

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

MIM SOFTWARE INC.
Petitioner

v.

PROGENICS PHARMACEUTICALS, INC.
Patent Owner

U.S. PATENT NO. 11,894,141
Filing Date: July 12, 2022
Issue Date: February 6, 2024
Title: NETWORK FOR MEDICAL IMAGE ANALYSIS, DESIGN SUPPORT
SYSTEM, AND RELATED GRAPHICAL USER INTERFACE (GUI)
APPLICATIONS

Inter Partes Review No.: IPR2025-00726

DECLARATION OF DR. BRUCE ROSEN

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EXHIBIT LIST

No.	Description
Ex1001	U.S. Patent No. 11,894,141 (“the Patent”)
Ex1002	Declaration of Dr. Rosen
Ex1003	Dr. Rosen Curriculum Vitae
Ex1004	Prosecution History File of the Patent (Application No. 17/862,528)
Ex1005	U.S. Patent Application Publication No. 2016/0203263 (“Maier”)
Ex1006	U.S. Patent Application Publication No. 2007/0081712 (“Huang”)
Ex1007	PCT Patent Application Publication No. 2015/058151 (“Armor”)
Ex1008	U.S. Patent No. 10,112,974 (“Neumaier”)
Ex1009	U.S. Patent No. 10,815,200 (“Cardinale”)
Ex1010	Giesel et al., “ ¹⁸ F-Labelled PSMA-1007 shows similarity in structure, biodistribution and tumour uptake to the theragnostic compound PSMA-617,” <i>European Journal of Nuclear Medicine and Molecular Imaging</i> 43(10):1929-1930 (June 2016) (“Giesel”)
Ex1011	Weineisen et al., “ ⁶⁸ Ga- and ¹⁷⁷ Lu-Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies,” <i>Journal of Nuclear Medicine</i> 56(8):1169-1176 (2015) (“Weineisen”)
Ex1012	RESERVED
Ex1013	RESERVED
Ex1014	Second Amended Complaint, <i>Progenics Pharmaceuticals, Inc. v. MIM Software Inc.</i> , Case No. 1:24-cv-10437-PBS, Dkt. 25, April 5, 2024
Ex1015	Kaur, “Various Image Segmentation Techniques: A Review,” <i>International Journal of Computer Science and Mobile Computing</i> 3(5):809-814 (May 5, 2014) (“Kaur”)
Ex1016	Sharma, “Automated medical image segmentation techniques,” <i>Journal of Medical Physics</i> 35(1):3-14 (2010) (“Sharma”)
Ex1017	Greenspan, “Deep Learning in Medical Imaging: Overview and Future Promise of an Exciting New Technique,” <i>IEEE Transactions on Medical Imaging</i> 35(5):1153-1159 (May 2016) (“Greenspan”)
Ex1018	Litjens, “A Survey on Deep Learning in Medical Image Analysis,” <i>Medical Image Analysis</i> 42:60-88 (Dec. 2017) (“Litjens”)
Ex1019	Shen, “Deep Learning in Medical Image Analysis,” <i>Annual Review of Biomedical Engineering</i> 19:221-248 (2017) (“Shen”)

Ex1020	Seifert et al., “Hierarchical Parsing and Semantic Navigation of CT Data,” Medical Imaging 2009: Image Processing, Proceedings of SPIE Vol. 7259, pp. 725902-1 to 725902-8 (2009) (“Seifert”)
Ex1021	Afshar-Oromieh et al., “Radiation dosimetry of 68Ga-PSMA-11 (HBED-CC) and preliminary evaluation of optimal imaging timing,” European Journal of Nuclear Medicine and Molecular Imaging 43:1611-1620 (2016) (“Afshar-Oromieh”)

I. INTRODUCTION

1. I have been retained by GE HealthCare Technologies Inc. (“GEHC”) and its wholly owned subsidiary, MIM Software Inc. (“MIM”), to provide a declaration in support of MIM’s Petition for *Inter Partes* Review of U.S. Patent No. 11,894,141 (“the Patent”) (Ex1001). The opinions presented here are my own and are based on my own personal knowledge.

2. The Patent contains claims that recite systems and methods for computing disease risk indices for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer.

3. I have been asked to prepare this declaration explaining the reasons and bases for my opinions that claims 1-3 and 6-35 of the Patent are unpatentable. As discussed below, I have concluded that these claims would have been obvious to the person of ordinary skill in the art at the time of the alleged invention in light of prior art patent publications including U.S. Patent Application Publication No. 2016/0203263 (“Maier”) (Ex1005), U.S. Patent Application Publication No. 2007/0081712 (“Huang”) (Ex1006), PCT Patent Application Publication No. 2015/058151 (“Armor”) (Ex1007), U.S. Patent 10,112,974 (“Neumaier”), (Ex1008), U.S. Patent No. 10,815,200 (“Cardinale”), and scientific journal articles by Giesel (“Giesel”) (Ex1010) and Weineisen (“Weineisen”) (Ex1011).

4. In reaching my opinions, I relied on the documents cited herein and

on my decades of knowledge and experience in the fields of radiology and nuclear medicine (outlined in Section II).

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

II. QUALIFICATIONS AND EXPERIENCE

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

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

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

9. I received my Radiology Residency training from the MGH, which I completed in 1987, and which included training in nuclear medicine. I was

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

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

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

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

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

14. I have been elected as a member of the National Academy of Inventors and the US National Academy of Medicine of the National Academies of Science. I have also been elected as a Fellow of the American Academy of Arts

and Sciences.

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

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

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

III. COMPENSATION AND PRIOR TESTIMONY

17. With respect to this matter, I am working as an independent consultant. I am being compensated at an hourly rate of \$850 USD, plus expenses,

for the time I spend working on this matter. Prior to my engagement in the present case, I never worked as a consultant for MIM, and I have never been adverse to Progenics in any proceeding. I own no stock in MIM and am aware of no other financial interest I have relating to MIM or Progenics. My compensation is not contingent upon the outcome of this matter.

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

IV. LEGAL STANDARDS

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

A. Priority Date

20. I have been asked to assume that the priority date of the Patent is October 27, 2016.

B. Claim Construction

21. I understand that in an *inter partes* review proceeding the claims of a

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

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

23. I understand that “extrinsic evidence” may also be considered when determining the meaning of a claim term. I understand there are different sources of extrinsic evidence, including dictionaries, inventor testimony, expert testimony, and learned treatises. I understand that intrinsic evidence is generally favored over extrinsic evidence, and that extrinsic evidence may not be used to contradict the

meaning of the claim term when read in light of the intrinsic evidence.

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

C. Anticipation

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

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

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

D. Obviousness

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

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

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

31. I understand that an obviousness determination can be based on a single prior art reference, a combination of multiple prior art references, or a

combination of prior art references and the patentee's admissions regarding the scope and content of the prior art.

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

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

one of ordinary skill in the art;

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

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

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

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

36. I understand that secondary considerations of non-obviousness may

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

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

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

38. I have been informed that a person of ordinary skill in the art is a hypothetical person who is presumed to have known all the relevant art at the time

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

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

40. I have undertaken to consider the knowledge the POSITA would have had as of October 27, 2016, which is the date I have been asked to assume is the priority filing date for the Patent. When I refer to the POSITA in this declaration

in my discussion of the Patent, I am referring to a person of ordinary skill in the art as of that date.

V. TECHNOLOGICAL BACKGROUND

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

A. Medical Imaging Modalities

42. Medical imaging is a non-invasive technology for visualizing and quantifying the structure inside the human body – as well as its function – thus aiding clinicians in the diagnosis and treatment of various medical conditions and diseases. Over the last century, the science of medical imaging has developed into a robust and diverse field, encompassing a wide range of techniques and technologies designed to address the myriad organs and tissues in the body, as well as the many different disease or disorder states.

1. Anatomical Imaging

43. Some medical imaging techniques and technologies are designed to visualize anatomical structures within the human body. Examples of structural imaging techniques that produce “anatomical images” include standard 2D X-ray

radiography, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI). Each of these technologies is valuable for visualizing, in high resolution, the shape, size, and position of different anatomical structures including organs, tissues, and anomalies.

2. Functional Imaging

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

45. The operational differences between PET and SPECT cameras are not relevant here. What is relevant is that PET and SPECT imaging scanners are both designed to visualize metabolic and physiological activity through detection of

radiation from a radionuclide or radiotracer. To perform nuclear medicine imaging, radionuclides are purposefully introduced into a patient's body in the form of a radiopharmaceutical (or radiotracer). Radiopharmaceuticals are compounds that include a biologically active delivery molecule labeled with a radiation emitting radionuclide. The delivery molecule is selected to target a cell or tissue associated with a particular disease or metabolic activity of interest. The molecules are chosen based on their ability to accumulate preferentially in certain tissues or organs, and many delivery molecules targeting different organs or disease states have been created. Thus, the delivery molecule that is selected will determine how the radiopharmaceutical behaves inside the human body and will direct the radiation emitting radionuclide toward specific organs or tissues in the body. As is pertinent here, many delivery molecules have been developed to target various types of cancer tissue.¹

46. As the radionuclides decay, they emit radiation that is detected by the PET or SPECT scanner, which will collect and compile, from multiple views

¹ One of the most common radiopharmaceuticals is [¹⁸F]-FDG (fluorodeoxyglucose), which is a glucose analog labeled with a radionuclide. [¹⁸F]-FDG is taken up by cells with high metabolic activity, but is not fully metabolized, allowing it to accumulate in these cells. This is particularly useful in oncology for detecting and monitoring tumors since cancer cells typically exhibit increased metabolic activity.

around the patient's body, many 2D projections of all detected radiation emitted from the patient. Using powerful computer algorithms that account for the precise direction from which the radiation was detected, the PET and SPECT scanners will then generate a reconstructed 3D image in which areas of high emission due to high radionuclide accumulation are depicted as high intensity "hotspots." This allows PET and SPECT cameras to achieve visualization and quantification of specific physiological processes and diseases within the body.

B. Image Registration and Composite Images

47. Anatomical images provide clear structural information regarding the location, shape, and size of organs and other tissues. Nuclear medicine functional images provide complementary information regarding physiological activity but often lack the clarity necessary to provide important structural context, such as the location of hotspots relative to other tissues. Complex diseases, such as many types of cancer, often require both structural and functional imaging to properly inform healthcare professionals with respect to diagnosis, dosimetry, and other clinical decisions. Therefore, it has long since been known to register, overlay, fuse or otherwise combine anatomical and functional images together for concurrent display in a composite image.

48. Image registration is the process of aligning two or more images so that corresponding points in each image match. Although many advanced

registration techniques have been developed, they can be summarized using the broad categories of rigid registration and non-rigid registration.

49. Rigid registration is most effectively employed when registering multi-modality images (*e.g.*, CT and SPECT) that were obtained at approximately the same time such that the patient remains in essentially the same position (*e.g.*, when the images are obtained using a hybrid imaging system). Rigid registration is accomplished by adjusting one complete image in six degrees of freedom relative to the other image before overlaying them – for example by translating or rotating one image relative to the other.

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

C. Image Segmentation

51. Image segmentation is the partition of an image – anatomical or functional – into meaningful regions or objects based on some physical criteria of

the image itself, such as intensity, color, texture, shape, or motion. *See generally* Ex1015, Ex1016. Image segmentation is essential for many medical image analysis tasks, such as detecting lesions or tumors, classifying tissues, contouring the overall shape or volume of organs, and localizing anatomical landmarks. In the past, radiologists manually segmented 3D volumes, 2D slice-by-slice, which was a laborious task that made comprehensive, whole-body analyses impractical. Eventually, numerous automated segmentation techniques were developed that greatly improved medical image analysis. *See generally* Ex1015, Ex1016. Although there are many types of image segmentation techniques, I will focus on some of the most common, including methods that use machine learning algorithms.

1. Region Growing

52. Region-based segmentation methods group points of image data in the form of pixels or voxels for 2D and 3D images, respectively, based on their similarity or homogeneity within a predefined region. Ex1015, 811. For example, region growing methods start from a seed pixel or voxel and iteratively add neighboring pixels or voxels that satisfy a similarity criterion, such as intensity range or variance. One particular use case of region-based segmentation is the accurate delineation of organ boundaries in CT scans.

2. Edge Detection

53. Edge-based segmentation methods detect the boundaries or contours of regions or objects by differentiating and isolating pixels or voxels where the stored data indicates a significant change in intensity, color, or texture relative to its neighbors. Ex1015, 811. Detected edge pixels or voxels are then connected into continuous curves or surfaces that are output in the processed image. In practice, edge-based methods have been successfully used in segmenting anatomical structures in medical images, such as detecting the boundaries of tumors.

3. Thresholding

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

4. Clustering

55. Clustering methods use machine learning to group pixels or voxels into homogenous clusters based on their similarity or proximity in a feature space,

such as intensity, color, texture, and/or location. Ex1016, 10-11. The object of clustering is to find natural groupings of pixels or voxels based on their characteristics such that members of one cluster are more similar to each other than to members of other clusters. The most common form of clustering divides the pixels or voxels of an image into a predetermined number of clusters and then iteratively reassigns each pixel or voxel to a different cluster until an optimization function is minimized – meaning that further reassignment among the clusters would not produce more homogenous clusters.

5. Artificial Neural Networks

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

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

58. Deep learning is a specialized subset of machine learning that uses artificial neural networks with many layers (hence “deep”) to analyze and

iteratively learn from data such as images. An artificial neural network is a computational model inspired by the highly interconnected structure of neurons in the human brain. It consists of interconnected nodes (like neurons) organized in layers. Each connection between neurons in adjacent layers has an associated weight, and the selected weight for each connection of the cumulative network determines the ability of the network to accurately predict outcomes (*e.g.*, whether an image contains the number “8”).

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

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

a particular organ that the neural network has been trained to look for. In this way, artificial neural networks can segment organs or bones in a medical image by accurately predicting which pixels in the image correspond to a particular organ or bone.

VI. THE '141 PATENT AND PROSECUTION HISTORY

61. The Patent, entitled “NETWORK FOR MEDICAL IMAGE ANALYSIS, DECISION SUPPORT SYSTEM, AND RELATED GRAPHICAL USER INTERFACE (GUI) APPLICATIONS,” was filed on July 12, 2022, and issued on February 6, 2024. Ex1001, cover. I have been instructed by counsel to conservatively treat October 27, 2016, as the priority date of the Patent, which is the filing date of priority Provisional Application No. 62/413,936.

62. According to the Patent, the disclosed invention “relates generally to systems and methods for creation, analysis, and/or presentation of medical image data.” Ex1001, 1:22-24. More specifically, however, I understand from the independent claims of the Patent (*i.e.*, claims 1, 24, 27, and 31-35), that the claimed invention relates to systems and methods computing “[a] risk index value indicative of cancer state or progression in the patient.” Ex1001, 37:36-40, 39:37-41, 40:22-25, 41:56-60, 42:29-33, 43:4-8, 44:13-17.

63. According to the Patent, “commonly available nuclear medicine cameras, known as single-photon emission computerized tomography (SPECT) or

positron emission tomography (PET) cameras, found in most hospitals throughout the world” are used by physicians “to determine the presence and the extent of disease in a patient.” Ex1001, 1:33-50. For example, “[a]n oncologist may use images from a targeted PET or SPECT study of a patient as input in her assessment of whether the patient has a particular disease, e.g., prostate cancer, what stage of the disease is evident, what the recommended course of treatment (if any) would be, whether surgical intervention is indicated, and likely prognosis.” Ex1001, 2:7-13. Additionally, the Patent explains that “[t]here are also a number of radiopharmaceuticals available for imaging particular kinds of cancer” including “the small molecule diagnostic 1404” which can be used for “the detection of primary and metastatic prostate cancer.” Ex1001, 1:55-64. But, despite the known use of PET and SPECT cameras to diagnose particular kinds of cancer using a variety of known radiopharmaceuticals, the Patent suggests that “there remains a need for systems and methods for improved analysis of medical imaging studies and communication of those results, diagnoses, prognoses, treatment recommendations, and associated risks to a patient.” Ex1001, 2:58-61 (emphasis added).

64. In pertinent part, the Patent describes a “network-based (e.g., cloud based) decision support system” (and method) comprising a processor and a memory having instructions stored thereon, wherein the instructions, when

executed by the processor, cause the processor to: (i) receive and store a plurality of medical images associated with a patient in a database (e.g., PET/SPECT/CT/MRI/US and composites thereof); and (iii) “automatically analyze [] one or more of the medical images [e.g., to compute a risk index [e.g., Bone Scan Index (BSI)] and/or a risk map.” Ex1001, 3:46-65, 4:4-6 (emphasis added).

65. The Patent states that its “automatic analysis” of the one or more medical images comprises any one or more of:

(a) automated fusion of the (e.g., PET, SPECT, CT, Mill [*sic*], and/or US) image(s) of the tissue;

(b) geographic identification of one or more organs, organ structures, sub-organs, organ regions, and/or other regions of the imaged tissue of the patient and production of a 3D image of the geographically identified tissue with PET, SPECT, CT, MM [*sic*], and/or US data overlaid;

(c) computation of risk information comprising one or more risk indices, a risk field, or a risk map using data from the database, the image(s) of the tissue, and/or the 3D image in (b); and

(d) use of the risk information computed in (c) (e.g., and data from the database) to produce a 3D risk picture for the patient.

Ex1001, 4:18-32.

66. Additionally, the Patent states that its “automatic analysis” of the one

or more medical images can be carried out using machine learning algorithms, including artificial neural networks, to perform tasks such as: (i) segmentation of tissue regions in CT scans, Ex1001 28:8-17; (ii) classification of hotspots in nuclear medicine images (e.g., PET or SPECT) as cancerous lesions, Ex1001, 27:4-8; and (iii) predicting a risk index value, Ex1001, 27:27-33.

67. “Hotspots,” according to the Patent, are “localized regions of high intensity in nuclear medicine images,” Ex1001, 15:66-16:2, that can be “classified as corresponding to cancerous lesions,” Ex1001, 27:4-8. According to the Patent, Figure 4, which is reproduced below, depicts “a screenshot of a GUI window showing representative full body gamma camera images showing hotspots automatically identified by the system, with corresponding overall computed BSI values for a particular image set obtained at a given time.” Ex1001, 13:66-14:4.

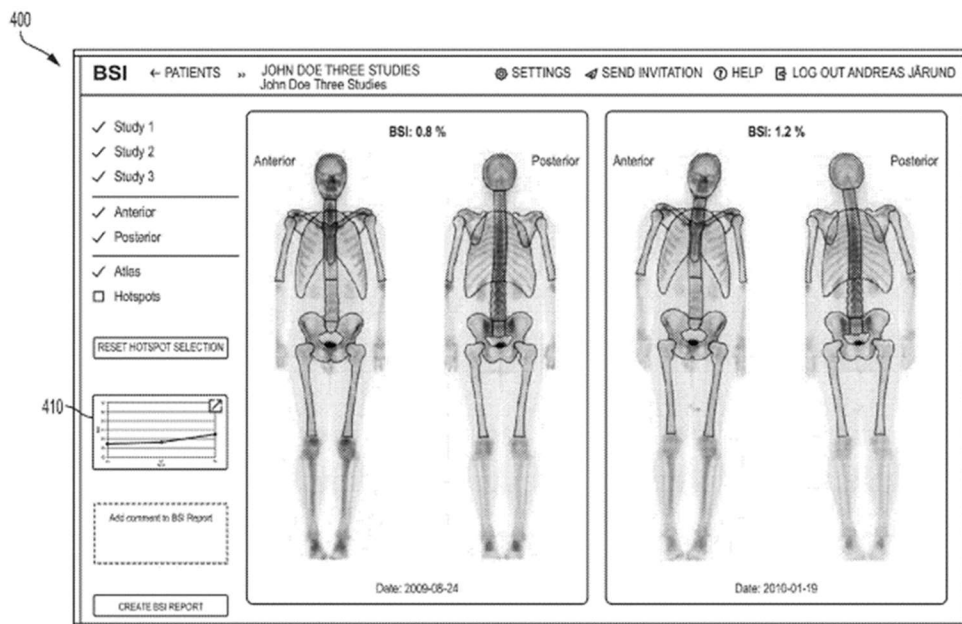


FIG. 4

I note that the images in Fig. 4 also include graphical overlays that identify the geographic locations of bones and skeletal regions in the functional SPECT images.

68. According to some embodiments described in the Patent, a nuclear medicine image, such as a PET scan, and an anatomical image, such as a CT scan, are combined as a composite image by overlaying the anatomical image with the nuclear medicine image. Ex1001, 27:64-66. As used in the Patent, “overlaying one image (e.g., a CT scan) with another (e.g., a PET scan) refers to establishing a mapping between coordinates and/or pixels or voxels of the two images that that [sic] represent the same physical locations (e.g., within the patient).” Ex1001, 27:66-28:3.

69. According to the Patent:

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

Ex1001, 28:3-13 (emphasis added). The Patent further explains that:

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

Ex1001, 28:24-30.

70. Importantly, the Patent purports to use the 3D boundaries of specific tissue regions that have been transferred to nuclear medicine images, such as PET images, to calculate risk indices and produce the risk map. For example, the Patent explains that a “[Bone Scan Index or ‘BSI’] value is a risk index that is a numeric value that quantifies the fraction of the total skeleton of the patient that is involved by cancerous tissue (e.g., tumors), based on [] detected hotspots.” Ex1001, 27:34-37. According to the Patent, BSI is computed by segmenting a whole-body scan of the patient “to geographically identify boundaries of regions... that correspond to... the patient’s skeleton.” Ex1001, 26:31-35. “Hotspots corresponding to cancerous tissue lesions within the patient’s skeleton, once detected, can be used to determine a risk index that provides a measure of disease state for the patient.”

Ex1001, 27:9-12.

71. Similarly, the Patent states:

[O]nce the 3D boundaries of the various regions are identified within the PET scan, one or more risk indices can be computed in a similar fashion to that described above with regard to BSI. In particular, in certain embodiments, intensity values of the PET scan in relation to (e.g., within and/or outside of) the 3D boundaries of the identified regions can be used to determine levels of cancerous tissue within the identified regions, e.g., based on features of detected hotspots (e.g., detected hotspots corresponding to metastases). Risk indices can then be computed based on the determined cancerous tissue levels. For example, hotspots within the PET scan can be identified, and, based on features such as their size, number, and distribution with respect to the identified regions, used to compute one or more risk indices.

Ex1001, 28:41-55.

72. Additionally, with respect to the production of the risk map, the Patent states that, according to some embodiments, a composite image can be automatically analyzed by: (i) “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 (e.g., such that portions of the nuclear medicine image falling within and/or outside of the 3D boundaries can be differentiated from each other)”; and (ii) computing “a value of each of one or more risk indices and/or [] a risk map using the nuclear medicine image with the identified 3D boundaries of the one or more region(s).” Ex1001, 5:6-20 (emphasis added), 6:3-16, 7:60-8:7, 8:57-9:3.

73. The Patent states that the computed risk indices and/or risk map are stored, e.g., for “display of a graphical representation of the determined values of the one or more risk indices for the patient (e.g., causing display of a graph showing variation in the determined values of the one or more risk indices for the patient over time),” Ex1001, 10:4-10, and used for “generating a radiologist report for a patient according to the patient images and/or risk index/risk map,” Ex1001, 30:64-65. The output of the “decision support system” described in the Patent may be an “automatically or semi-automatically generated radiologist report 510,” an embodiment of which is depicted in Fig. 5 (which is reproduced below) and

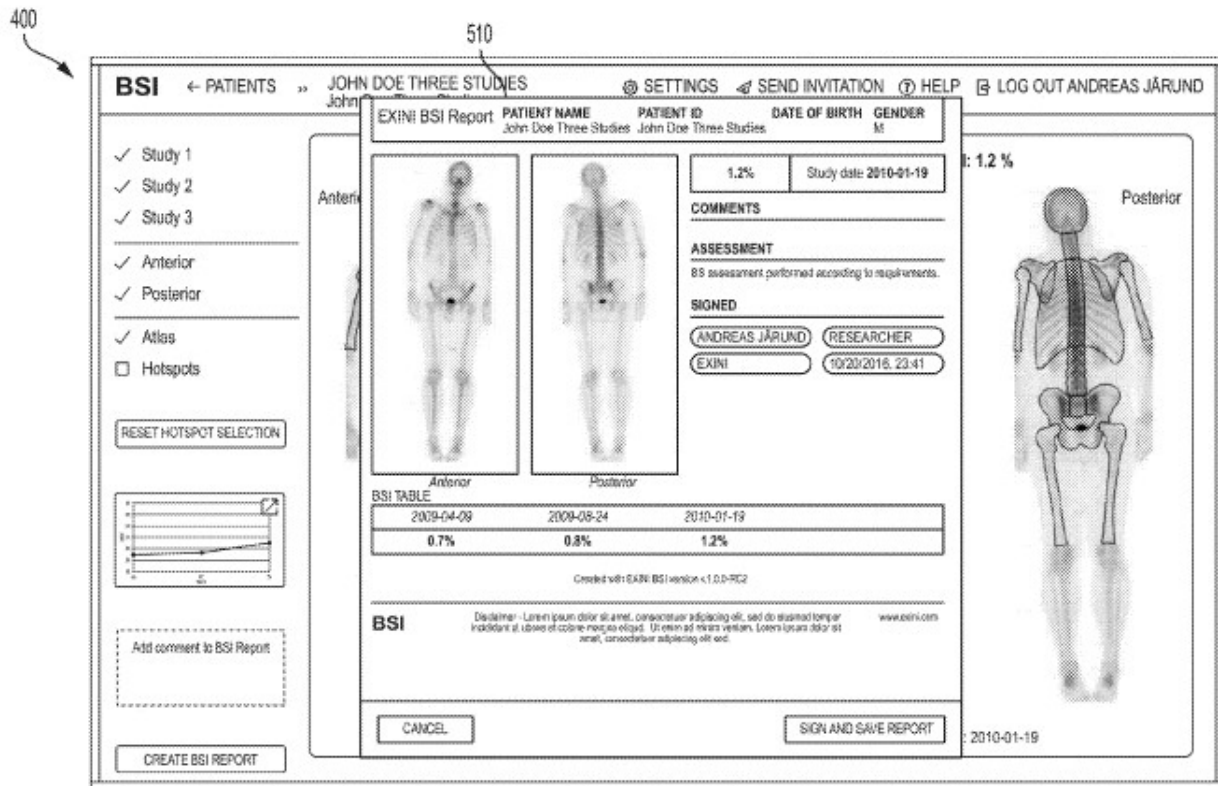


FIG. 5

includes a display of both BSI values over time and a risk map for the study date. Ex1001, 30:43-46, 4:13-15 (“generate a radiologist report for a patient according to one or more medical images for the patient”).

74. According to the Patent:

A radiologist report is a technical evaluation of the PET or SPECT images prepared by a radiologist for a physician who requested the imaging study and includes, for example, the type of study performed, the clinical history, a comparison between images, the technique used to perform the study, the radiologist’s observations and findings, as well as overall impressions and recommendations the radiologist may have based on the imaging study results.

Ex1001, 2:14-22 (emphasis added).

75. Thus, the Patent purports to address the need for improved analysis of medical imaging studies and communication of those results by disclosing systems and methods that: (i) receive and store medical images in a database, (ii) access one or more medical images from the database; (iii) automatically analyze the one or more medical images using a machine learning algorithm to calculate a risk index and/or a risk map; and (iv) communicate the calculated risk index and/or risk map, for example, in an automatically or semi-automatically generated radiologist report.

76. Additionally, the Patent briefly mentions using its accumulated image data to update – by applying a machine learning algorithm – its process for automatically analyzing medical images. For example, the Patent refers to “application of machine learning algorithms to update [a] process by which images are analyzed (e.g., updating segmentation and/or classification routines based on [the] growing image database).” Ex1001, 3:10-13. Similarly, Fig. 6, which is reproduced below, refers to applying a machine learning algorithm to update a process for the automatic analysis of “FUNCTION (III),” where function III refers to the automatic analysis of medical images “to compute a risk index (e.g., BSI) and/or to generate a risk map.” Ex1001, 30:61-67. However, no such use for updating the machine learning algorithm is required by the issued claims.

