Health Policy and Technology (2016) 5, 47–64

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/hlpt

LITERATURE REVIEW

De innovatione: The concept of innovation for medical technologies and its implications for healthcare policy-making

Ciani Oriana[a,b,*], Armeni Patrizio[a], Boscolo Paola Roberta[a], Cavazza Marianna[a], Jommi Claudio[a,c], Tarricone Rosanna[a,d]

[a]*CERGAS – Centre for Research on Health and Social Care Management, Bocconi University, Milan, Italy*
[b]*University of Exeter Medical School, Exeter, United Kingdom*
[c]*Department of Pharmaceutical Sciences, Università del Piemonte Orientale, Novara, Italy*
[d]*Department for Institutional Analysis and Public Management, Bocconi University, Milan, Italy*

Available online 22 October 2015

KEYWORDS
Innovation;
Medical devices;
Health technologies;
Healthcare policy making

Abstract
Innovation is constantly evoked as an imperative to drive growth, however identifying an actionable and agreed upon definition that applies to different settings and purposes is not trivial. In healthcare, innovation has often been described in relation to pharmaceuticals. Defining innovation allows for proper recognition and rewarding, thus fostering present and future innovativeness in the system. Current definitions adopted by payers are focused on therapeutic added value and more specifically include clinically significant benefit, large health gains, and favorable risk-benefit balance at an acceptable cost. However, they may not be fully adequate to assess medical devices. Based on a systematic review of the academic literature in the field, we aim at summarizing acceptable definitions of innovation in relation to medical devices. Based on the innovation management and economics theory, proposed definitions have been classified according to the source of innovation, to the degree of discontinuity introduced and to the impact associated to the technology. They have also been compared with definitions adopted for drugs by main healthcare reimbursement agencies. Decision-making in healthcare often favors static allocative efficiency at the expense of incentives to innovate and obtaining valuable innovation, that is dynamic allocative efficiency. In the long run, this attitude may artificially shrink net returns from innovation and rebound on the sustainability of the

*Correspondence to: CERGAS – Centre for Research on Health and Social Care Management, Bocconi University, Via Roentgen 1, 20136 Milan, Italy. Tel.: +390258362605; fax: +390258362598.
E-mail address: oriana.ciani@unibocconi.it (O. Ciani).

http://dx.doi.org/10.1016/j.hlpt.2015.10.005

healthcare systems, an undesirable consequence that a farsighted shared notion of innovation should try to prevent.

Contents

Introduction

The word "innovation" comes from the Latin noun *innŏvātĭo*. In lay language use, it refers to the act or process of introducing new ideas, devices, or methods or to the new ideas, devices, or methods themselves [1]. In business, economics and politics, the term is often evoked as an imperative to drive growth, [2] especially in times of financial crisis for companies, markets and economic institutions in general [3]. Although the subject has risen to the core of the debate in many disciplines, including economics and management theory, and their subfield known as innovation studies, [4-6] identifying an actionable and agreed upon definition that applies to different settings and purposes is not trivial.

In healthcare, the need to define innovation in relation to health technologies comes with the assumption that recognizing and appropriately rewarding innovation will foster present and future innovativeness in the system [7]. In many jurisdictions, health policy initiatives are discussed or in place where innovation is a critical element, often described in relation to pharmaceutical products [8-11]. New target or novel pharmacological mechanism, method of synthesis, pharmacokinetic, pharmacodynamic, pharmacogenetic or therapeutic features are properties of medicinal products that can lead to their innovative status [12]. However, the International Society of Drug Bulletins has explicitly distinguished between innovation that produces therapeutic advance, in terms of efficacy, safety, and convenience to patients, and innovation from a purely commercial (e.g. new molecules that do not produce any added value) and technological (e.g. biotech products *vs* chemical products) viewpoints [13]. More specifically, the Italian Society of Hospital Pharmacists has agreed on three criteria to recognize therapeutic advance. They are evidence from an intervention successful in at least one randomised superiority trial where the control group is treated according to the current best practice and the primary endpoint is clinically relevant [14]. Aronson and colleagues propose an intentional definition for innovation in drug therapy that includes more selective parameters, i.e. clinically significant benefit, large health gains, favorable risk-benefit balance at an acceptable cost [7].

