UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ELEKTA INC.,
Petitioner

v.

BEST MEDICAL INTERNATIONAL, INC.,
Patent Owner.

Case No.: IPR 2020-00074

U.S. Patent No. 6,393,096

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,393,096

TABLE OF CONTENTS

I. INTRODUCTION 1

A. Declaration Evidence 1

II. MANDATORY NOTICES UNDER 37 C.F.R. §42.8(a)(1)....................2

A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1)) 2

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

C. Counsel (37 C.F.R. § 42.8(b)(3)) and Service Information (37 C.F.R. § 42.8(b)(3)-(4)) 2

III. CERTIFICATION (37 C.F.R. § 42.104(A)) AND PAYMENT OF FEES (37 C.F.R. § 42.10) 3

IV. IDENTIFICATION OF CLAIMS AND GROUNDS (37 C.F.R. § 42.104(a),(B)) 4

A. Non-Patent Literature....................4

1. Niemierko-RONSC....................6

2. Goitein-1992 7

3. Mohan-1994....................8

V. TECHNOLOGY BACKGROUND....................8

VI. BACKGROUND....................18

A. Overview of the ’283 patent....................18

A. Relevant Prosecution History....................22

B. Cited References....................23

1. Niemierko-RONSC....................23

2. Goitein-1992 24

3. Mohan-1994 24

VII. PERSON OF ORDINARY SKILL IN THE ART ("POSITA") 25

VIII. CLAIM CONSTRUCTION (37 C.F.R. § 42.104(B)(3)) 25

ARGUMENTS 26

IX. GROUND #1: NIEMIERKO-RONSC COMPARED TO CLAIMS 1, 10, 22, 25 26

A. Claim 1. "A method of determining an optimized radiation beam arrangement for applying radiation to a tumor target volume while minimizing radiation of a structure volume in a patient, comprising the steps of…" ..... **Error! Bookmark not defined.**

B. Claim 10: "The method of claim 1…" **Error! Bookmark not defined.**

C. Claim 22: "A method of determining an optimized radiation beam arrangement for applying radiation to a tumor target volume while minimizing radiation of a structure volume in a patient, comprising the steps of…" ..... **Error! Bookmark not defined.**

D. Claim 25: "An apparatus for determining an optimized radiation beam arrangement for applying radiation to a tumor target volume while minimizing radiation of a structure volume in a patient, comprising…" ..... **Error! Bookmark not defined.**

X. GROUND #2: NIEMIERKO RONSC IN VIEW OF GOITEIN COMPARED TO CLAIMS 23, 24, 26, 33, 40, 44 26

A. Claim 23: "The method of claim 22…" ..... **Error! Bookmark not defined.**

B. Claim 24: "The method of claim 22…" ..... **Error! Bookmark not defined.**

C. Claim 26: "The method of claim 25…" ..... **Error! Bookmark not defined.**

D. Claim 33: "A method of determining an optimized radiation beam arrangement for applying radiation to at least one tumor target volume while minimizing radiation to at least one structure volume in a patient, comprising the steps of…”.... **Error! Bookmark not defined.**

E. Claim 40: “A method of determining an optimized radiation beam arrangement for applying radiation to at least one tumor target volume while minimizing radiation of at least one structure volume in a patient, comprising the steps of…”.... **Error! Bookmark not defined.**

F. Claim 44: “The method of claim 40…”........... **Error! Bookmark not defined.**

XI. GROUND #3: NIEMIERKO RONSC IN VIEW OF MOHAN 1994 COMPARED TO 6..40

A. Claim 6: “The method of claim 1…”. **Error! Bookmark not defined.**

XII. GROUND #4: NIEMIERKO RONSC IN VIEW OF GOITEIN 1992 IN FURTHER VIEW OF MOHAN 1994 COMAPRED TO CLAIMS 27, 28, 34, 42, 46 61

A. Claim 27: “The apparatus of claim 25, further comprising…” .. **Error! Bookmark not defined.**

B. Claim 28: “The apparatus of claim 27…”......... **Error! Bookmark not defined.**

C. Claim 34: “The method of claim 33…”........... **Error! Bookmark not defined.**

D. Claim 42: The method of claim 40... . **Error! Bookmark not defined.**

E. Claim 46: “The method of claim 44…”........... **Error! Bookmark not defined.**

XIII. MOTIVATION TO COMBINE CITED REFERENCES............................63

XIV. SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS DO NOT NEGATE OBVIOUSNESS..67

XV. SUMMARY CHARTS..68

XVI. CONCLUSION..68

TABLE OF AUTHORITIES

Page(s)

Cases

Best Med. Int'l, Inc. v. Accuray, Inc.,
No. 2:10-cv-1043, 2010 U.S. Dist. LEXIS 128367 (W.D. Pa. Dec. 2, 2010) 25

Best Medical International, Inc. v. *Elekta Inc. and Elekta Limited*,
Civil Action 1:19-cv-03409-MLB 2

Best Medical International, Inc. v. *Varian Medical Systems, Inc. et al*,
Civil Action 1:18-cv-01599 2

Chore-Time Equip., Inc. v. Cumberland Corp.,
713 F.2d 774 (Fed. Cir. 1983) 25

GoPro, Inc. v. *Contour IP Holding LLC*,
898 F.3d 1170 (Fed. Cir. 2018) 4, 5

LG Elec., Inc. v. *Advanced Micro Devices, Inc*.,
IPR2015-00329, Paper 13 (PTAB Jul. 10, 2015) 6, 7, 8

Medtronic Inc. v. *NuVasive Inc*.,
IPR2014-00087, Paper 44 (PTAB Apr. 3, 2015) 67

Ohio Willow Wood Co. v. *Alps South, LLC*,
735 F.3d 1333 (Fed. Cir. 2013) 67

Okajima v. Bourdeau,
261 F.3d 1350 (Fed. Cir. 2001) 25

Wyers v. *Master Lock Co*.,
616 F.3d 1231 (Fed. Cir. 2010) 67

Statutes

35 U.S.C. §103 26

35 U.S.C. §§ 311-319 1

Other Authorities

37 C.F.R. 42.100(b) 25

37 C.F.R. §42.8(A)(1)..2

(37 C.F.R. § 42.8(b)(1))...2

(37 C.F.R. § 42.8(b)(2))...2

(37 C.F.R. § 42.8(b)(3))...2

(37 C.F.R. § 42.8(b)(3)-(4))..2

37 C.F.R. § 42.8(b)(4)..3

(37 C.F.R. § 42.10) 3

37 C.F.R. § 42.10(b) 3

37 C.F.R. § 42.100 *et seq*...1

(37 C.F.R. § 42.104(A))...3

(37 C.F.R. § 42.104(A),(B)) 4

(37 C.F.R. § 42.104(B)(3)) 25

LIST OF EXHIBITS

Exhibit #	Description
1001	U.S. Patent No. 6,393,096 **("'096 patent")**
1002	Prosecution History of U.S. Patent Application No. 09/320,980, which matured into U.S. Patent No. 6,393,096
1003	Declaration of Prof. Joao Seco
1004	Niemierko, Andrzej, *Random search algorithm (RONSC) for optimization of radiation therapy with both physical and biological end points and constraints*, International Journal of Radiation Oncology* Biology* Physics 23.1 (1992): 89-98, PubMed P.M.I.D.: 1572834 **("Niemierko-RONSC")**
1005	Science Direct (Elsevier) Online Publication History of Niemierko-RONSC
1006	Goitein, Michael, *The comparison of treatment plans*. Seminars in radiation oncology, Vol. 2. No. 4. WB Saunders, 1992, PubMed P.M.I.D.: 10717041 **("Goitein-1992")**
1007	Science Direct (Elsevier) Online Publication History of Goitein-1992
1008	Mohan, Radhe, *et al.*, *The potential and limitations of the inverse radiotherapy technique*. Radiotherapy and Oncology 32(3) (1994): 232-248, PubMed P.M.I.D.: 7816942 **("Mohan-1994")**
1009	Elsvier Publication History of Mohan-1994
1010	Declaration of Librarian, Marla Hirth
1011	Boyer Declaration # 1 on the State of the Art in the 1990s **("Boyer SOA Declaration")**
1012	*Curriculum vitae* of Prof. Joao Seco
1013	Carol, M. P., *Where we go from here: one person's vision*, pages 243-252 in Sternick, ES, The Theory and Practice of Intensity-Modulated Radiation Therapy, Madison, WI, Advanced Medical Publishing (1997) ("Carol 1997")
1014	Carol, Mark P., et al., *3-D planning and delivery system for optimized conformal therapy*, International Journal of Radiation Oncology• Biology• Physics 24 (1992): 156 ("Carol 1992")
1015	Carol, Mark P., *Peacock™: A system for planning and rotational delivery of intensity-modulated fields*, International Journal of Imaging Systems and Technology 6.1 (1995): 56-61 ("Carol 1995")
1016	NOT USED
1017	January 11, 2013 Order from *Best Med. Int'l, Inc. v. Accuray, Inc.*, No. 2:10-cv-1043, 2013 U.S. Dist. LEXIS 4452 (W.D. Pa. Jan. 11, 2013)

Exhibit #	Description
1018	Lawrence, Theodore, *et al.*, "*The use of 3-D dose volumn analysis to predict radiation hepatitis,*" Int., J. Radiation Oncology Bio. Phys. Vol. 23 (1992);781-788 ("Lawrence 1992").
1019	Webb, S., "*Optimisation of conformal radiotherapy dose distribution by simulated annealing*," Physics in Medicine & Biology 34.10 (1989): 1349 ("Webb 1989")
1020	Webb, S., "*Optimization of conformal radiotherapy dose distributions by simulated annealing: II. Inclusion of scatter in the 2D technique*," Physics in Medicine & Biology 36.9 (1991): 1227 ("Webb 1991")
1021	Hill, R. W., Curran, B. H., Strait, J. P., & Carol, M. P. (1997). Delivery of intensity modulated radiation therapy using computer controlled multileaf collimators with the CORVUS inverse treatment planning system. In *Proceedings of the 12th International Conference on the Use of Computers in Radiation Therapy* (pp. 394-397). ("Carol 1997b")
1022	Rosen, I. I., Lam, K. S., Lane, R. G., Langer, M., & Morrill, S. M. (1995). Comparison of simulated annealing algorithms for conformal therapy treatment planning. International Journal of Radiation Oncology• Biology• Physics, 33(5), 1091-1099. ("Rosen 1995")
1023	PCT Publication No. WO 98/17349 to Carol et al. ("'349 application")
1024	Attachments to Ex. 1010 (Hirth Declaration) p. 1-288
1025	Attachments to Ex. 1010 (Hirth Declaration) p. 289-end

I. INTRODUCTION

Elekta Inc. ("Elekta" or "Petitioner") requests that the Board institute *inter partes* review ("IPR") of and cancel claims 1, 18, 21, 22, 23, 24, 31, 32, 33, 34, 36, 37, 38, 40, 43, 44, 45, 46 ("Challenged Claims") of U.S. Patent No. 6,393,096 ("the '096 patent") (Ex. 1001), assigned to Best Medical International, Inc. ("BMI" or "Patent Owner"), in accordance with 35 U.S.C. §§311-319 and 37 C.F.R. §42.100 *et seq*.

A. Declaration Evidence

This Petition is supported by declaration testimony of Professor Joao Seco ("Seco Declaration") (Ex. 1003), which incorporates by reference declaration testimony of Dr. Arthur Boyer ("Boyer SOA Declaration") (Ex. 1011), and declaration testimony of Marla Hirth (Ex. 1010). The Seco Declaration describes the '096 patent, the person of ordinary skill in the art in the relevant time frame, interpretation of certain terms in the '096 patent, the state of the art of the '096 patent, the scope and content of the prior art compared to the claims of the '096 patent, and the rationales for combining prior art elements. The Boyer Declaration describes the general state of the art in radiotherapy in the 1990s. The Hirth Declaration describes the authenticity and public availability of the cited references.

II. MANDATORY NOTICES UNDER 37 C.F.R. §42.8(A)(1)

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

Petitioner identifies Elekta Limited (UK), Elekta Holdings U.S., Inc. and Elekta AB as real parties in interest without admitting that they are in fact real parties in interest. Elekta Limited (UK), Elekta Holdings U.S., Inc. and Elekta AB have agreed to be bound by the estoppel provisions of 35 U.S.C. 315(e) to the same extent as Petitioners.

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

Patent Owner asserted the ’096 patent in *Best Medical International, Inc.* v. *Elekta Inc. and Elekta Limited*, Civil Action No. 1:19-cv-03409-MLB (currently pending in the Northern District of Georgia, and previously pending in the District of Delaware as Civil Action No. 1:18-cv-01600-MN) and *Best Medical International, Inc*. v. *Varian Medical Systems, Inc. et al*, Civil Action No. 1:18-cv-01599 (currently pending in the District of Delaware).

