

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. 10,665,346
Filing Date: December 18, 2019
Issue Date: May 26, 2020
Title: NETWORK FOR MEDICAL IMAGE ANALYSIS, DESIGN SUPPORT
SYSTEM, AND RELATED GRAPHICAL USER INTERFACE (GUI)
APPLICATIONS

Inter Partes Review No.: IPR2025-00630

DECLARATION OF DR. BRUCE ROSEN

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EXHIBIT LIST

No.	Description
Ex1001	U.S. Patent No. 10,665,346 (“the Patent”)
Ex1002	RESERVED
Ex1003	Dr. Rosen Curriculum Vitae
Ex1004	Prosecution History File of the Patent (Application No. 16/718,839)
Ex1005	U.S. Patent Application Publication No. 2012/0123253 (“Renisch”)
Ex1006	U.S. Patent Application Publication No. 2015/0063667 (“Sprenicz”)
Ex1007	U.S. Patent Application Publication No. 2011/0007954 (“Suehling”)
Ex1008	U.S. Patent Application Publication No. 2016/0203263 (“Maier”)
Ex1009	U.S. Patent Application Publication No. 2016/0335395 (“Wu”)
Ex1010	U.S. Patent No. 9,028,800 (“D’Souza”)
Ex1011	RESERVED
Ex1012	U.S. Patent Application Publication No. 2016/0180042 (“Menon”)
Ex1013	Second Amended Complaint, <i>Progenics Pharmaceuticals, Inc. v. MIM Software Inc.</i> , Case No. 1:24-cv-10437-PBS, Dkt. 25, April 5, 2024.
Ex1014	RESERVED
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, Suehling, et al., “Hierarchical Parsing and Semantic Navigation of CT Data,” <i>Medical Imaging 2009: Image Processing</i> , Proceedings of SPIE Vol. 7259, pp. 725902-1 to

	725902-8 (2009) (“Seifert”)
Ex1021	RESERVED
Ex1022	Gandaglia, “Distribution of metastatic sites in patients with prostate cancer: A population-based analysis,” <i>The Prostate</i> 74(2):210-216 (2014) (“Gandaglia”)
Ex1023	Guntur, “Bone as an endocrine organ.” <i>Endocrine Practice</i> . 18(5):758-762 (2012) (“Guntur”)
Ex1024	U.S. Patent Application Publication No. 2010/0032575 (“Iagaru”)

I. INTRODUCTION

1. I have been retained by GE HealthCare Technologies Inc. (“GEHC”) and its wholly owned subsidiary, MIM Software Inc. (“MIM”), to provide a declaration in support of MIM’s Petition for *Inter Partes* Review of U.S. Patent No. 10,665,346 (“the Patent”) (Ex1001). The opinions presented here are my own and are based on my own personal knowledge.

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

3. I have been asked to prepare this declaration explaining the reasons and bases for my opinions that claims 1-13 of the Patent are unpatentable. As discussed below, I have concluded that these claims are anticipated and/or would have been obvious to the person of ordinary skill in the art at the time of the alleged invention in light of prior art patent publications including U.S. Patent Application Publication No. 2012/0123253 (“Renisch”) (Ex1005), U.S. Patent Application Publication No. 2015/0063667 (“Sprencz”) (Ex1006), U.S. Patent Application Publication No. 2011/0007954 (“Suehling”) (Ex1007); U.S. Patent Application Publication No. 2016/0203263 (“Maier”) (Ex1008), U.S. Patent Application Publication No. 2016/0335395 (“Wu”) (Ex1009), U.S. Patent No. 9,028,800 (“D’Souza”) (Ex1010), and U.S. Patent Application Publication No.

2016/0180042 (“Menon”) (Ex1012).

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

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

II. QUALIFICATIONS AND EXPERIENCE

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

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

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

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

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

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

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

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

14. I have been elected as a member of the National Academy of

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

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

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

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

III. COMPENSATION AND PRIOR TESTIMONY

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

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

IV. LEGAL STANDARDS

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

A. Priority Date

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

B. Claim Construction

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

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

23. I understand that “extrinsic evidence” may also be considered when determining the meaning of a claim term. I understand there are different sources of extrinsic evidence, including dictionaries, inventor testimony, expert testimony,

and learned treatises. I understand that intrinsic evidence is generally favored over extrinsic evidence, and that extrinsic evidence may not be used to contradict the meaning of the claim term when read in light of the intrinsic evidence.

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

C. Anticipation

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

26. I understand that an element is inherently disclosed in a reference if it necessarily is present in that which is described in the reference. Thus, a prior art

reference, even without expressly referring to a claim limitation, may nonetheless anticipate by inherency.

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

D. Obviousness

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

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

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

31. I understand that an obviousness determination can be based on a single prior art reference, a combination of multiple prior art references, or a combination of prior art references and the patentee's admissions regarding the scope and content of the prior art.

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

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

use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

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

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

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

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

achieving the claimed invention.

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

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

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

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

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

40. I have undertaken to consider the knowledge the POSITA would have had as of October 27, 2016, which is the date I have been asked to assume is the priority filing date for the Patent. When I refer to the POSITA in this declaration in my discussion of the Patent, I am referring to a person of ordinary skill in the art as of that date.

V. TECHNOLOGICAL BACKGROUND

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

A. Medical Imaging Modalities

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

1. Anatomical Imaging

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

2. Functional Imaging

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

and detect radiation emitted from the patient to reconstruct 3D medical images.

45. The operational differences between PET and SPECT cameras are not relevant here. What is relevant is that PET and SPECT imaging scanners are both designed to visualize metabolic and physiological activity through detection of radiation from a radionuclide or radiotracer. To perform nuclear medicine imaging, radionuclides are purposefully introduced into a patient's body in the form of a radiopharmaceutical (or radiotracer). Radiopharmaceuticals are compounds that include a biologically active delivery molecule labeled with a radiation emitting radionuclide. The delivery molecule is selected to target a cell or tissue associated with a particular disease or metabolic activity of interest. The molecules are chosen based on their ability to accumulate preferentially in certain tissues or organs, and many delivery molecules targeting different organs or disease states have been created. Thus, the delivery molecule that is selected will determine how the radiopharmaceutical behaves inside the human body and will direct the radiation emitting radionuclide toward specific organs or tissues in the body. As is pertinent here, many delivery molecules have been developed to target various types of cancer tissue.¹

¹ One of the most common radiopharmaceuticals is [18F]-FDG (fluorodeoxyglucose), which is a glucose analog labeled with a radionuclide. (*cont'd*)

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

B. Image Registration and Composite Images

47. Anatomical images provide clear structural information regarding the location, shape, and size of organs and other tissues. Nuclear medicine functional images provide complementary information regarding physiological activity but often lack the clarity necessary to provide important structural context, such as the location of hot spots relative to other tissues. Complex diseases, such as many types of cancer, often require both structural and functional imaging to properly

[18F]-FDG is taken up by cells with high metabolic activity, but is not fully metabolized, allowing it to accumulate in these cells. This is particularly useful in oncology for detecting and monitoring tumors since cancer cells typically exhibit increased metabolic activity.

inform healthcare professionals with respect to diagnosis, dosimetry, and other clinical decisions. Therefore, it has long since been known to register, overlay, fuse or otherwise combine anatomical and functional images together for concurrent display in a composite image.

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

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

50. Non-rigid registration permits deformation of one image or parts of the image by, for example, stretching, shearing, or bending. Thus, if the patient's head is in a slightly different position in PET and CT images taken at different times, non-rigid registration can apply a different technique to the head portion of the image than is applied to the rest of the image to obtain the most accurate

alignment of the whole body. Similarly, when registering pre- and post-treatment images of a tumor, non-rigid registration can accurately align the images despite changes in the tumor's shape and size.

C. Image Segmentation

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

1. Region Growing

52. Region-based segmentation methods group points of image data in the form of pixels or voxels for 2D and 3D images, respectively, based on their

similarity or homogeneity within a predefined region. Ex1015 at 811. For example, region growing methods start from a seed pixel or voxel and iteratively add neighboring pixels or voxels that satisfy a similarity criterion, such as intensity range or variance. One particular use case of region-based segmentation is the accurate delineation of organ boundaries in CT scans.

2. Edge Detection

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

3. Thresholding

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

functional images; and (ii) identification of bone in CT images.

4. Clustering

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

5. Artificial Neural Networks

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

57. Machine learning is a subset of AI that focuses on the development of algorithms that allow computers to learn from, and make predictions based on, data. Instead of being explicitly programmed to perform a task, machine learning

algorithms are trained on large datasets and use statistical techniques to identify patterns and make decisions based on predictions.

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

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

60. Most pertinent to medical image segmentation, Convolutional Neural Networks (CNNs) are artificial neural networks specially adapted for analyzing images. *See generally* Ex1017, Ex1018, Ex1019. At a high level, CNNs are constructed of convolutional layers of nodes that apply filters to the input image,

looking for hierarchical patterns (e.g., edges, curves, circles), and creating feature maps that depict detected patterns. Eventually, fully connected layers of the CNN evaluate the features extracted by the convolutional layers to make final predictions including, for example, whether a particular pixel of an image is part of a particular organ that the neural network has been trained to look for. In this way, artificial neural networks can segment organs or bones in a medical image by accurately predicting which pixels in the image correspond to a particular organ or bone.

VI. THE '346 PATENT AND PROSECUTION HISTORY

61. The Patent, entitled “NETWORK FOR MEDICAL IMAGE ANALYSIS, DECISION SUPPORT SYSTEM, AND RELATED GRAPHICAL USER INTERFACE (GUI) APPLICATIONS,” was filed on December 18, 2019, and issued on May 26, 2020. Ex1001, cover. I have been instructed by counsel to conservatively treat October 27, 2016, as the priority date of the Patent, which is the filing date of priority Provisional Application No. 62/413,936.

62. According to the Patent, the disclosed invention “relates generally to systems and methods for creation, analysis, and/or presentation of medical image data.” *Id.* at 1:19-21. More specifically, however, I understand from the preambles of the only two independent claims of the Patent (i.e., claims 1 and 13), that the *claimed* invention relates to systems and methods “for generating a disease risk

map for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer.” *Id.* at 35:46-49, 36:43-45.

63. According to the Patent, “commonly available nuclear medicine cameras, known as single-photon emission computerized tomography (SPECT) or positron emission tomography (PET) cameras, found in most hospitals throughout the world” are used by physicians “to determine the presence and the extent of disease in a patient.” *Id.* at 1:30-47. For example, “[a]n oncologist may use images from a targeted PET or SPECT study of a patient as input in her assessment of whether the patient has a particular disease, e.g., prostate cancer, what stage of the disease is evident, what the recommended course of treatment (if any) would be, whether surgical intervention is indicated, and likely prognosis.” *Id.* at 2:4-10. Additionally, the Patent explains that “[t]here are also a number of radiopharmaceuticals available for imaging particular kinds of cancer” including “the small molecule diagnostic 1404” which can be used for “the detection of primary and metastatic prostate cancer.” *Id.* at 1:51-61. But, despite the known use of PET and SPECT cameras to diagnose particular kinds of cancer using a variety of known radiopharmaceuticals, the Patent suggests that “there remains a need for systems and methods for improved analysis of medical imaging studies and communication of those results, diagnoses, prognoses, treatment recommendations, and associated risks to a patient.” *Id.* at 2:55-58 (emphasis added).

64. The Patent describes “a software tool ... featuring a graphical user interface (GUI) element ... for ... presentation of a 3D risk image corresponding to a patient organ (and/or other tissue) for comparison with reference images (e.g., for use in communication of results to [a] patient as a decision-making support).” *Id.* at 3:15-20 (emphasis added). “For example, a patient for whom a risk of cancer is detected can display a map indicating areas and/or degrees of risk and can compare this risk map with those of others for whom a given course of treatment is recommended.” *Id.* at 3:26-30 (emphasis added).

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

place of the image of the tissue.” *Id.* at 3:43-4:12 (emphasis added).

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

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

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

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

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

Id. at 4:15-29 (emphasis added).

67. Additionally, the Patent states that its “automatic analysis” of the one or more medical images can be carried out using machine learning algorithms, including artificial neural networks, to perform tasks such as: (i) segmentation of tissue regions in CT scans (*id.* at 26:50-55); (ii) classification of hot spots in

nuclear medicine images (e.g., PET or SPECT) as cancerous lesions (*id.* at 25:41-45); and (iii) predicting a risk index value (*id.* at 25:64-26:3).

68. “Hotspots,” according to the Patent, are “localized regions of high intensity in nuclear medicine images” (*id.* at 15:52-53) that can be “classified as corresponding to cancerous lesions” (*id.* at 25:41-42). According to the Patent, Figure 4, which is reproduced below, depicts “a screenshot of a GUI window showing representative full body gamma camera images showing hotspots automatically identified by the system.” *Id.* at 13:53-56. I note that the images in Fig. 4 also include graphical overlays that identify the geographic locations of bones and skeletal regions in the functional SPECT images.

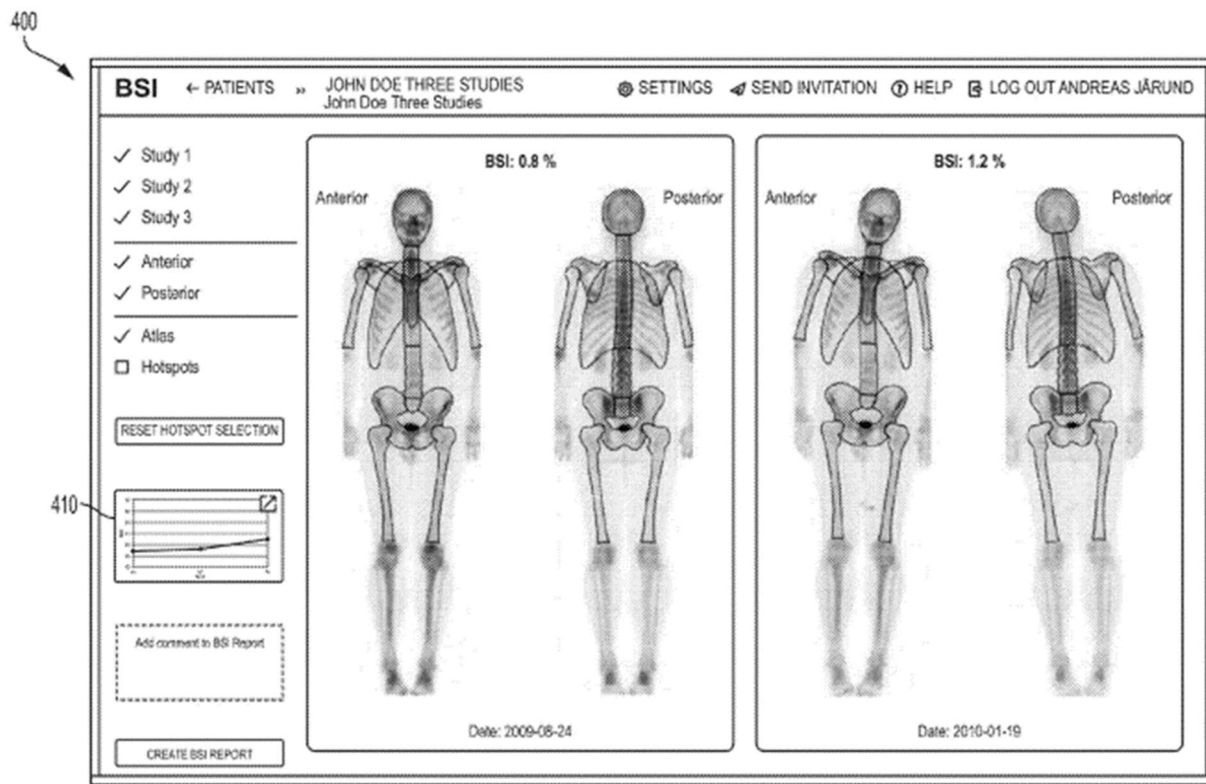


FIG. 4

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

70. According to the Patent:

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

Id. at 26:40-50 (emphasis added). The Patent further explains that:

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

of the PET image falling within and/or outside of the identified 3D boundaries can be accurately identified.

Id. at 26:61-66.

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

72. Similarly, the Patent states:

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

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

Id. at 27:11-25.

73. Additionally, with respect to the production of the risk map, the Patent states that, according to some embodiments, a composite image can be automatically analyzed by: (i) “using the composite image to geographically identify a 3D boundary for each of one or more regions of imaged tissue ... within the nuclear medicine image (e.g., such that portions of the nuclear medicine image falling within and/or outside of the 3D boundaries can be differentiated from each other)”; and (ii) generating “a risk map using the nuclear medicine image with the identified 3D boundaries of the one or more region(s).” *Id.* at 4:62-5:17 (emphasis added).

74. The output of the “decision support system” described in the Patent is an “automatically or semi-automatically generated radiologist report 510,” an embodiment of which is depicted in Fig. 5, which is reproduced below. *Id.* at 29:14-16, 4:10-12 (“generate a radiologist report for a patient according to one or

more medical images for the patient”).

400

510

BSI ← PATIENTS » JOHN DOE THREE STUDIES SETTINGS SEND INVITATION HELP LOG OUT ANDREAS JÄRUND

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CANCEL SIGN AND SAVE REPORT

2010-01-19

FIG. 5

75. According to the Patent:

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

Id. at 2:11-19 (emphasis added).

76. Thus, the Patent purports to address the need for improved analysis of

medical imaging studies *and communication of those results* by disclosing systems and methods that: (i) access one or more medical images from a database; (ii) automatically analyze the one or more medical images using a machine learning algorithm to generate a risk map; and (iii) display the risk map, for example, in an automatically or semi-automatically generated radiologist report.

77. Additionally, the Patent briefly mentions using its accumulated image data to update – by applying a machine learning algorithm – its process for automatically analyzing medical images. For example, the Patent refers to “application of machine learning algorithms to update [a] process by which images are analyzed (e.g., updating segmentation and/or classification routines based on [the] growing image database).” *Id.* at 3:7-10. Similarly, Fig. 6,

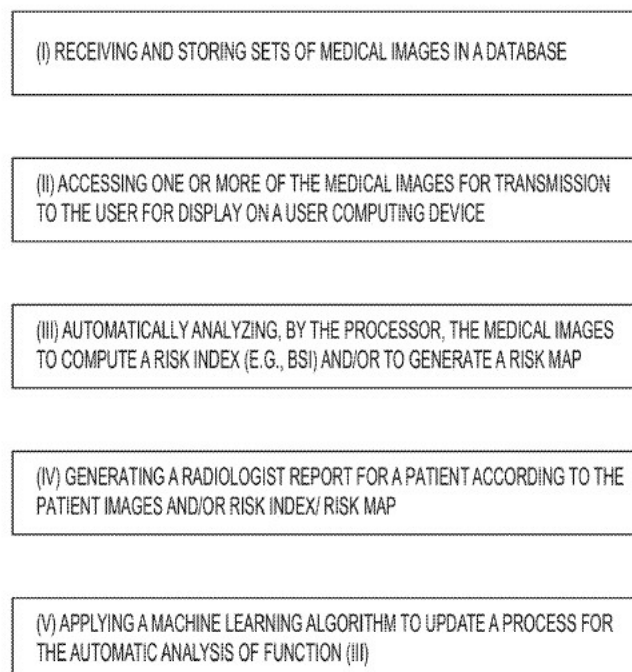


FIG. 6

which is reproduced here, refers to applying a machine learning algorithm to update a process for the automatic analysis of “FUNCTION (III),” where function III refers to the automatic analysis of medical images to “generate a risk map.”

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

79. The Patent issued from U.S. Patent Application No. 16/718,839 (“the Application”), which was filed December 18, 2019. The Applicant requested and was granted Track One prioritized examination. Ex1004 pp. 3, 142.

80. The Application was filed simultaneously with a preliminary amendment. *Id.* at 8-9. As amended for examination, the claim set included only two independent claims, 1 and 63, which correspond to issued claims 1 and 13 of the Patent, respectively. Amended claim 1, which is representative of the other independent claim, read as follows for examination:

A network-based system for generating a disease risk map for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer, the system comprising:

a processor; and

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

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

(ii) perform an analysis of the one or more medical images associated with the particular patient using a machine learning algorithm, to generate the risk map, wherein the risk map comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer or risk of recurrence of cancer; and

(iii) cause display of the risk map via a graphical user interface (GUI) for presentation and/or review of the risk map by a user.

Id. at 124-125 (emphasis added). Thus, as examined, the claimed system and method for generating a disease risk map, merely produced a “visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer.”

81. The Examiner did not issue an Office Action rejection of any examined claims. Instead, the Examiner initiated a telephone interview with the Applicant on February 7, 2020. Ex1004 p.169. During that interview, the Examiner suggested amendments to the independent claims “that may overcome the prior art of record.” *Id.* Agreement was reached and the Examiner issued a Notice of Allowance, with accompanying Examiner’s claim amendments, on February 21, 2020. *Id.* at 159-168.

82. With the agreement of the Applicant, the Examiner amended independent claim 1 as follows:

Claim 1. (Currently Amended) A network-based system for generating a disease risk map for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer, the system comprising:

a processor; and

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

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

(ii) perform an analysis of the one or more medical images associated with the particular patient using a machine learning algorithm, to generate the risk map, wherein the risk map comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer or risk of recurrence of cancer; and

(iii) cause display of the risk map via a graphical user interface (GUI) for presentation [[and/]]or review of the risk map by a user,

wherein the analysis of the one or more medical images comprises creation of a 3D image of the one or more regions of risk of cancer or risk of recurrence of cancer overlaid on the one or more medical images, and wherein the 3D image comprises geographic identification of one or more specific tissue region(s) overlaid on the one or more medical images.

Id. at 165. Thus, in addition to the originally claimed “overlaid ... graphical denotations marking one or more regions of risk of cancer,” the Examiner also

required for patentability “geographic identification of one or more specific tissue regions(s) overlaid on the one or more medical images.” *Id.* (emphasis added).

83. The only other independent claim, claim 63, which corresponds to issued claim 13, was similarly amended.

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

Based on applicant’s amendment, with respect to claim 1, representative of claim 63, the closest prior art of record [US2016/0335395] (WU), reference is directed to image processing systems. More particularly, embodiments of the invention relate to cloud-based medical image processing systems with tracking capability, but does not teach or suggest, among other things, “perform an analysis of the one or more medical images associated with the particular patient using a “machine learning algorithm”, to generate the risk map, wherein the risk map comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer or risk of recurrence of cancer; and display of the risk map via a graphical user interface (GUI) for presentation or review of the risk map by a user, wherein the medical images comprises creation of a 3D image of the one or more regions of risk of cancer or risk of recurrence of cancer “overlaid” on the one or more medical images, and wherein the 3D image comprises geographic identification of one or more “specific tissue” region(s)

overlaid on the one or more medical images”.

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

Id. at 167 (internal quotations in original) (underlining added for emphasis at the same locations).

85. The Examiner’s stated reasons for allowance, including the Examiner’s emphasis of particular claim terms, informs and confirms my understanding of the scope of the amended claims, as allowed.

A. The Claims of the Patent

86. I address below claims 1-13 of the Patent.

1. Claim 1

87. Independent claim 1 of the Patent reads:

A network-based system for generating a disease risk map for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer, the system comprising:

a processor; and

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

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

(ii) perform an analysis of the one or more medical

images associated with the particular patient using a machine learning algorithm, to generate the risk map, wherein the risk map comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer or risk of recurrence of cancer; and

(iii) cause display of the risk map via a graphical user interface (GUI) for presentation or review of the risk map by a user,

wherein the analysis of the one or more medical images comprises creation of a 3D image of the one or more regions of risk of cancer or risk of recurrence of cancer overlaid on the one or more medical images, and wherein the 3D image comprises geographic identification of one or more specific tissue region(s) overlaid on the one or more medical images.

Ex1001 at 35:46-36:7.

2. Claim 2

88. Claim 2 depends from claim 1 and further states “wherein the one or more medical images comprise one or more magnetic resonance images (MRIs).”

Id. at 36:8-10.

3. Claim 3

89. Claim 3 depends from claim 1 and further states “wherein the one or more medical images comprise (i) one or more PET/CT image(s) or (ii) one or more SPECT/CT image(s).” *Id.* at 36:11-13.

4. Claim 4

90. Claim 4 depends from claim 1 and further “wherein the visual representation of tissue is at least a portion of one of the one or more medical images of the particular patient.” *Id.* at 36:14-16.

5. Claim 5

91. Claim 5 depends from claim 1 and further states “wherein the cancer is prostate cancer.” *Id.* at 36:18-19.

6. Claim 6

92. Claim 6 depends from claim 1 and further states “wherein the visual representation of tissue comprises a visual representation of bone.” *Id.* at 36:20-21.

7. Claim 7

93. Claim 7 depends from claim 1 and further states “wherein the one or more specific tissue region(s) comprise one or more members selected from the group consisting of organs, organ structures, sub-organs, and organ regions.” *Id.* at 36:22-24.

8. Claim 8

94. Claim 8 depends from claim 1 and further states “wherein the one or more specific tissue region(s) comprise one or more particular bones.” *Id.* at 36:26-27.

9. Claim 9

95. Claim 9 depends from claim 1 and further states “wherein the instructions cause the processor to generate a radiologist report for the particular patient based at least in part on the analysis of the one or more medical images.” *Id.* at 36:28-31.

10. Claim 10

96. Claim 10 depends from claim 9, which in turn depends from claim 1, and further states “wherein the radiologist report comprises the one or more medical images and the risk map.” *Id.* at 36:33-34.

11. Claim 11

97. Claim 11 depends from claim 9, which in turn depends from claim 1, and further states “wherein the radiologist report comprises one or more reference images or reference risk maps.” *Id.* at 36:35-37.

12. Claim 12

98. Claim 12 depends from claim 1 and further states “wherein the instructions cause the processor to apply a machine learning algorithm to update a process for automatically analyzing the one or more medical images using accumulated image data in the database.” *Id.* at 36:38-42.

13. Claim 13

99. Independent claim 13 of the Patent is nearly the same as independent claim 1 except that it recites a method instead of a system. Claim 13 reads:

A method for generating a disease risk map for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer, the method comprising:

(i) accessing, by a processor, one or more medical images associated with a particular patient from a database;

(ii) automatically analyzing, by the processor, using a machine learning algorithm, the one or more medical images to generate the risk map, wherein the risk map comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer or risk of recurrence of cancer; and

(iii) causing, by the processor, display of the risk map via a graphical user interface (GUI) for presentation or review of the risk map by a user,

wherein step (ii) comprises creation of a 3D image of the one or more regions of risk of cancer or risk of recurrence of cancer overlaid on the one or more medical images, and wherein the 3D image comprises geographic identification of one or more specific tissue region(s) overlaid on the one or more medical images.

Id. at 36:43-65.

VII. OPINIONS REGARDING CLAIM CONSTRUCTION

A. Ordinary and Customary Meaning

100. Unless otherwise stated herein, I interpret the terms of the Patent's claims as having their ordinary and customary meaning.² After having reviewed the Patent specification and its prosecution history, I do not see any need to deviate from the plain and ordinary meaning of the claim language based on, for example, disclaimer, disavowal, or unique lexicography.

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

B. "Risk Map" (Claims 1, 10, 11, and 13)

102. The only claim term that I believe requires interpretation for the purpose of my declaration is the term "risk map," which is used in claims 1, 10, 11, and 13 of the Patent.

103. As used in the Patent specification, the term "risk map" means 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 id.*

² I reserve the right, in the district court litigation brought by Patent Owner against Petitioner, to identify other claim terms and phrases that might require construction. Such additional terms – not addressed here – might be material to the determination of infringement of the accused instrumentalities, even if they are not relevant based on the features of the prior art cited in this Petition.

at 3:17-18 (“risk image corresponding to a patient organ (and/or other tissue)”), 28-29 (“a map indicating areas and/or degrees of risk ... [i.e.,] risk map”); 4:3:10 (“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, e.g., wherein the risk map is displayed as an overlay of the ... image of the tissue, or is in place of the image of the tissue.”).

104. As expressly defined within the Patent claims, the risk map “comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer or risk of recurrence of cancer.” *Id.* at 35:59-62, 36:50-54. This definition is consistent, in my opinion, with the use of “risk map” in the Patent specification.

105. I understand that the Patent Owner, Progenics Pharmaceuticals, Inc., has accused Petitioner, MIM, of infringing at least claim 1 of the Patent. Ex1013, ¶¶62-66. I do not consider myself bound by the Patent Owner’s interpretation of the Patent’s terms, but I have considered the Patent Owner’s allegations of infringement as part of my claim construction analysis.³ Specifically, the Patent

³ 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 (*cont’d*))

Owner alleges that one of Petitioner's accused products satisfies the third limitation of claim 1 of the Patent (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)." Ex1013, ¶66 (emphasis added). Thus, I understand the Patent Owner to assert that displaying a visual representation of tissue overlaid with segmented tumors, which are also referred to more generally as segmented lesions, satisfies the claimed "visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer" (i.e., "risk map"). This interpretation, in my opinion, is at least consistent with the use of "risk map" in the Patent specification and claims.

