

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. 11,424,035
Filing Date: June 24, 2020
Issue Date: August 23, 2022
Title: NETWORK FOR MEDICAL IMAGE ANALYSIS, DECISION SUPPORT
SYSTEM, AND RELATED GRAPHICAL USER INTERFACE (GUI)
APPLICATIONS

Inter Partes Review No.: IPR2025-00725

**PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 11,424,035**

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EXHIBIT LIST

No.	Description
Ex1001	U.S. Patent No. 11,424,035 (“the Patent”)
Ex1002	Declaration of Dr. Rosen
Ex1003	Dr. Rosen Curriculum Vitae
Ex1004	Prosecution History File of the Patent (Application No. 16/938,488)
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	RESERVED
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”)
Ex1022	RESERVED
Ex1023	RESERVED
Ex1024	RESERVED
Ex1025	RESERVED
Ex1026	Electronic Order, <i>Progenics Pharmaceuticals, Inc. v. MIM Software Inc.</i> , Case No. 1:24-cv-10437-PBS, Dkt. 69, October 8, 2024.
Ex1027	Amended Joint Statement, <i>Progenics Pharmaceuticals, Inc. v. MIM Software Inc.</i> , Case No. 1:24-cv-10437-PBS, Dkt. 75, January 31, 2025.
Ex1028	Scheduling Order, <i>Progenics Pharmaceuticals, Inc. v. MIM Software Inc.</i> , Case No. 1:24-cv-10437-PBS, Dkt. 85, March 5, 2025.

CLAIMS APPENDIX

Limitation	Claim Language
Claim 1	
[1(pre)]	<i>A network-based decision support system comprising:</i>
[1(a)]	<i>a processor; and a memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to:</i>
[1(b)]	<i>(i) receive and store a plurality of medical images in a database, each medical image associated with a corresponding patient;</i>
[1(c)]	<i>(ii) access one or more of the medical images associated with a particular patient from the database upon user request for transmission to the user for display on a user computing device;</i>
[1(d)]	<i>(iii) automatically analyze the one or more medical images using a machine learning algorithm; and</i>
[1(e)]	<i>(iv) generate a radiologist report for the particular patient according to the one or more medical images for the patient,</i>
[1(f)]	<i>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</i>
[1(g)]	<i>and following administration to the patient of an imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide,</i>
[1(h)]	<i>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</i>
[1(i)]	<i>(b) computing, using the nuclear medicine image with the identified 3D boundary(ies) of the one or more region(s), a risk map comprising a graphical denotation marking a region of risk of cancer or risk of recurrence of cancer.</i>
Claim 2	
[2]	<i>The system of claim 1, wherein the nuclear medicine image is a SPECT scan.</i>
Claim 3	
[3]	<i>The system of claim 1, wherein the imaging agent comprises a metal chelated to the PSMA binding agent, and wherein the metal is the radionuclide.</i>

Claim 4	
[4]	<i>The system of claim 3, wherein the imaging agent comprises ^{99m}Tc-MIP-1404.</i>
Claim 5	
[5]	<i>The system of claim 1, wherein the nuclear medicine image is a PET scan.</i>
Claim 6	
[6]	<i>The system of claim 5, wherein the radionuclide is a radioisotope of a halogen.</i>
Claim 7	
[7]	<i>The system of claim 5, wherein the imaging agent comprises [18F]DCFPyL.</i>
Claim 8	
[8]	<i>The system of claim 5, wherein the radionuclide is a radioisotope of gallium (Ga).</i>
Claim 9	
[9]	<i>The system of claim 1, wherein the system is a cloud-based system.</i>
Claim 10	
[10]	<i>The system of claim 1, wherein the processor is a processor of one or more network of Internet host servers.</i>
Claim 11	
[11]	<i>The system of claim 1, wherein the cancer is prostate cancer.</i>
Claim 12	
[12]	<i>The system of claim 11, wherein the cancer is metastatic prostate cancer.</i>
Claim 13	
[13]	<i>The system of claim 1, wherein the imaged tissue comprises bone.</i>
Claim 14	
[14]	<i>The system of claim 1, wherein the imaged tissue comprises a prostate of the patient.</i>
Claim 15	
[15]	<i>The system of claim 1, wherein at step (b), the instructions cause the processor to compute a value of each of one or more risk indices, each risk index value indicative of cancer state or progression in the patient.</i>
Claim 16	
[16]	<i>The system of claim 15, 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</i>

	<i>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.</i>
Claim 17 [17]	
[17(a)]	<i>The system of claim 15, wherein at step (b) 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</i>
[17(b)]	<i>computing the value of the risk index based on the determined cancerous tissue levels within the one or more regions.</i>
Claim 18	
[18(pre)]	<i>A method comprising performing, by a processor of a server computing service, (i) to (v) as follows:</i>
[18(a)]	<i>(i) receiving and storing, by the processor, a plurality of medical images in a database, each medical image associated with a corresponding patient;</i>
[18(b)]	<i>(ii) accessing, by the processor, one or more of the medical images associated with a particular patient from the database upon user request for transmission to the user for display on a user computing device;</i>
[18(c)]	<i>(iii) automatically analyzing, by the processor, the one or more medical images using a machine learning algorithm; and</i>
[18(d)]	<i>(iv) generating, by the processor, a radiologist report for the particular patient according to the one or more medical images for the patient,</i>
[18(e)]	<i>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</i>
[18(f)]	<i>and following administration to the patient of an imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide,</i>
[18(g)]	<i>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</i>

[18(h)]	<i>(b) computing, using the nuclear medicine image with the identified 3D boundary(ies) of the one or more region(s), a risk map comprising a graphical denotation marking regions of risk of cancer or risk of recurrence of cancer.</i>
Claim 19	
[19]	<i>The method of claim 18, wherein the nuclear medicine image is a SPECT scan.</i>
Claim 20	
[20]	<i>The method of claim 19, wherein the imaging agent comprises a metal chelated to the PSMA binding agent, and wherein the metal is the radionuclide.</i>
Claim 21	
[21]	<i>The method of claim 20, wherein the imaging agent comprises ^{99m}Tc-MIP-1404.</i>
Claim 22	
[22]	<i>The method of claim 18, wherein the nuclear medicine image is a PET scan.</i>
Claim 23	
[23]	<i>The method of claim 22, wherein the radionuclide is a radioisotope of a halogen.</i>
Claim 24	
[24]	<i>The method of claim 23, wherein the imaging agent comprises $[^{18}\text{F}]\text{DCFPyL}$.</i>
Claim 25	
[25]	<i>The method of claim 22, wherein the radionuclide is a radioisotope of gallium (Ga).</i>
Claim 26	
[26]	<i>The method of claim 18, wherein the processor is a processor of a cloud-based system.</i>
Claim 27	
[27]	<i>The method of claim 18, wherein the processor is a processor of one or more network or Internet host servers.</i>
Claim 28	
[28]	<i>The method of claim 18, wherein the cancer is prostate cancer.</i>
Claim 29	
[29]	<i>The method of claim 28, wherein the cancer is metastatic prostate cancer.</i>
Claim 30	
[30]	<i>The method of claim 18, wherein the imaged tissue comprises bone.</i>

Claim 31	
[31]	<i>The method of claim 18, wherein the imaged tissue comprises a prostate of the patient.</i>
Claim 32	
[32]	<i>The method of claim 18, wherein step (b) comprises computing a value of each of one or more risk indices, each risk index value indicative of cancer state or progression in the patient.</i>
Claim 33	
[33]	<i>The method of claim 32, 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.</i>
Claim 34	
[34]	<i>The method of claim 33, 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.</i>
Claim 35 [35]	
[35(a)]	<i>The method of claim 32, wherein step (b) comprises, for at least one risk index of the one or more risk indices, computing 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</i>
[35(b)]	<i>computing the value of the risk index based on the determined cancerous tissue levels within the one or more regions.</i>
Claim 36	
[36(pre)]	<i>A method for tracking prostate cancer progression and treatment efficacy over time, for one or more patient(s), the method comprising:</i>
[36(a)]	<i>(a) repeatedly receiving and storing in a database, over time, by a processor of a computing device, 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;</i>
[36(b)(1)]	<i>(b) for each of the one or more patient(s), automatically analyzing,</i>

	<i>by the processor, using a machine learning algorithm, the series of medical images for the patient to determine</i>
[36(b)(2)]	<i>(i) 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</i>
[36(b)(3)]	<i>(ii) a risk map comprising a graphical denotation marking a region of risk of cancer or risk of recurrence of cancer;</i>
[36(c)]	<i>and (c) for each of the one or more patient(s), storing, by the processor, (i) the determined values of the one or more risk indices, each indicative of prostate cancer state or progression, and (ii) the risk map, for the patient for further processing or causing, by the processor, display of a graphical representation of the determined values of the one or more risk indices for the patient,</i>
[36(d)]	<i>wherein the series of medical images for a particular patient of the one or more patient(s) comprises a composite images of the particular patient, each composite image comprising a CT scan overlaid with a corresponding nuclear medicine image acquired at a substantially same time as the CT scan</i>
[36(e)]	<i>and following administration to the patient of an imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide,</i>
[36(f)]	<i>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 corresponding nuclear medicine image; and</i>
[36(g)]	<i>using the corresponding nuclear medicine image with the identified 3D boundary(ies) of the one or more region(s) to compute (i) the value of each of the one or more risk indices and (ii) the risk map.</i>
Claim 37 [37]	
[37(a)]	<i>The method of claim 36, 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</i>
[37(b)]	<i>(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</i>

	<i>radiopharmaceutical,</i>
[37(c)]	<i>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.</i>
Claim 38	
[38]	<i>The method of claim 37, wherein the medical images of [the] 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.</i>
Claim 41	
[41(pre)]	<i>A system for tracking prostate cancer progression and treatment efficacy over time, for one or more patient(s), the system comprising:</i>
[41(a)]	<i>a processor; and memory having instructions stored thereon, wherein the instructions, when executed by the processor, cause the processor to:</i>
[41(b)]	<i>(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;</i>
[41(c)(1)]	<i>(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</i>
[41(c)(2)]	<i>(i) 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</i>
[41(c)(3)]	<i>(ii) a risk map comprising a graphical denotation marking a region of risk of cancer or risk of recurrence of cancer;</i>
[41(d)(1)]	<i>and (c) for each of the one or more patient(s), store (i) the determined values of the one or more risk indices, each indicative of prostate cancer state or progression, and (ii) the risk map, for the patient for further processing or cause display of a graphical representation of the determined values of the one or more risk</i>

	<i>indices for the patient,</i>
[41(e)]	<i>wherein the series of medical images for a particular patient of the one or more patient(s) comprises a composite images of the particular patient, each composite image comprising a CT scan overlaid with a corresponding nuclear medicine image acquired at a substantially same time as the CT scan</i>
[41(f)]	<i>and following administration to the particular patient of an imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide,</i>
[41(g)]	<i>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 corresponding nuclear medicine image; and</i>
[41(h)]	<i>using the corresponding nuclear medicine image with the identified 3D boundary(ies) of the one or more region(s) to compute (i) the value of each of the one or more risk indices and (ii) the risk map.</i>
Claim 42 [42]	
[42(a)]	<i>The system of claim 41, 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</i>
[42(b)]	<i>(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,</i>
[42(c)]	<i>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.</i>
Claim 43	
[43]	<i>The system of claim 42, wherein the medical images of [the] 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</i>

	<i>patient is metastatic.</i>
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I. MANDATORY NOTICES (37 C.F.R. §42.8(A)(1))

A. Real Party-in-Interest (37 C.F.R. §42.8(b)(1))

The real parties-in-interest are Petitioner MIM Software Inc. (“Petitioner”); Petitioner’s parent company, GE HealthCare Technologies Inc.; and Petitioner’s insurer, AIG Specialty Insurance Company.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Progenics Pharmaceuticals, Inc. (“Progenics,” “Patent Owner”) has asserted U.S. Patent No. 11,424,035 (“the Patent”) against Petitioner in *Progenics Pharmaceuticals, Inc. et al v. MIM Software Inc.*, 1:24-cv-10437-PBS (D. Mass.) (“MA Litigation”). Ex1014. The earliest date of service is March 15, 2024.

Petitioner has filed a Petition for *Inter Partes* Review of U.S. Patent No. 10,665,346 in IPR2025-00630. The Patent and U.S. Patent No. 10,665,346 are related as, *e.g.*, continuations of an in-common parent application issued as U.S. Patent No. 10,762,993.

Petitioner is filing, contemporaneously with this petition, a Petition for *Inter Partes* Review of U.S. Patent No. 11,894,141 in IPR2025-00726. U.S. Patent No. 11,894,141 is a continuation of the application that issued as this Patent.

C. Lead and Back-up Counsel and Service Information (37 C.F.R. §42.8(b)(3)-(4))

Lead counsel is Jeff Metzcar (No. 52,027) at THOMPSON HINE LLP, 10050 Innovation Drive, Suite 400, Dayton, OH 45342;

Jeff.Metzcar@thompsonhine.com. Backup counsel is David R. Jaglowski (No. 58,514) at THOMPSON HINE LLP, 41 South High Street, Suite 1700, Columbus, Ohio 43215; David.Jaglowski@thompsonhine.com. Supplemental backup counsel is Marla R. Butler (to be admitted *pro hac vice*) at THOMPSON HINE LLP, Two Alliance Center, 3560 Lenox Road Suite 1600, Atlanta, Georgia 30326; Marla.Butler@thompsonhine.com. Petitioner consents to email service at the following address: IPDocket@ThompsonHine.com.

II. INTRODUCTION AND RELIEF REQUESTED

Petitioner requests *inter partes* review (IPR) and a finding that claims 1-38 and 41-43 (the “challenged claims”) of U.S. Patent No. 11,424,035 (“the Patent,” Ex1001) are not patentable.

The Patent claims systems and methods for automatically analyzing one or more “composite” medical images of a patient, using “a machine learning algorithm,” so as to generate “a radiologist report for the particular patient” or otherwise compute a “risk map” and the value of one or more “risk indices” that would subsequently be communicated to a radiologist or other user. *See, e.g.*, Ex1001, claims 1, 36. The Patent does not describe the machine learning algorithm except in general terms as “e.g., artificial neural networks (ANNs); e.g., convolutional neural networks (CNNs),” Ex1001, 26:62-65, and expansively describes the risk map as comprising “a graphical denotation marking a region of

risk of cancer or risk of recurrence of cancer”, *see, e.g.*, Ex1001, claim 1, and “risk indices” as simply being “numeric values indicative of prostate cancer state and/or progression in the patient,” *see, e.g.*, Ex1001, claims 15, 36.

