

UNITED STATES PATENT AND TRADEMARK OFFICE

---

BEFORE THE PATENT TRIAL AND APPEAL BOARD

---

MIM SOFTWARE INC.,  
*Petitioner,*

v.

PROGENICS PHARMACEUTICALS, INC.,  
*Patent Owner.*

---

IPR2025-00726  
U.S. Patent No. 11,894,141

---

**DECLARATION OF MILAN SONKA, PH.D.**

## TABLE OF CONTENTS

I.	INTRODUCTION .....	1
II.	QUALIFICATIONS .....	1
III.	MATERIALS CONSIDERED .....	2
IV.	LEGAL PRINCIPLES .....	4
	A. Priority Date .....	4
	B. A Person of Ordinary Skill in the Art .....	4
	C. Claim Construction.....	5
	D. Novelty and Non-Obviousness.....	6
V.	TECHNOLOGY BACKGROUND.....	8
	A. Medical Imaging Techniques .....	9
	B. Image Analysis .....	13
	C. Deep Learning and Convolutional Neural Networks.....	15
VI.	THE PRIOR ART .....	21
	A. Maier.....	21
	B. Huang .....	21
	C. Armor .....	21
	D. Neumaier, Cardinale, Giesel, and Weineisen.....	22
VII.	THE '141 PATENT AND ITS PROSECUTION HISTORY .....	22
	A. The '141 Patent .....	22
	B. Prosecution History of the '141 Patent .....	25
VIII.	CONSTRUCTION OF TERMS OF THE '141 PATENT .....	27
	A. A “network-based system” .....	28

B.	A “database” .....	33
IX.	ANALYSES OF THE PETITION GROUNDS .....	38
A.	Maier in view of Huang and Armor fails to render claims 1-3, 6-9, 13-26, 32-35 obvious.....	38
1.	Claim 1 .....	38
a.	Maier and Huang fail to render the element “wherein the one or more medical images comprise a ... CT scan overlaid with a nuclear medicine image” obvious.....	40
b.	Maier, Huang, and Armor fail to render the “PSMA binding agent” element obvious. ....	43
c.	Maier, Huang, and Armor do not disclose “using the composite image to geographically identify...” .....	48
d.	Maier, Huang, and Armor fail to render the element “computing, using the nuclear medicine image with the identified 3D boundary(ies) of the one or more region(s), a value of each of one or more risk indices, each risk index value indicative of cancer state or progression in the patient” obvious. ....	51
e.	Conclusion .....	54
B.	Maier in view of Huang and Armor, in further view of Neumaier, fails to render any of claims 6-11 obvious .....	54
C.	Maier in view of Huang and Armor, further in view of Cardinale and/or Giesel, fails to render claims 6 and 12 obvious .....	55
D.	Huang in view of Armor and Maier fails to render claims 27 and 31 obvious. ....	55
1.	Claims 27 and 31.....	55
a.	Huang fails to disclose risk indices that are indicative of “prostate cancer state or progression.” .....	55

b.	Maier, Huang, and Armor fail to render the “PSMA binding agent” element obvious. ....	56
c.	Huang does not disclose “using the composite image to geographically identify a 3D boundary . . . ,” as recited by the claims. ....	57
d.	Huang, Armor, and Maier fail to render obvious “computing the value of each of the one or more risk indices using the nuclear medicine image with the identified 3D boundary(ies) of the one or more region(s),” as recited by the claims. ....	57
e.	Conclusion .....	58
E.	Huang in view of Armor and Maier, further in view of Giesel and Weineisen, fails to render claims 28-30 obvious. ....	58
X.	CONCLUSION.....	58

## PATENT OWNER'S EXHIBIT LIST

EXHIBIT	DESCRIPTION
EX2001	Defendant's Memorandum of Law in Support of its Motion to Stay Pending <i>Inter Partes</i> Review, <i>Progenics Pharmaceuticals v. MIM Software Inc.</i> , Civil Action No. 1:24-cv-10437-PBS, Dkt. 89, Apr. 8, 2025.
EX2002	PACER Docket, <i>Progenics Pharmaceuticals v. MIM Software Inc.</i> , Civil Action No. 1:24-cv-10437-PBS (as of June 11, 2025).
EX2003	Defendant's Motion to Dismiss the Second Amended Complaint, <i>Progenics Pharmaceuticals v. MIM Software Inc.</i> , Civil Action No. 1:24-cv-10437-PBS, Dkt. 43, June 17, 2024.
EX2004	Motion to Dismiss Hearing Transcript (excerpted pp. 1, 4-6), <i>Progenics Pharmaceuticals v. MIM Software Inc.</i> , Civil Action No. 1:24-cv-10437-PBS, Oct. 8, 2024.
EX2005	Order Granting in Part and Denying in Part Defendant's Motion to Dismiss the Second Amended Complaint, <i>Progenics Pharmaceuticals v. MIM Software Inc.</i> , Civil Action No. 1:24-cv-10437-PBS, Dkt. 72, Jan. 14, 2025.
EX2006	Motion to Stay Hearing Transcript (excerpted pp. 1, 5-6), <i>Progenics Pharmaceuticals v. MIM Software Inc.</i> , Civil Action No. 1:24-cv-10437-PBS, May 12, 2025.
EX2007	Order Granting in Part and Denying in Part Defendant's Motion to Stay Pending <i>Inter Partes</i> Review, <i>Progenics Pharmaceuticals v. MIM Software Inc.</i> , Civil Action No. 1:24-cv-10437-PBS, Dkt. 102, May 13, 2025.
EX2008	MIM's Invalidity and Noninfringement Contentions, Civil Action No. 1:24-cv-10437-PBS.
EX2009	U.S. District Courts, Judicial Caseload Profile 2024 (D. Mass. excerpted).
EX2010	MIM's Responses & Objections to Plaintiffs' First Set of Interrogatories (excerpted pp. 1, 13-14), Civil Action No. 1:24-cv-10437-PBS.
EX2011	<i>Cancer Control Month, 2025 – The White House</i> (Apr. 3, 2025).

EXHIBIT	DESCRIPTION
EX2012	<i>NIH Strategic Plan for Data Science FY 2025-2030</i> , Nat'l Institutes of Health.
EX2013	Rowe, S.P. et al., <i>PET Imaging of Prostate-Specific Membrane Antigen in Prostate Cancer: Current State of the Art and Future Challenges</i> , Prostate Cancer & Prostatic Diseases (2016).
EX2014	Declaration of Dr. Milan Sonka.
EX2015	Curriculum Vitae of Dr. Milan Sonka.
EX2016	RESERVED
EX2017	Crisan, et al., <i>Radiopharmaceuticals for PET and SPECT Imaging: A Literature Review over the Last Decade</i> , International Journal of Molecular Sciences 23(9):5023 (2022).
EX2018	<i>PET Scans</i> , CancerQuest, Emory Winship Cancer Institute (2025).
EX2019	Rowe, S.P., et al., <i>PSMA-Based [<sup>18</sup>F]DCFPyL PET/CT Is Superior to Conventional Imaging for Lesion Detection in Patients with Metastatic Prostate Cancer</i> , Molecular Imaging and Biology 18(3):411-419 (2016).
EX2020	<i>FDA Approves First PSMA-Targeted PET Imaging Drug for Prostate Cancer</i> , Oncology Practice Management (2020).
EX2021	<i>FDA Approves Second PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer</i> , Food and Drug Administration (2021).
EX2022	<i>Atlas-Based vs. AI Auto-Contouring in Clinical Practice</i> , MIM Software Inc. (2023).
EX2023	Brown, <i>Machine Learning, Explained</i> , MIT Sloan (Apr. 21, 2021).
EX2024	RESERVED
EX2025	Krizhevsky, et al., <i>ImageNet Classification with Deep Convolutional Neural Networks</i> , Advances in Neural Information Processing Systems 25 (2012).
EX2026	Deng, et al., <i>ImageNet: A large-scale hierarchical image database</i> , IEEE Conference on Computer Vision and Pattern Recognition (2009).
EX2027	Bushberg, J.T., et al., <i>The Essential Physics of Medical Imaging</i> (2012), Ch. 1, Sec. 1.1, pp. 3-15.

EXHIBIT	DESCRIPTION
EX2028	Bushberg, J.T., et al., <i>The Essential Physics of Medical Imaging</i> (2012), Ch. 3, Sec. 3.1, pp. 33-38.
EX2029	Kelleher, <i>Deep Learning</i> (2019), Ch. 1, “What Is Machine Learning?,” pp. 9-17.
EX2030	Kelleher, <i>Deep Learning</i> (2019), Ch. 1, “The Key Ingredients of Machine Learning,” pp. 22-30.
EX2031	Kelleher, <i>Deep Learning</i> (2019), Ch. 3, “Neural Networks: The Building Blocks of Deep Learning,” pp. 65-67.
EX2032	Kelleher, <i>Deep Learning</i> (2019), Ch. 4, “The Era of Deep Learning,” pp. 143-145.
EX2033	Kelleher, <i>Deep Learning</i> (2019), Ch. 4, “Layer-Wise Pretraining Using Autoencoders,” pp. 145-148.
EX2034	Kelleher, <i>Deep Learning</i> (2019), Ch. 4, “Weight Initialization and ReLU Activation Functions,” pp. 148-153.
EX2035	Kelleher, <i>Deep Learning</i> (2019), Ch. 4, “The Virtuous Cycle: Better Algorithms, Faster Hardware, Bigger Data,” pp. 153-156.
EX2036	<i>Gleason Score</i> , Cleveland Clinic Health Library (last visited July 12, 2025).

I, Milan Sonka, hereby declare as follows:

## **I. INTRODUCTION**

1. I have been retained by Progenics Pharmaceuticals, Inc. (“Progenics”) to provide expert opinions in this *Inter Partes* Review (IPR). I am being compensated for my time at my customary rate of \$715 per hour for my work on this matter. I am being paid for my time regardless of the outcome of this IPR. Beyond the compensation I received for my time in this matter, I will not be affected in any way, positively or negatively, by the outcome of this case.

## **II. QUALIFICATIONS**

2. I am Professor of Electrical and Computer Engineering in the College of Engineering at the University of Iowa. I also hold the Lowell C. Battershell Chair in Biomedical Imaging, am the co-director of the Iowa Institute for Biomedical Imaging, and am the Director of the Iowa Initiative for Artificial Intelligence. I also hold secondary appointments at the University of Iowa in the Applied Mathematical and Computational Sciences, Ophthalmology and Visual Sciences, Radiation Oncology, and Biomedical Engineering departments.

3. I earned my Ph.D. in Technical Cybernetics-Digital Image Analysis from the Czech Technical University of Prague in 1983.