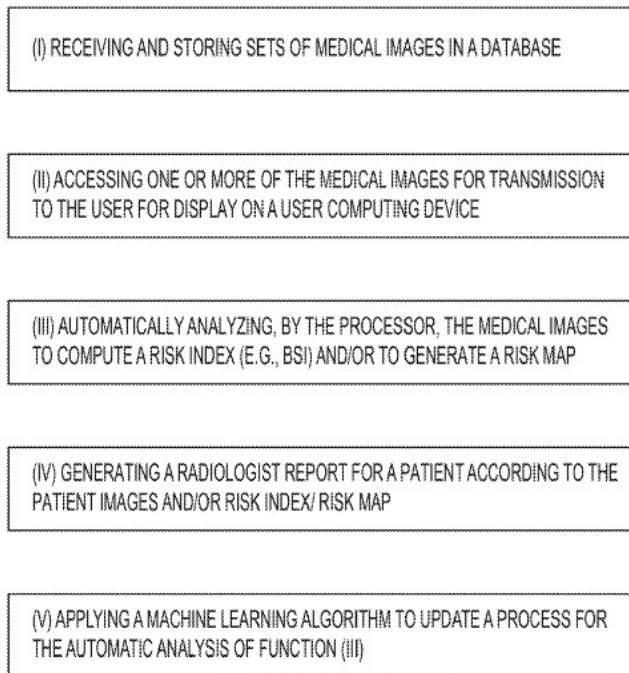


FIG. 6

77. I have reviewed the prosecution file history of the Patent, Ex1004, which is available digitally from the United States Patent and Trademark Office website, www.uspto.gov.

78. The Patent issued from U.S. Patent Application No. 17/862,528 (“the Application”), which was filed July 12, 2022.

79. Prior to examination, on September 23, 2022, the Applicant filed a preliminary amendment substantially amending the independent claims (then claims 1, 19, 40, and 45, corresponding to issued claims 1, 24, 27, and 31, respectively) to (i) require the processor to perform each of the receiving, accessing, automatically analyzing, and generating functions or steps (items (i)-(iv), respectively, of claims 1 and 19), (ii) require the automatic analysis to use “a machine learning algorithm” (item (iii) of claims 1 and 19, and item (b) of claims 40 and 45), and (iii) add “wherein” transition and subsequently recited limitations appearing thereafter (claims 1, 19, 40, and 45), among other amendments.

80. Amended claim 1, which is representative of amended claim 19, read as follows for examination:

A network-based decision support system comprising:

a processor; and

a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor

to ~~perform one or more functions (i) to (v) as follows:~~

(i) receive and store a plurality of medical images in a database, each medical image associated with a corresponding particular patient;

(ii) access one or more of the medical images ~~and/or related data~~ associated with a particular patient from the database ~~upon user request for transmission to the user for display on a user computing device;~~

(iii) automatically analyze the one or more ~~[[of the]]~~ medical images using a machine learning algorithm; and²

(iv) generate a radiologist report for ~~[[a]]~~ the particular patient according to the one or more ~~[[of the]]~~ medical images for the patient~~[[; and]]~~,

~~(v) apply a machine learning algorithm to update a process for automatically analyzing one or more medical images using accumulated image data in the database~~

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

² “and” was added in a second preliminary amendment, filed on October 27, 2022, which did not otherwise amend the independent claims.

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, wherein the instructions cause the processor to automatically analyze the composite image by:

(a) 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

(b) 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.

Ex1004, pp. 128-129. Thus, as examined, the claimed decision support system and method required an analysis, using a machine learning algorithm, of a “composite image” comprising a CT scan overlaid with a nuclear medicine image to compute a value of a risk index.

81. Amended claim 45, which is representative of amended claim 40, read as follows for examination:

A system for tracking prostate cancer progression and treatment efficacy over time, for one or more patient(s), the system comprising:

a processor; and

a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to:

(a) 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, for each of the one or more patient(s), a series of medical images taken over time;

(b) for each of the one or more patient(s), automatically analyze the series of medical images for the patient, using a machine learning algorithm, to determine values of one or more risk indices for each medical image of the series, thereby tracking determined values of the one or more risk indices over a course prostate cancer progression and treatment for the patient; and

(c) for each of the one or more patient(s), store the determined values of the one or more risk indices, each indicative of prostate cancer state or progression, for the patient for further processing and/or cause display of a graphical representation of the determined values of the one or more risk indices for the patient,

wherein the series of medical images for a particular patient of the one or more patient(s) comprises a CT scan overlaid with a nuclear medicine image acquired at a substantially same time as the CT scan and following administration to the particular patient

of an imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide, and wherein step (b) comprises:

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 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).

Ex1004, pp.134-135. Thus, as examined, the claimed system and method more broadly required an analysis, using a machine learning algorithm, of a CT scan overlaid with a nuclear medicine image to compute a value of a risk index, without express definition of a “composite image,” but with a subsequent reference to “the composite image” which must have antecedent basis in the recited overlaid images.

82. The Examiner did not issue an Office Action rejecting any of the examined claims. Instead, the Examiner initiated a telephone interview with the Applicant on September 18, 2023. where the Examiner suggested “ways to clarify the independent claim [*sic*] or amend the claim [*sic*] that may overcome the prior art of record and requested a Terminal Disclaimer.” Ex1004, p.223. Agreement was reached, a terminal disclaimer over U.S. Patent Nos. 10,340,046, 10,762,993, 10,665,346, and 11,424,035 was filed on September 19, 2023, and the Examiner

issued a Notice of Allowance, with accompanying Examiner's claim amendments, on November 1, 2023.³ Ex1004, pp.223, 215-219, 283-299.

83. With the agreement of the Applicant, the Examiner amended claim 1, which is representative of method claim 19 (issued claim 24), as follows:

A network-based decision support system comprising:

a processor; and

a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to:

(i) receive and store a plurality of medical images in a database, each medical image associated with a corresponding patient;

(ii) access one or more of the medical images associated with a particular patient from the database;

(iii) automatically analyze the one or more medical images using a machine learning algorithm; and

(iv) generate a radiologist report for the particular patient

³ An initial Notice of Allowance was mailed on September 27, 2023, then, subsequently, a Corrected Notice of Allowance was mailed on November 1, 2023.

according to the one or more medical images for the patient,

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 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:

(a) 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

(b) 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, and

wherein the system is a cloud-based system.

Ex1004, pp.287-288.

84. With the agreement of the Applicant, the Examiner also amended claim 45 (issued claim 31), which is representative of method claim 40 (issued claim 27), as follows:

A system for tracking prostate cancer progression and treatment efficacy over time, for one or more patient(s), the system comprising:

a processor; and

a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to:

(a) 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, for each of the one or more patient(s), a series of medical images taken over time;

(b) for each of the one or more patient(s), automatically analyze the series of medical images for the patient, using a machine learning algorithm, to determine values of one or more risk indices for each medical image of the series, thereby tracking determined values of the one or more risk indices over a course prostate cancer progression and treatment for the patient; and

(c) for each of the one or more patient(s), store the determined values of the one or more risk indices, each indicative of prostate cancer state or progression, for the patient for further processing and/or cause display of a graphical representation of the determined values of the one or more risk indices for the patient

wherein the series of medical images for a particular patient of the one or more patient(s) comprises a CT scan overlaid with a nuclear medicine image acquired 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, and wherein step (b) comprises:

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 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), and

wherein the system is a cloud-based system.

Ex1004, pp.290-291.

85. With the agreement of the Applicant, the Examiner also added new independent claims 68-71 (issued claims 32-35), which in lieu of the “system is a cloud-based system” and “processor [is] a processor of a cloud-based system” amendments, added a concluding “wherein” clause requiring “tracking determined values of at least the first risk index for the first patient over time” (claims 32 and 34), or a concluding “wherein” clause specifying that the value of the particular risk index is computed by “determining a corresponding cancerous tissue level... based on intensity values of the nuclear medicine image...” and “computing the value of the risk index based on the determined cancerous tissue levels...” (claims 33 and 35). Ex1004, pp.292-297.

86. The Examiner's Notice of Allowance also set forth the Examiner's reasons for allowing the claims as amended by the Examiner. The Examiner stated:

Based on applicant's amendment, with respect to claim 1, representative of claims 19, 40, 45 and 68-71 and, the closest prior art of record (WU and Zhao), WU reference is directed to image processing systems. More particularly, embodiments of the invention relate to cloud-based medical image processing systems with tracking capability, and Zhao reference directed to medical information processing systems. More particularly, embodiments of the invention relate to medical data processing using an evolving contextual clinical data (ECCD) engine. But neither WU nor Zhao teach or suggest, among other things, "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”.

These key features in combination with the other features of the claimed invention are neither taught nor suggested by (WU and Zhao) prior art of record.

Ex1004, pp.297-298 (internal quotations in original).

87. The Examiner’s stated reasons for allowance, including the Examiner’s express quotation of particular phrases in the claim, informs and confirms my understanding of the scope of the amended claims, as allowed.

88. [INTENTIONALLY OMITTED]

A. The Claims of the Patent

89. I address below claims 1-3 and 6-35 of the Patent.

1. Claim 1

90. Independent claim 1 of the Patent reads:

A network-based decision support system comprising:

a processor; and

a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to:

(i) receive and store a plurality of medical images in a database,

each medical image associated with a corresponding patient;

- (ii) access one or more of the medical images associated with a particular patient from the database;
- (iii) automatically analyze the one or more medical images using a machine learning algorithm; and
- (iv) generate a radiologist report for the particular patient according to the one or more medical images for the patient,

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 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:

- (a) 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
- (b) 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, and wherein the system is a cloud-based system.

Ex1001, 37:8-41.

2. Claim 2

91. Claim 2 depends from claim 1 and further states “wherein the plurality of medical images in the database comprise a series of medical images of a first patient taken over time, and wherein the instructions cause the processor to determine a value of at least a first risk index for each medical image of the series, thereby tracking determined values of at least the first risk index for the first patient over time.” Ex1001, 37:42-48.

3. Claim 3

92. Claim 3 depends from claim 2, which in turn depends from claim 1, and further states “wherein the instructions cause the processor to correlate the determined values of the first risk index with one or more prognostic values, thereby providing an objective metric of cancer state, progression, outlook, or treatment efficacy.” Ex1001, 37:49-53.

4. Claim 6

93. Claim 6 depends from claim 1 and further states “wherein the nuclear medicine image is a PET scan.” Ex1001, 37:58-59.

5. Claim 7

94. Claim 7 depends from claim 6, which in turn depends from claim 1, and further states “wherein the radionuclide is a radioisotope of a halogen.” Ex1001, 37:60-61.

6. Claim 8

95. Claim 8 depends from claim 7, which in turn depends from claims 6 and 1, and further states “wherein the imaging agent comprises [18F]DCFPyL.” Ex1001, 37:62-63.

7. Claim 9

96. Claim 9 depends from claim 7, which in turn depends from claims 6 and 1, and further states “wherein the halogen is fluorine-18 [18F].” Ex1001, 37:64-65.

8. Claim 10

97. Claim 10 depends from claim 6, which in turn depends from claim 1, and further states “wherein the radionuclide is a radioisotope of gallium (Ga).” Ex1001, 37:66-67.

9. Claim 11

98. Claim 11 depends from claim 10, which in turn depends from claims 6 and 1, and further states “wherein the imaging agent comprises 68Ga-PSMA-11.” Ex1001, 38:1-2.

10. Claim 12

99. Claim 12 depends from claim 6, which in turn depends from claim 1, and further states “wherein the imaging agent comprises 18F-PSMA-1007.” Ex1001, 38:3-4.

11. Claim 13

100. Claim 13 depends from claim 1 and further states:

...wherein the instructions cause the processor to, for at least one risk index of the one or more risk indices, compute the value of the risk index by:

determining, for each of the one or more regions, a corresponding cancerous tissue level within the region based on intensity values of the nuclear medicine image within the 3D boundary of the region; and
computing the value of the risk index based on the determined cancerous tissue levels within the one or more regions.

Ex1001, 38:5-14.

12. Claim 14

101. Claim 14 depends from claim 1 and further states “wherein the cancer is prostate cancer.” Ex1001, 38:15-16.

13. Claim 15

102. Claim 15 depends from claim 14, which in turn depends from claim 1, and further states “wherein the cancer is metastatic prostate cancer.” Ex1001, 38:17-18.

14. Claim 16

103. Claim 16 depends from claim 1 and further states:

...wherein the instructions cause the processor to automatically

analyze the composite image by, at step (a):

using the machine learning algorithm to geographically identify, within the CT scan of the composite image, the 3D boundary(ies) for each of the one or more region(s); and transferring the 3D boundary(ies) to the nuclear medicine image.

Ex1001, 38:19-27.

15. Claim 17

104. Claim 17 depends from claim 1 and further states:

...wherein the nuclear medicine image is a PET scan and the instructions cause the processor to automatically analyze the composite image by, at step (b):

computing the value of at least one particular risk index of the one or more risk indices based on intensity values of the PET scan in relation to the identified 3D boundary(ies).

Ex1001, 38:28-34.

16. Claim 18

105. Claim 18 depends from claim 17, which in turn depends from claim 1, and further states:

wherein the instructions cause the processor to automatically analyze the composite image by, at step (b):

computing the value of at least one particular risk index of the one or more risk indices based on intensity values of the PET scan within one or more of the identified 3D boundary(ies) within [the] PET scan.

Ex1001, 38:35-41.

17. Claim 19

106. Claim 19 depends from claim 17, which in turn depends from claim 1, and further states:

wherein the instructions cause the processor to automatically analyze the composite image by:

identifying one or more hotspots within the PET scan; and
at step (b), computing the value of the particular risk index based one or more features of the one or more hotspots together with the identified 3D boundary(ies).

Ex1001, 38:42-48.

18. Claim 20

107. Claim 20 depends from claim 19, which in turn depends from claims 17 and 1, and further states “wherein the one or more features comprise one or more members selected from the group consisting of: a size of the one or more hotspots, a number of the one or more hotspots, and a distribution of the one or more hotspots.” Ex1001, 38:49-53.

19. Claim 21

108. Claim 21 depends from claim 19, which in turn depends from claims 17 and 1, and further states:

wherein the instructions cause the processor to automatically analyze the composite image by, at step (b):

compute the value of the particular risk index based on one or more members selected from the group consisting of:

a total number of identified hotspots within one or more of the 3D boundary(ies);

a total volume of detected hotspots within one or more of the 3D boundary(ies);

an average intensity of detected hotspots within one or more of the 3D boundary(ies); and

a maximal intensity of detected hotspots within one or more of the 3D boundary(ies).

Ex1001, 38:54-38:67.

20. Claim 22

109. Claim 22 depends from claim 1 and further states “wherein the one or more regions of imaged tissue comprise one or more members selected from the group consisting of: organs, organ structures, sub-organs, and organ regions.”

Ex1001, 39:1-4.

21. Claim 23

110. Claim 23 depends from claim 1 and further states “wherein the one or more regions of imaged tissue comprise bone or a prostate of the patient.”

Ex1001, 39:5-7.

22. Claim 24

111. Independent claim 24 of the Patent is nearly the same as independent claim 1 except that it recites a method instead of a system. Claim 24 reads.

A method comprising performing, by a processor of a server computing device, (i) to (iv) as follows:

- (i) receiving and storing, by the processor of a server computing device, said processor a processor of a cloud-based system, a plurality of medical images in a database, each medical image associated with a particular corresponding patient;
- (ii) accessing, by the processor, one or more of the medical images associated with a particular patient from the database;
- (iii) automatically analyzing, by the processor, the one or more medical images using a machine learning algorithm; and
- (iv) generating, by the processor, a radiologist report for the particular patient according to the one or more medical images for the patient,

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 acquired 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, wherein the method comprises automatically analyzing the composite image by:

- (a) 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
- (b) 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, 39:8-41.

23. Claim 25

112. Claim 25 depends from claim 24 and further states “wherein the plurality of medical images in the database comprise a series of medical images of a first patient taken over time, and wherein the method comprises determining a value of at least a first risk index for each medical image of the series, thereby tracking determined values of at least the first risk index over time.” Ex1001, 39:42-47.

24. Claim 26

113. Claim 26 depends from claim 25, which in turn depends from claim 24, and further states “wherein the receiving and storing of the plurality of medical images comprises repeatedly receiving and storing, over time, a plurality of medical images of the first patient, each obtained at a different time, to obtain the series of medical images of the first patient.” Ex1001, 39:48-52.

25. Claim 27

114. Independent claim 27 of the Patent reads:

A method for tracking prostate cancer progression and treatment efficacy over time, for one or more patient(s), the method comprising:

- (a) repeatedly receiving and storing in a database, over time, by a processor of a computing device, said processor a processor of a cloud-based system, a plurality of medical images for each of the one or more patient(s) to obtain, for each of the one or more patient(s), a series of medical images taken over time;
- (b) for each of the one or more patient(s), automatically analyzing, by the processor, using a machine learning algorithm, the series of medical images for the patient to determine values of one or more risk indices for each medical image of the series, thereby tracking determined values of the one or more risk indices over a course [of] prostate cancer progression and treatment for the patient; and

(c) for each of the one or more patient(s), storing, by the processor, the determined values of the one or more risk indices, each indicative of prostate cancer state or progression, for the patient for further processing and/or causing, by the processor, display of a graphical representation of the determined values of the one or more risk indices for the patient,

wherein the series of medical images for a particular patient of the one or more patient(s) comprises a CT scan overlaid with a nuclear medicine image acquired 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, and wherein step (b) comprises:

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 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, 39:53-40:25.

26. Claim 28

115. Claim 28 depends from claim 27 and further states:

...wherein the series of medical images for the particular patient of

the one or more patient(s) comprises:

- (i) a first image subseries comprising one or more medical images obtained using a first nuclear imaging modality each following administration to the particular patient of a first radiopharmaceutical; and
- (ii) a second image subseries comprising one or more medical images obtained using a second nuclear imaging modality each following administration to the particular patient of a second radiopharmaceutical,

such that the values of the one or more risk indices determined in step (b) for the particular patient comprise a first subseries of values of a first risk index determined by automated analysis of the first image subseries and a second subseries of values of a second risk index determined by automated analysis of the second image subseries.

Ex1001, 40:26-43.

27. Claim 29

116. Claim 29 depends from claim 28, which in turn depends from claim 27, and further states “wherein the medical images of first image subseries are obtained over a first period of time, when prostate cancer of the particular patient is localized, and the medical images of the second image subseries are obtained over a second period of time, when prostate cancer of the particular patient is metastatic.” Ex1001, 40:44-49.

28. Claim 30

117. Claim 30 depends from claim 29, which in turn depends from claims 28 and 27, and further comprises “comprising using PET-CT imaging for evaluating prostate cancer in both localized and metastatic states.” Ex1001, 40:50-52.

29. Claim 31

118. Independent claim 31 of the Patent is nearly the same as independent claim 27 except that it recites a system instead of a method. Claim 31 reads:

A system for tracking prostate cancer progression and treatment efficacy over time, for one or more patient(s), the system comprising:

a processor; and

a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to:

(a) 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, for each of the one or more patient(s), a series of medical images taken over time;

(b) for each of the one or more patient(s), automatically analyze the series of medical images for the patient, using a machine learning algorithm, to determine values of one or more risk indices for each medical image of the series, thereby tracking determined values of the one or more risk indices over a course [of] prostate cancer progression and treatment for the patient; and

(c) for each of the one or more patient(s), store the determined values of the one or more risk indices, each indicative of prostate cancer state or progression, for the patient for further processing and/or cause display of a graphical representation of the determined values of the one or more risk indices for the patient

wherein the series of medical images for a particular patient of the one or more patient(s) comprises a CT scan overlaid with a nuclear medicine image acquired 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, and wherein step (b) comprises:

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 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), and

wherein the system is a cloud-based system.

Ex1001, 40:53-41:26.

30. Claim 32

119. Independent claim 32 of the Patent is nearly the same as independent claim 1, but substitutes “wherein the system is a cloud-based system” with different “wherein...” clause after item (b). Claim 32 reads:

A network-based decision support system comprising:

a processor; and

a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to:

- (i) receive and store a plurality of medical images in a database, each medical image associated with a corresponding patient;
- (ii) access one or more of the medical images associated with a particular patient from the database;
- (iii) automatically analyze the one or more medical images using a machine learning algorithm; and
- (iv) generate a radiologist report for the particular patient according to the one or more medical images for the patient,

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 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:

- (a) 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

(b) 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, and wherein the plurality of medical images in the database comprise a series of medical images of a first patient taken over time, and wherein the instructions cause the processor to determine a value of at least a first risk index for each medical image of the series, thereby tracking determined values of at least the first risk index for the first patient over time.

Ex1001, 41:27-67.

31. Claim 33

120. Independent claim 33 of the Patent is nearly the same as independent claim 1, but substitutes “wherein the system is a cloud-based system” with another different final “wherein...” clause after item (b). Claim 33 reads:

A network-based decision support system comprising:

a processor; and

a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to:

- (i) receive and store a plurality of medical images in a database, each medical image associated with a corresponding patient;
- (ii) access one or more of the medical images associated with a particular patient from the database;

(iii) automatically analyze the one or more medical images using a machine learning algorithm; and

(iv) generate a radiologist report for the particular patient according to the one or more medical images for the patient,

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 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:

(a) 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

(b) 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, and

wherein, for at least one particular risk index of the one or more risk indices, the instructions cause the processor to compute the value of the particular risk index by:

determining, for each of the one or more regions, a corresponding cancerous tissue level within the region based on intensity values of the nuclear medicine image within the 3D boundary of the

region; and

computing the value of the particular risk index based on the determined cancerous tissue levels within the one or more regions.

Ex1001, 42:1-43.

32. Claim 34

121. Independent claim 34 of the Patent is nearly the same as independent claim 24, but substitutes “said processor a processor of a cloud-based system” in step (i) with a “wherein...” clause after item (b). Claim 34 reads:

A method comprising performing, by a processor of a server computing device, (i) to (iv) as follows:

- (i) receiving and storing, by the processor of a server computing device, a plurality of medical images in a database, each medical image associated with a particular corresponding patient;
- (ii) accessing, by the processor, one or more of the medical images associated with a particular patient from the database;
- (iii) automatically analyzing, by the processor, the one or more medical images using a machine learning algorithm; and
- (iv) generating, by the processor, a radiologist report for the particular patient according to the one or more medical images for the patient,

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 acquired 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, wherein the method comprises automatically analyzing the composite image by:

- (a) 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
- (b) 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,

wherein the plurality of medical images in the database comprise a series of medical images of a first patient taken over time, and wherein the instructions cause the processor to determine a value of at least a first risk index for each medical image of the series, thereby tracking determined values of at least the first risk index for the first patient over time.

Ex1001, 42:44-43:15

33. Claim 35

122. Independent claim 35 of the Patent is nearly the same as independent claim 24, but substitutes “said processor a processor of a cloud-based system” in step (i) with a different “wherein...” clause after item (b). Claim 35 reads:

A method comprising performing, by a processor of a server computing device, (i) to (iv) as follows:

- (i) receiving and storing, by the processor of a server computing device, a plurality of medical images in a database, each medical image associated with a particular corresponding patient;
- (ii) accessing, by the processor, one or more of the medical images associated with a particular patient from the database;
- (iii) automatically analyzing, by the processor, the one or more medical images using a machine learning algorithm; and
- (iv) generating, by the processor, a radiologist report for the particular patient according to the one or more medical images for the patient,

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 acquired 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, wherein the method comprises automatically analyzing the composite image by:

- (a) 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
- (b) 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, and
wherein, for at least one particular risk index of the one or more
risk indices, the method comprises computing, by the processor,
the value of the particular risk index by:
determining, for each of the one or more regions, a
corresponding cancerous tissue level within the region based
on intensity values of the nuclear medicine image within the
3D boundary of the region; and
computing the value of the risk index based on the determined
cancerous tissue levels within the one or more regions.

Ex1001, 43:16-44:28.

VII. OPINIONS REGARDING CLAIM CONSTRUCTION

A. Ordinary and Customary Meaning

123. Unless otherwise stated herein, I interpret the terms of the Patent's claims as having their ordinary and customary meaning.⁴ After having reviewed the Patent specification and its prosecution history, I do not see any need to deviate from the plain and ordinary meaning of the claim language based on, for example,

⁴ I reserve the right, in the district court litigation brought by Patent Owner against Petitioner, to identify other claim terms and phrases that might require construction. Such additional terms – not addressed here – might be material to the determination of infringement of the accused instrumentalities, even if they are not relevant based on the features of the prior art cited in this Petition.

disclaimer, disavowal, or unique lexicography.

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

B. "Risk Indices" and/or "Risk Index" (Claims 1, 24, 27, 31-35, and various dependent claims)

125. I believe that the term "risk indices" and singular form "risk index" requires interpretation for the purpose of my declaration. These terms are used in independent claims 1, 24, 27, 31-35, and various dependent claims of the Patent.

126. As used in the Patent specification, the term "risk index" means, for example, "values... corresponding to numeric values indicative of prostate cancer state and/or progression in the patient (e.g., numeric values identifying a particular cancer stage; e.g., numeric values corresponding to a determined overall survival rate for the patient)." Ex1001, 9:62-10:1, 11:57-62. The Patent explains that such "risk indices... can be computed based on automated analysis of intensity variations in whole-body scans obtained following administration of ^{99m}Tc MDP to a patient" and "other radiopharmaceuticals can also be used in a similar fashion." Ex1001, 16:5-12, 16:60-67. The Patent further explains that "[a] risk index may be determined based on the determined cancerous tissue levels within one or more regions, directly, e.g., as the cancerous tissue level within a single region, or determined from cancerous tissue levels in multiple regions (e.g., as an average;

e.g., as a scaled sum; e.g., as a ratio; etc.), or even using machine learning approaches,” and provides an example of a Bone Scan Index (BSI) value as a risk index. Ex1001, 27:27-37.

127. As expressly defined in certain claims of the Patent, a risk index or risk index value is “indicative of cancer state or progression” (claims 1, 24, 27, 31-35), Ex1001, 37:39-40, 39:40-41, 40:6-7, 41:5-6, 41:59-60, 42:32-33, 43:6-7, 44:16-17, and may be computed by:

...determining, for each of [] one or more regions, a corresponding cancerous tissue level within the region based on intensity values of the nuclear medicine image within the 3D boundary of the region; and

computing the value of the risk index based on the determined cancerous tissue levels within the one or more regions.

(claims 13, 33, and 35), Ex1001, 38:5-14, 42:34-43, 44:18-28, or, *e.g.*, by:

...computing the value of at least one particular risk index of the one or more risk indices based on intensity values of the PET scan within one or more of the identified 3D boundary(ies) within PET scan.

(claims 17-21, quoting claim 18), Ex1001, 38:28-67. These limitations, requiring at most the computation of a risk index based on intensity values of a nuclear medicine image within one bounded region (or, as in claim 20, a size, number, or distribution of hotspots together with such 3D boundary(ies)), are consistent, in my

opinion, with the use of “risk index” in the parent claims and the Patent specification.

128. I understand that the Patent Owner, Progenics Pharmaceuticals, Inc., has accused Petitioner, MIM, of infringing at least claim 1 of the Patent. Ex1014, ¶¶85-93. I do not consider myself bound by the Patent Owner’s interpretation of the Patent’s terms, but I have considered the Patent Owner’s allegations of infringement as part of my claim construction analysis.⁵ Specifically, the Patent Owner alleges that one of Petitioner’s accused products satisfies sub-step (b) of the fourth limitation of claim 1 of the Patent (*i.e.*, “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 indicative of cancer state or progression in the patient”) because it “compute[s] ‘Advanced Therapy Response’ statistics like [Standardized Uptake Value (SUV)] peak and tumor burden.” Ex1014, ¶93 (emphasis added). In addition, the Patent Owner alleges that “[Total Tumor Volume (TTV)] and [mean Standardized Uptake Value

⁵ See *Toshiba Corp. v. Gold Charm Ltd.*, IPR2016-00462, Paper 29, pp.14-16 (accepting, as persuasive, the patent owner’s prior statements and allegations regarding claim scope), citing *Hewlett-Packard Co. v. MPHJ Tech. Inv., LLC*, IPR2013-00309, Paper 35, pp.20-22 (using patent owners’ demand letter as an aid in construing certain claim phrases).