The Patent was not rigorously compared against the prior art. The Examiner allowed the claims, without any rejections, after entering an Examiner’s Amendment. In the written record, specifically the Notice of Allowance, only one reference (Wu) was discussed, identified as “the closest prior art of record,” and evaluated against the claims, despite lacking a majority of the limitations recited therein yet disclosed in other prior art, *e.g.*, the use of a “machine learning algorithm,” the use of “composite images,” the administration of PSMA-binding imaging agents, and computing a “risk map.” *See* Ex1004, pp.232-233.

This Petition presents systems and methods of analyzing medical images that were not discussed in the written record of the Patent or the Patent’s predecessor applications. *See* Ex1005 (“Maier”); Ex1006 (“Huang”); Ex1007 (“Armor”). Additional references disclosing particular PSMA-binding imaging agents and their use with particular nuclear medicine imaging modalities (and use in so-called “theranostic” procedures) are presented in connection with various dependent claims. Although Maier and Huang were cited in a Notice of References Cited, and Armor was disclosed in an Information Disclosure Statement, the Examiner evidently did not properly consider such references, as

each is closer prior art in more (albeit not all) respects. For example, Maier discloses, in addition to the medical image processing aspects of Wu, the use of a “machine learning algorithm” and the computation of a “risk map” for a wide range of medical imaging applications. Huang discloses, in addition to the tracking aspects of Wu, the use of a “machine learning algorithm,” the use of “composite images,” and the identification and use of 3D boundaries (particularly, organ boundaries) so as to suppress or compensate for normal physiologic update of an imaging agent in such images. And Armor and/or various additional references not previously considered by the examiner discloses the use of PSMA-binding imaging agents with “composite” imaging so as to specifically identify primary and/or metastatic prostate cancer in such imaging.

As detailed in this Petition and supporting Declaration from Dr. Rosen, Ex1002, challenged claims 1-38 and 41-43 of the Patent are unpatentable as obvious in view of the presented prior art.

III. GROUNDS FOR STANDING AND FEES

Petitioner certifies that the Patent is available for *inter partes* review and Petitioner is not barred or estopped from requesting review.

The undersigned authorizes the charge of any required fees to Deposit Account No. 20-0809.

IV. THE PATENT AND PROSECUTION HISTORY

A. Specification

The Patent describes generation of “a 3D risk image corresponding to a patient organ (and/or other tissue) for comparison with reference images.”

Ex1001, 3:17-19.¹ “For example, a patient for whom a risk of cancer is detected can display a map indicating areas and/or degrees of risk and can compare this risk map with those of others for whom a given course of treatment is recommended.”

Ex1001, 3:26-30. An example risk map comprises “a visual representation (e.g., 3D representation) of tissue (e.g., an organ or other part of the body) with graphical denotations (e.g., texture- or color-coding) marking regions of risk of current disease..., e.g., cancer.” Ex1001, 4:3-7.

To produce the risk map, the Patent uses nuclear medicine images (*e.g.*, PET or SPECT) to identify regions of risk of cancer and anatomical images (*e.g.*, CT) to identify specific tissue regions such as organs and bones. To identify the regions of risk of cancer, the Patent explains that “hotspots” are “localized regions of high intensity in nuclear medicine images,” Ex1001, 16:3-5, that can be “classified as corresponding to cancerous lesions...,” Ex1001, 25:60-61. To identify specific

¹ Unless otherwise indicated, all emphasis, ellipses, and bracketed language has been added in the quotations and citations presented herein.

tissue regions, the Patent explains that:

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, 27:16-23.

The Patent also explains that “overlaying one image (e.g., a CT scan) with another (e.g., a PET scan) refers to establishing a mapping between coordinates and/or pixels or voxels of the two images that that [*sic*] represent the same physical locations (e.g., within the patient).” Ex1001, 27:9-13. Accordingly, “[o]nce the 3D boundaries of various regions are identified within a CT scan... the identified 3D boundaries can be transferred to [a] PET image” such that “regions of the PET image falling within and/or outside of the identified 3D boundaries can be accurately identified.” Ex1001, 27:34-40. Thus, “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 with the identified regions, e.g., based on features of detected hotspots.” Ex1001, 27:55-59.

Figure 4 of the Patent, below, depicts “full body gamma camera images showing hotspots automatically identified by the system” and includes graphical overlays delineating skeletal areas. Ex1001, 13:66-14:1, 29:47-48.

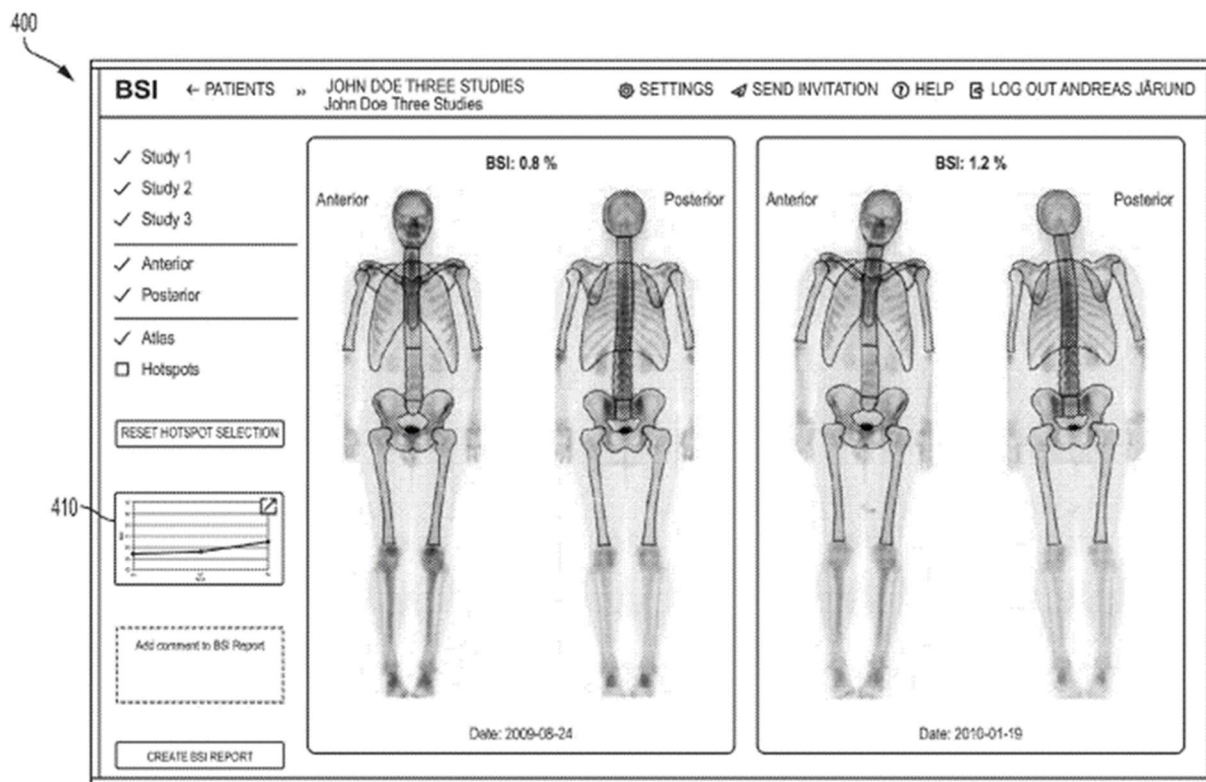


FIG. 4

As for the use of machine learning algorithms, the Patent states, but only generally, that machine learning algorithms can perform tasks such as: (i) segmentation of tissue regions in CT scans, Ex1001, 27:23-27; (ii) classification of hotspots as cancerous lesions, Ex1001, 26:37-43; and/or (iii) updating the process by which images are analyzed “(e.g., updating segmentation and/or classification routines based on [the] growing image database)...,” Ex1001, 3:7-10, Fig. 6. However, the claims do not appear to include any language analogous to that of item (iii). The Patent does not describe the machine learning algorithm except in general terms as “artificial neural networks (ANNs)” and “convolutional neural networks (CNNs).” Ex1001, 25:52-54.

B. Prosecution History

The Patent was filed on July 24, 2020 as a continuation claiming priority to provisional application no. 62/413,936, filed Oct. 27, 2016. Ex1001. On April 28, 2022, following an examiner-initiated interview, the Office mailed a Notice of Allowance with an Examiner's Amendment. Ex1004, pp.219-279. The Patent subsequently issued with four independent claims. Those four form two related sets of one system claim and one substantially identical method claim. The claims of the Patent, as they were presented for examination, recited only generic features such as receiving and storing, accessing, automatically analyzing, and generating reports from the analysis of one or more medical images, with added modest specificity, such as analysis "using a machine learning algorithm," medical images comprising a "composite image comprising a CT scan overlaid with a nuclear medicine image" following administration of a "Prostate Specific Membrane Antigen (PSMA) binding agent," and computing both "[a] risk index value indicative of cancer state or progression in the patient" and "a risk map comprising a graphical denotation marking... risk..." Ex1004, pp.127-128 (exemplary preliminary amendment of claim 19).

In the Examiner's Amendment, one such set was amended by the examiner to remove the requirement to calculate a risk index value. Ex1004, pp.226-228 (issued as claims 1 and 18). The other was amended by the examiner to add

requirements to determine such a risk map. Ex1004, pp.229-232 (issued as claims 35 and 41). Revealingly, for, example, the examiner amended claim 45 (issued claim 41) to include several “risk map”-related limitations, including: “automatically analyze the series of medical images for the patient using a machine learning algorithm to determine... a risk map comprising a graphical denotation marking a region of risk of cancer or risk of recurrence of cancer”; “for each of the one or more patient(s), store... the risk map”; “wherein the series of medical images... comprises a composite images of the particular patient”; and “using the corresponding nuclear medicine image with the identified 3D boundary(ies) of the one or more regions to compute... the risk map.” Ex1004, pp.230-232. The Examiner’s Reasons for Allowance stated that the closest prior art reference failed to disclose these added and certain other previously recited limitations. Ex1004, pp.232-233. However, as presented below, such limitations, and significant combinations thereof, are clearly present in Maier, Huang, and/or Armor.

V. IDENTIFICATION OF CHALLENGE

Petitioner requests review of challenged claims 1-38 and 41-43 of the Patent under 35 U.S.C. §103 as follows:

Ground	Prior Art	Claims Challenged
A	Maier in view of Huang and Armor	1-7, 9-24, 26-35
B	Maier in view of Huang and Armor, in further view of Neumaier	5-8, 22-25
C	Huang in view of Armor	36, 41
D	Huang in view of Armor, in further view of Giesel and Weineisen	37-38, 42-43

VI. LEVEL OF SKILL IN THE ART

A person of ordinary skill in the art (“POSITA”) would include a person with a medical (MD) degree and/or an advanced degree in Computer Engineering, Computer Science, Physics, or other field related to computer imaging, and at least 3 years of field experience with medical imaging devices, such as PET/CT or SPECT/CT systems. Ex1002, ¶39.

VII. CLAIM CONSTRUCTION (37 C.F.R. §42.100(b))

Except for the terms “risk map” and “risk indices” (and derivative term “risk index”) the claim terms of the Patent do not require an express construction.

A. “Risk Map” (Claims 1, 18, 36, and 41)

The term “risk map” does not have a well-established ordinary and customary meaning. Therefore, Petitioner looks to the intrinsic evidence to determine the meaning within the Patent.

The claims themselves internally define a risk map as “comprising a

graphical denotation marking a region of risk of cancer or risk of recurrence of cancer.” Ex1001, 36:51-52, 37:66-67; 39:1-3; 40:65-67. This description is consistent with the Patent specification, which similarly describes a risk map as an image corresponding to a patient organ or other tissue that indicates areas and/or degrees of cancer risk with graphical denotations such as texture or color. *See* Ex1001, 3:17-18 (“risk image corresponding to a patient organ (and/or other tissue)”), 3:28-29 (“a map indicating areas and/or degrees of risk... [i.e.,] risk map”); 4:3-7 (“a risk map, e.g., a visual representation... of tissue (e.g., an organ or other part of the body) with graphical denotations (e.g., texture- or color-coding) marking regions of risk of current disease..., e.g., cancer”).

As a matter of extrinsic evidence, the Patent Owner has asserted that Petitioner infringes claim 1 of the Patent, Ex1014, ¶¶62-66, and that Petitioner’s accused product satisfies the third element of claim 1 (*i.e.*, “cause display of the risk map via a graphical user interface (GUI)...”) because it “displays the risk map (i.e., tumor segmentation) via a graphical user interface (GUI).” Ex1014, ¶66. Based on this allegation, Patent Owner’s position appears to be that displaying segmented tumors (*i.e.*, segmented lesions) overlaid on a visual representation of tissue (*e.g.*, a medical image) constitutes display of a “risk map.” *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).

Accordingly, for the purpose of this Petition, the term “risk map” may be construed according to any of the following:

- (1) “an image corresponding to a patient organ or other tissue that indicates areas and/or degrees of cancer risk with graphical denotations such as texture or color,” consistent with the Patent specification;
- (2) “a visual representation of tissue overlaid with graphical denotations marking one or more regions of cancer or risk of recurrence of cancer,” consistent with the definition in the Patent claims; and
- (3) “a visual representation of tissue overlaid with segmented lesions,” consistent with Patent Owner’s allegations in litigation against Petitioner.

These constructions differ, if at all, only in the degree to which they expressly recite particular details.

B. “Risk Indices” and “Risk Index” (Claims 15, 17, 32, 35-37, and 41-42)

The terms “risk indices” and “risk index” do not have a well-established ordinary and customary meaning. Therefore, Petitioner looks to the intrinsic evidence to determine their meaning within the Patent.