4. I was an Assistant Professor at the Czech Technical University of Prague from 1984-1990, before moving to the University of Iowa, where I have been a professor since 1990.

5. For the past 35 years, as the head of a research group at the University of Iowa, I have researched and developed techniques for semi-automated and automated analysis of medical images, including foundational research in quantitative medical image analysis and medical image segmentation, and development of artificial intelligence (AI) and machine learning (ML) techniques for prediction of disease outcomes and image analysis.

6. I was elected as a Fellow of the Institute of Electrical and Electronics Engineers (IEEE) in 2002 for my contributions to medical image analysis and computer vision. I am also a Fellow of the American Institute for Medical and Biomedical Engineering, a Fellow of the Medical Image Computing and Computer-Aided Intervention Society, and a Fellow of the National Academy of Inventors.

7. My curriculum vitae is provided herewith as EX2015.

### **III. MATERIALS CONSIDERED**

8. In forming my opinions, I have read U.S. Patent No. 11,894,141 (the “141 Patent”) (EX1001) and reviewed relevant parts of its prosecution history. I have also reviewed the Petitioner’s Petition for *Inter Partes* Review (IPR) dated March 14, 2025 (the “Petition”) along with the accompanying Declaration of Dr.

Rosen (EX1002). I have also reviewed the following references, which the Petitioner cited in their Petition against the '141 Patent:

- U.S. Patent Application Publication No. 2016/0203263 (“Maier”) (EX1005);
- U.S. Patent Application Publication No. 2007/0081712 (“Huang”) (EX1006);
- U.S. Patent Application Publication No. 2015/058151 (“Armor”) (EX1007);
- U.S. Patent No. 10,112,974 (“Neumaier”) (EX1008);
- U.S. Patent No. 10,815,200 (“Cardinale”) (EX1009);
- Giesel et al., “<sup>18</sup>F-Labelled PSMA-1007 shows similarity in structure, biodistribution and tumour uptake to the theragnostic compound PSMA-617,” *European Journal of Nuclear Medicine and Molecular Imaging* 43(10):1929-1930 (June 2016) (“Giesel”) (EX1010); and
- Weineisen et al., “<sup>68</sup>Ga- and <sup>177</sup>Lu-Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies,” *Journal of Nuclear Medicine* 56(8):1169-1176 (2015) (“Weineisen”) (EX1011).

9. I have also reviewed other references that illuminate the state of the art as of October 27, 2016, which I have been instructed to use as the “priority date” of the '141 Patent. I have also called upon my extensive knowledge and experience in the field of medical imaging, medical image analysis, and artificial intelligence and machine learning.

10. I reserve the ability to review documents, deposition transcripts, or other information provided to me after the date of this Declaration and to supplement my opinions based upon such review.

#### **IV. LEGAL PRINCIPLES**

11. I have been informed of the following legal standards by Patent Owner's attorneys. I am not an attorney, but I have applied these understandings in my analysis herein.

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

12. I have been instructed to assume for purposes of my analysis that October 27, 2016, is the "priority date" for assessing the state of the art and for determining what is "prior art" when considering whether the claims of the '141 Patent would have been obvious.

##### **B. A Person of Ordinary Skill in the Art**

13. I have been asked to develop and offer opinions related to how a person of ordinary skill in the art ("POSA") would have understood the '141 Patent and the relevant references cited herein as of the priority date (October 27, 2016).

14. I have been informed and understand that certain factors may be considered in determining the level of ordinary skill in the art, for example, (1) the types of problems encountered in the art, (2) the prior art solutions to these problems, (3) the rapidity with which innovations are made, (4) the sophistication of the technology, and (5) the educational level of active workers in the field.

15. It is my opinion that a POSA for purposes of the '141 Patent would include a person with 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.

16. I consider myself to be at least a POSA and to have been at least a POSA as of the priority date, October 27, 2016.

**C. Claim Construction**

17. I have been informed and understand that, in an IPR proceeding, the claims of a patent are to “be construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b), including construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.100(b).

18. Specifically, I have been informed and understand that under the standard set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*), the claims of a patent are given their ordinary and customary meaning as would be understood by a POSA at the time of the invention. I have been informed that a *Phillips* construction of a claim is based on the entire record, including both intrinsic evidence (*i.e.*, the claims, specification, and prosecution history) as well as extrinsic

evidence (*e.g.*, dictionary definitions and expert testimony). I have applied this standard in formulating my opinions in this matter.

19. I reserve the right to supplement my opinions in view of any additional information regarding the interpretation of the claims of the '141 Patent that becomes available to me and any matters raised by the parties, the Board, and/or other experts in this matter.

**D. Novelty and Non-Obviousness**

20. I have been informed that to be valid patent claims must be novel and nonobvious. 35 U.S.C. §§ 102 and 103.

21. I have been informed that a patent claim is not novel if it is anticipated by a prior art reference. I have been informed that in order for a prior art reference to anticipate a claim, that prior art reference must disclose each and every limitation as set forth in the claim.

22. I have been informed and understand that a patent claim is obvious if the differences between what is set forth in the claims and what is disclosed in the prior art are such that what is claimed would have been obvious to a POSA as of the patent's priority date (October 27, 2016 in the case of the '141 Patent). I have been informed and understand that a POSA is presumed to have knowledge of all of the relevant art as of the priority date. I have further been informed and understand that as part of the analysis of whether a patent claim is obvious, I should consider: (a) the

scope and content of the prior art; (b) the level of ordinary skill in the art; (c) the differences between what is claimed and the prior art; and (d) any secondary considerations that may indicate that the claim is not obvious.

23. I have been informed and understand that obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so; and that a reasonable expectation of success in achieving the subject matter of the claim at issue must also be shown. Further, I have been informed and understand that the teaching, suggestion, or motivation test is flexible and that an explicit suggestion to combine the prior art is not necessary – the motivation to combine may be implicit and may be found in the knowledge of one of ordinary skill in the art, from the nature of the problem to be solved, market demand, or common sense. In undertaking an obviousness analysis, I have been informed and understand that I may take into account the inferences and creative steps that a person of ordinary skill would have employed in reviewing the prior art at the time of the invention. If the claimed invention combines elements known in the prior art and the combination yields results that would have been predictable to a person of ordinary skill at the time of the invention, then this evidence would make it more likely that the claim was obvious.

24. I have been informed and understand that an obviousness analysis must also take into account any “secondary considerations” or, as they are sometimes called, objective indicia of non-obviousness. These secondary considerations can include: (i) a long-felt but unsolved need for the solution provided by the patent claim; (ii) unexpected results that arise from what is provided in the patent claim; (iii) unsuccessful attempts by others to find the solution provided by the patent claim; (iv) industry skepticism regarding what is provided in the patent claim; (v) praise from others in the field; (vi) commercial success of a product due to the merits of what is provided in the patent claim; and (vii) copying by others of what is claimed in the patent. I further understand that a “nexus” must exist between the claimed invention and the evidence proffered on secondary considerations. Such secondary considerations, when present, offer objective information as to the state of the art at the time of the invention and provide a check to hindsight analysis.

## **V. TECHNOLOGY BACKGROUND**

25. The '141 Patent is generally directed to computer-implemented methods and systems for analyzing medical images that facilitate decision making in the context of cancer diagnosis, monitoring, and treatment. As such, in order to frame my analysis and provide the proper context for my opinions, I provide the following overview of relevant technology at issue in this Petition.

## **A. Medical Imaging Techniques**

26. Medical imaging (e.g., image acquisition) technologies provide a valuable way to detect and monitor disease in a non-invasive fashion. There are many different medical imaging techniques (or “modalities”), each relying on different physical mechanisms to create images and having different benefits and shortcomings. EX2027, 3. Often images produced by different types of medical imaging modalities convey different information. Accordingly, multiple different types of images may be acquired and relied on, for example by physicians, to make decisions about patient diagnosis, treatment, and prognosis.

27. For example, anatomical imaging modalities are a class of imaging techniques that produce images showing detailed anatomical structures, like organs and bones, within a patient. More specifically, intensity variations (e.g., light and dark regions) within anatomical images typically reflect the differences in physical properties of various tissue regions within a patient’s body, which, in turn, impact the way tissue absorbs, reflects, or otherwise interacts with electromagnetic radiation (e.g., x-rays), magnetic fields, or pressure waves. Examples of anatomical imaging techniques are computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US).

28. Functional imaging techniques, on the other hand, reflect physiological properties and activity in a subject. They are often acquired using molecular probes

administered to the subject and have intensity variations that reflect a spatial distribution of a probe within an imaged portion of the subject.

29. Nuclear medicine images are a type of functional image. EX2027, 11. Examples of nuclear medicine images include positron emission tomography (PET) images and single photon emission tomography (SPECT) images. EX2027, 14. PET and SPECT images are three-dimensional images.

30. Each of these nuclear medicine images is obtained by administering a specific type of probe – namely, a radiolabeled imaging agent, referred to as a radiopharmaceutical, containing a radioactive isotope, referred to as a radionuclide – to a patient. EX2027, 11. The radiopharmaceutical distributes throughout the patient’s body (as explained further, below, often selectively concentrating in regions associated with or exhibiting a particular molecular behavior, which, in turn, may be indicative of disease) and images are formed by detecting radiation emitted by the radionuclide as it decays, from within the patient. Accordingly, rather than conveying information that directly reflects the physical structures and properties of tissue within a patient, nuclear medicine images map the spatial distribution of radiopharmaceutical within the patient and thus relay information about tissue molecular properties or function.

31. The composition of a given radiopharmaceutical dictates (i) the type of nuclear medicine imaging modality that it is compatible with and (ii) the manner in

which the radiopharmaceutical distributes throughout a patient's body and, thus, the particular types and stages of disease for which it serves as a useful probe.