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

Petitioner designates Tamara D. Fraizer (Reg. No. 51,699) as lead counsel for this matter. Petitioner also designates Christopher W. Adams (Reg. No. 62,550) and Vid R. Bhakar (Reg. No. 42,323) as back-up counsel for this matter.

Postal mailings and hand-deliveries for lead and back-up counsel should be addressed to: Tamara D. Fraizer, Squire Patton Boggs (US) LLP, 1801 Page Mill Road, Suite 110, Palo Alto, CA 94304-1043 (Telephone: (650) 843-3201;Fax: (650) 843-8777).

Pursuant to 37 C.F.R. §42.8(b)(4), Petitioner consents to e-mail service at: tamara.fraizer@squirepb.com; sfripdocket@squirepb.com.

For compliance with 37 C.F.R. §42.10(b), a Power of Attorney is also filed concurrently herewith.

III. CERTIFICATION (37 C.F.R. § 2.104(A)) AND PAYMENT OF FEES (37 C.F.R. §42.10)

Petitioner certifies that the '096 patent is available for IPR and Petitioner and the real parties-in-interest are not barred or estopped from requesting IPR on the grounds identified herein.

The complaint referenced in Section II.B was served within the last 12 months. Neither the Petitioner nor its real parties-in-interest (or privies), have been served with any other complaint alleging infringement of the '096 patent.

The undersigned authorizes the USPTO to charge any fees due during this proceeding to Deposit Account No. 07-1850.

IV. IDENTIFICATION OF CLAIMS AND GROUNDS (37 C.F.R. §42.104(A),(B))

The application for the ‘096 patent was filed on May 27, 1999 by Nomos Corporation, the Patent Owner’s predecessor-in-interest. This application claimed priority to U.S. Provisional Application No. 60/087,049, which was filed on May 27, 1998 Ex. 1001 at cover page; Ex. 1002 at 6, 11.

Because the filing date of the ’096 patent (and all applications to which it claims priority) is before the effective date of the AIA (March 16, 2013), the pre-AIA statute applies.

For purposes of this IPR, Petitioner treats May 27, 1998 as the effective filing date of the cited provisional applications, as the “Alleged Priority Date” for all Challenged Claims. To the extent that the Patent Owner demonstrates a date of conception earlier than this, then the Petitioner shall reserve the right to adjust the “Alleged Priority Date” accordingly.

Petitioner relies on the following references:

A. Non-Patent Literature

The non-patent prior art references on which Petitioner relies are identified below. Each of these references qualifies as a printed publication under §102(b).

Whether a reference constitutes a printed publication under §102(b) is a legal conclusion based on underlying factual determinations. *GoPro, Inc.* v. *Contour IP*

Holding LLC, 898 F.3d 1170, 1173-74 (Fed. Cir. 2018) (opinion modified on other grounds). The Federal Circuit has "interpreted §102 broadly, finding that even relatively obscure documents qualify as prior art so long as the relevant public has a means of accessing them." *Id.* at 1174. A reference is "publicly accessible if it was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *Id.*

Each of the references below is an authentic copy of the article from its respective publication. *See* Ex. 1010 at ¶¶106-109,100-102 and 92-95. Each of the references below has (i) either a date stamp from the National Library of Medicine or (ii) a copyright office stamp from the Library of Congress, Copyright Office, each of which signify when such institution processed the article. *Id*. at ¶¶96-97,103 and 109. *See SAP America, Inc*. v. *Realtime Data, LLC*, IPR2016-00783, 2016 WL 667819 (PTAB Oct. 5, 2016) (noting sufficient indicia of public availability included copyright date, ISBN number, and Library of Congress Cataloging-in-Publication Data).

None of the following references are listed on the face of the '096 patent and therefore they were not considered by the Examiner during prosecution.

1. Niemierko-RONSC

Niemierko-RONSC is a printed publication bearing a copyright date of 1992 and first published by the American Society for Therapeutic Radiation and Oncology (ASTRO) in the International Journal of Radiation Oncology*Biology*Physics, Volume 23, Issue 1, 1992, pages 89-98. *See* Ex. 1004 at 89; see *LG Elec., Inc*. v. *Advanced Micro Devices, Inc*., IPR2015-00329, Paper 13 at 12 (PTAB Jul. 10, 2015) (copyright date is prima facie evidence of publication).

Niemierko-RONSC also includes numerous other indicia of its public accessibility, including National Library of Medicine (NLM) and Library of Congress (LOC) publication data (Ex. 1010 at ¶¶96-97) and publisher information (Ex. 1005).

Niemierko-RONSC was cited by other references prior to the Alleged Priority Date, including (i) Mohan-1994 and (ii) Rosen 1995. Ex. 1010 at ¶98. *See also Spitzer* v. *Aljoe*, No. 13-cv-05442-MEJ, 2016 WL 3275148 at *3 (N.D. Cal. Jun. 15, 2016) (taking judicial notice of the publicly availability of a document located on Google Scholar).

Thus, Niemierko-RONSC was publicly accessible a year before the Alleged Priority Date, and is §102(b) prior art.

2. Goitein-1992

Goitein-1992 is a printed publication bearing a copyright date of 1992 and first published by W.B. Saunders Company, in Seminars in Radiation Oncology, Volume 2, Issue 4, October 1992, pages 246-256. Ex. 1006 at cover pages,; *see LG Elec., Inc.*, IPR2015-00329, Paper 13 at 12 (PTAB Jul. 10, 2015).

Goitein-1992 also includes numerous other indicia of its public accessibility, including NLM publication data (Ex. 1010 at ¶103) and publisher information (Ex. 1007).

Goitein-1992 was cited by other references prior to the Alleged Priority Date. Ex. 1010 at 104. *See also Spitzer* at *3 . For example, (i) Jain, Nilesh L., and Michael G. Kahn. *Clinical decision-support systems in radiation therapy*. (1993) (published "1993-01-01")[1]and (ii) Purdy, James A., et al. *Advances in 3-dimensional radiation treatment planning systems: room-view display with real time interactivity*. International Journal of Radiation Oncology* Biology* Physics 27.4 (1993): 933-944, cited Goitein-1992.

Thus, Goitein-1992 was publicly accessible a year before the Alleged Priority Date, and is §102(b) prior art.

3. Mohan-1994

Mohan-1994 is a printed publication bearing a copyright date of 1994 and first published by Elsevier Science Ireland Ltd. in Radiotherapy & Oncology Volume 32, Issue 3, September 1994, pages 232-248. Ex. 1008 at 232; *see LG Elec., Inc.*, IPR2015-00329, Paper 13 at 12 (PTAB Jul. 10, 2015) (copyright date is prima facie evidence of publication).

Mohan-1994 also includes numerous other indicia of its public accessibility, including NLM publication data (Ex. 1010 at ¶109) and publisher information (Ex. 1009).

Based on the Hirth Declaration, Mohan-1994 was cited by other references prior to the Alleged Priority Date. Ex. 1010 at ¶110. *See also Spitzer* at *3.

Thus, Mohan-1994 was publicly accessible a year before the Alleged Priority Date, and is §102(b) prior art.

V. TECHNOLOGY BACKGROUND

The ’096 patent states that it pertains to “a method and apparatus for conformal radiation therapy of tumors with a radiation beam having a pre-determined, constant beam intensity.” Ex. 1001 at 1:10-12

Conventional medical linear accelerators (LINACs) have been used since the 1970s to treat tumors with an intense beam of radiation. Ex. 1011 at ¶¶15-24. The goal of “radiation therapy” is, and always has been, to target the tumor and avoid damage to healthy tissues. *Id.* at ¶¶10-14; Ex. 1003 at ¶101. The problem is that critical organs may be near the tumor, and therapeutic radiation must pass through normal, healthy tissues to reach the tumor. Ex. 1011 at ¶¶10-14. Radiation can damage or kill cells, depending on the amount of exposure. *Id.* So, treatment planners strive to define a treatment regime that will deliver a lethal dose of radiation to the tumor and tolerable doses to the critical organs and healthy tissues. *Id.*

One way to do this is by using a radiation beam shaped to match the outline of the tumor. Ex. 1011 at ¶¶28-33, Fig. A, I. This is the principle of **conformal radiation therapy**. *Id.* at 31. Historically, the outline of the radiation beam was shaped to conform to the outline of the tumor with blocks or specially built forms. *Id.* at ¶28, Fig. G. To further help avoid damaging healthy tissues, the radiation is delivered in treatment "fractions" over days or weeks, giving healthy cells time to recover. *Id.* at ¶12. An additional way to ensure the radiation to healthy tissues is tolerable is to deliver the radiation from different directions, with a portion of the dose given from each direction. *Id.* at ¶13. The dose concentration is highest where the beams intersect ("the isocenter"), which should be at the tumor. *Id.* at ¶¶16-17, Figs. A, B.

By the early 1990s, **multileaf collimators** (**MLCs**) were used with LINACs. Ex. 1011 at ¶¶34-35, Fig. H. They could accurately shape (or collimate) the radiation beam using narrow leaves of tungsten, that were easily positioned under control of a computer. *Id.* at ¶¶22, 29, 31. The radiation source with the MLC could be moved in an arc around the patient, so radiation could be delivered from different directions. *Id.* at ¶¶16, 18, 19, Fig. B.

Also by the early 1990s, more advanced patient imaging techniques and 3D computational models were available to help identify a better combination of directions and beam shapes for radiation therapy. *Id*. at ¶25, Fig. F; Ex. 1003 at ¶103. Radiation therapy using these capabilities became known as **three dimensional conformal radiation therapy** (**3DCRT**). *Id.* at ¶34.

Such 3DCRT treatment plans were more complicated than previous approaches, so **cumulative dose-volume histograms** (**CDVHs**) were commonly used to guide evaluations of proposed 3DCRT plans. Ex. 1011 at ¶¶42-49, Fig. J; Ex. 1003 at ¶119. The concept of the CDVH goes back to the 1980s. Ex. 1011 at ¶¶27, 40; Ex. 1003 at ¶119. A CDVH is a graph that provides information about the distribution of the dose delivered to each “structure” (the tumor, each critical organ). *Id.* at ¶42. The CDVH shows how much of a structure receives a dose equal to or greater than a specified dose. *Id*. The CDVH gives no spatial information about the delivered dose, meaning it does not provide information about *where* in the structure the dose is delivered. *Id.* (Spatial information would be shown, for example, in images with isodose lines. *Id.* at ¶¶41-42.)

The use of the MLC, advanced imaging techniques, computational 3D modeling in radiation therapy, and dose-volume data enabled a special type of 3DCRT, namely, **intensity-modulated radiation therapy** (**IMRT**). *Id.* at ¶¶34, 59.

In IMRT, the amount of radiation delivered by a beam can vary on a scale less than the width of the beam. *Id.* at ¶60. The intensity of the beam is modulated by applying radiation from one direction through multiple differently shaped MLC openings. *Id*. at ¶¶62-63, Fig. L. The necessary shapes are determined by mathematically decomposing the radiation beam into many small "beamlets," each of which can have a different "intensity" depending on the period of time the radiation is allowed to pass through the MLC for that gantry angle position. *Id.* at ¶61, Fig. K. "Beam weights" specify the intensity of the beamlets in the beam, and are referred to collectively as an "intensity map." *Id.* at ¶¶61, 65; Ex. 1003 ¶110.

The development of IMRT required a fundamental change in the process of treatment planning. In conventional **forward treatment planning**, values for treatment delivery parameters are selected by the planner and the resulting dose distribution is then determined and examined. *Id.* at ¶¶56, 68; Ex. 1003 at ¶102. Treatment parameters are adjusted to improve the plan until the prescription goal, e.g., the desired CDVH or dose constraint, is deemed to be sufficiently met. Ex. 1011 at ¶¶56, 68; Ex. 1003 at ¶¶122-123. This approach was not practical for complicated IMRT plans. *Id.* at ¶69.

This led to **inverse planning**, in which the planner starts by specifying a desired dose distribution, defining a few parameters such as the beam direction, and then working backwards (in "inverse") to find the collimator settings that produce the desired dose distribution. *Id.* at ¶¶69, 70; Ex. 1003 at ¶¶103-104. The computations are difficult even for a computer, because there may be hundreds of beam weights determined for each beam. *Id.* at ¶67. Thus, IMRT planning is not possible without computers. *Id.* at ¶¶67, 84.

Moreover, it is usually not possible to mathematically (analytically) determine a single best 3DCRT treatment plan. *Id.* at ¶¶58, 84. It certainly was not feasible given the computational capabilities of computers in the early 1990s and it is not possible for IMRT plans. *Id.* Therefore, as early as 1989, iterative optimization methods were used in 3DCRT radiation therapy treatment planning, and even to this day, iterative optimization methods are required for IMRT radiation therapy treatment planning. *Id.*; Ex. 1003 at ¶105.

