explained above in Section IX.C.1 is rendered obvious by the combination of Baker in view of Zhao. As I explain here, it is my opinion that claim 19 is rendered obvious by Baker in view of Zhao and in further view of Suehling.

**a) Preamble: “The method of claim 1, wherein the target tissue regions comprise one or more background tissue regions and wherein the method comprises:”**

348. Independent claim 1 – from which claim 19 depends – recites, in

pertinent part, the steps of “receiving ... a 3D anatomical image” and “automatically identifying ... using one or more machine learning modules, for each of a plurality of target tissue regions, a corresponding target volume of interest (VOI) within the 3D anatomical image.” Ex1001, 79:8-18. The preamble of claim 19 adds that the target tissue regions recited in claim 1 include “one or more background tissue regions.”

349. The Patent describes the “background tissue regions” as being “e.g., a background tissue region in which significant radiopharmaceutical uptake occurs under normal circumstances and is not necessarily indicative of presence of cancerous lesions.” Ex1001, 8:57-65. Examples of background tissue regions, according to the Patent, include “a bladder (e.g., a urinary bladder), a kidney, a duodenum, a small intestine, a spleen, a liver, a pancreas, a stomach, an adrenal gland, a rectum, and testes.” *Id.* at 18:48-52 (emphasis added).

350. Baker automatically segments target tissue regions in 3D anatomical images using machine learning, as I explained in Section IX.C.1.c) above. For example, Baker states: “[A]utomated segmentation of CT scans can be performed to identify 3D boundaries of specific organs (e.g., a prostate, lymph nodes, a lung or lungs) ... as well as other regions of imaged tissue, such as particular bones and an overall skeletal region of the patient.” Ex1008, [0137]. Additionally, Baker expressly describes segmenting the liver (Ex1008, [0038]), which the Patent lists

among the examples of background tissue regions (Ex1001, 7:65-8:2). Thus, Baker discloses the features of the preamble of claim 19.

351. As I explained in Section VIII.E above, Suehling likewise receives one or more 3D medical images (*id.* at [0025], Fig. 1 (102)) and automatically segments the one or more images into lesion search regions using a machine learning algorithm (*id.* at [0026]-[0028]). The one or more images can be an anatomical CT image or a composite PET/CT image, for example. *Id.* at [0025], [0036]. The search regions correspond to target tissue regions including particular organs and bones such as the brain, liver, spleen, kidneys, and spine. *Id.* at [0007], [0027]. Additionally, Suehling describes creating “search regions outside of the organs and bones” (*id.* at [0007]) including “specific search areas for lymph nodes” (*id.* at [0029], Fig. 3). Suehling states that “the segmented organs and bone structures[] are ... used to define the lesion search regions outside the organs and bones, in order to exclude the detected organs and bones from these search regions.” *Id.* at [0029] (emphasis added).

352. Ultimately, each search region defined by Suehling is searched *separately* using “a separate region-specific detector ... trained based on annotated training data for each region.” *Id.* at [0033]. Thus, whether I consider the organ and bone search regions to be the background or the regions outside the organs and bones (e.g., lymph nodes) to be the background, Suehling also discloses target

tissue regions that are one or more “background tissue regions” as recited in the preamble.

353. Accordingly, it is my opinion that Baker in view of Zhao in further view of Suehling renders obvious this limitation.

**b) Limitation 19(a): “at step (e), using the 3D segmentation map to identify, within the 3D functional image, as at least a portion of the one or more 3D volumes, one or more 3D background tissue volume(s), each corresponding a particular background tissue region; and”**

354. Step (e) of independent claim 1 recites, in pertinent part, “identifying, within the 3D functional image, one or more 3D volume(s), each corresponding to an identified target VOI.” Ex1001, 79:26-28. Limitation 19(a) adds that the identified 3D volumes should include “one or more 3D background tissue volume(s), each corresponding to a particular tissue region.”

355. As I explained in the immediately preceding Section, Baker discloses segmenting target tissue regions in 3D anatomical images into organ volumes, including the liver, which the Patent lists as an example of a background tissue region. As I explained in Section IX.C.1.f) above, Baker also discloses transferring the segmented organ volumes from the anatomical image to the functional image. Ex1008, [0138]. Additionally, as I explained in Sections IX.C.1.d) and IX.C.1.f) above, it would have been obvious to a POSITA to implement Baker’s

segmentation using segmentation masks as encouraged by Zhao and, thus, use a segmentation map representing a plurality of segmentation mask to identify 3D volumes in the functional image. Accordingly, it is my opinion that Baker in view of Zhao discloses limitation 19(a).