The claims themselves internally define a risk index value as “indicative of cancer state or progression” (claims 15, 32, 36, 41), Ex1001, 37:13-16, 38:28-31, 39:5-7, 41:1-3, and being computable 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 level” (claims 17 and 35), Ex1001, 37:25-25, 38:43-52. This is consistent with the Patent specification, which similarly describes risk index values as “numeric values indicative of prostate cancer state and/or progression in the patient (e.g., numeric values identifying a particular cancer stage...),” Ex1001, 9:62-10:1, 11:57-62, or “based on automated analysis of intensity variations” in functional images, Ex1001, 16:8-13, 16:65-17:3.

As a matter of extrinsic evidence, the Patent Owner has asserted that Petitioner infringes claim 1 of U.S. Patent No. 11,894,141, Ex1014, ¶¶85-93, which is a continuation of the Patent. Patent Owner asserts that Petitioner’s accused product satisfies substep (b) of the fourth limitation of claim 1 of the ’141 patent (*i.e.*, “computing, using the nuclear medicine image with the identified 3D boundary(ies) of [] 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 computes statistics like SUVpeak, tumor burden, total tumor volume, and SUVmean. Ex1014, ¶93. Based on this allegation, Patent Owner’s position appears to be that computing such maximums, means, and/or volumes constitutes computation of a “risk index.” *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).

Accordingly, for the purpose of this Petition, the terms “risk indices” and “risk index” may be construed according to any of the following:

- (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; 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,” which is consistent with Patent Owner’s allegations in the MA Litigation.

These differ, if at all, only in the degree to which they expressly recite particular details.

VIII. DETAILED EXPLANATION OF GROUNDS FOR INVALIDITY

A. Summary of the Prior Art

1. US2016/0203263 (“Maier”)

Maier is a U.S. patent application published on July 14, 2016. Ex1005. It is prior art under 35 U.S.C. §102(a)(1) and (a)(2).

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. Ex1005, [0014]. Maier receives one or more medical images from a medical imaging system or database and 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 calculates quantitative metrics related to the patient's risk of future health outcomes, such as lung cancer and other cardiopulmonary disease, Ex1005, [0007], [0021], and automatically generates a report that includes the patient's medical images and such risk metrics, Ex1005, [0026], [0041], Fig. 3.

2. US2007/0081712 ("Huang")

Huang is a U.S. patent application published on April 12, 2007. Ex1006. It is prior art under 35 U.S.C. §102(a)(1) and (a)(2).

Huang discloses a learning-based framework for whole-body landmark detection, segmentation, and change quantification in single- and multi-mode medical images. Ex1006, [0002]. Huang applies that framework in semi-automatic and fully automated systems and methods for hotspot detection, segmentation, and change quantification in such images, including PET/CT and SPECT/CT images. Ex1006, [0074]-[0075]. Huang discloses the training and use of "discriminative classifiers and detectors for organs, tissue regions, or anatomical

sections,” Ex1006, [0072]-[0073], and that such classifiers can be used to suppress or compensate for hotspots that appear so due to normal physiological uptake, Ex1006, [0099], such as by applying organ- or region-specific thresholding so as to identify hotspots which exceed such threshold(s), Ex1006, [0114].

3. WO/2015/058151 (“Armor”)

Armor is a Patent Cooperation Treaty application published on April 23, 2015. Ex1007. It is prior art under 35 U.S.C. §102(a)(1) and (a)(2).

Armor discloses radiolabeled compounds that selectively bind to prostate specific membrane antigen (PSMA), Ex1007 [0002], and are used to differentiate cancerous tissue from normal or benign tissue and to evaluate the progress of prostate cancer in patients. Ex1007, [0008]. Armor discloses that a variety of radionuclides are useful for radioimaging, Ex1007, [0007], and 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].

4. US10,112,974 (“Neumaier”)

Neumaier is a U.S. patent issued from a PCT patent application, designating the United States, filed on August 24, 2015. Ex1008. It is prior art under 35 U.S.C. §102(a)(2).

Neumaier discloses the preparation and use of PSMA-specific PET

radiotracers including [^{18}F]DCFPyL. Ex1008, title, 1:10-13. Neumaier otherwise discloses the prior, clinical use of the PSMA-specific PET radiotracer [^{68}Ga]HBED-CC (50), also known as [^{68}Ga]PSMA-11. Ex1008, 64:30-47; Ex1001, 18:17-19; Ex1021, abstract.

5. Giesel

Giesel is a scientific journal article published by the European Journal of Nuclear Medicine and Molecular Imaging on June 25, 2016. Ex1010, p.1929. 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). It is prior art under 35 U.S.C. §102(a)(1).

Giesel discloses an ^{18}F -labeled, PET-imaged PSMA-binding agent, ^{18}F -PSMA-1007, as part of a “theragnostic tandem” with ^{177}Lu -PSMA-617, and that (1) these are used for the imaging and treatment of metastatic castration-resistant prostate cancer (mCRPC), and (2) ^{18}F -PSMA-1007 is superior to ^{68}Ga -PSMA-11 for imaging due to its possible large-scale production, at high activity, and its longer-lived radioisotope. Ex1010, p.1929 (first and last paragraphs). Giesel also discloses “theragnostic” use, where ^{177}Lu -PSMA-617 is used both therapy and nuclear medicine imaging (albeit not stated, SPECT imaging). Ex1010, p.1929 (third paragraph), figure.

6. **Weineisen**

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, p.1169. An interested member of the public could have reasonably located this reference by searching the publisher's websites (*e.g.*, jnm.snmjournals.org), the National Library of Medicine's PubMed® database, or the article's DOI reference. It is prior art under 35 U.S.C. §102(a)(1).

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

B. Ground A: Maier in view of Huang and Armor Renders Obvious Claims 1-7, 9-24, and 26-35.

1. Independent Claim 1

a) [1(pre)]²: “A network-based decision support system comprising:”

Maier discloses the limitations of the preamble, to the extent it is limiting. Ex1005, [0014], [0042], [0045], [0047]; Ex1002, ¶¶162-164. Maier discloses “systems and methods for automatically analyzing a patient’s one or more medical images” to provide “quantitative metrics related to the patient’s current health status and their risks for future health outcomes.” Ex1005, [0014]. Those metrics constitute decision support systems for both physicians and patients. Ex1002, ¶160. Indeed, a report “may be used by the referring physician to plan an interventional procedure” Ex1005, [0026], or the “format and content may be specifically tailored... for influencing the patient’s behavior,” Ex1005, [0042].

Maier’s system is “network-based.” Ex1002, ¶163. Namely, Maier implements its system through a combination of personal computers, tablets, mobile devices, and servers constituting “connected parts of a computer network,” including “the Internet.” Ex1005, [0045], [0047].

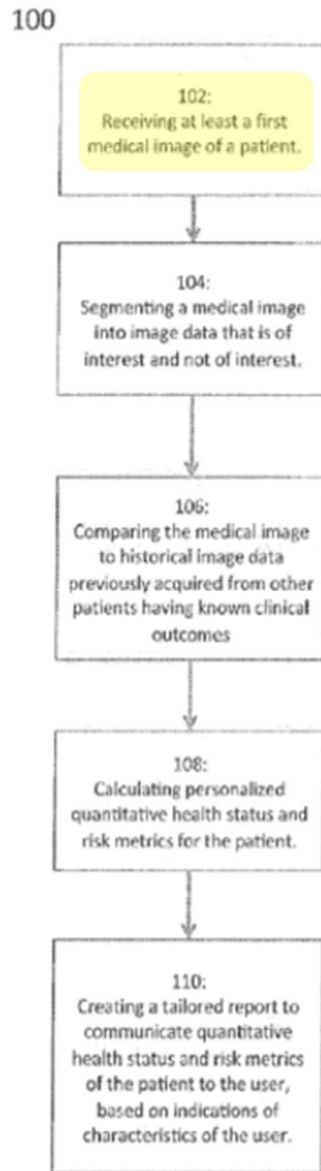
² The enclosed Claims Appendix includes the challenged claim language with bracketed reference characters identifying the respective limitations referenced in this Petition.

b) [1(a)]: “a processor; and a memory having instructions... executed by the processor... to:”

Maier discloses these limitations, which are generic recitations of structures present in any computer-implemented system like Maier’s. Ex1005, [0045]-[0046]; Ex1002, ¶¶165-166. Maier teaches that its system may include a processor and a memory. Ex1005, [0045] (“A system may include random access memory (RAM), one or more processing resources such as a central processing unit (CPU)...”), and the memory contains “applications or programs,” *i.e.*, instructions, which are executed by the processor to run the system, Ex1005, [0046]. Ex1002, ¶165.

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

Maier discloses this limitation. Ex1005, [0024], [0027], [0037], [0043]-[0044]; Ex1002, ¶¶167-168. Maier’s system interacts with a plurality of medical images, and stores the plurality of medical images in a database. Ex1005, [0024],[0027], Fig. 1. Indeed, Maier describes “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]. *See also* Ex1005, [0043]-[0044], [0037] (use of PACS database).



Maier, FIG. 1*

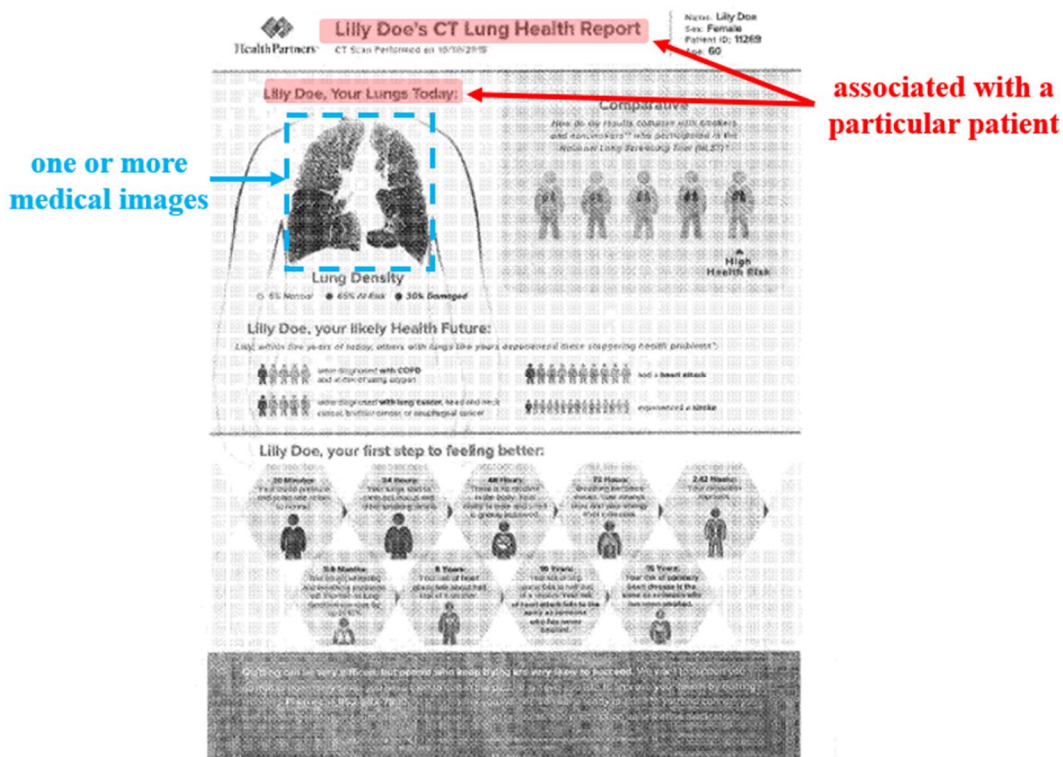
A POSITA would have recognized that comparing images and calculating values related to those images necessarily requires storing the images in a database. Ex1002, ¶167.

Therefore, Maier discloses this claim limitation.

- d) [1(c)]: “(ii) access one or more of the medical images associated with a particular patient from the database upon user request for transmission to the user for display on a user computing device;”**

Maier discloses these limitations. Ex1005, [0024], [0026], [0037], [0043]-[0045]; Ex1002, ¶¶169-170. At least when a report is generated, the processor must access the medical images discussed. *See* Section VIII.B.1.c).

A POSITA would recognize that Maier must access such medical images from a database. Ex1002, ¶169. But Maier also states that the first step of its method – receiving medical images – may occur “via a manual push by a user.” Ex1005, [0043], Figs. 1-2. Furthermore, Figure 3 of Maier depicts a user report



Maier, FIG. 3*

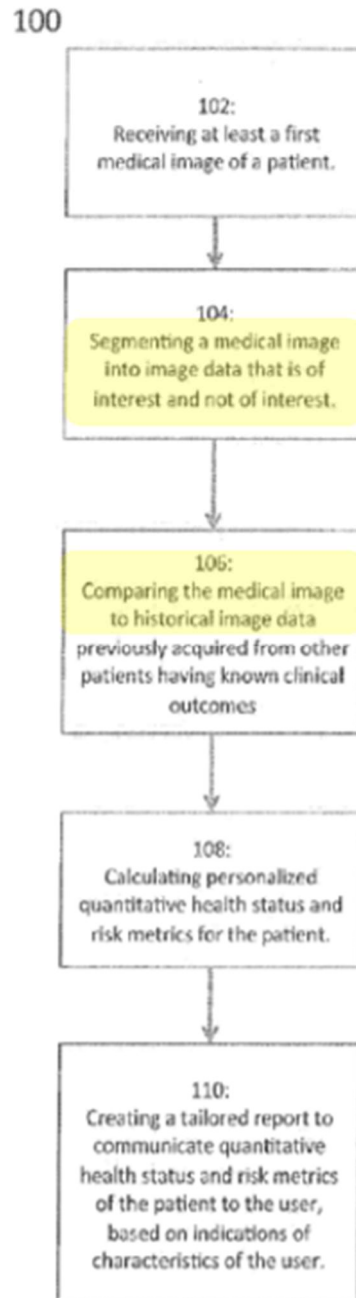
transmitted to the user including at least one accessed medical image. *See also* Ex1005, [0026] (defining Figure 3 as “a simple image of the patient’s lungs, comprising only the portion of their CT images that correspond to lung tissue”). Such accessed medical images may be displayed on a “user computing device.” Maier teaches that “a system or any portion thereof may be a personal computer.” Ex1005, [0045]. The generated report may be displayed “in a user readable format,” Ex1005, abstract, on the computer’s output device, such as “a computer monitor, flat-screen display, or other visual display...,” Ex1005, [0045]; Ex1002, ¶169. *See also* Ex1005, [0037] (“generating a PDF report which is wrapped in a DICOM or HL7 wrapper for communication to a Picture Archiving and Communication System (PACS) where it can be accessed and read by a user”).