32. In particular, the radioactive decay properties of the radionuclide component of a radiopharmaceutical determine the specific imaging modality that it can be used with. PET imaging detects radioactive decay that results in positron emission,<sup>1</sup> and thus relies on radionuclides that are short half-life positron-emitting isotopes, such as carbon-11 (<sup>11</sup>C) and fluorine-18 (<sup>18</sup>F), as well as gallium-68 (<sup>68</sup>Ga). EX2017, 2, 11. SPECT imaging, on the other hand, detects the direct emission of gamma radiation and use gamma-emitting radionuclides, such as <sup>99m</sup>Tc, <sup>123</sup>I, <sup>131</sup>I, <sup>111</sup>In, <sup>67</sup>Ga, <sup>201</sup>Tl, <sup>81m</sup>Kr, <sup>133</sup>Xe. *Id.*, 4

33. The manner in which an administered radiopharmaceutical is distributed throughout a patient depends upon the particular radiopharmaceutical and the patient's physiological status. For example, the radiopharmaceutical

---

<sup>1</sup> In a PET scanner, positron emission is detected by observing/measuring a characteristic byproduct of positron emission – specifically, simultaneously emitted and oppositely directed pairs of photons (gamma rays) that result from the annihilation of a positron-electron pair – as opposed to the positrons themselves. *See, e.g.*, EX2028, 37.

fluorodeoxyglucose (FDG) is an  $^{18}\text{F}$ -labeled form of glucose and thus concentrates most heavily in tissue with high metabolic activity. EX2018, 3. Since cancer cells are typically characterized by higher metabolic activity than surrounding normal cells, PET images acquired with FDG can be used to detect cancer lesions, which typically appear as “hot spots” within images. *Id.*, 4. FDG, however, is not specific to cancer, and may also be absorbed by other cells with high metabolic activity, including areas of inflammation and infection. *Id.* FDG is also limited in its ability to detect slower growing cancers, which absorb less glucose. *Id.* Other radiopharmaceuticals, like F-18 sodium fluoride ( $^{18}\text{F}$ -NaF) and  $^{99\text{m}}\text{Tc}$ -methyl diphosphonate ( $^{99\text{m}}\text{Tc}$ -MDP) tend to accumulate within new bone and were used to detect bone metastases. Like FDG, however, these tracers target cancer cells indirectly, via the propensity of cancer cells to divide rapidly, and thus are also limited in their sensitivity and specificity.

34. Nevertheless, in 2016, men with known or suspected prostate cancer were typically evaluated and followed using conventional imaging modalities – namely, contrast-enhanced computed tomography in the chest, abdomen, and pelvis. EX2019, 412. New imaging agents, including PET imaging agents, were being researched and developed. *Id.* Among these new imaging agents, PSMA targeting radiopharmaceuticals had been developed, but were still being assessed for their clinical utility to detect and stage prostate cancer, with some of the first in-human

evaluations of the new small-molecule PSMA inhibitors<sup>2</sup> that would ultimately obtain approval from the Food and Drug Administration (FDA) for PET imaging just taking place in 2015. EX2019, 412. It would take another four years for the first PSMA-targeted PET imaging drug for prostate cancer to be approved by the FDA, in December of 2020. EX2013, 1.

## **B. Image Analysis**

35. While radiologists and physicians have various medical imaging modalities and techniques at their disposal, the selection of exactly which types of images to obtain, and exactly how to interpret one or more of these images is not straightforward. To the contrary, the task of determining, for example, whether a particular patient has cancer, how severe it is, and what course of action to take is laborious, error prone, and highly subjective, often varying from physician to

---

<sup>2</sup> The first molecular imaging agent targeting PSMA was an indium-111-labeled monoclonal antibody (ProstaScint®), which could be used for SPECT (not PET) imaging, but suffered from a number of intrinsic limitations that made it an ultimately unsuccessful agent. EX2013, 1. The two small-molecule PSMA inhibitors that have ultimately obtained FDA approval for PET – <sup>68</sup>Ga-PSMA-11 and [<sup>18</sup>F]DCFPyL – only obtained FDA approval in 2020 and 2021, respectively. EX2020, 1; EX2021, 1.

physician. In efforts to facilitate and standardize medical image analysis, researchers in the image processing and computer vision fields have sought to develop computer algorithms that automate various tasks associated with medical image analysis.

36. Conventional image analysis techniques aim to craft a detailed series of step-by-step instructions for computers to follow in order to, for example, classify whether an image contains a particular object, like a lesion – referred to as “classification” or “object detection,” or to delineate complex boundaries of certain structures of interest within an image – referred to as “segmentation.”

37. For example, a simple conventional image segmentation technique is thresholding, whereby regions of an image are identified as part of one object or another based on whether their intensity values are above or below a particular threshold value or lie within a given range. EX1016, 7. This simple approach is best suited to segmenting objects that have uniquely high or low intensity values in an image, such as bones which tend to appear brighter in CT images than soft-tissue, and, even so, selection of proper threshold values may be challenging and performance may be impacted by image variability and presence of artifacts. EX1016, 7.

38. Another common conventional image segmentation technique is atlas-based segmentation. Atlas image segmentation relies on one or more templates, referred to as atlas images, in which various structures of interest, like organs or

bones, have been manually delineated. When a new image of a patient is received, one of the atlas images is registered with the new patient image, and the manually delineated contours from the atlas image are transferred to the new patient image. Atlas-based segmentation continues to be used in medical image analysis products today, even as newer techniques have been developed. *See* EX2022, 1.

### **C. Deep Learning and Convolutional Neural Networks**

39. Machine learning techniques are different from conventional computer programs. Machine learning generally refers to the development and use of algorithms that allow computers to extract, or “learn,” desired functionality from datasets in an automated fashion. EX2023, 1; EX2029, 11. Thus, machine learning algorithms do not require a human programmer to explicitly create a detailed series of instructions for the computer to follow to perform a specific task. *Id.* Instead, machine learning algorithms involve a two-step process comprising a training phase and an inference phase. EX2029, 12. During training, examples from a training dataset are repeatedly provided to a computational model, the parameters of which are refined to optimize performance on a specified task (and on examples from the training dataset) according to desired behavior or output (like labeling an image as comprising a dog, cat, etc.). *Id.* During inference, once trained, the (trained) computational model can be provided with new data not previously included in the

training dataset and generate output reflecting the trained model's predictions based on information derived from the new input data. *Id.*, 14.

40. Machine learning algorithms can be trained (e.g., can “learn”). Supervised machine learning algorithms are trained using labeled datasets. EX2023, 4; EX2030, 26. In labeled datasets, each example is labeled with the desired output (e.g., “ground truth”) that the machine learning algorithm is intended to reproduce. EX2030, 26.

41. There are also different computational models that can be used in connection with, and optimized via, machine learning techniques. These include simpler statistical models, like models based on Bayes' theorem (e.g., Naïve Bayes' classifiers), and more complex models, like neural networks.

42. While the term “neural network,” is, today, closely associated with machine learning, machine learning and neural networks are distinct terms and convey different ideas. That is, as explained above, machine learning refers to the development and use of algorithms that allow computers to extract, or “learn,” functions from datasets in an automated fashion.

43. A neural network, however, is a particular computational model inspired by the structure of a human brain. EX2031, 65. In this model, the weights of each neuron's excitations in a neural network can be used as adjustable parameters. While the weights can be determined using machine learning, the term “neural

network” is distinct from the term “machine learning.” A neural network is a type of model, whereas machine learning refers to algorithms that allow computers to extract, or “learn,” functions from datasets in an automated fashion. EX2023, 1.

44. Conventional artificial neural networks are shallow – they do not have many hidden layers. Before the confluence of multiple breakthroughs in the 2010’s, this was generally viewed as a requirement for any practical application, because multiple hidden layers were challenging and impractical to train. *See* EX2032, 143.

45. An important implication of the restriction to shallow neural networks is that conventional neural networks are not able to operate efficiently directly on raw, low-level data, like image pixels. EX2030, 23; EX1018, 1. Instead, they operated on limited and predefined sets of “handcrafted” features that could be extracted from raw low-level data. EX2030, 23-24; EX1018, 1. For example, a shallow neural network tasked with classifying an image would not operate directly on the image itself, but, instead, would require a pre-processing routine to extract features (things like a maximum intensity, variance in image intensity, a relative weight of different colors, etc.) from the image that, in turn, would be fed as input to the neural network. The task of designing sets of handcrafted features that would allow neural networks to effectively perform various desired tasks was a challenging, labor intensive, and highly subjective process that relied on human expertise.

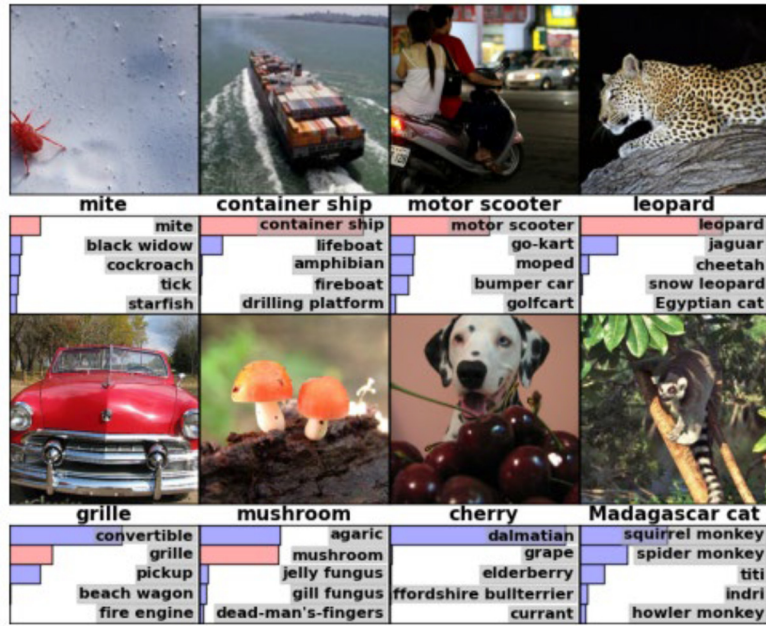
EX2030, 23, 30. As a result, ultimately, traditional shallow neural networks failed to lead to commercially viable levels of performance and practical accuracy.

46. Deep-learning techniques (i) use neural networks with many hidden layers (hence, deep) and (ii) train them to learn complex patterns from data, including raw or low-level data (like image pixels or voxels). In doing so, deep-learning methods overcome key challenges that made conventional neural networks impractical.

47. Before 2012, deep learning algorithms were not considered viable for certain imaging applications. Limitations in learning algorithms, computational power, computer hardware, and the availability of sufficiently large datasets made training neural networks with multiple hidden layers impractical. EX2024, 143. Only in 2012, the confluence of (i) new algorithmic approaches, (ii) hardware improvements, and (iii) the creation of and access to large, labeled datasets that could be used paved the way for a breakthrough. In particular, on the algorithm side, new techniques like Glorot initialization, rectified linear units (ReLU's), and dropout techniques, greatly improved the ability to train deep neural networks. EX2034, 152. In terms of hardware, training was also dramatically improved via the discovery that graphical processing units (GPUs) could be used to train neural networks much more efficiently than conventional computer processing units (CPUs), which was made widely accessible via NVIDIA's release of its CUDA programming language in

2007. EX2035, 153-154. Finally, the ImageNet database, created via a massive crowdsourcing effort, provided a huge hierarchical repository of millions of labeled images that could be used to train supervised image classifiers. EX2025, 1; EX2026, Abstract. By taking advantage of new algorithms, improved hardware capabilities, and the large ImageNet database, a convolutional neural network (CNN), referred to as AlexNet was able to achieve record performance on the ImageNet Large Scale Visual Recognition Challenge (ILSVRC). EX2025, Abstract, 7-8. This December 2012 report is now considered a watershed moment that led to the use of deep learning for image analysis tasks. EX1018, 2.