(SUVmean)] are risk indices that indicate cancer state or progression.” Ex1014, ¶93. Thus, I understand the Patent Owner to assert that computing a value characterizing a region/tumor, such as Standardized Uptake Value metrics (peak or mean) or volume, or characterizing multiple regions/tumors, such as the aforementioned metrics or tumor burden in an organ (including, for example, BSI), satisfies the recited “[value] indicative of cancer state or progression” (*i.e.*, “risk index”). This interpretation, in my opinion, is at least consistent with the use of “risk indices” and “risk index” in the Patent specification and claims.

129. Accordingly, the term “risk indices” and related term “risk index” may be construed according to any of the following for the purpose of my declaration:

- (1) “numeric value(s) indicative of cancer state and/or progression in the patient within one or more regions,” which is consistent with the Patent specification;
- (2) “value(s) indicative of cancer state and/or progression in the patient within one or more regions,” which is consistent with the definition in the Patent claims;
- (3) “value(s) indicative of cancer state and/or progression in the patient within one or more regions, including but not limited to uptake values, tumor volumes, and other values derived therefrom,” which is consistent

with Patent Owner's allegations in the district court Complaint against Petitioner.

VIII. SUMMARY OF THE PRIOR ART

A. US2016/0203263 ("Maier")

130. Maier is a U.S. patent application, filed on January 8, 2016, and published on July 14, 2016. Ex1005, cover. I understand, therefore, that Maier is prior art to the Patent, even if I assume that the Patent is entitled to a priority date of October 27, 2016. I note that the Examiner included Maier in a Notice of References Cited which accompanied a Notice of Allowance mailed on September 27, 2023, Ex1004, p.224, but did not specifically discuss Maier in the written record.

131. Maier discloses computer-implemented systems and methods for assessing medical images and communicating a patient's health status and risk by automatically generating a report tailored for the intended user. Ex1005, [0014]. The medical images evaluated by Maier can include anatomical images, such as CT or MR images, and/or functional images, such as PET or SPECT images, and can be whole body images or images of specific tissue regions such as the lung, prostate, liver, or bone. Ex1005, [0015]-[0017]. According to Maier, the disclosed systems and methods can be used for "screening for disease, prognosis or diagnosis of diseases, base-line assessments, treatment planning, treatment follow-up, or

other user education regarding tissue state.” Ex1005, [0018]. Maier discusses the systems and methods in the context of quantitative risk metrics for lung cancer and other cardiopulmonary disease, Ex1005, [0007], [0021], however the disclosed systems and methods are not limited to a particular disease or pathology. Ex1005, [0018].

132. With reference to Fig. 1, which is reproduced below, Maier describes receiving one or more medical images from a medical imaging system or image database (102), optionally segmenting the one or more images into image data that is of interest and image data that is not of interest (104), and comparing the one or more medical images to reference images from other patients having known clinical outcomes (106). Ex1005, [0027]. Based on the comparison, Maier further discloses calculating quantitative metrics related to the patient’s risk of future health outcomes (108), and automatically generating a report providing the results of the analysis, including the image of interest and the calculated risk metric(s) (110). Ex1005, [0027].

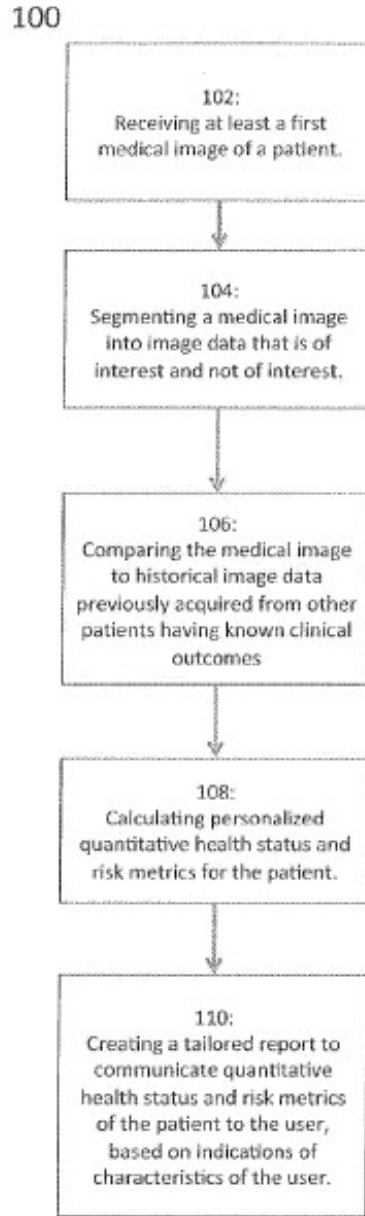


FIG. 1

133. Maier discloses that the step of comparing the patient's medical images to the historical reference images can be performed directly or indirectly. Ex1005, [0023]. Indirect comparison could involve evaluating the presence and/or amount of an imaging biomarker in the patient's image, where the biomarker is

defined based on comparison images of other individuals for whom the corresponding health status or medical outcome is known. Ex1005, [0020], [0031]. Direct comparison could involve identifying similar imaging features between the patient's medical image(s) and the comparison image(s) such as textual patterns of image intensity, distribution of CT densities in a tissue region, and size of an anatomical feature, as well as extracting only particular regions or anatomies of interest from the image(s), Ex1005, [0022]-[0023]. Maier further discloses that a direct comparison may involve “any type of algorithm that tests for similarities between the image data of interest and the comparison image data, including unsupervised machine learning algorithms of all varieties.” Ex1005, [0032].

134. With reference to Fig. 3, which is reproduced below, Maier discloses that the report produced from its comparisons can include the patient's own medical images with overlaid graphical denotations highlighting regions of risk and reference images of others for comparison. Ex1005, [0026], [0041]. The report can also include “quantitative measures of the amount of likely [disease] present (e.g., statistics for the amount of likely disease present in each individual [region]).” Ex1005, [0026], Fig. 3 (“Lung Density... 30% Damaged”). *See also* Ex1005, [0021] (correlation with, and imaging biomarkers for, development of lung cancer).

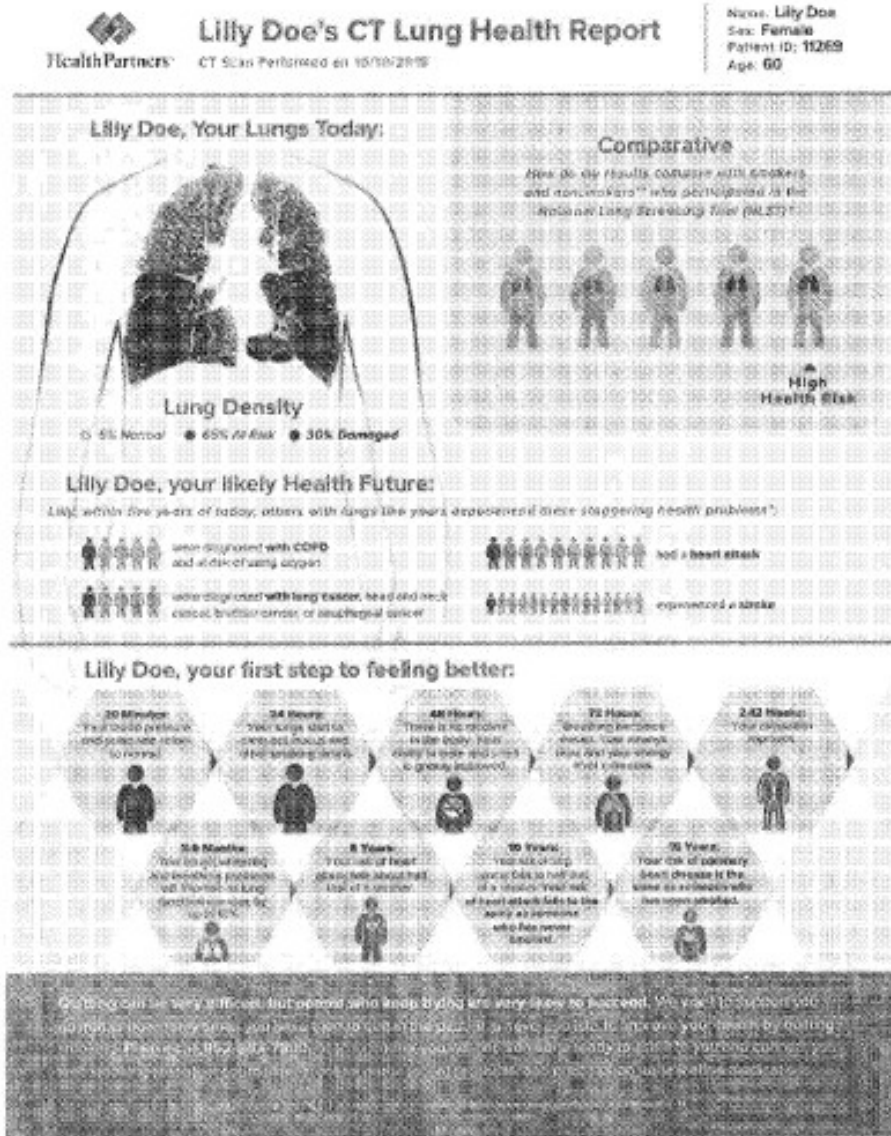


FIG. 3

B. US2007/0081712 (“Huang”)

135. Huang is a U.S. patent application, filed on October 3, 2006, and published on April 12, 2007. Ex1006, cover. I understand, therefore, that Huang is prior art to the Patent, even if I assume that the Patent is entitled to a priority

date of October 27, 2016. I note that the Examiner included Huang in a Notice of References Cited which accompanied a Notice of Allowance mailed on September 27, 2023, Ex1004, p.224, but did not specifically discuss Huang in the written record.

136. Huang discloses a learning-based framework for whole-body landmark detection, segmentation, and change quantification in single- and multi-mode medical images. Ex1006, [0002]. In particular, Huang references the use of “fused PET/CT images,” which “combine[] the functional imaging PET with an anatomical imaging computed tomography (CT),” and may be acquired from a single imaging device, and reports that such images and devices have “showed considerable promise for disease staging and therapy planning and monitoring.” Ex1006, [0011]. Huang subsequently discloses semi-automatic and fully automated systems and methods for hotspot detection, segmentation, and change quantification “in PET, or PET/CT images, and other imaging modalities such as PET/MR, PET/CT/MR, SPECT, SPECT/CT, SPECT/CT/MR, etc.,” Ex1006, [0074]-[0075].

137. Huang discloses that applications of the framework include the detection of anatomical landmarks, organs, or tissue regions in CT, PET, PET/CT, and other types of images, as well as the training of “discriminative classifiers and detectors for organs, tissue regions, or anatomical sections” such as the kidneys,

liver, heart, bladder, brain, lung, etc. Ex1006, [0072]. Huang, in particular, discloses that in multi-modal imaging such as PET/CT, image volumes may be used “jointly,” where in a first scenario of classifier training and detection, separate PET and CT classifiers are trained and then, for new volumes, the PET classifier is applied to the PET volume and the CT classifier is applied to the CT volume and “[t]hen the PET detection results and CT detection results are fused to prune false detections.” Ex1006, [0130]. In a second scenario of classifier training and detection, one classifier is trained on “joint” features of the PET/CT volumes and, for new volumes, “the trained classifier works on the ‘joint’ features.” Ex1006, [0130].

138. Huang discloses or suggests application of such trained classifiers of organs and tissue regions to its systems and methods for hotspot detection, segmentation, and change quantification. Ex1006, [0072]-[0073]. In general, Huang reports that on a fused image, *e.g.*, a PET/CT image, abnormalities that are seen on the functional PET portion can be located on the CT portion, and “this enables the interpreting physician to make a more informed decision about whether the hot-spot on PET is indeed an abnormality, and if so, where [it] is located anatomically.” Ex1006, [0011]. Huang subsequently discusses automatically separating hot pots that correspond to normal physiology (such as certain organs) from pathological hotspots (such as tumors), Ex1006 [0098], by enabling a

computer to understand on which organs or tissue region a hotspot is located, where “[t]he basic idea is to first detect normal physiological organs or regions that often induce high FDG uptake, such as the heart, kidney bladder, and brain,” then segment hotspots on the organ or region, and then suppress or compensate for segmented hotspots that appear so due to normal physiological uptake. Ex1006, [0099]. Huang’s trained classifiers of organs and tissue regions provide a basis for that understanding.

139. In addition, Huang reasons that because “because FDG uptakes by different organs or tissues have large variations, a global thresholding on the converted SUV volumes often fails to provide good hot-spot candidates” and “organ-specific or region-specific thresholding is very attractive.” Ex1006, [0114]. Thus, Huang subsequently discloses that “one can first detect, segment and separate organs or regions that have different ranges in SUV values, then apply organ- or region-specific thresholding” so as to identify hotspots which have SUV values above the organ- or region-specific threshold. Ex1006, [0114]. Huang’s trained classifiers of organs and tissue regions provide a basis for that detection, segmentation, and separation.

C. WO2015/058151 (“Armor”)

140. Armor is a Patent Cooperation Treaty application, filed on October 17, 2014, and published on April 23, 2015. Ex1008, cover. I understand,

therefore, that Armor is prior art to the Patent, even if I assume that the Patent is entitled to a priority date of October 27, 2016. I note that Armor was included in an Information Disclosure Statement filed on May 27, 2021, Ex1004, pp.177-182, 179, but neither the Examiner nor the Applicant specifically discussed or cited Armor in the written record.

141. Armor discloses radiolabeled compounds that selectively bind to prostate specific membrane antigen (PSMA). Ex1007, [0002]. In particular, Armor discloses “Tc-99m labeled PSMA targeting radioimaging agents” that are used to differentiate cancerous tissue from normal or benign tissue and to evaluate the progress of prostate cancer in patients. Ex1007, [0008]. The Armor compounds are for use with “any nuclear medicine tomographic imaging technique that is suitable for detecting gamma radiation,” such as single-photon emission computed tomography combined with conventional computed tomography (SPECT/CT). Ex1007, [0009]. However Armor otherwise reports that “[a] variety of radionuclides are known to be useful for radioimaging, Ex1007, [0007], and acknowledges that other clinical drugs incorporate other radionuclides imaged by other means, Ex1007, [0003]. In general, Armor teaches that “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].

D. US10,112,974 (“Neumaier”)

142. Neumaier is a PCT patent application, filed on August 24, 2015, which subsequently entered the U.S. national stage on February 24, 2017 and was granted on October 30, 2018. I understand, therefore, that Neumaier is prior art to the Patent, even if I assume that the Patent is entitled to a priority date of October 27, 2016. Neumaier was not disclosed by the Applicant, or cited by the Examiner, during the prosecution of the Patent.

143. Neumaier discloses, in pertinent part, the preparation of PSMA-specific PET radiotracers such as [¹⁸F]DCFPyL 1-10. Ex1008, title, 1:10-13. In general, Neumaier reports that the imaging of prostate cancer with PET isotope labelled PSMA ligands (PSMA binding agents) is of “considerable importance in clinical diagnosis.” Ex1008, 5:60-62. Neumaier reports that, in 2015, the only PSMA PET tracer used in clinics was [⁶⁸Ga]HBED-CC (50),⁶ and that in contrast to [⁶⁸Ga], [¹⁸F] has a longer half life and is more accessible, so that “[¹⁸F]DCFPyL 1-10... could represents [*sic*] an adequate alternative for [⁶⁸Ga]HBED-CC (50) for research and patient care.” Ex1008, 64:30-47.

⁶ [⁶⁸Ga]HBED-CC (50) is also referred to as [⁶⁸Ga]PSMA-11. Ex1001, 18:17-19; Ex1021, abstract.

E. US10,815,200 (“Cardinale”)

144. Cardinale is a U.S. Patent issued from a bypass continuation of a PCT patent application, designating the United States, filed on August 24, 2015. I understand, therefore, that Geisel is prior art to the Patent, even if I assume that the Patent is entitled to a priority date of October 27, 2016.

145. Cardinale discloses ¹⁸F-tagged PSMA-binding agents and their use as imaging agents for prostate cancer. Ex1009, title. Cardinale reports that its compounds, including ¹⁸F-PSMA-1007, were tested in PET imaging and “showed a great potential as possible tracer [*sic*] for the detection of prostate cancer and its metastases.” Ex1009, 46:44-54. Cardinale praises its compounds as having advantageous hepatobiliary versus renal clearance, Ex1009, 46:63-67, and claims that its compounds are “perfectly suited for the primary diagnosis of prostate cancer and local recurrence,” Ex1009, 47:1-4.

F. Geisel

146. Giesel is a scientific journal article published by the European Journal of Nuclear Medicine and Molecular Imaging on June 25, 2016. Ex1010, 1929. In my opinion, an interested member of the public could have reasonably located this reference by searching the Open Access collection of Springerlink.com, the National Library of Medicine’s PubMed® database, or the article’s DOI reference (*e.g.*, at crossref.org). I understand, therefore, that Geisel is prior art to the Patent,

even if I assume that the Patent is entitled to a priority date of October 27, 2016.

147. Geisel discusses two PSMA targeted radiotracers: ^{177}Lu -PSMA-167 and ^{18}F -PSMA-1007. Ex1010, p.1929. Geisel teaches that while the “biochemical and radiological responses to radionuclide therapy with ^{177}Lu -PSMA-167 targeting prostate-specific membrane antigen (PSMA) make it a promising approach to the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC),” it is “reported to have slower tumor accumulation and clearance kinetics” than other prior art PSMA tracers. Ex1010, p.1929. A new compound, ^{18}F -PSMA-1007, was developed “based on the scaffold of PSMA-617.” Ex1010, p.1929. Geisel discloses that ^{177}Lu -PSMA-167 and ^{18}F -PSMA-1007 “seem to be a perfect theragnostic tandem” “due to the preferred physical characteristics of ^{18}F for PET imaging and the possibility for large-scale production in a cyclotron” compared to prior art PSMA tracers. Ex1010, p.1929. While not explicitly stated in Giesel, in my opinion a POSITA would understand that Giesel’s theragnostic use involving ^{177}Lu -PSMA-617 nuclear medicine imaging constitutes SPECT imaging. See Ex1010, p.1929 (third paragraph & figure).

G. Weineisen

148. Weineisen is a scientific journal article published by the Society of Nuclear Medicine and Molecular Imaging, Inc. in the Journal of Nuclear Medicine on June 25, 2016. Ex1011, 1169. In my opinion, an interested member of the

public could have reasonably located this reference by subscribing to the journal or by searching the Society's and/or the journal's website (*e.g.*, jnm.snmjournals.org), the National Library of Medicine's PubMed® database, or the article's DOI reference. I understand, therefore, that Weineisen is prior art to the Patent, even if I assume that the Patent is entitled to a priority date of October 27, 2016.

149. Weineisen discloses ⁶⁸Ga- and ¹⁷⁷Lu-labeled PSMA-binding agents as part of another “theranostic” tandem, and that these are used for the imaging and treatment of metastatic castration-resistant prostate cancer (mCRPC). Ex1011, p.1169. Weineisen discloses “theranostic” use where ⁶⁸Ga-labeled PSMA-binding agents are imaged via PET/CT to confirm primary and (therapeutically determinative) metastatic prostate cancer, and ¹⁷⁷Lu-labeled PSMA-binding agents are imaged via SPECT/CT for dosimetry and other calculations, *e.g.*, (further) “therapy planning” and cycles. Ex1011, pp.1169 (second paragraph), 1173-1174 (including Fig. 6). Weineisen praises the tandem for “high contrast in PET imaging and therapeutic effectiveness with no detectable side effects,” its ⁶⁸Ga-labeled PSMA-binding agent as having “high potential for the detection of metastatic PC” and use in theranostics, and its ¹⁷⁷Lu-labeled PSMA-binding agent as “feasible, safe, and effective in metastatic PC.” Ex1011, pp.1175-1176.

IX. DETAILED OPINIONS REGARDING INVALIDITY

150. As detailed below, claims 1-3 and 6--35 of the Patent are unpatentable as obvious in view of the prior art. I rely principally on two combinations of references: (1) Maier (Ex1005) in view of Huang (Ex1006) and Armor (Ex1007), and (2) Huang (Ex1006) in view of Armor (Ex1007) and Maier (Ex1005). Both Maier and Huang were included in a Notice of References Cited which accompanied a Notice of Allowance mailed on September 27, 2023, Ex1004, p.224, but neither reference or their combination was discussed in the written record of the Patent or that of the Patent's parent (U.S. Application No. 16/938,488) or other predecessor (U.S. Application Nos. 16/418,527 and 15/794,220) patent applications. Armor was included in an Information Disclosure Statement filed on January 10, 2023, Ex1004, pp.176-190, 179, but likewise was not discussed in the written record of the Patent. Each of the presented combinations teach or at least suggest the combination of every limitation of the independent claims of the Patent, and most of the further limitations of the remaining claims.

151. The following table sets forth the combination of prior art that renders obvious each of claims 1-3 and 6-35:

Ground	Prior Art	Basis	Claims Challenged
A	Maier in view of Huang and Armor	Obviousness	1-3, 6-9, 13-26, 32-35
B	Maier in view of Huang and Armor, further in view of Neumaier	Obviousness	6-11
C	Maier in view of Huang and Armor, further in view of Cardinale and/or Giesel	Obviousness	6, 12
D	Huang in view of Armor and Maier	Obviousness	27, 31
E	Huang in view of Armor and Maier, further in view of Giesel and Weineisen	Obviousness	28-30

A. Ground A, Obviousness over Maier in view of Huang and Armor

1. Independent Claim 1

a) Preamble: “A network-based decision support system comprising:”

152. I understand that the preamble of a claim is typically just a statement of intended use, but may, in some circumstances, include limitations on the scope of the claim. For the purposes of providing a thorough analysis, I will assume that the preamble of claim 1 is limiting and I will address it like any other claim limitation. As I explain further below, it is my opinion that Maier discloses “[a] network-based decision support system.”

153. Meier discloses “systems and methods for automatically analyzing a patient’s one or more medical images and creating at least one report that provides

quantitative metrics related to the patient’s current health status and their risks for future health outcomes.” Ex1005, [0014]. These constitute decision support functions for physicians and patients alike. Maier discloses that the report “may be used by the referring physician to plan an interventional procedure.” Ex1005, [0026]. *See also* Ex1005, [0042] (The “format and content may be specifically tailored... to be most effective for influencing the patient’s behavior.”). In addition, Meier discloses that the systems and methods “may be integral portions of a single computer or server or may be connected parts of a computer network.... such as the Internet,” Ex1005, [0047], where “any portion thereof may be a personal computer (e.g., desktop or laptop), tablet computer, mobile device (e.g., personal digital assistant (PDA) or smart phone), server (e.g., blade server or rack server)... or any other suitable device or combination of devices,” Ex1005, [0045]. Thus, such functions may be provided as part of a network-based decision support system.

154. Accordingly, it is my opinion that Maier discloses all the limitations of the preamble of claim 1.

- b) Limitation 1(a): “a processor; and a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to:”**

155. Maier discloses these limitations, which are nothing more than generic

recitations of structures found in any computer-implemented system. Specifically, Maier discloses that “[t]he computer-implemented methods of this disclosure may utilize any computer-based system” where “[a] system may include random access memory (RAM), one or more processing resources such as a central processing unit (CPU) or hardware or software control logic, ROM, and/or other types of nonvolatile memory.” Ex1005, [0045]. In addition, Maier discloses that “[o]ne or more processors may execute applications or programs to run systems or methods of the present disclosure, or portions thereof, stored as executable programs or program code in the memory, or received from the Internet or other network.” Ex1005, [0046].

156. Accordingly, it is my opinion that Maier discloses limitation 1(a).

c) Limitation 1(b): “(i) receive and store a plurality of medical images in a database, each medical image associated with a corresponding patient;”

157. Maier discloses that “the computer-implemented method 100 comprises the computer-automated steps of: receiving at least a first medical image of a patient, said medical image having been obtained from a medical imaging system, as shown at 102.” Ex1005, [0027], Fig. 1. Although it would be virtually inherent to store such an image, Maier also discloses that “the algorithm may... comprise comparing the patient’s image(s) to the patient’s own image(s), such as previously obtained image(s) for the patient, and calculating values related to the

change in the patient's own image(s)." Ex1005, [0024]. Thus, Maier's systems and methods must inherently receive and store a plurality of medical images in a database, at least so as to allow for the described past-to-present comparison as well as future comparisons. Although a database may be any collection of data, Maier also discloses the use of a Picture Archiving and Communications System (PACS) database and use for multiple patients. Ex1005, [0043]-[0044], [0037]. Thus, Maier expressly discloses a database and an association of the images (and eventual reports) with corresponding patients.

158. Accordingly, it is my opinion that Maier discloses limitation 1(b).

d) Limitation 1(c): "(ii) access one or more of the medical images associated with a particular patient from the database;"

159. It is my opinion that Maier discloses these limitations. As previously described, Maier discloses the use of a PACS database. Ex1005, [0044], [0037]. Maier further discloses that the system and method "may receive the medical images directly as a DICOM send/push from a medical imaging system, or via a secondary routing decision by a separate device based on the contents of the DICOM tags in the medical images, or via a manual push by a user." Ex1005, [0043], Figs. 1-2. Maier yet further discloses that "the computer-implemented method 100 comprises... receiving at least a first medical image of a patient... [and] analyzing the image data of interest by comparing it to comparison image

data, as shown at 106,” Ex1005, [0027], where “[t]he algorithm may additionally or alternatively comprise comparing the patient’s image(s) to the patient’s own image(s), such as previously obtained image(s) for the patient,” Ex1005, [0024]. Thus, one or more images associated with a particular patient are accessed from the PACS or other database.

160. Accordingly, it is my opinion that Maier discloses limitation 1(c).

e) Limitation 1(d): “(iii) automatically analyze the one or more medical images using a machine learning algorithm; and”

161. It is my opinion that Maier discloses this limitation. As previously described, Meier discloses “systems and methods for automatically analyzing a patient’s one or more medical images and creating at least one report that provides quantitative metrics related to the patient’s current health status and their risks for future health outcome.” Ex1005, [0014]. Specifically, Maier discloses that “the computer-implemented method 100 comprises... receiving at least a first medical image of a patient... [and] analyzing the image data of interest by comparing it to comparison image data, as shown at 106,” Ex1005, [0027], where “step 106 may comprise a direct on-the-fly comparison of the image data of interest to comparison image data” and “[t]his comparison may comprise any type of algorithm that tests for similarities between the image data of interest and the comparison image data, including unsupervised machine learning algorithms of all

varieties,” Ex1005, [0032]. This constitutes automatic analysis of the image(s) by a machine learning algorithm.

162. Although I do not believe that the Patent Owner has given the claim term “machine learning algorithm” a definition that is different than its plain and ordinary meaning, I have noted that the Patent states that “approaches, based on machine learning techniques (e.g., artificial neural networks (ANNs); e.g., convolutional neural networks (CNNs)) may also be used.” Ex1001 at 26:63-65. Maier likewise discloses that “[t]he on-the-fly image comparison may be... unconstrained (e.g., neural networks and other unsupervised machine-learning algorithms).” Ex1005, [0023].