Therefore, Maier discloses this claim limitation.

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

Maier discloses this limitation. Ex1005, [0014], [0027], [0032]; Ex1002, ¶¶171-173. Maier’s system and method includes “receiving at least a first medical image of a patient” and “analyzing the image data of interest by comparing it to comparison image data.” Ex1005, [0027], Fig. 1 (elements 104, 106). This analysis is computer-automated. Ex1005, [0027]. Maier teaches that this comparison “may comprise... unsupervised machine learning algorithms of all

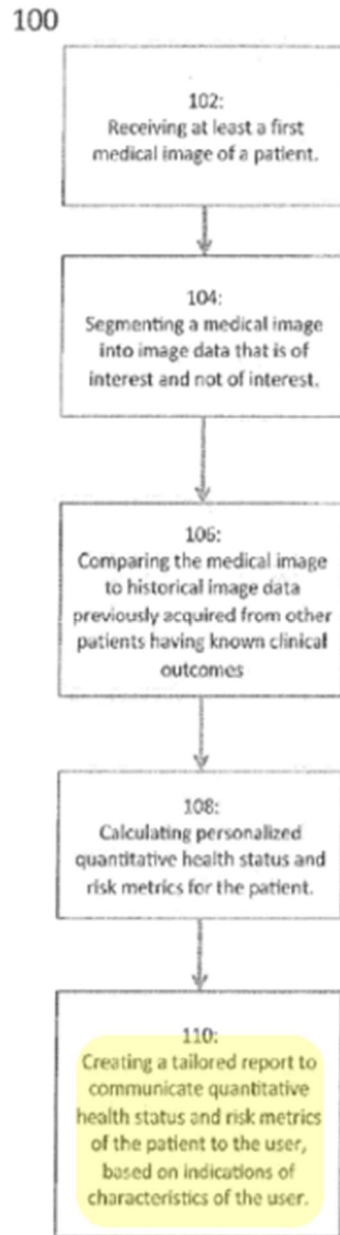
varieties.” Ex1005, [0032], [0023]. This constitutes automatic analysis of the image(s) by a machine learning algorithm. Ex1002, ¶¶171-172.



Maier, FIG. 1*

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

Maier discloses this limitation. Ex1005, [0014], [0036]; Ex1002, ¶¶174-175. First, Maier discloses creating a report for a particular patient to be viewed by



Maier, FIG. 1*

a radiologist. Ex1005, [0014] (“Multiple reports may be created for the same patient from the same medical images, wherein each of the multiple reports may be differently tailored for... a patient [or] ...a radiologist...”). Second, Maier teaches that a radiologist may review and annotate a user report. Ex1005, [0036] (“[V]oice recognition software... 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...”). Furthermore, a POSITA would understand that such a radiologist report is necessary to satisfy the standard of care in the art. *See* Ex1002, ¶174.

Therefore, Maier discloses this claim limitation.

- g) [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”**

Maier in view of Huang renders obvious this limitation. Ex1006, [0002]-[0004], [0011], [0098], [0130]; Ex1002, ¶176-182. While Maier does not disclose this limitation, Huang does, and a POSITA would have been motivated to combine the references to arrive at the claim limitation.

(1) Huang discloses the limitation.

Huang teaches a “learning-based framework for whole-body landmark detection, segmentation, and change quantification in single-mode and multi-mode medical images.” Ex1006, [0002]. Huang further teaches that “positron emission

tomography (PET)” is a nuclear medical whole-body imaging technique. Ex1006, [0003].

Huang combines “the functional imaging PET with an anatomical imaging computed tomography (CT).” Ex1006, [0011]. “[T]he acquisition of clinical quality PET and CT scans, accurately aligned, from a single imaging device” creates “a fused PET/CT image [where] abnormalities that are seen on PET can be located... on CT...,” Ex1006, [0011], and PET and CT images obtained from such a “single imaging device” are obtained at substantially the same time. Ex1002, ¶¶177-178.

(2) Rationale to combine.

- **Analogous art**

Huang is analogous art to Maier. Both references are within the same field of endeavor of anatomical and nuclear medical imaging, including segmentation and quantification of said images. Ex1002, ¶177. *See, e.g.*, Ex1005, [0002], [0005], [0015]-[0016], [0018], [0031]; Ex1006, abstract, [0002]-[0004], [0011].

- **Teaching, suggestion, motivation**

A POSITA would have found it obvious, with a reasonable expectation of success, to incorporate Huang’s fused PET/CT imaging into the system and method of Maier. Ex1002, ¶¶178-180; *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 417-418 (2007).

Improved physician decision-making: Maier may create a report including CT images to help “plan an interventional procedure” and “facilitate[e] the physician’s quick assessment” of the patient’s health. Ex1005, [0026]. Huang explains that a fused PET/CT image “enables the interpreting physician to make a more informed decision” about treatment, such as identifying and locating abnormalities. Ex1006, [0011]. Indeed, Huang recognizes that hotspots can be produced by “normal physiology,” *i.e.*, various organs, or “pathology, such as tumor or inflammations.” Ex1006, [0098]. “[T]o separate normal hot-spots from pathological hot-spots,” an “understanding of whole-body context” is required. Ex1006, [0098]. Thus, a POSITA would be prompted to combine Huang’s superior fused PET/CT image with Maier to better inform the physician. Ex1002, ¶179.

- **Combination according to known methods to yield predictable results.**

A POSITA would have recognized that Maier could be predictably combined with Huang’s composite images. Ex1002, ¶180. First, both Maier and Huang’s inventions operate on PET, SPECT, and/or CT images. *Compare* Ex1005, [0015] *with* Ex1006, [0130]. For example, because Huang reports obtaining a fused PET/CT image from a single imaging device, a POSITA would have recognized that the “composite” image would be a compatible “instrumentation source” for Maier. Ex1005, [0015]; Ex1006, [0011], [0130]

(explaining that “PET detection results and CT detection results are fused to prune false detections...”). Indeed, Huang’s fused PET/CT image operates the same way in combination with Maier as it does separately. Like Maier, Huang segments the PET/CT image into data of interest and analyzes said data. Ex1005, Fig. 1; Ex1006, Fig. 6, [0130]. And just as Maier would operate on the fused PET/CT image, Huang teaches that its “training and detection steps can be performed on the two image modalities jointly.” Ex1006, [0130]. Therefore, a POSITA would have recognized the results of this Maier-Huang combination were predictable.

- **Reasonable expectation of success**

A POSITA would have had a reasonable expectation of success in using Huang’s multi-modal images with Maier. Ex1002, ¶181. Both references are directed to medical image processing to identify cancerous tumors and lesions. Moreover, Huang recognizes the value of using multi-modal image results “in the areas of disease staging and therapy planning and monitoring.” Ex1006, [0011]. *See also* Ex1006, [0130]. A POSITA would therefore have expected Huang’s multi-modal images to operate successfully in Maier, which creates a report of “the patient’s current health status and their risks for future health outcomes.” Ex1005, abstract.

h) [1(g)]: “and following administration to the patient of an imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide”

Maier in view of Huang further in view of Armor renders obvious this limitation. Ex1007, [0002]-[0004], [0006]-[0007], [0009], [0056], [0064], [0078]; Ex1002, ¶¶183-187. Maier and Huang disclose administering a radiolabeled³ imaging agent⁴ to the patient. Ex1005, [0005] (“...the presence or non-presence of important imaging biomarkers for cancer... drives clinical decision-making...”); Ex1006, [0003] (“[PET] using [FDG] is a nuclear medicine medical whole-body imaging technique that produces a three-dimensional image of functional processes in the body.... FDG-PET imaging is essential and effective for detection, diagnosis and prognosis of tumors.”); Ex1002, ¶183. While they do not teach a radiolabeled PSMA-binding agent, Armor discloses such an agent, and a POSITA would have found it obvious to combine these references to arrive at this claim limitation.

(1) Armor discloses the limitation.

Armor’s disclosure relates to “imaging of prostate cancer (PCa) tissue to

³ *E.g.*, fluorine-18 deoxyglucose (“FDG”).

⁴ *I.e.*, an imaging biomarker such as a functional imaging agent. *See also* Ex1005, [0031].

differentiate cancerous tissue from normal tissue or benign prostate tissue,” including “determining the ratio of the uptake of a radiolabeled compound that selectively binds to [PSMA]...” Ex1007, [0002]. Armor reports that “[a] variety of radionuclides are known to be useful for radioimaging,” Ex1007, [0007], and 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 ^{99m}Tc-labeled anti-PSMA inhibitors, Ex1007, [0056], [0064], that can be imaged 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]; Ex1002, ¶184.

(2) Rationale to combine.

- **Teaching, suggestion, motivation.**

Improve cancer diagnosis and monitoring: Armor notes 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,” where “a PSMA targeted radiotracer would be an ideal imaging agent for diagnosis of prostate cancer and to evaluate the extent of disease progression...” Ex1007, [0006]. Thus, a POSITA

would have been motivated to combine Armor with Maier, whose system and method is used for “diagnosis of diseases” and “treatment follow-up.” Ex1005, [0018]. *See also* Ex1002, ¶184.

Compatibility with Maier and Huang’s multi-modal imaging: Armor generally references radiolabeled compounds “that selectively bind[] to prostate specific membrane antigen (PSMA),” Ex1007, [0002], which include, but are not limited to the specific radiolabeled compounds disclosed therein. *See* Ex1007, [0003] (“Most clinical drugs of this class are diagnostic agents incorporating a gamma-emitting nuclide...”). Armor discloses two radiolabeled Tc-99m anti-PSMA inhibitors – including ^{99m}Tc-MIP-1404 – that selectively bind to PSMA, Ex1007, [0056], [0064], and are imaged using SPECT/CT, Ex1007, [0009], however the Patent admits that, in April 2015, other radiolabeled PSMA-binding agents, such as [¹⁸F]DCFPyL, imaged by Positron Emission Tomography (PET), were known. Ex1001, 1:65-2:6. Maier in view of Huang is compatible with both SPECT/CT and PET (and, necessarily, PET/CT) imaging, such that any of such unnamed-but-known compounds could have been selected and used.

- **Simple substitution of one known element for another to obtain predictable results.**

A POSITA would have recognized that element [1(g)] simply substitutes the radiolabeled agent of the Maier-Huang combination (FDG) with a radiolabeled

PSMA-binding agent. Armor informs the POSITA that such agents were known in the art and were compatible with PET, SPECT, and CT imaging techniques. *E.g.*, Ex1007, [0002]-[0004], [0006]-[0007]. Therefore, A POSITA could have predictably substituted Armor’s PSMA-binding agents into the Maier-Huang combination to predictably arrive at this claim limitation. Ex1002, ¶185.

- **Reasonable expectation of success.**

A POSITA would have had a reasonable expectation of success in using Armor’s PSMA-binding agent with the Maier-Huang combination. Ex1002, ¶186. All three references discuss administering a functional imaging agent followed by functional imaging. Specifically, Huang and Armor disclose functional nuclear medicine imaging in combination with CT, including PET/CT and SPECT/CT. Furthermore, Armor praises PSMA-targeted radiotracers as “ideal” imaging agents for cancer diagnoses like those provided by the Maier-Huang combination. Ex1007, [0006].

Accordingly, Maier in view of Huang and Armor renders obvious limitation [1(g)].

- i) **[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”**

Maier in view of Huang renders obvious this claim limitation. Ex1005, [0028]; Ex1006 [0072]-[0075], [0099], [0114], [0140]; Ex1002, ¶¶188-194. Maier teaches that its processor analyzes medical images. Ex1005, [0027]-[0028], and this process is automatic, Ex1005, [0021] (“[A] computer-implemented algorithm... may measure, automatically and without any user input... and calculate a risk metric...”). Ex1002, ¶188. While Maier does not teach automatic analysis of a composite image, Huang teaches this, and a POSITA would have found it obvious to combine these references to arrive at this claim limitation.

(1) Huang teaches the limitation.

Huang detects “organs, [and] tissue regions” in anatomical CT, nuclear PET, and composite PET/CT images. Ex1006, [0072]. *See also* Ex1006, [0075], [0130] (composite SPECT/CT). Huang trains “discriminative classifiers and detectors” to analyze those images, including creating “3D bounding boxes” of organs. Ex1006, [0072]. Specifically, Huang teaches two scenarios for analyzing fused multi-modal images. In one, for example, PET and CT classifiers are used separately. Ex1006, [0130]. After each classifier is applied to its respective volume, the “detection results are fused to prune false detections.” Ex1006, [0130]. In another, a “single classifier” is trained on both volumes of the PET/CT image and applied to “joint features” of the PET and CT portions of a new composite image. Ex1006, [0130]. These disclose using PET/CT, or SPECT/CT “composite” images to

identify 3D boundaries, *e.g.*, those of organs, within a nuclear medicine image component. Ex1002, ¶¶189-190.

(2) Rationale to combine.

- **Teaching, suggestion, motivation.**

Improved, organ-specific identification: Huang discloses a basic method of (1) detecting normal organs or regions that often induce high FDG uptake; (2) segmenting the hotspots; and (3) suppressing, or compensating for, hotspots that arise due to normal physiological uptake. *See* Ex1006, [0099]. Also, because organs can vary significantly in FDG uptake, organs may be thresholded on an organ-by-organ basis. Ex1006, [0114]. “Using a whole-body context,” *i.e.*, a fused PET/CT or SPECT/CT image, allows the system to first detect and separate individual organs and regions and then apply organ- or region-specific suppression or thresholds. Ex1006, [0114]. These provide an express teaching, suggestion, or motivation use such multi-modality or “composite” images for such purposes within the nuclear medicine, *e.g.*, PET or SPECT, image component. Ex1002, ¶¶189-190.

Compatibility with machine-learning algorithms: Maier automatically analyzes medical images via machine learning algorithms. *See* Section VIII.B.1.e). Huang also uses machine learning algorithms. As presented in Section VIII.B.1.i)(1) above, Huang teaches, *e.g.*, that a single classifier may be applied to

joint features of a fused multi-modal image. Huang discloses that this scenario is an “application of a general learning-based framework.” Ex1006, [0072]. This informs the POSITA that the classifier is trained using machine learning.