106. Accordingly, the term "risk map" may be construed according to any of the following for the purpose of my Declaration:

- (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," which is consistent with the Patent specification;
- (2) "a visual representation of tissue overlaid with graphical denotations

regarding claim scope), citing *Hewlett-Packard Co. v. MPHJ Tech. Inv., LLC*, IPR2013-00309, Paper 35, pp.20-22 (using patent owners' demand letter as an aid in construing certain claim phrases).

marking one or more regions of cancer or risk of recurrence of cancer,” which is consistent with the definition within the Patent claims; and

(3) “a visual representation of tissue overlaid with segmented lesions,” which is consistent with Patent Owner’s allegations in the district court Complaint against Petitioner.

VIII. SUMMARY OF THE PRIOR ART

A. US2012/0123253 (“Renisch”)

107. Renisch is a United States patent application that published on May 17, 2012. Ex1005, cover. I understand, therefore, that Renisch is prior art to the Patent, even if I assume that the Patent’s priority date is October 27, 2016. As far as I can tell from the references cited within the Patent and the Patent’s prosecution history, Renisch was not disclosed to, or considered by, the Patent Office during examination of the Patent.

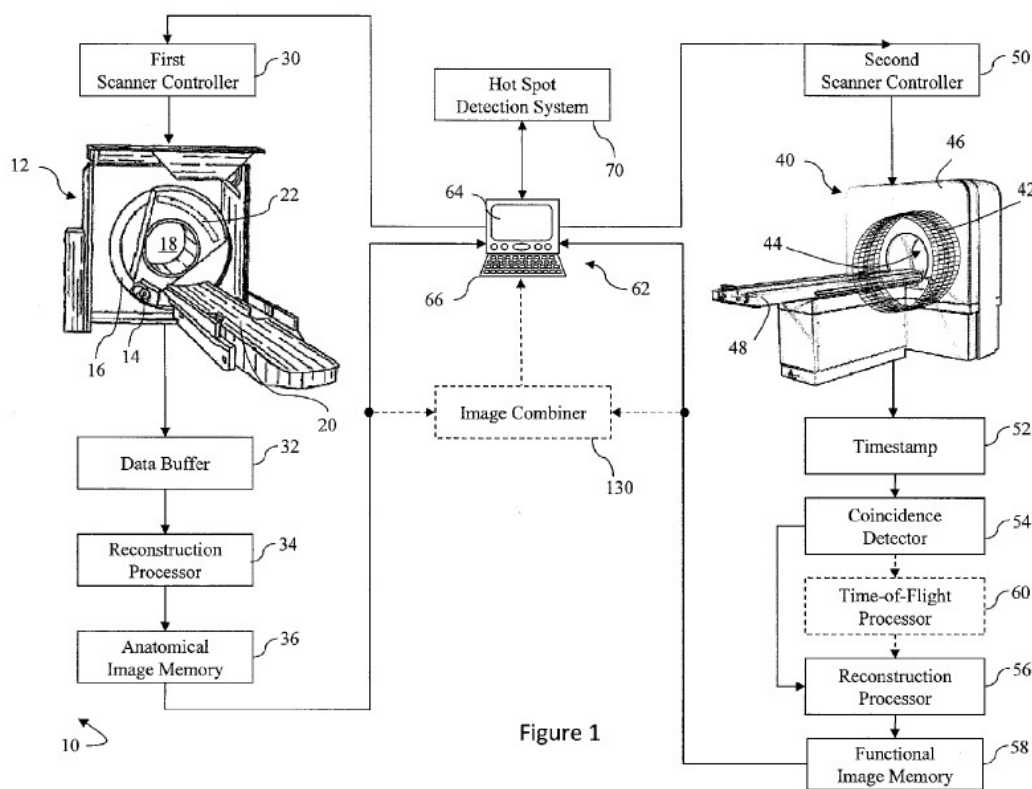
108. Renisch teaches that, as of its filing date, nuclear medicine imaging was being increasingly used in cancer imaging due to the success of tracers such as FDG. *Id.* at [0003]. FDG, when injected into a patient, accumulates in regions of high metabolic activity, including cancerous tumors. *Id.*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

109. Renisch also teaches that, as of its filing date, the current clinical

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

110. Renisch discloses a hot spot detection system for automatically segmenting and quantifying hot spots in functional images, such as PET or SPECT images. *Id.* The hot spot detection system includes: (i) a segmentation unit to segment anatomical images (e.g., CT or MR images) into regions corresponding to anatomical structures; (ii) a classification unit to classify the identified hot spots according to their location relative to the segmented anatomical structures; (iii) a suppression unit to suppress detected hot spots based on the results of the classification unit (e.g., if the hot spots are classified as being located within a normal functioning organ that is expected to have high physiological uptake); and (iv) an identification unit that identifies unsuppressed hot spots as either a potential cancerous lesion or not a lesion. *Id.*

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



112. Referring now to Fig. 2, which is reproduced below, a segmentation unit 76 of the hot spot detection system 70 automatically segments the received anatomical images into regions that correspond to anatomical structures such as the brain, heart, bladder, liver, and kidneys. *Id.* at [0025]. The segmentation can be

model-based, using atlas images, or can be accomplished using machine learning algorithms such as clustering or artificial neural networks. *Id.* at [0027].

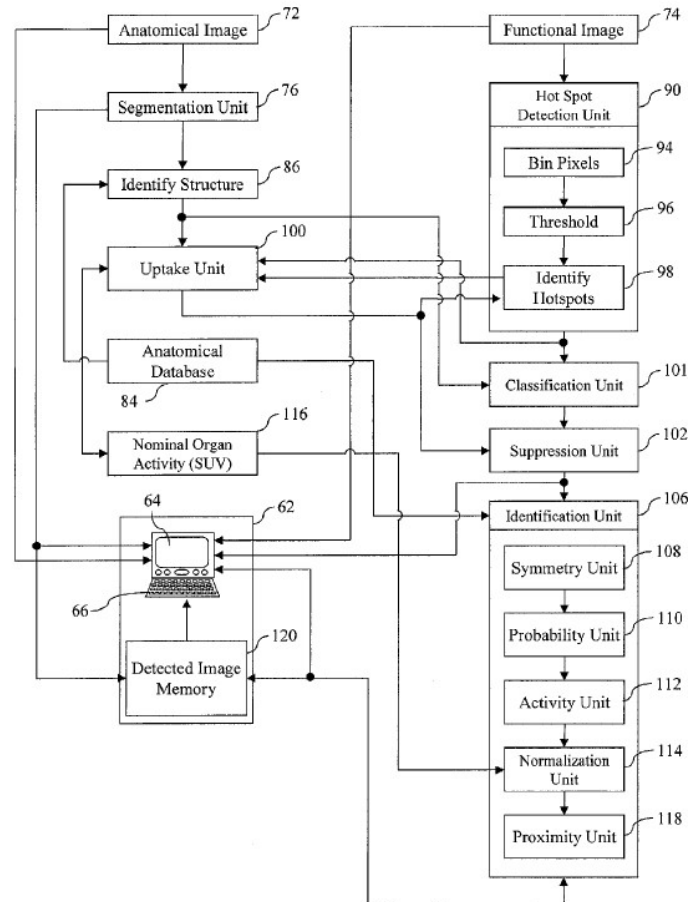


Figure 2

113. Renisch teaches that “[s]egmentation can ... be helpful for accurately determining a location of the hot spots relative to the patient’s anatomy” and “anatomical regions identified in the anatomical first image representation [] can be carried over to the functional second image representation [] in order to delineate anatomical structures in the second image representation.” *Id.* at [0025], [0034].

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

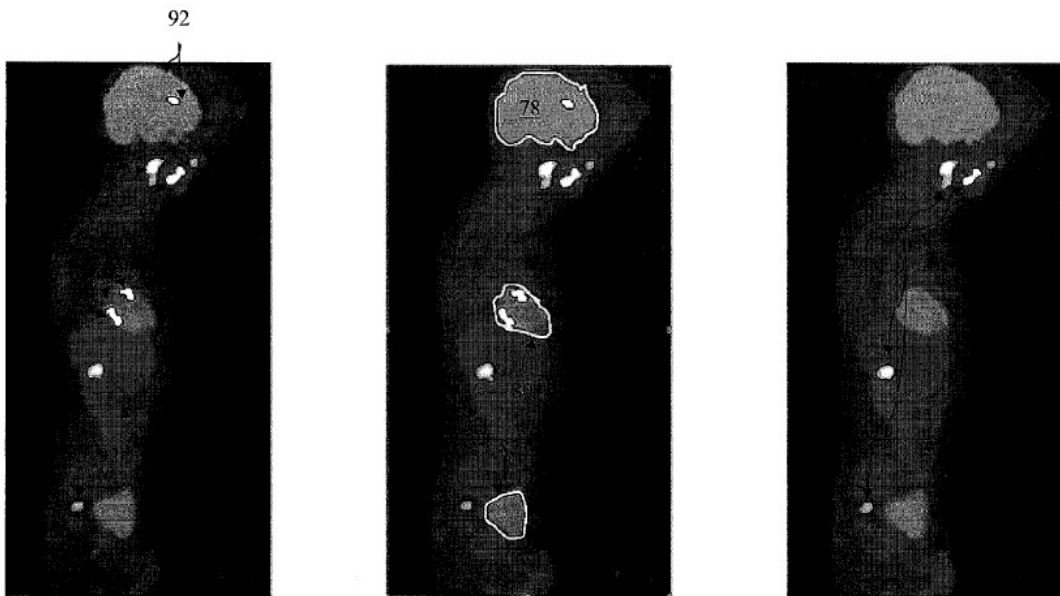


Figure 3A

Figure 3B

Figure 3C

115. Additionally, Renisch expressly states that the segmented anatomical and functional images can be combined for concurrent display on a graphical user

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

B. US2015/0063667 (“Sprencz”)

116. Sprencz is a U.S. patent application published on March 5, 2015. Ex1006, cover. I understand, therefore, that Sprencz is prior art to the Patent, even if I consider the Patent to be entitle to a priority date of October 27, 2016. As far as I can tell, Sprencz was not disclosed to, or considered by, the Examiner during examination of the Patent.

117. Sprencz teaches that, as of its filing date, it had become increasingly common for patients to be subjected to multiple imaging scans using different imaging modalities to acquire different, and complementary, pieces of information. *Id.* at [0002]. For example, a patient might be imaged using a computed tomography (CT) or magnetic resonance (MR) imaging system to obtain detailed

anatomical information, as well as a positron emission tomography (PET) imaging system to obtain functional information. *Id.* Furthermore, Sprenzc teaches that, as of its filing date, programs had been constructed to “register an anatomical and a functional image thereby showing, in a single image, both anatomical and functional information.” *Id.*

118. Sprenzc discloses a network-based system for automatically detecting, segmenting, displaying, and quantifying bone lesions using multi-modality 3D imaging data. *Id.* at Abstract, [0011], [0041]-[0044], [0048]-[0050], [0055]-[0056]. With reference to Fig. 1, which is reproduced below, Sprenzc discloses a CPU 12 that controls the system, and which may be connected via a network to one or more remotely located imaging system 20, workstation 28, and image databases 18. *Id.* at [0023]-[0027].

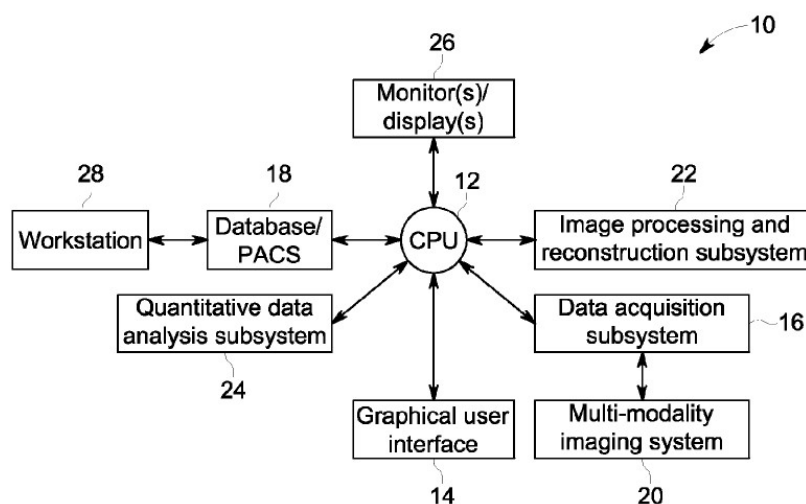


FIG. 1

119. With reference to Fig. 4, which is reproduced below, Sprenzc

discloses a technique for quantifying bone lesions that begins with accessing and selecting, from a database, at least one 3D anatomical image and at least one corresponding 3D functional image for a patient. *Id.* at [0041]. If the images have

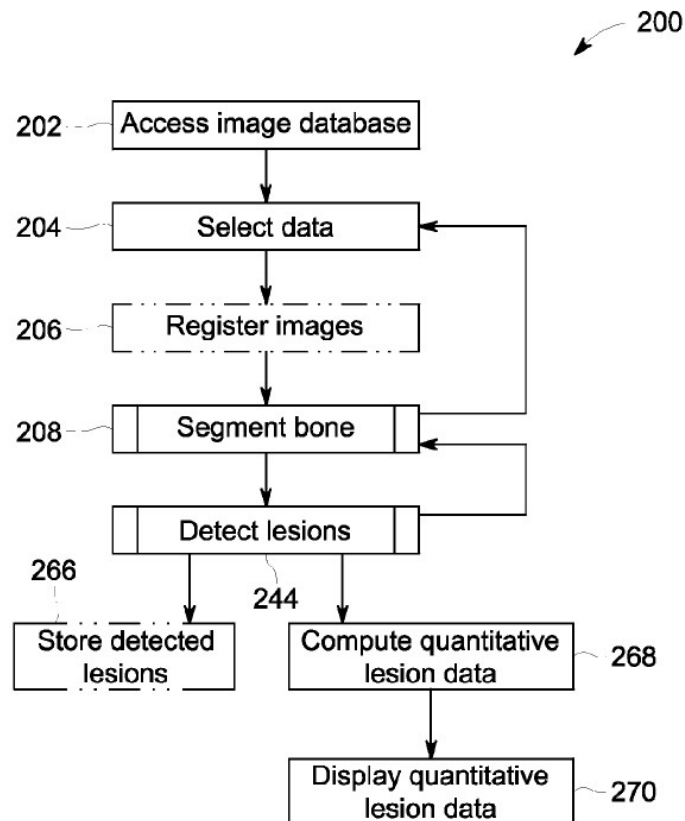


FIG. 4

not already been registered, Sprencz describes registering the acquired images to accurately overlie the anatomical data and the functional image data. *Id.* at [0042]. The anatomical image is automatically segmented to identify the patient's 3D bone volume. *Id.* at [0043]-[0046], Fig. 5. The segmentation can be accomplished by thresholding or using machine learning algorithms such as "clustering." *Id.* at

[0045]. The functional image is likewise segmented to identify lesions using a thresholding algorithm, and the lesions are classified as either bone lesions or non-bone lesions by comparing the location of each lesion with the location of the segmented skeletal volume. *Id.* at [0048]-[0049], [0052]. The segmentation results are then displayed and used to calculate quantitative lesion data such as the total bone lesion volume in comparison to the total bone volume. *Id.* at [0050], [0053]-[0054].

120. Referring now to Fig. 7, which is reproduced below, Sprenzc displays the segmented skeletal volume and the segmented bone lesion candidates in a

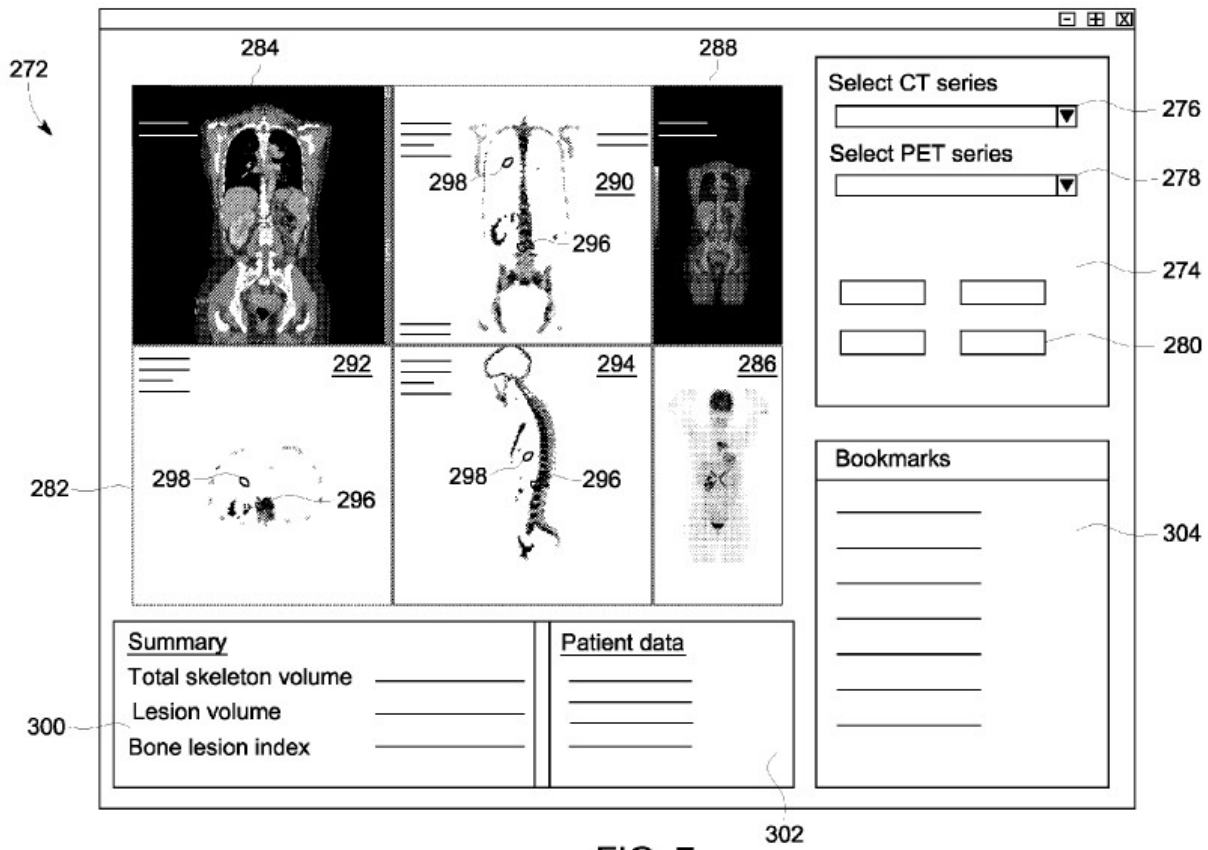


FIG. 7

variety of ways. For example, Sprencz states: “Images of the lesion candidates are generated ... and displayed as an overlay on the patient skeletal image generated from the segmented skeletal structure output from the bone segmentation subroutine.” *Id.* at [0050]. In one embodiment, “the segmented skeletal structure from a CT image series is projected into a PET image that includes the lesion candidates.” *Id.* (emphasis added).

121. Additionally, with specific reference to Fig. 7, Sprencz states:

According to an exemplary embodiment, GUI 272 includes an image display region 282 that is separated into multiple windows in order to display multiple images. For example, image display 282 may include a first window 284 that displays a CT image, a second window 286 that displays a corresponding PET image, and a third window 288 that displays the CT image overlaid on the PET image. Fourth, fifth, and sixth windows 290, 292, 294 include various views of the segmented skeletal volume obtained from the CT image using bone segmentation subroutine 210 overlaid with contours of lesion candidates 296, 298 detected using lesion detection subroutine 246. In alternative embodiments, image display region 282 includes one or more selected images corresponding to the multi-modality image series and the detected lesions. Image display region 282 may further be configured to display bone lesions and non-bone lesions in different colors or with different shading to visually distinguish detected bone lesions from non-bone lesions. As one example, a lesion candidate classified as a bone lesion, such as lesion candidate 296, may be displayed with

a red contour, and a lesion candidate classified as a non-bone lesion, such as lesion candidate 298, may be displayed with a blue contour. According to various embodiments, image display region 282 may be configured as an interactive workspace to permit a user to interact with the images to perform various tasks including, for example, manually identify lesion candidates, delete an automatically identified lesion, and/or change the classification of an automatically detected lesion, as non-limiting examples.

Id. at [0056].

122. As depicted in Fig. 7, Sprencz also produces a report summarizing patient information, parameters associated with image acquisition, and the quantitatively measured data, including total skeleton volume, the total volume of bone lesions and non-bone lesions, the total tumor burden, and the calculated bone lesion index. *Id.* at [0057].

C. US2011/0007954 (“Suehling”)

123. Suehling is a U.S. patent application published on January 13, 2011. Ex1007, cover. I understand, therefore, that Suehling is prior art to the Patent, even if I assume that the Patent is entitled to a priority date of October 27, 2016. As far as I can tell, Suehling was not disclosed to, or considered by, the Examiner during examination of the Patent.

124. Suehling discloses a network-based system for automatically

detecting, segmenting, and displaying lesions in a 3D medical image such as a CT image. *Id.* at Abstract, Fig. 1, [0006]. The system can detect lesions throughout the body, including in lymph nodes, organs, and bone, and automatically labels lesions by location so that lesion detection results can be navigated on a region-by-region basis (e.g., displaying only liver lesions or only lung lesions). *Id.* at [0042]-[0043].

125. With reference to Figs. 1 and 2, which are reproduced below,

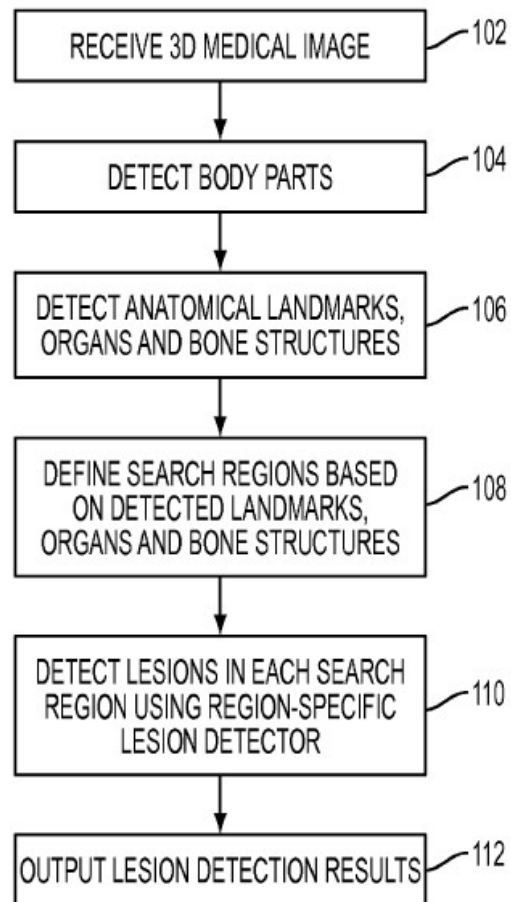


FIG. 1

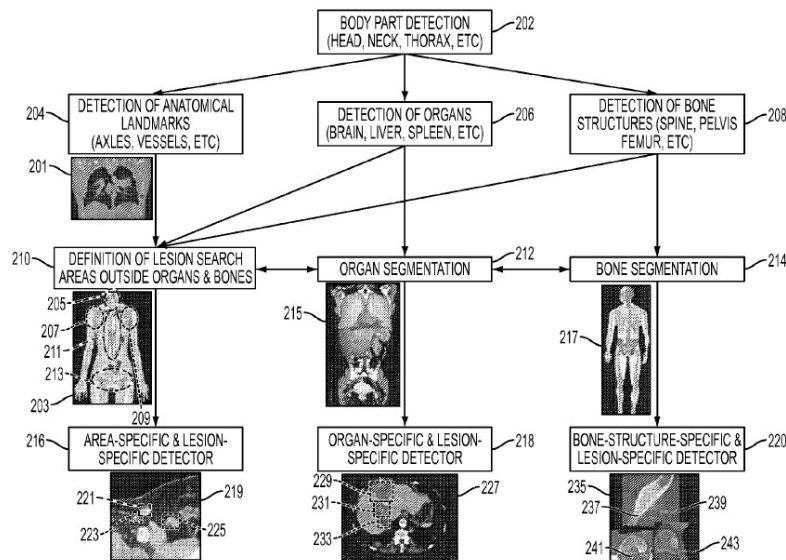


FIG. 2

Suehling receives a 3D medical image and automatically segments the image into search regions corresponding to particular organs and bones such as the brain, liver, spleen, kidneys, lungs, heart, spine, pelvis, femur, etc. *Id.* at [0026]-[0031]. Anatomical segmentation is accomplished using “well known organ segmentation techniques” including machine learning algorithms such as “Marginal Space Learning.” *Id.* at [0030]. Suehling then detects lesions in each of the search regions using a trained region-specific lesion detector. *Id.* at [0032]-[0033]. The region-specific lesion detectors likewise use trained machine learning algorithms including clustered marginal space learning. *Id.*

126. Referring to Fig. 2 above, Suehling states: “Image 215 of FIG. 2 shows exemplary organ segmentation results” (*id.* at [0030]) and “[i]mage 227 shows lesions 229, 231, and 233 detected in an exemplary segmented organ” (*id.* at

[0033]). Likewise, Suehling states: “Image 217 of FIG. 2 shows exemplary bone segmentation results” (*id.* at [0031]) and “[i]mage 235 shows lesions 237, 239, 241, and 243 detected in exemplary segmented bone structures” (*id.* at [0033]).

127. Suehling further discloses that the results of lesion detection can be displayed and filtered in a variety of ways. For example, “the lesion detection results can be displayed by displaying a probability map resulting from probability scores calculated by the lesion detectors.” *Id.* at [0034], [0045]. Or, “[i]t is also possible to display a fused image resulting from combining the probability map with the medical image data.” *Id.* Additionally, as depicted in Fig. 7, which is reproduced below, “lesion detection results can be displayed on an interactive pictogram, as a list of findings, within a 3D rendering of the image data, and/or as a graphical overlay of the original image data.” *Id.* at [0041]. According to Suehling, “[a]s illustrated in FIG. 7, the interactive display 700 displays detected lesions in various slices 702 and 704 of the medical image data, a 3D rendering 706 of the image data, a zoomed-in portion 708, and in corresponding locations in a 3D model of a body 710.” *Id.*

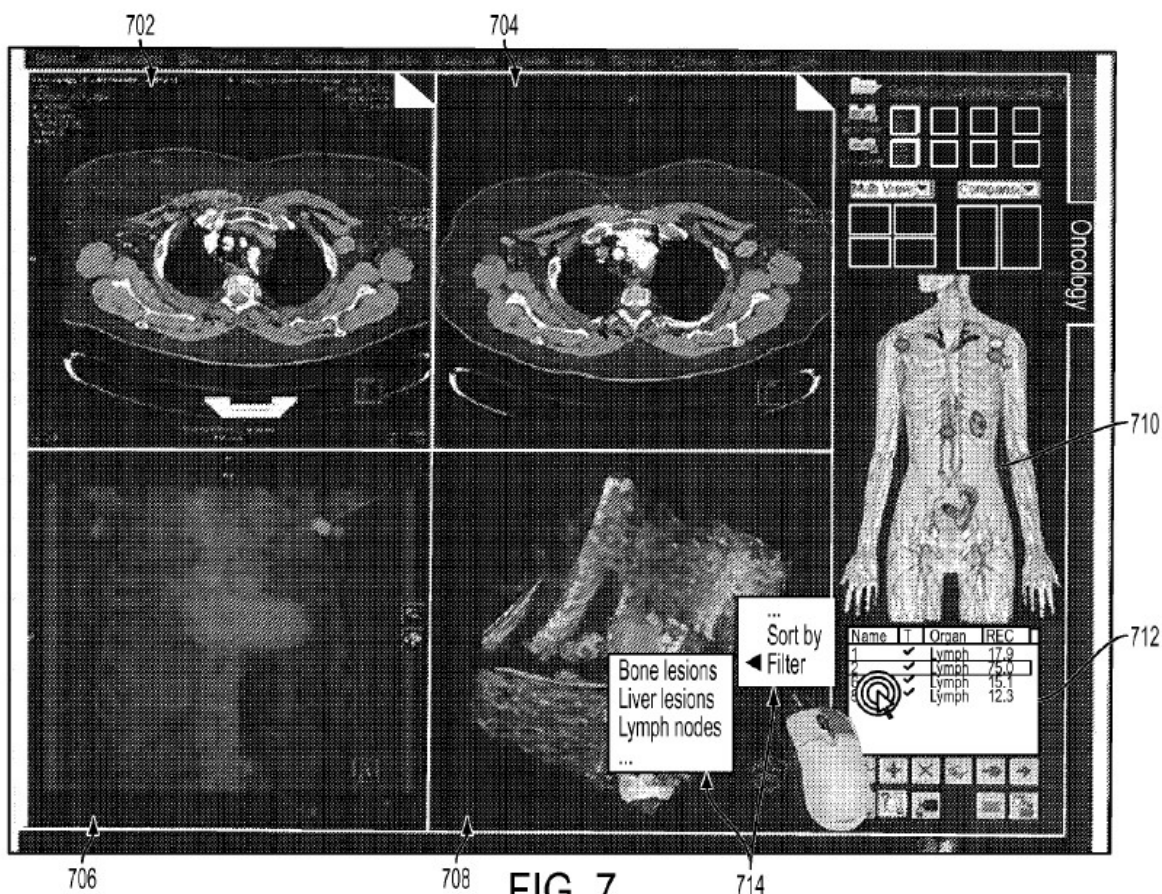


FIG. 7

D. US2016/0203263 (“Maier”)

128. Maier is a U.S. patent application, filed on January 8, 2016, and published on July 14, 2016. Ex1008, cover. I understand, therefore, that Maier is prior art to the Patent, even if I assume that the Patent is entitled to a priority date of October 27, 2016.