163. Accordingly, it is my opinion that Maier discloses limitation 1(d).

f) Limitation 1(e): “(iv) generate a radiologist report for the particular patient according to the one or more medical images for the patient,”

164. As previously discussed, Meier discloses “systems and methods for automatically analyzing a patient’s one or more medical images and creating at least one report that provides quantitative metrics related to the patient’s current health status and their risks for future health outcome.” Ex1005, [0014]. More specifically, Maier discloses that “[m]ultiple reports may be created for the same patient from the same medical images, wherein each of the multiple reports may be differently tailored for different types of intended users of the reports” and “a

‘user’ may be, for example, a patient, a patient’s guardian or caregiver, a primary care physician, [or] ...a radiologist.” Ex1005, [0014] (emphasis added). Even more specifically, Maier discloses that the system and method “may write the quantitative health status and/or risk metrics to a file according to a data file format that has been previously defined” where “[t]his data file format may be previously defined by the input requirements of a voice recognition software application, which converts the speech of a radiologist to text and then combines the text with the contents of the data file to create a user-readable report for review by a user.” Ex1005, [0036] (emphasis added). Thus, Maier discloses the generation of a radiologist report in addition to other user reports. In addition to these disclosures, a radiologist’s involvement would have been expected since Maier discloses analyzing an image by “segmenting the image into data that is of interest and image data that is not of interest,” Ex1005, [0027], *e.g.*, by “creating a mask of ones and zeros corresponding to... voxels with CT density less than a threshold value,” Ex1005, [0038], and such segmentations (especially “automatic” segmentations) as well as acquired imagery must be reviewed by a radiologist to satisfy a customary standard of care. Thus, Maier would have been understood by a POSITA to disclose the generation of a radiologist report for the particular patient according to the patient’s medical image(s).

165. Accordingly, it is my opinion that Maier discloses limitation 1(e).

- g) Limitation 1(f): “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”**

166. Maier discloses that “[t]he medical image(s) or medical image data for the patient’s image(s) as well as the comparison image(s) may be from a variety of different sources, including, but not limited to magnetic resonance imaging (MRI), computed tomography (CT), two-dimensional planar x-ray (either plain film converted to digital, or digital x-ray images), X-ray mammography, positron emission tomography (PET), ultrasound (US), or single-photon emission computed tomography (SPECT).” Ex1005, [0015] (emphasis added). Maier further discloses that “[t]he patient’s image(s) as well as the comparison image(s) may be anatomical images in nature, or they may be functional images that provide information about the tissue physiology or functioning.” Ex1005, [0016]. However, Maier does not expressly disclose a composite of an anatomical, *e.g.*, CT, and functional, *e.g.*, PET or SPECT, image.

167. Maier discloses systems and methods for analyzing medical images and creating a report that are generally applicable to medical imaging tasks. Ex1005, title, [0002]. Maier expressly teaches that its systems and methods “are not limited to a particular disease, pathology, or type of treatment.” Ex1005, [0018]. Maier also expressly teaches that “the presence or non-presence of

important imaging biomarkers for cancer” (such as physiological metrics derived from functional imaging exams, Ex1005, [0031]) “drives clinical decision-making in a more or less aggressive direction depending on the individual patient’s likelihood of having cancer.” Ex1005, [0005]. Indeed, Maier’s report can help “facilitate[e] the physician’s quick assessment” of the patient’s health and “plan an interventional procedure.” Ex1005, [0026]. In that regard, Huang discloses that “[p]ositron emission tomography (PET) using fluorine-18 deoxyglucose (FDG) is a nuclear medicine medical whole-body imaging technique that produces a three dimensional image of functional processes in the body” where “[t]umors in FDG-PET appear as ‘hot-spots’ due to increased FDG uptake.” Ex1006, [0003]. Huang explains that, in 2006 (prior to Maier and Huang), “tumor segmentation in PET is performed manually by the physician or semi-automatically” where “[u]n-supervised object segmentation involves a trade-off between sensitivity and specificity” and “[i]n cancer imaging, a second modality such as CT [] often provides better resolution and object delineation” but “the difference in attenuation between tumor and healthy tissue in CT is low and segmentation algorithms often fail when used on CT data alone.” Ex1006, [0013]. Thus, Huang discloses and teaches an invention “directed to [a] learning-based framework for whole-body landmark detection, segmentation, and change quantification in single-mode and multi-mode medical images,” Ex1006, [0002] (emphasis added), and constitutes

analogous prior art.

168. In particular, Huang suggests that “[a] new technology, PET/CT, combines the functional imaging PET with an anatomical imaging computed tomography (CT), and allows the acquisition of clinical quality PET and CT scans, accurately aligned, from a single imaging device.” Ex1006, [0011] (emphasis added). Huang further explains that “[o]n a fused PET/CT image, abnormalities that are seen on PET can be located, and possibly also confirmed, on CT, and this enables the interpreting physician to make a more informed decision about whether the hot-spot on PET is indeed an abnormality, and if so, where the abnormality is located anatomically.” Ex1006, [0011] (emphasis added). Such “fused PET/CT image[s]” are one example of the claim-recited “composite” image(s), however Huang also discloses use with “other imaging modalities such as PET/MR, PET/CT/MR, SPECT, SPECT/CT, SPECT/CT/MR, etc.” Ex1006, [0075]. *See also* Ex1006, [0130]. Therefore, in my opinion, Maier and Huang provide an express teaching, suggestion, or motivation for a POSITA to combine the reference to improve the physician’s decision-making.

169. It is my opinion that a POSITA would have been motivated, based on the express teachings of Maier and Huang, to modify Maier’s systems and methods to include the multi-mode medical imaging approach of Huang, *e.g.*, the fused (or “composite”) PET/CT or SPECT/CT imaging approach disclosed in Huang, for

imaging, analysis, and reporting as applied to cancerous lesions or tumors. As quoted above, Huang teaches that such fusion or combination allows the involved tissue to be anatomically located on CT so that a PET result can be evaluated in context. Indeed, Huang teaches or otherwise explains that “[s]ince both normal physiology, such as heart, kidney, or bladder, and pathology, such as tumor or inflammations, produce hot-spots, one issue... is to separate normal hot-spots from pathological hot-spots, an issue that requires the understanding of whole-body context.” Ex1006, [0098]. These provide an express teaching, suggestion, or motivation to use composite anatomical and functional imaging modalities as otherwise described in Huang for determining the presence of imaging biomarkers for cancer and a patient’s likelihood of having cancer.

170. Besides the express motivation included above, the combination of imaging modalities as described would merely constitute combining existing prior art elements according to known methods to yield predictable results. Specifically, Maier discloses each of the imaging modalities individually, Huang discloses PET/CT imaging from a single imaging device, and Huang also discloses registration and storage of PET/CT, SPECT/CT, and other multi-modal images for “joint” use. Ex1005, [0015]; Ex1006, [0011], [0130] (“In multi-modal images such as PET/CT, PET/MRI, or SPECT/CT, the functional and structure images are registered by the imaging hardware in a global coordinate system” and “[t]hus,

training and detection steps can be performed on the two image modalities jointly” and explaining that “PET detection results and CT detection results are fused to prune false detections”). A POSITA would have recognized that Huang’s PET/CT image would be a compatible “instrumentation source” in Maier. Ex1005, [0015]; Ex1006, [0011]. Acquiring a “composite” PET/CT or SPECT/CT image would merely have required use of Huang’s referenced “single imaging device,” or pre-registration and reception of multi-modal imagery, *see* Ex1006, [0011], [0130], with the acquired composite image then being stored and accessed as described in Maier. In my opinion, Huang’s fused PET/CT image operates the same way in combination with Maier as it does separately. Like Maier, Huang segments the data of its PET/CT image to isolate and analyze the data of interest. Ex1005, Fig. 1; Ex1006, Fig. 6, [0130]. Both Maier and Huang operate on the fused PET/CT image. See Ex1006, [0130] (“training and detection steps can be performed on the two image modalities jointly”). Therefore, a POSITA would have found this to have been an obvious and straightforward modification according to Maier’s and Huang’s disclosures of known devices and methods.

171. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in combining Maier and Huang. In addition to Maier and Huang both being within the same field of medical image processing, both describe the implementation of similar image processing tasks, including

image acquisition, storage, access, and segmentation for evaluation of pre-cancerous or cancerous lesions and tumors in particular organs. Therefore, Huang's multi-mode imaging techniques would have been readily applicable to, and easily implemented with, Maier's systems and methods. In addition, Huang expressly states that "[r]etrospective studies performed with PET/CT prototypes showed considerable promise, particularly in the areas of disease staging and therapy planning and monitoring." Ex1006, [0011].

172. Accordingly, it is my opinion that Maier in view of Huang discloses limitation 1(f).

h) Limitation 1(g): "and following administration to the patient of an imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide,"

173. As previously discussed in Section IX.A.1.g), Maier expressly teaches analysis for "the presence or non-presence of important imaging biomarkers for cancer" using "physiological metrics derived from functional imaging exams," Ex1005, [0005], and Huang discloses the use of fluorine-18 deoxyglucose (FDG), where cancerous lesions or tumors "in FDG-PET appear as 'hot-spots' due to increased FDG uptake," Ex1006, [0003]. However, while FDG is a radiolabeled imaging agent, neither Maier nor Huang disclose a radiolabeled PSMA-binding agent.

174. Armor discloses “technology [] generally related to the imaging of prostate cancer (PCa) tissue to differentiate cancerous tissue from normal tissue or benign prostate tissue,” and, particularly, radiolabeled compounds “that selectively bind[] to prostate specific membrane antigen (PSMA).” Ex1007, [0002]. Armor reports that “[a] variety of radionuclides are known to be useful for radioimaging,” Ex1007, [0007], as well as that “small molecule compounds that selectively bind PSMA and carry an appropriate radionuclide... can be used to selectively treat prostate cancer,” Ex1007, [0078]. Armor most specifically discloses that “^{99m}Tc-labeled anti-PSMA inhibitors, Formula (1) and Formula (2) compounds (^{99m}Tc-MIP-1404 and ^{99m}Tc-MIP-1405 respectively)... are highly specific radiolabeled agents for imaging PCa” that “selectively bind[] to prostate-specific membrane antigen (PSMA),” Ex1007, [0056], [0064], and that “[i]maging of the subject following administration of the gamma-emitting transition metal complex conjugated to a targeting moiety can be performed using... single-photon emission computed tomography combined with conventional computed tomography (SPECT/CT),” Ex1007, [0009], but acknowledges that other clinical drugs incorporate other radionuclides imaged by other means, Ex1007, [0003]. I have also noted that the background of the Patent admits that, in April 2015, specific examples of other radiolabeled PSMA-binding agents, such as [¹⁸F]DCFPyL, imaged by Positron Emission Tomography (PET), were known. Ex1001, 1:65-2:6.

These provide an express teaching, suggestion, or motivation to use radiolabeled anti-PSMA inhibitors (binding agents) in the multi-mode imaging of the Maier-Huang combination described above.

175. Besides the express motivation included above, the combination of imaging modalities and radiolabeled imaging agent as described would constitute a simple substitution of one known element for another to obtain predictable results. As previously discussed, Maier teaches that “suitable tissue types include lung, prostate, breast...” and numerous others, Ex1005, [0017], and Huang teaches that “[t]umors in FDG-PET appear as ‘hot-spots’ due to increased FDG uptake,” Ex1006, [0003]. Claim limitation 1(g) substitutes FDG with a radiolabeled PSMA-binding agent. Armor teaches PSMA-binding agents that are compatible with the PET, SPECT, and CT imaging techniques discussed in Maier and Huang. Ex1007, [0002]-[0004], [0006]-[0007]. Therefore, in applications where the suitable tissue type or tissue of interest is specifically the prostate and prostate-associated cancerous lesions, tumors, and metastases, a POSITA would have found substituting a radiolabeled anti-PSMA inhibitor (PSMA-binding agent) for a radiolabeled metabolic agent such as FDG, and selecting a suitable functional/anatomical imaging modality pair, to have been an obvious and straightforward modification according to Armor’s disclosure of such imaging agents and methods of use.

176. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in combining Maier and Huang and Armor. In addition to each being within the same field of medical image processing, each describes functional imaging after administration of physiological imaging agent, variously described as a contrast agent, a metabolic agent, or a PSMA-binding agent. Furthermore, Huang and Armor both describe the use of functional nuclear medicine imaging in combination with CT in the form of PET/CT, SPECT/CT, and/or other “composite” imaging modalities. Therefore, Armor’s PSMA-binding imaging agents would have been readily applicable to, and easily implemented with, the Maier-Huang combination described above. In addition, Armor expressly states that “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].

177. Accordingly, it is my opinion that the Maier-Huang combination in view of Armor (*i.e.*, Maier in view of Huang and Armor) discloses limitation 1(g).

- i) **Limitation 1(h): “wherein the instructions cause the processor to automatically analyze the composite image by: (a) 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”**

178. Maier discloses that the computer implemented method may involve

“segmenting the image into data that is of interest and image data that is not of interest.” Ex1005, [0027]. Specifically, Maier discloses that “[s]egmenting the image into image data that is of interest and image data that is not of interest at step 104 may include distinguishing image data that is relevant for a particular analysis, diagnosis, prognosis, assessment, treatment planning, treatment follow-up, or other determination,” and provides a specific example of “segmenting lung parenchyma from the background anatomy and discarding the background anatomy for the purpose of calculating the quantitative status and risk metrics.” Ex1005, [0028]. For example, Maier teaches that “a computer-implemented algorithm of the present disclosure may measure, automatically and without any user input or intervention, the relative volume of low-density tissue in the upper lobes of the lung, and calculate a risk metric [for lung cancer].” Ex1005, [0021].

179. To the extent that Maier does not itself expressly disclose analyzing a composite image and/or using the composite image to identify the recited 3D boundary within the nuclear medicine image, Huang discloses using trained discriminative classifiers and detectors “in CT, MRI, PET, PET/CT or other types of images” for identifying “organs, tissue regions, or anatomical sections such as kidney, liver, heart, bladder, brain, lung, ...etc.,” Ex1006, [0072] (emphasis added), and teaches that whole-body context interpretation “enables the computer to understand on which organs or tissue regions each hot-spot is located, hence

making it possible to separate normal hot-spots from pathological ones,” Ex1006, [0099]. Huang further teaches that “[t]he basic idea is to first detect normal physiological organs or regions that often induce high FDG uptake, such as the heart, kidney bladder, and brain,” then segment hotspots, and “[t]hen a segmented hot-spot which is considered a hot-spot due to normal physiological uptake is suppressed or compensated for.” Ex1006, [0099]. Huang yet further teaches that “because FDG uptakes by different organs or tissues have large variations.... organ-specific or region-specific thresholding is very attractive,” and discloses or suggests that “[u]sing a whole-body context... one can first detect, segment and separate organs or regions that have different ranges in SUV values, then apply organ- or region-specific thresholding,” where “[f]or instance, one can first detect and segment the lung, the liver, and other organs... [t]hen a threshold is chosen for the lung... [and a] different threshold can be chosen for the liver” Ex1006, [0114]. These provide an express teaching, suggestion, or motivation use the PET/CT, SPECT/CT, or other multi-modality “composite” images to identify one or more 3D boundaries, *e.g.*, those of organs, within the nuclear medicine, *e.g.*, PET or SPECT, image component, to produce improved organ-specific identification.

180. Huang also discloses that in registered multi-modal images such as PET/CT, “training and detection steps can be performed on the two image modalities jointly” where in a first scenario, separate PET and CT classifiers are

used and, at run-time, the PET classifier is applied to the PET volume and the CT classifier is applied to the CT volume and “[t]hen the PET detection results and CT detection results are fused to prune false detections.” Ex1006, [0130]. In a second scenario, “one single classifier” trained on PET/CT volumes is used and “[d]uring detection... the trained classifier works on the ‘joint’ features.” Ex1006, [0130]. Such classifiers are trained machine learning algorithms, *i.e.*, the product of “a general learning-based framework” for the detection of the 3D boundaries of such organs, or tissue regions, in such images, Ex1006, [0072], and these provide an express teaching, suggestion, or motivation to use Huang’s disclosed classifiers and detectors in “composite” PET/CT and/or SPECT/CT images to identify 3D boundaries of organs and the like for use in the nuclear medicine image when determining the presence of imaging biomarkers for cancer and a patient’s likelihood of having cancer.

181. Besides the express motivation described above, the combination of multi-mode imaging with organ segmentation, *i.e.*, the identification of 3D boundaries in the combined imaging modalities, would constitute the use of a known technique to improve similar devices, methods, or products in the same way. Maier discloses a prior art automated medical image processing system that may include “segmenting the at least one medical image into voxels corresponding to a tissue of interest and voxels not of interest” and identifies such tissues as

including, among others, individual organs. Ex1005, [0008], [0017]. Maier also expressly teaches that “suitable tissue types include lung, prostate, breast...” and numerous others, Ex1005, [0017], and that the “image data of interest” may be “physiological metrics derived from functional imaging exams,” Ex1005, [0031]. A POSITA would understand that claim 1(h) improves upon Maier’s system by introducing composite medical imaging, wherein 3D boundaries of tissue, such as organs, are identified. However, this improvement is disclosed by Huang, which uses trained discriminative classifiers and detectors “in CT, MRI, PET, PET/CT or other types of images” for identifying “organs, tissue regions, or anatomical sections such as kidney, liver, heart, bladder, brain, lung, ...etc.,” Ex1006, [0072], and teaches (similarly to the physician interpretation mentioned in Ex1006, [0011]) that whole-body context interpretation “enables the computer to understand on which organs or tissue regions each hot-spot is located, hence making it possible to separate normal hot-spots from pathological ones,” Ex1006, [0099]. Segmenting or otherwise identifying 3D boundaries in registered PET/CT or SPECT/CT imagery could have been implemented via the systems and methods described by Huang, and, in particular, the disclosed, trained “classifiers and detectors” expressly taught by Huang. *See* Ex1006, [0130]. Therefore, and for the same rationales discussed above in Section IX.A.1.g), a POSITA would have found implementing segmentation from a “composite” image to “geographically identify

a 3D boundary” for a region, such as an organ, within the nuclear medicine image to have been an obvious and straightforward modification according to Huang’s disclosure of such functions and methods.

182. Furthermore, it is my opinion that combining multi-mode imaging with organ segmentation would merely constitute combining existing prior art elements according to known methods to yield predictable results. As discussed above, Maier and Huang combined disclose this claim limitation. In my opinion, Huang’s analysis of a composite medical image would perform the same function in Maier’s system as it does separately. Both Maier and Huang separate the regions and data of interest from the background anatomy. Ex1005, [0028]; Ex1006, [0114]. Therefore, a POSITA could have predictably added Huang to Maier to arrive at this claim limitation.

183. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in combining Maier and Huang in this respect. In addition to each being within the same field of medical image processing, each describes applying image segmentation to identify organs in connection with the analysis of the imagery and generation of reports. Ex1005, [0028], [0036]; Ex1006, [0072], [0078]. Huang expressly states that “[r]etrospective studies performed with PET/CT prototypes showed considerable promise, particularly in the areas of disease staging and therapy planning and monitoring,” Ex1006,

[0011], and, furthermore in connection with a system implementing automated identification of pathological hotspots, that “[a]n implemented system... 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... PET/CT images, and other imaging modalities such as PET/MR, PET/CT/MR, SPECT, SPECT/CT, SPECT/CT/MR, etc.” Ex1006, [0073]-[0075].

184. Accordingly, it is my opinion that Maier in view of Huang and Armor discloses limitation 1(h).

- j) Limitation 1(i): “(b) 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,”**

185. As previously discussed in Section IX.A.1.i), Maier discloses “segmenting the image into data that is of interest and image data that is not of interest,” Ex1005, [0027], Fig. 1 (step 104), such as “segmenting lung parenchyma from the background anatomy and discarding the background anatomy for the purpose of calculating the quantitative status and risk metrics,” Ex1005, [0028]. *See also* Fig. 1 (“Step 108 calculating personalized quantitative health status and risk metrics for the patient.”). This constitutes a computation, using identified 3D boundary(ies), *e.g.*, of an organ such as the lungs, of one or more risk indices. Maier further discloses that the computer-implemented method includes “using the

comparison to calculate personalized quantitative health status and risk metrics for the patient; and creating a report tailored for the intended user of the report to communicate the patient's personalized quantitative health status and risk metrics....” where “the quantitative health status and risk metrics may be related to one or any combination of: ...emphysema, lung cancer, decreased lung function,” and others. Ex1005, [0007] (emphasis added). In particular, Maier explains that “step 108 may comprise calculating one or more health status metrics that are simply measured anatomical or physiological quantities.... In other embodiments, the health status metrics may be more complex calculations comparing a patient's data to a reference population, or identifying actual presence of burden of disease.” Ex1005, [0035]. The report produced by Maier can also include “quantitative measures of the amount of likely [disease] present (e.g., statistics for the amount of likely disease present in each individual [region]).” Ex1005, [0026], Fig. 3 (“Lung Density... 30% Damaged”). All of these are consistent with any of the constructions of a “risk index” proposed in Section VII.B above. Specifically, (1) “numeric value(s),” such as physiologic uptake of an agent, burden of disease metrics, or amount of disease, “indicative of cancer state and/or progression in the patient within one or more regions,” (2) “value(s),” such as the aforementioned, “indicative of cancer state and/or progression in the patient within one or more regions,” and (3) “value(s) indicative of cancer state and/or progression in the

patient within one or more regions, including but not limited to uptake values, tumor volumes, and other values derived therefrom,” such as the aforementioned and/or Maier’s “actual presence of burden of disease,” *e.g.*, the percent of the lung that is damaged.

186. To the extent that Maier does not expressly disclose analyzing a composite image and/or using the nuclear medicine portion of a composite image to compute a risk index, Huang teaches those functions. In addition to the portions of Huang cited in connection with the previous limitations, Huang discloses an exemplary embodiment that is read upon by limitation 1(i), where:

In PET images, because FDG uptakes by different organs or tissues have large variations, a global thresholding on the converted SUV volumes often fails to provide good hot-spot candidates. For example, tumors in the lung may have lower SUV values than normal tissue in the liver. Hence to automatically generate good hot-spot candidates, organ-specific or region-specific thresholding is very attractive. Using a whole-body context according to an embodiment of the invention, one can first detect, segment and separate organs or regions that have different ranges in SUV values, then apply organ- or region-specific thresholding. For instance, one can first detect and segment the lung, the liver, and other organs, or detect and separate the thorax and abdomen regions. Then a threshold is chosen for the lung, such as the mean SUV value in the lung region, and hot-spot candidates can be generated in the lung which have SUV values above the threshold. A different threshold can be chosen for the liver, such as the mean SUV value in the liver, and hot-spot candidates can be generated in the liver.

Ex1006, [0114] (emphasis added). *See also* [0098]-[0099] (explaining that Huang’s “learning-based method... can be used to provide [an] understanding” of

how “to separate normal hot-spots from pathological hot-spots...”). Such a whole-body context, as described in Ex1006, [0072]-[0075], [0098]-[0099], and [0130] as previously discussed, is provided for and applied by the Maier-Huang combination as set forth in Sections IX.A.1.g) and IX.A.1.i) above, and the rationales expressed in the context of those limitations apply equally here with respect to the consequent result. Those described SUV values (above an SUV threshold) are values of, or inputs to more complex indicators of, “cancer state and/or progression in the patient within one or more regions,” *see* Ex1006, [0009] (“Most approaches to hot-spot segmentation and the quantitative measurement of tumor volume use the standard uptake value (SUV)... [and] [p]hysicians and radiologists have used this measure for normalization across time points for different patients, and the maximum SUV values are used for grading tumors”), and those statements provide an express teaching, suggestion, or motivation to apply the functions provided by the prior-addressed limitations to the calculation and identification of pathological SUV value regions (which are pathological with respect to identified organ boundaries) within a nuclear medicine image of a “composite” image, and subsequent calculation of one or more risk indices, such as grading.

187. Armor also discloses analyzing a composite image and/or using the nuclear medicine portion of a composite image to compute a risk index. Armor is directed to “Methods of Using SPECT/CT Analysis for Staging Cancer,” Ex1007,

cover, and discloses that “[t]he present inventors have shown that the uptake levels of both compounds directly correspond with the Gleason score,” Ex1007, [0064], where “[t]he ratio of tumor uptake to background (T/B ratio), moreover, was observed to directly correlate with the Gleason score” and “[t]his correlation provides a rationale for replacing conventional prostate biopsies for determination of Gleason scores, with the method provided herein for determination of prostate cancer and the extent of the disease,” Ex1007, [0066]. These provide an express teaching, suggestion, or motivation to apply the functions provided by the Maier-Huang-Armor combination to the calculation and identification of pathological SUV value regions (which are pathological with respect to identified organ boundaries) within the nuclear medicine image of a “composite” image, and subsequent calculation of one or more risk indices, such as grading or Gleason score.

188. Computing such SUV and other values and, in particular, grading or Gleason score, constitutes computation of a risk index under any of the constructions proposed in Section VII.B above in that uptake values (*e.g.*, SUV values), uptake ratios over background (T/B ratio), and, especially, Gleason score, are all numeric or other values indicative “of cancer state and/or progression in the patient,” and SUV peak, standing alone, is alleged by the Patent Owner to constitute such an index. *See* Ex1014, ¶93.

189. Besides the express motivation(s) included above, the combination of multi-modal imaging, a radiolabeled PSMA-selective imaging agent, and application to the calculation of a risk metric for, *e.g.*, prostate cancer as described, would constitute a simple substitution of one known element for another to obtain predictable results. As discussed previously, Maier teaches the use of functional imaging and that “suitable tissue types include lung, prostate, breast...” and numerous others, Ex1005, [0017], and Armor teaches that uptake of radiolabeled anti-PSMA inhibitors (PSMA-binding agents) is selective for prostate cancer, Ex1007, [0006]. Therefore, in applications where the suitable tissue type or tissue of interest is specifically the prostate and prostate-associated cancerous lesions, tumors, and metastases, a POSITA would have found substituting a radiolabeled anti-PSMA inhibitor (PSMA binding agent) for a radiolabeled metabolic agent such as FDG and calculating uptake values (*e.g.*, SUV values), uptake ratios over background (T/B ratio), and Gleason score to have been an obvious and straightforward modification according to Armor’s disclosure of the diagnostic imaging agents, methods of use, and attendant calculations for radiologist and physician or other user reports.

190. It is my opinion that a POSITA would have had a reasonable expectation of success in combining Maier and Huang and Armor in this respect for the same reasons explained in Sections IX.A.1.h) and IX.A.1.i), since the

resultant risk indices were merely the application of known mathematical calculations and correlations to the PSMA-binding-agent-measured uptake or SUV values (above a threshold) within an identified 3D boundary applied to a nuclear medicine image.

191. Accordingly, it is my opinion that Maier in view of Huang and Armor discloses limitation 1(i).

k) Limitation 1(j): “and wherein the system is a cloud-based system.”

192. It is my opinion that Maier discloses this limitation. As discussed in Section IX.A.1.a), Meier discloses that the systems and methods “may be integral portions of a single computer or server or may be connected parts of a computer network.... such as the Internet,” Ex1005, [0047], where “any portion thereof may be a personal computer (e.g., desktop or laptop), tablet computer, mobile device (e.g., personal digital assistant (PDA) or smart phone), server (e.g., blade server or rack server)... or any other suitable device or combination of devices,” Ex1005, [0045]. In addition Maier further discloses that “[a]ny commercial or freeware web browser or other application capable of retrieving content from a network and displaying pages or screens may be used,” Ex1005, [0046] (emphasis added), and that “[t]he report may be uploaded by the method to a cloud storage bank for retrieval by a user,” Ex1005, [0037] (emphasis added). These constitute the

components of, and applications for accessing, a cloud-based system.

193. Although I do not believe that the Patent Owner has given the claim term “cloud-based” a definition that is different than its plain and ordinary meaning, I have noted that the Patent purports to display “an exemplary cloud computing environment” in Fig. 7, shown below, which consists simply of various “resource providers” and “computing devices” interconnected through a “network.” Maier, as detailed above, likewise discloses various resources that are provided as “connected parts of a computer network.... such as the Internet.” Therefore, consistent with the Patent disclosure, I understand Maier to disclose that its systems and methods may be provided as a “cloud-based,” network-connected system.