- **Combining prior art elements according to known methods to yield predictable results.**

A POSITA would have found it obvious to combine Huang’s composite medical imaging with Maier. *See* Section VIII.B.1.g)(2). Huang discloses two scenarios where such images are analyzed to create “3D bounding boxes” of organs. Ex1006, [0072], [0130]. Thus, Maier and Huang teach every element of this claim limitation. Moreover, Huang’s analysis to create 3D boundary(ies) of organs or tissues would perform the same function in Maier, which separates organs or regions of interest from background anatomy. *See* Ex1005, [0028]. Thus, a POSITA could have predictably added Huang’s analysis of composite medical images into Maier. Ex1002, ¶192.

- **Known technique to improve similar devices in the same way.**

A POSITA would have recognized that this claim limitation improves upon the base system of Maier by employing composite medical imaging to identify 3D boundaries of organs within the nuclear medicine image. But Huang also uses “composite” images, such as fused PET/CT images, to identify 3D bounding boxes of organs, and a POSITA would have been readily able to implement Huang’s

improved, composite medical imaging in Maier to arrive at this limitation. Ex1002, ¶191. *See also* Section VIII.B.1.g)(2) (discussing rationale to combine Huang’s composite medical images with Maier).

- **Reasonable expectation of success.**

A POSITA would have had a reasonable expectation of success in combining Maier and Huang. Ex1002, ¶193. In addition to the rationales provided in Section VIII.B.1.g)(2), Huang teaches that its system which automatically identifies hotspots is “fast (real time), robust and accurate, and can be used as a practical application on a regular basis for hot-spot detection, segmentation, and change quantification” in fused PET/CT or SPECT/CT images. Ex1006, [0075]. *See also* Ex1006, [0073]-[0074].

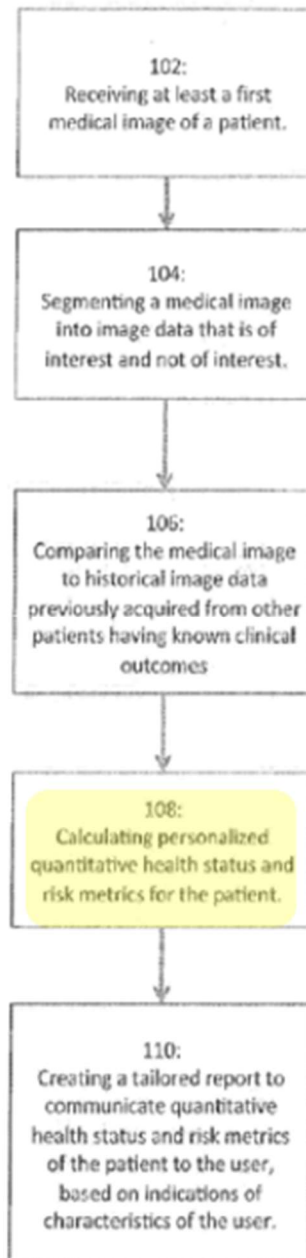
Therefore, Maier in view of Huang renders obvious this claim limitation.

j) **[1(i)]: “(b) computing, using the nuclear medicine image with the identified 3D boundary(ies) of the one or more region(s) a risk map comprising a graphical denotation marking a region of risk of cancer or risk of recurrence of cancer.”**

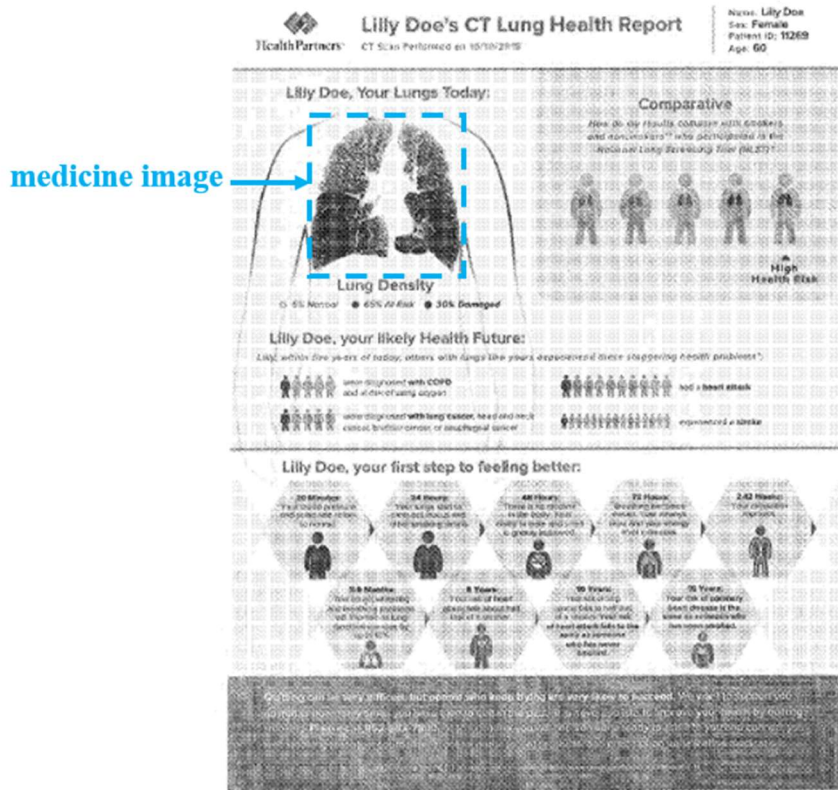
Maier in view of Huang renders obvious this claim limitation. Ex1005, [0007], [0027]-[0028]; Ex1006, [0011], [0072]-[0075], [0098]-[0099], [0114], [0130]; Ex1007 [0064], [0066]; Ex1002, ¶¶195-199. Maier explains that the medical image could be a nuclear medicine image, such as a PET image, Ex1005,

[0015], and segments that image into data that is of interest and data that is not, Ex1005, [0027]. For example, Maier “segment[s] lung parenchyma from the background anatomy” in such images. Ex1005, [0028]. For example, Maier calculates, and generates a report which includes, regions of risk related to “emphysema, lung cancer, decreased lung function,” and others, Ex1005, [0007], Figs. 1 and 3. As shown in Fig. 3, below, the medical image contains lighter and darker shading representing regions of risk of cancer, and below the image is a legend for interpreting graphically displayed levels of risk. There, the risk map and legend indicate that 5% of Lilly Doe’s lungs are “normal,” 30% are “at risk,” and 65% are “damaged.” In the image, corresponding color/shading is applied to regions of the image. Thus, Maier discloses computing a “risk map,” as that term is defined under each of Petitioner’s proposed constructions in Section VII.A. While Maier does not teach computation using a composite image, Huang teaches this, and a POSITA would have found it obvious to combine these references to arrive at this claim limitation. Ex1002, ¶¶196-197.

100

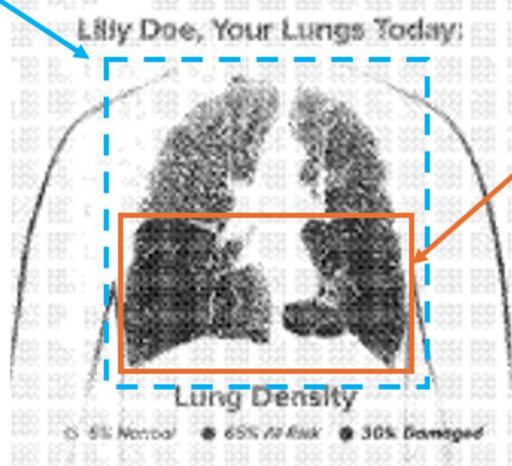


Maier, FIG. 1*



Maier, FIG. 3*

medicine image



“a risk map comprising a graphical denotation marking a region of risk of cancer or recurrence of cancer”

Maier, FIG. 3*

(1) Huang teaches the limitation.

Huang teaches multi-modal composite imaging, including PET/CT and SPECT/CT. Section VIII.B.1.g)(1). For example, PET nuclear medicine imaging uses FDG uptake to identify hotspots, and CT imaging allows a user to know where abnormalities are located anatomically. Ex1006, [0011]. Thus, in a “whole-body context... one can first detect, segment and separate organs or regions,” *i.e.*, identify 3D boundaries, via CT imaging and then apply “organ- or region-specific thresholding” in PET or SPECT imaging. Ex1006, [0114]. Huang teaches that joint-imaging modalities like PET/CT “enable[] the computer to understand on which organs or tissue regions each hot-spot is located... to separate normal hot-spots from pathological ones...” Ex1006, [0098]-[0099]; Ex1002, ¶196. *See also* Ex1006, [0009], [0072]-[0075], [0130]. Huang further teaches “quantify[ing] changes for the hot-spot based on the segmentation results and produc[ing] reports,” including “a visualization of the segmented results.” Ex1006, [0078]. A POSITA would recognize this as computing a risk map, fully as claimed. Ex1002, ¶197.

(2) Rationale to combine

A POSITA would have implemented this in the Maier-Huang-Armor combination for the same reasons explained for limitations [1(g)] and [1(h)] above, *see* Sections and VIII.B.1.h)(2) and VIII.B.1.i)(2), since the resultant risk map(s)

were merely applications of known mathematical calculations to PSMA-binding-agent-measured uptake within an identified 3D boundary, *e.g.*, the prostate or, specifically, a prostate tumor. Ex1002, ¶¶196-197.

Therefore, Maier in view of Huang and Armor renders obvious claim 1.

2. Claim 2: “The system of claim 1, wherein the nuclear medicine image is a SPECT scan.”

The Maier-Huang-Armor combination of claim 1 renders obvious this claim limitation. Ex1005, [0015]; Ex1006, [0075]; Ex1002, ¶¶200-203. Maier discloses that the patient’s medical images may be single-photon emission computed tomography, or SPECT, Ex1005, [0015], and Huang further teaches that its composite image modality may be PET/CT or SPECT/CT, Ex1006, [0075]. Ex1002, ¶201. A POSITA would have recognized that Huang’s described advantages for PET/CT composite images would apply equally to a SPECT/CT composite image. Ex1002, ¶202. *See also* Section VIII.B.1.g)(2) (rationale to combine Maier and Huang).

Therefore, Maier in view of Huang and Armor renders obvious claim 2.

3. Claim 3: “The system of claim 2, wherein the imaging agent comprises a metal chelated to the PSMA binding agent, and wherein the metal is the radionuclide.”

The Maier-Huang-Armor combination of claim 2 renders obvious this claim limitation. Ex1007, [0013], [0057]; Ex1002, ¶¶204-206. As discussed in Section VIII.B.1.h), Armor discloses two radiolabeled anti-PSMA inhibitors: Formula (1)

and Formula (2). Armor teaches that a “radionuclide chelating group” is bonded to the compounds represented by, *e.g.*, Formula (1), “via a linker” and that “[t]he transition metal radionuclide used for imaging is technetium-99m.” Ex1007, [0013]. Thus, in both Formulas (1) and (2), there is a chelated metal radionuclide. Ex1007, [0057] (“The radiolabel chelator is attached to the side chain carboxyl residue (Formula (1)) or the side chain amine group (Formula (2)) through an intervening linker.”); Ex1002, ¶205.

Therefore, Maier in view of Huang and Armor renders obvious claim 3.

4. Claim 4: “The system of claim 3, wherein the imaging agent comprises ^{99m}Tc -MIP-1404.”

The Maier-Huang-Armor combination of claim 3 renders obvious this claim element. Ex. 1002, ¶¶207-209. Armor teaches that its Formula (1) is ^{99m}Tc -MIP-1404. Section VIII.B.1.h).

5. Claim 5: “The system of claim 1, wherein the nuclear medicine image is a PET scan.”

The Maier-Huang-Armor combination of claim 1 renders obvious this claim limitation. Ex1002, ¶¶210-212; Section VIII.B.1.g) and corresponding rationales to combine Maier and Huang. *See also, e.g.*, Ex1006, [0011] (suggested use of single machine PET/CT imaging); Ex1007, [0002], [0007], [0078] (suggested use of radiolabeled PSMA-binding compounds generally); Ex1001, 1:65-2:6 (admitted prior use of PSMA-binding [^{18}F]DCFPyL with PET imaging).

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

The Maier-Huang-Armor combination of claim 1 renders obvious this claim limitation. Ex1002, ¶¶213-217; Section VIII.B.1.g) and corresponding rationales to combine Maier and Huang; Section VIII.B.1.h) and corresponding rationales to combine Maier, Huang, and Armor; Section VIII.B.5 and cited support. The selection of a nuclear imaging modality, such as PET, and the selection of a PSMA-binding agent comprising a correspondingly useful radionuclide that is a radioisotope of a halogen, such as ^{18}F in the combination of PET/ ^{18}F]DCFPyl, is taught by Armor given the Patent-admitted knowledge of the combination by a POSITA, Ex1002, ¶214, and would have been readily applicable to, and easily implemented with, the Maier-Huang combination of limitation [1(f)], Ex1002, ¶¶215-216.

Therefore, Maier in view of Huang and Armor renders obvious claim 6.

7. Claim 7: “The system of claim 5, wherein the imaging agent comprises ^{18}F]DCFPyL.”

The Maier-Huang-Armor combination of claim 1 renders obvious this claim limitation. Ex1002, ¶¶218-221; Section VIII.B.6 and all cited support. Likewise, the selection of PET/ ^{18}F]DCFPyl is taught by Armor given the Patent-admitted knowledge of the combination by a POSITA, Ex1002, ¶219, and would have been readily applicable to, and easily implemented with, the Maier-Huang combination

of limitation 1(f). Ex1002, ¶220.

Therefore, Maier in view of Huang and Armor renders obvious claim 7.

8. Claim 9: “The system of claim 1, wherein the system is a cloud-based system.”

The Maier-Huang-Armor combination of claim 1 renders obvious this claim limitation. Ex1005, [0037], [0046]-[0047]; Ex1002, ¶¶222-225. The term “cloud-based system” is entitled to its plain and ordinary meaning, and the Patent itself explains that a cloud-based system is one where computing device(s) are connected to resource providers via a network. Ex1005, Fig. 7.

