



Analysis of patent innovation in the field of brachytherapy

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ABSTRACT

PURPOSE To characterize inventions and assess trends in brachytherapy innovation based on brachytherapy-related patents awarded across the past 2 decades and provide insights that will help inform future research and entrepreneurship in the field.

METHODS The United States Patent and Trademark Office database was searched for patents awarded between 1999 and 2018 with a classification code corresponding to the broadest brachytherapy search category. Patent characteristics were stratified and compared by geographic location, affiliation, and theme of invention.

RESULTS There were 202 brachytherapy-related patents awarded from 2009 to 2018, which indicates a 56% increase in patent productivity and brachytherapy innovation compared with the previous decade from 1999 to 2008. Patents had an industry affiliation in 83% of cases from 1999 to 2008 and in 76% of cases from 2009 to 2018. Meanwhile, academic participation in brachytherapy patent innovation rose from 4% to 11% in that time. The focus and theme of inventions evolved across time, with *radiation sources* being the most common theme from 1999 to 2008 and falling to third place in 2009–2018. Conversely, development of brachytherapy-related patents involving *exogenous agents* such as drug-conjugates, radiosensitizers, and adjuncts to treatment increased substantially in the subsequent decade. While no collaboration was observed between academia and industry between 1999 and 2008, notable partnerships emerged in the subsequent decade which amounted to almost 5% of all patents awarded between 2009 and 2018.

CONCLUSIONS There has been an increase in overall brachytherapy patent production over time, and this has been accompanied by a greater variety of distinct patent themes. Collaboration between industry and academia is rare. Knowledge of brachytherapy patents may inform future research innovation in this field. © 2020 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

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Introduction

Brachytherapy was invented over a century ago. Arrived at separately by Pierre Curie in 1901 and Alexander Graham Bell in 1903, this idea took hold of the oncology world and altered the landscape of cancer therapy. Radium sources were placed into tumor beds at St. Luke's Hospital in New York by 1905, whereas Dr. William Myers at Ohio State University began the development of several different radioisotopes including ¹²⁵I, ⁶⁰Co, and ¹⁹⁸Au for use in clinical brachytherapy.(1) The invention of radiation released through transperineally inserted needles soon followed in 1917, which heralded the beginning of interstitial prostate cancer brachytherapy.(2)

Innovation in the field of brachytherapy has continued, and inventors often seek patent approval for these advancements. Brachytherapy patents are classified by the United

States Patent and Trademark Office (USPTO) as utility patents which cover the creation or improvement of a machine, product, or process, and receive a patent term valid for 20 years from the date at which the application was filed. Using the USPTO database, this study aimed to characterize innovations within the field of brachytherapy in the past 2 decades. This information may provide insight into the characteristics of upcoming clinical advancements within the field and better inform future research and development in this area.

Methods

Institutional review board approval was not required as all information for this study was publicly available online. The USPTO website was searched for filed and awarded patents within the field of brachytherapy within the decade of January 1st, 2009 through December 31st, 2018, in addition to the previous decade from January 1st, 1999 through December 31st, 2009. Specifically, the current USPTO Cooperative Patent Classification code “A61N5/1001”, corresponding to the broadest brachytherapy search criteria

classified as “using radiation sources introduced into or applied onto the body; brachytherapy,” was applied in the appropriate fields. Characteristics of each patent were recorded to include patent file number, title, abstract, file date, award date, country of assignee, affiliation of assignee, and the number of inventors.

The time interval between patent filing and award by the USPTO was calculated for each patent from 2009 to 2018. Assignee affiliation was classified as individual, industry, academic, or combination of industry-academia. Cases of multiple assignees listed from differing affiliations were recorded and included in the analysis. Two reviewers (M.M. and A.V.P.) classified the theme of invention, which was assigned to each patent based on title and abstract claim of assignee. Definition of each patent theme was summarized as described (Table 1). Frequency of themes was assessed overall, and differences between academic, industry, and individual assignee themes were analyzed. Differences between U.S. and international patents were similarly evaluated. The number of patents awarded to each corporation and academic institution, location, and theme thereof was compiled and summarized for comparison.