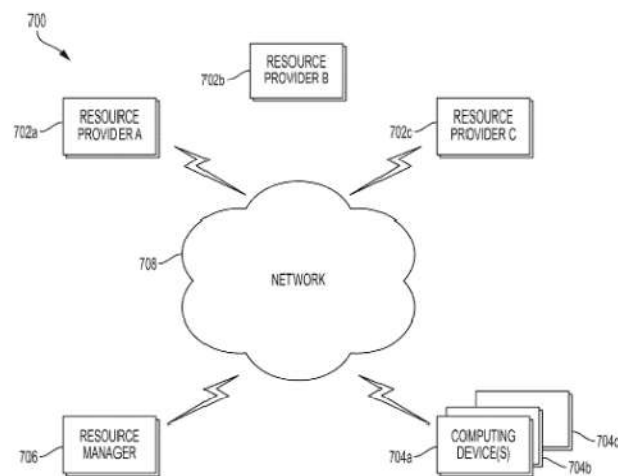


FIG. 7

194. Because the combined references disclose and render obvious every

limitation of claim 1, it is my opinion that Maier in view of Huang and Armor render claim 1 unpatentable as obvious.

2. **Claim 2: “The system of claim 1, wherein the plurality of medical images in the database comprise a series of medical images of a first patient taken over time, and wherein the instructions cause the processor to determine a value of at least a first risk index for each medical image of the series, thereby tracking determined values of at least the first risk index for the first patient over time.”**

195. Claim 2 depends from claim 1, which I explained above in Section IX.A.1 is rendered obvious by Maier in view of Huang and Armor. It is my opinion that at least Huang and Armor disclose the additional limitation of claim 2.

196. Maier discloses that “the computer-implemented method 100 comprises... receiving at least a first medical image of a patient... [and] analyzing the image data of interest by comparing it to comparison image data, as shown at 106,” Ex1005, [0027], where “[t]he algorithm may additionally or alternatively comprise comparing the patient’s image(s) to the patient’s own image(s), such as previously obtained image(s) for the patient,” Ex1005, [0024] (emphasis added). *See also* Ex1005, [0018] (use for base-line assessments and treatment follow-up). However, Maier does not expressly disclose calculating a risk index for each image, thereby tracking risk index values over time.

197. In connection with the Maier-Huang-Armor combination, Huang discloses that “[t]he assessment of tumor size and volume is important for patient

prognosis as well as for evaluation of treatment effectiveness and follow up,” Ex1006, [0003], and provides systems and methods “for quantifying changes across sub-volumes of digitized images,” where such a method includes “providing a plurality of new digitized images, said images representing a same patient at different time points, ...and quantifying changes in the sub-volume of interest over the different images of one or more properties including intensity, volume, shape, topology, location, and texture,” Ex1006, [0022] (emphasis added). Huang then expressly teaches that “[a]t step 65, a change quantification of one or more properties such as intensity, volume, shape, topology, location, and texture is applied to quantify changes for the hot-spot based on the segmentation results and produce reports,” where “[p]ossible change quantification mechanisms include: (1) Grading of the hot-spot (tumor) at each time point based on the maximum SUV values, and comparing the change in grading over time; [and] (2) Comparing the segmented hot-spot volumes over time, e.g., by quantifying the change in tumor volume size...” Ex1006, [0078] (emphasis added). In my opinion, these disclosures constitute disclosures of calculating a “risk index” as used in the Patent. *See* VII.B

198. Armor also discloses that “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]

(emphasis added), as well as a method for monitoring a status of prostate cancer in a human subject, Ex1007, [0019], a method of monitoring the efficacy of prostate cancer treatment, Ex1007, [0287], and a method of evaluating a human subject suspected of harboring a prostate tumor that is repeated periodically, Ex1007, [0189], [0206], in addition to the calculation of a risk index such as a Gleason score as discussed in IX.A.1.j) above. In my opinion, these disclosures also constitute disclosures of calculating a “risk index” as used in the Patent.

199. Both of these provide an express teaching, suggestion, or motivation to apply the functions provided by the system of claim 1 (the calculation and identification of pathological SUV value regions within the nuclear medicine image of a “composite” image to generate a risk index) to the calculation of risk indices (and unrecited, but attendant, objective of providing such information in a report as otherwise disclosed by Maier) for a series of images acquired over time so as to track values of the risk index over time.

200. Besides the express motivation included above, the calculation of risk indices at past and current points in time, rather than a change since one past point in time, would constitute the use of a known technique to improve similar devices, methods, or products in the same way. A POSITA would have recognized that claim 16 improves upon Maier to the extent that Maier only measures the change in risk indices compared to one point in time. However, as discussed for parent

claim 1 in Section IX.A.1.j), Maier discloses calculating and reporting “the patient's personalized quantitative health status and risk metrics...,” *see* Ex1005, [0007], [0026], [0035], including changes therein. Huang teaches calculating and reporting values at each point in time (as well as changes therein), Ex1006, [0078], thus providing greater context to the changes occurring therebetween, and Armor teaches evaluating the extent of disease progression periodically, including calculation of a Gleason score, thus providing a basis for discriminating low grade disease from higher grade disease and for selecting a therapeutic protocol, Ex1007, [0097], [0139]. Such calculations could readily have been implemented by conducting Maier’s comparisons, potentially for more than one past point in time, and reporting the values themselves in addition to the change occurring therebetween. Therefore, a POSITA would have found implementing such calculations to have been an obvious and straightforward modification according to Huang’s and Armor’s respective disclosures of such calculations and reports.

201. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in further combining Maier, Huang and Armor in the Maier-Huang-Armor combination for the reporting of such metrics over time. Such calculations were already required to produce Maier’s disclosed reports of change, and would merely be potentially repeated for additional past medical images and points in time in a series of more than two points in time. Therefore,

such calculations would have been readily applicable to, and easily implemented with, Maier's systems and methods.

202. Because the references disclose and render obvious every limitation of claim 2, including the limitations of claim 1 from which claim 2 depends, it is my opinion that Maier in view of Huang and Armor render claim 2 unpatentable as obvious.

3. **Claim 3: "The system of claim 2, wherein the instructions cause the processor to correlate the determined values of the first risk index with one or more prognostic values, thereby providing an objective metric of cancer state, progression, outlook, or treatment efficacy."**

203. Claim 3 depends from claim 2, which I explained above in Section IX.A.2 is rendered obvious by Maier in view of Huang and Armor. It is my opinion that the combination also discloses the additional limitation of claim 3.

204. As previously discussed in Sections IX.A.1.j) and IX.A.2, Armor discloses that "[t]he ratio of tumor uptake to background (T/B ratio), moreover, was observed to directly correlate with the Gleason score," Ex1007, [0066]. Armor further discloses that "Gleason score [] is used as a prognostic marker for the aggressiveness of prostate cancer," Ex1007, [0064] (emphasis added), and that "[u]sing [a] correlation between Gleason score and the stage of a prostate cancer condition and the correlation between the T/B ratio and Gleason score it will be possible to evaluate the status of a patient with prostate cancer condition," Ex1007,

[0139]. This constitutes a correlation of the determined values of a risk index (*e.g.*, T/B ratio) with a prognostic value (*e.g.*, Gleason score) as at least an objective metric of cancer state and progression.

205. Because the references disclose and render obvious every limitation of claim 3, including the limitations of claims 2 and 1 from which claim 3 depends, it is my opinion that Maier in view of Huang and Armor render claim 3 unpatentable as obvious.

4. Claim 6: “The system of claim 1, wherein the nuclear medicine image is a PET scan.”

206. Claim 6 depends from independent claim 1, which I explained above in Section IX.A.1 is rendered obvious by Maier in view of Huang and Armor. It is my opinion that the combination also discloses the additional limitation of claim 6.

207. As previously discussed in Section IX.A.1.g), Huang suggests that “[a] new technology, PET/CT, combines the functional imaging PET with an anatomical imaging computed tomography (CT), and allows the acquisition of clinical quality PET and CT scans, accurately aligned, from a single imaging device.” Ex1006, [0011] (emphasis added). Huang further explains that “[o]n a fused PET/CT image, abnormalities that are seen on PET can be located, and possibly also confirmed, on CT, and this enables the interpreting physician to make a more informed decision about whether the hot-spot on PET is indeed an

abnormality, and if so, where the abnormality is located anatomically.” Ex1006, [0011] (emphasis added). Via this and the other portions of Huang discussed in Section IX.A.1.g), Huang provides (1) an express teaching, suggestion, or motivation to combine the imaging modalities as described in Huang, (2) a rationale for combining existing prior art elements (in this context, PET and CT imaging) according to known methods to yield predictable results, and (3) a rationale for the use of a known technique (composite nuclear medicine and anatomical imaging, in this context, PET/CT imaging) to improve Maier’s similar devices, methods, and products in the same way. Furthermore, as discussed in Section IX.A.1.h), Armor teaches or otherwise references radiolabeled compounds “that selectively bind[] to prostate specific membrane antigen (PSMA),” where “[a] variety of radionuclides are known to be useful for radioimaging,” Ex1007, [0007], and “small molecule compounds that selectively bind PSMA and carry an appropriate radionuclide... can be used to selectively treat prostate cancer,” Ex1007, [0002], [0007], and [0078], respectively. I have also noted that the background of the Patent admits that, in April 2015, specific examples of such compounds were known, such as [¹⁸F]DCFPyL. Ex1001, 1:65-2:6.

208. Because the references disclose and render obvious every limitation of claim 6, including the limitations of claim 1 from which claim 6 depends, it is my opinion that Maier in view of Huang and Armor render claim 6 unpatentable as obvious.

5. Claim 7: “The system of claim 6, wherein the radionuclide is a radioisotope of a halogen.”

209. Claim 7 depends from claim 6, which I explained above in Section IX.A.4 is rendered obvious by Maier in view of Huang and Armor. It is my opinion that Armor also discloses the additional limitation of claim 7.

210. As previously discussed in Sections IX.A.4 and IX.A.1.h), while Armor more specifically discusses the compounds and performance of Formulas (1) and (2), Armor discloses that “[a] variety of radionuclides are known to be useful for radioimaging...,” Ex1007, [0007] (emphasis added), and that other clinical drugs incorporate other radionuclides imaged by other means, Ex1007, [0003]. Also, as previously discussed in Section IX.A.4, the Patent admits to the use of [¹⁸F]DCFPyL for PET imaging in the prior art. Ex1001, 1:65-2:6. These provide an express teaching, suggestion, or motivation to use an anti-PSMA inhibitor (binding agent) radiolabeled with a radioisotope of a halogen (*e.g.*, ¹⁸F) in the multi-mode imaging of the Maier-Huang combination as otherwise described above.

211. In my opinion, combining Maier and Huang with Armor’s anti-PSMA inhibitor merely constitutes combining prior art elements according to known methods to yield predictable results. Maier and Huang, with Armor’s radionuclide that is a radioisotope of a halogen, discloses every limitation of claim 7. A POSITA could have easily combined Armor’s PSMA-binding agent with Maier

and Huang, as Armor discloses that it is compatible with “nuclear medicine tomographic imaging technique[s]” like PET and SPECT. Ex1007, [0008]. Furthermore, Armor is directed to a treatment of prostate cancer, and Maier discloses that its system and method can be used to treat a variety of organs, including the prostate. Ex1005, [0017]; Ex1007, [0002].

212. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in combining Maier and Huang and these alternate Armor imaging agents. In addition to each being within the same field of medical image processing, each describes functional imaging after administration of physiological imaging agent, whether a contrast agent, a metabolic agent, or a PSMA-binding agent. Furthermore, Huang and Armor both describe the use of functional nuclear medicine imaging in combination with CT in the form of PET/CT, SPECT/CT, and/or other “composite” imaging modalities. Therefore, Armor’s suggested PSMA-binding imaging agents would have been readily applicable to, and easily implemented with, the Maier-Huang combination as described above. In addition, Armor expressly states that “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].

213. Because the references disclose and render obvious every limitation of

claim 7, including the limitations of claims 6 and 1 from which claim 7 depends, it is my opinion that Maier in view of Huang and Armor render claim 7 unpatentable as obvious.

6. Claim 8: “The system of claim 7, wherein the imaging agent comprises [18F]DCFPyL.”

214. Claim 8 depends from claim 7, which I explained above in Section IX.A.5 is rendered obvious by Maier in view of Huang and Armor. It is my opinion that Armor also discloses the additional limitation of claim 8.

215. As previously discussed in Sections IX.A.4 and IX.A.1.h), Armor discloses small molecule compounds that selectively bind PSMA and carry an appropriate radionuclide for selectively treating prostate cancer, Ex1007, [0078], and the Patent admits to the use of [18F]DCFPyL for PET imaging in the prior art, Ex1001, 1:63-2:4. These provide an express teaching, suggestion, or motivation to use a radiolabeled anti-PSMA inhibitor (binding agent) such as such as [18F]DCFPyL in the multi-mode imaging of the Maier-Huang combination as otherwise described above.

216. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in combining Maier and Huang and these alternate Armor imaging agents. In addition to each being within the same field of medical image processing, each describes functional imaging after administration

of physiological imaging agent, whether a contrast agent, a metabolic agent, or a PSMA-binding agent. Furthermore, Huang and Armor both describe the use of functional nuclear medicine imaging in combination with CT in the form of PET/CT, SPECT/CT, and/or other “composite” imaging modalities. Therefore, Armor’s suggested PSMA-binding imaging agents would have been readily applicable to, and easily implemented with, the Maier-Huang combination described above. In addition, Armor expressly states that “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].

217. Because the references disclose and render obvious every limitation of claim 10, including the limitations of claims 7 and 1 from which claim 8 depends, it is my opinion that Maier in view of Huang and Armor render claim 8 unpatentable as obvious.

7. Claim 9: “The system of claim 7, wherein the halogen is fluorine-18 [18F].”

218. Claim 9 depends from claim 7, which I explained above in Section IX.A.5 is rendered obvious by Maier in view of Huang and Armor. It is my opinion that Armor also discloses the additional limitation of claim 9.

219. Claim 9 differs from claim 8 only in that the imaging agent

comprising a radionuclide is more generally recited to comprise fluorine-18 [¹⁸F]. However, as previously discussed in Section IX.A.6, the Patent admits to the use of [¹⁸F]DCFPyL for PET imaging in the prior art, Ex1001, 1:63-2:4, in which the radionuclide is fluorine-18. Accordingly, claim 9 is rendered obvious by Maier in view of Huang and Armor (given the knowledge of the POSITA admitted by the Patent) for the same reasons explained in Section IX.A.6.

220. Because the references disclose and render obvious every limitation of claim 9, including the limitations of claims 7 and 1 from which claim 9 depends, it is my opinion that Maier in view of Huang and Armor render claim 9 unpatentable as obvious.

8. Claim 13: “The system of claim 1, wherein the instructions cause the processor to, for at least one risk index of the one or more risk indices, compute the value of the risk index by:”

221. Claim 13 depends from claim 1, which I explained above in Section IX.A.1 is rendered obvious by Maier in view of Huang and Armor. Claim 13 specifies computation of the risk index by:

determining, for each of the one or more regions, a corresponding cancerous tissue level within the region based on intensity values of the nuclear medicine image within the 3D boundary of the region; and

computing the value of the risk index based on the determined cancerous tissue levels within the one or more regions.

It is my opinion that each of Maier, Huang, and Armor also disclose the additional limitation of claim 13.

222. As previously discussed in Section IX.A.1.j), (1) Maier explains that “step 108 may comprise calculating one or more health status metrics that are simply measured anatomical or physiological quantities” or “metrics... identifying actual presence of burden of disease,” Ex1005, [0035] (emphasis added), including “e.g., statistics for the amount of likely disease present in each individual [region],” Ex1005, [0026], Fig. 3 (“Lung Density... 30% Damaged”), (2) Huang teaches that SUV values (above an organ- or region-specific SUV threshold) are used to generate hot-spot candidates in such organs or tissues (regions), Ex1006, [0114], and that maximum SUV values are used for grading tumors, Ex1006, [0009], and (3) Armor teaches that uptake levels and T/B ratios of at least its studied compounds correlate with, and provide a rationale for replacing conventional prostate biopsies for, “determination of Gleason scores[] ...for determination of prostate cancer and the extent of the disease,” Ex1007, [0064], [0066]. Rationales for the obviousness of a combination of these have already been explained in Section IX.A.1.j) in the context of parent claim 1.

223. Uptake and SUV values are, of course, determined from intensity values of the nuclear medicine image within the 3D boundary of a region, such as the lungs, liver, or prostate (as disclosed by Maier, Huang, and Armor as

previously discussed). Cancerous tissue levels and attendant risk indices, such as volume fraction, Ex1005, [0021], maximum SUV or volume with SUV above mean SUV or a threshold, Ex1006, [0114] and [0009], and T/B ratio and Gleason score, Ex1007, [0064], [0006], are calculated from such uptake or SUV values. Thus, these calculations constitute a calculation of the value of the risk index based on determined cancerous tissue levels, which are in turn based on intensity values of the nuclear medicine image within the 3D boundary of the region, as recited.

224. Because the references disclose and render obvious every limitation of claim 13, including the limitations of claim 1 from which claim 13 depends, it is my opinion that Maier in view of Huang and Armor render claim 13 unpatentable as obvious.

9. Claim 14: “The system of claim 1, wherein the cancer is prostate cancer.”

225. Claim 14 depends from claim 1, which I explained in Section IX.A.1 above is rendered obvious by Maier in view of Huang and Armor. It is my opinion that Armor discloses the additional limitation of claim 14.

226. As previously discussed in Section IX.A.1.g), Maier expressly teaches that its systems and methods “are not limited to a particular disease, pathology, or type of treatment.” Ex1005, [0018]. Maier also expressly teaches that “the presence or non-presence of important imaging biomarkers for cancer” (such as

physiological metrics derived from functional imaging exams, Ex1005, [0031]) “drives clinical decision-making in a more or less aggressive direction depending on the individual patient’s likelihood of having cancer.” Ex1005, [0005]. However, Maier does not expressly disclose an application to prostate cancer.

227. Armor teaches that a “critical challenge in imaging prostate cancer” is “differentiat[ing] clinically significant disease from silent or indolent disease within the prostate, as well as the identification of metastatic and recurrent disease.” Ex1007, [0006]. Armor, as otherwise described in Section IX.A.1.h), discloses “technology [] generally related to the imaging of prostate cancer (PCa) tissue to differentiate cancerous tissue from normal tissue or benign prostate tissue” where “the present technology relies on determining the ratio of the uptake of a radiolabeled compound that selectively binds to prostate specific membrane antigen (PSMA), which is overexpressed on the surface of prostate cancer tumors to the uptake of the same compound by a control tissue to differentiate clinically significant disease from silent or indolent disease within the prostate.” Ex1007, [0002] (emphasis added). Armor discloses further that “[i]maging of the subject following administration of the gamma-emitting transition metal complex conjugated to a targeting moiety can be performed using any nuclear medicine tomographic imaging technique that is suitable for detecting gamma radiation,” which includes SPECT/CT such as in the Maier-Huang combination. Ex1007,

[0009]. *See also* Section IX.A.1.h). These provide an express teaching, suggestion, or motivation to use radiolabeled anti-PSMA inhibitors (binding agents) in multi-mode imaging in Maier for the detection of prostate cancer.

228. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in combining Maier and Huang and Armor for the detection of prostate cancer. In addition to each being within the same field of medical image processing, each describes functional imaging after administration of physiological imaging agent, whether a contrast agent, a metabolic agent, or PSMA-binding agent. Furthermore, Huang and Armor both describe the use of functional nuclear medicine imaging in combination with CT in the form of PET/CT, SPECT/CT, and/or other “composite” imaging modalities. Therefore, Armor’s PSMA-binding imaging agents would have been readily applicable to, and easily implemented with, the Maier-Huang-Armor combination described above. In addition, Armor expressly states that “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].

229. Because the references disclose and render obvious every limitation of claim 14, including the limitations of claim 1 from which claim 14 depends, it is my opinion that Maier in view of Huang and Armor render claim 14 unpatentable

as obvious.

10. Claim 15: “The system of claim 14, wherein the cancer is metastatic prostate cancer.”

230. Claim 15 depends from claim 14, which I explained above in Section IX.A.10 is rendered obvious by Maier in view of Huang and Armor. It is my opinion that Armor also discloses the additional limitation of claim 12.

231. Claim 15 differs from claim 14 only in that the prostate cancer is specified to be metastatic prostate cancer. However, Armor expressly discloses that “compounds according to the present technology permit the detection of primary and metastatic prostate cancer tumors,” Ex1007, [0002], where “[t]he small molecule PSMA inhibitor represented by Formula (1) rapidly detects primary and metastatic PCa with high specificity,” Ex1007, [0100]. *See also* Ex1007, [0116]-[0121]. The rationales presented for the obviousness of claim 14 in Section IX.A.9 apply equally to claim 15.

232. Because the references disclose and render obvious every limitation of claim 15, including the limitations of claims 14 and 1 from which claim 15 depends, it is my opinion that Maier in view of Huang and Armor render claim 15 unpatentable as obvious.

11. Claim 16: “The system of claim 1, wherein the instructions cause the processor to automatically analyze the composite image by, at step (a):”

233. Claim 16 depends from claim 1, which I explained above in Section IX.A.1 is rendered obvious by Maier in view of Huang and Armor. Claim 16 specifies analysis of the composite image by:

using the machine learning algorithm to geographically identify, within the CT scan of the composite image, the 3D boundary(ies) for each of the one or more region(s); and

transferring the 3D boundary(ies) to the nuclear medicine image.

It is my opinion that the combination also discloses the additional limitation of claim 16.

234. As previously discussed in Section IX.A.1.g), Huang discloses that “[a] new technology, PET/CT, combines the functional imaging PET with an anatomical imaging computed tomography (CT), and allows the acquisition of clinical quality PET and CT scans, accurately aligned, from a single imaging device.” Ex1006, [0011] (emphasis added). Huang further explains that “[o]n a fused PET/CT image, abnormalities that are seen on PET can be located, and possibly also confirmed, on CT.” Ex1006, [0011] (emphasis added). Further, as previously discussed in Section IX.A.1.i), Huang teaches that whole-body context interpretation (*e.g.*, correlation of PET abnormalities and CT location) “enables the

computer to understand on which organs or tissue regions each hot-spot is located,” where “a segmented hot-spot which is considered a hot-spot due to normal [organ] physiological uptake is suppressed or compensated for.” Ex1006, [0099]. As also there, Huang yet further teaches that “because [] uptakes by different organs or tissues have large variations.... organ-specific or region-specific thresholding is very attractive,” and discloses or suggests that “[u]sing a whole-body context... one can first detect, segment and separate organs or regions that have different ranges in SUV values, then apply organ- or region-specific thresholding.” Ex1006, [0114]. As yet also discussed there, this is accomplished with trained classifiers, *i.e.*, machine learning algorithms. Ex1006, [0072-0075]; [0130]. Of course, using such organ- or region-specific thresholding of SUV values in a functional image, *e.g.*, PET or SPECT image, based on locations from an “aligned” anatomical image, *e.g.*, CT image, inherently involves a “transfer” of organ or region locations, and thus organ or region 3D boundaries, to the nuclear medicine functional image insofar as voxels of the latter image within the location of the organ or tissue are divided from voxels of the latter image outside of such location prior to organ- and region-specific calculations for, *e.g.*, the claim-recited and art-disclosed indices.

235. Although I do not believe that the Patent Owner has given the claim term “transfer” a definition that is different than its plain and ordinary meaning, I

have noted that the Patent states only that:

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

Ex1001, 28:24-30 (emphasis added), and does not describe any literal, indirect (e.g., 3D digital mask), or other specific “transfer” process or format. Huang likewise discloses using “aligned” or “pre-registered” PET and CT scans, Ex1006, [0011], [0130], where regions of the PET image falling within or outside of organ or tissue 3D boundaries are identified and selectively used, based on such identification, in the calculation of organ- and region-specific calculations for, e.g., the claim-recited and art-disclosed indices.

236. Because the references disclose and render obvious every limitation of claim 16, including the limitations of claim 1 from which claim 16 depends, it is my opinion that Maier in view of Huang and Armor render claim 16 unpatentable as obvious.

12. Claim 17: “The system of claim 1, wherein the nuclear medicine image is a PET scan and the instructions cause the processor to automatically analyze the composite image by, at step (b): computing the value of at least one particular risk index of the one or more risk indices based on intensity values of the PET scan in relation to the identified 3D boundary(ies).”

237. Claim 17 depends from claim 1, which I explained above in Section IX.A.1 is rendered obvious by Maier in view of Huang and Armor. It is my opinion that the combination also discloses the additional limitation of claim 17.

238. As previously discussed in the context of claim 6, Section IX.A.4 above, Huang suggests the use of PET/CT imaging and provides (1) an express teaching, suggestion, or motivation to combine the imaging modalities in Huang, (2) a rationale for combining existing prior art elements (in this context, PET and CT imaging) according to known methods to yield predictable results, and (3) a rationale for the use of a known technique (composite nuclear medicine and anatomical imaging, in this context, PET/CT imaging) to improve Maier's similar devices, methods, and products in the same way. Furthermore, as discussed in Section IX.A.1.h), Armor discloses "small molecule compounds that selectively bind PSMA and carry an appropriate radionuclide" that can be used with radioimaging to selectively treat prostate cancer. Ex1007, [0078], [0007], and the background of the Patent admits that specific examples of compounds for use with PET imaging, such as [¹⁸F]DCFPyL, were known. Ex1001, 1:65-2:6.

239. As previously discussed in Section IX.A.1.j), Huang teaches that SUV values (above an organ- or region-specific SUV threshold) are used to generate hot-spot candidates in such organs or tissues (regions), Ex1006, [0114], and that maximum SUV values are used for grading tumors, Ex1006, [0009]. In fact,

Huang expressly teaches that in a PET/CT study, “[p]ossible change quantification mechanisms include: (1) Grading of the hot-spot (tumor) at each time point based on the maximum SUV values, and comparing the change in grading over time...” Ex1006, [0076]-[0078], [0078] (emphasis added). The former inherently requires an analysis of intensity values in the PET scan in relation to identified 3D boundaries in order to implement such organ- or region-specific thresholds, while the latter inherently requires an analysis of intensity values in the PET scan in relation to the identified 3D boundaries of a lesion. Also as previously discussed, Armor teaches that uptake levels, and thus image intensity values, of at least its studied compounds “directly correspond with the Gleason score,” Ex1007, [0064], thus providing “a rationale for replacing conventional prostate biopsies for determination of Gleason scores, with the method provided herein for determination of prostate cancer and the extent of the disease,” Ex1007, [0066]. These also inherently require an analysis of intensity values in relation to identified 3D boundaries in order to replace a prostate biopsy for the determination of such a score. Rationales for the obviousness of a combination of these have already been explained in Section IX.A.1.j) in the context of the parent limitation.

240. Because the references disclose and render obvious every limitation of claim 17, including the limitations of claim 1 from which claim 17 depends, it is my opinion that Maier in view of Huang and Armor render claim 17 unpatentable

as obvious.

13. Claim 18: “The system of claim 17, wherein the instructions cause the processor to automatically analyze the composite image by, at step (b): computing the value of at least one particular risk index of the one or more risk indices based on intensity values of the PET scan within one or more of the identified 3D boundary(ies) within [the] PET scan.”

241. Claim 18 depends from claim 17, which I explained above in Section IX.A.12 is rendered obvious by Maier in view of Huang and Armor. It is my opinion that the combination also discloses the additional limitation of claim 18.

242. Claim 18 differs from claim 17 only in that intensity values are of the PET scan “within one or more of the identified 3D boundary(ies) within PET scan” rather than “in relation to the identified 3D boundary(ies).” However, as previously discussed in Section IX.A.12, Huang and Armor teach the analysis of SUV and other uptake values within the identified 3D boundaries of organs, tissues, and lesions for calculations of lesion volume, T/B ratio, Gleason score or other grading, and the like. Ex1006, [0009], [0078]; Ex1007, [0064], [0066]. These inherently require an analysis of intensity values within identified 3D boundaries in order to implement organ- or region-specific thresholds or calculate grading with respect to particular organs or tissues.