129. Maier discloses computer implemented systems and methods for assessing medical images and communicating a patient’s health status and risk by automatically generating a report tailored for the intended user. *Id.* at [0014]. The

medical images evaluated by Maier can include anatomical images, such as CT or MR images, and/or functional images, such as PET or SPECT images, and can be whole body images or images of specific tissue regions such as the lung, prostate, liver, or bone. *Id.* at [0015]-[0017]. According to Maier, the disclosed systems and methods can be used for “screening for disease, prognosis or diagnosis of diseases, base-line assessments, treatment planning, treatment follow-up, or other user education regarding tissue state.” *Id.* at [0018]. Additionally, the disclosed systems and methods are not limited to a particular disease or pathology. *Id.*

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

100

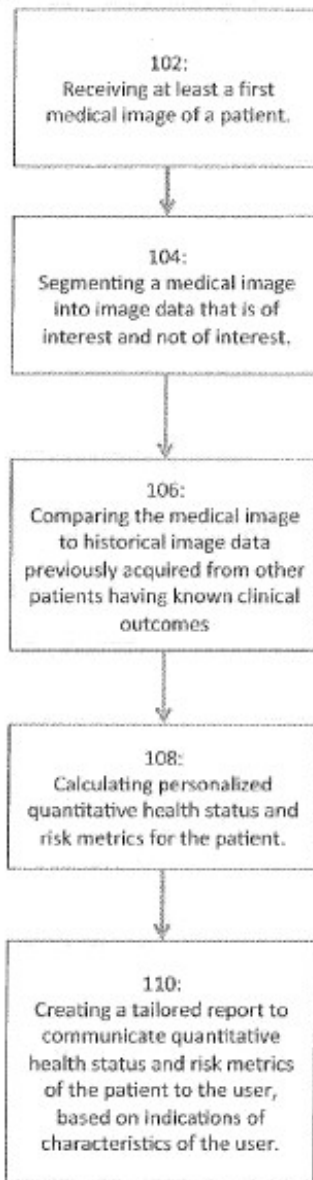


FIG. 1

131. Maier discloses that the step of comparing the patient's medical images to the historical reference images can be performed directly or indirectly using model-based algorithms or unconstrained machine-learning neural networks. *Id.* at [0023]. Indirect comparison could involve evaluating the presence and/or

amount of an imaging biomarker in the patient's image, where the biomarker is defined based on comparison images of other individuals for whom the corresponding health status or medical outcome is known. *Id.* at [0020], [0031]. Direct comparison could involve calculating metrics related to the degree of similarity between the patient's image and a comparison image. *Id.* at [0022], [0032]. Maier states that "[t]his comparison may comprise any type of algorithm that tests for similarities between the image data of interest and the comparison image data, including unsupervised machine learning algorithms of all varieties." *Id.* at [0032].

132. With reference to Fig. 3, which is reproduced below, the report produced by Maier can include the patient's own medical images with overlaid graphical denotations highlighting regions of risk and reference images of others for comparison. *Id.* at [0026], [0041].



133. Wu is a U.S. patent application, filed on July 28, 2016, and published on November 17, 2016. Ex1009, cover. I understand, therefore, that Wu is prior art to the Patent, even if I assume that the Patent is entitled to a priority date of

October 27, 2016. I note that the Examiner cited Wu as the closest known prior art reference during prosecution of the Patent.

134. Wu teaches that advanced image processing of 3D medical images, such as segmentation or registration of CT and PET images, was first performed using computer workstations. *Id.* at [0005], [0007]. However, as Wu explains, the use of workstation-based advanced image processing systems had many limitations. *Id.* For example, the user must physically go to the workstation and only one person can use the workstation at a time. *Id.*

135. Accordingly, Wu discloses a network-based server for providing advanced processing of medical images over a network, such as the Internet. *Id.* at [0027], [0029]-[0033], Figs. 1A and 1B. As explained by Wu, “a cloud server, also referred to as an image processing server, has the capability of processing one or more medical images to allow multiple participants to view and process the images either independently or in a collaborated manner or conferencing environment.” *Id.* at [0027]. Examples of image processing tasks include automatic preprocessing such as “bone removal, ... registration, ... segmentation of structures, and auto-3D operations.” *Id.* at [0043].

F. U.S. Patent No. 9,028,800 (“D’Souza”)

136. D’Souza is a U.S. Patent issued on May 12, 2015. Ex1010, cover. I understand, therefore, that D’Souza is prior art to the Patent, even if I assume that

the priority date of the Patent is October 27, 2016.

137. D’Souza discloses compositions of ^{18}F -labeled molecules and their uses in PET and SPECT nuclear medicine imaging, including ^{18}F -labeled PSMA for use in imaging prostate cancer. *Id.* at Abstract, 12:19-26, 49, 35:42-49, 36:17-24, 37.

138. D’Souza teaches that “Positron Emission Tomography (PET) has become one of the most prominent functional imaging modalities in diagnostic medicine” and that “ ^{18}F FDG is the most widely used PET imaging agent in oncology.” *Id.* at 2:15-21. D’Souza also explains that “there is a keen interest in developing other labeled compounds for functional imaging to complement and augment anatomic imaging methods ..., especially with the hybrid PET/computed tomography systems currently in use.” *Id.* at 22-27.

139. D’Souza teaches that “[t]he type of disease or conditions that may be imaged is limited only by the availability of a suitable delivery molecule for targeting a cell of tissue associated with the disease or condition.” *Id.* at 4:49-54. D’Souza also teaches that “virtually any delivery molecule can be attached to ^{18}F for imaging purposes” (*id.* at 3:57-58) and that “[m]any such delivery molecules are known” (*id.* at 4:51-57) including “PSMA [prostate specific membrane antigen]” (*id.* at 12:19-49). D’Souza expressly discloses that “ ^{18}F -labeled peptides, proteins and/or antibodies are of use for imaging of cancer” including, for

example, “prostate cancer.” *Id.* at 36:22-37.

G. US2016/0180042 (“Menon”)

140. Menon is a U.S. patent application published on June 23, 2016. Ex1012, cover. I understand, therefore, that Menon is prior art to the Patent, even if I assume that the Patent is entitled to a priority date of October 27, 2016.

141. Menon describes an automated triaging decision support tool 22 that utilizes machine learning and a feedback loop to continuously refine (i.e., update) the tool. *Id.* at [0010], [0032], [0055], [0078], [0103]-[0104], [0180], [0189], [0195]. The tool takes, as input, various patient clinical factors, the patient’s medical images, and estimated hospital transfer and treatment times. *Id.* at [0104], [0110]. The tool automatically outputs risk analysis and treatment recommendations, including recommendations as to whether the patient should be transferred to another hospital immediately. *Id.* at [0104]-[0109], [0189]. Additionally, the tool uses this output information and accumulated imaging data in a feedback loop to refine the tool using machine learning. *Id.* at [0180], [0189]. For example, Menon states: “The tool 22 may continue to refine the model ... using machine learning and improve its predictive accuracy using new information that will be available when the product is being tested real time and when the product is in clinical use.” *Id.* at [0195].

IX. DETAILED OPINIONS REGARDING INVALIDITY

142. As detailed below, claims 1-13 of the Patent are unpatentable as anticipated and/or obvious in view of the prior art. I rely principally on three alternative primary references, Renisch (Ex1005), Sprencz (Ex1006), and Suehling (Ex1007) – none of which was considered by the Examiner during examination of the Patent. Each of Renisch, Sprencz, and Suehling, describe, or at least suggest, every limitation of the independent claims of the Patent and most of the limitations of the remaining claims.

143. The following table sets forth the prior art that anticipates and/or the combination of prior art that renders obvious each of claims 1-13:

Ground	Prior Art	Basis	Claims Challenged
A	Renisch	Anticipation	1-7, 9-10, 13
B	Renisch in view of Wu	Obviousness	1-7, 9-10
C	Renisch, or Renisch in view of Wu, each in view of the Applicant's Admitted Prior Art ("AAPA") or D'Souza	Obviousness	5
D	Renisch, or Renisch in view of Wu, each in view of Sprencz	Obviousness	8
E	Renisch, or Renisch in view of Wu, each in view of Maier	Obviousness	9-11
F	Renisch, or Renisch in view of Wu, each in view of Menon	Obviousness	12
G	Sprencz	Anticipation	1-10, 13
H	Sprencz in view of AAPA or D'Souza	Obviousness	5
I	Sprencz in view of Maier	Obviousness	11
J	Suehling	Anticipation	1-10, 13

K	Suehling in view of Maier	Obviousness	11
L	Suehling in view of Menon	Obviousness	12

A. Grounds A and B, Anticipation by Renisch or Obviousness over Renisch with Wu

1. Independent Claim 1

- a) Preamble: “A network-based system for generating a disease risk map for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer, the system comprising:”**

144. I understand that the preamble of a claim is typically just a statement of intended use, but may, in some circumstances, include limitations on the scope of the claim. For the purposes of providing a thorough analysis, I will assume that the preamble of claim 1 is limiting and I will address it like any other claim limitation. As I explain further below, it is my opinion that Renisch discloses “[a] network-based system for generating a disease risk map for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer.”

145. Renisch teaches that regions of high radiotracer uptake in nuclear medicine images are known as “hot spots,” and that hot spots indicate regions of high metabolic activity, which may be cancerous lesions caused by tumor growth. Ex1005 at [0003], [0029]. Renisch also teaches that accurate quantification of lesion activity in nuclear medicine images is essential for staging and monitoring the response to treatment for many types of cancer. *Id* at [0003].

146. A “risk map,” as I have interpreted it for this Petition, can be: (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”; (2) “a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer or risk of recurrence of cancer”; and/or (3) “a visual representation of tissue overlaid with segmented lesions.” *Supra*, ¶106. Renisch satisfies all three definitions.

147. Renisch discloses a “hot spot detection system” that “identifies ... regions of high uptake as one of potential lesion and non-potential lesion.” *Id.* at [0006]. Hot spots that exceed a certain threshold are “highlighted ... with a color overlay” (92) as depicted (in grayscale) in Fig. 3A below. *Id.* at [0029].

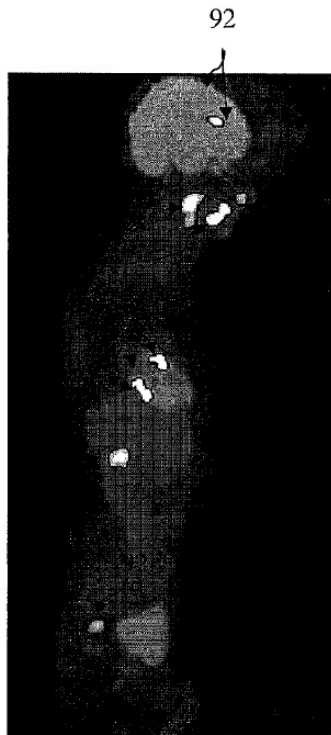


Figure 3A

Additionally, Renisch discloses that “[an] anatomical first image representation and [a] functional second image representation” can be “superimposed in different colors” and “the outline of the functional second image representation hotspots can be superimposed on the first [anatomical] image representation.” *Id.* at [0037] (emphasis added). Thus, Renisch describes segmenting regions of high uptake in a functional image, identifying those regions as potential lesions or non-potential lesions, and overlaying the outline of those regions on a corresponding anatomical image. It is, therefore, my opinion that Renisch discloses the claimed “system for generating a disease risk map for use as a decision-making support for evaluating risk of cancer.”

148. It is also my opinion that the hot spot detection system disclosed by Renisch is a network-based system as claimed. The Patent states: “[t]he components of the system can be interconnected by any form of ... communication network” and “[e]xamples of communications networks include a local area network (LAN), a wide area network (WAN), and the Internet.” Ex1001 at 35:19-24. With reference to Fig. 1, which is reproduced below, Renisch discloses a hot spot detection system 70 connected to a workstation/GUI 62 that is connected to a first anatomical imaging scanner 12 (e.g., an MRI or CT scanner) and a second functional imaging scanner 40 (e.g., a PET or SPECT scanner). EX1005 at [0020], [0022], [0023]. Each of these components is a computer system, and all are

connected for sharing data – making them part of at least a local area network. *Id.* at Fig. 1 (showing, e.g., two-way connection between the hotspot detection system 70 and the workstation 62). The hot spot detection system 70 receives data from the anatomical image memory 36 of the first imaging scanner 12 and from the functional image memory of the second imaging scanner 40. *Id.* at [0025]. Workstation 62 provides instructions, including scanning sequences and protocols to the respective scan controllers (30, 50) of the first and second imaging systems. *Id.* at [0023]. Additionally, the results of the hot spot detection system are shared with the workstation 62 for visualization on the display device 64. *Id.* at [0033].

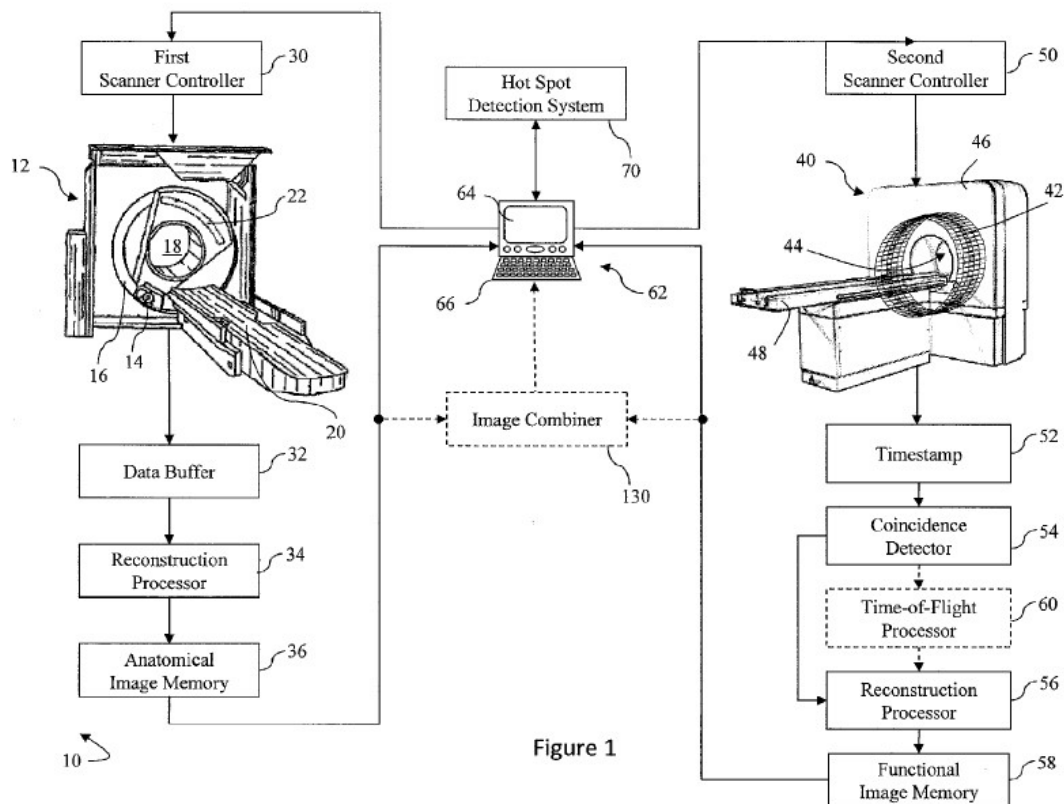


Figure 1

It is my opinion, therefore, that Renisch discloses a network-based system for

generating a disease risk map.

149. However, if Renisch does not disclose a “network-based system” as claimed, then Wu discloses this limitation. Wu discloses a server that provides advanced image processing services for medical images over a network, such as the Internet. Ex1009 at [0027], [0029]-[0033], [0035], [0094], Figs. 1A, 1B, and 2. Examples of image processing services provided by Wu over a network include services like those described in Renisch, such as e.g., “registration” of anatomical and functional images and “segmentation of structures” such as organs. *Id.* at [0043], [0118]. Additionally, Wu supplies the express motivation to provide medical image processing services via an internet-based server by explaining that early workstation-based systems had numerous limitations. *Id.* at [0007]. As taught by Wu, a network-based client-server system overcomes these limitations because a network server can provide advanced image processing services to multiple clients, simultaneously and remotely. *Id.* at [0008], [0027], [0035].

150. Accordingly, even if the hot spot detection system described in Renisch was not network-based, a POSITA would have been motivated, based on the express teachings in Wu, to implement Renisch over a network so the user did not need to physically go to a single workstation and so more than one user could simultaneously and remotely use the hot spot detection system. Ex1009 at [0007], [0008], [0035].

151. It is my opinion that a POSITA implementing Renisch would have looked to Wu because Renisch and Wu are in the same field of medical image processing. Additionally, it is my opinion that a POSITA would have found it obvious to modify Renisch's hot spot detection system to be a network-based system based on Wu's express teaching, suggestion, or motivation to provide medical image processing services over a client-server network, including the Internet. Ex1009, at [0035].

152. Besides this express motivation, combining Renisch and Wu would have merely amounted to combining existing prior art elements according to known methods to yield predictable results. Renisch discloses a prior art automated medical image processing system. Wu discloses cloud-based servers for providing medical image processing. Converting Renisch's hot spot detection system into a network-based system could have been implemented via the methods described by Wu. *E.g.*, Ex1009, Fig. 2, [0041]-[0049]. For example, Renisch's hot spot detection system (Ex1005, Fig. 1 (70)) could be implemented as an "image processing system" on a server (Ex1009, Fig. 2 (109)) that serves multiple client workstations (Ex1009, Fig. 2 (202, 203) (*e.g.*, corresponding to the workstation depicted in Renisch (Ex1005, Fig. 1 (62)) over a network (Ex1009, Fig. 2 (201)). Implementing Renisch's hot spot detection system on a server over a network would have been an obvious and straight forward modification

according to Wu's known methods.

153. Additionally, or alternatively, combining Renisch and Wu would have merely amounted to applying a known technique to a known device to yield predictable results. Renisch discloses a prior art device for providing advanced processing of medical images. Wu discloses prior art techniques for networking computers together. Networking computers together to share data and provide services remotely, as in Wu, was a standard, well-known technique before the presumed priority date of the Patent (i.e., October 27, 2016). Ex1009 at [0008]-[0009]. Indeed, Renisch itself describes and depicts connecting a workstation to multiple imaging scanners to receive imaging data therefrom. Ex1005, Fig. 1, [0025]. Implementing Renisch in a network, as taught by Wu, would merely have led to the predictable result of providing the functionality of Renisch to multiple remote users simultaneously, for example multiple physicians in the same hospital or network of hospitals.

154. Additionally, it is my opinion that a POSITA would have had a reasonable expectation of success in combining Renisch and Wu. In addition to Renisch and Wu both being within the same field of medical image processing, both describe the implementation of similar image processing tasks, including image registration and segmentation. Therefore, Wu's network techniques would be readily applicable to, and easily implemented with, Renisch's hot spot detection

system. And a POSITA would have expected success combining Renisch and Wu since it's really just a changed from a wired/local network (Renisch) to a wireless/remote network (Wu) for which the reasonable expectation of success would be well-known to a POSITA in 2016.

155. Renisch alone discloses all the limitations of the preamble of claim 1. In addition, or in the alternative, Renisch in view of Wu teaches all the limitations of the preamble of claim 1.

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

156. Renisch discloses these limitations, which are nothing more than generic recitations of structures found in any computer implemented system. *See, e.g.,* Ex1005 at Fig. 1 (showing hot spot detection system 70 and workstation 62, both of which necessarily contain a processor and memory having stored instructions). With reference to Fig. 2, which is reproduced below, Renisch discloses a hot spot detection system that comprises various functional units (e.g., segmentation unit 76) that Renisch alternatively describes as “processors” or “algorithms”. *Id.* at [0014], [0030] (“uptake unit, processor, or algorithm”), [0031] (“classification unit, processor, or algorithm”), [0032] (“identification unit, processor, or algorithm”), [0034] “quantification unit also includes a probability

unit, processor, or algorithm”). A POSITA would understand from this description that the described functional units could be different algorithms (i.e., stored instructions) that are carried out on a single processor, or multiple processors that carry out respective stored instructions to perform the respective described functions.

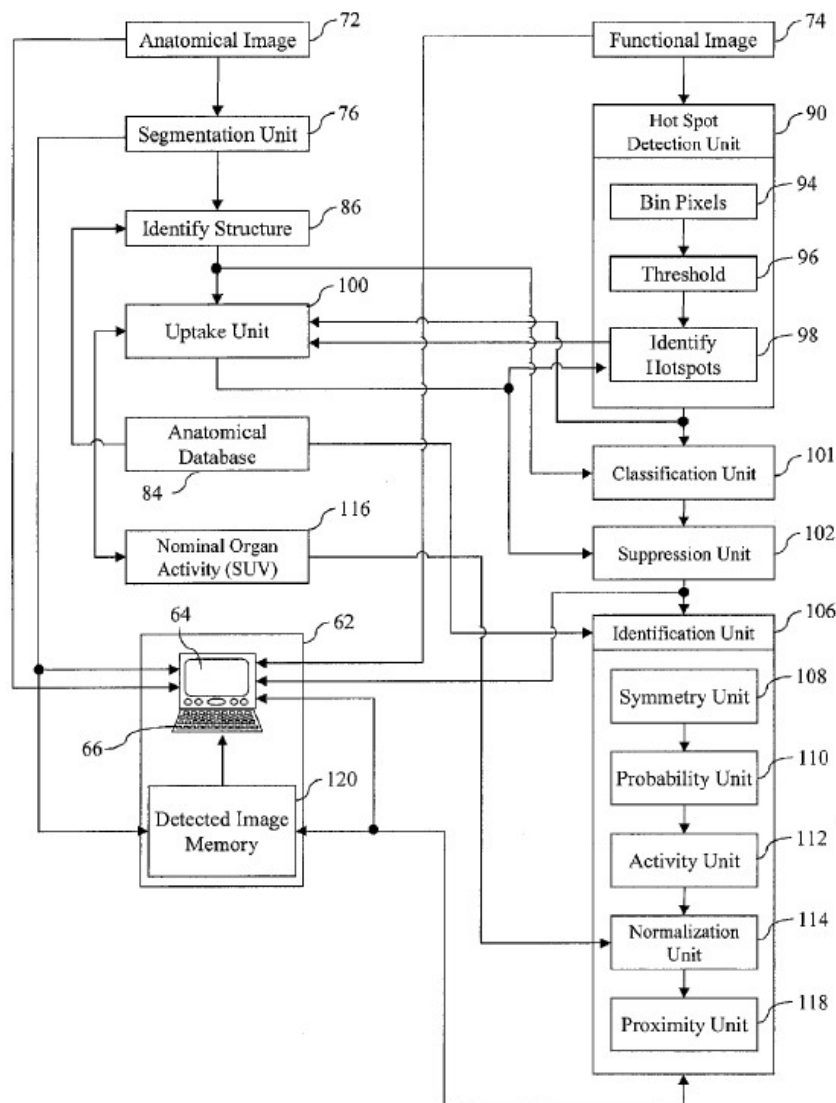


Figure 2

157. Accordingly, it is my opinion that Renisch discloses limitation 1(a).

c) Limitation 1(b): “(i) access one or more medical images associated with a particular patient from a database;”

158. It is my opinion that Renisch discloses this limitation. *Id.* at [0025], Fig. 1 (70, 62, 36, 58), Fig. 2 (72, 74, 76, 90). With reference to Fig. 1 of Renisch above (*supra*, ¶148), the disclosed diagnostic system 10 includes a hot spot detection system 70 that is connected to a workstation 62, which is connect to an anatomical image memory 36 of a first scanner 12 and a functional image memory 58 of a second scanner 40. With reference to Fig. 2 of Renisch above (*supra*, ¶156), an anatomical image 72 is passed to a segmentation unit 76 of the hot spot detection system, and a functional image 74 is passed to a hot spot detection unit 90 of the hot spot detection system. Renisch expressly states: “[W]ith reference to FIG. 1 and further reference to FIGS. 2 and 3B, the diagnostic system 10 includes a hot spot detection system 70 for automatic detection of a region of interest (ROI) pertaining to a lesion and automatic quantification of metabolic activity in detected lesions based on anatomical images 72 from the anatomical image memory 36 and functional images 74 from the functional image memory 58.” *Id.* at [0025] (emphasis added). Additionally, although it hardly seems necessary to state it, the anatomical and functional images that are accessed from a database are associated with a particular patient as claimed. For example, Renisch explains that the first scanner 12 and the second scanner 40 can be separate, as shown in Fig. 1, or

contiguous to each other, where “[a] common support moves the ... patient sequentially through the imaging regions.” *Id.* at [0024] (emphasis added). Thus, the anatomical and functional images are each intended to be associated with the same patient.

159. Accordingly, it is my opinion that Renisch discloses limitation 1(b).

- d) **Limitation 1(c): “(ii) perform an analysis of the one or more medical images associated with the particular patient using a machine learning algorithm, to generate the risk map, wherein the risk map comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer or risk of recurrence of cancer; and”**

160. It is my opinion that Renisch discloses these limitations. As previously described, Renisch discloses “a hot spot detection system 70 for automatic detection of a region of interest (ROI) pertaining to a lesion ... based on anatomical images 72 from the anatomical image memory 36 and functional images 74 from the functional image memory 58.” *Id.* at [0025]. Renisch states that “[a] segmentation unit 76 segments the anatomical first image representation 72 into regions which correspond to anatomical structures.” *Id.* Renisch further states that “[t]he segmentation unit 76 is capable of employing different types of segmentation methods” including, for example, “segmentation methods such as clustering ..., neural network, and the like.” *Id.* at [0027]. Clustering and artificial

neural networks are both examples of machine learning algorithms. *See, e.g.,* Ex1016 at pp.10-11. Thus, Renisch performs an analysis of one or more medical images using a machine learning algorithm as claimed. Additionally, Renisch uses the results of its machine learning segmentation to produce a risk map as claimed.

161. Renisch discloses that “a hot spot detection unit 90 detects from the functional image representation 74 regions of high intensity” that “potentially can be caused by tumor growth.” Ex1005 at [0029]. Regions of high intensity above a certain threshold are “highlighted ... with a cover overlay” and further evaluated *based on their location relative to segmented organs* to determine if they are lesions or just normal physiological uptake. *Id.* at [0029]-[0032].

162. Renisch discloses that “image combiner 130 combines the anatomical first image representation and the functional second image representation into a combined image for concurrent display.” *Id.* at [0037]. In particular, Renisch discloses that “the images can be superimposed in different colors, the outline of the functional second image representation hotspots can be superimposed on the [anatomical] first image representation, the outline of the segmented anatomical structures of the anatomical first image representation can be superimposed on the functional second image representation, ... or the like.” *Id.* (emphasis added). Renisch also states that “[t]he segmented and unsegmented anatomical images, ... map of quantified hot spots, and superimposed combinations thereof” are

generated and “stored” in the “memory 120 of a workstation or graphic[al] user interface 62.” Thus, Renisch also generates the claimed “risk map” comprising “a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer.”