However, health technologies are not to be intended as drugs only. Medical devices have an estimated market of roughly €100 billion in Europe only, and account for about 7.5% of the healthcare expenditure in most publicly funded healthcare systems [15]. Besides the extreme diversity and heterogeneity of products falling under this classification, medical devices are known to differ from drugs in many respects. For instance, for many of them, especially the implantable devices, their performance and use are heavily dependent upon organizational settings, training, competence, and experience of the operator. As long as clinicians and their staff do not reach the plateau of the learning curve, it is difficult to assess the value of new devices. There might be cases when the plateau is never reached. This happens when new devices are quickly replaced by newer generations. Because of their short life cycle, medical devices do not often benefit from patenting. Moreover, due to different regulatory and coverage requirements or unavoidable facts (e.g. difficult, impossible or unethical blinding in clinical trials), the evidence on added value at market launch is less robust than for drugs. The value of devices is also more challenging to assess because they have often multiple indications (e.g. CT-scan, MRI) or are embedded into procedures or services. Devices are often diagnostics and their contribution to final health outcomes depend on how the information provided is treated by the end-users and on what happens to patients afterwards, therefore it is not easy to parcel out the contributions of each single components to final outcomes [16-18].

As a consequence, definitions of innovation for medicinal products may not be fully adequate to assess medical devices, as the properties that drive innovativeness are different, and scales and thresholds set to capture the additional benefit of innovative molecules may not be representative of the marginal benefit produced by other medical technologies. For instance, if we agreed that therapeutic advance is an important dimension to capture and we used the definition provided by the Italian Society of Hospital Pharmacists [14], a very small fraction of hundreds of medical devices recently introduced in the market would be considered as innovative since only few of them could claim to base their clinical evidence on "at least one randomised superiority trial where the control group is treated according to the current best practice and the primary endpoint is clinically relevant". Take the example of MitraClip (Abbott Vascular Inc. Menlo Park, CA), an implantable device launched in 2008 allowing a fully percutaneous approach for mitral regurgitation in non-operable and high risk patients whose prognosis is very poor if left untreated. No randomized controlled trials (RCTs) looking at the appropriate comparator have been completed so far, nevertheless in 2015 the total number of implants worldwide amounts to 17.000 already [19]. Does it mean that Mitraclip is not innovative till a RCT will tell us so or does it mean we do not know how much innovative it is in terms of therapeutic added benefit versus its current best practice till a RCT will measure the number of life years or quality-adjusted life years (QALYs) gained by those patients treated with Mitraclip? Provided it is ethical to randomize patients with poor prognosis to the current best practice (i.e. medical therapy) when observational evidence already exists on the efficacy of Mitraclip, in the example given the definition and measurement of innovation overlap.

No matter how much narrow or wide it is, the definition of innovation endorsed by regulators or decision-makers will certainly have wide implications for the patients or end-users, the industry, the citizens and the policy-makers. For instance, analyzing how innovation in healthcare is defined might help to lay bare the spill over effects on different stakeholders as well as for the entire system of care and beyond, and eventually provide guidance to decision-makers especially in this period when the new regulation of medical devices is under discussion at the EU [20].

Therefore, in this study we systematically search for definitions of innovation in relation to medical devices as emerging by the academic literature on the subject and classify them according to the major classifications proposed by the innovation management theory. The analysis aims at enlarging the viewpoint on innovation in medical technologies, providing healthcare policy-makers with useful insights in the implications of this broaden view such as fostering the diffusion of worthwhile innovation.

Methods

We performed a systematic review of the scientific peer reviewed literature discussing the concept of innovation in relation to medical technologies. This is a common