Maier discloses that its hardware and software components “may be divided among a plurality of locations and connected directly or through a global computer information network, such as the Internet.” Ex1005, [0047]. “Any commercial or freeware web browser... capable of retrieving content from a network” may be used to implement Maier. Ex1005, [0046]. Additionally, Maier’s report “may be uploaded... to a cloud storage bank[.]” Ex1005, [0037]. A POSITA would recognize these disclosures constitute a cloud-based system, as claimed. Ex1002, ¶¶223-224.

Therefore, Maier in view of Huang and Armor renders obvious claim 9.

9. Claim 10: “The system of claim 1, wherein the processor is a processor of one or more network or Internet host servers.”

The Maier-Huang-Armor combination of claim 1 renders obvious this claim

limitation. Ex1002, ¶226-228. Maier discloses that its system and method “may utilize any computer-based system,” including a “server (e.g., blade server or rack server), a network storage device, or any other suitable device.” Ex1005, [0045]. Moreover, the hardware and software components of Maier’s system may be “divided among a plurality of locations and connected directly or through a global computer information network, such as the Internet.” Ex1005, [0047]. Thus, Maier discloses that the processor may be that of a network server, including one on the Internet. Ex1002, ¶227.

Therefore, Maier in view of Huang and Armor renders obvious claim 10.

10. Claim 11: “The system of claim 1, wherein the cancer is prostate cancer.”

The Maier-Huang-Armor combination of claim 1 renders obvious this claim limitation. Ex1005, [0017]; Ex1006, [0006], [0009]; Ex1002, ¶229-233. While Maier makes clear that its system and method is “not limited to a particular disease...,” Ex1005, [0018], Armor’s disclosure is “generally related to the imaging of prostate cancer...,” Ex1007, [0002]. Ex1002, ¶230-231. *See also* Ex1005, [0005], [0031]; Ex1006, [0009].

a) Rationale to combine

- **Teaching, suggestion, motivation**

Specific improvement for specific application: Maier teaches that it can

analyze the prostate. Ex1005, [0017]. However, Armor recognizes challenges specific to prostate cancer, including “imaging” and “differentiat[ing] clinically significant disease from silent or indolent disease.” Ex1007, [0006]. Armor teaches that its technique “can be performed using any nuclear medicine tomographic imaging technique that is suitable for detecting gamma radiation,” including SPECT/CT. Ex1007, [0009]. Therefore, a POSITA using Maier to analyze potential prostate cancer would have been motivated to incorporate Armor’s specific improvements for detecting prostate cancer. Ex1002, ¶231.

- **Reasonable expectation of success:** The reasons to combine have been explained in the context of limitation [1(g)]. Ex1002, ¶232; Section VIII.B.1.h)(2).

Therefore, Maier in view of Huang and Armor renders obvious claim 11.

11. Claim 12: “The system of claim 11, wherein the cancer is metastatic prostate cancer.”

The Maier-Huang-Armor combination of claim 11 renders obvious this claim limitation. Ex1002, ¶¶234-236. Armor further discloses that “[c]ompounds according to the present technology permit the detection of primary and metastatic prostate cancer tumors...” Ex1007, [0116].

12. Claim 13: “The system of claim 1, wherein the imaged tissue comprises bone.”

The Maier-Huang-Armor combination of claim 1 renders obvious this claim

limitation. Ex1002, ¶¶237-241. Maier teaches imaging of “a bone lesion,” Ex1005, [0017], Huang teaches that “to detect whole-body metastatic spread in bones, one needs to find the bones first,” Ex1006, [0071] (and “Bone Segmentation in PET-CT images,” Ex1006, [0124]-[0128]), and Armor teaches that “[i]n yet another embodiment, the tissue imaged is bone tissue,” Ex1007, [0077].

Therefore, Maier in view of Huang and Armor renders obvious claim 13.

13. Claim 14: “The system of claim 1, wherein the imaged tissue comprises a prostate of the patient.”

The Maier-Huang-Armor combination of claim 1 renders obvious this claim limitation. Ex1002, ¶¶242-247. Maier and Armor respectively teach, *e.g.*, that “suitable tissue types include lung, prostate, breast, ...bone, etc.,” Ex1005, [0017], and the imaging of the prostate for “replacing conventional prostate biopsies for determination of Gleason scores,” Ex1007, [0066]. Furthermore, Huang teaches the identification of “organs... such as kidney, liver, heart, bladder, brain, lung, ...etc.,” Ex1006, [0072], even if not specifically the prostate.

Therefore, Maier in view of Huang and Armor renders obvious claim 14.

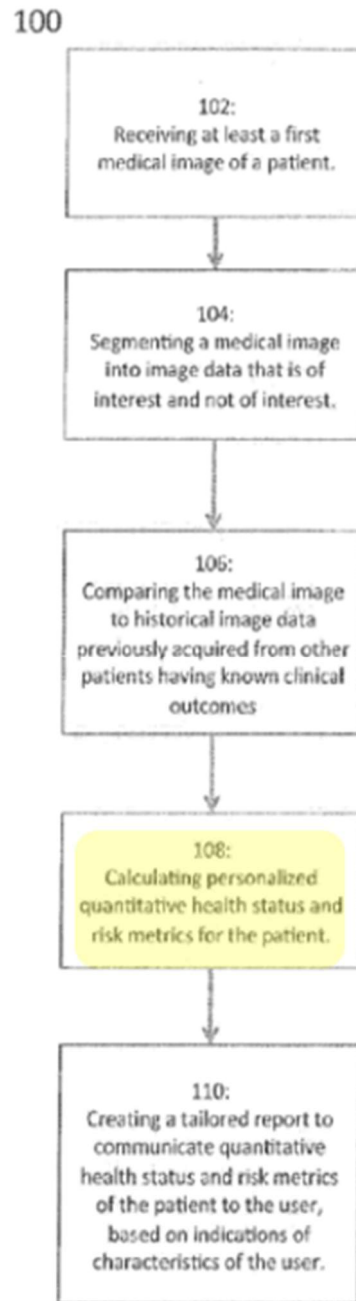
14. Claim 15: “The system of claim 1, wherein at step (b), the instructions cause the processor to compute a value of each of one or more risk indices... indicative of cancer state or progression in the patient.”

The Maier-Huang-Armor combination of claim 1 renders obvious this claim limitation, under any proposed construction of “risk indices” discussed in Section

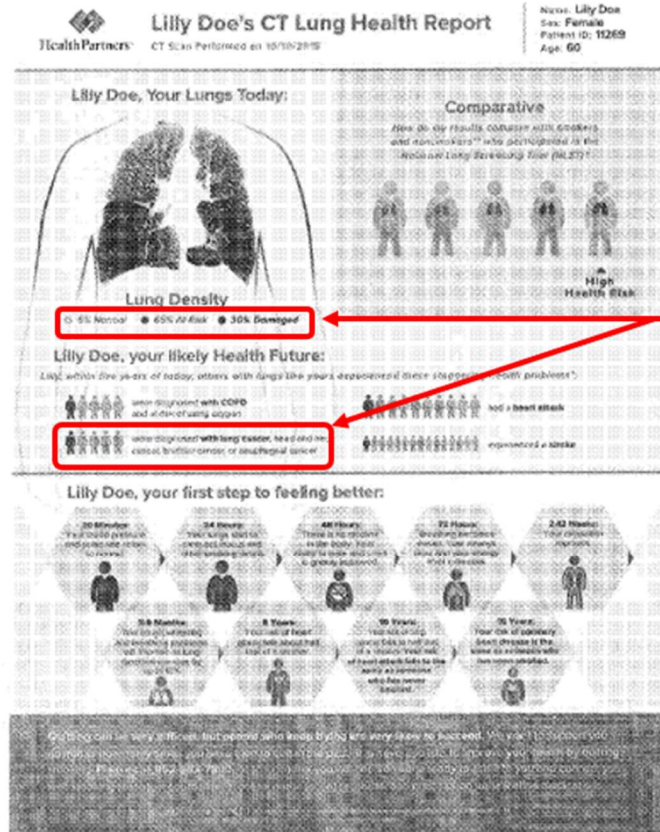
VII.B. Ex1005, [0007], [0026]-[0028], [0035]; Ex1006, [0011], [0072]-[0075], [0098]-[0099], [0114], [0130]; Ex1007 [0064], [0066]; Ex1002, ¶¶248-256.

First, Maier explains that the medical image could be a nuclear medicine image, such as a PET image, Ex1005, [0015], and segments that image into data that is of interest and data that is not, Ex1005, [0027]. For example, Maier “segment[s] lung parenchyma from the background anatomy” to calculate exemplary “quantitative status and risk metrics.” Ex1005, [0028]. For example, Maier calculates, and generates a report which includes, quantitative health status and risk metrics related to “emphysema, lung cancer, decreased lung function,” and others, Ex1005, [0007], such as “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], [0035], Figs. 1 and 3. As shown in Fig. 3, below, the report includes a legend for interpreting graphically displayed levels of risk. There, the legend indicates that 5% of the patient’s lungs are “normal,” 30% are “at risk,” and 65% are “damaged.” Adjoining the legend are other, graphical representations of the patient’s risk relative to a population for, here, lung cancer among others. Thus, Maier discloses computing a “risk index” as that term is defined under each of Petitioner’s proposed constructions in Section VII.B. While Maier does not teach computation using a composite image, Huang teaches such computation, and a POSITA would have found it obvious to combine these

references to arrive at this claim limitation. Ex1002, ¶251.



Maier, FIG. 1*



risk indices
"indicative of cancer state or progression"

Maier, FIG. 3*

(1) Huang teaches the limitation.

Huang teaches that joint-imaging modalities like PET/CT "enable[] the computer to understand on which organs or tissue regions each hot-spot is located... to separate normal hot-spots from pathological ones..." Ex1006, [0098]-[0099]. *See also* Ex1006, [0009], [0072-0075], [0130]. A POSITA would recognize this as computing a risk index, fully as claimed. Ex1002, ¶251.

(2) Armor teaches the limitation.

Armor teaches multi-modal composite imaging, at least using SPECT/CT.

Section VIII.B.1.h)(1). Armor discloses that uptake levels of its compounds directly correspond with a risk index, *i.e.*, the Gleason score for tumors in the prostate. Ex1007, [0064]. Specifically, “[t]he ratio of tumor uptake to background... directly correlate[d] with the Gleason score” and “provides a rationale for replacing conventional prostate biopsies for determination of Gleason scores...” Ex1007, [0066]. A POSITA would recognize this as computing a risk index, fully as claimed. Ex1002, ¶¶252-253.

(3) Rationale to combine.

A POSITA would have implemented this in the Maier-Huang-Armor combination for the same reasons explained for limitations [1(g)] and [1(h)] above, *see* Sections VIII.B.1.h)(2) and VIII.B.1.i)(2), since the resultant risk indices were merely applications of known mathematical calculations to the PSMA-binding-agent-measured uptake within an identified 3D boundary, *e.g.*, the prostate or, specifically, a prostate tumor. Ex1002, ¶¶251-255.

Accordingly, Maier in view of Huang and Armor renders obvious claim 15.

15. Claim 16: “The system of claim 15, wherein the plurality of medical images... comprise a series of medical images... taken over time, and... determine[ing] a value of at least a first risk index for each... , thereby tracking determined values of at least the first risk index... over time.”

The Maier-Huang-Armor combination of claim 15 renders obvious this claim limitation. Ex1006, [0022], [0078]; Ex1007, [0097], [0139], [0206];

Ex1002, ¶¶257-264. Maier discloses a database comprising a series of medical images of a first patient taken over time. Ex1005, [0024] (“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[.]”); Ex1002, ¶255. *See also* Ex1005, [0018], [0027]. While Maier does not teach tracking using a composite image, Huang and Armor teach such tracking, and a POSITA would have found it obvious to combine these references to arrive at this claim limitation.

a) Huang and Armor each disclose calculating a risk index for each image to determine values of the risk index over time.

Huang discloses this limitation. Ex1006, [0022] (“[A] method for quantifying changes across sub-volumes of digitized images including providing a plurality of new digitized image... representing a same patient at different time points... and quantifying changes in the sub-volume of interest over the different images[.]”). Huang’s method includes “change quantification mechanisms” such as “[g]rading of the hot-spot (tumor) at each time point...” Ex1006, [0078]. Additionally, Armor discloses a method of evaluating a patient suspected of prostate cancer that is “repeated periodically.” Ex1007, [0206]. Moreover, Armor teaches calculating a risk index. *E.g.*, Ex1007, [0015] (“[A]ssigning a severity level in terms of Gleason score...”). A POSITA would have recognized such grades as determined values of a “risk index” as used in the Patent. Ex1002, ¶¶259-260.

b) Rationale to combine

- **Use of known technique to improve similar devices in the same way.**

A POSITA would understand claim 16 of the Patent, which recites calculating risk indices for multiple points in time, as being taught by Huang and Armor, and an improvement over Maier, which arguably measures only the change since a previous point in time. *See* Ex1005, [0007], [0026], [0035]; Ex1002, ¶262. Through the latter lens, Huang and Armor can be seen as comparable improvements: Huang teaches calculating and reporting values at each point in time, while Armor evaluates disease progression periodically. Ex1006, [0078]; Ex1007, [0097], [0139]. A POSITA could have readily applied the teachings and/or improvement to Maier, as it simply amounts to iterations of the same calculations already performed by Maier and display of the values, not just a change. Ex1002, ¶¶262-263.

Therefore, Maier in view of Huang and Armor renders obvious claim 16.

16. Claim 17

- a) [17(pre)]: “The system of claim 15, wherein at step (b) the instructions cause the processor to... compute the value of the risk index by:**

The Maier-Huang-Armor combination of claim 15 renders obvious this claim limitation. Ex1005, [0021]; Ex1006, [0009], [0114]; Ex1007, [0064], [0066]; Ex1002, ¶¶265-268. *See also* Section VIII.B.14.

- b) **[17(a)]: “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**

The Maier-Huang-Armor combination of claim 15 renders obvious this claim limitation. First, Huang teaches that SUV values above a specific threshold are used to generate hot-spot candidate in regions, such as organs or tissues. Ex1006, [0114], and that maximum SUV values are used to grade tumors. Ex1006, [0009]. Similarly, Armor teaches that uptake levels and T/B ratios of its compounds can be used to determine the presence and extent of prostate cancer. Ex1007, [0064]. A POSITA would have recognized that SUV values and uptake levels are determined from intensity values of the nuclear medicine image, and from within the 3D boundary of a region such as an organ or tissue as previously explained. Ex1002, ¶¶266-267.