163. Accordingly, it is my opinion that Renisch discloses limitation 1(c).

e) Limitation 1(d): “(iii) cause display of the risk map via a graphical user interface (GUI) for presentation or review of the risk map by a user,”

164. It is my opinion that Renisch discloses this limitation. Renisch discloses “[a] workstation or graphic user interface 62” that “includes a display device 64 ... which a clinician can use to ... display image data, and the like.” *Id.* at 0023]. Renisch also states that the results of its image analysis “are visualized on the display device 64” and “[t]he user is asked to confirm or edit the selected hot spots, i.e. high uptake regions ... before a summary report is generated.” *Id.* at [0033]; *see also id.* at [0037] (identifying the combination of images that can be displayed including “the outline of the hotspots ... superimposed on the [anatomical] first image”).

165. Accordingly, it is my opinion that Renisch discloses limitation 1(d).

f) Limitation 1(e): “wherein the analysis of the one or more medical images comprises creation of a 3D image of the one or more regions of risk of cancer or risk of recurrence of cancer overlaid on the one or more medical images, and wherein the 3D image

comprises geographic identification of one or more specific tissue region(s) overlaid on the one or more medical images.”

166. It is my opinion that Renisch discloses these limitations. Fundamentally, Renisch discloses segmenting 3D anatomical images into specific tissue regions, such as specific organ volumes (*id.* at [0025]), and transferring those segmented anatomical regions to a 3D functional nuclear medicine image so that regions of high radiotracer uptake in the functional image (i.e., hot spots) can be compared to the organ locations to evaluate if those hot spots are cancerous lesions or just normal physiological uptake (*id.* at [0025], [0031]). Additionally, Renisch describes the possibility of displaying every conceivable combination of the analyzed anatomical and/or functional images with segmented organs and/or segmented lesions superimposed thereon. *Id.* at [0036]-[0037].

167. Renisch states that the imaging scanners (12, 40) that supply the images to be analyzed produce 3D anatomical and functional images. *Id.* at [0021] (“reconstructs 3D image representations from the acquired imaging data”), [0022] (“acquisition of three-dimensional imaging data”). Renisch also states that “[t]he segmented and unsegmented anatomical images, the function [sic] images, the functional image with high uptake organs suppressed, in image or map of quantified hot spots, and superimposed combinations thereof are stored in a detected image memory 120 of a workstation or graphic user interface 62.” *Id.* at

[0036]. More specifically, Renisch states that “the outline of the functional second image representation hotspots can be superimposed on the first image representation” (id. at [0037]), which is a 3D anatomical image. Thus, I understand that Renisch discloses the claimed “creation of a 3D image of the one or more regions of risk of cancer or risk of recurrence of cancer overlaid on the one or more medical images.”

168. Additionally, Renisch teaches that “[t]he anatomical regions identified in the anatomical first image representation 72 can be carried over to the functional second image representation 74 in order to delineate anatomical structures in the second image representation 74.” *Id.* at [0034], [0008]. Specifically, Renisch states that “the outline of the segmented anatomical structures of the anatomical first image representation can be superimposed on the functional second image representation.” *Id.* at [0037] (emphasis added). Additionally, Renisch shows in Fig. 3B, which is reproduced below, the production of a risk map comprising a medical image overlaid with the outlines of segmented organs and containing color overlays of identified lesions. *Id.* at [0016], [0025] (referring to Fig. 3B as depicting the segmented brain, heart, and bladder). Thus, I understand that Renisch also teaches the claimed creation of a 3D image of one or more regions of risk of cancer “wherein the 3D image comprises geographic identification of one or more specific tissue region(s) overlaid on the one or more medical images.”

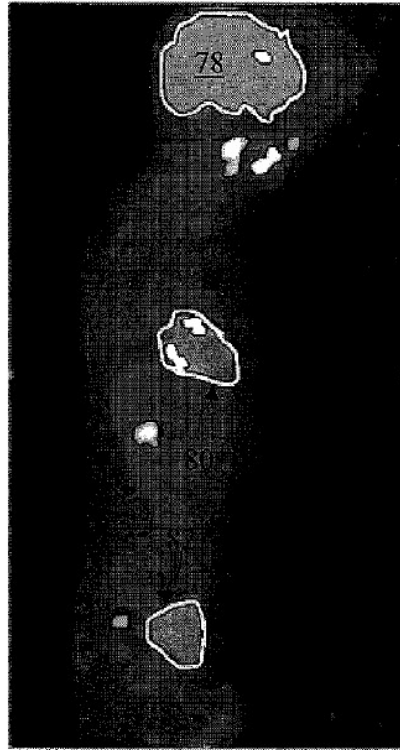


Figure 3B

See also, id. at [0036] (“The segmented ... anatomical images, ... the functional image with high uptake organs suppressed, in image or map of quantified hot spots, and superimposed combinations thereof are stored.”) (emphasis added).

169. Accordingly, it is my opinion that Renisch discloses limitation 1(e).

170. Because Renisch discloses every limitation of claim 1, it is my opinion that Renisch anticipates claim 1 and renders it unpatentable. Alternatively, if Renisch does not disclose a “network-based” system, as recited in the preamble of claim 1, then it is also my opinion that Renisch in combination with Wu

discloses every limitation of claim 1 and renders it unpatentable as obvious.

2. Claim 2: “The system of claim 1, wherein the one or more medical images comprise one or more magnetic resonance images (MRIs).”

171. Claim 2 depends from claim 1, which I explained above in Section IX.A.1 is anticipated by Renisch and/or rendered obvious by the combination of Renisch in view of Wu. Claim 2 further states “wherein the one or more medical images comprise one or more magnetic resonance images (MRIs).”

172. It is my opinion that Renisch discloses the limitations of claim 2. Renisch states: “With reference to FIG. 1, a diagnostic system 10 includes a first imaging system, a diagnostic imaging scanner 12 such as a computed tomography (CT) imaging scanner, an MRI scanner, or the like for obtaining anatomical diagnostic images.” *Id.* at [0020] (emphasis added), [0026] (stating that the anatomical image 72 and functional image 74 can both be “MR” images).

173. Because Renisch discloses every limitation of claim 2, including the limitations of claim 1 from which claim 2 depends, it is my opinion that claim 2 is anticipated by Renisch. In addition, it is also my opinion that claim 2 is rendered unpatentable as obvious in view of the combination of Renisch with Wu, as applied to claim 1 in Section IX.A.1.

3. Claim 3: “The system of claim 1, wherein the one or more medical images comprise (i) one or more PET/CT image(s) or (ii) one or more SPECT/CT image(s).”

174. Claim 3 depends from claim 1, which I explained above in Section IX.A.2 is anticipated by Renisch and/or rendered obvious by the combination of Renisch with Wu. It is my opinion that Renisch also discloses the additional limitations of claim 3 “wherein the one or more medical images comprise (i) one or more PET/CT image(s) or (ii) one or more SPECT/CT image(s).”

175. As I explained above in Section IX.A.1, Renisch discloses a diagnostic system that includes a first anatomical imaging system, which could be a CT scanner, a second functional imaging system, which could be a PET or SPECT scanner, and a hot spot detection system for automatic detection and quantification of lesions from anatomical and functional images. *Id.* at [0020], [0022], [0025]. Renisch also states “[a]lthough the anatomical and functional scanners are illustrated separate, it is to be appreciated that they can be combined” such as “combined PET/CT, SPECT/CT, [and] SPECT/MRI.” *Id.* at [0024]. Images from a hybrid PET/CT scanner would include a PET image and CT image. Likewise, images from a hybrid SPECT/CT scanner would include a SPECT image and a CT image.

176. Renisch further discloses that “an optional image combiner 130 combines the anatomical first image representation and the functional second

image representation into a combined image for concurrent display” (id. at [0037]) and the “anatomical images, the function[al] images, ... and superimposed combinations thereof are stored in a detected image memory 120 of a workstation or graphic user interface 62” (id. at [0036]). Thus, it is my opinion that Renisch discloses the limitations of claim 3.

177. Because Renisch discloses every limitation of claim 3, including every limitation of claim 1 from which it depends, it is my opinion that claim 3 is anticipated by Renisch. Additionally, claim 3 is rendered unpatentable as obvious based on the combination of Renisch and Wu as applied to claim 1.

4. Claim 4: “The system of claim 1, wherein the visual representation of tissue is at least a portion of one of the one or more medical images of the particular patient.”

178. Claim 4 depends from claim 1, which I explained above in Section IX.A.2 is anticipated by Renisch and/or rendered obvious by the combination of Renisch with Wu. Claim 1 states that the claimed risk map “comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer.” It is my opinion that Renisch also discloses the additional limitations of claim 4: “wherein the visual representation of tissue is at least a portion of one of the one or more medical images of the particular patient.”

179. With respect to the risk map produced by Renisch, Renisch states: “The segmented and unsegmented anatomical images, the function[al] images, the

functional image with high uptake organs suppressed, in image or map of quantified hot spots, and superimposed combinations thereof are stored in a detected image memory 120 of a workstation or graphic user interface 62.” *Id.* at [0036] (emphasis added). Additionally, Renisch states that “the outline of the functional second image representation hotspots can be superimposed on the first image representation, the outline of the segmented anatomical structures of the anatomical first image representation can be superimposed on the functional second image representation, ... or the like.” Thus, the visual representation of tissue in the risk map produced by Renisch includes at least a portion of the one or more anatomical/functional images. As I already explained in Section IX.A.1.c) above, the anatomical and functional medical images are each associated with a particular patient.

180. Because Renisch discloses every limitation of claim 4, including every limitation of claim 1 from which claim 4 depends, it is my opinion that claim 4 is anticipated by Renisch. Additionally, it is my opinion that Renisch in view of Wu renders claim 4 unpatentable as obvious in the same manner that the combination of Renisch and Wu are applied to claim 1 in Section IX.A.1 above.

5. Claim 5: “The system of claim 1, wherein the cancer is prostate cancer.”

181. Claim 5 depends from independent claim 1, which I explained above

in Section IX.A.1 is anticipated by Renisch and/or rendered obvious by the combination of Renisch with Wu. It is my opinion that Renisch also inherently discloses the additional limitation of claim 5, “wherein the cancer is prostate cancer.”

182. Renisch discloses the detection of cancerous lesions – generally – and is not limited to any particular cancer type. Indeed, Renisch depicts the detection and quantification of lesions throughout the body (e.g., Figs. 3A-3C) and describes the calculation of “total tumor burden,” which would account for metastatic cancer that has spread throughout the body. Ex1005 at Figs. 3A-3C, [0032], [0034] (“Assessing lymph nodes ... is a critical component in determining whether a tumor is likely to have metastasized.”). Imaging cancer throughout the body, including the pelvic region where the prostate is located, would necessarily include imaging prostate cancer if it is present.

183. In my experience, prostate cancer is one of the most prevalent and deadly forms of cancer because it is known to metastasize throughout the body. Therefore, it is my opinion that a POSITA, reading the broad disclosure of Renisch would understand that its teachings apply to the detection and quantification of prostate cancer, as well as other forms of metastatic cancer.

184. Renisch explains that “[n]uclear medicine imaging has been increasingly used in cancer imaging due to the success of the tracer [18F]-

fluorodeoxyglucose (FDG).” *Id.* at [0003]. By 2014, other publications characterized [18F] FDG as “the most widely used PET imaging agent in oncology.” Ex1010 at 2:20-21. A POSITA would know that FDG is capable of imaging prostate cancer, as well as many other forms of cancer. Ex1024 at [0004], [0006]-[0007], [0024], [0056], Table 1.

185. As of the filing date of Renisch in June 2010, prostate specific membrane antigens (“PSMAs”) for targeted prostate cancer imaging were not yet commercially available or clinically approved. Thus, in my experience, other radiopharmaceuticals such as 18F FDG PET or 99mTc-MDP SPECT would have been used by clinicians to image metastatic prostate cancer as of the publication date of Renisch.

186. It is my opinion, based on my knowledge and experience, that a person practicing the invention disclosed in Renisch, i.e., imaging the whole body to detect cancerous lesions using radio-labeled FDG, would necessarily detect prostate cancer if it was present. Accordingly, I believe that Renisch inherently discloses the imaging of prostate cancer even if it does not expressly state it.

187. Because Renisch discloses every limitation of claim 5, it is my opinion that claim 5 is anticipated by Renisch. In addition, it is my opinion that Renisch in combination with Wu render claim 5 unpatentable as obvious in the same manner as the combination of Renisch and Wu are applied to claim 1 above.

6. Claim 6: “The system of claim 1, wherein the visual representation of tissue comprises a visual representation of bone.”

188. Claim 6 depends from independent claim 1, which I explained above in Section IX.A.1 is anticipated by Renisch and/or rendered obvious by the combination of Renisch and Wu. Claim 1 states that the claimed risk map “comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer.” It is my opinion that Renisch also discloses the additional limitation of claim 6: “wherein the visual representation of tissue comprises a visual representation of bone.”

189. As discussed in Section IX.A.5, Renisch discloses the generation of a risk map comprising a visual representation of tissue, such as an anatomical CT image or functional PET image, overlaid with one or more outlined lesions and outlined organ contours. Ex1005 at [0036]-[0037], Fig. 3B. As depicted in Figs. 3A-3C, exemplary functional images produced by Renisch include at least head and torso images. Corresponding anatomical images of the same regions – as required for segmenting the organs – would necessarily include a visual representation of bones located in the image of the head and torso. Renisch expressly states that “the outline of the functional second image representation hotspots can be superimposed on” these anatomical images, and “[these] anatomical images, ... the functional image with high uptake organs suppressed, in

image or map of quantified hot spots, and superimposed combinations thereof” are generated and stored. Thus, it is my opinion that Renisch discloses embodiments in which the visual representation of tissue includes bones, as claimed.

190. Because Renisch teaches every limitation of claim 6, it is my opinion that claim 6 is anticipated by Renisch. In addition, it is my opinion that the combination of Renisch and Wu, as applied to claim 1 in Section IX.A.1 above, also renders claim 6 unpatentable as obvious.

7. Claim 7: “The system of claim 1, wherein the one or more specific tissue region(s) comprise one or more members selected from the group consisting of organs, organ structures, sub-organs, and organ regions.”

191. Claim 7 depends from claim 1, which I explained above in Section IX.A.1 is anticipated by Renisch and/or rendered obvious by the combination of Renisch and Wu. Claim 1 recites the “creation of a 3D image of [] one or more regions of risk of cancer ... wherein the 3D image comprises geographic identification of one or more *specific tissue region(s)* overlaid on the one or more medical images.” Ex1001 at 36:1-7 (emphasis added). Claim 7 adds the limitation: “wherein the one or more specific tissue region(s) comprise one or more members selected from the group consisting of organs, organ structures, sub-organs, and organ regions.” It is my opinion that Renisch discloses the additional limitation of claim 7.

192. As previously explained, Renisch states that “[t]he anatomical regions identified in the anatomical first image representation 72 can be carried over to the functional second image representation 74 in order to delineate anatomical structures in the second image representation 74.” Ex1005 at [0034]. Additionally, Renisch states that “the outline of the segmented anatomical structures of the anatomical first image representation can be superimposed on the functional second image representation.” *Id.* at [0037]. For example, Fig. 3B of Renisch (*supra*, ¶168) depicts a functional image in which potential lesions have been identified by a “color overlay” and segmented organs (i.e., brain, heart, bladder) are geographically identified by overlaid graphical “outline[s]”. *Id.* at [0025], [0029], [0037], [0015]-[0016]. Thus, Renisch discloses the geographic identification of organs overlaid on one or more medical images.

193. Because Renisch discloses all the limitations of claim 7, it is my opinion that Renisch anticipates claim 7. Additionally, it is my opinion that Renisch in combination with Wu, as applied to claim 1 in Section IX.A.1 above, also renders claim 7 unpatentable for obviousness.

8. Claim 9: “The system of claim 1, wherein the instructions cause the processor to generate a radiologist report for the particular patient based at least in part on the analysis of the one or more medical images.”

194. Claim 9 depends from claim 1, which I explained above in Section

IX.A.1 is anticipated by Renisch and/or rendered obvious by the combination of Renisch with Wu. It is my opinion that Renisch also discloses the additional limitations of claim 9: “wherein the instructions cause the processor to generate a radiologist report for the particular patient based at least in part on the analysis of the one or more medical images.”

195. Renisch discloses that “[a]n identification unit, processor, or algorithm 106 is configured to calculate metrics” including, but not limited to, “total tumor burden, glycolytic volume, SUV, average activity, maximum activity, minimum activity, homogeneity, and the like.” *Id.* at [0032]. Additionally, Renisch states that “the results of the identification unit 106 are visualized on the display device 64” and “[t]he user is asked to confirm or edit the selected hot spots, i.e. high uptake regions, using the input device 66 before a summary report is generated.” *Id.* at [0033] (emphasis added). Thus, Renisch generates a report, and that report is based on the analysis of the one or more medical images to produce quantitatively calculated metrics, as well as final confirmation by the user (i.e., radiologist) of lesion candidates.

196. Because Renisch discloses every limitation of claim 9, it is my opinion that Renisch anticipates claim 9. In addition, it is my opinion that the combination of Renisch and Wu, as applied to claim 1 in Section IX.A.1 above, also renders claim 9 unpatentable as obvious.

9. Claim 10: “The system of claim 9, wherein the radiologist report comprises the one or more medical images and the risk map.”

197. Claim 10 depends from claim 9, which I explained in Section IX.A.8 above is anticipated by Renisch and/or rendered obvious by the combination of Renisch and Wu. It is my opinion that Renisch also discloses the additional limitations of claim 10: “wherein the radiologist report comprises the one or more medical images and the risk map.”

198. The Patent describes generating a “risk map, e.g., a visual representation (e.g., 3D representation) of tissue (e.g., an organ or other part of the body) with graphical denotations (e.g., texture- or color-coding) marking regions of risk of current disease or risk of recurrence of disease, e.g., cancer, e.g., wherein the risk map is displayed as an overlay of the PET/SPECT/CT/MRI/US/-combined/derived/fused image of the tissue, or is in place of the image of the tissue.” Ex1001 at 4:2-10 (emphasis added). From this, I understand that a risk map, as used in the Patent, can be overlaid on a medical image or can comprise another visual representation of tissue, e.g., an illustration of an organ or region of the body with graphical denotations marking regions of risk. This interpretation is at least somewhat confirmed by dependent claim 4 of the patent, which purports to *narrow* independent claim 1 by stating “wherein the visual representation of tissue is at least a portion of the one or more medical images of the particular patient.”

Thus, the “visual representation of tissue” can be something other than a “medical image” – like a model or illustration.

199. Renisch discloses that the results of its hot spot detection system may be visualized on a display device, and a user (e.g., radiologist) is “asked to confirm or edit the selected hot spots ... before a summary report is generated.” Ex1005 at [0033]. Without Renisch including any suggestion to the contrary, I conclude that the images presented to the user for confirmation and editing are also included in the summary report after confirmation and editing, if any.

200. As I previously explained in Sections IX.A.1 and IX.A.7, Renisch produces risk maps, as claimed, comprising graphical denotations of one or more regions of risk of cancer, such as outlined or color-coded lesions, overlaid on medical images, such as anatomical and/or functional images, on which the outline of segmented anatomical structures, such as organs, are superimposed. Ex1005 at [0036]-[0037], Fig. 3B I understand, therefore, that the risk maps produced by Renisch satisfy both the “risk map” and the “one or more medical images” limitations of claim 10. Specifically, the risk maps produced by Renisch include one or more of the patient’s medical images.

201. Separately, Renisch also explains that its generated risk maps and medical images can be displayed concurrently side-by-side. *Id.* at [0036]-[0037]. For example, Renisch states: “[T]he outline of the functional second image

representation hotspots can be superimposed on the first [anatomical] image representation, the outline of the segmented anatomical structures of the anatomical first image representation can be superimposed on the functional second image representation, the first and second image representations can be displayed side by side with a common scale, or the like.”

202. Thus, whether the summary report generated by Renisch displays a single risk map comprising segmented lesions over a medical image or a risk map side-by-side with a medical image, it is my opinion that the summary report generated by Renisch discloses all the limitations of claim 10.

10. Independent Claim 13

203. Independent claim 13 of the Patent is nearly identical to independent claim 1, which I explained in Section IX.A.1 above is anticipated by Renisch and/or rendered obvious by Renisch in view of Wu. Whereas claim 1 is directed to “[a] network-based system for generating a disease risk map,” claim 13 is directed to “[a] method for generating a disease risk map.” Whereas claim 1 recites a “processor and memory” having stored instructions for performing a series of steps, claim 13 recites essentially the same steps performed “by a processor.” Unlike claim 1, however, claim 13 does not state that the method/system is “network-based” – either in the preamble or the body of the claim. My only purpose for combining Wu with Renisch relative to claim 1 was to address the

possibility that Renisch is not explicit enough in stating that it is a network-based system. Claim 13 does not include a “network-based” limitation. Accordingly, it is my opinion that claim 13 is anticipated by Renisch for the same reasons I explained in Section IX.A.1 above and that the combination of Renisch with Wu is not needed to render claim 13 unpatentable.

a) Preamble: “A method for generating a disease risk map for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer, the method comprising:”

204. The preamble of claim 13 is essentially the same as the preamble of claim 1 except that claim 13 recites a “method” whereas claim 1 recites a “network-based system.” Assuming the preamble is considered a limitation on the scope of the claim, it is my opinion that Renisch discloses the limitations of the preamble for the same reasons provided in Section IX.A.1.a) above.

b) 13(a): “(i) accessing, by a processor, one or more medical images associated with a particular patient from a database;”

205. This limitation is essentially identical to limitation 1(b) which is addressed in Section IX.A.1.c) above. The only difference is that, whereas limitation 1(b) relates to instructions that cause a processor to “access one or more medical images ...,” limitation 13(a) recites “accessing, by a processor, one or more medical images” Accordingly, it is my opinion that Renisch discloses

limitation 13a) for the same reasons explained in Section IX.A.1.c) above.

- c) **13(b): “(ii) automatically analyzing, by the processor, using a machine learning algorithm, the one or more medical images to generate the risk map, wherein the risk map comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer or risk of recurrence of cancer; and”**

206. This limitation is essentially identical to limitation 1(c) which is addressed in Section IX.A.1.d) above. The only difference is that, whereas limitation 1(c) relates to instructions that cause a processor to “perform an analysis of the one or more medical images associated with the particular patient using a machine learning algorithm ...,” limitation 13(b) recites “automatically analyzing, by the processor, using a machine learning algorithm, the one or more medical images” I note that limitation 13(b) explicitly recites “*automatically* analyzing, by the processor.” Nevertheless, my analysis of limitation 1(c) above already assumed that the claimed analysis – performed by a processor executing stored instructions – was automatic. Nevertheless, I repeat here, for the avoidance of doubt, that Renisch discloses “a hot spot detection system [] for *automatic* detection of a region of interest (ROI) pertaining to a lesion and *automatic* quantification of metabolic activity in detected lesions based on anatomical images ... and functional images.” Ex1005 at [0025] (emphasis added). Accordingly, it is my opinion that Renisch discloses limitation 13(b) for the same reasons explained

in Section IX.A.1.d) above.

- d) **13(c): “(iii) causing, by the processor, display of the risk map via a graphical user interface (GUI) for presentation or review of the risk map by a user,”**

207. This limitation is essentially identical to limitation 1(d) which is addressed in Section IX.A.1.e) above. The only difference is that, whereas limitation 1(d) relates to instructions that cause a processor to “cause display of the risk map ... ,” limitation 13(c) recites “causing, by the processor, display of the risk map” Accordingly, it is my opinion that Renisch discloses limitation 13(c) for the same reasons explained in Section IX.A.1.e) above.

- e) **13(d): “wherein step (ii) comprises creation of a 3D image of the one or more regions of risk of cancer or risk of recurrence of cancer overlaid on the one or more medical images, and wherein the 3D image comprises geographic identification of one or more specific tissue region(s) overlaid on the one or more medical images.”**

208. This limitation is essentially the same as limitation 1(e), which I address in Section IX.A.1.f) above. The only difference is that, whereas limitation 1(e) recites “wherein the analysis of the one or more medical images comprises ...,” limitation 13(d) recites “wherein step (ii) comprises ...,” where step (ii) of claim 13 is the step of “automatically analyzing, by the processor, ... the one or more medical images” Accordingly, it is my opinion that Renisch anticipates limitation 13(d) for the same reasons I provided in Section IX.A.1.f) above.

209. Because it is my opinion that Renisch discloses all the limitations of claim 13, it is also my opinion that Renisch anticipates claim 13.

B. Ground C, Obviousness over Renisch, or Renisch in view of Wu, each in view of the Applicant's Admitted Prior Art or D'Souza

1. Claim 5: "The system of claim 1, wherein the cancer is prostate cancer."

210. Claim 5 depends from claim 1, which I explained in Section IX.A.1 above is anticipated by Renisch and/or rendered obvious by Renisch in view of Wu. If, however, Renisch does not sufficiently disclose that the cancer being imaged is prostate cancer, then the Patent admits, or in the alternative D'Souza discloses, that systems and techniques for imaging prostate cancer were known in the prior art. It is my opinion that it would have been obvious to use Renisch for imaging prostate cancer based on the knowledge of a POSITA, as evidenced by the applicant admitted prior art ("AAPA"). Alternatively, it is my opinion that the combined teachings of Renisch and D'Souza render claim 5 obvious.

211. As I explained in Section IX.A.5 above, Renisch discloses a system for imaging and analyzing cancerous lesions, generally. Renisch is not limited to any particular type of cancer. With reference to Figs. 3A-3C of Renisch, the region of the body evaluated for cancer includes at least the region extending from the patient's head to the patient's pelvis, which would include the patient's prostate. Indeed, Renisch describes calculating "total tumor burden," which

includes metastatic cancer that has spread throughout the body. Ex1005 at Figs. 3A-3C, [0032], [0034]. Prostate cancer is one of the most common cancers to spread (i.e., metastasize) throughout the body, and thus a POSITA would immediately know that a primary use of the teachings of Renisch is to evaluate prostate cancer. *See generally* Ex1022 (describing the prevalence of metastatic prostate cancer). It stands to reason, therefore, that Renisch either teaches the imaging of prostate cancer or, at the very least, discloses a system that could image prostate cancer given the appropriate motivation and radiotracer.

212. The AAPA in the Background Section of the Patent demonstrates the knowledge of a POSITA at the time of the effective filing date of the Patent and supplies the motivation and teaching to use a nuclear medicine imaging device like Renisch for imaging prostate cancer. The Patent admits that “single-photon emission computerized tomography (SPECT) [and] positron emission tomography (PET) cameras” are “commonly available nuclear medicine cameras ... found in most hospitals throughout the world.” Ex1001 at 1:39-43. Renisch is such a diagnostic system, having a functional PET or SPECT scanner. Ex1005 at [0022]. The Patent also admits that “[t]here are also a number of radiopharmaceuticals available for imaging particular kinds of cancer” including prostate cancer. Ex1001 at 1:49-61. Specifically, the Patent states:

For example, the small molecule diagnostic 1404 targets the

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

Id. at 1:52-61. Additionally, the Patent admits:

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

Id. at 1:62-2:3.

213. Accordingly, a POSITA would have known that a nuclear medicine imaging device, like the ones disclosed in Renisch (PET or SPECT), could be used to image prostate cancer, and a POSITA would have had a reasonable expectation of success in doing so using known PSMA tracers identified in the AAPA. It is also my opinion, therefore, that Renisch renders claim 5 obvious based on the knowledge of a POSITA, as evidenced by the AAPA.

214. Renisch also teaches the use of ^{18}F -labeled fluorodeoxyglucose (FDG) as an example of a radiotracer used to image cancer with a PET scanner. *Id.* at [0003], [0023].

215. D'Souza states that "Positron Emission Tomography (PET) has become one of the most prominent functional imaging modalities in diagnostic medicine" and that " ^{18}F FDG is the most widely used PET imaging agent in oncology." Ex1010 at 2:15-21. D'Souza also states that "[t]he skilled artisan will realize that virtually any delivery molecule can be attached to ^{18}F for imaging purposes," (*id.* at 3:57-58) and "[t]he type of disease or conditions that may be imaged is limited only by the availability of a suitable delivery molecule for targeting a cell or tissue associated with the disease or condition" (*id.* at 4:51-64). For example, D'Souza discloses that " ^{18}F -labeled peptides, proteins and/or antibodies are of use for imaging cancer" including "prostate cancer." *Id.* at 36:22-37. Specifically, D'Souza discloses PAP (prostatic acid phosphatase), PSA (prostate-specific antigen), and PSMA (prostate-specific membrane antigen), which are examples of target antigens useful in imaging prostate cancer. *Id.* at 12:19-49.

216. Additionally, D'Souza explains that "[m]ethods of imaging using labeled molecules are well known in the art, and any such known methods may be used with the ^{18}F -labeled molecules disclosed herein." *Id.* at 35:42-49, 36:4-21.