Table 1
Descriptions of patent themes

Patent theme	Patent description
Treatment delivery	Radiotherapy procedure, for purposes of delivering radiation directly to tumor or specified tissue
Exogenous agents	Radiosensitizers and adjuncts to brachytherapy treatment
Radiation source	Material, apparatus, or method for generation of X-ray radiation or emission source
Microparticles	Microparticles used for radiotherapy, sensitization, or radioimaging
Treatment planning	Methods for enhancing treatment that include systems for detection, tracking, and placement of treatment
Body insert/catheter	Physical elements introduced into a body or cavity for purposes of delivering radiation
Positioning	Methods for arranging radiation treatment with respect to one or more regions of interest in a system
Radioisotope infusion system	Construction, maintenance, and operation of a strontium rubidium radioactive eluate system
Radiation shielding	Patents related to the protecting of nontarget structures during brachytherapy treatment
Radiation dosing	Inventions specifying mechanisms for measuring and applying precise amounts of radiation
Imaging	Technology that specifies imaging modalities used for or related to brachytherapy treatment
Radioactive seeds	Seeds implanted into target structures for delivery of radiation to intended site
Robotic tissue radiation applicator	Instrument for applying a radioactive substance to a biological tissue
Mobile radiation therapy structure	Integrated radiation setup and system dispatched to a patients home for delivery of brachytherapy treatment
Cardiac pacer	Pacing electrodes implanted for delivery of one or more intended pacing pulses
Fiducials	System and method for placement of object markers for purposes of enhanced planning within an imaging system
Calibration	Protocol and instrument specifying the measurement of dispensing of correct levels of radioactivity
Diagnostic test	Patents which describe tissue sampling, blood hormone measurement, or evaluation of a lesion for purposes of diagnosis
Pulse generation	Conductor including a carbon nanotube that contains radioactive particles for purposes of generating an electric current
Oral stenting device	Patent specifically related to a device for stabilizing the mouth and jaw for precise delivery of radiation
RNAi prostate cancer treatment	Local prolonged release of one or more nucleotide-based RNAi agents for treatment of prostate cancer
Fractionation	Method or protocol for delivery of radiation divided by specific time period and dosing
Device sterilization	Disinfection of surgical equipment including catheters used for brachytherapy
Respiratory gating	Control apparatus adapted to receive respiration state information and control the output of an X-ray source
Suture containing radioactivity	Suture containing beta radiation emitting element tritium embedded into polypropylene material
Spinal disc directed treatment	Implant element structured to have a therapeutic effect within a spinal disc
Sheath apparatus for X-ray probe	Cover material for a probe to allow air present within a void region to escape as the probe is inserted into a cavity

Table 2

International (Non-U.S.) patent awards by country from 2009 to 2018 vs. 1999–2008

A. Non-U.S. international patent productivity by country 2009–2018		
International country	Patent count (51 Patents)	%
The Netherlands	13	25.5
Germany	10	19.6
Canada	6	11.8
France	4	7.8
Israel	4	7.8
Switzerland	4	7.8
South Korea	2	3.9
China	2	3.9
Australia	1	2.0
Japan	1	2.0
Italy	1	2.0
Great Britain	1	2.0
Taiwan	1	2.0
Sweden	1	2.0
B. Non-U.S. international patent productivity by country 1999–2008		
Country	Patents	%
Sweden	10	33.33
Germany	8	26.67
The Netherlands	4	13.33
Belgium	2	6.67
Japan	1	3.33
Switzerland	1	3.33
Norway	1	3.33
Canada	1	3.33
Russia	1	3.33
Great Britain	1	3.33

Results

In total, 202 brachytherapy-related patents were awarded by the USPTO in the decade between January 1st, 2009 through December 31st, 2018, and 129 patents were awarded between January 1, 1999 through December 31, 2009. Of the most recent patents awarded from 2009 to 2018, 15% ($n = 30$) had one inventor, 26% ($n = 52$) had two inventors, 23% ($n = 46$) had three inventors, and 36% had 3 inventors (maximum number of 14 inventors; median of three inventors). The median time interval between patents being filed and awarded was 209 days (minimum of 102 days from filing to award, maximum of 1843 days).