Iterative optimization is used in IMRT to find the "best" plan, where "best" depends on the specified goal. Ex. 1011 at ¶72; Ex. 1003 at ¶106. An "objective" or "cost" function is a mathematical description of that goal. *Id.* The iterative process entails evaluating a sequence of possible solutions to try and find the best one, without having to look at all the possibilities. Ex. 1011 at ¶71; Ex. 1003 at ¶111. In radiation treatment planning, each potential solution is defined by the values of chosen variables such as the beam weights. Ex. 1011 at ¶¶65-57; Ex. 1003 at ¶110. Each potential solution has an associated value of the cost function, calculated according to the values of the variables that define the potential solution. *Id.* at ¶72.

The cost function characterizes the possible solutions, and provides a "landscape" of all cost function values (elevations) that can be searched to find the solution (location) having the best (e.g. minimum) value of the cost function. *Id.* at ¶¶72, 79. The landscape may have a single minimum, which means there is one best and easy-to-find solution. Ex. 1011 at ¶80; Ex. 1003 at ¶113. Most problems are more complex, with multiple local minima and one global minimum. Ex. 1011 at ¶79; Ex. 1003 at ¶¶114-115.

Stochastic algorithms, such as simulated annealing, were used in the early 1990s for such problems because they can escape a local minimum. Ex. 1011 at ¶81; Ex. 1003 at ¶¶114-117. This is because, from one iteration to the next, each possible solution is chosen with some random probability (stochastically) and that solution may be better or worse than the last possible solution. Ex. 1003 at ¶¶111-112, 114-117. The advantages of simulated annealing, and its variants, were well known in the art prior to the filing date of the '096 patent. Ex. 1011 at ¶105; Ex. 1003 at ¶118.

Many kinds of cost functions and constraints on cost functions were known and used in radiation therapy treatment planning by the mid-1990s. *Id.* at ¶72; Ex. 1003 at ¶¶108-109. Almost always, different cost functions are specified for the socalled "partial volumes" of the total patient body. Ex. 1011 at ¶¶73, 77; Ex. 1003 at ¶107. One partial volume is the tumor; other partial volumes are organs-at-risk (OAR) (e.g. the heart, bladder, rectum, spine). Ex. 1011 at ¶73.

The conflicting goals of radiation treatment planning (for the tumor, a high dose to destroy the diseased tissue; for the OARS, a low dose to avoid treatment complications) can be implemented by combining cost functions. *Id.* at ¶74. For example, the total cost function may focus on delivering a certain high dose to the target, while allowing some radiation to critical organs. At the other extreme, the total cost function may focus on minimizing the radiation of a critical organ, while delivering as much dose to the tumor as possible. Most often, a total cost function will be somewhere in the middle, specifying a dosage goal for the target and other dosage goals or constraints for the critical organs. In all of these examples, weighting factors can be used to emphasize one goal relative to another. *Id.*

As noted in the '096 patent, one approach commonly used was to specify the goal (i.e., define the cost function) for the tumor in terms of **tumor control probability (TCP).** *Id.* at ¶75. As its name suggests, TCP was based on the empirical mathematical relationship between the dose received by a small volume of tissue (a "voxel" in the 3D planning model) and the likelihood that the tissue would die as a result of treatment. *Id.* Analogously, the goal for an organ at risk (OAR) could be specified in terms of **non-tumor complication probability (NTCP),** calculated based on the relationship between the dose received by the normal tissue and the likelihood of permanent damage. *Id.* Such calculations were computationally intensive. *Id.*

Another approach, not discussed in the ’096 patent, was simpler. It was based on the dose volume data commonly used to create CDVHs for evaluation of treatment plans. Ex. 1011 at ¶76; Ex. 1003 at ¶¶122-123. In this approach, goals (and the associated cost function) were defined in terms of the radiation dose to be received by a particular volume. *Id.* For example, one goal might be to deliver 60Gy to the entire tumor, with no part of the tumor to receive more than 90Gy. *Id.* Another goal could be that no more than 50% of the organ receives more than 30Gy. *Id.* This approach is mathematically simpler than TCP/NTCP calculations, but presumes an understanding of the relationship between the amount of radiation and its effect on the tumor and healthy tissue. Ex. 1003 ¶124.

The relationship between dose volume data and TCP/NTCP is understandable with rules-of-thumb based on empirical studies. Ex. 1011 at ¶49. But there were also rigorous mathematical studies of this relationship by Lyman and others from the 1980s. Ex. 1011 at ¶48; Ex. 1003 at ¶121. These studies provided tools to understand how changes to the CDVH for a partial volume would change the underlying TCP/NTCP. *Id.*

Iterative optimization methods for 3DCRT treatment planning using dose-volume-based cost functions, and applied to partial volumes, were thus known and used before the filing of the ’096 patent.

They had even been disclosed by the patent applicant. *Id.* at ¶¶88-98. For example, Mark Carol, named inventor on the ’096 patent, reported in 1992, “[w]e have developed a 3-D conformal treatment planning and delivery system” that provides “a way of creating and delivering spatially modulated conformal therapy plans” where the goal is to “increase the dose to the entire target volume while keeping the dose to critical normal structures within accepted limits.” Ex. 1014 at Purpose and Conclusion; *see also* Ex. 1011 at ¶¶88-89; Ex. 1003 at ¶¶124-25. More than a year before the Alleged Priority Date, Carol described the Nomos Peacock™ treatment planning system, noting nearly all of the elements of the purported invention of the ’096 patent. Ex. 1015 at 57-58; *see also* Ex. 1011 at ¶¶94-98; Ex. 1003 at ¶¶126-27.

Further, in Carol 1997b, Dr. Mark Carol explains that the cost function in CORVUS was constructed using CDVH’s: “An interface has been implemented that supports the entry of partial volume information for each structure, out of which cumulative dose volume histogram curves are generated and used as the goal by the optimizer. Ex. 1021 at 317. The ’096 patent states that “the physician may be able to draw the desired target and structure CDVH curve 100, 200 graphically using a mouse or other pointing device and the System would then present the numeric values representing the target goals corresponding to the desired CDVH curves 100, 200.” Ex. 1001 at 7:37-42. The CDVH curve may be constructed from “partial volume data… entered by the user during the Prescription Panel step ...” *Id.* at 6:62-63. This approach is the same as the approach described in Carol 1997b. Ex. 1003 at ¶128; Ex. 1021 at 317-318.

Moreover, Nomos Corporation’s ’349 application, which published on April 30, 1998, (**approximately 27 days before the earliest effective filing date of the ’096 patent**) and was not considered by the Examiner, also discloses most of the Challenged Claims in the ’096 patent. Ex. 1003 at at ¶129.

The Peacock system, as described in Carol’s publication (e.g. Carol 1995) and the ’096 patent, was based on the work of Steve Webb.[2] The patent acknowledges this, stating:

> Except for the foregoing detailed description of the cost function utilized in the present system, the details of the foregoing simulated annealing techniques are known in the art and are described 45 in such publications as "Optimization of Conformal Radiotherapy Dose Distributions by Simulated Annealing," S. Webb, Physics and Medical Biology, Vol. 34, PP. 1349-1370 (1989); and "Optimization of Conformal Radiotherapy Dose Distributions by Simulated Annealing:

> 2. Inclusion of Scatter in the 2d Technique," S. Webb, Physics and Medical Biology, vol.36, pp. 1227-1237, (1991)[3] . . . .

Ex. 1001 at 8:41-51 (emphasis added). The ’096 patent explicitly refers to the invention as “an ***improved*** optimized treatment planning system,” with a “***modified*** cost function.” Ex. 1001 at 5:54-55, 57-58. In short, the patent admits that, other than its modification of the cost function, everything in the ’096 patent was known.

As demonstrated in this Petition, supported by the declaration of Joao Seco (Ex. 1003), the cost-function approach described in the ’096 patent would have been obvious to a person of skill in the art, and all of the Challenged Claims should be found invalid as obvious in view of the prior art references relied on in this Petition.

VI. BACKGROUND

A. Overview of the ’096 patent

The ’096 patent relates to “a method and apparatus for conformal radiation therapy of tumors with a radiation beam having a pre-determined, constant beam intensity.” Ex. 1001 at 1:10-12; Ex. 1003 at ¶¶133-134. It uses a “cost function based on a comparison of desired partial volume data . . . and proposed partial volume data

[3] Carol similarly cites to these two publication. Ex. 1020 at 61; *see also* Ex. 1011 at ¶99.

. . . for target tumors and tissue structures." Ex. 1001 at Abstract; Ex. 1003 at ¶¶133-134.

The '096 patent discloses an "optimizer," and an "optimization method." Ex. 1001 at 5:54-6:2, 12:28-32. As stated, the optimizer arrives at the optimal beam arrangement "by computationally increasing the proposed bean weight iteratively, incorporating cost functions to ensure that an iterative change in the beam weight would not result in an unacceptable exposure to the volumes of tissue or other structures. . ."*Id.* at 5:39-43. Thus, the '096 patent contemplates optimization methods for 3DCRT and IMRT. Ex. 1003 at ¶136.

The '096 patent describes only stochastic optimization methods, specifically, simulated annealing, and admits that such methods were known in the art. Ex. 1003 at ¶¶137-138. Indeed, the Detailed Description of the '096 patent begins with this admission: "Simulated annealing radiotherapy planning (SARP) methods are well known in the art to compute optimized radiation beam arrangements to meet objective parameters of a physician with regard to conflicting treatment objectives of a tumor volume and its surrounding structures." Ex. 1001 at 5:3-7. These "[e]xisting SARP methods utilize systematic algorithms to calculate a proposed, optimized beam arrangement." *Id.* at 5:7-9.

The '096 patent further indicates that its "invention" is limited to the cost function for such a optimization method disclosed in column 5. Ex. at 1003 at ¶139.

Figure 2 is purported to provide "a procedure for creating a treatment plan utilizing the system of the present invention." Ex. 1001 at 6:3-4. The process through optimization is described in columns 5 to 6, but the '096 patent admits at column 8, lines 41-44, that ***"[e]xcept for the foregoing detailed description of the cost function*** utilized in the present system, ***the details of the foregoing simulated annealing techniques are known in the art***."

The '096 patent is directed to a specific cost function for use in simulated annealing radiotherapy planning systems, and states "the SARP method will produce an optimized treatment plan, based on the treatment objectives as expressed by the cost function incorporated in the SARP algorithm." *Id.* at 5:50-53.

The cost function provides for a "determination of whether, when any change is made to the strengths of the beams being used to treat the patient, the resultant dose distribution is closer to the result desired by the user." *Id.* at 10:37-40; Ex. 1003 at ¶140. The patent explains the cost function with respect to "familiar CDVH curves 100, 200" shown in Figures 3, 4 (Figure 1, below), which it says "are used . . . to establish partial volume data representing dosage limits and other parameters . . . for each target and structure to establish the input parameters for the cost function of the present invention . . . ." Ex. 1001 at 6:48-56.

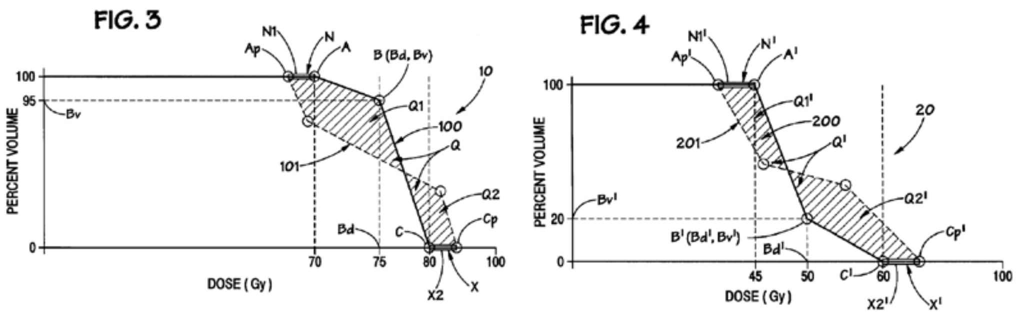

Figure 1. Figures 3 and 4, ’096 patent.

These CDVH curves “are created from partial volume data” that “generally describes what percent of the volume of a tumor or structure can receive how much dose.” Ex. 1001 at 6:59-60, 6:67-7:1; Ex. 1003 at ¶142. Such CDVHs and use of partial volume data, including identifying dosage limits on a CDVH, was known. *Id.* at ¶141-42.

The patent further states that, “[i]n the cost function of the present invention, each region, or zone, of the CDVH is assigned a relative weight, according to the importance of that region, or zone, of the CDVH. A zone cost is then calculated for the target and each structure,” and the cost is the sum of the zone costs. Ex. 1001 at 13:4-8, 19-32. “[T]he cost function of the present invention” is defined as the sum of these costs for the target and structure(s). *Id.* at 9:10-10:50.