Rationale to combine: The reasons to combine have been explained in the context of claim 15. Ex1002, ¶266; Section VIII.B.14.

- c) **[17(b)]: “computing the value of the risk index based on the determined cancerous tissue levels within the one or more regions.”**

Second, a POSITA would have recognized that risk indices such as volume fraction, Ex1005, [0021], SUV_{peak} or volume (with SUV above SUV_{mean} or a threshold), Ex1006, [0114] and [0009], or T/B ratio or Gleason score, Ex1007,

[0064], [0006], are calculated based on “determined cancerous tissue levels,” themselves based on intensity values, both as fully recited in the claim. Ex1002, ¶267; Section VIII.B.14.

Therefore, the Maier-Huang-Armor combination of claim 15, as explained in this Section, renders obvious this overall claim limitation ([17]).

17. Claims 18-24, 26-33, and 35

Claim 18 recites “[a] method comprising performing, by a processor of a server computing device,” steps which are substantively identical to the “network-based decision-support system” functions recited in claim 1, addressed above. Similarly, dependent claims 19-24, 26-33, and 35 are substantively identical to dependent claims 2-7 and 9-17, discussed above. For those reasons discussed above and the additional reasons in the table below, Maier in view of Huang and Armor render obvious claims 18-24, 26-33, and 35. Ex1002, ¶¶269-296, 303.

Limitation	Reasoning {referenced limitation}
[18(pre)]	See Sections VIII.B.1.a), VIII.B.1.b) {[1(pre)]-[1(a)]}
[18(a)]	See Section VIII.B.1.c) {[1(b)]}
[18(b)]	See Section VIII.B.1.d) {[1(c)]}
[18(c)]	See Section VIII.B.1.e) {[1(d)]}
[18(d)]	See Section VIII.B.1.f) {[1(e)]}
[18(e)]	See Section VIII.B.1.g) {[1(f)]}
[18(f)]	See Section VIII.B.1.h) {[1(g)]}
[18(g)]	See Section VIII.B.1.i) {[1(h)]}
[18(h)]	See Section VIII.B.1.j) {[1(i)]}
[19]	See Section VIII.B.2 {[2]}
[20]	See Section VIII.B.3 {[3]}
[21]	See Section VIII.B.4 {[4]}

[22]	See Section VIII.B.5 {[5]}
[23]	See Section VIII.B.6 {[6]}
[24]	See Section VIII.B.7 {[7]}
[26]	See Section VIII.B.8 {[9]}
[27]	See Section VIII.B.9 {[10]}
[28]	See Section VIII.B.10 {[11]}
[29]	See Section VIII.B.11 {[12]}
[30]	See Section VIII.B.12 {[13]}
[31]	See Section VIII.B.13 {[14]}
[32]	See Section VIII.B.14 {[15]}
[33]	See Section VIII.B.15 {[16]}
[35]	See Section VIII.B.16 {[17]}

18. Claim 34: “The method of claim 33, wherein the receiving and storing... comprises repeatedly receiving and storing, over time, a plurality of medical images..., each obtained at a different time, to obtain [a] series of medical images of the first patient.”

Maier in view of Huang and Armor renders obvious this claim limitation. Ex1005, [0024], [0027]; Ex1006, [0022]; Ex1007, [0189], [0206]; Ex1002, ¶¶297-302. First, claim 34 depends from claim 33, and, thus, (as identified in the table above), the obviousness arguments and rationales referenced via the table of Section VIII.B.17 apply to claim 34.

Second, Maier discloses receiving at least a first medical image of a patient and, *e.g.*, “comparing the patient’s image(s) to the patient’s own image(s), such as previously obtained image(s) for the patient.” Ex1005, [0024], [0027]. *See also* Ex1005, [0018] (use for base-line assessments and treatment follow-up). Thus, Maier contemplates repeating such receiving and storing, as fully claimed.

Ex1002, ¶298.

Third, Huang discloses a method commencing with “providing a plurality of new digitized images... representing a same patient at different time points...” Ex1006, [0022], and Armor likewise teaches a method of evaluating and re-evaluating a patient with a suspected tumor over time, Ex1007, [0189], [0206]. *See also* Ex1006, [0003]; Ex1007, [0019], [0287]. Thus, Huang and Maier also contemplate repeating such receiving and storing, as fully claimed. Ex1002, ¶¶299-300.

Rationale to combine: The reasons to combine have been explained in the context of claims 16 and 11-14 and 16. Ex1002, ¶301; Sections VIII.B.15 and VIII.B.10-VIII.B.13.

C. Ground B: Maier in view of Huang and Armor, further in view of Neumaier, Renders Obvious Claims 5-8 and 22-25.

1. Claim 5

The Maier-Huang-Armor combination of claim 1, further in view of Neumaier, renders obvious this claim limitation. Ex1008, 1:9-12, 64:13-15, 64:29-46, 83:56-84:32; Ex1002, ¶¶304-308. Armor teaches a “PSMA targeted radiotracer” to diagnose prostate cancer and its progression. Ex1007, [0006]. Neumaier expands upon this concept with “PSMA-specific PET tracers such as [¹⁸F]DCFPyL.” Ex1008, 1:9-12. Neumaier teaches using such PSMA PET tracers “for imaging prostate cancer cells or prostate cancerous tissue.” Ex1008, 64:13-15; Ex1002, ¶305.

a) Rationale to combine.

- **Teaching, suggestion, motivation**

Improved tumor detection: Neumaier compares [^{18}F]DCFPyL to the [^{68}Ga]PSMA- tracer used in clinics prior to the [^{18}F]DCFPyL invention. Ex1008, 64:29-46. Neumaier praises [^{18}F]DCFPyL's longer half-life (110 minutes compared to 68 minutes) and "accessib[ility] in high amounts... permit[ting] the centralized production and regional distribution... for clinical use." Ex1008, 64:30-37; Ex1002, ¶305. Also, kidneys uptake much less [^{18}F]DCFPyL than the prior art [^{68}Ga]-PSMA tracer. Ex1008, 64:40-41. Neumaier reports that these characteristics "should improve the detection of tumor lesions in the abdomen." Ex1008, 64:41-42.

More accessible compound: Armor discloses " ^{99m}Tc -labeled anti-PSMA inhibitors for SPECT/CT imaging, Ex1007, [0056], but does not speak to the availability of those compounds. In contrast, Neumaier teaches that [^{18}F]DCFPyL incorporates a readily-accessible radioisotope. Ex1008, 64:42-46 ("Therefore, taking into an easy accessibility of [^{18}F]DCFPyL 1-10... represents an adequate alternative... for research and patient care."). Thus, in an environment where Armor's specific compounds are not available, a POSITA would be motivated to substitute Armor's SPECT/CT composite imaging with Neumaier's PET/CT imaging based on [^{18}F]DCFPyL. Ex1002, ¶306.

- **Reasonable expectation of success**

A POSITA would have had a reasonable expectation of success in combining Neumaier's imaging agents with the Maier-Huang-Armor combination(s). Ex1002, ¶307. Like Maier-Huang-Armor, Neumaier is directed to the field of medical image processing, *e.g.*, Ex1008, 1:14-18, and describes functional imaging after administration of an imaging agent – in the case of Neumaier, after that of a PSMA-binding agent, *e.g.*, Ex1008, 83:56-84:32. 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 model, “[¹⁸F]DCFPyL 1-10 displays imaging characteristics nearly identical to those of [⁶⁸Ga]HBED-CC (50)...” Ex1008, 64:37-39.

Therefore, Maier in view of Huang and Armor, in further view of Neumaier, renders obvious claim 5.

2. Claim 6

The Maier-Huang-Armor-Neumaier combination of claim 5 renders obvious this claim limitation. Ex1002, ¶¶309-311. A POSITA would recognize that Neumaier's radionuclide, [¹⁸F], is a radioisotope of a halogen. Ex1002, ¶310.

Rationale to combine: The reasons to combine have been explained in the context of claim 5. *See* Section VIII.C.1.a).

3. Claim 7

The Maier-Huang-Armor-Neumaier combination of claim 5 renders obvious this claim limitation. Ex1002, ¶¶312-314. Neumaier discloses [¹⁸F]DCFPyL as an improved imaging agent over the prior art. Ex1002, ¶313. *See* Section VIII.C.1 and rationales to combine.

4. Claim 8: “The system of claim 5, wherein the radionuclide is a radioisotope of gallium (Ga).”

The Maier-Huang-Armor-Neumaier combination of claim 5 renders obvious this claim limitation. Ex1002, ¶¶315-319. As presented in Section VIII.C.1, Neumaier compares [¹⁸F]DCFPyL to the prior art radionuclide PSMA-binding tracer [⁶⁸Ga]HBED-CC (50). *E.g.*, Ex1008, 64:29-39. A POSITA would recognize this prior art radionuclide as a radioisotope of gallium (Ga), and usable as claimed. Ex1002, ¶¶316-318.

5. Claims 22-25

As presented in Section VIII.B.17, claims 22-24 are substantively identical to claims 5-7. For those same reasons, claim 25 is substantively identical to claim 8 as addressed in the immediately preceding Section. Therefore, for the reasons described below, the Maier-Huang-Armor-Neumaier combination of claims 5-8 renders obvious claims 22-25. Ex1002, ¶¶320-323.

Limitation	Reasoning {referenced limitation}
[22]	<i>See</i> Section VIII.C.1 {[5]}
[23]	<i>See</i> Section VIII.C.2 {[6]}
[24]	<i>See</i> Section VIII.C.3 {[7]}
[25]	<i>See</i> Section VIII.C.4 {[8]}

D. Ground C: Huang in view of Armor Renders Obvious Claims 36 and 41.

1. Independent Claim 36

- a) [36(pre)]: “A method for tracking prostate cancer progression and treatment efficacy over time, for one or more patient(s), the method comprising:”

Huang in view of Armor renders obvious this claim limitation. Ex1006, [0003], [0006], [0019], [0022], [0098], [0189], [0206], [0287]; Ex1002, ¶¶324-329. Huang emphasizes the importance “of tumor size and volume” on “patient prognosis” and “evaluation of treatment effectiveness and follow up...,” Ex1006, [0003], and to track cancer progression and treatment over time, Huang discloses a method “for quantifying changes...” with digitized images... representing a same patient at different points in time,” Ex1006, [0022]. Ex1002, ¶325.

While Huang’s method is not expressly applied to prostate cancer, Armor’s disclosure “generally relate[s] to the imaging of prostate cancer (PCa) tissue to differentiate cancerous tissue from normal tissue or benign prostate tissue.” Ex1007, [0002]. Ex1002, ¶326. *See also* Ex1006, [0006], [0019], [0189], [0206], [0287].

Rationale to combine: *See* Sections VIII.B.1.h)(2) (reasons to combine

Huang's composite imaging and Armor's PSMA binding agents) and VIII.B.10; (reasons for application to prostate cancer); Ex1002, ¶¶326-328.

Therefore, Huang in view of Armor renders obvious this claim limitation.

- b) [36(a)]: “(a) repeatedly receiving and storing in a database, over time, by a processor of a computing device, a plurality of medical images... to obtain, for each of the one or more patient(s), a series of medical images taken over time;”**

Huang, in view of Armor discloses and renders obvious this claim limitation. Ex1006, [0022], [0074], [0149]; Ex1007, [0019], [0287], [0149]; Ex1002, ¶¶330-333. Huang discloses “providing... digitized images, said images representing a same patient at different time points,” for quantification and evaluation of tumor properties, Ex1006, [0022], 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]. Armor similarly discloses a method for monitoring prostate cancer in a patient and a method for monitoring the effectiveness of cancer treatment, Ex1006, [0019], [0287], and, additionally, a method of evaluating a patient suspected of prostate cancer that is “repeated periodically,” Ex1007, [0189], [0206]. Ex1002, ¶¶330-331.

Huang teaches that its method is performed by a processor of a computing device, Ex1006, [0149] (“[A] computer system 191 for implementing the present invention can comprise... a central processing unit (CPU) 192 [and] a memory

193... [and] can be implemented as a routine 197 that is stored in memory 193 and executed by the CPU 192,” Ex1006, [0149]. A POSITA would recognize this disclosure constitutes performance on a processor of a computing device, and, with regard to the Patent’s corresponding system claim, a memory with stored instructions for such performance. Ex1002, ¶¶330, 364.

Rationale to combine: The reasons to combine have been explained in the context of limitation [36(pre)]. *See* Section VIII.D.1.a); Ex1002, ¶¶330-332.

Therefore, Huang in view of Armor renders obvious this claim limitation.

- c) **[36(b)(1)]: “(b) for each of the one or more patient(s), automatically analyzing..., using a machine learning algorithm, the series of medical images for the patient to determine...”**

Huang discloses this claim limitation. Ex1006, [0062], [0072], [0099], [0130]; Ex1002, ¶¶334-335. Huang discloses using trained discriminative classifiers and detectors “in CT, MRI, PET, PET/CT or other types of images” for identifying, *e.g.*, organs, 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 trained classifiers used with registered multi-modal images such as PET/CT. Ex1006, [0130]; Section VIII.B.1.i). 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]; Ex1002; ¶334.

Therefore, Huang discloses this claim limitation.

- d) **[36(b)(2)]: “(i) 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”**

Huang, alone and in combination with Armor, discloses this claim limitation. Ex1002, ¶¶336-342. This limitation is substantively identical to a combination of claims 15 and 16, addressed in Sections VIII.B.14 and VIII.B.15, albeit without certain recited requirements which subsequently appear in limitations [36(f)] and [36(g)], addressed below. Ex1002, ¶¶336-338.

Rationale to combine: *See* Sections VIII.B.14 and VIII.B.15.b) (reasons to combine Huang’s and Armor’s calculation and tracking of risk indices); Ex1002, ¶¶339-341.

Therefore, Huang in view of Armor renders obvious this claim limitation.

- e) **[36(b)(3)]: “(ii) a risk map comprising a graphical denotation marking a region of risk of cancer or risk of recurrence of cancer;”**

Huang discloses this claim limitation. Ex1006, [0078]-[0079]; Ex1002, ¶¶343-344. Huang’s method segments cancerous lesions or tumors according to

SUV values and thresholds, may provide “a visualization of the segmented results,” and may render “segmented volumes... together with the fused PET/CT image for visual inspection and comparison.” Ex1006, [0078]-[0079]. A POSITA would recognize that computing such segmented volumes for rendering with the PET/CT, SPECT/CT, or other image constitutes determining a risk map. Ex1002, ¶343.