48. While the performance of the AlexNet CNN spurred interest in deep learning techniques, the AlexNet report demonstrated performance of a CNN on an image classification task. EX2025, Abstract, 7. That is, given an example image, the AlexNet CNN was tasked with outputting a label for the image – i.e., “mite”, “container ship”, etc. (as shown in Fig. 1, below). EX2025, Figure 4. It would take several more years for deep learning techniques like CNNs to be developed for performance on the more challenging task of image segmentation – which requires delineating complex boundaries of objects within an image. EX1018, 5-6. Namely, neural network architectures that could adequately avoid degradations in resolution when performing segmentation would not appear until around 2015, when the U-net architecture was proposed. EX1018, 5-6.



**Fig. 1 Example test images and the five most probable labels for each predicted by the AlexNet CNN. EX2025, Figure 4.**

49. Accordingly, around 2016, deep learning approaches like CNNs were a nascent technology in computer vision and image analysis, and their adoption in the medical field in particular was gradual. Even years later (into the 2020s), challenges associated with machine learning techniques have made medical professionals skeptical of machine learning-based techniques, although they clearly provide advantages in terms of robustness and reliability, e.g., in comparison with more conventional atlas-based approaches. EX2022, 1 (“While some clinicians have embraced the technology, others remain skeptical about its ability to provide accurate results in clinical practice.”).

## **VI. THE PRIOR ART**

### **A. Maier**

50. Maier (EX1005) discloses a “computer implemented method for assessing and communicating a patient’s health status and risk,” primarily in relation to smoking-related diseases like “myocardial infarction, Chronic Obstructive Pulmonary Disease (COPD), emphysema, lung cancer, decreased lung function, COPD exacerbations, coronary artery disease, and stroke.” EX1005, [0007]. Maier’s approach involves extracting values of features like numbers or percentages of voxels with intensities below or above a threshold intensity, mean image intensity within a region, etc., from CT images of a given patient and correlating these “imaging biomarkers” with values from historical patient populations having known clinical outcomes, analogous to how, for example, the BRCA1 and BRCA2 genes are genetic biomarkers for breast cancer risk and cholesterol levels are biomarkers for heart disease risk. EX1005, [0007]-[0008].

### **B. Huang**

51. Huang (EX1006) describes CAD tools for fluorine-18 deoxyglucose (FDG) PET imaging. EX1006, [0002], [0003], [0006], [0051], [0098], [0108].

### **C. Armor**

52. Armor (EX1007) discloses Tc-99m labeled PSMA targeting agents (a gamma-emitting transition metal complex conjugated to a targeting moiety), suitable for SPECT imaging. EX1007, [0008]. Armor also describes a method of evaluating

a human subject suspected of harboring a prostate tumor that uses his SPECT imaging compounds, but otherwise appears to involve a conventional approach that relies on users (e.g., physicians) manually marking, and comparing uptake within, different circular regions of interest on images. EX1007, [0008], [0096] (requiring placing “[c]ircular regions of interest with a diameter of approximately 20 pixels” on regions adjacent to the prostate gland and recording counts in that region as background).

#### **D. Neumaier, Cardinale, Giesel, and Weineisen**

53. Neumaier (EX1008), Cardinale (EX1009), Giesel (EX1010), and Weineisen (EX1011) each discloses methods for synthesizing particular radiopharmaceutical compounds or analyses of their characteristics, via otherwise conventional imaging techniques. EX1008, Abstract, 1:1-13; EX1009, 2:64-67; EX1010, 1929; EX1011, 1169, 1171.

### **VII. THE '141 PATENT AND ITS PROSECUTION HISTORY**

#### **A. The '141 Patent**

54. The '141 Patent is generally directed to technologies for improving the ability of doctors and patient to detect and monitor cancer (particularly prostate cancer) progression and treatment over time. The specification, for example, begins by describing the disclosed technology as directed to “decision-making tools for use by medical practitioners and/or their patients, e.g., to aid in the process of making decisions about a course of cancer treatment and/or to track treatment and/or the progress of a disease.” EX1001, 2:66-3:3.

55. As of the priority date (October 27, 2016), there was a need for innovative solutions to increase the accuracy, reliability, and consistency of medical imaging analysis, especially for (but not limited to) cancer diagnosis and treatment. The '141 Patent describes a technology for addressing this need via a combination of insight into the promise of deep-learning technologies, specific ways in which they could be applied to analyze specific types of medical images, and how providing these capabilities in the format of a network-based platform could be especially valuable in the context of cancer diagnosis and treatment.

56. To begin with, the '141 Patent describes inventive processes for accessing anatomical and functional images, automatically segmenting organs, identifying regions of cancer within relevant organs, and then using the organ segmentation with the functional image information and/or identified cancer regions to determine values of risk indices that provide indications of cancer state or progression.

57. The '141 Patent reflects multiple key innovations. One of those innovations was to leverage machine learning (“ML”) techniques, e.g., convolutional neural networks (“CNNs”), to perform organ segmentation in 3D images (e.g., 3D CT scans). Patent Owner recognized that ML could be used to geographically identify 3D boundaries of particular tissue regions in an overall more accurate and robust manner with desirable scan-to-scan reproducibility than had been possible

previously. Patent Owner was thus able to combine the ML-identified 3D tissue region boundaries with the detailed functional (e.g., radiopharmaceutical probe distribution) information provided by nuclear medicine imaging modalities, like PET and/or SPECT. This new and improved method dramatically increased the accuracy and reproducibility of tissue and organ segmentation. The resulting capability to provide valuable anatomical context to demarcations of cancer risk, where it is often impossible to obtain, inaccurate, or subjective. This is especially significant because, as described in the '141 Patent, cancer is often best detected via nuclear medicine imaging approaches, like 3D PET or 3D SPECT. Nuclear medicine techniques, however, do not capture features of anatomy and structure of organs and/or tissues at sufficiently high resolution. They thus cannot always reliably distinguish between different organs or tissue regions. As described in the '141 Patent, accurate and reliable 3D boundaries of tissue regions (e.g., as determined via ML-based analysis of anatomical, CT images) can be transferred to 3D PET or SPECT images that map the distribution of administered radiopharmaceuticals (which, in certain cases, can be highly sensitive to specific cancers). EX1001, 28:41-67. This allows, for example, for values of risk indices that reflect or are based on cancer tissue load in specific organs and tissue regions to be determined in a robust and accurate fashion. *Id.*

58. Another key innovation of the '141 Patent was combining the insight about ML techniques with the insight that taking advantage of remote networking by

uploading medical images to, and accessing them from, databases via network-based systems would be especially valuable in the context of cancer diagnosis, monitoring, and treatment.

59. Finally, the '141 Patent leverages particular radiopharmaceuticals – PSMA binding agents – that, around the time of filing, were in early stages of being studied for its potential for prostate cancer diagnosis. The '141 Patent thus combines insight into the promise of those imaging agents together with the above-described image analysis techniques and network-based delivery platform to provide a comprehensive solution tailored for assisting physicians and patients from prostate cancer diagnosis, to monitoring, and through treatment.

60. As such, the claimed methods provide numerous advantages over prior art methods.

### **B. Prosecution History of the '141 Patent**

61. I have reviewed relevant parts of the publicly available prosecution history of the '141 Patent. The Application for the '141 Patent was filed on July 12, 2022, claiming priority to U.S. Provisional Application 62/413,936 filed on October 27, 2016. EX1004, 113. The '141 Patent issued on February 6, 2024. EX1004, 307.

62. It appears that, during prosecution, the Examiner considered the Maier, Huang, and Armor references that the Petition asserts against the independent claims, requested amendments, and then allowed the claims in their current form.

63. For example, during prosecution, the Examiner identified six references on his “Notice of References Cited,” two of which were the Huang and Maier references, which the Petition relies on for its arguments against the independent claims. EX1004, 224. The Patent Owner also appears to have cited the Petition’s third main reference, Armor, in an Information Disclosure Statement (IDS) submitted to the Office on January 10, 2023. *See* EX1004, 179. On September 19, 2023, the Examiner also signed the IDS, noting at the bottom that “ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.H.A./.” The Examiner did not line through the Armor reference. EX1004, 242.

64. On September 18, 2023, as reflected in the Examiner’s interview summary, the Examiner conducted “a telephone interview, which was initiated by the examiner with applicant’s representative,” and “Examiner suggested ways to clarify the independent claim or amend the claim that may overcome **the prior art of record** and requested a Terminal Disclaimer, and agreement was reached.” EX1004, 223 (emphasis added). In granting the claims, the Examiner stated: “Based on telephone on September 18, 2023, with respect to cancellation of claims 3-10, 15, 17-18, 22-39, 43-44, 46-49, 52, and amended claims 1, 19, 40, 45, 55, 59, 67 and new claims 68-71, also **review of prior art of record**, all have been fully considered and are persuasive.” EX1004, 286 (emphasis added).

65. Subsequently, the Examiner issued a Notice of Allowance, highlighting the following features that appear in the claims:

automatically analyze the one or more medical images using a machine learning algorithm; and generate a radiologist report for the particular patient, wherein the one or more medical images comprise a composite image of the particular patient, comprising a CT scan “overlaid” with a nuclear medicine image obtained at a same time as the CT scan and following administration to the patient of an imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide, wherein the instructions cause the processor to automatically analyze the composite image by: using the “composite image” to geographically identify a “3D boundary” for each of one or more regions of imaged tissue within the nuclear medicine image; and computing, using the nuclear medicine image with the identified 3D boundary of the one or more region, a value of each of one or more risk indices, each risk “index value” indicative of cancer state or progression in the patient, and wherein the system is a cloud-based system.

EX1004, 297-298.

66. It thus appears, in my opinion, that the references that Petition relies on for its challenges against claims 1, 24, 27, and 31-35 (the independent claims) are identical to the Maier, Huang, and Armor references that were considered during prosecution of the ’141 Patent.

### **VIII. CONSTRUCTION OF TERMS OF THE ’141 PATENT**

67. I have been asked to provide my opinion on how a POSA would understand several terms used in the claims of the ’141 Patent under the *Phillips* construction standard of which I have been informed (as discussed in Section IV.C, above).