243. Because the references disclose and render obvious every limitation of claim 18, including the limitations of claims 17 and 1 from which claim 18

depends, it is my opinion that Maier in view of Huang and Armor render claim 18 unpatentable as obvious.

14. Claim 19: “The system of claim 17, wherein the instructions cause the processor to automatically analyze the composite image by:”

244. Claim 19 depends from claim 17, which I explained above in Section IX.A.12 is rendered obvious by Maier in view of Huang and Armor. Claim 19 specifies analysis of the composite image by:

identifying one or more hotspots within the PET scan; and

at step (b), computing the value of the particular risk index based one or more features of the one or more hotspots together with the identified 3D boundary(ies).

It is my opinion that the combination also discloses the additional limitation of claim 19.

245. As discussed in Section IX.A.12, Huang teaches that SUV values (above an organ- or region-specific SUV threshold) are used to generate hot-spot candidates in PET scans of organs or tissues, Ex1006, [0114]. This constitutes the identification of a hotspot within a PET scan, as well as calculation based on a feature, *e.g.*, uptake/intensity and/or location, together with an identified 3D boundary, *e.g.*, the boundary of an organ such as the lungs or liver. As further discussed in Section IX.A.12, Huang teaches the analysis of SUV/intensity values

of lesions for, for example grading, and otherwise teaches, as discussed in Section IX.A.1.i), that “a segmented hot-spot which is considered a hot-spot due to normal physiological uptake is suppressed or compensated for” so that “only pathological or abnormal hot-spots remain as bright spots in the PET or PET/CT image.” Ex1006, [0099]. This constitutes computation of a risk index, *e.g.*, a grading, based on a feature of the hotspot, *e.g.*, hotspot maximum SUV, together with an identified 3D boundary, *e.g.*, that of an organ where such maximum SUV must exceed an organ-specific SUV threshold. Armor similarly teaches the calculation of an imaging-based Gleason score based on SPECT/CT imaging of the prostate as a replacement for conventional prostate biopsies. Ex1007, [0064], [0066]. This constitutes computation of a risk index, *e.g.*, a grading, based on a feature of the hotspot, *e.g.*, hotspot maximum SUV, together with an identified 3D boundary, *e.g.*, that of the prostate.

246. Because the references disclose and render obvious every limitation of claim 19, including the limitations of claims 17 and 1 from which claim 19 depends, it is my opinion that Maier in view of Huang and Armor render claim 19 unpatentable as obvious.

15. Claim 20: “The system of claim 19, wherein the one or more features comprise one or more members selected from the group consisting of: a size of the one or more hotspots, a number of the one or more hotspots, and a distribution of the one or more hotspots.”

247. Claim 20 depends from claim 19, which I explained above in Section IX.A.14 is rendered obvious by Maier in view of Huang and Armor. It is my opinion that the combination also discloses the additional limitation of claim 20.

248. Huang teaches, in addition to the grading discussed in connection with parent claims 17 and 19 in Sections IX.A.12 and IX.A.14, that calculating “one or more properties such as intensity, volume, shape, topology, location, and texture... to quantify changes for the hot-spot based on the segmentation results and produce reports.” Ex1006, [0078] (emphasis added). In fact, Huang expressly teaches “(2) Comparing the segmented hot-spot volumes over time, e.g., by quantifying the change in tumor volume size... performing volume subtraction... etc.” Ex1006, [0078]. This constitutes at least feature of a size of one or more hotspots.

249. Because the references disclose and render obvious every limitation of claim 20, including the limitations of claims 19, 17, and 1 from which claim 20 depends, it is my opinion that Maier in view of Huang and Armor render claim 20 unpatentable as obvious.

16. Claim 21: “The system of claim 19, wherein the instructions cause the processor to automatically analyze the composite image by, at step (b):”

250. Claim 21 depends from claim 19, which I explained above in Section IX.A.14 is rendered obvious by Maier in view of Huang and Armor. Claim 21 specifies analysis of the composite image by causing the processor to:

compute the value of the particular risk index based on one or more members selected from the group consisting of:

a total number of identified hotspots within one or more of the 3D boundary(ies);

a total volume of detected hotspots within one or more of the 3D boundary(ies);

an average intensity of detected hotspots within one or more of the 3D boundary(ies); and

a maximal intensity of detected hotspots within one or more of the 3D boundary(ies).

It is my opinion that the combination also discloses the additional limitation of claim 21.

251. As previously discussed in Section IX.A.12, Huang teaches that SUV values (above an organ- or region-specific SUV threshold) are used to generate hot-spot candidates in PET scans of organs or tissues, Ex1006, [0114], and that maximum SUV values are used for grading tumors, Ex1006, [0009]. In fact, Huang expressly teaches that in a PET/CT study, “[p]ossible change quantification mechanisms include: (1) Grading of the hot-spot (tumor) at each time point based on the maximum SUV values, and comparing the change in grading over time...” Ex1006, [0076]-[0078], [0078] (emphasis added). This constitutes computing a

value of a risk index, *e.g.*, grading, based upon a maximal intensity of a detected hotspot, *e.g.*, maximum SUV, within an identified 3D boundary, *e.g.*, an organ-, tissue-, or lesion-encompassing boundary.

252. Because the references disclose and render obvious every limitation of claim 21, including the limitations of claims 19, 17, and 1 from which claim 21 depends, it is my opinion that Maier in view of Huang and Armor render claim 21 unpatentable as obvious.

17. Claim 22: “The system of claim 1, wherein the one or more regions of imaged tissue comprise one or more members selected from the group consisting of: organs, organ structures, sub-organs, and organ regions.”

253. Claim 22 depends from claim 1, which I explained above in Section IX.A.1 is rendered obvious by Maier in view of Huang and Armor. It is my opinion that at least each of Maier, Huang, and Armor disclose the additional limitation of claim 2.

254. Maier expressly teaches that “suitable tissue types include lung, prostate, breast, ...bone, etc.,” Ex1005, [0017], and provides a specific example of “segmenting lung parenchyma from the background anatomy and discarding the background anatomy for the purpose of calculating the quantitative status and risk metrics,” Ex1005, [0028]. Huang discloses using trained discriminative classifiers and detectors “in CT, MRI, PET, PET/CT or other types of images” for identifying

“organs, tissue regions, or anatomical sections such as kidney, liver, heart, bladder, brain, lung, ...etc.,” Ex1006, [0072], and provides a specific example where “[f]or instance, one can first detect and segment the lung, the liver, and other organs... [t]hen a threshold is chosen for the lung... [and a] different threshold can be chosen for the liver” Ex1006, [0114]. Armor discloses imaging of the prostate and “replacing conventional prostate biopsies for determination of Gleason scores, with the method provided herein for determination of prostate cancer and the extent of the disease,” Ex1007, [0066]. These constitute organs and/or organ structures.

255. Because the references disclose and render obvious every limitation of claim 22, including the limitations of claim 1 from which claim 22 depends, it is my opinion that Maier in view of Huang and Armor render claim 22 unpatentable as obvious.

18. Claim 23: “The system of claim 1, wherein the one or more regions of imaged tissue comprise bone or a prostate of the patient.”

256. Claim 23 depends from claim 1, which I explained above in Section IX.A.1 is rendered obvious by Maier in view of Huang and Armor. It is my opinion that at least each of Maier, Huang, and Armor disclose the additional limitation of claim 2.

257. Maier expressly teaches that “suitable tissue types include lung, prostate, breast, ...bone, etc.,” and further provides a specific example where “the tissue region may be a breast tumor, a liver tumor, a bone lesion, and/or a head/neck tumor.” Ex1005, [0017]. Huang teaches that “to detect whole-body metastatic spread in bones, one needs to find the bones first,” Ex1006, [0071], and, in addition to the previously described discriminative classifiers, further discloses systems and methods for “Bone Segmentation in PET-CT images,” Ex1006, [0124]-[0128]. Armor discloses imaging of the prostate, Ex1007, [0066], as well as that “[i]n yet another embodiment, the tissue imaged is bone tissue,” Ex1007, [0077], and a comparison of “whole-body ^{99m}Tc-MIP-1404 SPECT/CT imaging with conventional bone scan” that showed “increased accuracy and specificity... versus conventional bone scan.” Ex1007, [0116]-[0121]. These variously constitute imaging of bone or the prostate.

258. Because the references disclose and render obvious every limitation of claim 23, including the limitations of claim 1 from which claim 23 depends, it is my opinion that Maier in view of Huang and Armor render claim 23 unpatentable as obvious.

19. Independent Claim 24

259. Independent claim 24 of the Patent is nearly identical to independent claim 1, which I explained in Section IX.A.1 above is rendered obvious by Maier

in view of Huang and Armor. Whereas claim 1 is directed to “[a] network-based decision-support system,” claim 24 is directed to “[a] method comprising performing, by a processor of a server computing device,” steps which duplicate functions implicitly recited in claim 1 as decision-support system functions. Whereas claim 1 recites a “a processor[] and a memory” having stored instructions for performing a series of functions, claim 24 recites essentially the same steps performed by such a processor where “said processor [is] a processor of a cloud-based system.” Whereas claim 1 recites instructions causing the processor to “(i) receive and store...,” (ii) access...,” and the like, claim 24 recites “(i) receiving and storing, by the processor, ...,” “(ii) accessing, by the processor, ...,” and the like. Claim 24 otherwise differs only immaterially in reciting (presented as a pseudo-amendment markup): (1) the images being “associated with a particular corresponding patient...;” (2) “the composite image comprising a CT scan overlaid with a nuclear medicine image ~~obtained~~ acquired at a substantially same time...;” and (3) “the ~~instructions cause the processor to~~ method comprises automatically ~~analyze~~ analyzing the composite image by:”

260. Accordingly, it is my opinion that claim 24 is rendered obvious by Maier in view of Huang and Armor for the same reasons explained in Section IX.A.1 above. I will briefly discuss the individual limitations of claim 24 below in a similar manner as was done for claim 1 above for the sake of the record.

a) Preamble: “A method comprising performing, by a processor of a server computing device, (i) to (iv) as follows:”

261. For the purposes of providing a thorough analysis, I will assume that the preamble of claim 24 is limiting and I will address it like any other claim limitation. As I explain further below, it is my opinion that Maier discloses “[a] method comprising performing, by a processor of a server computer device,” various attendant steps.

262. Maier discloses these limitations, which are nothing more than generic recitations of structures found in almost any post-Internet computer-implemented method. Specifically, Maier discloses that “[o]ne or more processors may execute applications or programs to run systems or methods of the present disclosure, or portions thereof, stored as executable programs or program code in the memory, or received from the Internet or other network.” Ex1005, [0046]. Otherwise, as previously discussed in Section IX.A.1.k), Maier further discloses that the processor may be that of a network server, including one on the Internet. Ex1005, [0045], [0047].

263. Accordingly, it is my opinion that Maier discloses all the limitations of the preamble of claim 24.

- b) Limitation 24(a): “(i) receiving and storing, by the processor of a server computing device, said processor a processor of a cloud-based system, a plurality of medical images in a database, each medical image associated with a particular corresponding patient;”**

264. This limitation is essentially identical to limitation 1(b), which is addressed in Section IX.A.1.c) above, in combination with limitation 1(j), which is addressed in Section IX.A.1.k) above. The only differences are that: (1) whereas limitation 1(b) uses the verbs “receive and store,” limitation 24(a) uses the phrase “receiving and storing, by the processor, ...;” (2) limitation 24(a) references the processor introduced in the preamble, which is addressed in Section IX.A.19.a) above; and (3) limitation 24(a) specifies that the processor is one of a “cloud-based system,” which is addressed in Section IX.A.1.k) above. Accordingly, it is my opinion that Maier discloses limitation 21(a) for the same reasons explained in Sections IX.A.1.c), IX.A.19.a), and IX.A.1.k).

- c) Limitation 24(b): “(ii) accessing, by the processor, one or more of the medical images associated with a particular patient from the database;”**

265. This limitation is essentially identical to limitation 1(c) which is addressed in Section IX.A.1.d) above. The only difference is that, whereas limitation 1(c) uses the verb “access,” limitation 24(b) uses the phrase “accessing, by the processor, ...” Accordingly, it is my opinion that Maier discloses limitation

18(b) for the same reasons explained in Section IX.A.1.d).

- d) Limitation 24(c): “(iii) automatically analyzing, by the processor, the one or more medical images using a machine learning algorithm; and”**

266. This limitation is essentially identical to limitation 1(d) which is addressed in Section IX.A.1.e) above. The only difference is that, whereas limitation 1(d) uses the verb phrase “automatically analyze,” limitation 24(c) uses the phrase “automatically analyzing, by the processor, ...” Accordingly, it is my opinion that Maier discloses limitation 24(c) for the same reasons explained in Section IX.A.1.e).

- e) Limitation 24(d): “(iv) generating, by the processor, a radiologist report for the particular patient according to the one or more medical images for the patient,”**

267. This limitation is essentially identical to limitation 1(e) which is addressed in Section IX.A.1.f) above. The only difference is that, whereas limitation 1(e) uses the verb “generate,” limitation 24(d) uses the phrase “generating, by the processor, ...” Accordingly, it is my opinion that Maier discloses limitation 18(d) for the same reasons explained in Section IX.A.1.f).

- f) Limitation 24(e): “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 acquired at a substantially same time as the CT scan”**

268. This limitation is essentially identical to limitation 1(f) which is addressed in Section IX.A.1.g) above. The only difference is that, whereas limitation 1(f) recites “a nuclear medicine image obtained at a substantially same time,” limitation 24(e) recites “a nuclear medicine image acquired at a substantially same time.” This difference is immaterial. Accordingly, it is my opinion that Maier in view of Huang discloses and renders obvious limitation 24(e) for the same reasons explained in Section IX.A.1.g).

g) Limitation 24(f): “and following administration to the patient of an imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide,”

269. This limitation is identical to limitation 1(g) which is addressed in Section IX.A.1.h) above. Accordingly, it is my opinion that Maier in view of Huang and Armor discloses and renders obvious limitation 24(f) for the same reasons explained in Section IX.A.1.h).

h) Limitation 24(g): “wherein the method comprises automatically analyzing the composite image by: (a) 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”

270. This limitation is essentially identical to limitation 1(h) which is addressed in Section IX.A.1.i) above. The only difference is that, whereas limitation 1(h) recites that instructions cause the processor to perform the

subsequent functions, limitation 24(g) recites that “the method comprises automatically analyzing...” This difference is immaterial. Accordingly, it is my opinion that Maier in view of Huang and Armor discloses and renders obvious limitation 24(g) for the same reasons explained in Section IX.A.1.i).

- i) Limitation 24(h): “(b) 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.”**

271. This limitation is identical to limitation 1(i) which is addressed in Section IX.A.1.j) above. Accordingly, it is my opinion that Maier in view of Huang and Armor discloses and renders obvious limitation 24(h) for the same reasons explained in Section IX.A.1.j).

272. Because the combined references disclose and render obvious every limitation of claim 24, it is my opinion that Maier in view of Huang and Armor render claim 24 unpatentable as obvious.

20. Claim 25: “The method of claim 24, wherein the plurality of medical images in the database comprise a series of medical images of a first patient taken over time, and wherein the method comprises determining a value of at least a first risk index for each medical image of the series, thereby tracking determined values of at least the first risk index over time.”

273. This limitation is essentially identical to that of claim 2 which is addressed in Section IX.A.2 above. The only differences are that: (1) the claim

differs in its preamble, which reflects a method dependency of the same character as the corresponding system claim dependency; (2) whereas claim 2 recites “the instructions cause the processor to determine...,” claim 25 recites “the method comprises determining...,” and (3) whereas claim 2 refers to “tracking determined values of at least the first index for the first patient over time,” claim 25 omits the reference to “for the first patient” quoted therefrom. Accordingly, it is my opinion that Huang and Armor disclose and render obvious the additional limitation of claim 25 for the same reasons explained in Section IX.A.2, and Maier in view of Huang and Armor render claim 25 unpatentable as obvious.

21. Claim 26: “The method of claim 25, wherein the receiving and storing of the plurality of medical images comprises repeatedly receiving and storing, over time, a plurality of medical images of the first patient, each obtained at a different time, to obtain the series of medical images of the first patient.”

274. Claim 26 depends from claim 25, which I explained above in Section IX.A.20 (via referenced Section IX.A.2) is rendered obvious by Maier in view of Huang and Armor. It is my opinion that each of Maier, Huang, and Armor disclose the additional limitation of claim 34.

275. As previously discussed in referenced Section IX.A.2, Maier discloses that “the computer-implemented method 100 comprises... receiving at least a first medical image of a patient... [and] analyzing the image data of interest by comparing it to comparison image data, as shown at 106,” Ex1005, [0027], where

“[t]he algorithm may additionally or alternatively comprise comparing the patient’s image(s) to the patient’s own image(s), such as previously obtained image(s) for the patient,” Ex1005, [0024] (emphasis added). *See* also Ex1005, [0018] (use for base-line assessments and treatment follow-up). Thus, Maier discloses repeatedly receiving and storing, over time, medical images of the first patient, each expressly disclosed as being obtained at a different time – at baseline (prior to treatment), at treatment follow-up (after treatment), and the like – to obtain the series of medical images.

276. Huang discloses that “[t]he assessment of tumor size and volume is important for patient prognosis as well as for evaluation of treatment effectiveness and follow up,” Ex1006, [0003], and provides systems and methods “for quantifying changes across sub-volumes of digitized images,” where such a method includes “providing a plurality of new digitized images, said images representing a same patient at different time points, ...and quantifying changes in the sub-volume of interest over the different images of one or more properties including intensity, volume, shape, topology, location, and texture,” Ex1006, [0022] (emphasis added).

277. Armor discloses “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] (emphasis

added), as well as a method for monitoring a status of prostate cancer in a human subject, Ex1007, [0019], a method of monitoring the efficacy of prostate cancer treatment, Ex1007, [0287], and a method of evaluating a human subject suspected of harboring a prostate tumor that is repeated periodically, Ex1007, [0189], [0206].

278. Rationales for the combination of such teachings have been provided in at least Section IX.A.2 above and apply equally here with respect to the consequent result.

279. Because the combined references disclose and render obvious every limitation of claim 26, including the limitations of claims 25 and 24 from which claim 26 depends, it is my opinion that Maier in view of Huang and Armor render claim 26 unpatentable as obvious.

22. Independent claim 32

280. Independent claim 32 of the Patent is nearly identical to independent claim 1, which I explained in Section IX.A.1 above is rendered obvious by Maier in view of Huang and Armor. Claim 32 repeats, verbatim, each of the preamble and limitations 1(a)-1(i) of claim 1; however, rather than including limitation 1(j) (“and wherein the system is a cloud-based system”), claim 32 includes, verbatim, the additional limitation of claim 2, which directly depends from claim 1. Dependent claim 2 is also rendered obvious by Maier in view of Huang and Armor, as I explained in Section IX.A.2 above.

281. Accordingly, it is my opinion that claim 32 is rendered obvious by Maier in view of Huang and Armor for the same reasons explained in Sections IX.A.1 and IX.A.2 above (excluding, for sake of clarity, my discussion of limitation 1(j) in Section IX.A.1.k), which is not required by claim 32).

23. Independent claim 33

282. Independent claim 33 of the Patent is nearly identical to independent claim 1, which I explained in Section IX.A.1 above is rendered obvious by Maier in view of Huang and Armor. Claim 33 repeats, verbatim, each of the preamble and limitations 1(a)-1(i) of claim 1; however, rather than including limitation 1(j) (“and wherein the system is a cloud-based system”), claim 33 essentially includes the additional limitation of claim 13, which directly depends from claim 1. Dependent claim 13 is also rendered obvious by Maier in view of Huang and Armor, as I explained in Section IX.A.8 above. Other than the omission of limitation 1(j), claim 33 differs only immaterially from the incorporated and recited limitations of claim 13 in concluding (presented as a pseudo-amendment markup): (1) “wherein ~~the instructions cause the processor to~~, for at least one particular risk index of the one or more risk indices, the instructions cause the processor to compute the value of the particular risk index by;” and (2) “computing the value of the particular risk index based on...”

283. Accordingly, it is my opinion that claim 33 is rendered obvious by Maier in view of Huang and Armor for the same reasons explained in Sections IX.A.1 and IX.A.8 above (excluding, for sake of clarity, my discussion of limitation 1(j) in Section IX.A.1.k), which is not required by claim 33).

24. Independent claim 34

284. Independent claim 34 of the Patent is nearly identical to independent claim 24, which I explained in Section IX.A.19 above (via referenced Section IX.A.1) is rendered obvious by Maier in view of Huang and Armor. Claim 34 repeats, verbatim, each of the preamble and limitations 24(b)-24(i) of claim 24; however, rather than including all of limitation 24(a), claim 34 omits “said processor a processor of a cloud-based system,” and then concludes by essentially including the additional limitation of claim 25, which directly depends from claim 24. Dependent claim 25 is also rendered obvious by Maier in view of Huang and Armor, as I explained in Section IX.A.20 above (via referenced Section IX.A.2). Other than the omission of the aforementioned portion of limitation 24(a), claim 34 differs only immaterially from the incorporated and recited limitations of claim 25 in concluding (presented as a pseudo-amendment markup): “and wherein the ~~method comprises determining~~ instructions cause the processor to determine a value of at least a first risk index...” and (2) “tracking determined values of at least the first index for the first patient over time.”

285. Accordingly, it is my opinion that claim 34 is rendered obvious by Maier in view of Huang and Armor for the same reasons explained in Sections IX.A.19 and IX.A.20 above (excluding, for sake of clarity, my discussion of “a processor of a cloud-based system” in Section IX.A.19.b), which is not required by claim 34).

25. Independent claim 35

286. Independent claim 35 of the Patent is nearly identical to independent claim 24, which I explained in Section IX.A.19 above (via referenced Section IX.A.1) is rendered obvious by Maier in view of Huang and Armor. Claim 35 repeats, verbatim, each of the preamble and limitations 24(b)-24(i) of claim 24; however, rather than including all of limitation 24(a), claim 34 omits “said processor a processor of a cloud-based system,” and then concludes by essentially including the additional limitation of claim 13 (which depends from corresponding system claim 1). Dependent claim 13 is also rendered obvious by Maier in view of Huang and Armor, as I explained in Section IX.A.8 above. Other than the omission of the aforementioned portion of limitation 24(a), claim 35 differs only immaterially from the combined limitations of claims 24 and 13 in concluding (presented as a pseudo-amendment markup): (1) “~~wherein the instructions cause the processor to~~, for at least one particular risk index of the one or more risk indices, the instructions cause the processor to compute the value of the particular

risk index by;” and (2) “computing the value of the particular risk index based on...”

287. Accordingly, it is my opinion that claim 35 is rendered obvious by Maier in view of Huang and Armor for the same reasons explained in Sections IX.A.19 and IX.A.8 above (excluding, for sake of clarity, my discussion of “a processor of a cloud-based system” in Section IX.A.19.b), which is not required by claim 35).

B. Ground B, Obviousness over Maier in view of Huang and Armor, further in view of Neumaier

1. Claim 6: “The system of claim 1, wherein the nuclear medicine image is a PET scan.”

288. Claim 6 depends from claim 1, which I explained above in Section IX.A.1 is rendered obvious by Maier in view of Huang and Armor, and, in my opinion, as explained above in Section IX.A.4, is itself rendered obvious by Maier in view of Huang and Armor. However, if Armor’s express teaching, suggestion, or motivation to use a radiolabeled anti-PSMA inhibitor (PSMA-binding agent) is not in itself sufficient, Neumaier discloses the additional limitation of claim 6.

289. As previously discussed in Section IX.A.4, Armor discloses that “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]. In that regard, Neumaier expressly

discloses the preparation of “PSMA-specific PET tracers such as [¹⁸F]DCFPyL” and their use. Ex1008, 1:9-12, 66:44-65:18. Neumaier reports that the imaging of prostate cancer with PET isotope labelled PSMA ligands (PSMA binding agents) is of “considerable importance in clinical diagnosis,” Ex1008, 5:60-62, and otherwise explains that “[s]o far the only PSMA PET tracer used in clinics is [⁶⁸Ga]HBED-CC (50),” Ex1008, 64:29-35. While Armor does not disclose the availability of its specific ^{99m}Tc-MIP-1404 and ^{99m}Tc-MIP-1405 compounds, Neumaier teaches the synthesis and use of [¹⁸F]DCFPyL “for imaging prostate cancer cells or prostate cancerous tissue,” Ex1008, 64:13-15, and that “taking into an easy accessibility of [¹⁸F]DCFPyL 1-10 according to the present invention it could represent [*sic*] an adequate alternative for [⁶⁸Ga]HBED-CC (50) for research and patient care,” Ex1008, 64:29-46. [¹⁸F]DCFPyL has a longer half-life. Ex1008, 64:34-35. And a patient’s kidneys uptake less [¹⁸F]DCFPyL than the prior art [⁶⁸Ga]HBED-CC. Ex1008, 64:41-42. Neumaier concludes that [¹⁸F]DCFPyL “should improve the detection of tumor lesions in the abdomen.” Ex1008, 64:42-43. This is an express teaching, suggestion, or motivation to use a radiolabeled PSMA binding agent for the PET imaging component of the Maier-Huang-Armor combination described above.

290. Besides the express motivation included above, Armor discloses that PSMA targeted radiotracers may be radiolabeled with variety of radionuclides,

Ex1007, [0006]-[0007], and further discloses the administration of “^{99m}Tc-labeled anti-PSMA inhibitors, Formula (1) and Formula (2) compounds (^{99m}Tc-MIP-1404 and ^{99m}Tc-MIP-1405 respectively)” for SPECT/CT imaging, Ex1007, [0056]. Neumaier teaches other such radiolabeled PSMA selective imaging agents for PET imaging. Therefore, in circumstances where specific radioisotopes are not locally available, *see, e.g.*, Ex1008, 64:29-46 (discussing half-life, radioisotope generation, and other issues), other such radioisotopes and PSMA targeted radiotracers may be locally available, and a POSITA would have found substituting one radiolabeled anti-PSMA inhibitor for another to have been an obvious and straightforward modification according to Armor’s and Neumaier’s respective disclosures of such compounds and methods of use.

291. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in further combining the Maier-Huang-Armor combination with these alternate Neumaier imaging agents. In addition to each being within the same field of medical image processing, each reference describes functional imaging after administration of physiological imaging agent, whether a contrast agent, a metabolic agent, or a PSMA-binding agent. Furthermore, each of Armor and Neumaier describe the use of functional nuclear medicine imaging in combination with radiolabeled PSMA selective imaging agents. *E.g.*, Ex1008, 83:56-84:32. Therefore, Neumaier’s disclosed imaging agents would have been

readily applicable to the Maier-Huang-Armor combination described above. In addition, Armor expressly states that “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], and Neumaier expressly states that “In a suitable PSMA+ PCa mice model [18 F]DCFPyL 1-10 displays imaging characteristics nearly identical to those of [68 Ga]HBED-CC (50),” Ex1008, 64:37-39.

292. Because the combined references disclose and render obvious every limitation of claim 6, including the limitations of claim 1 from which claim 6 depends, it is my opinion that Maier in view of Huang and Armor, further in view of Neumaier, renders claim 6 unpatentable as obvious.

2. Claim 7: “The system of claim 6, wherein the radionuclide is a radioisotope of a halogen.”

293. Claim 7 depends from claim 6, which I explained above in Sections IX.A.4 and IX.B.1 is rendered obvious by Maier in view of Huang and Armor, or the combination further in view of Neumaier. In my opinion, as explained above in Section IX.A.5, claim 7 is itself rendered obvious by Maier in view of Huang and Armor. However, if Armor’s express teaching, suggestion, or motivation is not in itself sufficient, Neumaier discloses the additional limitation of claim 7.