The patent states that a beam arrangement optimized with the foregoing cost function “optimal beam arrangement is arrived at by computationally increasing the proposed beam weight iteratively, incorporating cost functions to ensure that an iterative change in the beam weight would not result in an unacceptable exposure to the volumes of tissue or other structures being subjected to the proposed dose." *Id.* at 5:39-44. "Patient Treatment" is the result of final step 808 in Figure 2. The '096 patent explains this only by stating, "the Delivery System step 808 is accomplished . . . in order to treat the tumor in the patient." Ex. 1001 at 16:34-37. The '096 patent does not provide any other explanation regarding application of an optimized radiation beam arrangement to a patient.

A. Relevant Prosecution History

U.S. Patent Application No. 09/320,980, which resulted in the '096 patent, was filed on May 27, 1999. *See* Ex. 1002 at 6. This application claims priority to US Provisional Patent Application No. 60/087,049, filed on May 27, 1999. *Id.* at 11.

Other than a Notice to File Missing parts that cited a missing inventor oath or declaration, and a missing filing fee, there were no intervening office actions from the Office. *Id*. at 69. The Examiner allowed the claims of the '980 application on September 7, 2000. *Id*. at 86. The Examiner did not consider the references in this Petition.

In the Notice of Allowance on September 7, 2000, the Examiner indicated that the prior art did not disclose:

> In the method and apparatus claimed, the claims address a method and apparatus of determining an optimized radiation beam arrangement for applying radiation to a tumor target where correspondence of a

> proposed beam arrangement with a CDVH is used and the radiation beam intensity is increased or decreased if the change leads to greater correspondence, or a CDVH is used as part of an iterative algorithm using a cost function to calculate correspondence of partial volume data associated with the proposed radiation beam arrangement with the partial volume data associated with the desired dose prescription, or providing the user with a range of input values indicating the importance of the values or the objects being irradiated. This feature is neither shown nor fairly suggested in the prior art.

Id. at 88. Contrary to this conclusion, the prior art references (individually or in combination) relied upon in this Petition disclose or suggest correspondence of a proposed beam arrangement with a CDVH as part of an interative algorithm.

B. Cited References

1. Niemierko-RONSC

Niemierko-RONSC discloses "[a] new algorithm for the optimization of 3-dimensional radiotherapy plans . . .[t]he RONSC algorithm (Random Optimization with Non-linear Score functions and Constraints)." Ex. 1004 at Abstract. It is "based on the idea of random search in the space of feasible solutions" and the author's "previous experience with mathematical programming algorithms . . . , especially with the refreshing idea of simulated annealing." *Id.* at Abstract, 91. The new algorithm "takes advantage of some specific properties of the dose distribution and derivable information such as dose-volume histograms." *Id.* at Abstract; Ex. 1003 at ¶¶159-166.

2. Goitein-1992

Goitein-1992 summarizes the use of dose-volume histograms and statistics in 3D radiation therapy treatment planning. Dr. Goitein explains the need to reduce the dimensionality of 3D treatment plans for purposes of comparing them, and the importance of visual displays enabling such comparison. He notes, "DVH's were first introduced precisely in order to compare treatment plans," citing his own work from 1983, and states acceptance of DVHs "has been rapid and widespread." Ex. 1006 at 251. Goitein-1992 explains how dose-volume histograms are created, interpreted, and used to compare and evaluate treatment plans. *Id.* at 251-52. He discusses use of dose statistics, which are "really nothing more than points on a cumulative DVH." *Id.* at 254. He notes that "minimum dose and dose range are often used as driving constraints on target volumes" and "maximum dose is often used as a driving constraint on a normal tissue volume," and that "[i]t is possible to assign a number that represent the extent to which a particular constraint is or is not met." *Id*.; Ex. 1003 at ¶¶167-172.

3. Mohan-1994

Mohan-1994 explored "the applicability of the inverse radiotherapy technique for designing optimized intensity distributions to achieve a desired dose distribution." Ex. 1008 at Abstract. Mohan-1994 used software developed by Bortfeld to find "optimum intensity distributions in a set of beams arranged around the target volume" subject to "constraints on the surrounding normal tissue dose." *Id.* at Abstract. Mohan-1994 "evaluated results both qualitatively and quantitatively using dose distribution displays[and] dose-volume histograms." *Id.* Importantly, Mohan studied two clinical cases, one of whom "was treated with the 3D conformal plan." *Id*. at 236; Ex. 1003 at ¶173.

VII. PERSON OF ORDINARY SKILL IN THE ART ("POSITA")

The level of skill in the art is generally evidenced by the prior art references. *See Chore-Time Equip., Inc. v. Cumberland Corp.*, 713 F.2d 774 (Fed. Cir. 1983); *see also Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). A POSITA would have undergraduate degree in science, computer science, engineering or math, and have additional training in radiation dosimetry, medical physics, medicine, or an equivalent field of study, with at least 2-3 years of computer programming experience and some clinical experience in radiation therapy or radiation therapy treatment planning. Ex. 1003 at ¶62.

VIII. CLAIM CONSTRUCTION (37 C.F.R. §42.104(B)(3))

In this proceeding, Petitioner submits that the claims should be construed in accordance with their ordinary and customary meaning as understood by one of ordinary skill in the art and the prosecution history. 37 C.F.R. 42.100(b).

ARGUMENTS

The Challenged Claims are unpatentable in view of the references cited for each ground below. Petitioner's arguments here are supported by the testimony of Joao Seco, Ph.D., Ex. 1003, which is incorporated by reference in full with respect to each claim below.

#	Grounds	Claims
I	§103 - Niemierko-RONSC	1, 18, 31, 32 and 34
II	§103 - Niemierko-RONSC in view of Goitein-1992	21, 22, 33, 37, 38, 40, 43, 45 and 46
III	§103 - Niemierko-RONSC in view of Mohan-1994	36
IV	§103 - Niemierko-RONSC in view of Goitein-1992 in further view of Mohan-1994	23, 24, 44

IX. GROUND #1: NIEMIERKO-RONSC COMPARED TO CLAIMS 1, 18, 31, 32 and 34

Niemierko-RONSC renders each of claims 1, 18, 31, 32 and 34 obvious.

A. Claim 1. "A method of determining an optimized radiation beam arrangement for applying radiation to a tumor target volume while minimizing radiation of a structure volume in a patient, comprising the steps of…"

To the extent that the preamble is limiting, Niemierko-RONSC discloses "***A method of determining an optimized radiation beam arrangement***," ("A new algorithm for the optimization of 3-dimentional radiotherapy plans is presented," Ex.

1004 at Abstract. "We term the algorithm RONSC which stands for: Random Optimization with Non-linear Score functions and Constraints." *Id.* at 91 ¶6. "[C]linically useful results can be obtained by limiting the optimization to . . . the beam weights and we have restricted ourselves to this case in this paper." *Id.* at 92 ¶1; *see also id.* at 92 ¶1.).

Niemierko-RONSC also discloses the algorithm is "***for applying radiation to a tumor target volume while minimizing radiation of a structure volume in a patient***," (RONSC is intended "to be able to reflect, as closely as possible, the main goal of radiotherapy, that is, eradication of the tumor tissue while the normal tissues are spared." *Id.* at 91 ¶5; *see also* 89 ¶1.).

See Ex. 1003 at ¶¶207-08.

Claim 1[a]: "using a computer to computationally obtain a proposed radiation beam arrangement;

Niemierko-RONSC discloses "***using a computer to computationally***," ("The optimization problem . . . is computationally very demanding. Ex. 1004 at 92 ¶¶1, 2. "The heuristic algorithm we have developed and presented here... allows one to find an optimal solution within minutes on presently available standard computer workstations." *Id.* at 97 ¶7.).

Niemierko-RONSC discloses "***obtain a proposed radiation beam arrangement***," ("[C]linically useful results can be obtained by limiting the optimization to . . . the beam weights and we have restricted ourselves to this case in this paper." *Id.*).

Ex. 1003 at ¶¶210-11.

Claim 1[b]: "using a computer to computationally change the proposed radiation beam arrangement iteratively,"

Niemierko-RONSC discloses "***using a computer to computationally***" as shown above in Section X.A.a and incorporated here.

Niemierko-RONSC discloses "***change the proposed radiation beam arrangement iteratively***," ("The parameters of the model (i.e. beam weight) are non-negative." Ex. 1004 at 92 #1. "The RONSC algorithm is implemented as follows:

> **1.** A starting point, $\overline{x}$ (the set of beam weights), is arbitrary[sic] selected.. . . .
>
> **2, 3.** Linear constraints are examined and[normalized]. . . .
>
> **4.** All parameters are normalized . . . .
>
> **5, 6.** Non-linear constrains . . . are examined and[if not satisfied, normalized] . . . .
>
> **7.** Parameters are normalized again . . . .
>
> **8.** Logical constraints are examined and if they are not satisfied a new solution is generated.
>
> **9.** When necessary, a penalty function is calculated.
>
> **10.** The value of the objective function (with penalty function) is calculated and compared with the best value found so far. If the new value is greater than the old one, the new solution (the $\overline{x}$ of the current iteration) becomes the new "optimal" solution 1. . .

> **11.** A new guess at a solution ($\overline{x}^{new}$) is made. This is done by random selection of a new point within a hypercube which surrounds the best solution found so far. . . . The algorithm to pick ($\overline{x}^{new}$). . . is[provided in equations (10) and (11) and is a function of R_i]. R_i is a random number generated for each parameter x_i ($-1 < R_i < 1$). . . .
>
> **12.** After some user-defined number of iterations . . . the size of the space within which solutions are sought is decreased . . . .
>
> **13.** The stopping criteria are inspected. The search will be stopped (and the best solution found presented as the optimal solution) when at least one of three criteria is fulfilled: . . .
>
> **14.** If none of the stopping criteria are met, steps 2-13 are repeated."

Id. at 93 ¶2 to 94 #14. *See also id.* at Fig. 4, "A new solution is randomly generated inside the subsequently diminishing sub-space of feasible solutions.").

See Ex. 1003 at ¶¶213-14.

Claim 1[c]: "incorporating a cost function at each iteration to approach correspondence of a CDVH associated with the proposed radiation beam arrangement to a CDVH associated with a predetermined desired dose prescription;"

Niemierko-RONSC discloses "***a cost function***," (". . . an objective[i.e. cost] function which scores the plan is maximized subject to a set of constraints, that is, inequalities and equalities defining the space of feasible solutions. Mathematically, the optimization goal is to find a solution (a vector of variables of the model, $\overline{x}$), which maximizes the objective function f(x) in the space of feasible solutions Ω, (i.e., solutions which satisfy all constraints):

$$f(\hat{x}) = \max_{\bar{x} \in \Omega_0} f(\bar{x}) \qquad (1)$$

Figure 2. Objective Function f(x),Niemierko-RONSC.

where $\overline{x}$ is the desired optimum. The space of feasible solutions Ω_0 is defined by constraints as follows . . . :"

$$\Omega_0 = \{\bar{x} \in \Omega \subset R^n : \bar{g}(\bar{x}) \leq \bar{C}_g, \quad \bar{h}(\bar{x}) = \bar{C}_h \text{ and logic of } (\bar{g}, \bar{h})\} \qquad (2)$$

and

$$f: R^n \rightarrow R^1, \quad \bar{g}: R^n \rightarrow R^{m_g}, \quad \bar{h}: R^n \rightarrow R^{m_h}. \qquad (3)$$

Figure 3. Space of Feasible Solutions for f(x), Niemierko-RONSC.

Ex. 1004 at 91 ¶¶7-8.).

Niemierko-RONSC discloses "***incorporating a cost function at each iteration***," ("**10.** The value of the objective function (with penalty function) is calculated and compared with the best value found so far. If the new value is greater than the old one, the new solution (the $\bar{x}$ of the current iteration) becomes the new "optimal" solution, . . .". *Id*. at 93, #10. "**14.** If none of the stopping criteria are met, steps 2-13 are repeated." *Id.* at 94, #14; *see also* steps 2-9, which relate to the application of constraints and calculation of the penalty.)

Niemierko-RONSC also discloses "***to approach correspondence of a CDVH associated with the proposed radiation beam arrangement to a CDVH associated with a predetermined desired dose prescription***," ("The inverse approach posits an ideal dose distribution and attempts to determine beam weights and compensator shapes that lead to a physical solution that is "as close as possible" to the ideal." *Id.* at 90 ¶4. "In our heuristic approach it is easy to handle even complex constraints such as, for example, dose-volume constraints. . . . (Figure 5a and 5b)." *Id.* at 94 ¶¶2, 3; Figures 4, 5.).

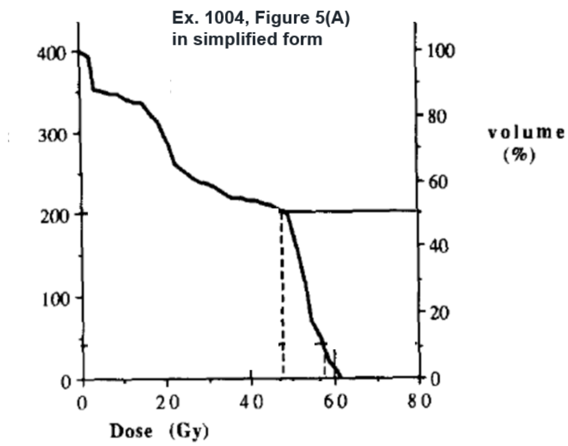

Figure 4. Simplified Fig. 5(A), Niemierko-RONSC.