- c) **Limitation 19(b): “excluding voxels of the 3D [sic] within the 3D background tissue from the voxels used to automatically detect the one or more hotspots at step (f).”**

356. Step (f) of independent claim 1 recites, in pertinent part, “automatically detecting ... within at least a portion of the one or more 3D volumes identified within the 3D functional image, one or more hotspots determined to represent lesions.” Ex1001, 79:29-32 (emphasis added). Limitation 19(b) appears to contain an error, but for the purpose of my analysis I assume that it adds the limitation: “excluding voxels of the 3D *functional image* within the 3D background tissue from the voxels used to automatically detect the one or more hotspots at step (f).”

357. Although Baker automatically segments background tissue volumes, including for example the liver (as identified in the Patent), Baker does not expressly describe excluding voxels within these regions from the voxels used to automatically detect hotspots. In my opinion, Suehling discloses this limitation.

358. As I explained in Section VIII.E above, Suehling generates a plurality

of distinct search regions and separately searches each region using “separate region-specific detectors.” Ex1006, [0033]. Because each region (e.g., organ) is searched separately for lesions, the voxels of the image outside the region (i.e., the background) are excluded from the search. For example, when defining the “specific search areas for lymph nodes,” Suehling states that the segmented organs and bones are used “to exclude the detected organs and bones from these search regions.” *Id.* [0029] (emphasis added). Likewise, Suehling describes using a “trained region-specific detector” based on “marginal space learning (MSL)” to search for lesions in each respective search region, and expressly states “MSL is applied to the restricted search space.” *Id.* at [0032] (emphasis added). Accordingly, Suehling fundamentally teaches excluding voxels (e.g., outside the search region) from the voxels used to automatically search for lesions (e.g., within the search region) using a region-specific detector.

359. Additionally, as I explained above, Suehling discloses embodiments in which anatomical images, such as CT images, are searched for lesions, as well as embodiments in which composite images, such as PET/CT images are searched for lesions. *Id.* at [0025], [0036]. In fact, Suehling teaches that “[t]he information of two imaging modalities may further improve the accuracy and robustness of the detection.” *Id.* at [0036]. Thus, Suehling also teaches that voxels of a 3D functional image are excluded from the voxels used to automatically detect lesions,

where those voxels include other segmented volumes in the “background,” i.e., currently outside the region presently being searched.

360. Accordingly, it is my opinion that Suehling discloses Limitation 19(b).

361. It is also my opinion that a POSITA would have been motivated to combine, and had reasonable expectation of success combining, Suehling with Baker in view of Zhao, thus rendering claim 19 obvious.

362. Whereas Baker describes segmenting one or more specific tissue regions and “determine[ing] levels of cancerous tissue within the identified regions,” (*id.* at [0140]), Baker does not expressly describe using different search criteria to identify lesions within respective regions. Nor, therefore, does Baker expressly describe restricting its lesion search to particular regions or excluding certain voxels from the voxels used to automatically search for lesions. Suehling, however, teaches the advantage of region-specific detectors and, therefore, restricted search areas. Suehling states that “[a] general lesion detection algorithm for the whole body is ... unlikely to yield reliable results” because “the appearance of the same lesion entity may differ between different body regions.” Ex1006, [0024]. Accordingly, in my opinion Suehling suggests “us[ing] body-region-specific detectors that exploit the typical context of a given region to detect lesions.” *Id.*

363. Accordingly, in my opinion Suehling supplies the teaching, suggestion, or motivation that would have led a POSITA to modify Baker (in view of Zhao), or to combine Baker (in view of Zhao) with Suehling, to arrive at the claimed invention. Whereas Baker is already concerned with determining cancerous tissue levels within particular tissue regions (e.g., the skeleton or prostate) for the purpose of computing risk indices, Suehling discloses a technique for improved lesion detection with such tissue regions using trained region-specific detectors. Accordingly, it is my opinion that a POSITA would have been motivated to improve Baker based on the teachings in Suehling.

364. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success combining Suehling with Baker (in view of Zhao). Each of Baker, Zhao, and Suehling are in the same field of 3D medical image analysis using machine learning to segment specific tissue regions. Baker already uses the segmented tissue regions to identify and quantify lesions within respective regions. Under the proposed combination/modification Baker would also use different regions-specific lesion search criteria in each region, as taught by Suehling. This could easily be accomplished based on the teachings of Zhao, which describes the use of segmentation masks produced from image segmentation like Baker and Suehling. Zhao states, for example, “an ROI mask can be used as a filter to determine a subset of image data ... that need be further analyzed and

processed.” Using the teachings of Zhao and Suehling, a POSITA could have easily used a segmentation mask to exclude voxels outside of a specific tissue region (e.g., skeleton) so as to apply a region-specific detector to voxel within the regions, as taught by Suehling.

365. Accordingly, it is my opinion that Baker in view of Zhao in further view of Suehling renders obvious claim 19.

**2. Dependent Claim 26: Wherein the Target Tissue Regions Comprise One Or More Background Tissue Regions**

366. Dependent claim 26 depends from claim 10 (system claim) and is essentially the same as dependent claim 19, which depends from claim 1 (method claim). Even the typographical error in claim 19 has been carried over to claim 26. Whereas claim 19 is a method claim that recites a series of steps, claim 26 is a system claim that recites “wherein the instructions cause the processor to” perform the same steps recited in claim 19. For the same reasons I explained in Sections IX.C.6 (claim 10) and IX.E.1 (claim 19) above, it is my opinion that claim 26 is rendered obvious by Baker in view of Zhao and in further view of Suehling.

**3. Dependent Claim 28: “The system of claim 26, wherein the particular target tissue region is selected from the group consisting of: a skeletal region comprising one or more bones of the subject, a lymph region, and a prostate region.”**

367. Dependent claim 28 depends from claim 26, which I explained in Section IX.E.2 is rendered obvious by Baker in view of Zhao in further view of

Suehling. Claim 28 further requires that the particular target tissue region be selected from the group consisting of a skeletal region comprising one or more bones of the subject, a lymph region, and a prostate region. In my opinion, Baker and Suehling each disclose this additional limitation.

368. As a preliminary matter, it is my opinion that claim 28 contains a typographical error and should further depend from claim 27. Several characteristics of the claims support this conclusion. For example, claim 28 refers to “the particular target tissue region.” Claim 26, however, only refers to “the target tissue regions” in the plural sense, where each target tissue region comprises “one or more background tissue regions.” In my opinion, because claim 26 makes reference to multiple target tissue regions, claim 28’s reference to a singular (i.e., “the particular”) target tissue region is at odds with the claim from which it depends. In my opinion, a more natural reading of claim 28 is that it depends from claim 27, which specifically defines “a particular target tissue region corresponding to a particular target VOI.” Ex1001, 82:22-23. Furthermore, I note that claim 27 is structured substantially identically to claim 20, while claim 28 is structured substantially identically to claim 21. *See* Ex1001, 81:30-41, 82:21-33. But while claim 21 further depends from claim 20, claim 28 does not further depend from claim 27. In my opinion, a POSITA would, upon reading the claims, understand that claim 28 ought to depend from claim 27.

369. As written, it is my opinion that claim 28 is obvious in light of Baker in view of Zhao in further view of Suehling. Baker teaches that “automated segmentation of CT scans can be performed to identify 3D boundaries of specific organs” including “a prostate” and “lymph nodes,” “as well as other regions of imaged tissue, such as particular bones and an overall skeletal region of the patient.” Ex1008, ¶ [0137]. Suehling also teaches that its “automatic lesion detection method ... can be used to detect lesions in various parts of the body including ... lymph nodes ... and bone structures.” Ex1006, [0021]. Additionally, as discussed in Section IX.E.1.c), each distinct search region defined by Suehling is searched *separately* using “a separate region-specific detector ... trained based on annotated training data for each region.” Ex1006, [0033]. Thus, for each region (e.g., organ), the voxels of the image outside the region (i.e., the background) are exclude from the search. For example, when defining the “specific search areas for lymph nodes,” Suehling states that the segmented organs and bones are used “to exclude the detected organs and bones from these search regions.” Ex1006, [0029].

370. Accordingly, in my opinion, Baker in view of Zhao in further view of Suehling renders obvious claim 28.

## **X. CONCLUSION**

371. For the foregoing reasons, it is my opinion that claims 1-5, 7-14, 16-

19, 22-26, and 28-32 of the Patent should be found unpatentable.

\* \* \*

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: April 4, 2025

/Bruce R. Rosen/  
Dr. Bruce R. Rosen