**A. A “network-based system”**

68. Claim 1 of the ’141 Patent begins with “A *network-based* decision support *system* comprising . . .” EX1001, 37:8 (emphasis added).

69. It is my opinion that a POSA, reading the term a “network-based . . . system” in the context of the claims and specification, would understand the term to mean a system involving interaction across multiple interconnected and physically dispersed computing devices. This interpretation is consistent with both the claim language and the detailed description of the claimed subject matter laid out in the specification of the ’141 Patent.

70. To begin with, the claim does not simply state “a system,” but, rather, states a “network-based . . . system.” The use of the term “network-based” would be given meaning by a POSA. In particular, it indicates that the claimed system is more than a single, isolated computer and, instead, is part of a network, which would be understood to mean multiple distinct computing devices.

71. The other elements of the claim further support, and make clear, that the system of claim 1 is connected with other computing devices. For example, the claim includes the steps of “access[ing] . . . one or more of the medical images associated with a particular patient from the database,” and “generat[ing] a radiologist report for the particular patient according to the one or more medical images for the patient.” EX1001, 37:16-17, 37:20-23. As explained below, in the context of the

'141 Patent, both of these steps point to interaction with other computing devices as part of a network.

72. The specification further supports the reading that “a network-based . . . system” means a system involving interaction across multiple interconnected and physically dispersed computing devices. The specification repeatedly describes the invention as distributed platform (e.g., a cloud-based platform) that provides for regular interaction by multiple users at potentially different locations and at different times, rather than a standalone machine.

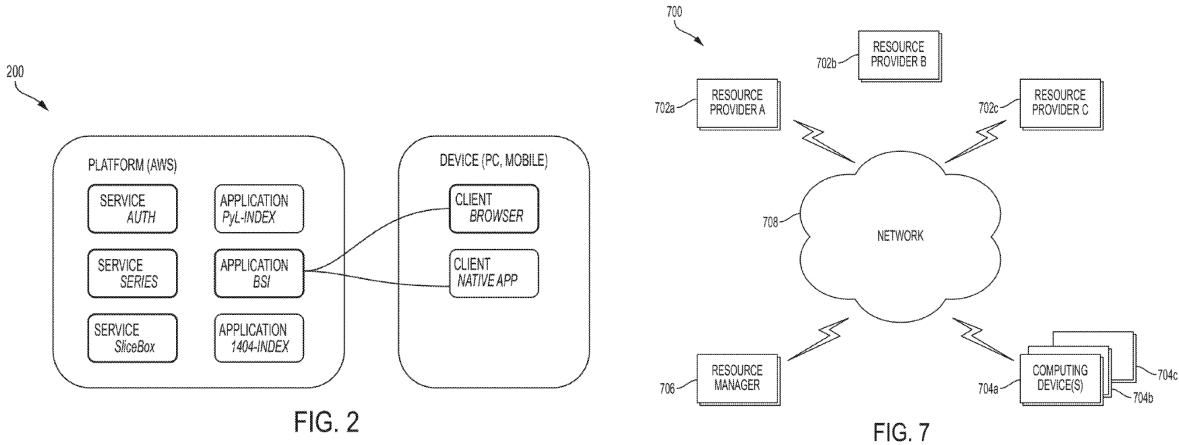
73. The specification states “For example, presented herein is a network-based (e.g., cloud-based) support platform allowing multiple users to store, access, analyze, and/or provide feedback regarding a given set of image data for a patient.” EX1001, 3:4-7.

74. Many figures in the Patent convey interactions between distinct computing devices, including between server and client devices, as well as cases where a user computing device is a mobile application that interacts with a cloud-based service.

75. For example, FIG. 1 shows an example mobile app providing access to three cloud-based services. EX1001, 13:52-54 (“FIG. 1 is a screenshot of a graphical user interface (GUI) showing mobile app icons for three cloud-based services...”).

FIGs. 3-6 all are described as relating to features of exemplary cloud-based embodiments. EX1001, 13:60-14:12.

76. FIGs. 2, 7, and 9 (reproduced below) show schematics relating to network-based platforms, where platform services are provided via distinct computing devices that serve a user, client, computing device, like a personal computer, mobile device, smart phone. EX1001, 13:55-57 (“FIG. 2 is a schematic showing the relationship between a platform and a computing device (e.g., personal computer or mobile computing device, e.g., smart phone); 14:13-14 (“FIG. 7 is a block diagram of an exemplary cloud computing environment...”); 14:18-20 (FIG. 9 is a block diagram of an example architecture for implementing the cloud based platform described herein, according to an illustrative embodiment.”).



**FIGs. 2 and 7, reproduced from the '141 Patent.**

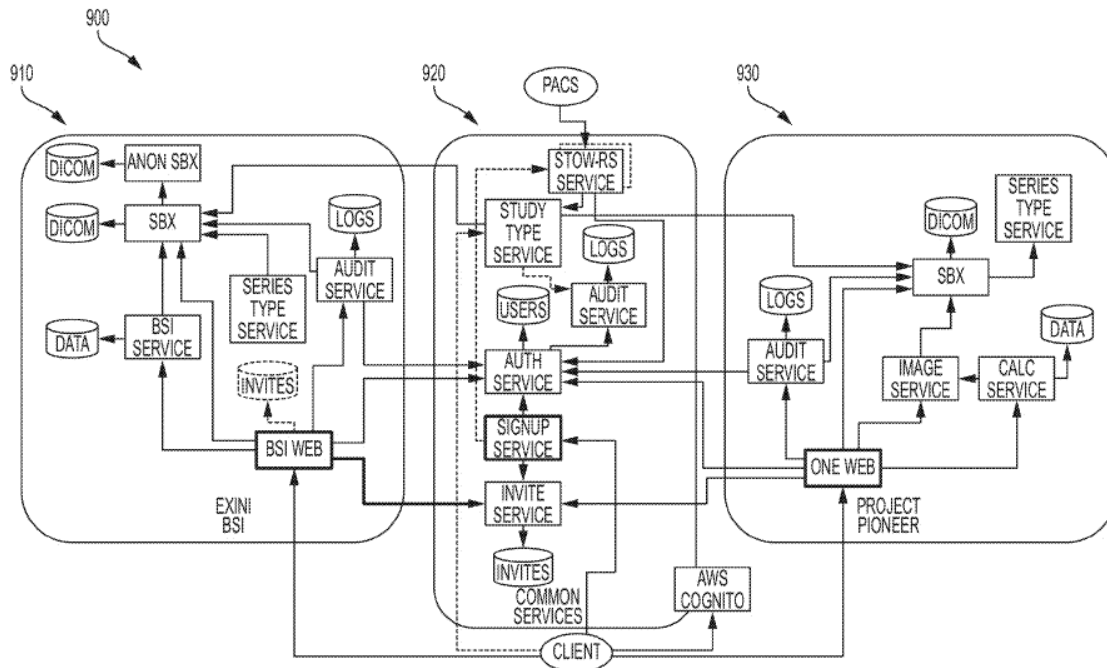


FIG. 9

**FIG. 9, reproduced from the '141 Patent.**

77. For example, FIG. 9 provides a detailed architecture for a cloud-based system involving multiple dispersed computing devices, including client and server devices. EX1001, FIG. 9 (among other things, including reference to “AWS COGNITO,” which is a cloud-based service provided by Amazon Web Services); FIG. 2 (referring also to “Platform (AWS)”). The specification of the '141 Patent describes, in detail, how the platform approach of the claimed technology can be implemented in a way that allows it to be dispersed across multiple datacenters, allowing parts of the platform to be scaled individually e.g., to meet high demand and ensure minimal downtime. EX1001, 29:48-30:29. The specification further explains that “[t]he computing system can include clients and servers. A client and server are

generally remote from each other and typically interact through a communication network.” EX1001, 36:54-56.

78. Moreover, the specification of the '141 Patent explains that the choice to structure the claimed technology as a network-based platform is linked with a key challenge that the technology of the '141 Patent aims to address, namely, improving the ability of doctors and patient to detect and monitor cancer – particularly prostate cancer – progression and treatment over time. The specification, for example, begins by describing the disclosed technology as directed to “decision-making tools for use by medical practitioners and/or their patients, e.g., to aid in the process of making decisions about a course of cancer treatment and/or to track treatment and/or the progress of a disease.” EX1001, 2:66-3:3. Throughout, the specification repeatedly emphasizes the ability to provide access to *multiple users* and to obtain, store, and analyze medical images that are obtained over the course of multiple visits to one or more doctors and/or clinical specialists. For example, the specification describes the following example practical/clinical benefits of the claimed network-based implementation:

In certain embodiments, the cloud-based platform facilitates evaluating prostate cancer progression and treatment efficacy over time. For example, as shown in the example process 1100 of the block flow diagram of FIG. 11, in certain embodiments medical images of a particular patient are repeatedly received and stored over time 1110, over the course of multiple visits to one or more doctors and/or clinical specialists (e.g., radiologists) by the patient.

...  
Notably, by virtue of the capability of the cloud-based platform described herein to receive, store, and analyze a variety of different medical image types, such as composite SPECT-CT images, whole-body scans, and composite PET-CT images, the medical images need not be of the same type.

EX1001, 31:43-63.

79. Thus, reading the claim language in the context of the specification, a POSA would understand that “a network-based . . . system” thus refers to a system involving interaction across multiple interconnected and physically dispersed computing devices.

**B. A “database”**

80. Claim 1 recites “receive and store a plurality of medical images in a *database*,” and “access one or more of the medical images associated with a particular patient from the *database*.” EX1001, 37:13-14; 37:16-17 (emphasis added). Similarly, claim 24 recites “receiving and storing, . . . , a plurality of medical images in a *database*,” and “accessing, . . . , one or more of the medical images associated with a particular patient from the *database*.” EX1001, 39:10-13; 39:15-17 (emphasis added).

81. It is my opinion that a POSA, reading the term a “database,” in the context of the claims and specification, would understand the term to mean a large, structured, set of data that contains multiple records that contain multiple fields (e.g., along with data-associated attributes thereof). They would, moreover, understand

that this definition is not synonymous with computer “memory.” This interpretation is consistent with both the claim language and the detailed description of the claimed subject matter laid out in the specification of the ’141 Patent.

82. To begin with, claim 1 uses both terms, “database,” and “memory,” and, true to their different meanings, uses them differently. Claim 1 states “system comprising . . . a *memory* having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to: . . . *access one or more of the medical images* associated with a particular patient *from the database.*” EX1001, 37:8-17 (emphasis added). Thus, a POSA would understand that the element “a database” is different from computer “memory” and that, as stated in claim 1, the recited database is a set of data that contains multiple patient images (i.e., records). Moreover, the fact that the claim specifies accessing medical images *associated with a particular patient* from the database would indicate to a POSA the presence of a structured store of data, such that medical images that are associated with not just any patient, but a *particular* (i.e., sought) *patient*, can be located and accessed.