Niemierko-RONSC shows (Figure 4 above) a "***CDVH associated with the proposed radiation beam arrangement***," (line starting at (dose 0, volume 100), going through (dose 48, volume 50) and sloping to (dose 62, volume 0). *Id.* at 95, Figure 5(A)).

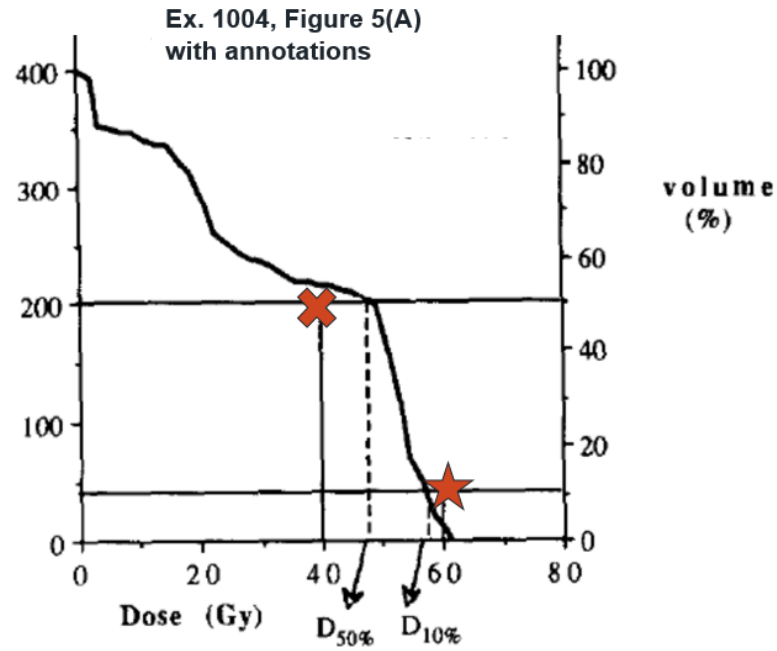

Figure 5. Annotated Fig. 5(A), Niemierko-RONSC.

Niemierko-RONSC shows (Figure 5 above) "***a predetermined desired dose prescription***," (Indicating: (1) as shown by the **star,** no more than 10% of the volume should receive a dose of more than 60 Gy; (2) as shown by the **X,** no more than 50% of the volume should receive a dose of more than 40 Gy. The "star" dose prescription is satisfied by the CDVH for the proposed beam arrangement, but the **X** dose prescription "is not satisfied." *Id.* at 95, Fig. 5(A) caption.).

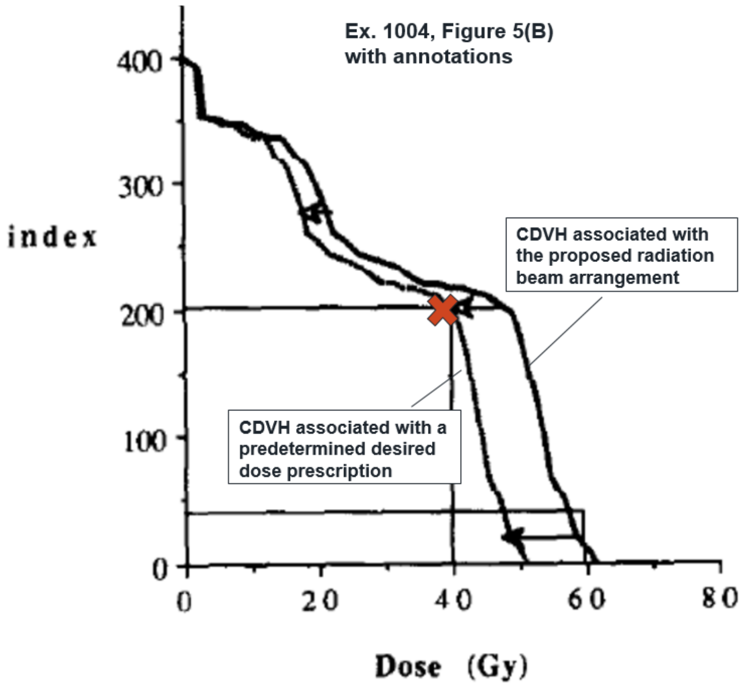

Figure 6. Annotated Fig. 5(B), Niemierko-RONSC.

Niemierko-RONSC shows (Figure 5 above) "***to approach correspondence of a CDVH associated with the proposed radiation beam arrangement to a CDVH associated with a predetermined desired dose prescription***," ("Constraints that are logical combinations of elemental constraints are clinically very useful. Their application is straightforward in our algorithm. The logical value of logically related constraints is examined after normalization of variables and, if satisfied, the objective function is calculated and evaluated; if not satisfied, the trial solution is discarded and a new solution is generated. Using the DVH in Figure 5 as an example; if the logical constraint was to have . . . the maximum dose to that organ smaller than 55 Gy, this logical constraint is satisfied (after re-normalization forced by the DVH constraints described above) because the maximum dose is less than 55 Gy . . . .Then, if the value of the objective function is greater than the previous optimum, this solution is accepted as the new optimum." *Id.* at 94 ¶4. Figure 5(B) shows "[t]he renormalized DVH" to the left of the DVH that was also shown in Figure 5(A), and arrows to the left indicate demonstrate that the "CDVH associated with the proposed radiation beam arrangement" "approach[es] correspondence" with "a CDVH associated with a predetermined desired dose prescription." *Id.* at Figure 5(B). *See also* Table 1, describing the objective functions and DVH constraints for three cases.).

See Ex. 1003 at ¶¶216-222.

Claim 1[d]: "comparing the dose distribution to a prescribed dose for the tumor volume and surrounding tissue structures, and"

Niemierko RONSC discloses "***comparing the dose distribution to a prescribed dose for the tumor volume and surrounding tissue structures, and increasing or decreasing radiation beam intensity if the change of the proposed beam arrangement leads to a greater correspondence to the desired dose prescription to obtain an optimized radiation beam arrangement***…" ("8. Logical constraints are examined and if they are not satisfied a new solution is generated." Ex. 1004 at 93 #8. "The logical value of logically related constraints is examined after normalization of variables and, if satisfied, the objective function is calculated and evaluated; if not satisfied, the trial solution is discarded and a new solution is generated." Id. at 94 ¶ 3. "The value of the objective function (with penalty function) is calculated and compared with the best value found so far. If the new value is greater than the old one, the new solution (the $\bar{x}$ of the current iteration) becomes the new "optimal" solution $\hat{x}$. Id. at 93 #10.)

Claim 1[e]: " increasing or decreasing radiation beam intensity if the change of the proposed beam arrangement leads to a greater correspondence to the desired dose prescription to obtain an optimized radiation beam arrangement."

Niemierko-RONSC discloses "***increasing or decreasing radiation beam intensity if the change of the proposed beam arrangement leads to a greater correspondence to the desired dose prescription to obtain an optimized radiation beam arrangement***," ("8. Logical constraints are examined and if they are not satisfied a new solution is generated." Ex. 1004 at 93 #8. "The logical value of logically related constraints is examined after normalization of variables and, if satisfied, the objective function is calculated and evaluated; if not satisfied, the trial solution is discarded and a new solution is generated." *Id.* at 94 ¶3. "The value of the objective function (with penalty function) is calculated and compared with the best value found so far. If the new value is greater than the old one, the new solution (the $\overline{x}$ of the current iteration) becomes the new "optimal" solution $\hat{x}$. *Id.* at 93 #10.).

See Ex. 1003 at ¶204.

B. Claim 18. "The method of claim 1, 2 or 14…"

Claim 18 depends from Claim 1. As disclosed in section X.A and incorporated here, Niemierko RONSC discloses this claimed limitation.

See Ex. 1003 at ¶225.

a. Claims 18[a]: "further comprising the step of allowing a radiation limit on the tissue structure to be exceeded by a set amount if such excess allows better conformation to the desired target CDVH curve."

As discloses in Section IX.A.b and IX.A.e and incorporated here, Niemierko RONSC discloses this claimed limitation.

"[T]he parameters are appropriately renormalized. . . . "In practice, one sometimes wishes to use two-sided constraints (e.g., require that the dose to the target lkie between a lower and an upper limit). Ex. 1004 at 92, ¶2.

See Ex. 1003 at ¶2.

C. Claim 31. "Apparatus for determining an optimized radiation beam arrangement for applying radiation to a tumor target volume while minimizing radiation of a structure volume in a patient, comprising a computer which is adapted to…"

To the extent that the preamble is limiting, for the reasons discussed in Section IX.A, Niemierko-RONSC discloses this limitation.

See Ex. 1003 at ¶264.

Claim 31[a]: "(a) computationally obtain a proposed radiation beam arrangement,"

For the reasons discussed in Section IX.A[a] and incorporated here, Niemierko-RONSC discloses this limitation.

See Ex. 1003 ¶266.

Claim 31[b]: "(b) computationally change the proposed radiation beam arrangement iteratively to conform to a target CDVH curve,"

For the reasons discussed in Section IX.A[b] and incorporated here, Niemierko-RONSC discloses this limitation.

See Ex. 1003 ¶268.

Claim 31[c]: " (c) incorporate a cost function at each iteration to approach correspondence of partial volume data associated with the proposed radiation beam arrangement to partial volume data associated with a predetermined desired dose prescription,"

For the reasons discussed in Section IX.A[c] and incorporated here, Niemierko-RONSC discloses this limitation.

See Ex. 1003 at ¶¶270-271.

Claim 31[d]: "(d) reject the change of the proposed radiation beam arrangement if the change of the proposed radiation beam arrangement leads to a lesser correspondence to the desired dose prescription and to accept the change of the proposed radiation beam arrangement if the change of the proposed radiation beam arrangement leads to a greater correspondence to the desired dose prescription to obtain an optimized radiation beam arrangement, and"

For the reasons discussed in Section IX.A[d], Niemierko-RONSC discloses this limitation.

See Ex. 1003 at ¶273.

Claim 31[e]: "(e) exceed the cost function by a set amount if such excess allows better conformation with the target CDHV curve."

For the reasons discussed in Section IX.B[a], Niemierko-RONSC discloses this limitation.

See Ex. 1003 at ¶273.

D. Claim 32. "The apparatus of claim 31…"

Claim 32 depends from claim 31. As discussed in Section IX. C and incorporated here, Niemierko-RONSC discloses the claimed limitation.

See Ex. 1003 at ¶276.

b. Claim 32[a]: "wherein the proposed radiation beam arrangement is changed by changing the beam weights."

As discussed in Section IX.A.b and incorporated here, Niemierko-RONSC discloses the claimed limitation.

See Ex. 1003 at ¶¶278-79.

E. Claim 34. "Apparatus for determining an optimized radiation beam arrangement for applying radiation to a tumor target volume while minimizing radiation of a structure volume in a patient, comprising a computer, including…"

To the extent that the preamble is limiting, as discussed above in Section IX.A and incorporated here, Niemierko RONSC meets this claimed limitation.

See Ex. 1003 at ¶283.

Claim 34[a]: "means for computationally obtaining a proposed radiation beam arrangement;"

As discussed above in Section IX.A.a and incorporated here, Niemierko RONSC meets this claimed limitation.

See Ex. 1003 at ¶285.

Claim 34[b]: "means for computationally changing the proposed radiation beam arrangement iteratively to conform to a CDHV curve;"

As discussed above in Section IX.A.b and incorporated here, Niemierko RONSC meets this claimed limitation.

See Ex. 1003 at ¶287.

Claim 34[c]: "means for incorporating a cost function at each iteration to approach correspondence of partial volume data associated with the proposed radiation beam arrangement to partial volume data associated with a predetermined desired dose prescription;"

As discussed above in Section IX.A.c and incorporated here, Niemierko RONSC meets this claimed limitation.

See Ex. 1003 at ¶289.

Claim 34[d]: "means for rejecting the change of the proposed radiation beam arrangement if the change of the proposed radiation beam arrangement leads to a lesser correspondence to the desired dose prescription and accepting the change of the proposed radiation beam arrangement if the change of the proposed radiation beam arrangement leads to a greater correspondence to the desired dose prescription to obtain an optimized radiation beam arrangement; and"

As discussed above in Section IX.A.d and incorporated here, Niemierko RONSC meets this claimed limitation.

See Ex. 1003 at ¶292.

Claim 34[e]: "means for adapting the radiation beam arrangement to exceed the cost function by a set amount if such excess allows better conformation with the target CDHV curve."

As discussed above in Section IX.B.a and incorporated here, Niemierko RONSC meets this claimed limitation.

See Ex. 1003 at ¶294.