The breakdown of patents' first assignee by country are presented in Table 2. The most common country of patents' first assignee was the United States by an overwhelming majority of all patents in each decade (75%, $n = 151$ from 2009 to 2018, 77%, $n = 99$ from 1999 to 2008). A breakdown of patents by individual states within the United States is presented in Table 3. The state of California led the way with roughly 30% of all patents in each decade.

Table 4 and Fig. 1 depict the themes assigned to the patents in each decade. A total of 24 unique themes were assigned to the 202 brachytherapy patents from 2009 to 2018

Table 3

U.S. patent productivity by state in 2009–2018 vs. 1999–2008

A. U.S. patent productivity by state 2009–2018		
U.S. state	U.S. patent count (151 patents)	%
California	48	31.8
New Jersey	27	17.9
Arizona	8	5.3
Minnesota	8	5.3
Pennsylvania	6	4.0
New York	6	4.0
Massachusetts	6	4.0
North Carolina	5	3.3
Ohio	5	3.3
Indiana	5	3.3
Florida	4	2.6
Montana	4	2.6
Colorado	3	2.0
Maryland	3	2.0
New Mexico	3	2.0
Washington	3	2.0
Virginia	3	2.0
Georgia	2	1.3
West Virginia	1	0.7
New Hampshire	1	0.7
B. U.S. patent productivity by state 1999–2008		
State	n	%
California	29	29.29
Massachusetts	23	23.23
Minnesota	15	15.15
Illinois	6	6.06
New York	5	5.05
North Carolina	3	3.03
Montana	3	3.03
Indiana	3	3.03
Florida	3	3.03
Georgia	3	3.03
Washington	1	1.01
Idaho	1	1.01
Michigan	1	1.01
Maryland	1	1.01
Ohio	1	1.01
New Jersey	1	1.01

(Table 4, Fig. 1). The three most common themes were *treatment delivery* (19.3%, $n = 39$), *exogenous agents* (15.8%, $n = 32$), and *radiation source* (9.4%, $n = 19$). The 151 patents filed from the United States exhibited similar themes with *treatment delivery* (23.8%, $n = 36$) and *exogenous agents* (17.2%, $n = 26$) being the two most common, followed by *radiation source* (7.9%, $n = 12$) and *microparticles* (7.9%, $n = 12$) tied for third most frequent. Of the 51 international patents in this study, the three most common themes were *radiation source* (13.7%, $n = 7$), *treatment planning* (13.7%, $n = 7$), and *radiation dosing* (13.7%, $n = 7$).

There were a total of 13 unique themes assigned to all patents awarded between 1999 and 2008, with *radiation source* (30.2%, $n = 39$), *treatment delivery* (29.5%, $n = 38$), and *body insert/catheter* (9.3%, $n = 12$)

Table 4
Overall frequency of brachytherapy-related themes from 2009 to 2018 vs. 1999–2008

(A) 2009–2018		
Theme	<i>n</i>	%
Treatment delivery	39	19.3
Exogenous agents	32	15.8
Radiation source	19	9.4
Microparticles	14	6.9
Treatment planning	12	5.9
Body insert/catheter	11	5.4
Positioning	10	5.0
Radioisotope infusion system	8	4.0
Radiation shielding	8	4.0
Radiation dosing	8	4.0
Imaging	7	3.5
Radioactive seeds	6	3.0
Robotic tissue radiation applicator	4	2.0
Mobile radiation therapy team structure	4	2.0
Cardiac pacer	4	2.0
Fiducials	3	1.5
Calibration	3	1.5
Diagnostic test	3	1.5
Pulse generation	2	1.0
Oral stenting device	1	0.5
RNAi-based prostate cancer treatment	1	0.5
Fractionation	1	0.5
Device sterilization	1	0.5
Respiratory gating	1	0.5
(B) 1999–2008		
Theme	<i>n</i>	%
Radiation source	39	30.2
Treatment delivery	38	29.5
Body insert/catheter	12	9.3
Radiation dosing	11	8.5
Imaging	8	6.2
Exogenous agents	5	3.9
Treatment planning	5	3.9
Radioactive seeds	3	2.3
Radiation shielding	2	1.6
Sheath apparatus for X-ray probe	2	1.6
Spinal disc directed treatment	1	0.8
Positioning	2	1.6
Suture containing radioactive element	1	0.8