83. The specification repeatedly confirms that “database” means a large, structured, set of data that contains multiple records that contain multiple fields. For example, when describing the cloud diagram in FIG. 7 above, the specification identifies “application servers and/or databases with storage and retrieval capabilities” as discrete network resources, separate from compute nodes. EX1001,

32:31-33. In the “Summary of Invention” section, the specification describes the claimed technology as “a network-based (e.g., cloud-based) support platform allowing multiple users to store, access, analyze, and/or provide feedback regarding a given set of image data for a patient,” and states that “[i]n certain embodiments, multiple (accredited) users can access the information, e.g., to weigh in on data interpretation.” EX1001, 3:4-17. A POSA would understand that this functionality would involve a large, structured, set of data that contains multiple records that contain multiple fields (e.g., medical image data, with records including not just image data, but also patient identifiers, dates, and the like).

84. Indeed, FIG. 3 of the ’141 Patent, reproduced below, illustrates exactly this, showing an example of a GUI window that “allows a user to enter information about a patient and upload and/or access medical images for the patient, e.g., series of images obtained over a period of time.” EX1001, 13:60-65.

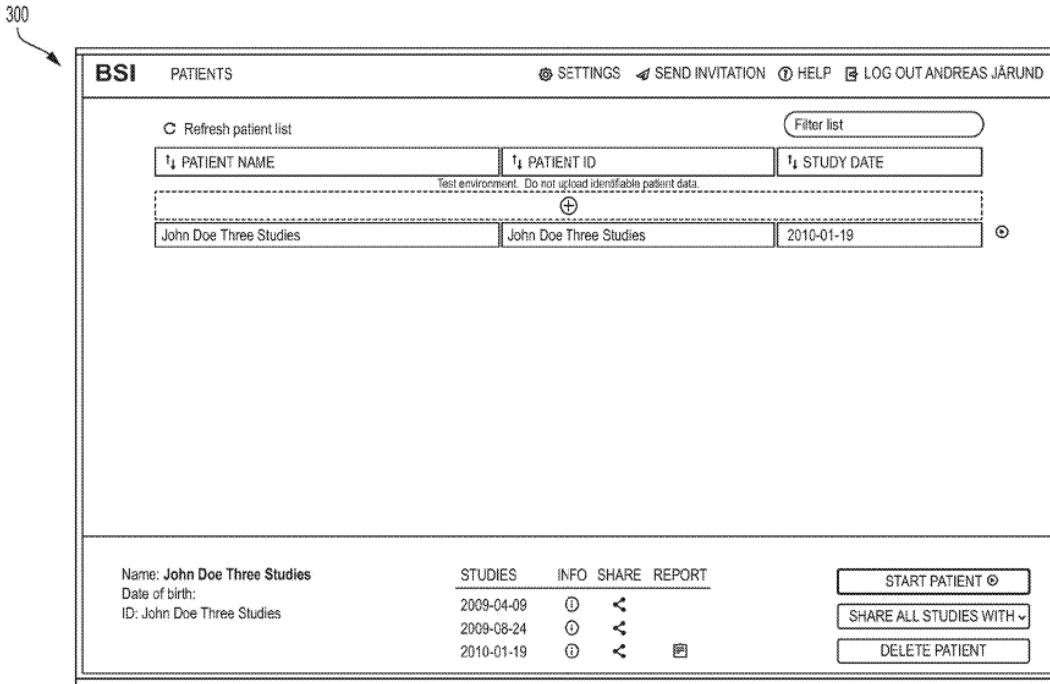


FIG. 3

**FIG. 3 reproduced from the '141 Patent.**

85. Finally, the specification makes clear that the element “database,” as used in the '141 Patent is a large, structured, set of data that contains multiple records that contain multiple fields, so as to allow the storage, retrieval, and analysis of multiple images taken over the course of a patient’s cancer diagnosis, any monitoring period, and treatment, as is often relevant for, e.g., prostate cancer. For example, the specification describes functionality like “repeatedly receive and store in a database over time, a plurality of medical images for each of the one or more patient(s) to obtain, . . . , a series of medical images taken over time (e.g., over the course of multiple visits to one or more doctor . . . thereby tracking determined values of the

one or more risk indices over a course of prostate cancer progression and treatment for the patient[.]” EX1001, 11:50-65.

86. A POSA would understand that this is different from how the specification describes computer “memory,” which, in contrast, is described as a hardware storage element. EX1001, 33:41-46 (“The memory 804 stores information within the computing device 800. In some implementations, the memory 804 is a volatile memory unit or units. In some implementations, the memory 804 is a non-volatile memory unit or units. The memory 804 may also be another form of computer-readable medium, such as a magnetic or optical disk.”); 35:19-27 (“The memory may include, for example, flash memory and/or NVRAM memory . . . The instructions can also be stored by one or more storage devices, such as one or more computer- or machine-readable mediums (for example, the memory 864 . . .”).

87. Therefore, it is my opinion that, having read the claim language and the specification of the ’141 Patent, a POSA would understand that a “database” refers to a large, structured, set of data that contains multiple records that contain multiple fields and that “database,” as used in the claims of the ’141 Patent, is different from computer “memory,” which is a hardware element.

## **IX. ANALYSES OF THE PETITION GROUNDS**

### **A. Maier in view of Huang and Armor fails to render claims 1-3, 6-9, 13-26, 32-35 obvious.**

#### **1. Claim 1**

88. Claims 1, 24, and 32-35 appear to be directed to Patent Owner's approach of using a machine learning algorithm to analyze medical images and determine values of risk indices that are indicative of cancer state or progression in a patient. The technology to which claim 1 is directed includes several key advances, and leverages insight into how they could be combined in a synergistic fashion to provide a valuable tool for tracking and aiding physicians over the course of a patient's prostate cancer progression and treatment.

89. For example, the Patent Owner recognized that machine learning could be used to geographically identify 3D boundaries of particular tissue regions in an overall more accurate and more robust manner with desirable scan-to-scan reproducibility than had been possible previously in commercial medical imaging software. The claims in the '141 Patent combine Patent Owner's insight into machine learning techniques with the insight that they could be leveraged in a particular way for a particular type of image, which, at the time the '141 Patent was effectively filed, was just beginning to show promise for sensitive diagnosis of prostate cancer.

90. The '141 Patent claims specify analysis of a composite image that comprising a CT scan overlaid with a nuclear medicine image acquired using a

PSMA binding agent. The '141 Patent claims describe analyzing these composite images by first, using the composite image to identify 3D boundaries of imaged tissue within the nuclear medicine image, and then, using the nuclear medicine image with the identified 3D boundaries to compute the risk indices. This approach is described in detail in the specification of the '141 Patent, for example at Section A.iv (“Positron Emission Tomography (PET) Scans”) and, as explained in further detail below, leverages the fact that complementary anatomical and functional information are provided by the CT scan and nuclear medicine image, respectively, and that this information can be combined by virtue of the overlay between the two images in a composite image, such as a PET/CT or SPECT/CT.

91. The claims of the '141 Patent combine machine learning techniques and new imaging approaches with the insight that taking advantage of remote networking by uploading medical images to, and accessing them from, databases via network-based systems would be especially valuable in the context of, for instance, cloud-based systems for cancer diagnosis and treatment.

92. As explained in further detail below, the Petition acknowledges that the primary reference, Maier, does not disclose key features, such as the particular types of images analyzed, particular radiopharmaceuticals used, and particular ways of analyzing those images, which are included in the claims. The Petition, however, alleges that combining Maier with two additional references – Huang and Armor –

cures this deficiency in Maier and renders the claims obvious. I disagree. Among other things, the three references that the Petition relies on relate to different approaches for analyzing or obtaining different types of images. The Petition's arguments, however, proceed in an element-wise fashion that glosses over significant incompatibilities between the cited references and fail to show that one of skill in the art would be motivated to, or even could, combine them to arrive at the claimed subject matter of the '141 Patent.

**a. Maier and Huang fail to render the element “wherein the one or more medical images comprise a ... CT scan overlaid with a nuclear medicine image” obvious.**

93. Claim 1 states “wherein the one or more medical images comprise a composite image of the particular patient, the composite image comprising a CT scan overlaid with a nuclear medicine image obtained at a substantially same time as the CT scan.” EX1001, 37:23-27. The Petition acknowledges that Maier fails to disclose this, but alleges that Huang discloses this element, and then argues that the combination of Maier and Huang render this claim element obvious. Pet., 23. Respectfully, I disagree.

94. In my opinion, based on my review, Maier and Huang are directed to fundamentally different imaging approaches, different ways of analyzing those images, and different purposes. Thus, contrary to the Petition's assertions, in my

opinion, it would not have been obvious for a POSA to combine the teachings of Huang and Maier to arrive at the claimed invention.

95. Having reviewed Maier, it is my opinion that Maier, throughout, is focusing almost entirely on analysis of CT (or MRI) images, with the aim of determining “imaging biomarkers” that correlate with various smoking-related diseases, like “myocardial infarction, Chronic Obstructive Pulmonary Disease (COPD), emphysema, lung cancer, decreased lung function, COPD exacerbations, coronary artery disease, and stroke.” EX1005, [0007]. Maier repeatedly explains that imaging biomarkers are characteristic patterns in images that are correlated with disease (again, focusing on smoking related diseases). *See, e.g.*, EX1005, [0031].

96. In contrast, in my opinion, Huang describes CAD tools for FDG PET images. That is, whereas Maier’s description focuses on analyzing single CT images to detect characteristic patterns that might correlate with lung disease, Huang’s analysis centers around the fact that in FDG-PET images tumors appear as hot spots. In my opinion, it is not clear how Maier could be applied to a PET/CT image, or how Maier’s approach of using machine learning to assign risk to imaging biomarkers would yield predictable results for a PET/CT image. Accordingly, Maier’s complicated correlations and various flavors of imaging biomarkers would be irrelevant in Huang, and it is not clear how, if at all, Huang’s FDG-PET imaging

approach would allow for assessing risk of all varieties of lung disease, including emphysema.

97. Additionally, the context in Maier for analyzing medical images is an “on-the fly comparison . . . that tests for similarities between the image data of interest and the comparison image data.” EX1005, [0032]. Huang does not perform any such step, and the Petition does not provide any indication as to how or why Huang would fit in with this step.