X. GROUND #2: NIEMIERKO RONSC IN VIEW OF GOITEIN COMPARED TO CLAIMS 21, 22, 33, 37, 38, 40, 43, 45 and 46

Niemierko-RONSC in combination with Goitein-1992 renders claims 21, 22, 33, 37, 38, 40, 43, 45 and 46 obvious.

A. Claim 21. "A method of determining an optimized radiation beam arrangement for applying radiation to a tumor target volume while minimizing radiation of a structure volume in a patient, comprising the steps of…"

To the extent the preamble is limiting, Niemierko RONSC discloses "***A method of determining an optimized radiation beam arrangement,***" ("A new algorithm for the optimization of 3-dimentional radiotherapy plans is presented," Ex. 1004 at Abstract. "We term the algorithm RONSC which stands for: Random Optimization with Non-linear Score functions and Constraints." *Id.* at 91 ¶ 6. "[C]linically useful results can be obtained by limiting the optimization to a subset of possible parameters, namely the beam weights and we have restricted ourselves to this case in this paper." *Id.* at 92 ¶ 1. "The parameters of the model (i.e. beam weight) are non-negative." *Id.* at 92 #1.)

Niemierko RONSC also discloses the algorithm is "***for applying radiation to a tumor target volume while minimizing radiation of a structure volume in a patient***" ("Optimization of radiation therapy is a very important and, at the same time, a very difficult problem…[with] the principle goal of radiotherapy [being]…the complete depletion of tumor cells while preserving normal structures…" *Id.* at 89 ¶ 1. The disclosed algorithm is intended "to be able to reflect, as closely as possible, the main goal of radiotherapy, that is, eradication of the tumor tissue while the normal tissues are spared." *Id.* at 91 ¶ 5.)

See Ex. 1003 at ¶¶228-29.

Claim 21[a] "(a) determining a desired CDVH associated with each target and structure;"

Goitein discloses "***associated with each target and structure***," ("The possibility of knowing the detailed dose distribution has a particular impact on normal tissue constraints. Whereas in the past it was usual to specify a single dose constraint for an organ, ie, no more than 25 Gy to the lung, it is now realistic to specify dose-volume constraints, ie, "no more than 25 Gy to 25% of the lung", or more elaborately, "no more than 15 Gy to half the lung; and no more than 25 Gy to 25% of the lung; and no more than 50 Gy to 10% of the lung". Even target volume (TV) dose constraints can be tailored: "minimum TV dose, 65 Gy; and at least 95% of the TV must receive at least 70 Gy; and maximum TV dose, 80 Gy". Goitein 1992 at 247 ¶ 6.)

Goitein discloses "determining a desired CDVH" Goitein 1992 also discloses "wherein the partial volume data is represented as a CDVH," ("A cumulative DVH is a graph of volume plotted against dose (horizontal axis), where the interpretation of the graph is that the ordinate of a point on the graph represents the volume which receives at least the dose associated with the point's abscissa; i.e., receives that dose or more. By definition, then, the value at the dose origin will be the full volume of the volume of interest because the entire volume receives at least zero dose… To determine the value of a cumulative DVH at any dose, one computes the area of the corresponding differential DVH to the right of that dose (since the cumulative DVH is that volume which receives the specified dose or more." Goitein 1992 at 251 ¶1-252 ¶2. Fig. 5 (reproduced below) illustrates a "[s]chematic representation indicating how differential and cumulative DVHs are constructed." *Id.* 1992 at 251 (Fig. 5).)

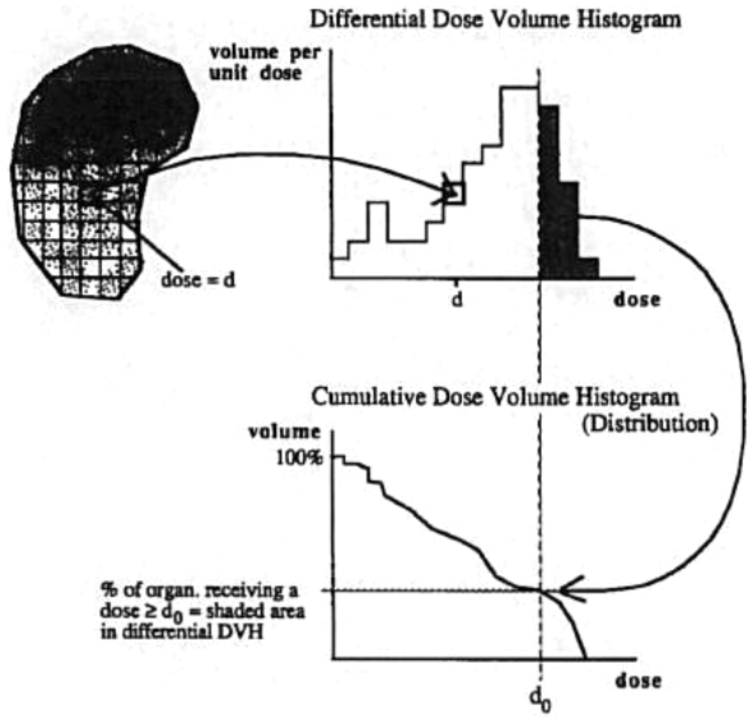

Figure 5. Schematic representation indicating how differential and cumulative DVHs are constructed.

A POSITA would have reason to refer to Goitein 1992, in view of Niemierko RONSC, because Niemierko RONSC discloses partial volume data and CDVHs (Figure 5) and Goitein discusses the relationship between partial volume data and CDVHs. In addition, the author of Niemierko RONSC thanks the author of Goitein 1992 for "helpful discussion." Niemierko RONSC at 89, *Acknowledgments.*

See also Ex. 1003 at ¶¶ 231-233.

Claim 21[b] "(b) using a computer to iteratively compare a cost of a radiation beam arrangement proposed during a given iteration to a radiation beam arrangement proposed during the previous iteration based on the relative costs associated with the proposed radiation beam arrangement, the costs being calculated by…"

As disclosed above in Section IX.A.c and incorporated here, Niemierko RONSC discloses “***a cost function***,” “***to determine a cost of the change to the set of proposed beam weights***,” “***compare a cost of a radiation beam arrangement proposed during a given iteration to a radiation beam arrangement proposed during the previous iteration based on the relative costs associated with the proposed radiation beam arrangement***,”

As disclosed above in Section IX.A.b and incorporated here, Niemierko RONSC discloses “***using a computer to iteratively***.”

Dr. Seco noted in his declaration that the “objective function” of Niemierko RONSC is a “cost function” as that term is used in the ’096 patent. The terms “objective function” and “cost function” are often used interchangeably in mathematical optimization and have similar meanings. The meaning of the term “objective function” may be more inclusive than the meaning of the term “cost function.” This is because an objective function may be maximized or minimized as part of an iterative optimization process, while a cost function is usually minimized. Niemierko RONSC discusses maximization of the objective function, while the ’096 patent discussed minimization of the cost function. But as noted in Niemierko RONSC, “It can easily be shown that minimization (as opposed to maximization) of an objective function and the use of constraints with the opposite direction of inequality to that used in expressions 1 or 2, can be resolved into the general form expressed in equations l-2.” *Id.* at 91 ¶ 10.

See also Ex. 1003 at ¶¶234-239.

Claim 21[c] “(1) determining a CDVH associated with each target and structure based on the proposed radiation beam arrangement of a given iteration;”

Niemierko RONSC discloses “***determining a CDVH associated with each target and structure based on the proposed radiation beam arrangement of a given iteration***,” (“In our heuristic approach it is easy to handle even complex constraints such as, for example, dose-volume constraints. To minimize the computational burden we use points randomly distributed throughout the volume(s) of interest.” *Id.* at p. 94R ¶1)

See also Ex. 1003 at ¶241.

Claim 21[d]: “(2) assigning cost zones to the desired CDVH and the proposed CDVH of a given iteration associated with each target and structure;”

Goitein 1992 discloses “***assigning cost zones to the desired CDVH and the proposed CDVH of a given iteration associated with each target and structure***,” (“It is possible to assign a number that represents the extent to which a particular constraint is or is not met, or to represent the degree of dose inhomogeneity within a target volume. This may be useful in interactive optimization where the user can observe the score(s), as well as the other estimators of the plan, while adjusting one or more of the free parameters, and, possibly, automated optimization schemes. Such scores are inherent in many of the published approaches to optimization. Ex. 1006 at 254 ¶6.”).

Claim 21[e]: “(3) assigning a weight value to each cost zone of each CDVH associated with each target and structure;”

As discloses in Section IX.A.b and incorporated here, Niemierko RONSC discloses this claimed limitation

Claim 21[f]: “(4) for each target and structure, multiplying the weight value of each zone by the quotient of a value representing the area of the zone of the CDVH associated with the proposed radiation beam arrangement and a value representing the area of the zone of the CDVH associated with the desired radiation beam arrangement;”

Goitein 1992 discloses “***assigning cost zones to the desired CDVH and the proposed CDVH of a given iteration associated with each target and structure***,” (“It is possible to assign a number that represents the extent to which a particular constraint is or is not met, or to represent the degree of dose inhomogeneity within a target volume. This may be useful in interactive optimization where the user can observe the score(s), as well as the other estimators of the plan, while adjusting one or more of the free parameters, and, possibly, automated optimization schemes. Such scores are inherent in many of the published approaches to optimization. ” Ex. 1006 at 254 ¶6).

See also Ex. 1003 at ¶245.

Claim 21[g]: " (5) summing the results of step (4) for each zone of each CDVH of each target and structure to obtain a total dosage cost;"

Niemierko RONSC discloses "(5) summing the results of step (4) for each zone of each CDVH of each target and structure to obtain a total dosage cost," ("The space of feasible solutions Q0 is defined by constraints as follows (Figure 1 shows a 2-dimensional example): [Equation 2 reproduced below]…"Ex. 1006 at 254 ¶6.").

$$\Omega_0 = \{\bar{x} \in \Omega \subset R^n : \bar{g}(\bar{x}) \leq \bar{C}_g, \quad \bar{h}(\bar{x}) = \bar{C}_h \text{ and logic of } (\bar{g}, \bar{h})\} \quad (2)$$

See also Ex. 1003 at ¶247.

Claim 21[h]: "(c) increasing or decreasing radiation beam intensity if the change of the proposed beam arrangement leads to a greater correspondence to the desired dose prescription;"

As disclosed in Section IX.B.a and incorporated here, Niemierko RONSC discloses this claimed limitation.

Niemierko RONSC discloses "***increasing or decreasing radiation beam intensity if the change of the proposed beam arrangement leads to a greater correspondence to the desired dose prescription***," ("8. Logical constraints are examined and if they are not satisfied a new solution is generated." Ex. 1004 at 93 #8. "The logical value of logically related constraints is examined after normalization of variables and, if satisfied, the objective function is calculated and evaluated; if not satisfied, the trial solution is discarded and a new solution is generated." *Id.* at 94 ¶ 3. "The value of the objective function (with penalty function) is calculated and compared with the best value found so far. If the new value is greater than the old one, the new solution (the $\overline{x}$ of the current iteration) becomes the new "optimal" solution $\hat{x}$. *Id.* at 93 #10.)

See also Ex. 1003 at ¶249.

c. Claim 21[i]: "(d) allowing a radiation limit on the tissue structure to be exceeded by a set amount if such excess allows better conformation to the desired target CDVH curve; and"

As discussed above in Section IX.B.a and incorporated here, Niemierko RONSC discloses this limitation.

See also Ex. 1003 at ¶251.

d. Claim 21[j]: "(e) repeating steps b through d until the proposed radiation beam arrangement has obtained an optimized radiation beam arrangement."

As discussed above in Sections IX.A.b and incorporated here, Niemierko RONSC discloses this claimed limitation.

See also Ex. 1003 at ¶253.

B. Claim 22. "The method of claim 21…"

Claim 22 depends from claim 21. As discussed above in Section X.A, Niemierko RONSC and Goitein 1992 disclose the claimed limitation.

See also Ex. 1003 at ¶254.

e. Claim 22[a]: "wherein the proposed radiation beam arrangement is calculated using simulated annealing radiation therapy planning methods."

Niemierko RONSC discloses ***wherein the proposed radiation beam arrangement is calculated using simulated annealing radiation therapy planning methods***," ("We based our approach on our previous experience with mathematical programming algorithms (7, 19, 20), especially with the refreshing idea of simulated annealing (references omitted)…" Ex. 1008 at 91R ¶2.)

See also Ex. 1003 at ¶256.

C. Claim 33. "The apparatus of claim 31…"

Claim 33 depends from claim 31. As discussed above in IX.C and incorporated here, Niemierko-RONSC discloses all of the claimed limitations.

See Ex. 1003 ¶280.

a. Claim 33[a]: "further comprising: a conformal radiation therapy apparatus in communication with the computer for applying the optimized radiation beam arrangement to the patient."