217. It is my opinion that a POSITA implementing Renisch would have looked to D'Souza because Renisch and D'Souza are in the same field of cancer imaging using radiotracers such as ^{18}F -labeled delivery molecules. Additionally, it is my opinion that a POSITA would have found it obvious to use D'Souza's ^{18}F -labeled molecules with Renisch's hot spot detection system to image prostate cancer based on D'Souza's express teaching that its disclosed ^{18}F -labeled molecules could be used to image prostate cancer and could be used with any known method of imaging using labelled molecules. Ex1010 at 35:42-36:37, 4:51-64.

218. Combining Renisch and D'Souza would have merely amounted to combining existing prior art elements (i.e., automated lesion detection systems and prostate-cancer-specific radiotracers) according to known methods (i.e., selecting a suitable delivery molecule for targeting a particular disease) to yield predictable results. D'Souza expressly teaches that many delivery molecules were known for imaging many different diseases, including prostate cancer. Ex1010 at 4:51-64, 36:22-37. Using Renisch's hot spot detection system to image prostate cancer could have been accomplished simply by selecting the appropriate prostate-cancer-specific delivery molecule as taught by D'Souza. *E.g.*, Ex1009, Fig. 2, [0041]-[0049]. Thus, implementing Renisch's hot spot detection system to image prostate cancer would have been an obvious and straight forward modification according to

D'Souza's express teachings.

219. Additionally, or alternatively, combining Renisch and D'Souza would have merely amounted to simple substitution of one known element (i.e., ^{18}F -labeled prostate cancer targeting molecules) for another (i.e., ^{18}F FDG) to obtain predictable results. Renisch discloses the use the ^{18}F FDG for imaging cancer generally. Ex1005 at [0003], [0023]. D'Souza teaches that although ^{18}F FDG is “the most widely used PET imaging agent in oncology..., there is a keen interest in developing other labeled compounds for functional imaging to complement and augment anatomic imaging methods.” Ex1010 at 2:20-25. D'Souza also discloses that “[e]xemplary target antigens of use for imaging or treating various diseases” include “PSA [prostate-specific antigen]” and “PSMA [prostate-specific membrane antigen]” (*id.* at 12:19-49) and that ^{18}F can be labeled with any of these antigens including PSMA (*id.* at 3:57-58, 4:51-64, claim 7). Therefore, it is my opinion that it would have been obvious to substitute ^{18}F -PSMA, as taught in D'Souza, for ^{18}F FDG, as disclosed in Renisch, based on the teaching and motivation expressed in D'Souza to “complement and augment” existing imaging methods with “other labeled compounds” including compounds targeted to particular diseases, such as prostate cancer. Ex1010 at 2:20-27, 36:22-37. Additionally, using an ^{18}F -labeled PSMA with the hot spot detection system of Renisch would merely have led to the predictable result of providing improved imaging of a particular cancer (i.e.,

prostate cancer).

220. It is also my opinion that a POSITA would have had a reasonable expectation of success in combining Renisch and D’Souza. Renisch already teaches the use of an ^{18}F -labeled molecule to image cancer using a PET scanner. Ex1005 at [0023]. Nothing in the disclosure of Renisch would discourage the use of a different ^{18}F -labeled molecule for the same purpose. Additionally, D’Souza expressly teaches that any of its disclosed disease-specific targeting molecules could be used with any known PET imaging technique. Ex1010 at 35:42-36:21. Therefore, the ^{18}F -labeled molecules of D’Souza would be readily applicable to, and easily implemented with, Renisch’s hot spot detection system. And a POSITA would have expected success combining Renisch and D’Souza in view of their complementary teachings.

C. Ground D, Obviousness over Renisch, or Renisch in view of Wu, each in view of Sprencz

1. Claim 8: “The system of claim 1, wherein the one or more specific tissue region(s) comprise one or more particular bones.”

221. Claim 8 depends from claim 1, which I explained in Section IX.A.1 above is anticipated by Renisch and/or rendered obvious by the combination of Renisch and Wu. Claim 1 requires “creation of a 3D image ... wherein the 3D image comprises geographic identification of one or more specific tissue region(s).” Ex1001 at 36:2-6. Claim 8 further adds “wherein the one or more

specific tissue region(s) comprise one or more particular bones.”

222. As I explained above in Section IX.A.1.e), Renisch, discloses the creation of a 3D image (e.g., CT or PET) that includes geographic identification of one or more specific tissue regions, including one or more organs (e.g., brain, heart, bladder, kidneys, liver, etc.). Ex1005 at [0021] (“reconstructs 3D image representations”), [0025], [0034], Fig. 3B, [0008] (“anatomical regions identified in the anatomical first image representation could be carried over to the functional second image representation in order to delineate anatomical structures there.”), [0037]. Renisch does not, however, expressly describe or depict geographic identification of one or more specific bones in a medical image. Sprenzc discloses this limitation.

223. Sprenzc, like Renisch, discloses a system for automatically detecting, segmenting, displaying, and quantifying lesions using multi-modality 3D imaging data. Ex1006 at Abstract, [0011], [0041]-[0044], [0048]-[0050], [0055]-[0056]. Unlike Renisch, however, Sprenzc specifically describes the identification and quantification of bone lesions. *Id.* at [0001].

224. As I explained in Section VIII.B above, Sprenzc discloses a system and technique for quantifying bone lesions that includes automatically segmenting an anatomical image (e.g., CT image) to identify the patient’s 3D bone volume. *Id.* at [0043]-[0046], Fig. 5. Segmented lesions identified throughout the body (as in

Renisch) can then be classified as either bone lesions or non-bone lesions by comparing the location of each lesion with the location of the segmented skeletal volume. *Id.* at [0048]-[0049], [0052]. Sprencz expressly states that the segmentation results can be displayed in a variety of ways. For example, Sprencz states: “Images of the lesion candidates are generated ... and displayed as an overlay on the patient skeletal image generated from the segmented skeletal structure output from the bone segmentation subroutine.” *Id.* at [0050]. Alternatively, “the segmented skeletal structure from a CT image series is projected into a PET image that includes the lesion candidates.” *Id.* (emphasis added). Thus, Sprencz discloses the limitations of claim 8 because the described overlays will display lesions on particular bones of the skeletal image.

225. It is my opinion that a POSITA would have been motivated to modify Renisch’s automatic hot spot detection system to also segment bones based on Sprencz’s express teaching that “[q]uantification of bone lesions using medical images is an important aspect of clinical diagnostics and therapy.” *Id.* at [0004]. Renisch already teaches the automatic calculation of quantitative metrics such as total tumor burden. Ex1005 at [0032]. Sprencz further teaches the calculation of additional diagnostic values such a “bone lesion index,” which is “a ratio of the total bone lesion volume to the total skeletal volume.” Ex1006 at [0054]. Thus, for the purpose of determining additional diagnostic values, including the total

tumor burden in the skeletal system, a POSITA would have been motivated to extend the automatic segmentation techniques described in Renisch beyond just the soft tissue organs expressly identified therein to also include bones, the structural organ of the body.

226. Combining Renisch and Sprencz, or Renisch in view of Wu with Sprencz, would have merely amounted to combining existing prior art elements according to known methods to yield predictable results. Renisch's lesion detection system and Sprencz's bone lesion detection system are both prior art to the Patent. To geographically locate lesions relative to anatomical structures (e.g., organs), Renisch teaches the segmentation of anatomical structures in anatomical images using a variety of known methods, including model-based methods, clustering, edge detection, region growing, principle component analysis, artificial neural networks, "and the like." Ex1005 at [0027]-[0028]. Likewise, to geographically locate lesions relative to anatomical structures (e.g., bones), Sprencz discloses the segmentation of anatomical structures in anatomical images using a variety of techniques that overlap with the techniques disclosed by Renisch, including thresholding, clustering, level set, and region growing. Ex1006 at [0045]. Thus, combining Sprencz with Renisch would have amounted to little more than applying the same or additional segmentation techniques, such as thresholding, in order to segment additional structures, such as bones.

227. Combining Sprencz with Renisch, or Renisch in view of Wu, would have led to the predictable result being able to segment additional anatomical structures and, therefore, calculate additional diagnostic metrics, including the tumor burden within the skeletal system. It is also my opinion that a POSITA would have had a reasonable expectation of success in view of the overlapping technology disclosed by Renisch and Sprencz, including their disclosure of common techniques for anatomical segmentation. In essence, combining Sprencz with Renisch would not change the operation of Renisch and would amount to little more than segmenting additional anatomical structures – specifically bones – using techniques already disclosed in Renisch (e.g., neural networks) or other standard techniques such as thresholding of CT images.

228. Because Renisch, or Renisch in view of Wu, each in view of Sprencz, teaches or suggests every limitation of claim 8, it is my opinion that claim 8 is rendered unpatentable as obvious by the references.

D. Ground E, Obviousness over Renisch, or Renisch in view of Wu, each in view of Maier

- 1. Claim 9: “The system of claim 1, wherein the instructions cause the processor to generate a radiologist report for the particular patient based at least in part on the analysis of the one or more medical images.**

229. Claim 9 depends from claim 1, which I explained in Section IX.A.1 above is anticipated by Renisch and/or rendered obvious by the combination of

Renisch and Wu. In Section IX.A.8 above, I explained that it is also my opinion that Renisch discloses the features of claim 9, thus rendering claim 9 unpatentable over Renisch and/or the combination of Renisch and Wu. Nevertheless, if Renisch’s “summary report” is not a “radiologist report for the particular patient based at least in part on the analysis of the one or more medical images,” as set forth in claim 9, then Maier discloses that limitation.

230. As I explained in Section XIII.D above, Maier discloses computer implemented systems and methods for assessing medical images and communicating a patient’s health status and risk by automatically generating a report tailored for the intended user, including for example a “radiologist.” Ex1008 at [0014], [0015]-[0016], [0026], [0041].

231. Maier describes receiving one or more medical images, comparing the one or more medical images to historical reference images from the same patient or other patients having known clinical outcomes, calculating quantitative metrics related to the patient’s risk of future health outcomes, and automatically generating a report providing the results of the analysis, including the image of interest and the calculated risk metrics. *Id.* at Fig. 1, [0027], [0035] (“In another embodiment, the health status metrics may be calculated by comparing a patient’s image data to their own image data that was acquired on a prior occasion.”).

232. As depicted in Fig. 3 of Maier (*supra*, ¶132), the report that is

produced can include the patient's own medical images overlaid with graphical denotations highlighting regions of risk side-by-side with reference images of others for comparison. *Id.* at [0026], [0041]. Maier also discloses that, in some embodiments, a software application “converts the speech of a radiologist to text and then combines the text with the contents of [a] data file to create a user-readable report for review by a user.” *Id.* at [0036] (emphasis added). Accordingly, Maier discloses the limitations of claim 9: automatic generation of “a radiologist report for the particular patient based at least in part on the analysis of the one or more medical images.”

233. Additionally, Maier provides the express motivation, suggestion, and teaching to combine its computer-implemented image analysis and report generating method with other diagnostic systems like Renisch. For example, Maier states that the disclosed method “may be implemented as a software application running in a hospital enterprise data center,” and “may receive [] medical images directly ... from a medical imaging system, or ... a separate device ..., or via a manual push by a user.” *Id.* at [0043]. Additionally, Maier states that “any system or information handling system used for the methods described herein may include any instrumentality or aggregate of instrumentalities operable to compute, calculate, determine, classify, process, transmit, receive, retrieve, originate, switch, store, display, communicate, manifest, detect, record, reproduce,

handle, or utilize any form of information.” *Id.* at [0045] (emphasis added). Renisch, as described in Section XIII.A, discloses a diagnostic system comprising one or more anatomical and functional imaging scanners. Ex1005 at Fig. 1, [0020]-[0022]. The anatomical and functional images produced by Renisch, including segmented images and superimposed combinations thereof, are stored in a “detected image memory.” Ex1005 at [0036]. Based on the express teachings in Maier, a POSITA would have been motivated to combine, and would have had a reasonable expectation of success in combining, Maier with Renisch because Maier expressly receives anatomical and/or functional images directly from medical imaging systems – like those disclosed in Renisch – or a separate device, including a database of a patient’s historical images – like the one disclosed in Renisch.

234. Additionally, or alternatively, combining Renisch, or Renisch in view of Wu, with Maier, would merely have amounted to combining prior art elements according to known methods to yield predictable results. The computer-implemented medical image analysis system disclosed in Renisch and the computer-implemented medical image analysis system disclosed in Maier are both prior art to the Patent. Their respective disclosed functionalities are additive and can be performed in parallel. In other words, combining Renisch with Maier does not require any alteration or modification of Renisch or Maier. The only thing

required to combine Renisch and Maier is to transfer image data acquired by Renisch to Maier according to well-known, standard methods that are expressly described in Maier. Ex1008 at [0043] (“the method may receive the medical images directly as a DICOM send/push from a medical imaging system”), [0045]-[0047], [0048] (“Information, ... data, etc. may be passed, forwarded, or transmitted via any suitable means including memory sharing, ... network transmission, etc.”). Alternatively, processed image data produced by Renisch, including segmented images and risk maps of quantified hot spots that are stored in Renisch’s “detected image memory” (Ex1005 at [0036]), could be supplied to Maier for analysis according to Maier’s disclosed process, including comparison of the patient’s images to the images of others for which medical outcomes are known or to the patient’s own historical images for tracking progress (Ex1008 at [0014], [0022], [0024]). In either case, neither Maier nor Renisch need to be modified or altered; they only need to be connected to share image data.

235. Accordingly, it is my opinion that it would have been obvious and straightforward for a POSITA to combine Maier with Renisch or Renisch in view of WU to yield the predictable result of automatically generating a tailored radiologist report using the image data produced by Renisch. Moreover, a POSITA would have had a reasonable expectation of success in combining Maier with Renisch, or Renisch in view of Wu, because the combination would merely

have amounted to transferring the data and images produce by Renisch to Maier using standard data transfer methods and formats (e.g., DICOM).

236. Accordingly, it is my opinion that Renisch, or Renisch in view of Wu, each in view of Maier, teach all the limitations of claim 9 and render claim 9 unpatentable as obvious.

2. Claim 10: “The system of claim 9, wherein the radiologist report comprises the one or more medical images and the risk map.”

237. Claim 10 depends from claim 9, which I explained in Section IX.D.1 above is rendered obvious by Renisch, or Renisch in view of Wu, each in view of Maier. As I also explained in Section IX.A.8 above, Renisch discloses the additional limitations of claim 10, i.e., the summary report generated by Renisch comprises the one or more medical images and the risk map generated by Renisch. Maier likewise discloses that the radiologist report it generates “may include a CT image with transparent color overlay indicating areas of [disease]” and “may also include a complete new set of images generated by the computer-implemented algorithm with transparent color overlays on the original gray-scale CT images to indicate the areas of likely [disease].” Therefore, it is my opinion that Renisch, or Renisch in view of Wu, each in view of Maier, also renders claim 10 unpatentable under the same rationales set forth in Section IX.D.1. For example, a POSITA would have been motivated to combine Renisch and Maier and would have had a

reasonable expectation of success in doing so, since neither Renisch nor Maier need to be modified in any way to implement such combination. When combined as proposed, the processed image data produced by Renisch, including the patient's current risk map, could be supplied to Maier for further processing (e.g., comparing the patient's current risk map to the risk map of others) and automatic generation of the radiologist's report according to Maier's disclosure.

3. Claim 11: “The system of claim 9, wherein the radiologist report comprises one or more reference images or reference risk maps.”

238. Claim 11 depends from claim 9, which I explained in Section IX.D.1 above is rendered obvious by the combination of Renisch, or Renisch in view of Wu, each in view of Maier. Maier also discloses the additional limitations of claim 11: “wherein the radiologist report comprises one or more reference images or reference risk maps.”

239. With reference to Fig. 3, which is reproduced below, an example of a report automatically generated by Maier includes not only the patient's medical images, but also comparative reference images (or risk maps) from others with known medical outcomes. Ex1008 at [0041].



MIM Ex1002

E. Ground F, Obviousness over Renisch, or Renisch in view of Wu, each in view of Menon

- 1. Claim 12: “The system of claim 1, wherein the instructions cause the processor to apply a machine learning algorithm to update a process for automatically analyzing the one or more medical images using accumulated image data in the database.**

241. Claim 12 depends from claim 1, which I explained in Section IX.A.1 above is anticipated by Renisch and/or rendered obvious by the combination of Renisch in view of Wu. Claim 12 recites the additional limitation: “wherein the instructions cause the processor to apply a machine learning algorithm to update a process for automatically analyzing the one or more medical images using accumulated image data in the database.” Ex1001 at 36:38-42 (emphasis added). I interpret this to refer to something akin to a machine learning feedback loop that improves the method by which automatic analysis of the medical images is performed – rather than updating the analysis of any particular medical image. I base my interpretation on the specification of the Patent, which states that the disclosed system supports software tools for “application of machine learning algorithms to update [the] process by which images are analyzed (e.g., updating segmentation and/or classification routines based on growing image database).” *Id.* at 3:6-10 (emphasis added). My interpretation is further informed by my understanding that machine learning algorithms that perform segmentation and/or classification tasks are trained using training data including labeled images. Thus,

the Patent seems to describe applying machine learning using additional training data – including the accumulated images that have been segmented and/or classified using the disclosed system – to update the routines by which future segmentation and/or classification will be performed. Menon discloses this limitation.

242. Menon describes an automated triaging decision support tool that utilizes machine learning and a feedback loop to continuously refine (i.e., update) the tool. Ex1012 at [0010], [0032], [0055], [0078], [0103]-[0104], [0180], [0189], [0195]. The tool takes, as input, various data, including the patient’s medical images (*id.* at [0104], [0110]), and automatically outputs risk analysis and treatment recommendations (*id.* at [0104]-[0109], [0189]). Additionally, the tool uses this output information and accumulated imaging data in a feedback loop to refine the tool using machine learning. *Id.* at [0180], [0189].

243. Menon states that “the tool [] may be refined with additional ... imaging data using machine learning, feedback, and validation data.” *Id.* at [0180] (emphasis added). Menon explains that “the tool [] generates and provides output data including triaging decision support ... and risk analysis” and “[t]his information is also used by the tool along with physician feedback to further refine the system model continuously.” *Id.* at [0189]. Additionally, Menon states: “The tool [] may continue to refine the model ... using machine learning and improve its

predictive accuracy using new information that will be available when the product is being tested real time and when the product is in clinical use.” *Id.* at [0195]. Accordingly, it is my opinion that Menon discloses the limitation recited in claim 12.

244. Renisch and Menon are in the same field of automated medical image analysis systems. It is my opinion that a POSITA would have been motivated to improve Renisch, or Renisch in view of Wu, as described in Menon, based on motivations supplied by Renisch and/or the common sense of a POSITA. For example, Renisch explains the value of accurate image segmentation, stating “[s]egmentation can ... be helpful for accurately determining a location of ... hot spots relative to the patient's anatomy.” Ex1005 at [0025]. Renisch further explains that this is important for the accurate removal of normal physiological uptake from functional images unrelated to potential cancer. *Id.* at [0004], [0025], [0031]. Common sense, therefore, dictates that improved segmentation, if possible, would be desirable to achieve even more accurate location of hot spots relative to the patient’s anatomy. Menon, which is within the same field of art, provides the means for improved image analysis by expressly teaching the application of machine learning using accumulated data (i.e., validated output) for continuously refining of the automatic image analysis system. Ex1012 at [0189] (“refine the system model continuously”). It is my opinion that a POSITA would have looked

to Menon to improve Renisch's automatic image analysis. Additionally, a POSITA would have had a reasonable expectation of success in making such an improvement because the concept and techniques for training machine learning algorithms are well-established, and the process of extending that training to include newly validated data in something akin to a feedback loop would simply use the same well-established training techniques. For example, the technique for training a machine learning algorithm to perform a classification task using labeled training data is a standard, well-established process. The additional process of using machine learning to refine or update the classification routine would use the same standard training technique except with validated classification output as the new training data.

245. Additionally, or alternatively, improving Renisch, or Renisch in view of Wu, with the teachings in Menon would merely have amounted to using a known technique (i.e., machine learning) to improve similar devices in the same way. Renisch and Menon are both automated medical image analysis systems. Renisch analyzes medical image to identify and quantify cancerous lesions. Menon analyzes medical images to assess the risk of stroke and provide treatment recommendations. Menon further teaches that machine learning can be used to continuously refine its analysis model with validated output and a feedback loop. Ex1012 at [0195], Fig. 22 (2210, 2218, 2220). Indeed, the use of machine learning

to refine and improve automated processes is a known technique – of which Menon is just one example. It is my opinion that it would have been obvious to a POSITA to apply the same technique to a similar medical image analysis system (Renisch) for the same purpose, which is to continually improve the analysis technique.

246. Accordingly, it is my opinion that Renisch, or Renisch in view of Wu, each in combination with Menon, teach all the limitations of claim 12 and render claim 12 unpatentable as obvious.

F. Ground G, Anticipation by Sprencz

1. Independent Claim 1

- a) Preamble: “A network-based system for generating a disease risk map for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer, the system comprising:”**

247. Assuming that the preamble is a limitation on the scope of claim 1, Sprencz discloses “[a] network-based system for generating a disease risk map for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer.” Ex1006 at Abstract, [0011], [0041]-[0044], [0048]-[0050], [0055]-[0056], Figs. 1, 4, 6, 7.

248. As I have previously defined it in Section VII.B, a “risk map” may be any of: (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, (2) a visual representation of tissue overlaid with graphical denotations marking one or more regions of cancer or risk of recurrence of cancer; or (3) a visual representation of tissue overlaid with segmented lesions. Sprencz produces a risk map that satisfies all these definitions.

249. Sprencz discloses a system that automatically detects, segments, and displays cancerous lesions using graphical denotations that clearly delineate the location of the lesions relative to a patient's skeletal structure. *Id.* at Abstract, [0011], [0023]-[0027], [0041]-[0044], [0048]-[0050], [0055]-[0056]. For example, Sprencz states that the disclosed “medical diagnostic tool ... includes a graphical user interface (GUI) constructed to display an image generated from overlaying a first image corresponding to ... skeletal data on a second image corresponding to ... bone lesion data.” *Id.* at [0011]. Sprencz also states that “[i]mages of the lesion candidates are generated ... and displayed as an overlay on the patient skeletal image....” *Id.* at [0050]. In one embodiment, “the segmented skeletal structure from a CT image series is projected into a PET image that includes the lesion candidates.” *Id.* Sprencz further teaches the display of “bone lesions and non-bone lesions in different colors or with different shading to visually distinguish detected bone lesions from non-bone lesions.” *Id.* at [0056]. Accordingly, it is my opinion that Sprencz discloses a system for generating a disease risk map as claimed.

250. Additionally, the system disclosed by Sprencz is network-based, as claimed. Referring to Fig. 1, which is reproduced below, Sprencz discloses a distributed system 10 controlled by a CPU 12 and including one or more remotely located imaging system 20, workstation 28, and image databases 18. *Id.* at [0023]-[0027].

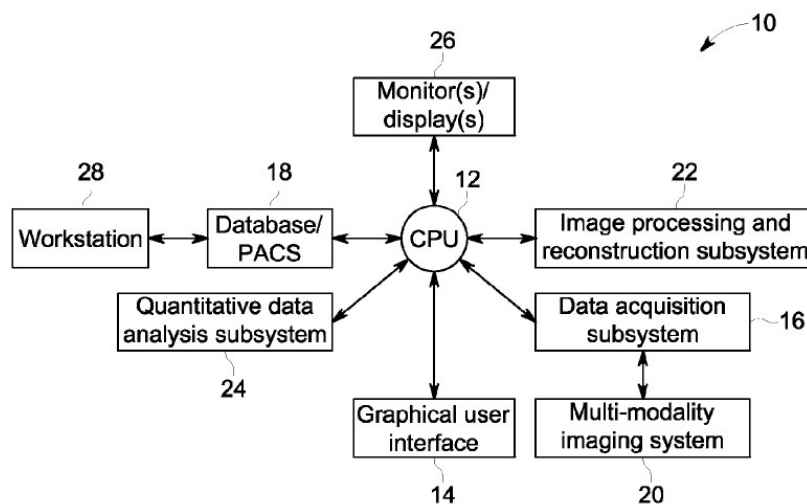


FIG. 1

251. With continuing reference to Fig. 1 above, Sprencz states:

[I]t is contemplated that a dedicated workstation 28 having a computer, monitor(s), and operably connected to the one or more databases may be used such that a physician may analyze the image and quantitative data remote from the scanner. As such, it is understood that systems and methods described herein may be used remotely from the treatment facility at which the patient is scanned.

Id. at [0026]. Additionally, Sprencz explains that “database 18 may be more than one database and remotely located from the site of data acquisition.” *Id.* at [0024].

Thus, I understand that the system disclosed in Sprencz is network-based and that its technique for obtaining, analyzing, and displaying images is carried out by a network of remotely located components.

252. It is my opinion that Sprencz discloses the features of the preamble of claim 1 to the extent they are limitations.

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

253. Sprencz discloses these limitations. *Id.* at [0009], [0023], [0041], [0061], Fig. 1. For example, Sprencz states that “the system 10 includes a central processor (CPU) 12 that controls the system 10.” *Id.* at [0023]. Additionally, Sprencz explains:

One skilled in the art will appreciate that embodiments of the invention may be interfaced to and controlled by a computer readable storage medium having stored thereon a computer program. The computer readable storage medium includes a plurality of components such as one or more of electronic components, hardware components, and/or computer software components. These components may include one or more computer readable storage media that generally stores instructions such as software, firmware and/or assembly language for performing one or more portions of one or more implementations or embodiments of a sequence.

Id. at [0061] (emphasis added). Sprenzc further states that “FIG. 4 sets forth a technique 200 for quantifying bone lesions in a patient using multi-modality three dimensional image data” and “technique 200 is performed by a computer processor such as, for example, CPU 12 of FIG. 1.” *Id.* at [0041].

254. Accordingly, it is my opinion that Sprenzc discloses limitation 1(a).

c) Limitation 1(b): “(i) access one or more medical images associated with a particular patient from a database;”

255. Sprenzc discloses this limitation. *Id.* at [0041], [0023], Fig. 1 (18), Fig. 4 (202), [0009] (“instructions that when executed by the computer causes the computer to access ...”), [0010] (“accessing an anatomical image data set acquired from a patient and accessing a function image data set acquired from the patient”), [0011] (“The computer processor is programmed to access the first and second image datasets.”). Sprenzc states:

FIG. 4 sets forth a technique 200 for quantifying bone lesions in a patient using multi-modality three dimensional image data. According to various embodiments, technique 200 is performed by a computer processor such as, for example, CPU 12 of FIG. 1. Technique 200 begins with step 202, by selecting and loading one or more exams to be processed by the computer system corresponding to one or more imaging sessions during which multi-modality image data was acquired from a patient of interest. The multi-modality image data includes at least one set of anatomical image data acquired from the

patient using an anatomical imaging modality, such as CT or MR for example, and at least one set of functional image data acquired from the patient using a functional imaging modality, such as PET or SPECT as examples.

Id. at [0041]. Additionally, with reference to Fig. 1 above (*supra*, ¶250), Sprencz states that “data acquisition subsystem 16 may access previously acquired data stored in database 18 or may acquire data directly from a multi-modality imaging sub-system 20” (*id.* at [0023]) where database 18 is labeled “PACS,” which a POSITA would understand stands for “picture archiving and communication system.”

256. Accordingly, it is my opinion that Sprencz discloses limitation 1(b).

- d) Limitation 1(c): “(ii) perform an analysis of the one or more medical images associated with the particular patient using a machine learning algorithm, to generate the risk map, wherein the risk map comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer or risk of recurrence of cancer; and”**

257. Sprencz discloses these limitations. *Id.* at [0041]-[0050], [0055]-[0056], [0011], Figs. 4-7. As I already explained in Section IX.F.1.a) above, Sprencz generates the claimed “risk map” comprising “a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer.” Additionally, as I explain further here, Sprencz generates the risk map by

performing an analysis of one or more medical images using a machine learning algorithm.

258. Sprencz states:

In accordance with an[] aspect of the invention, a medical diagnostic tool includes an image acquisition system configured to acquire multi-modality image data, a first database having stored thereon a first image dataset acquired from a patient using a first imaging modality, a second database having stored thereon a second image dataset acquired from the patient using a second imaging modality, and a computer processor. The computer processor is programmed to access the first and second image datasets. The computer processor is further programmed to segment the first image dataset to define a set of skeletal data, identify a location of a lesion candidate in the second image set, compare the location of the lesion candidate to the set of skeletal data, and classify the lesion candidate as one of a bone lesion and a non-bone lesion based on the comparison to define a set of bone lesion data. In addition, the computer processor is programmed to calculate a lesion burden based on a ratio of the set of bone lesion data and the set of skeletal data. The medical diagnostic tool also includes a graphical user interface (GUI) constructed to display an image generated from overlaying a first image corresponding to the set of skeletal data on a second image corresponding to the set of bone lesion data.