constituting the three most common themes overall. Among the 99 U.S. patents awarded between 1999 and 2008, *treatment delivery* (33.3%, *n* = 33), *radiation source* (25.3%, *n* = 25), and *body insert/catheter* (10.1%, *n* = 10) were the most common themes. The most prominent themes observed among the 30 international patents awarded were *radiation source* (46.7%, *n* = 14), *radiation dosing* (23.3%, *n* = 7), and *treatment delivery* (16.7%, *n* = 5).

From 2009 to 2018 vs. 1999–2008, respectively, patents had an industry affiliation in 76% (*n* = 154) vs. 83% (*n* = 107) of cases, whereas 11% (*n* = 22) vs. 4% (*n* = 5) of patents were characterized by an academic affiliation and 5% (*n* = 10).

No collaboration between any academic institution and industry corporation was observed in the decade between

1999 and 2008. In contrast, there were 5% (*n* = 10) of instances in which an academic institution partnered with an industry corporation for creation of an invention between 2009 and 2018. Of all patents awarded, 8% (*n* = 16) vs. 13% (*n* = 17) were assigned to individual inventors. Appendix Table I shows a breakdown of themes across industry vs. academic vs. individual vs. collaborative patents.

Appendix Table II provides a breakdown of industrial patent production by company. From 2009 to 2018, Oraya Therapeutics Inc. led patent award productivity (*n* = 18), followed by Pop Test Oncology LLC (*n* = 10) and Bracco Diagnostics Inc. (*n* = 8). These top three companies accounted for almost one-quarter of all industry patent production (23.4%, *n* = 36 of 154). There were 19 companies which produced greater than two patents in the past decade, which accounted for over half of all patents awarded during this period (50.4%, *n* = 102 of 202) and approximately two-thirds of all industry-specific patents in this period (66%, *n* = 102 of 154). Individual industry patent leaders from 1999 to 2008 consisted of Photoelectron corporation from Massachusetts, United States (*n* = 14), Medtronic from California, United States (*n* = 13), and Radi Medical Systems from Sweden (*n* = 10). Overall, there were nine different companies responsible for production of more than two patents in this era, which accounted for approximately 65% of all industry patents produced (*n* = 70 of 107).

Appendix Table III provides a breakdown of academic patent production by academic institution. From 2009 to 2018, the University of Zurich (*n* = 3), Stanford University (*n* = 2), Johns Hopkins University (*n* = 2), University of New Mexico (*n* = 2), Korea Institute of Science and Technology (*n* = 2), Wake Forest University (*n* = 2), and Virginia Commonwealth University (*n* = 2) were responsible for production of multiple patents. From 1999 to 2008, the Regents of University of California was the only institution with two patents, whereas Duke University, Florida Institute of Technology, and University of Rochester were all responsible for producing one patent a piece.

Discussion

Within the last 2 decades, 331 patents related to brachytherapy have been granted to assignees from 18 different countries. There has been roughly a 50% increase in brachytherapy patent productivity in the last decade, resulting in increased diversity of individual countries, states, and distinct themes of focus in the most recent decade compared with the previous decade. Overall, there is greater variety in brachytherapy patent themes over time, although prominent themes remain on *treatment delivery*, *exogenous agents*, and *radiation source*. This study characterized brachytherapy patents over the last 2 decades to better inform future research in this area.