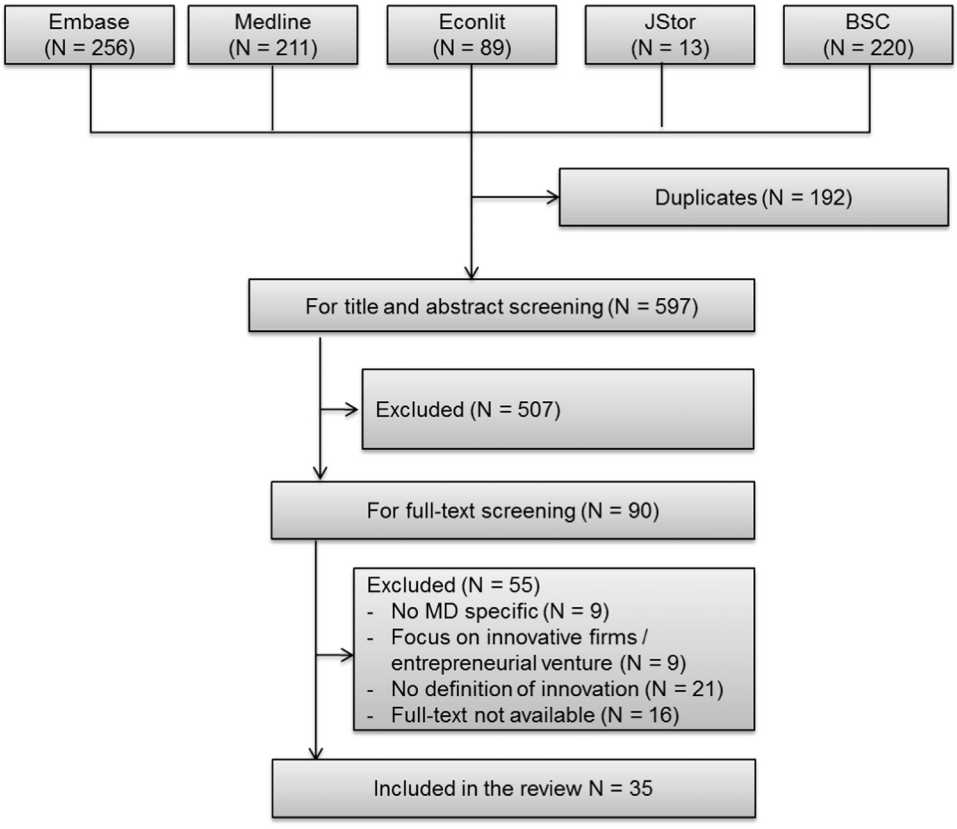

Fig. 1 Review selection process – flow diagram.

methodology in public health and comparative effectiveness research that seeks to systematically and explicitly identify, select, and appraise studies relevant to a particular research question, and to collect and analyse data from the studies that are included in the review [21]. As our topic is broad and of interest across different disciplines, we searched several databases for scholarly work: Medline and Embase, collecting publications from the biomedical and clinical fields; Econlit, mainly indexing economic literature; BusinessSourceComplete and JStore, as comprehensive databases for policy, management and social sciences academic journals. We searched for articles that used both "innovation" and "medical devices" in their titles or abstracts (see Supplementary Material for search strategies) from the coverage start of each database up until April 2013. This search yielded 789 titles and abstracts that we downloaded on a citation manager library. After electronic deduplication, 597 entries remained for further investigation (Fig. 1). As we intentionally used a wide search filter, we introduced also articles where authors incidentally adopted both expressions without specifically providing a definition, rather relying on an alleged shared concept of "innovation". We therefore checked the abstracts to exclude those papers where "innovation" was not a major focus. In order to reduce subjective judgment to a minimum, two reviewers independently performed the screening on the abstracts, with involvement of a third reviewer and check of the full-text publication in case of disagreement. This screening resulted in a short list of 90 papers for full-text examination. Information about included publications was recorded according to a predefined template and stored in a local database. We collected data on general characteristics of the study and definitions and measures of innovation proposed by the authors. Systematic reviews usually include a quality appraisal step. However, quality checklists developed so far (e.g. Cochrane risk of bias assessment tool [22]) apply to situations where clinical studies (e.g. RCTs, observational studies) are assessed in order to evaluate health interventions. Our study aims are different hence we decided to present main study characteristics (i.e. journal, design, perspective, technologies under investigation) without building a *de novo* quality appraisal tool that would suit the aim of this study. We qualitatively analysed the papers to identify how they define innovation for medical technologies, either conceptually or – by means of specific measures – empirically. We then classified through thematic analysis [23] each of these applied definitions according to a framework previously identified from the innovation management and economics theory (see next paragraph). Finally, we contrast the applied definitions against current systems in place to value drug innovation, identify those aspects of innovation that are specific to medical devices and discuss implications for the purpose of the policy-making in healthcare.

Theoretical framework for analysis of retained studies

In order to structure the analysis of definitions of innovation in medical devices emerging from the systematic review, we relied on a framework previously proposed and generally accepted in the innovation management and economics community [24]. This framework includes three classifications that are briefly introduced below.