Id. at [0011] (emphasis added).

259. Additionally, with reference to Fig. 4, which is reproduced below, Sprencz states: “FIG. 4 sets forth a technique 200 for quantifying bone lesions in a patient using multi-modality three dimensional image data.” *Id.* at [0041].

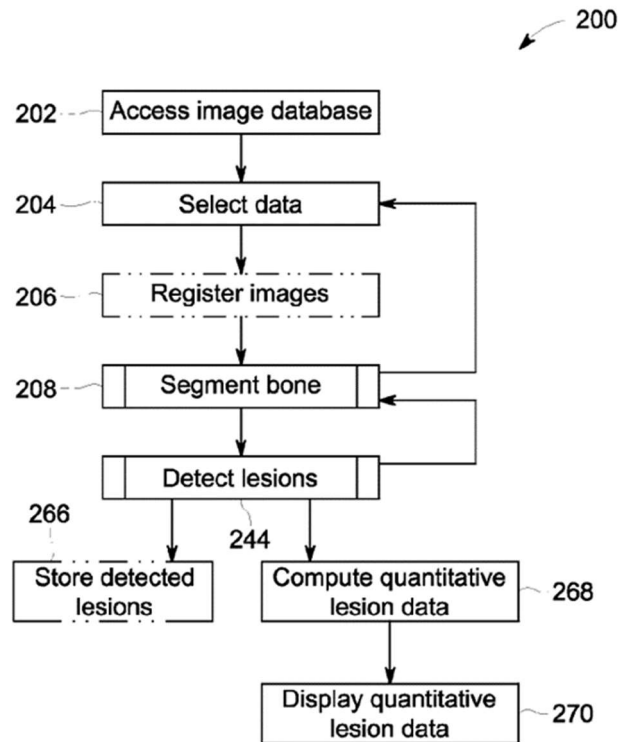


FIG. 4

“During step 208 an automatic bone segmentation is performed on the anatomical image data (e.g., data corresponding to the CT volume) using a bone segmentation subroutine.” *Id.* at [0043]. Although thresholding appears to be the primary segmentation technique that is contemplated, Sprencz also states that “one having skill in the art will recognize that embodiments of the invention may segment different anatomical region bone structures using alternative techniques, such as,

for example, clustering, level set, and region growing.” *Id.* at [0045] (emphasis added). Clustering is a well-known, unsupervised machine learning technique for image segmentation. Ex1016 (“Sharma”) at pp. 10-11. Thus, it is my opinion that Sprencz discloses the use of a machine learning algorithm to segment one or more medical images in the process of generating a risk map.

260. Continuing with reference to Fig. 4 above, Sprencz states that “after the bone segmentation subroutine 210 of step 208 is complete, technique 200 continues to step 244 wherein technique 200 uses the segmented anatomical image data output from bone segmentation subroutine 210 and the functional image data selected at step 204 to detect bone lesions using a lesion detection subroutine 246, as described in detail in FIG. 6.” *Id.* at [0048].

261. With reference to Fig. 6, which is reproduced below, Sprencz states:

Referring now to FIG. 6, the lesion detection subroutine 246 begins at step 248 by accessing the functional image data set corresponding to the image series selected at step 204 of technique 200. In step 250 lesion detection subroutine 246 automatically identifies possible lesion candidates in the functional image data set using a thresholding algorithm. In one embodiment, the possible lesion candidates are identified based on the standardize uptake values (SUV) of image voxels within the PET data series.

Id. at [0049].

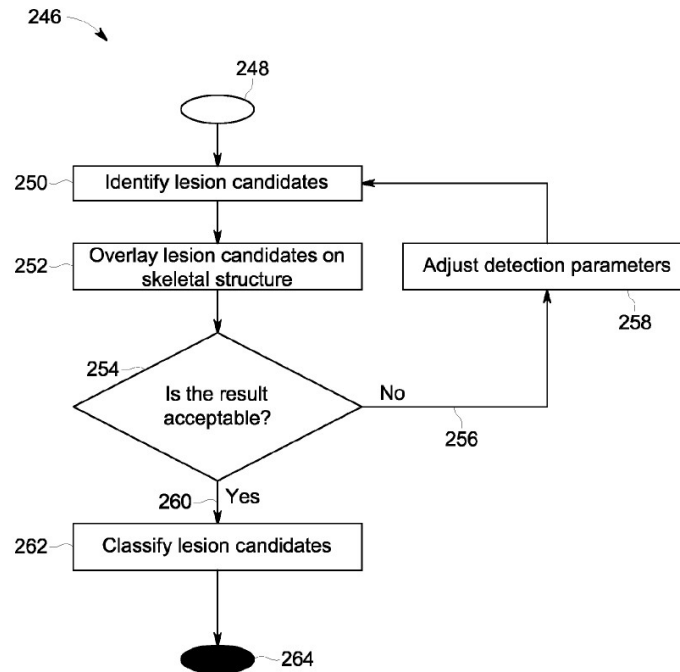


FIG. 6

262. With continuing reference to Fig. 6 above, and regarding the production of a risk map, Sprencz further discloses:

Images of the lesion candidates are generated in step 252 and displayed as an overlay on the patient skeletal image generated from the segmented skeletal structure output from bone segmentation subroutine 210 of FIG. 5. In one embodiment, the segmented skeletal structure from a CT image series is projected into a PET image that includes the lesion candidates.

Id. at [0050].

263. Accordingly, Sprencz discloses performing an analysis of an

anatomical and a functional image using a machine learning algorithm to segment the anatomical image. Sprencz also discloses using the segmented anatomical image to generate a risk map comprising a visual representation of tissue, including the skeletal structure, overlaid with graphical denotations marking one or more regions of risk of cancer (i.e., segmented lesion candidates). Thus, it is my opinion that Sprencz discloses limitation 1(c).

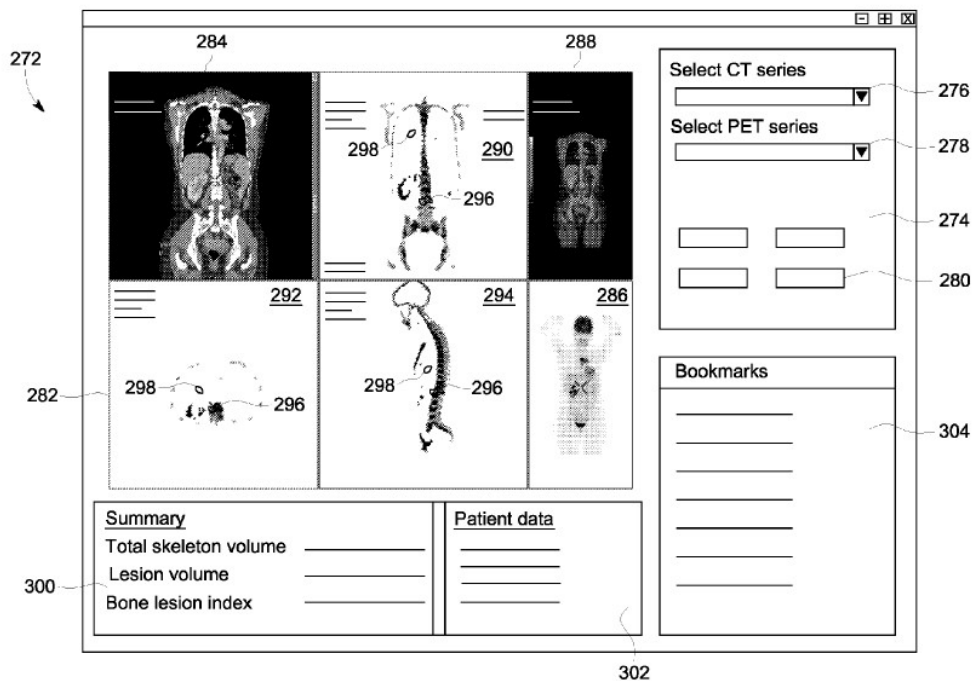
e) Limitation 1(d): “(iii) cause display of the risk map via a graphical user interface (GUI) for presentation or review of the risk map by a user”

264. Sprencz discloses this limitation. *See id.* at Fig. 1 (14), Fig. 7 (272), [0055]-[0056]. For example, with reference to Fig. 7, which is reproduced below, Sprencz states:

According to an exemplary embodiment, GUI 272 includes an image display region 282 that is separated into multiple windows in order to display multiple images. For example, image display 282 may include a first window 284 that displays a CT image, a second window 286 that displays a corresponding PET image, and a third window 288 that displays the CT image overlaid on the PET image. Fourth, fifth, and sixth windows 290, 292, 294 include various views of the segmented skeletal volume obtained from the CT image using bone segmentation subroutine 210 overlaid with contours of lesion candidates 296, 298 detected using lesion detection subroutine 246. In alternative embodiments, image display region 282 includes one or more selected images corresponding to the multi-modality image series and the

detected lesions. Image display region 282 may further be configured to display bone lesions and non-bone lesions in different colors or with different shading to visually distinguish detected bone lesions from non-bone lesions. As one example, a lesion candidate classified as a bone lesion, such as lesion candidate 296, may be displayed with a red contour, and a lesion candidate classified as a non-bone lesion, such as lesion candidate 298, may be displayed with a blue contour. According to various embodiments, image display region 282 may be configured as an interactive workspace to permit a user to interact with the images to perform various tasks including, for example, manually identify lesion candidates, delete an automatically identified lesion, and/or change the classification of an automatically detected lesion, as non-limiting examples.

Id. at [0056] (emphasis added).



265. Accordingly, it is my opinion that Sprencz discloses limitation 1(d).

- f) **Limitation 1(e): “wherein the analysis of the one or more medical images comprises creation of a 3D image of the one or more regions of risk of cancer or risk of recurrence of cancer overlaid on the one or more medical images, and wherein the 3D image comprises geographic identification of one or more specific tissue region(s) overlaid on the one or more medical images.”**

266. Sprencz discloses these limitations. *Id.* at [0011], [0050], [0056], [0041], [0052], Fig. 7. As I have already explained in Sections IX.F.1.a) and IX.F.1.d) above, Sprencz analyzes anatomical and functional images to generate a risk map as claimed. As I explain further here, the analysis performed by Sprencz includes “creation of a 3D image of the one or more regions of risk of cancer ... overlaid on the one or more medical images, and ... geographic identification of one or more specific tissue region(s) overlaid on the one or more medical images.”

267. Sprencz discloses a technique for quantifying bone lesions in a patient using “multi-modality three dimensional image data” including, for example, “three-dimensional CT and PET data.” *Id.* at [0041]. That technique includes segmenting an anatomical image to produce “a patient skeletal image representing the skeleton of the patient ... from a subset of the anatomical image data.” *Id.* at

[0043], [0046].⁴ After segmentation of the anatomical image is complete, the technique “uses the segmented anatomical image data ... and the functional image data ... to detect bone lesions.” *Id.* at [0048], [0052]. Lesion candidates are identified by thresholding the functional image to segment regions of image voxels above a set standardized uptake value (SUV).⁵ *Id.* at [0049]. Sprensz states that “[i]mages of the lesion candidates are generated ... and displayed as an overlay on the patient skeletal image generated from the segmented skeletal structure output.” *Id.* at [0050]; *see also id.* at [0056] (“various views of the segmented skeletal volume obtained from the CT image using [the] bone segmentation routine ... overlaid with contours of lesion candidates”). Additionally, Sprensz states that “[i]n one embodiment, the segmented skeletal structure from a CT image series is projected into a PET image that includes the lesion candidates.” *Id.* at [0050] (emphasis added); *see also id.* at [0011] (“display an image generated from overlaying a first image corresponding to the set of skeletal data on a second image

⁴ As is evident from the various available views of the segmented skeletal structure 290, 292, 294 in Fig. 7 of Sprensz, the segmentation is performed in three dimensions and produces a 3D skeletal volume.

⁵ As is evident from the appearance of the segmented lesion candidates 296, 298 in the various views of the segmented skeletal structure 290, 292, 294 of Fig. 7, the lesion segmentation is also performed in three dimensions to produce a 3D risk picture.

corresponding to the set of bone lesion data”). These disclosures anticipate limitation 1(e). Projecting the skeletal structure into a PET image constitutes geographic identification of one or more specific tissue regions overlaid on the medical images. Additionally, segmentation of the lesion candidate contours in the PET image – overlaid with a subset of the anatomical image (i.e., the skeletal structure) – constitutes creation of a 3D image of the regions of risk overlaid on the medical images.

268. Accordingly, it is my opinion that Sprencz discloses limitation 1(e).

269. Because Sprencz discloses all the limitations of claim 1, it is further my opinion that Sprencz anticipates claim 1, rendering it unpatentable.

2. Claim 2: “The system of claim 1, wherein the one or more medical images comprise one or more magnetic resonance images (MRIs).”

270. Claim 2 depends from claim 1, which I explained above in Section IX.A.1 is anticipated by Sprencz. Claim 2 further states “wherein the one or more medical images comprise one or more magnetic resonance images (MRIs).”

271. It is my opinion that Sprencz discloses the limitations of claim 2. *See id.* at [0022]-[0023], [0027], [0031], [0041]-[0042]. Sprencz states: “The operating environment of embodiments of the invention is described below with respect to a multi-modality imaging system that includes a positron emission tomography (PET) imaging system and one of an [sic] magnetic resonance (MR) imaging

system and a ... computed tomography (CT) imaging system.” *Id.* at [0022]. Sprencz further states that its multi-modality imaging system “may be a combined PET/MR system (as shown in FIG. 2), a combined PET/CT system (as shown in FIG. 3), a combined SPECT/MR system, or a combined SPECT/CT system, as non-limiting examples.” *Id.* at [0023]. The technique for quantifying bone lesions begins by accessing anatomical imaging data from a patient using an anatomical imaging modality, such as CT or MR. *Id.* at [0041].

272. Because Sprencz discloses every limitation of claim 2, including the limitations of claim 1 from which claim 2 depends, it is my opinion that claim 2 is anticipated by Sprencz.

3. Claim 3: “The system of claim 1, wherein the one or more medical images comprise (i) one or more PET/CT image(s) or (ii) one or more SPECT/CT image(s).”

273. Claim 3 depends from claim 1, which I explained above in Section IX.A.1 is anticipated by Sprencz. It is my opinion that Sprencz also discloses the additional limitations of claim 3. *See id.* at [0022]-[0023], [0033]-[0034], [0041]-[0042].

274. Sprencz states that its multi-modality imaging system “may be a combined PET/MR system (as shown in FIG. 2), a combined PET/CT system (as shown in FIG. 3), a combined SPECT/MR system, or a combined SPECT/CT system, as non-limiting examples.” *Id.* at [0023]. Sprencz further explains that it

may operate by registering separate three-dimensional CT and PET series or “where the multi-modality image data is acquired from a combined PET/CT ..., the acquired multi-modality image data may be automatically registered.” *Id.* at [0042].

275. Because Sprencz discloses every limitation of claim 3, including the limitations of claim 1 from which claim 3 depends, it is my opinion that claim 3 is anticipated by Sprencz.

4. Claim 4: “The system of claim 1, wherein the visual representation of tissue is at least a portion of one of the one or more medical images of the particular patient.”

276. Claim 4 depends from claim 1, which I explained above in Section IX.A.2 is anticipated by Sprencz. Claim 1 states that the claimed risk map “comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer.” It is my opinion that Sprencz also discloses the additional limitations of claim 4: “wherein the visual representation of tissue is at least a portion of one of the one or more medical images of the particular patient.”

277. As I have already explained in Sections IX.F.1.a) and IX.F.1.e) above, the risk map generated and displayed by Sprencz includes at least a portion of one or more medical images of the particular patient. For example, Sprencz states that “[i]mages of the lesion candidates are generated ... and displayed as an overlay on

the patient skeletal image.” *Id.* at [0050]. And, “[i]n one embodiment, the segmented skeletal structure from a CT image series is projected into a PET image that includes the lesion candidates.” *Id.* Additionally, with reference to Fig. 7 above (*supra*, ¶264), Sprenzc discloses that “[i]n alternative embodiments, image display region 282 [of GUI 272] includes one or more selected images corresponding to the multi-modality image series and the detected lesions.” Accordingly, it is my opinion that Sprenzc discloses the limitations of claim 4.

278. Because Sprenzc discloses every limitation of claim 4, including every limitation of claim 1 from which claim 4 depends, it is my opinion that claim 4 is anticipated by Sprenzc.

5. Claim 5: “The system of claim 1, wherein the cancer is prostate cancer.”

279. Claim 5 depends from independent claim 1, which I explained above in Section IX.A.1 is anticipated by Sprenzc. It is also my opinion that Sprenzc inherently teaches the additional limitation of claim 5, “wherein the cancer is prostate cancer.”

280. Sprenzc discloses the detection of cancerous lesions throughout the body – both bone lesions and non-bone lesions – and is not limited to any particular type of cancer. *See, e.g.*, Ex1006 at [0056] (“display bone lesions and non-bone lesions in different colors or with different shading to visually

distinguish detected bone lesions from non-bone lesions”). Accordingly, a person practicing the invention disclosed in Sprencz, i.e., imaging the whole body to detect bone and non-bone lesions, would necessarily detect prostate cancer if it was present. Stated differently, imaging prostate cancer would be the natural result of practicing Sprencz. Accordingly, I believe that Sprencz inherently discloses the imaging of prostate cancer even if it does not expressly state it.

281. Because Sprencz discloses all the limitations of claim 5, it is my opinion that Sprencz anticipates claim 5.

6. Claim 6: “The system of claim 1, wherein the visual representation of tissue comprises a visual representation of bone.”

282. Claim 6 depends from independent claim 1, which I explained above in Section IX.A.1 is anticipated by Sprencz. It is my opinion that Sprencz also teaches the additional limitation of claim 6, “wherein the visual representation of tissue comprises a visual representation of bone.” *Id.* at [0011], [0050], [0056], Fig. 7 (290, 292, 294).

283. As I explained in, for example, Sections IX.F.1.a), IX.F.1.e) above, Sprencz generates and displays risk maps that comprise segmented lesions overlaid on segmented medical images of the patient’s skeletal structure, including embodiments in which the skeletal structure from a CT image is projected into a PET image containing contoured lesions. For example, Sprencz states that

“[i]mages of the lesion candidates are generated ... and displayed as an overlay on the patient skeletal image.” *Id.* at [0050]. Similarly, with reference to Fig. 7 above (*supra*, ¶264), Sprencz states that “windows 290, 292, 294 include various views of the segmented skeletal volume obtained from the CT image ... overlaid with contours of lesion candidates.” *Id.* at [0056]. Accordingly, Sprencz discloses the limitations of claim 6.

284. Because Sprencz discloses all the limitations of claim 6, including all the limitations of claim 1 from which claim 6 depends, it is my opinion that Sprencz anticipates claim 6.

7. Claim 7: “The system of claim 1, wherein the one or more specific tissue region(s) comprise one or more members selected from the group consisting of organs, organ structures, sub-organs, and organ regions.”

285. Claim 7 depends from claim 1, which I explained above in Section IX.F.1 is anticipated by Sprencz. Claim 1 recites the “creation of a 3D image of [] one or more regions of risk of cancer ... wherein the 3D image comprises geographic identification of one or more *specific tissue region(s)* overlaid on the one or more medical images.” Ex1001 at 36:1-7 (emphasis added). Claim 7 adds the limitation: “wherein the one or more specific tissue region(s) comprise one or more members selected from the group consisting of organs, organ structures, sub-organs, and organ regions.” It is my opinion that Sprencz discloses the additional

limitation of claim 7.

286. As previously explained, Sprenzc discloses the generation and display of risk maps comprising 3D images that geographically identify the patient's skeletal structure overlaid on one or more medical images. *Id.* at [0050] (“In one embodiment, the segmented skeletal structure from a CT image series is projected into a PET image that includes the lesion candidates.”), [0056], Fig. 7.

287. A POSITA knows that the skeleton, which is made up of individual bones, is both a structural and functional endocrine organ. *See generally*, Ex1023. Although the Patent refers to both bones and organs at various locations, it never expressly redefines organs to not include bones. Nor does it expressly state that bones are not organs. Thus, it is my opinion that Sprenzc discloses the limitations of claim 7.

288. Because Sprenzc discloses all the limitations of claim 7, including all the limitations of claim 1 from which claim 7 depends, it is my opinion that Sprenzc anticipates claim 7.

8. Claim 8: “The system of claim 1, wherein the one or more specific tissue region(s) comprise one or more particular bones.

289. Claim 8 depends from claim 1, which I explained in Section IX.F.1 above is anticipated by Sprenzc. It is my opinion that Sprenzc also discloses the limitations of claim 8.

290. As I already explained in, for example, Section IX.F.7 above, Sprencz discloses the generation and display of risk maps that geographically identify a specific tissue region – namely the patient’s skeletal structure – which comprises “one or more particular bones” as claimed in claim 8. Accordingly, Sprencz discloses the limitations of claim 8.

291. Because Sprencz discloses all the limitations of claim 8, including all the limitations of claim 1 from which claim 8 depends, it is my opinion that Sprencz anticipates claim 8.

9. Claim 9: “The system of claim 1, wherein the instructions cause the processor to generate a radiologist report for the particular patient based at least in part on the analysis of the one or more medical images.”

292. Claim 9 depends from claim 1, which I explained in Section IX.F.1 above is anticipated by Sprencz. It is my opinion that Sprencz also discloses the limitations of claim 9: “wherein the instructions cause the processor to generate a radiologist report for the particular patient based at least in part on the analysis of the one or more medical images.” Ex1006 at [0055]-[0057], Fig. 7 (282, 300, 302).

293. The Patent states:

A radiologist report is a technical evaluation of the PET or SPECT images prepared by a radiologist for a physician who requested the imaging study and includes, for example, the type of study performed,

the clinical history, a comparison between images, the technique used to perform the study, the radiologist's observations and findings, as well as overall impressions and recommendations the radiologist may have based on the imaging study results.

Ex1001 at 2:11-19.

294. The Patent also shows, in Fig. 5 (*supra*, ¶74), an example of an automatically or semi-automatically generated radiologist report 510 displayed on a graphical user interface 400. *Id.* at 29:14-16. The report 510 contains, for example, the patient's name, the patient's medical images, the quantitatively calculated "BSI" (bone scan index), i.e., the ratio of bone lesion volume to total bone volume, and information regarding the study performed, including the date of the study.

295. With reference to Fig. 7, which is reproduced below, Sprenzc discloses that "portions of the selected anatomical and functional image series, visual representations of the lesion candidates, and the quantitative information calculated by technique 200 [including the ratio of total bone lesion volume to total bone volume] may be displayed on a graphical user interface (GUI) 272 as illustrated in FIG. 7." Ex1006 at [0055].

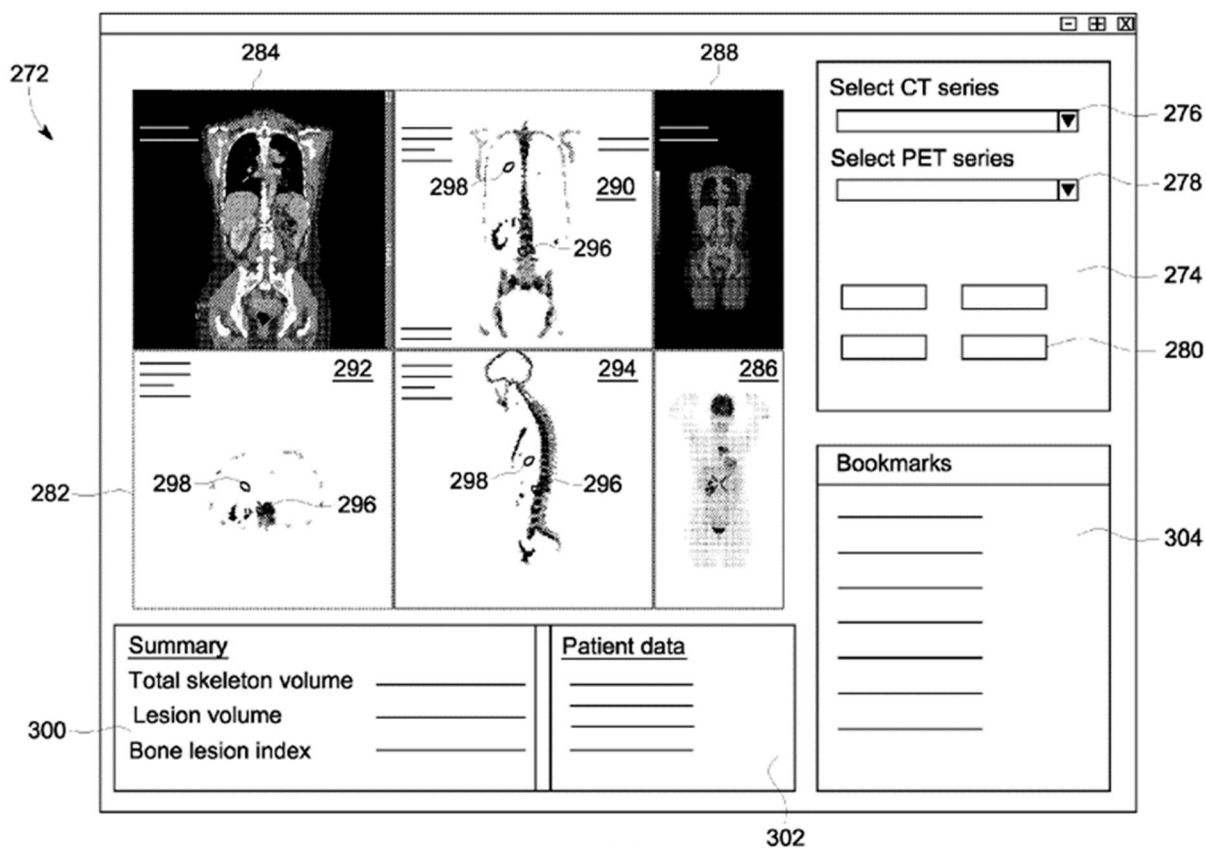


FIG. 7

296. With continuing reference to Fig. 7 above, Sprencz states:

Analysis display region 300 includes a visual display of the quantitative or statistical data computed in step 268 of technique 200. This data can include the total skeleton volume of the patient, the total volume of bone lesions and non-bone lesions, the total bone lesion volume (i.e., total tumor burden), the calculated bone lesion index, and other statistical information calculated during step 268. An information display region 302 is also located within in GUI 272 to provide the user with patient and scan information including, for example, name, age, the date of scans, and/or various parameters associated with the scans.

Ex1006 at [0057] (emphasis added).

297. It is my opinion that Sprencz discloses the limitations of claim 9, including an automatically generated radiologist report as described in the Patent. Accordingly, it is also my opinion that Sprencz anticipates claim 9.

10. Claim 10: “The system of claim 9, wherein the radiologist report comprises the one or more medical images and the risk map.”

298. Claim 10 depends from claim 9, which I explained in Section IX.F.9 above is anticipated by Sprencz. Claim 9 requires generation of a radiologist report. Claim 10 further requires that “the radiologist report comprises the one or more medical images and the risk map.” It is my opinion that Sprencz also discloses all the limitations of claim 10. *Id.* at Fig. 7, [0056].

299. With reference to Fig. 7 above, Sprencz states:

According to an exemplary embodiment, GUI 272 includes an image display region 282 that is separated into multiple windows in order to display multiple images. For example, image display 282 may include a first window 284 that displays a CT image, a second window 286 that displays a corresponding PET image, and a third window 288 that displays the CT image overlaid on the PET image. Fourth, fifth, and sixth windows 290, 292, 294 include various views of the segmented skeletal volume obtained from the CT image using bone segmentation subroutine 210 overlaid with contours of lesion candidates 296, 298 detected using lesion detection subroutine 246. In alternative

embodiments, image display region 282 includes one or more selected images corresponding to the multi-modality image series and the detected lesions.

Id. at [0056].

300. As I explained in Section IX.F.9, the information reported in Fig. 7 of Sprencz constitutes a “radiologist report.” That radiologist report contains both the original medical images and the claimed risk map comprising visual representations of tissue overlaid with graphical denotations of regions of risk of cancer (i.e., segmented lesions). *Id.*

301. Accordingly, it is my opinion that Sprencz anticipates claim 10.

11. Independent Claim 13

- a) Preamble: “A method for generating a disease risk map for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer, the method comprising:”**

302. The preamble of claim 13 is essentially the same as the preamble of claim 1 except that claim 13 recites a “method” whereas claim 1 recites a “network-based system.” Assuming the preamble is considered a limitation on the scope of the claim, it is my opinion that Sprencz discloses the limitations of the preamble for the same reasons provided in Section IX.F.1.a) above.