Niemierko-RONSC discloses "***conformal radiation therapy***," ("A clinically interesting and mathematically challenging type of constraint is the requirement to use in a plan exactly N beams. . . . This approach is quite natural because beams with relatively small weight contribute relatively less to the overall dose distribution, and rejecting them from the plan is only a small perturbation of the dose distribution." Ex. 1004 at ¶3; Table I. Optimization of beam weights, together with the use of dose volume constraints, indicates that the IMRT treatment plans optimized by RONSC were "conformal radiation therapy" plans.).

Niemierko-RONSC discloses "***applying the optimized radiation beam arrangement to the patient***," ("[O]ptimization of treatment plans in radiation therapy has not met with broad clinical acceptance. . . . previous investigations, . . . have short-changed the extremely difficult problem of computing clinically relevant objective functions. . . . No existing algorithm seemed to meet these requirements, so we were led to develop a new approach." Ex. 1004 at 91 ¶¶4-5. "[W]e have applied the RONSC algorithm to about a dozen clinical cases . . .." *Id.* at 95 ¶4. The RONSC algorithm . . . seems to be clinically useful." *Id.* at 97 ¶6.).

Thus, Niemierko-RONSC contemplated "applying" the optimized radiation beam arrangement. A POSITA would know that such radiation therapy plans were applied with a conformal radiation therapy apparatus.

Mohan-1994 discloses "***further comprising the step of applying the optimized radiation beam arrangement to the patient with a conformal radiation therapy apparatus***," ("The patient was treated with the 3D conformal plan plus the 9-Gy boost plan . . . ." Mohan-1994 at 236 ¶¶1-2.).

See Ex. 1003 at ¶¶ .

Mohan-1994 discloses "***. . . in communication with . . .***," ("Recent advances in computer technology and computer-controlled treatment machines have allowed us to attempt increasingly ambitious methods of planning and delivering complex 3D conformal treatments." Ex. 1008 at 232 ¶2. Mohan-1994"[W]e believe that computer-aided optimization is essential to the success of 3D conformal therapy. We envision that in the next important step for radiotherapy, most 3D conformal treatments will be optimized . . . . Such treatments will be delivered using computer-controlled machines employing dynamic multi-leaf collimators." *Id.* at 246 ¶2).

In view of these disclosures, it would have been obvious to a POSITA to have the radiation therapy apparatus for applying the radiation "in communication with" the computer as recited in claim 15.

See Ex. 1003 at ¶¶_.

D. Claim 37. "A method of determining an optimized radiation beam arrangement for applying radiation to at least one tumor target volume while minimizing radiation of at least one structure volume in a patient, comprising the steps of…"

To the extent that the preamble is limiting, for the reasons discussed in Section IX.A, Niemierko-RONSC discloses this limitation.

See Ex. 1003 at ¶298.-

b. Claim 37[a]: "determining desired partial volume data for each of the at least one target volume and structure volume associated with a desired dose prescription;"

Goitein discloses ***"for each of the at least one target volume and structure volume associated with a desired dose prescription,"*** ("[I]n the past it was usual to specify a single dose constraint for an organ, [e.g.] no more than 25 Gy to the lung, it is now realistic to specify dose-volume constraints,[e.g.] . . . "no more than 15 Gy to half the lung; and no more than 25 Gy to 25% of the lung; and no more than 50 Gy to 10% of the lung". Even target volume (TV) dose constraints can be tailored: "minimum TV dose, 65 Gy; and at least 95% of the TV must receive at least 70 Gy; and maximum TV dose, 80 Gy." Goitein-1992 at 247 ¶6.).

Goitein 1992 also discloses "***determining desired partial volume data for each of the at least one target volume and structure volume associated with a desired dose prescription***," ("A cumulative DVH is a graph of volume plotted against dose (horizontal axis), where the interpretation of the graph is that the ordinate of a point on the graph represents the volume which receives at least the dose associated with the point's abscissa; i.e., receives that dose or more. By definition, then, the value at the dose origin will be the full volume of the volume of interest because the entire volume receives at least zero dose… To determine the value of a cumulative DVH at any dose, one computes the area of the corresponding differential DVH to the right of that dose (since the cumulative DVH is that volume which receives the specified dose or more." Goitein 1992 at 251 ¶1-252 ¶2. Fig. 5 (reproduced below) illustrates a "[s]chematic representation indicating how differential and cumulative DVHs are constructed." *Id.* 1992 at 251 (Fig. 5).)

For the reasons discussed in Section IX.A.c and incorporated here, Niemierko-RONSC discloses "***determining desired partial volume data.***"

See Ex. 1003 at ¶¶_.

c. Claim 37[b]: "entering the desired partial volume data into a computer;"

Niemierko-RONSC discloses "***the partial volume data is entered directly into the computer***," ("[I]t is easy to handle even complex constraints such as . . . dose-volume constraints." Ex. 1004 at 94 ¶2. "[Q]uantitative information about the feasibility of a solution allows the user to modify the constraints, . . . we found that users almost always define the constraints in such a way that feasible solutions exist." Id. at 93 ¶2.).

Goitein-1992 also discloses "***the partial volume data is entered directly into the computer***," ("A valuable tool is to be able to use an interactive tool, such as a mouse-driven cursor, to point to a place on any one of the side-by-side images and have the value of the dose at that point be displayed numerically for each of the plans being compared." Goitein-1992Ex. 1006 at p. 249 ¶3.).

Ex. 1003 at ¶¶___.

d. Claim 37[c]: "in response to the desired partial volume data, using the computer to computationally approximate desired CDVHs for each of the at least one target and structure associated with the desired dose prescription; and"

For the reasons discussed in Section IX.A.c, Niemierko-RONSC disclose this limitation.

See Ex. 1003 at ¶¶_.

e. Claim 37[d]: "using the computer to computationally calculate the optimized radiation beam arrangement associated with the CDVHs approximated by the computer."

For the reasons discussed in Section IX.A.d, Niemierko-RONSC disclose this limitation.

See Ex. 1003 at ¶¶_.

E. Claim 38. "The method of claim 37, wherein the CDVHs approximated by the computer are approximated by the steps of …"

Claim 38 depends from claim 37 and, for the reasons discussed in Section X.D, Niemierko-RONSC and Goitein-1992 disclose all of the claimed limitations.

See Ex. 1003 at ¶311.

a. Claim 38[a]: "using the computer to computationally obtain a set of proposed beam weights;"

For the reasons discussed in Section IX.A.a and incorporated here, Niemierko-RONSC discloses this limitation.

See Ex. 1003 at ¶¶313-14.

b. Claim 38[b]: "using the computer to computationally change the set of proposed beam weights iteratively,"

For the reasons discussed in Sections IX.A.b and IX.A.c and incorporated here, Niemierko-RONSC discloses this limitation.

See Ex. 1003 at ¶¶315-20.

c. Claim 38[c]: "incorporating a cost function at each iteration to determine a cost of the change to the set of proposed beam weights; and"

For the reasons discussed in Section IX.A.c, Niemierko-RONSC discloses this limitation.

See Ex. 1003 at ¶¶.

d. Claim 38[d]: "rejecting the change to the set of proposed beam weights if the change to the set of proposed beam weights leads to a lesser correspondence to the desired CDVHs and accepting the change to the set of proposed beam weights if the change to the set of proposed beam weights leads to a greater correspondence to the desired CDVHs."

For the reasons discussed in Section IX.A.d, Niemierko-RONSC discloses this limitation.

See Ex. 1003 at ¶¶.

F. Claim 40. "The method of claim 38…"

Claim 40 depends from claim 38. As discussed in Section X.E and incorporated here, Niemierko RONSC and Goitein 1992 disclose this claimed limitation.

See Ex. 1003 at ¶¶.

a. Claim 40[a]: "further comprising the step of applying the optimized radiation beam arrangement to the patient with a conformal radiation therapy apparatus."

As discussed above in Section XI.C.a and incorporated here, Niemierko RONSC and Goitein 1992 disclose this claimed limitation.

See Ex. 1003 at ¶¶.

G. Claim 43. "A method of determining an optimized radiation beam arrangement for applying radiation to at least one tumor target volume while minimizing radiation to at least one structure volume in a patient, comprising the steps of…"

To the extent that the preamble is limiting, as discussed in Section IX.A and incorporated here, Niemierko RONSC discloses this claimed limitation.

See Ex. 1003 at ¶¶.

a. Claim 43[a]: "distinguishing each of the at least one tumor target volume and each of the at least one structure volume by target or structure type;"

"***Biologically Polymorphic***" means a structure for which "maximum dose received by any part of the structure is the primary factor in determining whether or not a complication occurs," such as the spinal cord. Ex. 1001 at 14:13-21. "***Biologically Uniform***" means a structure "where all portions of the BU structure perform the same function," such that "[o]verdosing one portion of the BU structure with a lethal dose to that portion of the BU structure may be acceptable as long as a sufficient portion of the BU structure is preserved." *Id.* at 14:24-31.

Ex. 1003 at ¶¶____.

b. Claim 43[b]: "determining desired partial volume data for each of the at least one target volume and structure volume associated with a desired dose prescription;"

Goitein discloses ***"for each of the at least one target volume and structure volume associated with a desired dose prescription**,"* ("[I]n the past it was usual to specify a single dose constraint for an organ, [e.g.] no more than 25 Gy to the lung, it is now realistic to specify dose-volume constraints,[e.g.] . . . "no more than 15 Gy to half the lung; and no more than 25 Gy to 25% of the lung; and no more than 50 Gy to 10% of the lung." Even target volume (TV) dose constraints can be tailored: "minimum TV dose, 65 Gy; and at least 95% of the TV must receive at least 70 Gy; and maximum TV dose, 80 Gy." Ex. 1006 at 247 ¶6.).

For the reasons discussed in Section X.C[a], Niemierko-RONSC discloses "***determining desired partial volume data.***"

Ex. 1003 at ¶¶____.

c. Claim 43[c]: "entering the desired partial volume data into a computer;"

Niemierko-RONSC discloses ***"the partial volume data is entered directly into the computer***," ("[I]t is easy to handle even complex constraints such as . . . dose-volume constraints." Ex. 1004 at 94 ¶2. "[Q]uantitative information about the feasibility of a solution allows the user to modify the constraints, . . . we found that users almost always define the constraints in such a way that feasible solutions exist." *Id.* at 93 ¶2.).

Goitein-1992 also discloses "***the partial volume data is entered directly into the computer***," ("A valuable tool is to be able to use an interactive tool, such as a mouse-driven cursor, to point to a place on any one of the side-by-side images and have the value of the dose at that point be displayed numerically for each of the plans being compared." Ex. 1006 at p. 249 ¶3.).

Ex. 1003 at ¶¶____.

d. Claim 43[d]: "providing a user with a range of values to indicate the importance of objects to be irradiated;"

Goitein 1992 discloses "***providing a user with a range of values to indicate the importance of objects to be irradiated***," ("The use of color-wash to represent dose, rather than the conventional isodose contours, is an important aid to rapid comprehension (for the 90% or so of individuals who have good color vision). A color-wash representation is one in which the color of an image at any point is based on the dose (or other displayed quantity) at that point. The intensity at any point, on the otherhand, is based on the pixel value of the CT data. As a result, the user has an impression of a semitransparent color overlay that simultaneously gives information about both dose and anatomy (this is, then, a 4D display)." at p. 248 ¶5.)

Ex. 1003 at ¶¶____.

e. Claim 43[e]: "providing the user with a range of conformality control factors; and"

Niemierko RONSC discloses "***using the computer to computationally calculate an optimized radiation beam arrangement***," ("13. The stopping criteria are inspected. The search will be stopped (and the best solution found presented as the optimal solution) when at least one of three criteria is fulfilled: (i) The solution has not been improved for the last 200 (or any user defined number) iterations; (ii) The size of the search space defined by the parameter MAX_STEP is smaller than the dose per fraction (or any user defined number); (iii) The total number of iterations reached the user defined limit—usually 400-1000." at p. 94L ¶#13.)

Ex. 1003 at ¶¶____.

f. Claim 43[f]: "using the computer to computationally calculate an optimized radiation beam arrangement."

Niemierko RONSC discloses "***using the computer to computationally calculate an optimized radiation beam arrangement***," ("In our heuristic approach it is easy to handle even complex constraints such as, for example, dose-volume constraints. To minimize the computational burden we use points randomly distributed throughout the volume(s) of interest. at p. 94R ¶1.)

Ex. 1003 at ¶¶____.

H. Claim 45. "The method of claim 43…"

Claim 45 depends from claim 43. As discussed in XI.G and incorporated here, Niemierko RONSC and Goitein 1992 disclose this claimed limitation.

Ex. 1003 at ¶¶____.

g. Claim 45[a]: "wherein the target or structure types are distinguished as either Biologically Uniform or Biologically Polymorphic."

As discussed in Section XI.G and incorporated herein, Niemierko RONSC and Goitein 1992 disclose this claimed limitation.