98. The Petition thus ignores the fundamental incompatibilities between Maier and Huang, and instead appears to argue that since they are both directed to diagnostics and because Huang states PET/CT imaging is useful for his specific application, one would be motivated to, and could, combine the two “to better inform the physician.” Pet., 25. In my opinion, that is overly simplistic and insufficient – there are many different medical diagnostics techniques, each serving a particular purpose, and working in a particular way. But that does not mean features of them would be obvious to combine with each other. To the contrary, Maier and Huang, as I explain above, perform distinct types of analyses, based on distinct principles, and for different purposes.

99. In addition, in my opinion, a POSA would not have a reasonable expectation of success in combining two fundamentally different approaches to image analysis. The Petition does not explain *how* Maier would be applied to a

PET/CT image. The Petition argues that, “because Huang reports obtaining a fused PET/CT image from a single imaging device, a POSITA would have recognized that the ‘composite’ image would be a compatible ‘instrumentation source’ for Maier.” Pet., 26. Maier focuses almost entirely on analyzing numerical features and calculating properties and textures from anatomical images, like CT (and MR) images (his “imaging biomarkers”). The Petition does not explain how or why a POSA would alter this approach to be used with a PET/CT image.

100. Thus, it is my opinion that the Petition fails to provide rationale as to why a POSA would combine Maier and Huang to arrive at the claimed limitation. Accordingly, Maier and Huang do not render the claim obvious for at least this reason.

101. Since claims 24 and 32-35 contain limitations identical in relevant part to this limitation in claim 1, it is my opinion that Petitioner’s references fail to render this limitation in claims 24 and 32-35 obvious for the same reasons.

**b. Maier, Huang, and Armor fail to render the “PSMA binding agent” element obvious.**

102. Claim 1 states a “composite image comprising a CT scan overlaid with a nuclear medicine image obtained at a substantially same time as the CT scan and following administration to the patient of an **imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide . . .**” EX1001, 37:24-30 (emphasis added).

103. The Petition claims Maier and Huang “disclose administering a radiolabeled imaging agent to the patient,” and that “[a] POSITA would have recognized that element [] simply substitutes the radiolabeled agent of the Maier-Huang combination (FDG) with a radiolabeled PSMA-binding agent.” Pet, 30-31. The Petition further contends that “Armor informs the POSITA that such agents were known in the art and were compatible with PET, SPECT, and CT imaging techniques,” and thus argues “[a] POSITA could have predictably substituted Armor’s PSMA-binding agents into the Maier-Huang combination to predictably arrive at this claim limitation.” *Id.* Respectfully, I disagree.

104. It is my opinion that the combination of Maier, Huang, and Armor fails to render the “PSMA binding agent” element obvious.

105. First, it is my opinion that Maier does not disclose any radiolabeled imaging agent suitable for use in nuclear medicine imaging, let alone one directed to prostate cancer specifically (like PSMA binding agent). The Petition argues that “Maier and Huang disclose administering a radiolabeled<sup>3</sup> imaging agent<sup>4</sup> to the patient,” and, in footnote 4, equates “imaging agent” to “an imaging biomarker such as a functional imaging agent.” Pet., 27. Maier, however, does not indicate that his imaging biomarkers equate to functional imaging agents. Maier’s imaging biomarkers are not physical compounds of any kind and are not administered to patients. Instead, Maier’s imaging biomarkers are quite different – namely, they

appear to be some kind of pattern or feature that can be calculated from an image. *See, e.g.*, EX1005, [0031]. Maier’s paragraph [0031] provided a laundry list of ways imaging biomarkers could be calculated. The only mention of an “agent” in this long list of “imaging biomarkers” is “metrics related to contrast agent uptake in MR or CT in tumors, or other vascularized tissues, etc.” EX1005, [0031]. A metric related to a contrast agent is not a radiolabeled imaging agent and, moreover, as explained above in Section V.A, MR and CT images are not nuclear medicine images and therefore do not use radiolabeled imaging agents that target specific types of cancer.

106. Second, while the Petition states that Huang describes a radiolabeled agent, that agent (as reflected in footnote 3 on pg. 27 of the Petition) is FDG. Huang, does not mention or suggest prostate cancer, let alone the idea of radiolabeled agents like PSMA that target specific types of cancer. As explained above, FDG is a glucose analogue and thus its uptake concentrates most heavily in tissue with high metabolic activity. EX2018, 3. Since cancer cells are typically characterized by higher metabolic activity than normal cells, PET images acquired with FDG can be used to detect cancer lesions, which typically appear as “hot spots” within images. *Id.* FDG, however, is not specific to cancer, and may also be absorbed by other cells with high metabolic activity, including areas of inflammation and infection. *Id.* In fact, Huang describes FDG as a glucose analogue that is absorbed preferentially by tissue with high metabolic activity. It is not specific to any cancer type. In contrast, PSMA

binding agents expressly bind specifically to prostate specific membrane antigen, a protein that is overexpressed in prostate cancer. In this way they exhibit molecular specificity to, and expressly target, prostate cancer tumors.

107. Thus, FDG operates in a fundamentally different way than a PSMA binding agent and FDG is non-specific, whereas PSMA expressly targets prostate cancer. Nothing in Huang suggests the use of a particular binding agent that acts via molecular specificity and targets a specific cancer type, let alone PSMA binding agents, which target a cancer-prostate cancer. Huang does not even mention the prostate or prostate cancer.

108. Third, having reviewed Armor, in my opinion, although Armor describes a PSMA binding agent for SPECT imaging, none of the agents described in Armor could be substituted for FDG, as the Petition claims. Pet., 30 (“A POSITA would have recognized that element [1(g)] simply substitutes the radiolabeled agent of the Maier-Huang combination (*FDG*) with a radiolabeled PSMA-binding agent which is specific to PET imaging.”) (emphasis added). Armor discloses PSMA binding agents that are labeled with <sup>99m</sup>Tc and are thus suitable for SPECT imaging. As I discussed above in Section V.A, PET and SPECT detect different kinds of radiation, and thus require different types of radionuclides. PET imaging detects radioactive decay that results in positron emission, and thus relies on radionuclides that are short half-life positron-emitting isotopes, such as carbon-11 (<sup>11</sup>C) and

fluorine-18 ( $^{18}\text{F}$ ), as well as gallium-68 ( $^{68}\text{Ga}$ ). EX2017, 2, 11. SPECT imaging, on the other hand, detects the direct emission of gamma radiation and use gamma-emitting radionuclides, such as  $^{99\text{m}}\text{Tc}$ ,  $^{123}\text{I}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$ ,  $^{67}\text{Ga}$ ,  $^{201}\text{Tl}$ ,  $^{81\text{m}}\text{Kr}$ ,  $^{133}\text{Xe}$ . *Id.*, 4. Thus, in my opinion, a POSA could not merely substitute Armor's SPECT-specific compounds for FDG, since that would result in a non-functioning system.

109. I also disagree with the Petition's statement that "Armor informs the POSITA that such agents were known in the art and were compatible with PET, SPECT, and CT imaging techniques." Pet, 30. The referenced passages in Armor passages are taken from the background section, where Armor sets out the need he aims to fill, stating, "Thus, a PSMA targeted radiotracer would be an ideal imaging agent for diagnosis of prostate cancer and to evaluate the extent of disease progression in a subject harboring prostate cancer." EX1007, [0006]. Armor addresses the desire for such an imaging agent by describing compounds that are suitable for SPECT imaging, and which are not simple substitutes for FDG.

110. Fourth, apart from disclosing PSMA binding agents, Armor is otherwise directed to a wholly conventional imaging technique, and it is my opinion that a POSA would not have a motivation to combine Armor with Huang. Armor describes image analysis that relies on users (e.g., physicians) to manually mark circular regions of interest on images. *See* EX1007, [0096]. Armor does not contemplate the shortcomings of a manual image analysis approach, let alone the

particular shortcomings in situations where images are repeatedly obtained and analyzed over the course of multiple visits (where Patent Owner’s insights into combining automated machine learning-based analysis with cloud-based systems are especially powerful). Neither Maier nor Huang appear to appreciate this point—the relevance of cloud-based systems in combination with the repeatability and robustness of automated approaches to situations where images are repeatedly obtained and analyzed over the course of multiple visits to one or more doctors—either.

111. Accordingly, it is my opinion that the combination of Maier, Huang, and Armor fails to render this element of claim 1 obvious.

112. Since claims 24 and 32-35 contain limitations identical in relevant part to this limitation in claim 1, it is my opinion that Petitioner’s references fail to render this limitation in claims 24 and 32-35 obvious for the same reasons.

**c. Maier, Huang, and Armor do not disclose “using the composite image to geographically identify...”**

113. Claim 1 recites “using the composite image to geographically identify a 3D boundary for each of one or more region of imaged tissue within the nuclear medicine image.” EX1001, 37:33-35. It is my opinion that Huang does not disclose this limitation, either alone or in view of Maier, and that it would not be obvious for a POSA to combine Maier with Huang to arrive at this limitation.

114. First, Huang does not disclose this claim limitation. The Petition claims that “Huang trains ‘discriminative classifiers and detectors’ to analyze [CT, PET, and composite PET/CT] images, including creating ‘3D bounding boxes’ of organs.” Pet., 31-32. But Huang’s “discriminative classifiers” do not segment organs and do not identify a 3D boundary for tissue regions. In particular, Huang explains that his detection framework uses (for a given landmark) a binary classifier, that takes an image as input and classifies the input image as either (i) a positive example of the landmark (i.e., the landmark is in the image) or (ii) a negative example of the landmark (i.e., the landmark is not in the image). Huang then scans his classifier in a sliding window fashion over a whole-body image, repeatedly classifying rectangular patches within the image. *See* EX1006, [0065], [0066], [0069], [0071], and [0072]. In my opinion, that is not segmentation, because all that Huang’s classifier returns is a 1 or a 0 for an entire rectangular patch. Segmentation requires determining a 3D boundary - i.e., a complex outline - of a given organ or bone.

115. Second, even were Huang to disclose this limitation (which, as explained above, it is my opinion that Huang does not), it would not be obvious for a POSA to combine Huang with Maier to arrive at this limitation, let alone the claims as a whole. As explained above, Huang’s approach is fundamentally distinct from Maier’s approach and therefore there is no teaching, suggestion, or motivation to combine Huang with Maier. The Petition first appears to argue that Huang provides

“[i]mproved, organ-specific identification,” and focuses on challenges with FDG imaging, but, in my opinion, this would not motivate a POSA to combine Huang with Maier. *See* Pet., 32. The Petition also notes that both Huang and Maier use machine learning algorithms, but in my opinion that does not provide rationale to combine either. *See* Pet., 33. In my opinion, a POSA would not have a motivation to combine two references simply because they both discuss machine learning.