Following the innovation management and economics theory, the retained studies from our systematic review, or the definitions of innovation provided by them, can be classified according to three broad dimensions: (i) the source of innovation, (ii) the degree of discontinuity introduced and (iii) the impact or consequences of innovation.

According to the first dimension, the source of innovation can be either an emerging need or problem (demand perspective) or the output of a knowledge-based process (supply perspective). Problemistic search [25] is the typical trigger of a demand-pull innovation process that sees innovation as the result of a searching activity aimed at coupling specific problems to solutions, i.e. innovation happens because individuals face problems and look for solutions. For example, we could see research on artificial pancreas as originating from the need to overcome long-term consequences in the diabetic population. The supply or technology-push perspective instead, [26] emphasizes the entrepreneurial aspects of the innovation process. A popular example of technology-push innovation is the touch screen technology. When it first appeared in the 1960s, there was not a precise call from its use. However, its potential started attracting investments from firms that further developed its applications and functions. Of course, both perspectives can be integrated into a single paradigm-trajectories framework [27]. Under this unifying framework, paradigm shifts and trajectories, i.e. developments within the same paradigm that advance innovation in a problem-solving perspective, coexist. Hence, technology-push and demand-pull innovation are not exclusive definitions, however the prevalent adoption of either one or the other has different implications in supervising the user-producer relationship. In healthcare demand and supply do not interact independently from the regulatory environment. This is particularly true in systems where public administration plays a major role by defining the amount of resources available to the healthcare system, translating needs into demand and structuring decisional systems for value-based allocation of scarce resources.

The degree of discontinuity, introduced vis-à-vis previous practice, is the second recurrent trait of technology innovation. According to this dimension, innovations are often considered as incremental or breakthrough [28,29]. Technological breakthroughs, or radical innovations, are viewed as a broad, arching process of scientific discovery and paradigm shifts, [27,30] often characterized by an era of ferment and following convergence into a dominant design or "standard" [31]. From a dynamic point of view, radical innovations usually create and define demands, thus triggering the development of a set of incremental innovations that may serve diverse nuances of the newly created needs [32].

Finally, innovation can be defined based on the type, degree and measure of its impact. Although one may argue on what constitute real impact, this approach seems suitable for public health authorities when assessing medical technologies as they are usually expected to be associated with measurable changes in terms of patients' benefits, quality of the service or costs.

Table 1 Main characteristics of included studies.

ID	First author	Journal	Year	Perspective	Type of study	Particular MDs subgroup considered in the study	Other technologies/ industry
1	Traijtenberg	Journal of Political Economy	1989	Patient	Quantitative	Computed tomography scanners	None
2	Littell	Health Affairs	1994	Industry	Quantitative	None	None
3	Anderson	Health Affairs	1994	Industry	Commentary	None	Colony-stimulating factors, erythropoietin
4	Citron	Journal of Biomedical Materials Research	1996	Industry / user	Commentary	None	Vaccines
5	Gullikson	Plant, technology and safety management Series	1996	User	Qualitative	None	None
6	Iserson	Seminars in Laparascopic Surgery	2002	User	Commentary	Minimally invasive surgery applied to laparascopic cholycistectomy	None
7	Roberts	National Academy of Engineering-Institute of Medicine Symposium	2003	Industry	Commentary	None	None
8	Morscher	Scandinavian Journal of Surgery	2003	User / industry	Commentary	Total hip replacement	None
9	Lexa	Journal of American College of Radiology	2004	Industry	Qualitative	Radiological technologies	None
10	Boyle	Expert Review of Medical Devices	2005	Industry	Commentary	None	None
11	Reitsma	Journal of the American College of Surgeons	2005	User	Quantitative	None	None
12	Djellal	Research Policy	2005	User	Qualitative	None	None
13	Lettl	Journal of Engineering & Technology Management	2007	User/industry	Qualitative	None	None
14	Ghodeswar	Journal of Services Research	2007	National Health System	Qualitative	Electromyography	None
15	Lettl	IEEE Transactions On Engineering Management	2008	User/industry	Qualitative	Medical robot system, computer-assisted navigation system for neurosurgery, computer-assisted navigation system for orthopedics, and radically new biocompatible implant	None
16	Editorial review (no authors listed)	Health Affairs	2008	Patient	Commentary	None	None
17	Chatterji	Health Affairs	2008	Industry	Quantitative	None	None
18	Graham	Berkeley Technology Journal	2009	Industry	Quantitative	None	IT-software and harware, biotechnologies
19	Karim	Management Science	2009	Industry	Quantitative	None	None
20	Consoli	Journal of Evolutionary Economics	2009	Industry	Qualitative	Coronary artery disease and glaucoma	None
21	Lambooij		2010	National Health System	Quantitative	Computed tomography scanners, MRI, lithotripters	None