Ex. 1003 at ¶¶____.

I. Claim 46. "The method of claim 43…"

Claim 45 depends from claim 43. As discussed in XI.G and incorporated here, Niemierko RONSC and Goitein 1992 disclose this claimed limitation.

Ex. 1003 at ¶¶____.

h. Claim 46[a]: "wherein the optimized radiation beam arrangement is calculated using different cost function parameters depending on the target or structure type."

Niemierko RONSC discloses "wherein the optimized radiation beam arrangement is calculated using different cost function parameters depending on the target or structure type," ("Table 1 presents performance statistics for three examples. In the first, tumor control probability was used as the objective function, and the constraints included normal tissue complication probability as well as dose volume and dose constraints. Complication probability constraints are more time-consuming than simple dose or dose-volume constraints." at 96L ¶ 2.)

Ex. 1003 at ¶¶____.

XI. GROUND #3: NIEMIERKO RONSC IN VIEW OF MOHAN 1994 COMPARED TO 36 and 44

Niemierko-RONSC in view of Mohan-1994 renders claims 36 and 44 obvious.

A. Claim 36. "The apparatus of claim 34…"

Claim 36 depends from claim 34. As discussed in IX.E and incorporated here, Niemierko RONSC discloses this claimed limitation.

Ex. 1003 at ¶¶____.

i. Claim 36[a]: "further comprising a conformal radiation therapy apparatus in communication with the computer for applying the optimized radiation beam arrangement to the patient."

Mohan 1994 discloses "***further comprising a conformal radiation therapy apparatus in communication with the computer for applying the optimized radiation beam arrangement to the patient.***," ("Recent advances in computer technology and computer-controlled treatment machines have allowed us to attempt increasingly ambitious methods of planning and delivering complex 3D conformal treatments." Ex. 1008 at 232 ¶ 2. "The planner-designed plan has two components. In the first component, 6 fields were used to deliver a uniform dose of 72 Gy to the target volume. The apertures of all fields were shaped to conform to the target volume. An additional 9 Gy was delivered by a second coned-down plan consisting of 6 different beams for which apertures were reshaped to exclude the rectum…The plan was normalized so that the isodose line that encompasses the target volume (but maintains the rectum dose below the desired dose level) was set to the prescription dose…The patient was treated with the 3D conformal plan plus the 9-Gy boost plan as described above." Mohan 1994 at 236 ¶¶ 1-2. "[W]e believe that computer-aided optimization is essential to the success of 3D conformal therapy. We envision that in the next important step for radiotherapy, most 3D conformal treatments will be optimized . . . . Such treatments will be delivered using computer-controlled machines employing dynamic multi-leaf collimators." Id. at 246 ¶ 2).

Ex. 1003 at ¶¶____.

B. Claim 44. "The method of claim 43…"

Claim 44 depends from claim 43. As discussed in XI.G and incorporated here, Niemierko RONSC and Goitein 1992 disclose this claimed limitation.

Ex. 1003 at ¶¶____.

a. Claim 44[a]: "further comprising the step of applying the optimized radiation beam arrangement to the patient with a conformal radiation therapy apparatus."

As discussed above in Section XI.C.a and incorporated here, Niemierko RONSC and Goitein 1992 disclose this claimed limitation.

See Ex. 1003 at ¶¶.

XII. GROUND #4: NIEMIERKO RONSC IN VIEW OF GOITEIN 1992 IN FURTHER VIEW OF MOHAN 1994 COMAPRED TO CLAIMS 23 and 24

Niemierko-RONSC in view of Goitein-1992, in further view of Mohan-1994, renders claims 23 and 24 obvious.

A. Claim 23. "The method of claim 21…"

Claim 23 depends from claim 21. As discussed above in Section XI.A, Niemierko RONSC and Goitein 1992 disclose the claimed limitation.

See also Ex. 1003 at ¶___.

a. Claim 23[a]: "further comprising the step of applying the optimized radiation beam arrangement to the patient using a conformal radiation therapy apparatus."

Niemierko RONSC discloses "conformal radiation therapy," ("A clinically interesting and mathematically challenging type of constraint is the requirement to use in a plan exactly N beams out of a total of A4 designed beams. . . . This approach is quite natural because beams with relatively small weight contribute relatively less to the overall dose distribution, and rejecting them from the plan is only a small perturbation of the dose distribution." Id. at ¶3; Table III. Optimization of beam weights, together with the use of dose volume constraints, indicates that the treatment plans optimized by RONSC were "conformal radiation therapy" plans.)

Niemierko RONSC discloses "applying the optimized radiation beam arrangement to the patient," ("[O]ptimization of treatment plans in radiation therapy has not met with broad clinical acceptance. As we mentioned in a companion paper (22) it seems to us that one reason optimization attempts have not been successful is that previous investigations, in order to reduce the mathematical difficulties of the problem, have short-changed the extremely difficult problem of computing clinically relevant objective functions. . . . No existing algorithm seemed to meet these requirements, so we were led to develop a new approach." Ex. 1004 at 91 ¶¶ 4-5. "To date we have applied the RONSC algorithm to about a dozen clinical cases, as well as a few artificially created test cases. A typical clinical example is fully described in a companion report." Id. at 95 ¶4. The RONSC algorithm . . . seems to be clinically useful." Id. at 97 ¶ 6.)

According to Dr. Seco, These disclosure indicate that Niemierko RONSC contemplated the optimized radiation beam arrangement as required by limitation [a] of claim 6. A POSITA would know that such radiation therapy plans were applied with a conformal radiation therapy apparatus.

Mohan 1994 also discloses "further comprising the step of applying the optimized radiation beam arrangement to the patient using a conformal radiation therapy apparatus," ("The planner-designed plan has two components. In the first component, 6 fields were used to deliver a uniform dose of 72 Gy to the target volume. The apertures of all fields were shaped to conform to the target volume. An additional 9 Gy was delivered by a second coned-down plan consisting of 6 different beams for which apertures were reshaped to exclude the rectum…The plan was normalized so that the isodose line that encompasses the target volume (but maintains the rectum dose below the desired dose level) was set to the prescription dose…The patient was treated with the 3D conformal plan plus the 9-Gy boost plan as described above." Mohan 1994 at 236 ¶¶ 1-2.)

Dr. Seco opines that a POSITA would have reason to combine Niemierko RONSC and Mohan 1994 because both are directed to computer-implemented optimization of conformal radiation therapy treatment planning. In addition, Mohan 1994 references Niermierko RONSC as an example of optimization in which "all beam parameters except beam weights are pre-selected and beam weights are adjusted by the optimization process." Mohan 1994 at 233 ¶ 2, citing (43).

See also Ex. 1003 at ¶___.

B. Claim 24. "The method of claim 22…"

Claim 24 depends from claim 22. As discussed above in Section XI.B, Niemierko RONSC and Goitein 1992 disclose the claimed limitation.

See also Ex. 1003 at ¶257.

a. Claim 24[a]: "further comprising the step of applying the optimized radiation beam arrangement to the patient using a conformal radiation therapy apparatus."

As discussed above in Section XII.A.a and incorporated here, Niemierko RONSC, Goitein 1992 and Mohan 1994 disclose the claimed limitation.

See Ex. 1003 at ¶¶ 259-263.

XIII. MOTIVATION TO COMBINE CITED REFERENCES

A POSITA would have reason to combine Niemierko-RONSC with Goitein-1992 and Mohan-1994 to render obvious all of the Challenged Claims. This is indicated by an examination of the references themselves and supported by the testimony of Prof. Seco. Ex. 1003 at _.

Importantly, all three prior art references are directed to methods and tools of 3D radiation therapy treatment planning in 1992-1994, and the use of dose-volume data in such planning, including use of CDVHs to compare and evaluate treatment plans. A POSITA would be motivated to combine these references to achieve a more efficient and/or easier to use treatment planning system. In view of these commonalities in subject matter and the use of dose-volume data to address optimization and evaluation of 3DCRT plans, a POSITA would have reason to combine the relevant teachings of Niemierko-RONSC, Goitein-1992 and Mohan-1994. Ex. 1003 at ¶_____.

A POSITA would also know that Andre Niemierko and Michael Goitein co-authored many publications in the field of 3D radiation therapy treatment planning during this time, including those cited in Niemierko-RONSC and Goitein-1992, and would look to publications of each in view of publications by the other. Ex. 1003 at _____. Indeed, Niemierko-RONSC "thank[ed] Michael Goitein… for helpful discussions," which would provide a POSITA reason to look to other Goitein publications including Goitein-1992. Ex. 1003 at 184. In addition, Mohan-1994 cites the Niemierko-RONSC publication, as well as nine publications authored by Goitein, including four co-authored by Niemierko and Goitein. Ex. 1003 at 187. Mohan-1994 also discloses "employ[ing] an adaptation of Goitein's model." Ex. 1008 at 235.

XIV. SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS DO NOT NEGATE OBVIOUSNESS

It is Patent Owner's burden of production to provide evidence of secondary considerations. *Medtronic Inc.* v. *NuVasive Inc*., IPR2014-00087, Paper 44 at 21 (PTAB Apr. 3, 2015). However,

Petitioner is not aware of any secondary considerations that would demonstrate non-obviousness in view of the art relied on in this Petition. The only aspect of the claimed invention that Patentee indicated to be novel was the modified cost function, and Petitioner is not aware of any use of, acclaim for or copying of, the described modified cost function. Moreover, a strong showing of obviousness, as here, overcomes secondary considerations. *See*, e.g., *Leapfrog Enters, Inc*. v. *Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007); *Dow Chemical Co.* v. *Halliburton Oil Well Cementing Co.*, 324 U.S. 320, 330 (1945) ("[Secondary] considerations are relevant only in a close case.").

Petitioner also is not aware of any nexus between any alleged commercial success and "the merits of the claimed invention." *Ohio Willow Wood Co*. v. *Alps South, LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013); *Wyers* v. *Master Lock Co*., 616 F.3d 1231, 1246 (Fed. Cir. 2010) ("[f]or objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention.").

Petitioner reserves the right to provide a full rebuttal to any secondary consideration evidence provided during this proceeding.

XV. SUMMARY CHARTS

XVI. CONCLUSION

For the reasons set forth above, Elekta requests that the Board institute *IPR* of and cancel the Challenged Claims.

Dated: DRAFT

DRAFT

TAMARA D. FRAIZER
Squire Patton Boggs (US) LLP
1801 Page Mill Road, Suite 110
Palo Alto, CA 94304-1043
Telephone: (650) 843-3201
Facsimile: (650) 843-8777
Email: tamara.frazier@squirepb.com

Registration No.: _______________

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 6,038,283 contains, as measured by the word-processing system used to prepare this paper, 13,896 words. This word count does not include the items excluded by 37 C.F.R. §42.24 as not counting towards the word limit.

Dated: October 18, 2019

/Tamara D. Fraizer/
TAMARA D. FRAIZER
Squire Patton Boggs (US) LLP
1801 Page Mill Road, Suite 110
Palo Alto, CA 94304-1043
Telephone: (650) 843-3201
Facsimile: (650) 843-8777
Email: tamara.frazier@squirepb.com

Registration No.: 51,699

CERTIFICATE OF SERVICE

The undersigned certifies pursuant to 37 C.F.R. §42.6(e) and §42.105 that on October 21, 2019, a true and correct copy of the foregoing will be served via USPS Express Mail on the Patent Owner at the following correspondence address of record as listed on PAIR:

Buchanan Ingersoll & Rooney, PC
P.O. Box 1404
Alexandria, VA 22313-1404

and was served via electronic mail upon counsel of record for the Patent Owner in the litigation pending before the U.S. District Court for the Northern District of Georgia entitled *Best Medical International, Inc., v. Elekta Inc. and Elekta Limited*, Case No. 1:19-cv-03409.

Anand Mohan Erin M. Dunston Buchanan Ingersoll & Rooney, PC Suite 500 1737 King Street Alexandria, VA 22314-2727 anand.mohan@bipc.com erin.dunston@bipc.com	Jason P. Camillo Buchanan Ingersoll-Pittsburg 301 Grant Street One Oxford Centre, 20th Floor Pittsburgh, PA 15219 jason.camillo@bipc.com
Philip L. Hirschhorn Jennifer Liu Buchanan Ingersoll & Rooney, PC 9th Floor 640 Fifth Avenue New York, NY 10019 philip.hirschhorn@bipc.com jennifer.liu@bipc.com	John Weldon Harbin Meunier Carlin & Curfman, LLC Suite 1300 999 Peachtree Street NE Atlanta, GA 30309 jharbin@mcciplaw.com

Dated: October 18, 2019

/Tamara D. Fraizer/
TAMARA D. FRAIZER
Squire Patton Boggs (US) LLP
1801 Page Mill Road, Suite 110
Palo Alto, CA 94304-1043
Telephone: (650) 843-3201
Facsimile: (650) 843-8777
Email: tamara.frazier@squirepb.com

Registration No.: 51,699