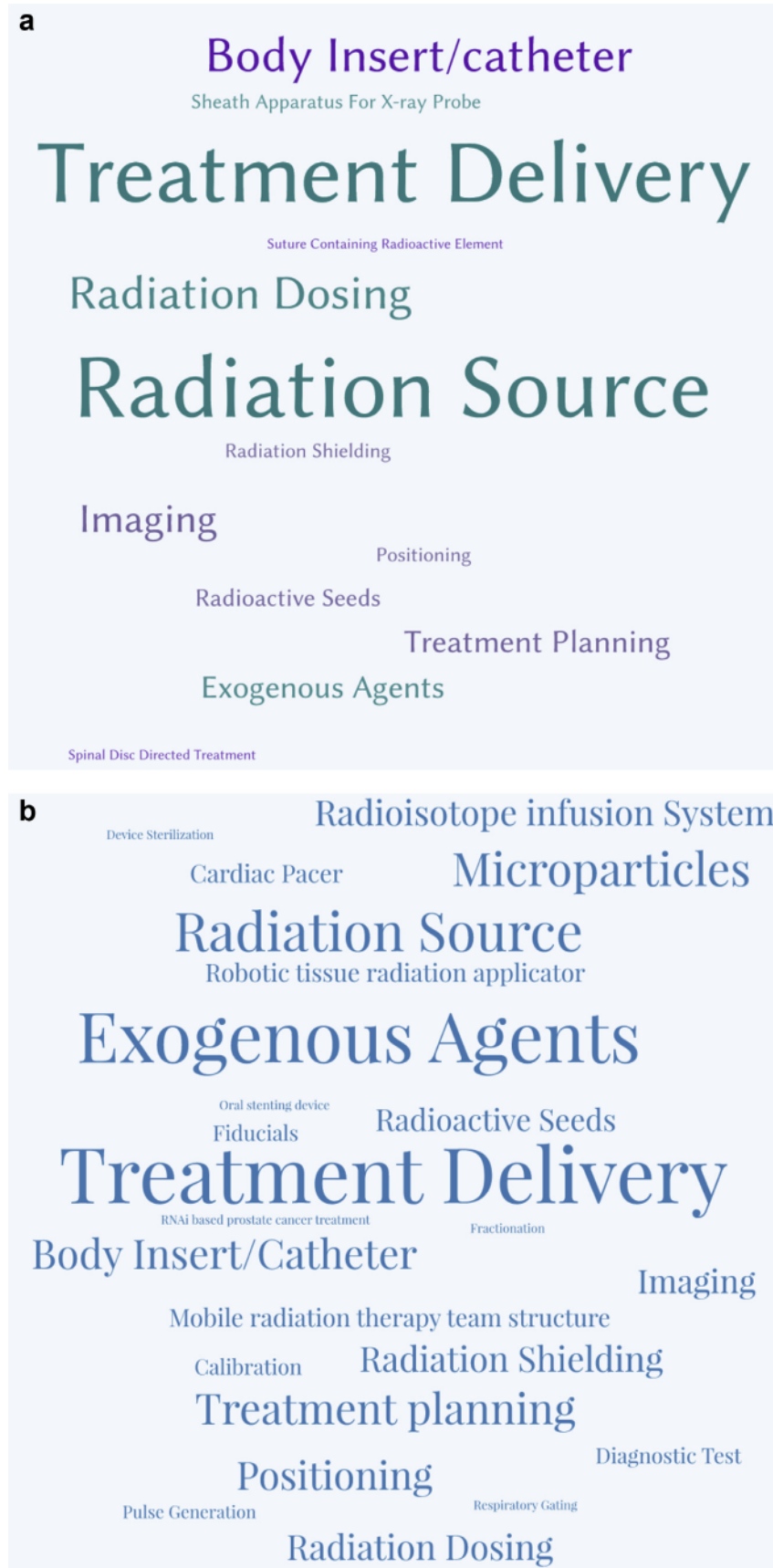


Fig. 1. (a) Patent theme word cloud 1999–2008. (b) Patent theme word cloud 2009–2018.

There has been a substantial increase in overall brachytherapy patent production over time, and the majority of USPTO brachytherapy patents have been awarded to assignees from the United States and industrial corporations. The United States accounted for approximately three-quarters of all patents awarded across each decade. California remained the leader across both decades, accounting for approximately 30% of all U.S. patents awarded in each era (Table 3). This is likely because of a higher concentration of top industry innovators such as Oraya Therapeutics, Medtronic, Xofigo, and Reflexion Medical in addition to academic contribution from Stanford University (Appendix Table III). Leading production among the remainder of U.S. states did however shift across time, with Massachusetts and Minnesota predominating alongside California from 1999 to 2008, whereas New Jersey was the second largest contributor from 2009 to 2018. This is because of a result of industrial entities in these regions, with Photoelectron Corporation from Massachusetts producing 14 patents and SciMed Life Systems from Minnesota being responsible for nine patents from 1999 to 2008 (Appendix Table II). In the subsequent decade, New Jersey earned its second-place designation among U.S. states because of production of 14 patents by industry entity Pop Test Technology and eight patents by Bracco diagnostics from 2009 to 2018.