Table 1 (*continued*)

ID	First author	Journal	Year	Perspective	Type of study	Particular MDs subgroup considered in the study	Other technologies/ industry
		International Journal of Technology Assessment in Health Care					
22	Galbrun	Systems Research & Behavioral Science	2010	User	Quantitative	Computed tomography	None
23	Ahn	Journal of Commercial Biotechnology	2010	Industry	Qualitative	Wound healing sector	PC and the digital industries
24	Weigel	European Planning Studies	2011	Industry	Qualitative	Surgery, orthopaedics and medical imaging	None
25	Atluri	Expert Review of Medical Devices	2011	User	Qualitative	Robotic surgery, valve repair	None
26	Moosmayer	International Journal of Business Research	2011	Industry	Quantitative	None	None
27	Suter	New England Journal of Medicine	2011	Industry	Quantitative	Knee implant	None
28	Morlacchi	Research Policy	2011	Industry	Qualitative	Left Ventricular Assist Device	None
29	Davey	Irish Journal of Management	2011	Industry	Qualitative	Stenting for vascular disease, engineered bladder	None
30	Chandra	National Bureau of economic research bulletin on Aging and Health	2011	User	Qualitative	None	None
31	Xu	Circulation	2012	Industry	Qualitative	Coronary artery stents	None
32	Pullen	Creativity and Innovation Management	2012	Industry	Quantitative	None	None
33	Chatterji	Organization Science	2012	Industry	Quantitative	None	None
34	Gosset	IEEE Pulse	2012	Industry	Commentary	None	None
35	Smith	Medical Care	2013	Industry	Qualitative	None	None

Results

In our systematic review, we identified 35 publications (see Supplementary Material) reporting a definition of innovation applied to medical technologies out of 90 full-text papers screened (Fig. 1). The main characteristics of the included studies are presented in Table 1. They were empirical studies, with either qualitative (15 out of 35, 43%) [33-47] or quantitative design (12 out of 35, 34%) [48-59], or commentary or opinion pieces from experts (8 out of 35, 23%) [60-67]. The vast majority of these studies adopted the perspective of the industry (20 out of 35, 57%), nine (26%) reflected the view of the users, either patients or professionals, [34,35,38,40,49,56,58,62,67] and two (6%) reflected the view of the National Healthcare System, [39,52] with the remainder (11%) taking a combination of those [41,42,61,64]. The industry perspective focuses on the innovation-related activities occurring within the firms such as inventing new products, processes, or services; conducting initial research and development; creating internal tools or processes to build or implement final products, processes, or services; and undertaking the risks and costs of making, selling, and marketing a commercial product [50]. User perspectives consider the role of users, usually clinicians or patients, in generating radically new ideas and concepts due to their specific need and problem-related context [41]; whereas the system perspective is broader and reflects on the general level of innovativeness within healthcare services or the whole country [52]. All papers referred to medical devices, however particular technologies used as good cases of innovation in healthcare were imaging and radiological technologies, [43,49,52,58] orthopedic prostheses, [57,64] robotic systems for computer-assisted surgery, [34,41] left-ventricular assistive devices [44] and stents for cardiovascular disease [36,37,47]. The discussion was often extended to innovation in different industries, such as the biotech pharmaceutical industry, [60,61] within the medical sector, or the IT and software industry, [33,50] beyond the healthcare field.

Applied definitions of medical technologies innovation

Definitions of innovation reported by study authors are tabulated in Table 2. They are analysed according to the three categories derived form the innovation management and economic theory introduced before.