- f) **[36(c)]: “and (c) ...storing, by the processor, ...(i) the determined values of the one or more risk indices... and (ii) the risk map, for the patient for further processing or causing, by the processor, display of a graphical representation of the determined values of the one or more risk indices for the patient,”**

Huang discloses this claim limitation. Ex1002, ¶¶345-346. “At step 65, a change quantification of one or more properties... 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..., (2) Comparing the segmented hot-spot volumes over time... [and] (3) providing a visualization of the segmented results” where “VOIs returned from different time points can be rendered as surfaces in different colors, or the segmented volumes can be rendered together with the fused PET/CT image for visual inspection and comparison.” Ex1006, [0078]. A POSITA would recognize that these functions constitute determining a value of a risk index and determining a risk map. Ex1002, ¶345. These functions are followed by storage of

such values and the risk map for further processing (*e.g.*, generation of, or subsequent delivery to users of, reports) and/or display of such values (*e.g.*, in the form of such delivered reports). Ex1002, ¶345.

- g) [36(d)]: “wherein the series of medical images... comprises a composite images..., each composite image comprising a CT scan overlaid with a corresponding nuclear medicine image acquired at a substantially same time as the CT scan”**

Huang alone and in combination with Armor, discloses this claim limitation. Ex1002, ¶¶347-349. This limitation is substantively identical to limitation [1(f)], addressed in Section VIII.B.1.g).

Rationale to combine: Huang discloses PET/CT. For SPECT/CT, *see* Section VIII.B.1.h)(2) (rationale for combination of imaging agents and modalities).

Therefore, Huang in view of Armor renders obvious this claim limitation.

- h) [36(e)]: “and following administration to the patient of an imaging agent comprising a Prostate Specific Membrane Antigen (PSMA) binding agent comprising a radionuclide,”**

Armor discloses this claim limitation. Ex1002, ¶¶350-354. This limitation is substantively identical to limitation [1(g)], addressed in Section VIII.B.1.h).

Rationales to combine: The reasons to combine have been explained in the context of limitation [1(g)]. Ex1002, ¶¶351-353; Section VIII.B.1.h)(2).

Therefore, Huang in view of Armor renders obvious this claim limitation.

- i) **[36(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 corresponding nuclear medicine image; and”**

Huang discloses this claim limitation. Ex1002, ¶¶355-356. This limitation is substantively identical to limitation [1(h)], addressed in Section VIII.B.1.i).

- j) **[36(g)]: “using the corresponding nuclear medicine image with the identified 3D boundary(ies) of the one or more regions to compute (i) the value of each of the one or more risk indices and (ii) the risk map.”**

Huang discloses this claim limitation. Ex1002, ¶¶357-360. This limitation is substantively identical to a combination of limitation [1(i)] and claim 15, as addressed in Sections VIII.B.1.j) and VIII.B.14.

Therefore, Huang in view of Armor renders obvious this claim limitation.

Therefore, Maier in view of Huang and Armor renders obvious claim 36.

2. Independent Claim 41

Claim 41 recites “[a] system” for the same purpose as the method of claim 36, with components and functions which are substantively identical to the components and steps of the method. For those reasons and the additional reasons in the table below, Huang in view of Armor renders obvious claim 41. Ex1002, ¶¶361-374.

Limitation	Reasoning {referenced limitation}
[41(pre)]	See Section VIII.D.1.a) {[36(pre)]}
[41(a)]	See Section VIII.D.1.b) {[36(a)] components}

[41(b)]	See Section VIII.D.1.b) {[36(a)] step}
[41(c)(1)]	See Section VIII.D.1.c) {[36(b)(1)]}
[41(c)(2)]	See Sections VIII.D.1.d), B.14 {[36(b)(2)], [15]}
[41(c)(3)]	See Sections VIII.D.1.e), VIII.B.1.j) {[36(b)(3))], 1[i]}
[41(d)]	See Section VIII.D.1.f) {[36(c)]}
[41(e)]	See Sections VIII.D.1.g), VIII.B.1.g) {[36(d)], [1(f)]}
[41(f)]	See Sections VIII.D.1.h), VIII.B.1.h) {[36(e)], [1(g)]}
[41(g)]	See Sections VIII.D.1.i), VIII.B.1.i) {[36(f)], [1(h)]}
[41(h)]	See Sections VIII.D.1.j), VIII.B.1.j) {[36(g)], [1(i)]}

E. Ground D: Huang in view of Armor, in further view of Giesel and Weineisen, Renders Obvious Claims 37-38 and 42-43.

1. Claim 37

- a) [37(a)]: “The method of claim 36, wherein the series of medical images... 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”

The Huang-Armor combination of claim 36 renders obvious this claim limitation. Ex1002, ¶376. As previously presented in Sections VIII.D.1.b)-VIII.D.1.e) and VIII.D.1.h), Huang in view of Armor discloses and renders 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.

Therefore, Huang in view of Armor renders obvious this claim limitation.

- b) [37(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,”**

Huang in view of Armor, further in view of Giesel and Weineisen, renders obvious this limitation. Ex1011, abstract, pp.1169, 1173-1175; Ex1010, p.1929; Ex1002, ¶¶377-380. While the Huang-Armor-Maier combination does not disclose this limitation, Giesel and Weineisen do, and a POSITA would have been motivated to combine the references to arrive at the claim limitation.

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 (mCRPC)].” Ex1011, abstract, p.1169 (first paragraph); Ex1010, p.1929. In such a process, a patient diagnosed with mCRPC, *e.g.*, via [¹⁸F]DCFPyL PET/CT as presented in Sections VIII.B.5 and VIII.B.7, is subsequently “staged” via ¹⁸F-PSMA-1007 or ⁶⁸Ga-PSMA-11 PET (or, as in Huang-Armor, and in Weineisen, PET/CT), Ex1010, p.1929, and therapeutically treated with ¹⁷⁷Lu-PSMA-617 and ensued SPECT/CT imaging/dosimetry, Ex1010, p.1929 (figure) and Ex1011, pp.1173-1174 (using alternate ⁶⁸Ga- and ¹⁷⁷Lu-PSMA- agents disclosed at p.1170). This constitutes performance of limitation [37(b)] with a second nuclear imaging modality (SPECT) and radiopharmaceutical (¹⁷⁷Lu-PSMA- agents). Ex1002, ¶378.

(1) Rationale to combine

- **Teaching, suggestion, motivation**

Improved therapeutic treatment: Giesel states that “¹⁸F-PSMA-1007 and ¹⁷⁷Lu-PSMA-617 seem to be a perfect theragnostic tandem.” Ex1010, p.1929. Weineisen also explains, in the context of a similar theranostic tandem, that “high contrast in PET imaging and therapeutic effectiveness with no detectable side effects qualifies ⁶⁸Ga-/¹⁷⁷-Lu-PSMA I&T to be a valid choice for the theranostic management of [prostate cancer].” Ex1011, p.1175. *See also* Ex1011, p.1176 (conclusion). ¹⁷⁷Lu-PSMA- agents also allow for *in vivo* dosimetry via SPECT/CT. Ex1011, pp.1174, 1169 (second paragraph). A POSITA would have expected an improvement in therapeutic treatment based upon these disclosures. Ex1002, ¶378.

- **Reasonable expectation of success**

In addition to the statements presented immediately above, 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 [prostate cancer].” Ex1011, p.1176; Ex1002, ¶379.

Therefore, Huang in view of Armor, further in view of Giesel and Weineisen, renders obvious this claim limitation.

- c) **[37(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.”**

The Huang-Armor-(Giesel-Weineisen) combination of limitations [36(a)]-[36(b)] renders obvious this limitation. Ex1002, ¶¶381-382. The “such that...” clause is merely the inherent consequence of performing the preceding limitations and recited determinations, *e.g.*, for “improving imaging and therapy planning” and dosimetry. Ex1011, pp.1169 (second paragraph), 1174; Ex1002, ¶381.

2. Claim 38: “The method of claim 37, wherein the medical images of [the] 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.”

The Huang-Armor-Giesel-Weineisen combination of claim 37 renders obvious this additional limitation. Ex1011, pp.1169, 1173-1174; Ex1007, [0010], [0121]; Ex1002, ¶¶383-385. As referenced in Section VIII.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], [0121]. Also, in addition to the diagnostic applications presented in Sections VIII.B.5 and VIII.B.7, Weineisen reports imaging, via ⁶⁸Ga-PSMA-agent PET/CT, with demonstrated uptake in a primary tumor, Ex1011, pp.1173, 1174

(second full paragraph). Further, as presented in Section VIII.E.1.b), Weineisen (and, inherently, Giesel, given the figure therein) change to SPECT/CT 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 (*e.g.*, Weineisen’s ¹⁷⁷Lu-PSMA I&T “endoradiotherapy”) is recommended. Ex1007, [0121]; Ex1002, ¶384.

Therefore, Huang in view of Armor, further in view of Giesel and Weineisen, renders obvious claim 38.

3. Claims 42-43

Claims 42 and 43 depend from independent claim 41. As presented in Section VIII.D.2, claim 41 is substantively identical to claim 36. Therefore, for those reasons and the additional reasons in the table below, Huang in view of Armor, further in view of Giesel and Weineisen, renders obvious claims 42-43. Ex1002, ¶¶386-387.

Limitation	Reasoning
[42(a)]	See Section VIII.E.1.a) {[37(a)]}
[42(b)]	See Section VIII.E.1.b) {[37(b)]}
[42(c)]	See Section VIII.E.1.c) {[37(c)]}
[43]	See Section VIII.E.2 {[38]}

IX. INSTITUTION IS APPROPRIATE

As explained in Section II, Petitioner presents substantially different prior art and arguments than those previously considered by the Office. 35 U.S.C. §325(d); *Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH*, IPR2019-01469, Paper 6 at 7-10 (PTAB Feb. 13, 2020) (precedential). Petitioner’s principal prior art was not properly and substantively considered by the Examiner during original prosecution, and other prior art concerning particular imaging agents, functions, and processes not available to the examiner.

Further, institution should not be denied under 35 U.S.C. §314(a) based on analysis of the *Fintiv* factors,⁵ which are relevant here because the Patent is also the subject of the pending MA Litigation.

The first factor is “whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted.” *Fintiv*, Paper 11, p.6. Petitioner MIM has not yet requested a stay. Petitioner will be filing additional petitions for IPR directed to other patents that are being asserted in the MA Litigation, and Petitioner plans to move to stay the MA Litigation if the petitions are granted. The court entered its scheduling order less than two weeks ago. Ex1028. As such, the

⁵ *Apple Inc. v. Fintiv Inc.*, IPR2020-00019, Paper 11 at 5-6 (PTAB March 20, 2020).

court is likely to grant a forthcoming motion to stay pending IPRs, and this factor weighs against denying institution.

The second factor is the “proximity of the court’s trial date to the Board’s projected statutory deadline for a final written decision.” *Fintiv*, Paper 11, p.6. The court adopted its case schedule less than two weeks ago and has not set a trial date. Ex1028, p.4. As a result, this factor also weighs against denying institution.

The third factor is “investment in the parallel proceeding by the court and the parties.” *Fintiv*, Paper 11, p.6. The MA Litigation is still in its infancy. Petitioner MIM answered the latest amended complaint less than five weeks ago, and the court adopted its case schedule less than two weeks ago. Thus far, the only deadline has been for the exchange of initial disclosures on February 28. Ex1027, pp.8-11. The parties have not taken any discovery, of which the court set deadlines falling between May 2026 and October 2026, “subject to change per local rule.” Ex1028, p.3. As such, this factor, too, weighs against denying institution.

The fourth factor is “overlap between issues raised in the petition and in the parallel proceeding.” *Fintiv*, Paper 11, p.6. This factor only further serves to highlight the lack of progress in the MA Litigation. Because the Patent Owner has not served infringement contentions and Petitioner has not served invalidity contentions, it is unknown to what extent the issues raised in this petition will overlap with those in the MA Litigation. As such, this factor should be, at worst,

neutral.

The fifth factor is “whether the petitioner and the defendant in the parallel proceeding are the same party.” *Fintiv*, Paper 11, p.6. “Although this factor may, standing alone, be neutral, under these circumstances in which the trial date is not set and may occur after [the panel’s] Final Written Decision date... the fifth *Fintiv* factor weighs against discretionary denial of institution.” *Fusion Orthopedics, LLC v. Extremity Medical, LLC*, IPR2023-00894, Paper 15, p.32 (Nov. 17, 2023).

The sixth factor is “other circumstances that impact the Board’s exercise of discretion, including the merits.” *Fintiv*, Paper 11, p.6. No other circumstances warrant denying the Petition given that the balance of the previously-discussed factors weigh in favor of instituting review. When “the Petitioner has set forth a reasonably strong case for the obviousness of most challenged claims,” “this factor weighs in favor of not exercising discretion to deny institution...” *Sand Revolution II, LLC v. Continental Intermodal Grp.-Trucking LLC*, IPR2019-01393, Paper 24, p.13 (PTAB June 16, 2020).

The Board should not deny institution under § 314(a) based on the *Fintiv* factors.

X. CONCLUSION

In light of the strength of the identified grounds and absence of discretionary policy considerations, the Board should institute review of the challenged claims.

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CERTIFICATION UNDER 37 C.F.R. § 42.24(D)

Pursuant to 37 C.F.R. §42.24(a)(1)(i), I certify that this paper includes 13811 words. In accordance with 37 C.F.R. §42.24(a)(1), this word count does not include a count of the words in a table of contents, a table of authorities, mandatory notices under §42.8, a certificate of service or word count, or appendix of exhibits or claim listing. Furthermore, in accordance with 37 C.F.R. §42.24(d), this word count is the word count of the word-processing system used to prepare the paper.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6 and 42.105, the undersigned hereby certifies that a true and correct copy of the Petition for *Inter Partes* Review in connection with U.S. Patent No. 11,424,035 and supporting evidence was served on March 14, 2025, upon agreement of the parties, via electronic mail on the following counsel of record for Patent Owner, Progenics:

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