294. As previously discussed in Section IX.B.1, Armor discloses that “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]. In that regard, Neumaier expressly discloses the preparation of “PSMA-specific PET tracers such as [18 F]DCFPyL” and their use. Ex1008, 1:9-12, 66:44-65:19, 86:27-87:32. This is an express teaching, suggestion, or motivation to use a PSMA binding agent radiolabeled with a radioisotope of a halogen, specifically fluorine, for the PET imaging component of the combination of claim 6, and the rationales for combination explained in Section IX.B.1 apply equally here.

295. Because the combined references disclose and render obvious every limitation of claim 6, including the limitations of claims 6 and 1 from which claim 7 depends, it is my opinion that Maier in view of Huang and Armor, further in view of Neumaier, renders claim 7 unpatentable as obvious.

3. Claim 8: “The system of claim 7, wherein the imaging agent comprises [18F]DCFPyL.”

296. Claim 8 depends from claim 7, which I explained above in Sections IX.A.5 and IX.B.2 is rendered obvious by Maier in view of Huang and Armor, or the combination further in view of Neumaier. In my opinion, as explained above in Section IX.A.6, claim 8 is itself rendered obvious by Maier in view of Huang

and Armor. However, if Armor's express teaching, suggestion, or motivation is not in itself sufficient, Neumaier discloses the additional limitation of claim 8.

297. As previously discussed in Section IX.B.1, Armor discloses that "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] (emphasis added). In that regard, Neumaier expressly discloses the preparation of "PSMA-specific PET tracers such as [18 F]DCFPyL," and their use, and their advantages. Ex1008, 1:9-12, 66:44-65:19, 86:27-87:32. This is an express teaching, suggestion, or motivation to use the very compound recited in the claim, and the rationales for combination explained in Section IX.B.1 apply equally here.

298. Because the combined references disclose and render obvious every limitation of claim 8, including the limitations of claims 7, 6, and 1 from which claim 8 depends, it is my opinion that Maier in view of Huang and Armor, further in view of Neumaier, renders claim 9 unpatentable as obvious.

4. Claim 9: "The system of claim 7, wherein the halogen is fluorine-18 [18F]."

299. Claim 9 depends from claim 7, which I explained above in Sections IX.A.5 and IX.B.2 is rendered obvious by Maier in view of Huang and Armor, or the combination further in view of Neumaier. In my opinion, as explained above

in Section IX.A.7, claim 9 is itself rendered obvious by Maier in view of Huang and Armor. However, if Armor's express teaching, suggestion, or motivation is not in itself sufficient, Neumaier discloses the additional limitation of claim 9.

300. Claim 9 differs from claim 8 only in that the imaging agent comprising a radionuclide is more generally recited to comprise fluorine-18 [18F]. However, as previously discussed in Section IX.B.3, Neumaier expressly discloses the preparation of "PSMA-specific PET tracers such as [18 F]DCFPyL" and their use, Ex1008, 1:9-12, 66:44-65:19, 86:27-87:32, in which the radionuclide is fluorine-18. Accordingly, claim 9 is rendered obvious by Maier in view of Huang and Armor, further in view of Neumaier, for the same reasons explained in Section IX.B.3.

301. Because the combined references disclose and render obvious every limitation of claim 9, including the limitations of claims 7, 6, and 1 from which claim 9 depends, it is my opinion that Maier in view of Huang and Armor, further in view of Neumaier, renders claim 9 unpatentable as obvious.

5. Claim 10: "The system of claim 6, wherein the radionuclide is a radioisotope of gallium (Ga)."

302. Claim 10 depends from claim 6, which I explained above in Section IX.A.4 is rendered obvious by Maier in view of Huang and Armor, or the combination further in view of Neumaier. At least Neumaier discloses the

additional limitation of claim 8.

303. As previously discussed in Section IX.B.1, Neumaier, which predates Armor, discloses that “[s]o far the only PSMA PET tracer used in clinics is [68 Ga]HBED-CC (50).” Ex1008, 64:29-39. This is an express teaching, suggestion, or motivation to use a PSMA binding agent radiolabeled with a radioisotope of gallium for the PET imaging component of the Maier-Huang-Armor combination described above.

304. Besides the express motivation included above, the combination of multi-modal imaging and a [68 Ga] radiolabeled PSMA-selective imaging agent would constitute a simple substitution of one known element for another to obtain predictable results for the same reasons explained in Section IX.B.1.

305. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in further combining the Maier-Huang-Armor combination with this Neumaier-disclosed imaging agent for the same reasons explained in Section IX.B.1.

306. Because the references disclose and render obvious every limitation of claim 10, including the limitations of claims 6 and 1 from which claim 10 depends, it is my opinion that Maier in view of Huang and Armor, further in view of Neumaier, renders claim 10 unpatentable as obvious.

6. Claim 11: “The system of claim 10, wherein the imaging agent comprises ⁶⁸Ga-PSMA-11.”

307. Claim 11 depends from claim 10, which I explained above in Section IX.B.5 is rendered obvious by Maier in view of Huang and Armor, further in view of Neumaier. At least Neumaier discloses the additional limitation of claim 11.

308. As previously discussed in Section IX.B.5, Neumaier discloses the PSMA PET tracer [⁶⁸Ga]HBED-CC (50). Ex1008, 64:29-39. [⁶⁸Ga]HBED-CC (50) is also referred to as [⁶⁸Ga]PSMA-11. Ex1001, 18:17-19; Ex1021, abstract. Accordingly, claim 11 is rendered obvious by Maier in view of Huang and Armor, further in view of Neumaier, for the same reasons explained in Section IX.B.5.

309. Because the references disclose and render obvious every limitation of claim 11, including the limitations of claims 10, 6, and 1 from which claim 11 depends, it is my opinion that Maier in view of Huang and Armor, further in view of Neumaier, renders claim 11 unpatentable as obvious.

C. Ground C, Obviousness over Maier in view of Huang and Armor, further in view of Cardinale and/or Giesel

1. Claim 6: “The system of claim 1, wherein the nuclear medicine image is a PET scan.”

310. Claim 6 depends from claim 1, which I explained above in Section IX.A.1 is rendered obvious by Maier in view of Huang and Armor, and, in my opinion, as explained above in Section IX.A.4, is itself rendered obvious by Maier in view of Huang and Armor. However, if Armor’s express teaching, suggestion,

or motivation to use an anti-PSMA inhibitor (PSMA-binding agent) radiolabeled with a positron-emitting radioisotope is not in itself sufficient, Cardinale and/or Geisel discloses the additional limitation of claim 6.

311. As previously discussed in Section IX.A.4, Armor discloses that “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]. In that regard, Cardinale expressly discloses “¹⁸F-tagged inhibitors of prostate specific membrane antigen (PSMA) and their use as imaging agents for prostate cancer,” Ex1009, title, which were applied in PET/CT scanning and, “in comparison to the other known PSMA-tracers the compounds of the present invention, particularly [¹⁸F]PSMA-1007, provide a very unique hepatobiliary clearance with very small clearance via the renal pathway.” Ex1009, 46:63-67. Cardinale teaches that the disclosed tracers “are perfectly suited for the primary diagnosis of prostate cancer and local recurrence” and “showed a great potential as possible tracer for the detection of prostate cancer and its metastases.” Ex1009, 47:1-4, 44-54. Giesel likewise discloses patient staging using ¹⁸F-PSMA-1007 PET scans as part of a “perfect theragnostic tandem.” Ex1010, 1929. These are an express teaching, suggestion, or motivation to use a radiolabeled PSMA binding agent for the PET imaging component of the Maier-Huang-Armor combination as described above.

312. Besides the express motivation included above, the combination of PET-based multi-modal imaging and an ^{18}F radiolabeled PSMA-selective imaging agent would constitute a simple substitution of one known element for another to obtain predictable results. As cited above, Armor discloses that PSMA targeted radiotracers may be radiolabeled with variety of radionuclides, Ex1007, [0006]-[0007], and further discloses the administration of “ $^{99\text{m}}\text{Tc}$ -labeled anti-PSMA inhibitors, Formula (1) and Formula (2) compounds ($^{99\text{m}}\text{Tc}$ -MIP-1404 and $^{99\text{m}}\text{Tc}$ -MIP-1405 respectively)” for SPECT/CT imaging, Ex1007, [0056]. Cardinale and Geisel teach other such radiolabeled PSMA selective imaging agents for PET imaging, where Geisel explains that “[a] PSMA-targeting ^{18}F -labelled PET tracer could be produced... [and] the half-life... would allow both late imaging beyond 1 h after injection and shipping to satellite institutions.” Ex1010, 1929. Therefore, in circumstances where specific radioisotopes such as $^{99\text{m}}\text{Tc}$ or ^{68}Ga are not locally available, other such radioisotopes and PSMA targeted radiotracers may be locally available, and a POSITA would have found substituting one radiolabeled anti-PSMA inhibitor for another to have been an obvious and straightforward modification according to Armor’s and Cardinale/Geisel’s respective disclosures of such compounds and methods of use.

313. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in further combining the Maier-Huang-Armor

combination with these alternate imaging agents. In addition to each being within the same field of medical imaging, each reference describes functional imaging after administration of physiological imaging agent, whether a contrast agent, a metabolic agent, or a PSMA-binding agent. Furthermore, each of Armor and Cardinale/Geisel describe the use of functional nuclear medicine imaging in combination with radiolabeled PSMA selective imaging agents. *E.g.*, Ex1009, 44-54; Ex1010, p.1929. Therefore, the Cardinale/Geisel disclosed imaging agents would have been readily applicable to the Maier-Huang-Armor combination described above. In addition, Armor expressly states that “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], and Geisel indicates “¹⁸F-PSMA-1007 is also a promising alternative to ⁶⁸Ga-PSMA-11 for diagnostic purposes.” Ex1010, 1929.

314. Because the references disclose and render obvious every limitation of claim 6, including the limitations of claim 1 from which claim 6 depends, it is my opinion that Maier in view of Huang and Armor, further in view of Cardinale and/or Giesel, renders claim 16 unpatentable as obvious.

2. Claim 12: “The system of claim 6, wherein the imaging agent comprises ¹⁸F-PSMA-1007.”

315. Claim 12 depends from claim 6, which I explained above in Section

IX.C.1 is rendered obvious by Maier in view of Huang and Armor, further in view of Cardinale and/or Giesel. Both Cardinale and Giesel disclose the additional limitation of claim 12.

316. As previously discussed in Section IX.C.1, Cardinale and/or Giesel disclose ¹⁸F-PSMA-1007 and its use. Accordingly, claim 12 is rendered obvious by Maier in view of Huang and Armor, further in view of Cardinale or Giesel, for the same reasons explained in Section IX.C.1.

D. Ground D, Obviousness over Huang in view of Armor and Maier

1. Independent Claim 27

a) Preamble: “A method for tracking prostate cancer progression and treatment efficacy over time, for one or more patient(s), the method comprising:”

317. For the purposes of providing a thorough analysis, I will assume that the preamble of claim 27 is limiting and I will address it like any other claim limitation. As I explain further below, it is my opinion that a combination of Huang and Armor renders “[a] method for tracking prostate cancer progression and treatment efficacy over time, for one or more patient(s),” obvious.

318. Huang discloses that “[t]he assessment of tumor size and volume is important for patient prognosis as well as for evaluation of treatment effectiveness and follow up,” Ex1006, [0003], and provides systems and methods “for quantifying changes across sub-volumes of digitized images,” where such a

method includes “providing a plurality of new digitized images, said images representing a same patient at different time points, ...and quantifying changes in the sub-volume of interest over the different images of one or more properties including intensity, volume, shape, topology, location, and texture,” Ex1006, [0022] (emphasis added). However, Huang does not expressly disclose application to the tracking of prostate cancer.

319. Armor discloses “technology [] generally related to the imaging of prostate cancer (PCa) tissue to differentiate cancerous tissue from normal tissue or benign prostate tissue,” Ex1007, [0002], and teaches that “[a] critical challenge in imaging prostate cancer (PCa) is to differentiate clinically significant disease from silent or indolent disease within the prostate, as well as the identification of metastatic and recurrent disease,” Ex1007, [0006]. Armor further teaches that “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] (emphasis added), as well as a method for monitoring a status of prostate cancer in a human subject, Ex1007, [0019], a method of monitoring the efficacy of prostate cancer treatment, Ex1007, [0287], and a method of evaluating a human subject suspected of harboring a prostate tumor that is repeated periodically, Ex1007, [0189], [0206]. These provide an express teaching, suggestion, or motivation to track prostate cancer progression

and treatment efficacy over time.

320. Besides the express motivation included above, the application to track prostate cancer progression and treatment would constitute a simple substitution of one known element for another to obtain predictable results. As previously discussed, Huang discloses “assessment... for patient prognosis as well as for evaluation of treatment effectiveness and follow up,” Ex1006, [0003], where assessment also includes “diagnosis and quantification of pathological changes,” Ex1006, [0098], and Armor teaches that uptake of radiolabeled anti-PSMA inhibitors (PSMA binding agents) is selective for prostate cancer, Ex1007, [0006]. Therefore, in applications where the suitable tissue type or tissue of interest is specifically the prostate and prostate-associated cancerous lesions, tumors, and metastases, a POSITA would have found a substitute, specific application to prostate cancer (and substitution of a prostate cancer targeting imaging agent and appropriate nuclear medicine imaging modality, as discussed below) to have been an obvious and straightforward modification according to Armor’s disclosure of appropriate imaging agents and methods of use.

321. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in combining Huang and Armor. In addition to each being within the same field of medical image processing, each describes functional imaging after administration of physiological imaging agent, whether a

metabolic agent or a PSMA-binding agent, for use in the diagnosis of, monitoring of progression of, and determination of post-treatment efficacy of, cancerous lesions and tumors. Furthermore, Huang and Armor both describe the use of functional nuclear medicine imaging and imaging agents in combination with CT in the form of PET/CT, SPECT/CT, and/or other “composite” imaging modalities (as discussed below). Therefore, Armor’s systems and methods would have been readily applicable to, and easily implemented with, Huang’s systems and methods. In addition, Armor expressly states that “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].

322. Accordingly, it is my opinion that Huang in view of Armor discloses and renders obvious all the limitations of the preamble of claim 27.

b) Limitation 27(a): “(a) repeatedly receiving and storing in a database, over time, by a processor of a computing device, said processor a processor of a cloud-based system, a plurality of medical images for each of the one or more patient(s) to obtain, for each of the one or more patient(s), a series of medical images taken over time;”

323. It is my opinion that the combination of Huang and Armor, further in view of Maier, disclose and render this limitation obvious. As previously discussed, Huang discloses “providing a plurality of new digitized images, said images representing a same patient at different time points,” for quantification and

evaluation of tumor properties, Ex1006, [0022] (emphasis added), where “[g]iven a... PET/CT study with volumes of a same patient at N time points, three clinical use cases for detection, segmentation and change quantification are described,” Ex1006, [0074] (emphasis added). Armor likewise discloses a method for monitoring a status of prostate cancer in a human subject, Ex1007, [0019], and a method of monitoring the efficacy of prostate cancer treatment, Ex1007, [0287]. It would be inherent to receive and store images at such earlier and current points in time, *i.e.*, repeatedly receive such images, to accomplish such change detection and monitoring, and a database may be any collection of data. In that regard, at least Huang discloses that “a computer system 191 for implementing the present invention can comprise, inter alia, a central processing unit (CPU) 192, a memory 193 and an input/output (I/O) interface 194a” where “[t]he memory 193 can include... disk drive, tape drive, etc., or a combinations thereof.” Ex1006, [0149]. Thus, such reception and storage is provided for by the Huang-Armor combination as set forth in Section IX.D.1.a) above, and the rationales expressed in the context of the preamble apply equally here with respect to the consequent gathering of patient image data.

324. With further regard to the requirement for “repeatedly receiving and storing... a plurality of medical images for each... of the one or more patient(s)” function, Huang expressly discloses that “[a]n implemented system... can be used

as a practical application on a regular basis for hot-spot detection, segmentation, and change quantification,” Ex1006, [0075] (emphasis added), and Armor teaches a method of evaluating a human subject suspected of harboring a prostate tumor that is repeated periodically, Ex1007, [0189], [0206]. These provide an express teaching, suggestion, or motivation to repeatedly acquire such imagery so as to track prostate cancer progression and treatment efficacy over time as described above.

325. With further regard to the requirement that “said processor is a processor of a cloud-based system,” and as otherwise explained in the context of limitation 1(j) of claim 1, in Section IX.A.1.k) above, Meier discloses that quite similar systems and methods for analyzing medical images “may be integral portions of a single computer or server or may be connected parts of a computer network.... such as the Internet,” Ex1005, [0047], where “[a]ny commercial or freeware web browser or other application capable of retrieving content from a network and displaying pages or screens may be used,” Ex1005, [0046] (emphasis added), and produced reports “may be uploaded by the method to a cloud storage bank for retrieval by a user,” Ex1005, [0037] (emphasis added). These constitute the components of a cloud-based system, where the processor may be that of the cloud-based system, *i.e.*, that of a server accessed by such web browsers via the Internet. This provides an express teaching, suggestion, or motivation to

implement such medical image analysis systems and methods as Internet-based or cloud-based systems.

326. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in combining Huang, Armor, and Maier. In addition to each being within the same field of medical image processing, each describes analyzing the results of functional imaging after the administration of a physiological imaging agent, whether a contrast agent, a metabolic agent or a PSMA-binding agent. *See* Ex1006, [0073]-[0074]; Ex1007, [0006]-[0007]; Ex1005, [0016]. Furthermore, Huang and Armor both describe the use of functional nuclear medicine imaging in combination with CT in the form of PET/CT, SPECT/CT, and/or other “composite” imaging modalities, while Maier teaches that analysis of anatomical, functional, and other medical images may be performed via servers, storage banks, and web browser clients communicating through the Internet, in what the Patent characterizes as a “cloud-based system.” Therefore, Armor’s application of PSMA-binding imaging agents and multi-modal imaging thereof to monitoring and periodic evaluation of prostate cancer, and the repeated reception and storage of images from that application for that purpose, would have been readily applicable to, and easily implemented with, a “cloud-based” implementation of Huang’s systems and methods.

327. Accordingly, it is my opinion that the Huang-Armor-Maier combination discloses and teaches limitation 27(a).

c)

(1) Limitation 27(b)(1): “(b) for each of the one or more patient(s), automatically analyzing, by the processor, using a machine learning algorithm, the series of medical images for the patient to determine...”

328. It is my opinion that Huang discloses this limitation. Huang discloses using trained discriminative classifiers and detectors “in CT, MRI, PET, PET/CT or other types of images” for identifying “organs, tissue regions, or anatomical sections such as kidney, liver, heart, bladder, brain, lung, ...etc.,” Ex1006, [0072], and teaches that whole-body context interpretation “enables the computer to understand on which organs or tissue regions each hot-spot is located, hence making it possible to separate normal hot-spots from pathological ones,” Ex1006, [0099]. In particular, Huang discloses classifiers where, in registered multi-modal images such as PET/CT, “training and detection steps can be performed on [] two image modalities jointly” where in a first scenario, separate PET and CT classifiers are used and, at run-time, the PET classifier is applied to the PET volume and the CT classifier is applied to the CT volume and “[t]hen the PET detection results and CT detection results are fused to prune false detections.” Ex1006, [0130]. In a second scenario, “one single classifier” trained on PET/CT volumes is used and

“[d]uring detection... the trained classifier works on the ‘joint’ features.” Ex1006, [0130]. Such classifiers are trained machine learning algorithms, *i.e.*, the product of a “learning-based framework” for the detection of such organs, or tissue regions, in such images, Ex1006, [0062], [0072], and these provide an express disclosure of the use Huang’s disclosed classifiers and detectors to analyze, *e.g.*, identify organs and the like in, medical images (such as the later, claim-recited “composite” images).

329. Accordingly, it is my opinion that the Huang-Armor-Maier combination discloses and teaches limitation 27(b).

(2) Limitation 27(b)(2): “...values of one or more risk indices for each medical image of the series, thereby tracking determined values of the one or more risk indices over a course [of] prostate cancer progression and treatment for the patient; and”

330. It is my opinion that both Huang and Armor disclose this limitation. Huang reports the well-known use of SUV values (above an SUV threshold) as inputs to more complex indicators of “cancer state or progression” (as discussed in Section IX.D.1.d) below), *see* Ex1006, [0009] (“Most approaches to hot-spot segmentation and the quantitative measurement of tumor volume use the standard uptake value (SUV)... [and] [p]hysicians and radiologists have used this measure for normalization across time points for different patients, and the maximum SUV values are used for grading tumors”), and those statements provide an disclosure of

calculating a value of a risk index. Thus, in addition to disclosing the repeated acquisition of images over time as previously discussed in Section IX.D.1.b), *see* Ex1006, [0003], [0022], [0074], Huang further expressly discloses that “[a]t step 65, a change quantification of one or more properties such as intensity, volume, shape, topology, location, and texture is applied to quantify changes for the hot-spot based on the segmentation results and produce reports,” Ex1006, [0078], and may be “fully automated to achieve hot-spot detection, segmentation, and change quantification,” Ex1006, [0083]. Specifically, Huang teaches that “[p]ossible change quantification mechanisms include: (1) Grading of the hot-spot (tumor) at each time point based on the maximum SUV values, and comparing the change in grading over time; [and] (2) Comparing the segmented hot-spot volumes over time, e.g., by quantifying the change in tumor volume size...” Ex1006, [0078] (emphasis added). This constitutes the calculation of risk indices (and an unrecited, but attendant, objective of providing such information in a report, as disclosed in Huang) for a series of images acquired at prior and current points in time so as to track the values of such risk indices.

331. Armor likewise discloses a method of evaluating a human subject suspected of harboring a prostate tumor that may be repeated periodically, Ex1007, [0189], [0206]. Armor further discloses that “[t]he present inventors have shown that the uptake levels of [Armor’s] compounds directly correspond with the

Gleason score,” Ex1007, [0064], where “[t]he ratio of tumor uptake to background (T/B ratio), moreover, was observed to directly correlate with the Gleason score” and “[t]his correlation provides a rationale for replacing conventional prostate biopsies for determination of Gleason scores, with the method provided herein for determination of prostate cancer and the extent of the disease,” Ex1007, [0066]. Armor yet further discloses “a non-surgical method of identifying a severity level of prostate cancer in a patient.... [by] determining a level of uptake of the compound in the prostate of the patient as a tumor (T) level; determining a level of uptake of the compound in a control tissue as a baseline (B) level; and assigning a severity level in terms of Gleason score if a ratio of T:B is at, or above, a predetermined threshold value.” Ex1007, [0017]. This constitutes the calculation of risk indices (and unrecited, but attendant, objective of providing such information in a report, as disclosed in Huang) for a series of images acquired at prior and current points in time, over a course of prostate cancer progression and treatment, so as to track the values of such risk indices. *See also* Ex1007, [0019] (method of monitoring a status of prostate cancer), [0287] (method of monitoring the efficacy of treatment).

332. All of these are consistent with any of the constructions proposed in Section VII.B above. Specifically, (1) “numeric value(s),” such as physiologic uptake of an agent (maximum SUV value) or amount of disease (segmented hot-

spot volumes), “indicative of cancer state and/or progression in the patient within one or more regions,” (2) “value(s),” such as the aforementioned values or subsequent grading, “indicative of cancer state and/or progression in the patient within one or more regions,” and (3) “value(s) indicative of cancer state and/or progression in the patient within one or more regions, including but not limited to uptake values, volumes, and other values derived therefrom” (emphasis added).

333. While Huang itself discloses the calculation of a risk index, Armor provides an express teaching, suggestion, or motivation to apply Huang’s systems and methods (the calculation and identification of pathological SUV value regions within the nuclear medicine image of a “composite” image) to the calculation of a risk index (and unrecited, but attendant, objective of providing such information in a report as otherwise disclosed by Maier) particular to prostate cancer, namely, the Gleason score.

334. Besides the express motivation included above, the calculation of a Gleason score would constitute a simple substitution of one known element for another to obtain predictable results. Huang discloses “[g]rading of the hot-spot (tumor) at each time point based on the maximum SUV values, and comparing the change in grading over time,” Ex1006, [0078], and Armor discloses a method of evaluating a human subject suspected of harboring a prostate tumor that may be repeated periodically, Ex1007, [0189], [0206], as well as a method of identifying a

severity level of prostate cancer, assigning severity level in terms of Gleason score, and monitoring the status of prostate cancer, Ex1007, [0015], [0068]-[0069]. Such calculations could readily have been implemented by conducting Huang's grading, for more than one past point in time (and a current point in time, if contemporaneous), using Armor's PSMA-binding agent(s) and disclosed correlation(s) to Gleason score. Therefore, a POSITA would have found implementing such calculations to have been an obvious and straightforward modification according to Huang's disclosure of such calculations and reports.

335. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in combining the Huang-Armor-Maier combination for the calculation of such indices over time with the aforementioned indices from Armor. Similar calculations were already required to so that "a segmented hot-spot which is considered a hot-spot due to normal physiological uptake is suppressed or compensated for," Ex1006, [0099], *i.e.*, distinguish a tumor uptake from organ background uptake, and would merely need to be performed and associated with the correlated Gleason scope. Therefore, such calculations would have been readily applicable to, and easily implemented with, Huang's systems and methods.

336. Accordingly, it is my opinion that the Huang-Armor combination discloses and teaches limitation 27(b)(1).

- d) **Limitation 27(c): “(c) for each of the one or more patient(s), storing, by the processor, the determined values of the one or more risk indices, each indicative of prostate cancer state or progression, for the patient for further processing and/or causing, by the processor, display of a graphical representation of the determined values of the one or more risk indices for the patient,”**

337. It is my opinion that Huang discloses this limitation. As previously discussed, Huang discloses that “[a]t step 65, a change quantification of one or more properties... is applied to quantify changes for the hot-spot based on the segmentation results,” Ex1006, [0078], where “[p]ossible change quantification mechanisms include: (1) Grading of the hot-spot (tumor) at each time point... [and] (2) Comparing the segmented hot-spot volumes over time...” Ex1006, [0078] (emphasis added). Huang yet further discloses that “at step 65, a change quantification... is applied to quantify changes... and produce reports,” Ex1006, [0078] (emphasis added), with storage and/or display by the processor at least in the form of such produced reports.

338. Accordingly, it is my opinion that the Huang-Armor-Maier combination discloses and teaches limitation 27(c).

- e) **Limitation 27(d): “wherein the series of medical images for a particular patient of the one or more patient(s) comprises a CT scan overlaid with a nuclear medicine image acquired at a substantially same time as the CT scan”**

339. Huang discloses that “[p]ositron emission tomography (PET) using fluorine-18 deoxyglucose (FDG) is a nuclear medicine medical whole-body imaging technique that produces a three dimensional image of functional processes in the body” where “[t]umors in FDG-PET appear as ‘hot-spots’ due to increased FDG uptake.” Ex1006, [0003]. Huang explains that, in 2006, “tumor segmentation in PET is performed manually by the physician or semi-automatically” where “[u]n-supervised object segmentation involves a trade-off between sensitivity and specificity” and “[i]n cancer imaging, a second modality such as CT [] often provides better resolution and object delineation” but “the difference in attenuation between tumor and healthy tissue in CT is low and segmentation algorithms often fail when used on CT data alone.” Ex1006, [0013]. Thus, Huang discloses an invention “directed to [a] learning-based framework for whole-body landmark detection, segmentation, and change quantification in single-mode and multi-mode medical images,” Ex1006, [0002] (emphasis added).

340. In particular, Huang discloses that “[a] new technology, PET/CT, combines the functional imaging PET with an anatomical imaging computed tomography (CT), and allows the acquisition of clinical quality PET and CT scans, accurately aligned, from a single imaging device.” Ex1006, [0011] (emphasis added). Huang further explains that “[o]n a fused PET/CT image, abnormalities that are seen on PET can be located, and possibly also confirmed, on CT, and this

enables the interpreting physician to make a more informed decision about whether the hot-spot on PET is indeed an abnormality, and if so, where the abnormality is located anatomically.” Ex1006, [0011] (emphasis added).