Definitions based on the source and boundary conditions of the innovative process

Building on the supply-driven perspective, [26] several authors view innovation as an entrepreneurial process entailing the series of steps taken from the idea to invention to development to commercialization [50,54,68]. Innovation in medical technologies has been described as the result of progress along three different pathways: advances in scientific understanding, improvement in the ability to develop new tools and learning in practice [44]. For instance, with implantable devices for advanced heart failure (i.e. left ventricular assistive devices) an essential aspect of the evolution is collective and cumulative learning or experience gained through the actual use of the technology. In such entrepreneurial perspective, the source of knowledge is not necessarily creative but innovation is also adoption, that is taking something that someone else had previously done and applying it in a different milieu [63]. Gelijns and Rosenberg [69] have described the path-dependent character and cross-disciplinary origin of medical device innovation [69]. In relation to the interdisciplinary aspect of medical innovation, different authors see medical innovation as an emergent, nondeterministic process generated from complex interactions across heterogeneous knowledge bases [49,53]. This links with the concept of "health innovation systems", valid for instance in cardiology and ophthalmology, based on the coexistence of institutionally-bound interactions among agents, so called "gateways of innovation" and "pathways of innovation" [36]. Similarly, medical innovations can be seen as complex bundles of new medical technologies and clinical services emerging from a highly distributed competence base [37]. In describing the success of hip replacement procedure, Morscher states that progress has been achieved in part through new implant materials and designs that provided improvements under the biomechanical profile. However, of at least equal importance, were advances in operative procedures and in clinical quality control (e.g. more complete documentation of implant and patient variables, establishment of implant registers) [64].

From a demand-pull perspective, innovation is a way to meet specific needs that firms or research have ignored or not yet figured out to address [48]. Scientific research is not the starting point of the innovation circle but, instead, it appears more like a necessary approach for dealing with solutions that fall outside the set of solutions suggested by current knowledge or practice. In this respect, the role of academia is functional to the interpretation of needs more than it is to the free search for solutions, as it identifies the clinical need for certain surgical instruments and diagnostic services and provide valuable scientific and clinical expertise during the early and later stages of development [60]. Problem-solving may be generated by the adaptation of existing elements that are modified, upgraded and improved to fit new conditions or a change in the needs [63]. Needs are perceived and expressed by users, who have been identified as a crucial factor not only for the uptake but also for the development of innovations, often contributing to the definition of a standard [70,71]. Users becoming entrepreneurs is a particularly common phenomenon in medicine, for instance surgeons often develop a new device in response to an issue experienced in practice and start a company to commercialize it [72,73]. Although in most areas of medicine what has been learned is much better characterized as the accumulation of relative small and local advances than as dramatic breakthroughs in understanding, [44,47] solutions are often found far from the *status quo* or from the existing set of answers. Unintended consequences of solutions may derive from uncertainty, unclear preferences and fluid participation to decisional processes, e.g. adoption decisions in a hospital setting [56]. If these three conditions occur together, then solutions and problems are coupled through a "garbage can" approach whereby consequences

Table 2 Definition of innovation for medical technologies provided by the authors of included studies.

Classification	First author	Year	Definition 1	Definition 2	Definition 3
A	Littell	1994	Several indicators of inputs and outputs associated with medical device innovation, including public- and private-sector research and development (R&D) investment, patent activity, product regulatory clearance patterns, and market acceptance trends.	It is a dynamic, continuous, and interactive process, rarely proceeding in a linear or predictable manner. Medical device innovation is characterized more often by small, incremental steps than by bold, technological bounds. The direction of the process is sensitive to a variety of forces, including the availability of funds, the reactions of users and regulators, and more general market trends.	
A	Anderson	1994	AHC faculties also have a major impact on the content of research and development programs in both the public and private sectors. They identify the clinical need for certain drugs, surgical instruments, and diagnostic services and provide valuable scientific and clinical expertise during their early and later stages of development.		
A	Roberts	2003	Radical innovations that introduce dramatic new capabilities occur, as well as incremental innovations in those products and processes that have previously existed. Invention that is wholly original indeed takes place.	But innovation also includes the adaptation of things that had come before but are now being modified, upgraded and improved to fit new conditions. Innovation is also adoption, taking something that someone else had previously done and applying it in a different milieu. Another way of distinguishing among innovations is that some are based upon science or research, where new knowledge gets applied, whereas others are clear cases of engineering problem-solving, applying primarily existing knowledge or techniques to newly defined problems.	Yet my personal experience,.[..], indicates that the medical device field contradicts all of the images I have just described. As my evidence will show, innovation in medical devices is by and large engineering-based problem-solving by primarily individuals or small firms, that is usually incremental in character, that seldom reflects long periods of basic research, and that does not in general depend upon recent generation of fundamental new knowledge.
A	Morscher	2003	For an orthopaedic surgeon research is, first of all, aimed at solving clinical problems.	For industry, on the other hand, research and development must follow the so-called "S-curves of development" and continuously and systematically be directed towards offering new products that will improve sales. Before the sales of a current product slow down, the next product of the same type must already be "in the pipeline". Industrial innovation is also directed at reducing manufacturing costs, in order to improve profitability.	