- b) 13(a): “(i) accessing, by a processor, one or more medical images associated with a particular patient from a database;”**

303. This limitation is essentially identical to limitation 1(b) which is addressed in Section IX.F.1.c) above. The only difference is that, whereas limitation 1(b) relates to instructions that cause a processor to “access one or more medical images ...,” limitation 13(a) recites “accessing, by a processor, one or more medical images” Accordingly, it is my opinion that Sprencz discloses limitation 13(a) for the same reasons explained in Section IX.F.1.c) above.

- c) 13(b): “(ii) automatically analyzing, by the processor, using a machine learning algorithm, the one or more medical images to generate the risk map, wherein the risk map comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer or risk of recurrence of cancer; and”**

304. This limitation is essentially identical to limitation 1(c) which I addressed in Section IX.F.1.d) above. The only difference is that, whereas limitation 1(c) relates to instructions that cause a processor to “perform an analysis of the one or more medical images associated with the particular patient using a machine learning algorithm ...,” limitation 13(b) recites “automatically analyzing, by the processor, using a machine learning algorithm, the one or more medical images” I note that limitation 13(b) explicitly recites “*automatically* analyzing, by the processor.” Nevertheless, my analysis of limitation 1(c) above already

assumed that the claimed analysis – performed by a processor executing stored instructions – was automatic. Nevertheless, I repeat here, for the avoidance of doubt, that Sprencz discloses that “an automatic bone segmentation is performed on the anatomical image data (e.g., data corresponding to the CT volume)” (Ex1006 at [0043]) using any of a variety of “alternative techniques, such as, for example, clustering,” (*id.* at [0045]) which is an unsupervised machine learning algorithm. Accordingly, it is my opinion that Sprencz discloses limitation 13(b) for the same reasons explained in Section IX.F.1.d) above.

d) 13(c): “(iii) causing, by the processor, display of the risk map via a graphical user interface (GUI) for presentation or review of the risk map by a user,”

305. This limitation is essentially identical to limitation 1(d) which I addressed in Section IX.F.1.e) above. The only difference is that, whereas limitation 1(d) relates to instructions that cause a processor to “cause display of the risk map ...,” limitation 13(c) recites “causing, by the processor, display of the risk map” Accordingly, it is my opinion that Sprencz discloses limitation 13(c) for the same reasons explained in Section IX.F.1.e) above.

e) 13(d): “wherein step (ii) comprises creation of a 3D image of the one or more regions of risk of cancer or risk of recurrence of cancer overlaid on the one or more medical images, and wherein the 3D image comprises geographic identification of one or more specific tissue region(s) overlaid on the one or more medical images.”

306. This limitation is essentially the same as limitation 1(e), which I address in Section IX.F.1.f) above. The only difference is that, whereas limitation 1(e) recites “wherein the analysis of the one or more medical images comprises ...,” limitation 13(d) recites “wherein step (ii) comprises ...,” where step (ii) of claim 13 is the step of “automatically analyzing, by the processor, ... the one or more medical images” Accordingly, it is my opinion that Sprenz anticipates limitation 13(d) for the same reasons I provided in Section IX.F.1.f) above.

307. Because it is my opinion that Sprenz discloses all the limitations of claim 13, it is also my opinion that Sprenz anticipates claim 13.

G. Ground H, Obviousness over Sprenz in view of the Applicant’s Admitted Prior Art or D’Souza

1. Claim 5: “The system of claim 1, wherein the cancer is prostate cancer.”

308. Claim 5 depends from claim 1, which I explained in Section IX.F.1 is anticipated by Sprenz. In Section IX.F.5 above, I explained that Sprenz also anticipates claim 5 because Sprenz’s general disclosure relating to the quantification of lesions throughout the body – without limitation to any particular radiopharmaceutical – would include, among the most prominent examples, prostate cancer, including metastatic prostate cancer. Nevertheless, if Sprenz does not anticipate claim 5, then it is my opinion that Sprenz renders claim 5 obvious because a POSITA would have been motivated to use Sprenz for imaging

prostate cancer based on the knowledge of a POSITA, as evidenced by the applicant admitted prior art (“AAPA”). Alternatively, it is my opinion that the combined teachings of Sprencz and D’Souza render claim 5 obvious.

309. As I explained in Section IX.F.5 above, Sprencz teaches the identification and quantification of lesions throughout the body, including bone lesions generally, which would have broad application to a wide variety of cancers. Sprencz does not appear to teach the use of any particular radiopharmaceutical, which leaves it open to the use of any known cancer-specific target molecule.

310. As I explained in Section IX.B.1 above, the AAPA in the Patent demonstrates the knowledge of a POSITA at the time of the effective filing date of the Patent. The Patent admits that functional nuclear medical imaging systems like the ones described in Sprencz were well-known. Ex1001 at 1:39-43. The Patent also admits that “[t]here are also a number of radiopharmaceuticals available for imaging particular kinds of cancer” including prostate cancer. *Id.* at 1:49-61. A POSITA would have known, therefore, that the systems and methods of Sprencz could be used to image prostate cancer. Additionally, the motivation to use Sprencz to image prostate cancer is supplied by the knowledge of POSITA, who would know that prostate cancer, including prostate cancer that has metastasized to the patient’s bones, is one of the most common and deadly forms of cancer. Therefore, a POSITA who was familiar with Sprencz and its teaching as to how to

image and quantify lesions throughout the body would have been motivated to use Sprencz to image prostate cancer specifically. Additionally, a POSITA would have had a reasonable expectation of success in doing so using known PSMA tracers identified in the AAPA.

311. Accordingly, it is my opinion that Sprencz renders claim 5 obvious based on the knowledge of a POSITA, as evidenced by the AAPA.

312. D'Souza discloses a wide range of ^{18}F -labeled molecules that are usable to image different diseases, including prostate cancer. Ex1010 at 3:57-58, 4:51-64, 36:22-37. Moreover, D'Souza teaches that its disclosed ^{18}F -labeled molecules can be used with any known method of imaging using labeled molecules (which would include Sprencz, which pre-dates D'Souza). *Id.* at 35:42-36:21, 4:60-64 (“Any known TAA[(tumor-associated antigen)]-binding antibody or fragment may be labeled with ^{18}F by the described methods and used for imaging and/or detection of tumors, for example by PET scanning or other known techniques.”).

313. In my opinion, a POSITA would have been motivated to combine the teachings of Sprencz and D'Souza and would have had a reasonable expectation of success in making such combination.

314. Combining Sprencz and D'Souza would have merely amounted to combining existing prior art elements (i.e., nuclear medicine imaging systems and

prostate-cancer-specific radiotracers) according to known methods (i.e., selecting a suitable delivery molecule for targeting a particular disease) to yield predictable results. D'Souza expressly teaches that many delivery molecules were known for imaging many different diseases, including prostate cancer. Ex1010 at 4:51-64, 36:22-37. Using Sprencz's automatic segmentation and lesion quantification system to image prostate cancer, including metastatic prostate cancer, could have been accomplished simply by selecting the appropriate prostate-cancer-specific delivery molecule as taught by D'Souza. *E.g.*, Ex1009, Fig. 2, [0041]-[0049]. Thus, implementing Sprencz to image prostate cancer would have been an obvious and straight forward modification according to D'Souza's express teachings.

315. Additionally, or alternatively, combining Sprencz and D'Souza would have merely amounted to simple substitution of one known element (i.e., ^{18}F -labeled prostate cancer targeting molecules) for another (i.e., the unidentified gamma ray emitting, cancer-targeting radiopharmaceutical implemented by Sprencz) to obtain predictable results. Sprencz discloses the use of an unidentified radiopharmaceutical for imaging cancer generally – both bone lesions and non-bone lesions. Ex1006 at [0031] (“detect gamma rays ... emitted from a subject”), [0049], [0052] (“classifying lesion candidates as being either bone lesions or non-bone lesions”), [0056] (“display bone lesions and non-bone lesions in different colors”). D'Souza teaches that “[m]any such delivery molecules are known”

(Ex1010 at 4:54) and that “[t]he type of diseases or conditions that may be imaged is limited only by the availability of a suitable delivery molecule for targeting a cell or tissue associated with the disease.” (id. at 4:51-53). The Patent admits, and D’Souza teaches that targeting molecules suitable for imaging prostate cancer were known. Ex1001 at 1:51-65; Ex1010 at 12:19-49 (e.g., “PSMA”). Therefore, it is my opinion that it would have been obvious to substitute ^{18}F -PSMA, as taught in D’Souza, for the unidentified radiopharmaceutical used in Sprencz, to achieve the predictable result of being able to image prostate cancer more accurately.

316. It is also my opinion that a POSITA would have had a reasonable expectation of success in combining Sprencz and D’Souza. Sprencz teaches the identification of cancerous lesions in functional nuclear medicine images produced by, for example, a PET scanner. Ex1006 at [0022]-[0023], [0033], [0041]. D’Souza expressly teaches that any of its disclosed disease-specific targeting molecules could be used with any known PET imaging technique. Ex1010 at 4:57-64, 35:42-36:21. Therefore, the ^{18}F -labeled molecules disclosed in D’Souza would be readily applicable to, and easily implemented with, the system disclosed in Sprencz, and a POSITA would have expected success combining Sprencz and D’Souza in view of their complementary teachings.

H. Ground I, Obviousness over Sprencz in view of Maier

1. Claim 11: “The system of claim 9, wherein the radiologist report comprises one or more reference images or reference risk maps.”

317. Claim 11 depends from claim 9, which I explained in Section IX.F.9 above is anticipated by Sprencz. Claim 9 requires the generation of a radiologist report. Claim 11 further requires that “the radiologist report comprises one or more reference images or reference risk maps.” Maier discloses the additional limitations of claim 11, and it would be obvious, in my opinion, to improve the report generated by Sprencz to include reference images for comparison, as taught by Maier.

318. The Patent purports to disclose a software tool with which “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 at 3:15-30 (emphasis added). Similarly, the Patent states that “[t]he patient can visually compare his risk map with a map representing a typical risk-level for which surgery would be recommended.” *Id.* at 3:32-35.

319. As I explained in Section IX.F.9 above, Sprencz automatically generates and displays, on a graphical user interface, a radiologist report that includes patient information, image scanning parameters, the patient’s medical

images, the patient's risk map, and calculated lesion metrics, including total lesion volume. Ex1006, at Fig. 7, [0056]-[0057]. Sprencz does not, however, clearly disclose that the generated radiologist report also includes reference images or risk maps of others for comparison.

320. As I explained in Section XIII.D above, Maier discloses computer implemented systems and methods for assessing medical images and communicating a patient's health status and risk by automatically generating a report tailored for the intended user, including for example a "radiologist." Ex1008 at [0014], [0015]-[0016], [0026], [0041]. More specifically, Maier discloses assessing a patient's health status and risk by comparing the patient's medical images to one or more comparison images from one more individuals for whom the corresponding health status and/or outcomes are known. *Id.* at [0014].

321. With reference to Fig. 3 of Maier (*supra*, ¶132), an example of a report automatically generated by Maier includes not only the patient's medical images, but also comparative reference images (or risk maps) from others with known medical outcomes. Ex1008 at [0041].

322. In my opinion, it would have been obvious and straightforward to improve the report generated by Sprencz by including one or more reference images and/or risk maps based on the express teachings and motivations supplied in Sprencz and Maier, respectively.

323. Sprencz states: “Quantification of bone lesions using medical images is an important aspect of clinical diagnostics and therapy.” Ex1006 at [0004].

324. Maier states that its disclosed systems and method “may be used for screening disease, prognosis or diagnosis of diseases, base-line assessments, treatment planning, treatment follow-up, or other user education regarding tissue state.” Ex1008 at [0018]. Additionally, Maier explains that “[t]he systems and methods of the present disclosure are not limited to any particular type or kind of tissue region.” *Id.* at [0016]. Suitable tissue types and regions include, for example, the “whole body,” “bone,” and “a bone lesion.” *Id.* at [0017]. Then, with reference to the disclosed method of comparing the patient’s medical images to reference medical images, Maier states: “[t]he quantitative status and/or risk metrics for the patient may ... be calculated based on the known health status and/or outcomes for the corresponding cohort.” *Id.* at [0022]. Accordingly, it is my opinion, that Sprencz and Maier themselves supply the express motivation to combine their teachings. Sprencz is directed to clinical diagnosis through quantification of bone lesions. Maier teaches that quantitative status and/or risk metrics can be calculated based on comparison to reference images with known outcomes. Therefore, a POSITA would have been motivated to improve diagnosis and quantification of bone lesions, as addressed in Sprencz, by comparing the patient’s images to reference images of cohorts with known medical results, as

taught by Maier.

325. It is further my opinion that a POSITA would have had a reasonable expectation of success in combining Sprencz and Maier in the manner proposed since the combination would have amounted to nothing more than including a comparison image in the report to improve diagnosis.

326. Additionally, or alternatively, improving the report generated by Sprencz based on the teachings of Maier would merely have amounted to applying a known technique to a known device, method, or product ready for improvement to yield predictable results. The practice of diagnosing and/or staging disease progression by comparing a patient's medical images to the images of others with known medical outcomes is as old as medical imaging itself – and is certainly disclosed *no later than* the publication of Maier. Although Sprencz may not expressly describe the use of reference images in its generated report, it would have been obvious based on standard medical practice and the teachings in Maier to include a reference image for the purpose of improving diagnosis and/or staging.

327. It is my opinion that a POSITA would have had a reasonable expectation of success in combining Maier with Sprencz in this manner because the combination would merely have amounted to adding one or more additional images to those already displayed on Sprencz's GUI.

328. Accordingly, it is my opinion that a POSITA would have motivated to

combine, and would have had a reasonable expectation of success in combining, Sprencz and Maier. It is also my opinion that Sprencz in view of Maier renders claim 11 unpatentable as obvious.

I. Ground J, Anticipation by Suehling

1. Independent Claim 1

- a) Preamble: “A network-based system for generating a disease risk map for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer, the system comprising:”**

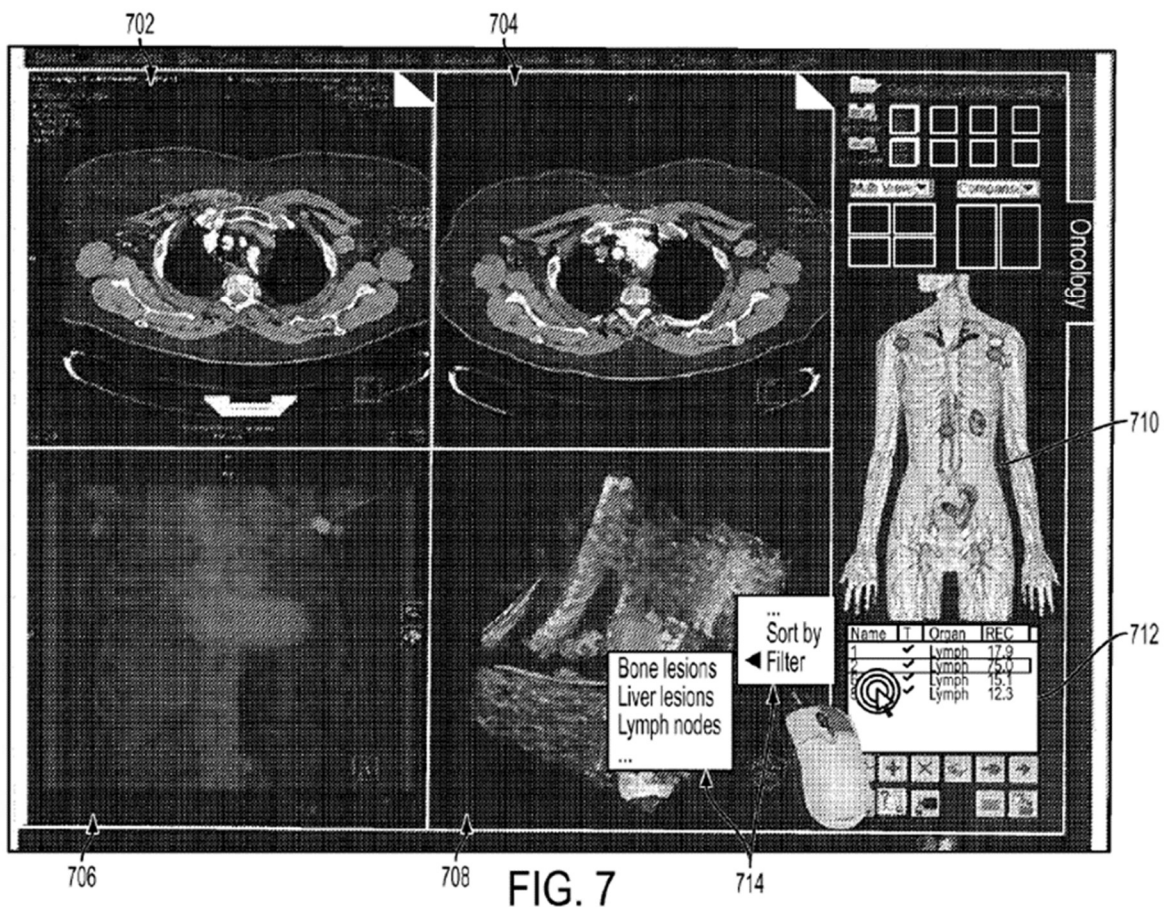
329. If the preamble is considered a limitation on claim 1, then Suehling discloses these limitations. Ex1007 at Abstract, [0006]-[0007], [0034], [0037], [0041], [0045], [0046], Fig. 5 (506), Fig. 7, Fig. 8, Fig. 9 (906). Suehling states that it discloses “a method and system for automatic detection of lesions in 3D medical images” including “lesions throughout the body, including in lymph nodes, organs, other soft tissue, and bone.” *Id.* at [0006]. Suehling also states that:

The lesion detection results can be output by displaying the lesion detection results on a display of a computer system. For example, the detected and segmented lesions can be displayed in combination with the received 3D image data. It is also possible that the lesion detection results be displayed by displaying a probability map resulting from probability scores calculated by the lesion detectors. It is also possible to display a fused image resulting from combining the probability map with the medical image data.

Id. at [0034] (emphasis added).

330. With reference to Fig. 7, which is reproduced below, Suehling states “the interactive display 700 displays detected lesions in various slices 702 and 704 of the medical image data, a 3D rendering 706 of the image data, a zoomed-in portion 708, and in corresponding locations in a 3D model of a body 710.”

Id. at [0041] (emphasis added).



331. With reference to Fig. 8, which is reproduced below, Suehling explains:

In addition to the display of detected lesion candidates, a “fuzzy” method of result visualization may be used. As described above, the probabilistic detection framework also outputs a probability map of each image voxel belonging to a given lesion entity. This probability map can be displayed similar to the display of PET/CT data. Augmenting morphological CT information, PET data displays metabolic activity of body regions where tumors usually stand out as areas with high image intensity. According to an embodiment of the present invention, the probability map can be displayed in a similar fashion to PET data. FIG. 8 illustrates displaying lesion detection results using a probability map. Image 802 of FIG. 8 shows a display of CT image data. As illustrated in FIG. 8, image 804 shows a probability map displayed alone and image 806 shows a probability map in a fused mode, overlaid on morphological image data. It is to be understood that the same display options may also be presented in 3D renderings.

Id. at [0045] (emphasis added).

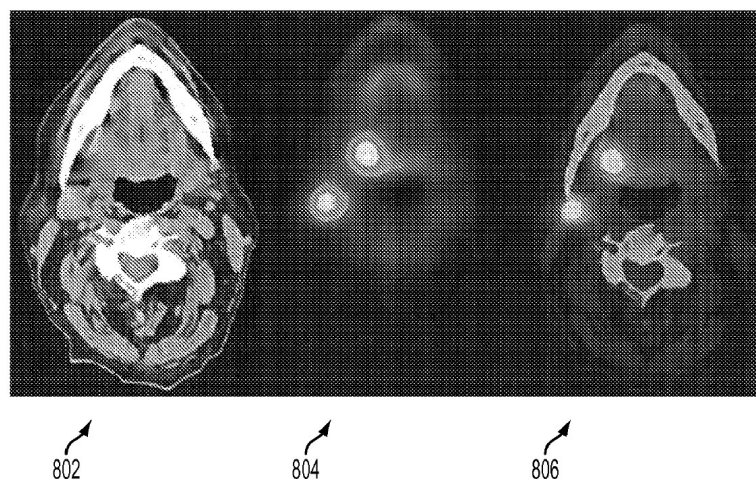


FIG. 8

332. Thus, Suehling discloses both: (i) displaying areas of risk of cancer (i.e., segmented lesions) overlaid on a visual representation of tissue; and (ii) displaying a map of degrees of risk of cancer (i.e., a probability map) overlaid on a visual representation of tissue. It is my opinion, therefore, that Suehling discloses a “system for generating a disease risk map for use as a decision-making support for evaluating risk of cancer,” as claimed in the preamble of claim 1.

333. Additionally, Suehling states that its disclosed system is network-based, as recited in the preamble of claim 1. For example, with reference to Fig. 5, Suehling states:

Upon arrival of new image data at the workstation/server 506, the fully automatic lesion detection pre-processing of the image data is triggered on the workstation/server 506 by exploiting the available RIS information, such as the requested procedure (e.g., “Abdomen tumor follow up staging”). The lesions can be automatically detected in the 3D medical image using the method of FIGS. 1 and 2 described above.

Id. at [0038] (emphasis added). Additionally, with reference to Fig. 9, Suehling states: “The above-described methods for automatic lesion detection ... and visualizing lesion detection results may be implemented on a computer” where “[t]he computer 902 ... includes one or more network interfaces 906 for communicating with other devices via a network.” *Id.* at [0046].

334. Therefore, it is my opinion that Suehling discloses all the limitations of the preamble of claim 1.

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

335. Suehling discloses these limitations. *Id.* at [0046], Fig. 9. As I explained above, Suehling states:

The above-described methods for automatic lesion detection, a clinical workflow integrating automatic lesion detection, and visualizing lesion detection results may be implemented on a computer using well-known computer processors, memory units, storage devices, computer software, and other components. A high level block diagram of such a computer is illustrated in FIG. 9. Computer 902 contains a processor 904 which controls the overall operation of the computer 902 by executing computer program instructions which define such operations. The computer program instructions may be stored in a storage device 912, or other computer readable medium (e.g., magnetic disk, CD ROM, etc.) and loaded into memory 910 when execution of the computer program instructions is desired. Thus, the steps of the methods of FIGS. 1, 2, 4, and 6 may be defined by the computer program instructions stored in the memory 910 and/or storage 912 and controlled by the processor 904 executing the computer program instructions.

Id. at [0046] (emphasis added).

336. Accordingly, it is my opinion that Suehling discloses limitation 1(a).

c) Limitation 1(b): “(i) access one or more medical images associated with a particular patient from a database;”

337. Suehling discloses this limitation. *Id.* at Fig. 1 (102), Fig. 4 (402), Fig. 5 (508, 502), [0024], [0025], [0037]. For example, Suehling states:

Referring to FIG. 1, at step 102, a 3D medical image is received. The medical image can be a 3D medical image (volume) generated using an imaging modality, such as CT and MR. The medical image can also be a 3D medical image generated using a hybrid imaging modality, such as PET/CT and PET/MR. The medical image can be received directly from an image acquisition device (e.g., MR scanner, CT scanner, etc.). It is also possible that the medical image can be received by loading a medical image that was previously stored, for example on a memory or storage of a computer system or a computer readable medium.

Id. at [0025] (emphasis added); *see also* [0037] (“Referring to FIG. 4, at step 402, a 3D medical image ... is received.”). The received medical images represent the “anatomy of a patient.” *Id.* at [0024].

338. Accordingly, it is my opinion that Suehling discloses limitation 1(b).

d) Limitation 1(c): “(ii) perform an analysis of the one or more medical images associated with the particular patient using a machine learning algorithm, to generate the risk map, wherein the risk map comprises a visual representation of tissue overlaid

with graphical denotations marking one or more regions of risk of cancer or risk of recurrence of cancer; and”

339. Suehling discloses these limitations. As I already explained in Section IX.I.1.a) above, Suehling generates the claimed “risk map” comprising “a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer.” *See id.* at [0041], Fig. 7, [0045], Fig. 8. Moreover, as I explain further here, Suehling also generates the claimed risk map by performing an analysis of one or more medical images associated with the patient using a machine learning algorithm.

340. As I explained in Section VIII.C above, the automatic analysis performed by Suehling begins with receiving a 3D medical image and automatically segmenting the image into search regions corresponding to particular organs and bones such as the brain, liver, spleen, kidneys, lungs, heart, spine, pelvis, femur, etc. *Id.* at [0026]-[0031], Fig. 1. Suehling discloses that anatomical segmentation of the 3D anatomical image is accomplished using “well known organ segmentation techniques” including trained machine learning algorithms such as “Marginal Space Learning.” *Id.* at [0030]. Suehling then detects lesions in each of the search regions using a trained region-specific lesion detector. *Id.* at [0032]-[0033]. The region-specific lesion detectors likewise use trained machine learning algorithms including clustered marginal space learning. *Id.*

341. A POSITA would know that marginal space learning (MSL), as described in Suehling, is a supervised machine learning technique used for classification and segmentation tasks. *See generally*, Ex1020.

342. Accordingly, it is my opinion that Suehling discloses limitation 1(c).

e) Limitation 1(d): “(iii) cause display of the risk map via a graphical user interface (GUI) for presentation or review of the risk map by a user”

343. Suehling discloses this limitation. Ex1007 at [0034], [0041], Fig. 5 (510), Fig. 7. For example, Suehling states:

At step 112, lesion detection results are output. The lesion detection results can be output by displaying the lesion detection results on a display of a computer system. For example, the detected and segmented lesions can be displayed in combination with the received 3D image data.... The lesion detection results can be displayed in an interactive display to provide intuitive navigation and assessment of the lesion detection results.

Id. at [0034] (emphasis added). Additionally, Suehling states:

At step 604, lesion detection results are automatically displayed. The lesion detection results can be displayed in an interactive display to provide intelligent navigation and assessment of the lesion detection results. For example, lesion detection results can be displayed on an interactive pictogram, as a list of findings, within a 3D rendering of the image data, and/or as a graphical overlay of the original image data.

Id. at [0041] (emphasis added). Suehling explains that “[t]he interactive display 700 can also provide the user with an option to accept, refine, or reject detected lesions.” *Id.* at [0043].

344. Accordingly, it is my opinion that Suehling discloses limitation 1(d).

- f) Limitation 1(e): “wherein the analysis of the one or more medical images comprises creation of a 3D image of the one or more regions of risk of cancer or risk of recurrence of cancer overlaid on the one or more medical images, and wherein the 3D image comprises geographic identification of one or more specific tissue region(s) overlaid on the one or more medical images.”**

345. Suehling discloses these limitations. *See id.* at [0033], [0036], [0041]-[0043], [0045], Fig. 2 (215, 217, 227, 229, 231, 233, 235, 237, 239), Fig. 7 (706, 710) (showing graphical overlay of segmented lesions on segmented anatomical structures, e.g., sortable by bone lesions, liver lesions, etc.). As I explained in Section IX.I.1.d) above, Suehling analyzes 3D medical images to produce a risk map by first segmenting a 3D anatomical image into 3D search regions corresponding to particular organs and bones. *Id.* at [0026]-[0031]. Suehling then detects lesions in each of the search regions (*id.* at [0032]-[0033]) and displays the lesion detection results “within a 3D rendering of the image data and/or as a graphical overlay of the original image data” (*id.* at [0041]). It is my opinion that this constitutes “creation of a 3D image of the one or more regions of risk of

cancer or risk of recurrence of cancer overlaid on the one or more medical images,” as claimed.