341. Accordingly, it is my opinion that the Huang-Armor-Maier combination discloses and teaches limitation 27(d).

f) Limitation 27(e): “and following administration to the patient of an imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide,”

342. Huang discloses the use of fluorine-18 deoxyglucose (FDG), where cancerous lesions or tumors “in FDG-PET appear as ‘hot-spots’ due to increased FDG uptake,” Ex1006, [0003]. However, while FDG is a radiolabeled agent, Huang does not disclose a radiolabeled PSMA-binding agent.

343. Armor discloses “technology [] generally related to the imaging of prostate cancer (PCa) tissue to differentiate cancerous tissue from normal tissue or benign prostate tissue,” and, particularly, radiolabeled compounds “that selectively bind[] to prostate specific membrane antigen (PSMA).” Ex1007, [0002]. Armor reports that “[a] variety of radionuclides are known to be useful for radioimaging,” Ex1007, [0007], as well as that “small molecule compounds that selectively bind PSMA and carry an appropriate radionuclide... can be used to selectively treat prostate cancer,” Ex1007, [0078]. Armor most specifically discloses that “^{99m}Tc-

labeled anti-PSMA inhibitors, Formula (1) and Formula (2) compounds (^{99m}Tc -MIP-1404 and ^{99m}Tc -MIP-1405 respectively)... are highly specific radiolabeled agents for imaging PCa” that “selectively bind[] to prostate-specific membrane antigen (PSMA),” Ex1007, [0056], [0064], and that “[i]maging of the subject following administration of the gamma-emitting transition metal complex conjugated to a targeting moiety can be performed using... single-photon emission computed tomography combined with conventional computed tomography (SPECT/CT),” Ex1007, [0009], but acknowledges that other clinical drugs incorporate other radionuclides imaged by other means, Ex1007, [0003]. I have also noted that the background of the Patent admits that, in April 2015, specific examples of other radiolabeled PSMA-binding agents, such as [^{18}F]DCFPyL, imaged by Positron Emission Tomography (PET), were known. Ex1001, 1:65-2:6. These provide an express teaching, suggestion, or motivation to use radiolabeled anti-PSMA inhibitors (binding agents) in the multi-mode imaging of Huang as described above.

344. Besides the express motivation included above, the combination of imaging modalities and radiolabeled imaging agent as described would constitute a simple substitution of one known element for another to obtain predictable results. As previously discussed, Huang teaches that “[t]umors in FDG-PET appear as ‘hot-spots’ due to increased FDG uptake,” Ex1006, [0003]. Therefore, in

applications where the suitable tissue type or tissue of interest is specifically the prostate and prostate-associated cancerous lesions, tumors, and metastases, a POSITA would have found substituting a radiolabeled anti-PSMA inhibitor (PSMA-binding agent) for a radiolabeled metabolic agent such as FDG, and selecting a suitable functional/anatomical imaging modality pair, to have been an obvious and straightforward modification according to Armor's disclosure of such imaging agents and methods of use.

345. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in combining Huang and Armor in this respect. In addition to both being within the same field of medical image processing, both describe functional imaging after administration of physiological imaging agent, whether a metabolic agent or a PSMA-binding agent. Furthermore, both describe the use of functional nuclear medicine imaging in combination with CT in the form of PET/CT, SPECT/CT, and/or other "composite" imaging modalities. Therefore, Armor's PSMA-binding imaging agents would have been readily applicable to, and easily implemented with, Huang's systems and methods as described above. In addition, Armor expressly states that "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].

346. Accordingly, it is my opinion that the Huang-Armor-Maier combination discloses limitation 27(e).

- g) Limitation 27(f): “and wherein step (b) comprises: 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”**

347. It is my opinion that Huang discloses this limitation. Huang discloses using trained discriminative classifiers and detectors “in CT, MRI, PET, PET/CT or other types of images” for identifying “organs, tissue regions, or anatomical sections such as kidney, liver, heart, bladder, brain, lung, ...etc.,” Ex1006, [0072] (emphasis added), and teaches that whole-body context interpretation “enables the computer to understand on which organs or tissue regions each hot-spot is located, hence making it possible to separate normal hot-spots from pathological ones,” Ex1006, [0099]. Huang further teaches that “[t]he basic idea is to first detect normal physiological organs or regions that often induce high FDG uptake, such as the heart, kidney bladder, and brain,” then segment hotspots, and “[t]hen a segmented hot-spot which is considered a hot-spot due to normal physiological uptake is suppressed or compensated for.” Ex1006, [0099]. Huang yet further teaches that “because FDG uptakes by different organs or tissues have large variations.... organ-specific or region-specific thresholding is very attractive,” and discloses or suggests that “[u]sing a whole-body context... one can first detect,

segment and separate organs or regions that have different ranges in SUV values, then apply organ- or region-specific thresholding,” where “[f]or instance, one can first detect and segment the lung, the liver, and other organs... [t]hen a threshold is chosen for the lung... [and a] different threshold can be chosen for the liver” Ex1006, [0114]. These provide an express disclosure of using the PET/CT, SPECT/CT, or other multi-modality “composite” images to identify one or more 3D boundaries, *e.g.*, those of organs, within the nuclear medicine, *e.g.* PET or SPECT, image component, for subsequent determination of whether the measured uptake is physiological or pathological, as well as potential determination of organ- or region-specific thresholds.

348. Accordingly, it is my opinion that the Huang-Armor-Maier combination discloses limitation 27(f).

h) Limitation 27(g): “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).”

349. It is my opinion that Huang discloses this limitation. In addition to the portions of Huang cited in connection with the previous limitations, Huang expressly teaches an exemplary embodiment that is read upon by the limitation, where:

In PET images, because FDG uptakes by different organs or tissues have large variations, a global thresholding on the converted SUV

volumes often fails to provide good hot-spot candidates. For example, tumors in the lung may have lower SUV values than normal tissue in the liver. Hence to automatically generate good hot-spot candidates, organ-specific or region-specific thresholding is very attractive. Using a whole-body context according to an embodiment of the invention, one can first detect, segment and separate organs or regions that have different ranges in SUV values, then apply organ- or region-specific thresholding. For instance, one can first detect and segment the lung, the liver, and other organs, or detect and separate the thorax and abdomen regions. Then a threshold is chosen for the lung, such as the mean SUV value in the lung region, and hot-spot candidates can be generated in the lung which have SUV values above the threshold. A different threshold can be chosen for the liver, such as the mean SUV value in the liver, and hot-spot candidates can be generated in the liver.

Ex1006, [0114] (emphasis added). Such a whole body context, as described in Ex1006, [0072]-[0075], [0099], and [0130] as previously discussed, is provided for and applied by the Huang-Armor-Maier combination as set forth in Sections IX.D.1.c) and IX.D.1.g) above. In addition, (1) Huang paragraph [0011], teaching the use of CT in PET/CT so that “abnormalities that are seen on PET can be located, and possibly also confirmed, on CT, and this enables... a more informed decision about whether the hot-spot on PET is indeed an abnormality, and if so, where the abnormality is located anatomically,” (2), Huang paragraphs [0098]-

[0099], teaching that whole-body context interpretation (in PET/CT, SPECT/CT, and other joint imaging modalities) “enables the computer to understand on which organs or tissue regions each hot-spot is located, hence making it possible to separate normal hot-spots from pathological ones,” and (3) Huang paragraphs [0072]-[0075], [0099], and [0130], teaching how to perform such context analysis, provide an express disclosure to, and of how to, apply the functions provided by the prior-addressed limitations to the calculation and identification of pathological SUV value regions within the nuclear medicine image of a “composite” image.

350. Accordingly, it is my opinion that the Huang-Armor-Maier combination discloses limitation 27(g).

351. Because the combined references disclose and render obvious every limitation of claim 27, it is my opinion that Huang in view of Armor and Maier renders claim 27 unpatentable as obvious.

2. Independent Claim 31

352. Independent claim 31 of the Patent is essentially identical to independent claim 27, which I explained in Section IX.D.1 above is rendered obvious by Huang in view of Armor and Maier. Whereas claim 27 is directed to “[a] method for tracking prostate cancer progression and treatment efficacy over time, for one or more patient(s), the method comprising: ...,” claim 31 is directed to a corresponding system and “system comprising: ...” Claim 31 subsequently

recites “a processor; and a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to” perform essentially the steps of the method of claim 27. For the steps themselves, claim 31 differs only immaterially (1) in grammatical form, (2) by replacing the phrase “by a processor of a computing device, said processor a processor of a cloud-based system” in limitation 31(b) with the concluding limitation “and wherein the system is a cloud-based system,” and (3) by slight difference in the location of the phrase “using a machine learning algorithm” in limitation 31(c). Grammatically, claim 31 differs only immaterially in reciting, *e.g.*, “(a) repeatedly receive and store..., by a processor, ...,” “(b) ... automatically analyze ..., by the processor, ...” and the like rather than “(a) repeatedly receiving and storing...,” “(b) ... automatically analyzing...,” and the like.

353. Accordingly, it is my opinion that claim 31 is rendered obvious by Huang in view of Armor and Maier for the same reasons explained in Section IX.D.1 above. I will briefly discuss the individual limitations of claim 31 below in a similar manner as was done for claim 27 above for the sake of the record.

- a) **Preamble: “A system for tracking prostate cancer progression and treatment efficacy over time, for one or more patient(s), the system comprising:”**

354. For the purposes of providing a thorough analysis, I will assume that the preamble of claim 31 is limiting and I will address it like any other claim

limitation. It is my opinion that Huang in view of Armor discloses and teaches “[a] system for tracking prostate cancer progression and treatment efficacy over time, for one or more patient(s)” in that this limitation is essentially identical to the preamble of method claim 27 which is addressed in Section IX.D.1.a) above. The only difference is that claim 31 is directed to a corresponding system, and the Huang-Armor combination discloses and teaches such a system. Ex1006, [0149]. Accordingly, it is my opinion that Huang in view of Armor discloses and renders obvious the limitations of the preamble for the same reasons explained in Section IX.D.1.a).

b) Limitation 31(a): “a processor; and a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to:”

355. Huang discloses these limitations, which are nothing more than generic recitations of structures found in any system implementing a computerized method. Specifically, Huang discloses that “a computer system 191 for implementing the present invention can comprise, inter alia, a central processing unit (CPU) 192, a memory 193 and an input/output (I/O) interface 194a” where “[t]he memory 193 can include... disk drive, tape drive, etc., or a combinations thereof,” as well as that “[t]he present invention can be implemented as a routine 197 that is stored in memory 193 and executed by the CPU 192.” Ex1006, [0149].

356. Accordingly, it is my opinion that Huang in view of Armor discloses and renders obvious limitation 31(a).

- c) **Limitation 31(b): “(a) 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, for each of the one or more patient(s), a series of medical images taken over time;”**

357. This limitation is essentially identical to limitation 27(a) which is addressed in Section IX.D.1.b) above. The only differences are that (1) limitation 31(b) omits the phrase “by a processor of a computing device, said processor a processor of a cloud-based system,” and (2) whereas limitation 27(a) uses the phrase “receiving and storing, by the processor,” limitation 31(b) uses the verbs “receive and store.” Accordingly, it is my opinion that Huang in view of Armor discloses and renders obvious limitation 31(b) for the same reasons explained in Section IX.D.1.b).

- d)

- (1) **Limitation 31(c)(1): “(b) for each of the one or more patient(s), automatically analyze the series of medical images for the patient, using a machine learning algorithm, to determine...”**

358. This limitation is essentially identical to limitation 27(b)(1) which is addressed in Section IX.D.1.c)(1) above. The only difference is that, whereas limitation 27(b)(1) uses the phrase “automatically analyzing, by the processor,”

limitation 31(c)(1) uses the verb phrase “automatically analyze.” Accordingly, it is my opinion that Huang in view of Armor discloses and renders obvious limitation 31(c)(1) for the same reasons explained in Section IX.D.1.c)(1).

(2) Limitation 31(c)(2): “...values of one or more risk indices for each medical image of the series, thereby tracking determined values of the one or more risk indices over a course [of] prostate cancer progression and treatment for the patient; and”

359. This limitation is identical to limitation 27(b)(2) which is addressed in Section IX.D.1.c)(2) above. Accordingly, it is my opinion that that Huang in view of Armor discloses and renders obvious limitation 31(c)(2) for the same reasons explained in Section IX.D.1.c)(2).

e) Limitation 31(d): “(c) for each of the one or more patient(s), store the determined values of the one or more risk indices, each indicative of prostate cancer state or progression, for the patient for further processing and/or cause display of a graphical representation of the determined values of the one or more risk indices for the patient”

360. This limitation is essentially identical to limitation 27(c) which is addressed in Section IX.D.1.d) above. The only difference is that, whereas limitation 27(c) uses the phrases “storing, by the processor” and “causing, by the processor,” limitation 31(d) uses the verbs “store” and “cause.” Accordingly, it is my opinion that Huang in view of Armor discloses and renders obvious limitation

31(d) for the same reasons explained in Section IX.D.1.d).

- f) Limitation 31(e): “wherein the series of medical images for a particular patient of the one or more patient(s) comprises a CT scan overlaid with a nuclear medicine image acquired at a substantially same time as the CT scan”**

361. This limitation is identical to limitation 27(d) which is addressed in Section IX.D.1.e) above. Accordingly, it is my opinion that that Huang in view of Armor discloses and renders obvious limitation 31(e) for the same reasons explained in Section IX.D.1.e).

- g) Limitation 31(f): “and following administration to the patient of an imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide,”**

362. This limitation is identical to limitation 27(e) which is addressed in Section IX.D.1.f) above. Accordingly, it is my opinion that Huang in view of Armor discloses and renders obvious limitation 31(f) for the same reasons explained in Section IX.D.1.f).

- h) Limitation 31(g): “and wherein step (b) comprises: 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**

363. This limitation is identical to limitation 27(f) which is addressed in Section IX.D.1.g) above. Accordingly, it is my opinion that that Huang in view of

Armor discloses and renders obvious limitation 31(g) for the same reasons explained in Section IX.D.1.g).

- i) **Limitation 31(h): “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),”**

364. This limitation is identical to limitation 27(g) which is addressed in Section IX.D.1.h) above. Accordingly, it is my opinion that that Huang in view of Armor discloses and renders obvious limitation 31(h) for the same reasons explained in Section IX.D.1.h).

- j) **Limitation 31(i): “and wherein the system is a cloud-based system.”**

365. This limitation is essentially identical to the phrase “by a processor of a computing device, said processor a processor of a cloud-based system” omitted from limitation 31(b) but recited in corresponding method limitation 27(a). As previously explained in Section IX.D.1.b) (via referenced Section IX.A.1.k), Maier discloses, and the Huang-Armor combination in view of Maier, *i.e.*, Huang in view of Armor and Maier, renders obvious limitation 31(i) for the same reasons explained in Section IX.D.1.b) above. Accordingly, it is my opinion that that Huang in view of Armor and Maier discloses and renders obvious limitation 31(i) for the same reasons explained in Section IX.D.1.b).

E. Ground E: Obviousness over Huang in view of Armor and Maier, further in view of Weineisen and/or Giesel

1. Claim 28

366. Claim 28 depends from claim 27, which I explained above in Section IX.D.1 is rendered obvious by Huang in view of Armor and Maier. As I explain below, it is my opinion that Huang in view of Armor and Maier, further in view of Giesel and Weineisen, renders obvious the claim limitation of claim 28.

- a) Limitation 28(a): “The method of claim 27, wherein the series of medical images for the particular patient of the one or more patient(s) comprises: (i) a first image subseries comprising one or more medical images obtained using a first nuclear imaging modality each following administration to the particular patient of a first radiopharmaceutical; and”**

367. It is my opinion that the combination of Huang, Armor, and Maier discloses and renders this limitation obvious. As previously explained in Sections IX.D.1.b)-IX.D.1.c)(2) and IX.D.1.f), Huang discloses using “images representing a same patient at different time points,” and “volumes of a same patient at N time points” for quantification and evaluation of tumor properties. Ex1006, [0022], [0074] (emphasis added). Armor likewise discloses a method for monitoring a status of prostate cancer in a human subject, Ex1007, [0019], and a method of monitoring the efficacy of prostate cancer treatment, Ex1007, [0287]. Huang also discloses automatic analysis using a machine learning algorithm for identifying

“organs... such as kidney, liver, heart, bladder, brain, lung, ...etc.” to separate normal hot-spots from pathological ones, and automated “[g]rading of the hot-spot (tumor) at each time point based on the maximum SUV values” and/or automated calculation of segmented hotspot volumes, with comparison of each over time. Ex1006, [0072], [0078] (emphasis added), [0099], [0130]. Armor further discloses ^{99m}Tc-labeled anti-PSMA inhibitors imaged with SPECT/CT, but acknowledges that other clinical drugs incorporate other radionuclides imaged by other means, Ex1007, [0009], [0003], and the Patent admits to prior means such as [¹⁸F]DCFPyL imaged by PET, Ex1001, 1:65-2:6, and thus, as taught by Huang, imaging by fused or “composite” PET/CT. Huang in view of Armor therefore disclose and render obvious the reception, storage, and analysis of at least one image obtained with administration of a PSMA-binding agent, *i.e.*, a first radiopharmaceutical, and the determination of at least one risk index value, over a course of progression and treatment for the reasons explained in Sections IX.D.1.b)-IX.D.1.c)(2) and IX.D.1.f).

- b) Limitation 28(b): “(ii) a second image subseries comprising one or more medical images obtained using a second nuclear imaging modality each following administration to the particular patient of a second radiopharmaceutical,”**

368. Huang in view of Armor and Maier does not expressly disclose a change in imaging modality and agent, *e.g.*, from PET/CT imaging using an ¹⁸F- or

⁶⁸Ga-tagged PSMA-binding agent, *see* Sections IX.C.1-IX.C.2 (focusing, in this context, on the Giesel article), to SPECT/CT imaging using a photon-emitting PSMA-binding agent, *see* Sections IX.D.1.f) and IX.D.1.h) (Armor's use of ^{99m}Tc-labeled anti-PSMA inhibitors with SPECT/CT to determine, for example, Gleason score). However, Giesel and Weineisen teach such a change when proceeding from initial diagnostic scanning to subsequent integrated treatment and imaging in a process referred to as "theranostics" (or, variantly, as "theragnostics").

369. Giesel and Weineisen teach a process of PSMA imaging & therapy (PSMA I&T), or "thera[g]nostic" treatment, for patients with metastatic and castration-resistant prostate cancer or "mCRPC." Ex1011, abstract, first paragraph; Ex1010, p.1929. In such a process, a patient diagnosed with mCRPC, *e.g.*, via ¹⁸F-PSMA- or ⁶⁸Ga-PSMA-agent PET/CT as explained in Sections IX.A.6 (Armor's general teaching of the use radioisotope-labelled PSMA-binding agents given Patent-admitted prior knowledge of [¹⁸F]DCFPyl PET) and/or IX.C.2 (Giesel's disclosure of ¹⁸F-PSMA-1007 PET/CT), is subsequently "staged" via ¹⁸F-PSMA-1007 or ⁶⁸Ga-PSMA-11 PET (or, as explained above and otherwise disclosed in Weineisen, PET/CT), Ex1010, p.1929, and therapeutically treated with an ¹⁷⁷Lu-PSMA-agent. Almost immediately following administration, the patient is imaged via SPECT/CT for dosimetry, *i.e.*, measurement of the amount of therapeutic ¹⁷⁷Lu-PSMA-agent taken up by the target lesion(s) or tumor(s), and for

other calculations concerning the lesions and tumors, such as “risk indices” concerning the current state of such lesions and tumors, the current state of such lesions or tumors as indicated by the theranostic tracer (versus the diagnostic or “staging”), and/or the planning of additional treatment cycles. See Ex1010, figure; Ex1011, pp.1173-1174. This theranostic administration and imaging constitutes performance of limitation 28(b) with a second nuclear imaging modality (SPECT) and radiopharmaceutical (the ^{177}Lu -PSMA-agent), and an express teaching, suggestion, or motivation to change from obtaining and using “a first image subseries comprising one or more medical images obtained using a first nuclear imaging modality... following administration... of a first radiopharmaceutical” to (but not necessarily exclusively to) obtaining and using “a second image subseries comprising one or more medical images obtained using a second nuclear imaging modality... following administration... of a second radiopharmaceutical” Specifically a POSITA would have expected such a change in radiopharmaceutical, and associated imaging modality, to improve therapeutic treatment, since Giesel writes that “ ^{18}F -PSMA-1007 and ^{177}Lu -PSMA-617 seem to be a perfect theragnostic tandem,” Ex1010, p.1929, and Weineisen explains that “high contrast in PET imaging and therapeutic effectiveness with no detectable

side effects qualifies ⁶⁸Ga-/¹⁷⁷-Lu-PSMA I&T⁷ to be a valid choice for the theranostic management of PC [(prostate cancer)],” Ex1011, pp.1173-74. A POSITA would also have expected an improvement in therapeutic treatment from their ability to perform *in vivo* dosimetry via the SPECT/CT image, rather than simply having knowledge of the bulk amount of the administered dose. *See* Ex1011, pp.1174, 1169 (second paragraph).

370. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in combining Huang, in view of Armor and Maier, with Giesel and Weineisen. In addition to each being within the same field of medical image processing, each reference describes functional imaging after administration of physiological imaging agent, whether a contrast agent, a metabolic agent, or a PSMA-binding agent. Furthermore, each of Armor, Giesel, and Weineisen describe the use of functional nuclear medicine imaging in combination with radiolabeled PSMA selective imaging agents. Therefore, Giesel’s and Weineisen’s disclosed imaging agents would have been readily applicable to the Huang-Armor-Maier combination described above. In addition,

⁷ Although Weineisen uses different ⁶⁸Ga- and ¹⁷⁷Lu-PSMA-agents, disclosed at Ex1011, p.1170, the theranostic concepts discussed in Giesel and Weineisen are more general, and I have taken note that these claims, 28-30, do not require any specific subclass or pair of radiolabeled PSMA-binding agents.

Armor expressly states that “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], Giesel describes its agents as a perfect theragnostic tandem,” Ex1010, p.1929, and Weineisen reports that in its “proof-of-concept study [of the theranostic tandem], ¹⁷⁷Lu-PSMA I&T endoradiotherapy was feasible, safe, and effective in metastatic PC [(prostate cancer)],” Ex1011, p.1176 (conclusion).

371. Accordingly, it is my opinion that Huang in view of Armor and Maier, further in view of Giesel and Weineisen, discloses limitation 28(b).

- c) **Limitation 28(c): “such that the values of the one or more risk indices determined in step (b) for the particular patient comprise a first subseries of values of a first risk index determined by automated analysis of the first image subseries and a second subseries of values of a second risk index determined by automated analysis of the second image subseries.”**

372. It is my opinion that Huang in view of Armor and Maier, further in view of Giesel and Weineisen, discloses this limitation. The claim’s “such that...” clause is simply an express statement of the inherent consequence of performing limitations 28(a) and 28(b). As shown in Giesel, and explained in Weineisen, the administration ¹⁷⁷Lu-PSMA I&T endoradiotherapy is “thera[g]nostic,” *i.e.*, used not only for therapy, but diagnostic imaging, dosimetry, further therapy planning, etc. *See* Ex1010, figure; Ex1011, pp.1169 (second paragraph).

373. Because the combined references disclose and render obvious every limitation of claim 28, it is my opinion that Huang in view of Armor and Maier, further in view of Giesel and Weineisen, renders claim 28 unpatentable as obvious.

2. Claim 29: “The method of claim 28, wherein the medical images of first image subseries are obtained over a first period of time, when prostate cancer of the particular patient is localized, and the medical images of the second image subseries are obtained over a second period of time, when prostate cancer of the particular patient is metastatic.”

374. Claim 29 depends from claim 28, which I explained above in Section IX.E.1 is rendered obvious by Maier in view of Huang and Armor, further in view of Giesel and Weineisen. It is my opinion that Huang in view of Armor and Maier, further in view of Giesel and Weineisen, discloses the additional limitation of claim 29.

375. As explained in Section IX.D.1.b), Huang and Armor disclose methods conducted over time, *e.g.*, “repeatedly,” to, and potentially through, a diagnosis of primary (localized) prostate cancer. *See, e.g.*, Ex1007, [0010] (“[T]he method provides a physician the necessary information to evaluate whether or not the subject has prostate cancer and whether the subject needs to undergo active surveillance or watchful-waiting or needs to undergo surgery, for instance radical prostatectomy, cryosurgery, radiation therapy, hormone (or androgen deprivation) therapy, chemotherapy, PSMA antibody-drug- conjugate, or combinations

thereof...”); [0121] (“Clinical care protocol in prostate cancer today recommends that if metastatic disease has reached bone, prostatectomy is contraindicated and systemic treatment recommended (e.g. chemotherapy).”). Also, in addition to the diagnostic applications presented in Sections IX.A.6 and IX.C.2, Weineisen reports imaging, via ^{68}Ga -PSMA-agent PET/CT, with demonstrated uptake in primary tumors and metastases. Ex1011, pp.1173 (“The primary prostate tumor..., as well as periprostatic tissue and urinary bladder invasion, was not concealed by radioactivity in the bladder.”), 1174 (“The baseline ^{68}Ga -PSMA-HBED-CC PET/CT scan in patient 3... demonstrated PSMA-mediated uptake in the primary tumor and multiple lymph node and bone metastases...”). Further, as previously discussed in Section IX.E.1.b), Weineisen (and, inherently, Giesel, given the figure therein) changes to SPECT/CT imaging during theranostic treatment of mCRPC for dosimetry and other “therapy planning.” Ex1011, pp.1174, 1169 (second paragraph). Indeed, Armor acknowledges that it is after metastasis that systemic treatment, such as radiation therapy, PSMA antibody-drug-conjugate, or combinations thereof (e.g., Weineisen’s ^{177}Lu -PSMA I&T “endoradiotherapy”) is recommended. Ex1007, [0121].

376. Because the combined references disclose and render obvious every limitation of claim 29, it is my opinion that Huang in view of Armor and Maier, further in view of Giesel and Weineisen, renders claim 29 unpatentable as obvious.

3. Claim 30: “The method of claim 29, comprising using PET-CT imaging for evaluating prostate cancer in both localized and metastatic states.”

377. Claim 30 depends from claim 39, which I explained above in Section IX.E.2 is rendered obvious by Maier in view of Huang and Armor, further in view of Giesel and Weineisen. It is my opinion that Huang in view of Armor and Maier, further in view of Giesel and Weineisen, discloses the additional limitation of claim 30.

378. It is my opinion that Huang in view of Armor and Maier, further in view of Giesel and Weineisen, discloses this limitation. As previously discussed in Section IX.E.2, Weineisen reports imaging, via ⁶⁸Ga-PSMA-agent PET/CT, with demonstrated uptake in primary tumors and metastases. Ex1011, pp.1173 (“The primary prostate tumor..., as well as periprostatic tissue and urinary bladder invasion, was not concealed by radioactivity in the bladder.”), 1174 (“The baseline ⁶⁸Ga-PSMA-HBED-CC PET/CT scan in patient 3... demonstrated PSMA-mediated uptake in the primary tumor and multiple lymph node and bone metastases...”). This constitutes using PET/CT imaging for evaluating prostate cancer in both primary (e.g., in the primary tumor) and metastatic (e.g., in lymph node and bone metastases) states.

379. Because the combined references disclose and render obvious every limitation of claim 30, it is my opinion that Huang in view of Armor and Maier,

further in view of Giesel and Weineisen, renders claim 30 unpatentable as obvious.

X. CONCLUSION

380. For the foregoing reasons, it is my opinion that claims 1-3 and 6-35 of the Patent should be found unpatentable.

* * *

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

Dated:

A handwritten signature in black ink, appearing to read 'Dr. Bruce Rosen', is written over a horizontal line. The signature is fluid and cursive.

Dr. Bruce Rosen