				Therefore, industrial innovation is aimed principally at the economic success and survival of companies. One consequence of these differences in goals is that today's innovation may well be tomorrow's revision	
A	Reitsma	2005	Innovation that falls under acceptable everyday routine variation [...] are done on as as-needed basis and might arise during a procedure or may be planned head for for the benefit of an individual patient.	Yet when otucomes of procedure are largely unpredictable because they have not been previously described, innovation becomes essentialy experimental and should be conducted, at some point, as a research project.	Differentiating between three categories of innovation (routine variation, innovation that is not formal research but requires formal review, research requireing IRB review)[...] Forms of surgical innovation fall under the existing definition of human subject research and should be treated as such. For those who fall short of meeting this definition [... such criteria are]: if an innovation is (yet) no part of a part of a formal investigation, if it is premeditated because the surgeon seeks to test a hunch or hypothesis, or theory; if it differs notably from the existing standard of care if the outcomes of the proceddure are not predictable [...]; and if it entails serious risks for complications.
A	Graham	2009	"innovation" in its Schumpeterian meaning—the series of steps taken from idea to invention to development to commercialization.	Four innovation-related activities: (a) inventing new products, processes, or services; (b) conducting initial research and development; (c) creating internal tools or processes to build or implement final products, processes, or services; and (d) undertaking the risks and costs of making, selling, and marketing a commercial product.	As is the case with many innovations in medical devices, Jeremy was a "user-innovator," seeing a practical problem in his medical practice that needed a practical response. He founded his company to offer a product to meet that need, and quickly secured a patent
A	Consoli	2009	The notion of medical innovation is as an emergent, nondeterministic process generated from complex interactions across heterogeneous knowledge bases.	Medical innovation thus understood [history of medicine] involves a variety of forms of knowledge whose evolutionary paths are rooted in the contexts in which they emerge and interact.	Medical innovation is an interactive process involving a broad set of disciplines, agencies and institutions with close relations emerging between firms, clinicians and academic scientists. More precisely, the process of division of labor — which in Hayekian terms can be configured as the dynamic division of knowledge in the economy—is distributed across technological fields, geographical domains and organizational units.
A	Lambooij	2010	Innovation measured in terms of technology's output improvement.		
A	Galbrun	2010	Technological breakthroughs may be generally viewed as a broad, arching process of scientific discovery and paradigm shifts, often characterized by convergence into a standard.		

Table 2 (*continued*)

Classification	First author	Year	Definition 1	Definition 2	Definition 3
A	Moosmayer	2011	Innovations can be described as serving existing or creating new market needs.	Radical innovations usually create a need and thus trigger a set of incremental innovations that may serve diverse nuances of the newly created need.	[...] the high importance of uncertainty as a prerequisite for radical innovations to become successful, which can be equally understood as risk and opportunity.
A	Morlacchi	2011	[...] medical practice evolves as a result of progress along three different pathways [...] advance in scientific understanding.[..] the improvement in the ability to develop new medical technologies. And learning in practice has been an extremely important feature of many medical advances.	In most areas [..] of medicine, what has been learned is much better characterized as the accumulation of relative small and local advances than as dramatic breakthroughs in understanding. [...] The design and development of new medical technologies, including the LVAD which is the focus of this paper, often has been stimulated and enabled by the advance of broad technologies whose principal uses and support lie outside the realm of medicine.	
A	Davey	2011	Health innovation consists of complex bundles of new medical technologies and clinical services emerging from a highly distributed competence base.	Health innovation systems are driven by the combination of institutionally bound interactions or 'gateways' of innovation and history-dependent trajectories of change often referred to as 'pathways' of innovation.	
A	Pullen	2012	In the field of high technology innovation is invention plus commercialization.	[Innovation measured as] 1. The performance that is achieved as a result of new product development is the innovation performance, 2. According to Booz et al. (1982) product innovativeness is the level of newness of the product to the market and the firm. In particular: newness to company and newness to market; new product-line and new-to-world products. In newness to company and to market: Improvements/Revision of existing products; Cost reduction; Addition to existing product -lines; Repositionings.	
A	Smith	2013	The FDA defines class III devices as "those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.		
B/A	Ahn	2010	Rosenberg has highlighted the fundamental contribution to medical device innovation made by individuals. Exceptionally gifted	Literature stresses the Importance of user involvement for innovation. Users are characterised by a need i.e. an unsolved	