346. It is also my opinion that Suehling discloses the additional claimed feature: “wherein the 3D image comprises geographic identification of one or more specific tissue region(s) overlaid on the one or more medical images.” Referring to Fig. 2, which is reproduced below, Suehling states: “Image 215 of FIG. 2 shows exemplary organ segmentation results” (*id.* at [0030] (emphasis added)) and “[i]mage 217 of FIG. 2 shows exemplary bone segmentation results” (*id.* at [0031]

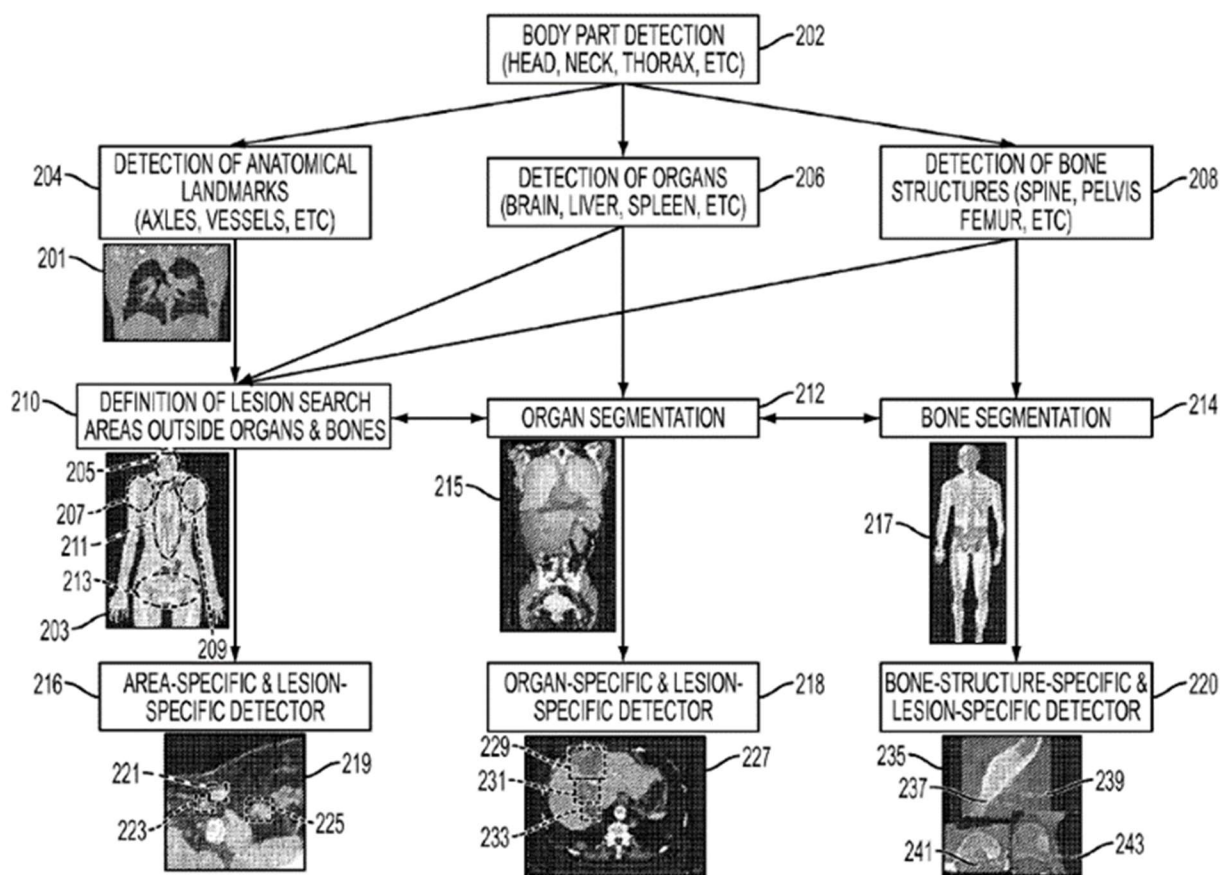


FIG. 2

(emphasis added)). By comparing image 215 to image 217 in Fig. 2, it is apparent that both images depict the geographic identification of one or more specific tissue regions (i.e., organ and bone boundaries) in the medical images. Additionally, in stark contrast to the appearance of the lungs in image 201, the segmented lungs in image 215 appear as a consistent gray scale while the ribs that surround the lungs are not visible. I interpret this as showing a color overlay of the 3D boundary of the segmented lungs. Moreover, in order for image 215 to “show” the results of organ segmentation, as described in Suehling, I believe that it must include some graphical overlay – as is more evident in image 217 showing segmented bones and non-bone structures whited out.

347. With continuing reference to Fig. 2 above, Suehling also states that “[i]mage 227 shows lesions 229, 231, and 233 detected in an exemplary segmented organ” (*id.* at [0033] (emphasis added)) and “[i]mage 235 shows lesions 237, 239, 241, and 243 detected in exemplary segmented bone structures” (*id.* at [0033] (emphasis added)). Both images are medical images that include more than just the segmented organ and segmented bone structures, respectively. Thus, in my opinion, these images, and the description of these images, disclose medical images overlaid with graphics (e.g., color or texture) to geographically identify specific tissue regions (i.e., segmented organs or bones) and segmented lesions showing regions of risk of cancer. Accordingly, it is my opinion that Suehling

discloses limitation 1(e).

348. Although it is not necessary to my opinion, I will also point out that, whereas Suehling primarily describes its invention relative to a single 3D anatomical image, such as a CT or MR image, Suehling also states: “The medical image can also be a 3D medical image generated using a hybrid imaging modality, such as PET/CT and PET/MR.” *Id.* at [0025] (emphasis added); *see also id.* at [0036] (“The information of two imaging modalities may further improve the accuracy and robustness of the detection.”). By referring to the hybrid image in the singular, I understand this to refer to a composite (or “fused”) image in which the anatomical (e.g., CT) and functional (e.g., PET) images have been overlaid and registered together. Accordingly, because Suehling generates segmented anatomical images that “show[] lesions ... in an exemplary segmented organ,” (*id.* at [0033]), and because Suehling also discloses embodiments in which the anatomical image is overlaid with a functional image to form a composite image, it is my opinion that the segmented structures generated by Suehling would necessarily be “overlaid” on one of the medical images (i.e., the functional PET image).

349. Therefore, it is my opinion that Suehling discloses limitation 1(e).

350. Additionally, since Suehling discloses every limitation of claim 1, it is my opinion that Suehling anticipates claim 1.

2. Claim 2: “The system of claim 1, wherein the one or more medical images comprise one or more magnetic resonance images (MRIs).”

351. Claim 2 depends from claim 1, which I explained in Section IX.I.1 above is anticipated by Suehling. Suehling also discloses the additional limitation of claim 2: “wherein the one or more medical images comprise one or more magnetic resonance images (MRIs).” For example, Suehling states that “[t]he present invention is directed to a method and system for automatic detection of lesions in 3D medical images, such as a computed tomography (CT) and magnetic resonance (MR) images.” *Id.* at [0020]. Suehling also states that the medical images it receives for analysis “can be a 3D medical image (volume) generated using an image modality, such as CT and MR.” *Id.* at [0025].

352. Accordingly, it is my opinion that Suehling anticipates claim 2.

3. Claim 3: “The system of claim 1, wherein the one or more medical images comprise (i) one or more PET/CT image(s) or (ii) one or more SPECT/CT image(s).”

353. Claim 3 depends from claim 1, which I explained in Section IX.I.1 is anticipated by Suehling. Suehling also discloses the additional limitation of claim 3. For example, Suehling states: “The medical images can also be a 3D medical image generated using a hybrid imaging modality, such as PET/CT and PET/MR.” *Id.* at [0025]. Additionally, Suehling states that its disclosed method “can be extended to use features from hybrid imaging modalities such as PET/CT and

PET/MR.” *Id.* at [0036].

354. Accordingly, it is my opinion that Suehling anticipates claim 3.

4. Claim 4: “The system of claim 1, wherein the visual representation of tissue is at least a portion of one of the one or more medical images of the particular patient.”

355. Claim 4 depends from claim 1, which I explained in Section IX.I.1 above is anticipated by Suehling. Suehling also discloses the additional limitations of claim 4. *See id.* at Fig. 2, Fig. 7, Fig. 8, [0034], [0041], [0045].

356. As I already explained in Section IX.I.1.d) above, Suehling discloses the generation of a risk map comprising a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer. Additionally, Suehling discloses that the visual representation of tissue over which the graphical denotations are overlaid is the medical image analyzed by Suehling. For example, Suehling states that “lesion detection results can be displayed ... within a 3D rendering of the image data and/or as a graphical overlay of the original image data.” *Id.* at [0041]. Additionally, or alternatively, with reference to Fig. 8, Suehling discloses that a “probability map” of each voxel belonging to a lesion candidate can be displayed “in a fused mode, overlaid on morphological image data.” *Id.* at [0045].

357. Accordingly, it is my opinion that Suehling anticipates claim 4.

5. Claim 5: “The system of claim 1, wherein the cancer is prostate cancer.”

358. Claim 5 depends from claim 1, which I explained in Section IX.I.1 above is anticipated by Suehling. It is my opinion that Suehling also inherently discloses the additional limitation of claim 5: “wherein the cancer is prostate cancer.”

359. Suehling, like Renisch, which is described in Section IX.A.5 above, discloses the detection of cancerous lesions – generally – and is not limited to any particular cancer type. Indeed, like Renisch, Suehling depicts the detection of lesions throughout the body. *Id.* at Figs. 2, 3, 7. Accordingly, the regions of risk of cancer detected by Suehling would necessarily include regions of risk of prostate cancer.

360. Because Suehling images the region of the prostate, as well as regions of metastatic prostate cancer, including the lymph nodes and bones, it is my opinion that Suehling discloses the limitations of claim 5. Accordingly, it is my opinion that Suehling anticipates claim 5.

6. Claim 6: “The system of claim 1, wherein the visual representation of tissue comprises a visual representation of bone.”

361. Claim 6 depends from claim 1, which I explained in Section IX.I.1 above is anticipated by Suehling. It is also my opinion that Suehling discloses the limitations of claim 6. For example, with reference to Fig. 2 above (*supra*, ¶346),

Suehling states that “[i]mage 235 shows lesions 237, 239, 241, and 243 detected in exemplary segmented bone structures.” *Id.* at [0033]. As another example, Suehling discloses that “lesion detection results can be displayed ... as a graphical overlay of the original image data” (*id.* at [0041]) where “detected lesions can be labeled with: lesion entity (e.g., liver, lymph node, bone, etc.)” (*id.* at [0042]) such that the user can “filter (hide or show) and sort finding according to different criteria, such as lesion entity (e.g., ‘show only liver lesions’)” (*id.* at [0043]). Thus, because Suehling can display lesions as a graphical overlay of the original image data and filter the display to show, e.g., only bone lesions, Suehling’s visual representation of tissue must include a visual representation of bone, as claimed. Additionally, with reference to Fig. 7 above (*supra*, ¶330), Suehling states that “the interactive display 700 displays detected lesions in various slices 702 and 704 of the medical image data,” where I note that slices 702 and 704 each include visual representation of at least one bone of the spine.

362. Accordingly, it is my opinion that Suehling anticipates claim 6.

7. Claim 7: “The system of claim 1, wherein the one or more specific tissue region(s) comprise one or more members selected from the group consisting of organs, organ structures, sub-organs, and organ regions.”

363. Claim 7 depends from claim 1, which I explained in Section IX.I.1 above is anticipated by Suehling. It is also my opinion that Suehling discloses the

limitations of claim 7 for reasons I explained in Section IX.I.1.f) above. Claim 1 requires creation of a “3D image [that] comprises geographic identification of one or more specific tissue region[s] overlaid on ... one or more medical images.” Claim 7 requires that the one or more specific tissue regions be selected from a group that includes organs.

364. As I explained in Section IX.I.1.f) above, Suehling shows and describes the geographic identification of one or more 3D organs (e.g., segmented lungs and bone) in a medical image. *See, e.g., id.* at Fig. 2 (215, 217), [0030] (“[E]ach detected organ can be segmented by detecting a position ... of the organ in the 3D medical image.”). Suehling states that “[t]he search region [for lesions] is defined for each detected organ by segmenting the detected organ” and “[i]mage 215 of FIG. 2 shows exemplary organ segmentation results.” *Id.* at [0030]. By comparing the appearance of image 215 to images 201, 203, and 217 in Fig. 2, it is clear that the organ segmentation results in image 215 are displayed (i.e., made visible) using one or more graphical overlays on the medical image such as color. Additionally, with continuing reference to Fig. 2 above (*supra*, ¶346), Suehling states that “[i]mage 227 shows lesions 229, 231, and 233 detected in an exemplary segmented organ.” *Id.* at [0033] (emphasis added). As I explained in Section IX.I.1.f), the segmented organs (e.g., lungs) appear as a graphical overlay on the 3D anatomical image and/or are overlaid on a functional image (e.g., PET) in

embodiments that utilize hybrid images (e.g., PET/CT).

365. Thus, it is my opinion that Suehling anticipates claim 7.

8. Claim 8: “The system of claim 1, wherein the one or more specific tissue region(s) comprise one or more particular bones.

366. Claim 8 depends from claim 1, which I explained in Section IX.I.1 above is anticipated by Suehling. It is also my opinion that Suehling discloses the limitations of claim 8 for reasons I explained in Section IX.I.1f) above. Claim 1 requires creation of a “3D image [that] comprises geographic identification of one or more specific tissue region[s] overlaid on ... one or more medical images.” Claim 8 requires that the one or more specific tissue regions comprise one or more particular bones.

367. As I explained in Section IX.I.1.f) above, Suehling shows and describes the geographic identification of one or more 3D segmented bones in a medical image. *See, e.g., id.* at Fig. 2 (214, 217), [0031] (“[E]ach bone structure can be segmented by detecting a position ... of the structure in the 3D medical image.”). Suehling states that “[t]he search region [for lesions] for each bone structure is defined by segmenting the detected bone structure,” and “[i]mage 217 of FIG. 2 shows exemplary bone segmentation results.” *Id.* at [0031]. Image 217 of Fig. 2 shows the segmented skeletal structure using some type of graphical overlay (e.g., color or texture) because the bones appear differently than all other

structures in the body. Additionally, with continuing reference to Fig. 2 above (*supra*, ¶346), Suehling states that “[i]mage 235 shows lesions 237, 239, 241, and 243 detected in exemplary segmented bone structures.” *Id.* at [0033] (emphasis added). As I explained in Section IX.I.1.f), the segmented bones appear as a graphical overlay on the anatomical image and/or are overlaid on a functional image (e.g., PET) in embodiments that utilize hybrid images (e.g., PET/CT).

368. Accordingly, it is my opinion that Suehling anticipates claim 8.

9. Claim 9: “The system of claim 1, wherein the instructions cause the processor to generate a radiologist report for the particular patient based at least in part on the analysis of the one or more medical images.

369. Claim 9 depends from claim 1, which I explained in Section IX.I.1 above is anticipated by Suehling. It is my opinion that Suehling also discloses the limitations of claim 9: “wherein the instructions cause the processor to generate a radiologist report for the particular patient based at least in part on the analysis of the one or more medical images.” *See id.* at [0009], [0022], [0035]-[0037], [0041], [0043], [0044], Fig. 7.

370. The Patent shows, in Fig. 5, an example of a radiologist report 510 provided on a graphical user interface. Ex1001 at 13:59-62. The Patent also states:

A radiologist report is a technical evaluation of the PET or SPECT images prepared by a radiologist for a physician who requested the imaging study and includes, for example, the type of study performed,

the clinical history, a comparison between images, the technique used to perform the study, the radiologist's observations and findings, as well as overall impressions and recommendations the radiologist may have based on the imaging study results.

Ex1001 at 2:11-19 (emphasis added).

371. Suehling discloses a “fully automatic lesion detection method ... integrated into a clinical workflow as a fully automatic pre-processing step that is executed before a users [sic] starts reads [sic] a scanned medical image.” Ex1007 at [0037]. The examined medical images can include hybrid images such as PET/CT images. *Id.* at [0036]. Suehling states:

The automatic lesion detection method allows all lesions in the body to be detected and assessed quantitatively, since existing segmentation algorithms can be triggered automatically in response to the lesion detection results during a fully automatic pre-processing phase before the 3D image data is actually read by a user. This saves time and additionally, yields the total tumor burden (diameter or volume) and not just the burden of some selected target lesions. The detected lesions and associated segmentations allow for easy navigation through the lesions according to different criteria, such as lesion size (typically the largest lesions are of highest interest), lesion location (e.g., axillary, abdominal, etc.), and appearance (e.g., necrotic, fatty core, calcifications, etc.). Further, automatic detection reduces the dependency of reading results on the user and allows for a fully automatic comparison of follow up data to highlight changes in the

detected lesions.

Id. at [0022]. For example, Suehling explains that “an interactive display may also be used in a follow-up scenario in which the current tumor burden is compared to one or more prior exams” and “lesions that changed (e.g., grew or shrank) may be highlighted” for example with “different color schemes.” *Id.* at [0044].

372. Additionally, Suehling teaches that detected lesions are automatically labeled according to their location, and the user is provided with “an option to accept, refine, or rejected detected lesions.” *Id.* at [0042]-[0043].

373. Thus, Suehling discloses the automatic production of a technical evaluation of, e.g., hybrid PET/CT images that includes, e.g., comparison between images and quantitatively calculated metrics such as total tumor burden. Ex1007 at [0035]-[0037], [0022]. The results of the automatic evaluation can be accepted or refined by a user on an interactive display (*id.* at [0043]) and saved (*id.* at [0038]), thus rendering the results a radiologist report.

374. It is my opinion that Suehling anticipates claim 9.

10. Claim 10: “The system of claim 9, wherein the radiologist report comprises the one or more medical images and the risk map.”

375. Claim 10 depends from claim 9, which I explained in Section IX.I.9 above is anticipated by Suehling. It is my opinion that claim 10 is also anticipated

by Suehling for the same reasons set forth in Section IX.I.9 above. As I already explained in Section IX.I.9, Suehling automatically produces a radiologist report that includes a technical evaluation of medical images, including identification of lesions, labeling of lesions by size and location, and quantitatively calculated metrics such as total tumor burden. As I also explained in Section IX.I.9, the radiologist report that Suehling automatically generates includes one or more of the examined medical images and/or risk maps, for example, in which lesions that have changed are highlighted.

376. Accordingly, is it my opinion that Suehling anticipates claim 10.

11. Independent Claim 13

- a) Preamble: “A method for generating a disease risk map for use as a decision-making support for evaluating risk of cancer or risk of recurrence of cancer, the method comprising:”**

377. The preamble of claim 13 is essentially the same as the preamble of claim 1 except that claim 13 recites a “method” whereas claim 1 recites a “network-based system.” Assuming the preamble is considered a limitation on the scope of the claim, it is my opinion that Suehling discloses the limitations of the preamble for the same reasons provided in Section IX.I.1.a) above.

- b) 13(a): “(i) accessing, by a processor, one or more medical images associated with a particular patient from a database;”**

378. This limitation is essentially identical to limitation 1(b) which is addressed in Section IX.I.1.c) above. The only difference is that, whereas limitation 1(b) relates to instructions that cause a processor to “access one or more medical images ...,” limitation 13(a) recites “accessing, by a processor, one or more medical images” Accordingly, it is my opinion that Suehling discloses limitation 13(a) for the same reasons explained in Section IX.I.1.c) above.

- c) **13(b): “(ii) automatically analyzing, by the processor, using a machine learning algorithm, the one or more medical images to generate the risk map, wherein the risk map comprises a visual representation of tissue overlaid with graphical denotations marking one or more regions of risk of cancer or risk of recurrence of cancer; and”**

379. This limitation is essentially identical to limitation 1(c) which I addressed in Section IX.I.1.d) above. The only difference is that, whereas limitation 1(c) relates to instructions that cause a processor to “perform an analysis of the one or more medical images associated with the particular patient using a machine learning algorithm ...,” limitation 13(b) recites “automatically analyzing, by the processor, using a machine learning algorithm, the one or more medical images” I note that limitation 13(b) explicitly recites “*automatically* analyzing, by the processor.” Nevertheless, my analysis of limitation 1(c) above already assumed that the claimed analysis – performed by a processor executing stored instructions – was automatic. Nevertheless, I repeat here, for the avoidance of

doubt, that Suehling discloses the automatic segmentation of anatomical structures and automatic detection of lesions in medical images using machine learning algorithms, including Marginal Space Learning. *Id.* at [0022], [0024], [0030], [0032], [0038]. Accordingly, it is my opinion that Suehling discloses limitation 13(b) for the same reasons explained in Section IX.I.1.d) above.

d) 13(c): “(iii) causing, by the processor, display of the risk map via a graphical user interface (GUI) for presentation or review of the risk map by a user,”

380. This limitation is essentially identical to limitation 1(d) which I addressed in Section IX.I.1.e) above. The only difference is that, whereas limitation 1(d) relates to instructions that cause a processor to “cause display of the risk map ...,” limitation 13(c) recites “causing, by the processor, display of the risk map” Accordingly, it is my opinion that Suehling discloses limitation 13(c) for the same reasons explained in Section IX.I.1.e) above.

e) 13(d): “wherein step (ii) comprises creation of a 3D image of the one or more regions of risk of cancer or risk of recurrence of cancer overlaid on the one or more medical images, and wherein the 3D image comprises geographic identification of one or more specific tissue region(s) overlaid on the one or more medical images.”

381. This limitation is essentially the same as limitation 1(e), which I address in Section IX.I.1.f) above. The only difference is that, whereas limitation 1(e) recites “wherein the analysis of the one or more medical images comprises

...,” limitation 13(d) recites “wherein step (ii) comprises ...,” where step (ii) of claim 13 is the step of “automatically analyzing, by the processor, ... the one or more medical images” Accordingly, it is my opinion that Suehling anticipates limitation 13(d) for the same reasons I provided in Section IX.I.1.f) above.

382. Because it is my opinion that Suehling discloses all the limitations of claim 13, it is also my opinion that Suehling anticipates claim 13.

J. Ground K, Obviousness over Suehling in view of Maier

1. Claim 11: “The system of claim 9, wherein the radiologist report comprises one or more reference images or reference risk maps.”

383. Claim 11 depends from claim 9, which I explained in Section IX.I.9 above is anticipated by Suehling. Claim 9 requires the generation of a radiologist report. Claim 11 further requires that “the radiologist report comprises one or more reference images or reference risk maps.” As I already explained in Sections IX.D.3 and IX.H.1 above, Maier discloses the additional limitations of claim 11. It is my opinion that it would be obvious to improve the report generated by Suehling to include reference images for comparison, as taught by Maier.

384. As I explained in Section IX.I.9 above, Suehling automatically evaluates a patient’s medical images and displays the results on an interactive graphical user interface, including the patient’s medical images, the patient’s risk map, and calculated metrics, such as total tumor burden. Ex1007 at [0022], [0041],

[0044]. Additionally, Suehling explains that the “interactive display may also be used in a follow-up scenario in which the current tumor burden is compared to one or more prior exams” and “lesions that changed (e.g., grew or shrank) may be highlighted” for example with “different color schemes.” *Id.* at [0044]. Suehling does not, however, clearly describe comparing the patient’s images to reference images or risk maps *of others*.

385. As I explained in Section XIII.D above, Maier discloses computer implemented systems and methods for assessing medical images and communicating a patient’s health status and risk by automatically generating a report tailored for the intended user, including for example a “radiologist.” Ex1008 at [0014], [0015]-[0016], [0026], [0041]. Like Suehling, Maier discloses assessing a patient’s health status and risk by comparing the patient’s medical images to the patient’s own prior images and calculating values related to the change in the patient’s own images. *Id.* at [0024]. Additionally, however, Maier also discloses assessing a patient’s health status and risk by comparing the patient’s medical images to one or more comparison images from one more individuals for whom the corresponding health status and/or outcomes are known. *Id.* at [0014].

386. With reference to Fig. 3 of Maier (*supra*, ¶132), an example of a report automatically generated by Maier includes not only the patient’s medical images, but also comparative reference images (or risk maps) from others with

known medical outcomes. Ex1008 at [0041].

387. In my opinion, it would have been obvious and straightforward to improve the report generated by Suehling simply by including one or more reference images and/or risk maps based on the express teachings and motivations supplied in Maier. Specifically, Maier teaches that comparison to a “corresponding cohort” permits quantitative calculation of “risk metrics” (Ex1008 at [0022]) that “may be used for screening disease, prognosis or diagnosis of diseases, base-line assessments, treatment planning, treatment follow-up, or other user education regarding tissue state” (*id.* at [0018]). Additionally, Maier explains that its teachings are applicable to any type of tissue and/or disease. *Id.* at [0016]-[0018]. Therefore, Maier supplies motivation to a POSITA to also include a reference image for comparison in the report generated by Suehling. Furthermore, in view of the teachings in Maier, a POSITA would have had a reasonable expectation of success in doing so since Maier and Suehling are in the same field and both already disclose comparison to a patient’s own prior images.

388. Accordingly, it is my opinion that a POSITA would have motivated to combine, and would have had a reasonable expectation of success in combining, Suehling and Maier. Specifically, it is my opinion that a POSITA would have been motivated to improve the report generated by Suehling to include a reference image as taught by Maier. Thus, it is my opinion that Suehling in view of Maier

renders claim 11 unpatentable as obvious.

K. Ground L, Obviousness over Suehling in view of Menon

- 1. Claim 12: “The system of claim 1, wherein the instructions cause the processor to apply a machine learning algorithm to update a process for automatically analyzing the one or more medical images using accumulated image data in the database.**

389. Claim 12 depends from claim 1, which I explained in Section IX.I.1 above is anticipated by Suehling. Claim 12 recites the additional limitation: “wherein the instructions cause the processor to apply a machine learning algorithm to update a process for automatically analyzing the one or more medical images using accumulated image data in the database.” As I previously explained in Section IX.E.1 above, I interpret this to refer to something akin to a machine learning feedback loop that improves the method by which automatic analysis of the medical images is performed – rather than updating the analysis of any particular medical image. Menon discloses this limitation.

390. As I explained in Section IX.E.1, Menon describes an automated triaging decision support tool that utilizes machine learning and a feedback loop to continuously refine (i.e., update) the tool. Ex1012 at [0010], [0032], [0055], [0078], [0103]-[0104], [0180], [0189], [0195]. The tool takes, as input, various data, including the patient’s medical images (*id.* at [0104], [0110]), and automatically outputs risk analysis and treatment recommendations (*id.* at [0104]-

[0109], [0189]). Additionally, the tool uses this output information and accumulated imaging data in a feedback loop to refine the tool using machine learning. *Id.* at [0180], [0189].

391. Menon states that “the tool [] may be refined with additional ... imaging data using machine learning, feedback, and validation data.” *Id.* at [0180] (emphasis added). Menon explains that “the tool [] generates and provides output data including triaging decision support ... and risk analysis” and “[t]his information is also used by the tool along with physician feedback to further refine the system model continuously.” *Id.* at [0189]. Additionally, Menon states: “The tool [] may continue to refine the model ... using machine learning and improve its predictive accuracy using new information that will be available when the product is being tested real time and when the product is in clinical use.” *Id.* at [0195]. Accordingly, it is my opinion that Menon discloses the limitation recited in claim 12.

392. Suehling and Menon are in the same field of automated medical image analysis systems. It is my opinion that a POSITA would have been motivated to improve Suehling, as described in Menon, based on motivations supplied by Suehling and/or the common sense of a POSITA. Suehling explains that “the appearance of the same lesion entity may differ between different body regions” and “[a] general lesion detection algorithm for the whole body is therefore

unlikely to yield reliable results.” Ex1007 at [0024]. Therefore, Suehling segments the body into distinct search regions (e.g., organs and bones) using trained detectors “trained based on annotated training data.” *Id.* at [0026], [0028] (“a specific detector trained for each individual landmark, organ, and bone structure”), [0030]. If the segmentation of anatomical structures is important to the accurate identification of lesions, as taught by Suehling, then it is a matter of common sense that improved segmentation, if possible, would produce more accurate lesion detection results. Additionally, if the segmentation process is based on annotated training data, as taught by Suehling, then it is a matter of common sense that additional or improved training data would improve the segmentation process. Menon, within the same field of art, expressly teaches the application of machine learning *using* accumulated data (i.e., validated output) to continuously refine an automatic image analysis system. Ex1012 at [0189] (“refine the system model continuously”). Thus, it is my opinion that a POSITA would have looked to Menon as a means to improve Suehling. Additionally, a POSITA would have had a reasonable expectation of success in making such an improvement because the concept and techniques for training machine learning algorithms are well-established, and the process of extending that training to include newly validated data in something akin to a feedback loop would simply use the same well-established training techniques. For example, the technique for training a machine

learning algorithm to perform a classification task using labeled training data is a standard, well-established process. The additional process of using machine learning to refine or update the classification routine would use the same standard training technique except with validated classification output as the new training data.

393. Additionally, or alternatively, improving Suehling with the teachings in Menon would merely have amounted to using a known technique (i.e., machine learning) to improve similar devices in the same way. Suehling and Menon are both automated medical image analysis systems. Suehling analyzes medical image to identify and quantify cancerous lesions. Menon analyzes medical images to assess the risk of stroke and provide treatment recommendations. Menon further teaches that machine learning can be used to continuously refine its analysis model with validated output and a feedback loop. Ex1012 at [0195], Fig. 22 (2210, 2218, 2220). Indeed, the use of machine learning to refine and improve automated processes is a known technique – of which Menon is just one example. It is my opinion that it would have been obvious to a POSITA to apply the same technique to a similar medical image analysis system (Suehling) for the same purpose, which is to continually improve the analysis technique.

394. Accordingly, it is my opinion that Suehling in combination with Menon, teach all the limitations of claim 12 and render claim 12 unpatentable as

obvious.

X. CONCLUSION

395. For the foregoing reasons, it is my opinion that claims 1-13 of the Patent should be found unpatentable.

* * *

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

Dated:

/ Dr. Bruce Rosen /
Dr. Bruce Rosen