There has been a greater variety of distinct themes regarding the focus of patents produced in addition to a shift in the most common themes observed. Themes that emerged as the most predominant categories for innovation across all brachytherapy patents from 2009 to 2018 related to advancements in treatment delivery, exogenous agents used as adjuncts to therapy, and radiation source production (Table 4). This was driven by United States and industry production, where the same three themes topped the list of patents awarded by the USPTO. This demonstrates a shift in focus for areas of innovation from the previous decade of 1999–2008, where radiation sources were the leading invention theme, followed by treatment delivery and body insert/catheter-related patents.

The rising interest in exogenous agents from 2009 to 2018 was not isolated to industrial corporations; it was the predominant patent theme produced at academic institutions during this time and accounted for almost one-third of all awarded innovations in academia (Appendix Table III). Themes involving exogenous agents exhibited a wide variety of purpose, with some serving as drug conjugates(3), adjuncts to brachytherapy treatment(4), or radiosensitizers for radiation treatment.(5) Interestingly, rather than developing a radiation therapy system from beginning to end, the vast majority of corporations and academic institutions focused on production in one particular category or theme. This was evident in academia, where all three patents filed by the University of Zurich concern radiation dosing, those by Stanford University relate to exogenous agents used as radiosensitizers, and Wake Forest

University which created two patents that both involve aspects of treatment delivery. Among the exception was Johns Hopkins University, which created separate patents relating to radiation source production(6) and treatment planning.(7)

Academic patents had distinct patterns of scope and themes from those of industry-affiliation. From 1999 to 2008, industrial corporations were responsible for the vast majority of patent production; academia played only a minor role in this decade, with five patents originating solely from U.S. institutions. Conversely, from 2009 to 2018, academic entities played a larger role with 14 different institutions producing 22 patents. Notably, international academic contribution rose significantly with the University of Zurich responsible for three separate patents involving radiation dosing, in addition to contributions from institutions in Canada, France, Korea, and Israel (Table 2).

Collaboration between industry and academia was rare, yet formation of well-developed relationships between these two entities is on the rise. While no collaboration was observed between any academic institution and industry corporation between 1999 and 2008, there were notable partnerships that formed in the subsequent decade which amounted to almost 5% of all patents awarded during this time (Appendix Table IV). Relationships between the University of Utah and Batelle Memorial Institute (private nonprofit company), Regents of the University of California and Varian Medical Systems, and Tsinghua University (CH) and Hon Hai Precision Industry (TW) were responsible for multiple patent filings. Such academia-industry relationships generally resulted through collaboration on one specific theme innovation. For instance, University of Utah and Batelle Memorial Institute have created two separate patents for radioactive seeds which are coated with fast-dissolving matrices that enable optimal delivery of radionuclides to a specific cancer site.(8, 9)

Industries commonly focused on one particular aspect of brachytherapy innovation. All 18 of Oraya Therapeutics patents relate to treatment delivery;(10) Pop Test Technology LLC has created 12 patents all pertaining to exogenous agents;(4) Bracco Diagnostics patented eight innovations specifically relating to a radioisotope infusion system.(11) Despite a consistency in theme by Oraya Therapeutics regarding treatment delivery systems, each patent included a separate indication for radiotherapy in cancer types such as ocular tumors, breast cancer, and CNS malignancies, as well as nonmalignant conditions such as carpal tunnel syndrome. Many patents such as those created by Pop Test Technology and Bracco Diagnostics did not specify a particular cancer type for use, indicating a desire for broad application of these products.

Smaller producers also tended to focus on one particular theme of invention, with Reflexion Medical creating six patents related solely to positioning,(12) Ethicon Endo-Surgery making five for the theme of body-insert/catheter,(13) and Brea LLC producing four patents related to

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