116. As the Petition does not indicate what a combination of Huang and Maier would be, it is my opinion that combining Huang with Maier would not be predictable and a POSA would have no reasonable expectation of success. The Petition argues that a POSA would have reasonably expected success because “Huang teaches that its system which automatically identifies hotspots is ‘fast (real time), robust and accurate, and can be used as a practical application on a regular basis for hot-spot detection, segmentation, and change quantification’ in fused PET/CT or SPECT/CT images.” Pet., 34. In my opinion, this conclusory assertion is insufficient. The question is whether a POSA would have had a reasonable expectation of success in combining the two very different references—not whether Huang considered his own invention to be fast and accurate. Thus, in my opinion, the Petition fails to establish a rationale to combine Huang and Maier to perform this limitation.

117. Since claims 24 and 32-35 contain limitations identical in relevant part to this limitation in claim 1, it is my opinion that Petitioner’s references fail to disclose or render this limitation in claims 24 and 32-35 obvious for the same reasons.

**d. Maier, Huang, and Armor fail to render the element “computing, using the nuclear medicine image with the identified 3D boundary(ies) of the one or more region(s), a value of each of one or more risk indices, each risk index value indicative of cancer state or progression in the patient” obvious.**

118. Claim 1 recites “computing, using the nuclear medicine image with the identified 3D boundary(ies) of the one or more region(s), a value of each of one or more risk indices, each risk index value indicative of cancer state or progression in the patient.” EX1001, 37:36-40. It is my opinion that Maier, Huang, and Armor do not disclose that limitation and a POSA would not have a motivation to combine those references.

119. The Petition argues that Maier discloses “computing a ‘risk index’” by generating reports that include “metrics” and “quantitative measures” of disease. Pet., 35 (referencing EX1005, [0028]). None of the referenced portions of Maier, however, discloses the use of the nuclear medicine image with the identified 3D boundaries for calculation of risk indices. The analysis in Maier predominantly uses CT images (and different types of disease than one would normally use PET for) and follows a fundamentally different way of analyzing images—comparing them to similar patients in a reference cohort rather than the approach of the claimed subject

matter, where the analysis is focused on the single image and its intrinsic information content. *See* EX1005, [0027] (explaining “analyzing the image data of interest by comparing it to comparison image data,” and, “based on the comparison,” then “calculating quantitative metrics related to the patient's current health status and/or their risks for future health outcomes”).

120. The Petition acknowledges that “Maier does not teach computation using a composite image,” but alleges that Huang does. Pet., 37. I am of the opinion that Huang does not. The Petition argues “Huang teaches that joint-imaging modalities like PET/CT ‘enable[] the computer to understand on which organs or tissue regions each hot-spot is located... to separate normal hotspots from pathological ones...’” and that “A POSITA would recognize this as computing a risk index, fully as claimed.” Pet., 38.

121. It is my opinion that a POSA would not recognize “enable[ing] the computer to understand on which organs or tissue regions each hot-spot is located... to separate normal hotspots from pathological ones,” *id.*, as to computation of a risk index, which involves computing a value of some kind that is indicative of cancer state and/or progression in a patient. Pet., 11-12. This action in Huang does not disclose any calculation of a value.

122. The Petition also alleges that Armor discloses computing risk indices. Pet., 38. But none of the referenced portions of Armor discloses the use of the nuclear

medicine image with the identified 3D boundaries for calculation of risk indices. The referenced paragraphs generally recites “ratio of tumor uptake to background” and “Gleason score,” but does not disclose how these are being computed, and do not explain how Armor uses the nuclear medicine image with the identified 3D boundaries in that computation.<sup>3</sup>

123. It thus is my opinion that a POSA would not recognize Armor as disclosing computing a risk index as claimed.

124. In sum, it is my opinion that a POSA would not have had reason to combine (i) Maier, who analyzes CT images to detect emphysema, (ii) Huang, who creates CAD tools for FDG-PET images to detect tumors (but does not mention any specific cancer type and does not even mention the prostate), and (iii) Armor, who is directed to PSMA binding agents for SPECT-CT imaging (which are incompatible with PET and therefore cannot be simply substituted for FDG), to arrive at the Patent Owner’s claimed subject matter.

125. The Petition’s argument that there would be any rational to combine appears to be based on the claim that “the resultant risk indices were merely

---

<sup>3</sup> Gleason scores are calculated via histology, by a pathologist looking at a sample, and not by analyzing a CT or PET image directly. *See* EX2036, 2.

applications of known mathematical calculations to PSMA-binding agent-measured uptake within an identified 3D boundary, e.g., the prostate or, specifically, a prostate tumor.” Pet., 39. But this conclusory statement, in my opinion, does not address the omissions in and incompatibilities between the cited explained above.

126. Since claims 24 and 32-35 contain limitations identical in relevant part to this limitation in claim 1, is my opinion that Petitioner’s references fails to render this limitation in claims 24 and 32-35 obvious for the same reasons.

**e. Conclusion**

127. Based at least on the above-explained reasons, it is my opinion that Maier in view of Huang and Armor fails to render independent claims 1, 24, and 32-35 obvious. For the same reasons, it is my opinion that the combination(s) fails to render dependent claims 2-3, 6-9, 13-23, and 25-26 obvious.

**B. Maier in view of Huang and Armor, in further view of Neumaier, fails to render any of claims 6-11 obvious**

128. For Ground B, the Petition adds further in view of Neumaier to Maier in view of Huang and Armor. That addition does not change the obviousness analysis discussed above for Ground A. Accordingly, for at least the reasons above, it is my opinion that Maier in view of Huang and Armor, further in view of Neumaier, fails to render claim 1 (or dependent claims 6-11) obvious.

**C. Maier in view of Huang and Armor, further in view of Cardinale and/or Giesel, fails to render claims 6 and 12 obvious**

129. For Ground C, the Petition adds further in view of Cardinale and/or Giesel to Maier in view of Huang and Armor. That addition does not change the obviousness analysis discussed above for Ground A. Accordingly, for at least the reasons above, it is my opinion that Maier, in view of Huang and Armor, in further view of Cardinale and/or Giesel, fails to render claim 1 (or dependent claims 6 and 12) obvious.

**D. Huang in view of Armor and Maier fails to render claims 27 and 31 obvious.**

**1. Claims 27 and 31**

**a. Huang fails to disclose risk indices that are indicative of “prostate cancer state or progression.”**

130. Claims 27 and 31 recite “track[ing] determined values of the one or more risk indices over a course [of] prostate cancer progression and treatment for the patient,” and “stor[ing] the determined values of the one or more risk indices, each indicative of prostate cancer state or progression.” EX1001, 39:67-40:7, 41:3-6. The Petition argues that Huang alone, or with Armor, discloses this limitation. The Petition relies on its arguments for disclosure and rationale to combine from dependent claim 2, “addressed in Sections VIII.B.1.j) and VIII.B.2.” Pet., 66-67. But dependent claim 2 does not recite a risk index indicative of *prostate cancer* state or progression, nor does dependent claim 2 recite tracking determined values of risk

indices over *a course of prostate cancer progression and treatment for the patient* as recited in these claims. The Petition’s discussion of dependent claim 2 fails to address this claim element. Instead, in regard to claim 2, the Petition states only: “While Maier does not teach tracking using a composite image, Huang and Armor teach this, and a POSITA would have found it obvious to combine these references to arrive at this claim limitation.” Pet., 40. Moreover, it is my opinion that Huang alone does not disclose this limitation because Huang fails to disclose prostate cancer or prostate generally and, as explained above, combining Huang with Armor would not be obvious given their distinctions and incompatibilities.

**b. Maier, Huang, and Armor fail to render the “PSMA binding agent” element obvious.**

131. Claims 27 and 31 recite medical images comprising “a CT scan overlaid with a nuclear medicine image obtained at a substantially same time as the CT scan and following administration to the patient of an **imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide . . .**” EX1001, 40:12-17, 41:11-16 (emphasis added). The Petition cross-references its disclosure and rationales-to-combine arguments relating to the PSMA binding agent limitation of claim 1. Pet., 68-69. The Petition argues that Armor discloses this limitation and that Huang in view of Armor and Maier renders it obvious. *Id.* For the reasons explained with regard to this limitation in claim 1 above, it is my opinion that the cited references fail to render this limitation obvious.

- c. Huang does not disclose “using the composite image to geographically identify a 3D boundary . . .,” as recited by the claims.**

132. Claims 27 and 31 recite “using the composite image to geographically identify a 3D boundary for each of one or more region of imaged tissue within the nuclear medicine image.” EX1001, 40:19-21, 41:18-20. The Petition argues Huang discloses this limitation and that it is “substantively identical” to the similar limitation in claim 1. Pet., 68-70. For the reasons explained with regard to this limitation in claim 1, it is my opinion that Huang does not disclose this limitation and it would not be obvious for a POSA to combine Huang, Maier, and Armor to arrive at this limitation.

- d. Huang, Armor, and Maier fail to render obvious “computing the value of each of the one or more risk indices using the nuclear medicine image with the identified 3D boundary(ies) of the one or more region(s),” as recited by the claims.**

133. Claims 27 and 31 recite “computing the value of each of the one or more risk indices using the nuclear medicine image with the identified 3D boundary(ies) of the one or more region(s).” EX1001, 40:22-25, 41:21-24. The Petition alleges Huang discloses this claim limitation, and Huang in view of Armor and Maier renders it obvious because it is “substantively identical” to the similar limitation in claim 1. Pet., 69-70. Accordingly, for the reasons explained with regard

to this limitation in claim 1, it is my opinion that the cited references fail to render this limitation obvious.

**e. Conclusion**

134. Based at least on the foregoing reasons, it is my opinion that Huang in view of Armor and Maier fails to render claims 27 and 31 obvious.

**E. Huang in view of Armor and Maier, further in view of Giesel and Weineisen, fails to render claims 28-30 obvious.**


135. For Ground E, the Petition adds further in view of Giesel and Weineisen to Huang in view of Armor and Maier. That addition does not change the obviousness analysis discussed above for Ground D. Accordingly, for at least the reasons above, it is my opinion that Huang in view of Armor and Maier, further in view of Giesel and Weineisen, fails to render claim 27 (or dependent claims 28-30) obvious.

**X. CONCLUSION**

136. For the reasons stated herein, it is my view that claims 1-3 and 6-35 of the '141 Patent are nonobvious over the cited art. I reserve the right to expand or modify my opinions as my analysis continues, and to supplement my opinions in response to any additional information that becomes available to me and any matters raised by the parties, the Board, and/or the opinions provided by other experts.

137. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct. I hereby declare that all the 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 so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code.

Date: 7/10/25

By:   
\_\_\_\_\_  
Milan Sonka