			individuals regularly triggered progress by crossing long-prevailing disciplinary boundaries.	problem, openness to new technologies, free space for creative thinking and access to interdisciplinary expertise.	
B/A	Xu	2012	Innovative medical devices make major contributions to patient welfare. [...] Medical device innovation occurs in both the public and private sectors and can generate substantial economic benefits.	Examining patent literature is a viable way of assessing the origins of transformative technology.	
B/A	Chatterji	2012	"[...] I looked at things and just naturally thought-"Okay, how can I make this better?"- Dr T. Fogarty, inventor of more than 70 surgical patents".	In the users' perspective, innovation is a way to meet often personal needs that firms have ignored or have not figure out to address.	[Innovation measured as] 1. Citations from outside their technology class. 2. Innovation in the early stages of the product life cycle where there is significant uncertainty over dominant design.
B	Iserson	2002	Innovations in medicine [...] fall into two broad categories: evolutionary and revolutionary. [...] Building on known scientific theory and learned skills, they pose few problems to physicians wishing to add them to their practice. Revolutionary developements are, in contrast, the "gee-whiz" breackthrough drugs or devices that change aspect of medical care. [...] Moreover, revolutionary developments typicallly have significant learning curves until physicians become confortable with their use.		
B	Djellal	2005	Innovation is considered subjectively, with the element of novelty being apprehended in relative rather than absolute terms. It is also considered extensively in order to encompass both innovations generated internally and those originating externally, that is those adopted from outside sources.	[This decision is reflected both] in the nature of the innovations taken into account (organizational, technological, product and service innovations, etc.) and in the degree of novelty those innovations display (radical innovations are included, of course, but so are minor or incremental innovations possibly resulting from a simple adaptation or change).	
B	Lettl	2007	The fact that our sample of innovative surgeons encountered the limits of conventional technologies motivated them to search for other, more workable solutions.		
B	Ghodeswar	2007	An innovation is defined as any product, idea or practice that is viewed as new by an individual or the adopting unit.	Incremental innovations make a marginal improvement over existing technology, semi-radical innovations represent a significant improvement over existing technology, and radical innovations represent a major or revolutionary technology advance.	

Table 2 (*continued*)

Classification	First author	Year	Definition 1	Definition 2	Definition 3
B	Lettl	2008	From lead user theory, we know that lead users generate radically new ideas and concepts due to their specific need and problem-related context.	Appendix provides a Degree of Innovativeness Tool grounded on dimensions related to the innovation process's uncertainty. In particular, there are: 1) Market dimension: 2) Technological dimension: 3) Organizational dimension.	
B	Chatterji	2008	One measure of the importance of a patented innovation involves counting the number of citations it receives in subsequent patents. […] A second way to measure the impact of a patented invention is to consider the breadth of technological space that it influences. Patents that influence follow-on technologies across a more diverse set of areas have a broader impact. BronwynHall and colleagues found that one additional citation increased the firm's market value by more than 3 percent.		
B	Weigel	2011	Innovation measured in terms of clinical indicators of improvement.		
B/C	Traijtenberg	1989	Product innovation can be thought of in terms of changes over time in the set of available products, in the sense that new brands apprear and that there improvements in the qualities of exiting products.		
C	Citron	1996	The impact has been most pronounced for those technologies that could mature to become technological breakthroughs, the major advancements in therapy.		
C	Gullikson	1996	Technology assessment is an essential tool for new medical technologies management that allows to control negative legal and economic consequences by assessing risk throughout the medical equipment lifecycle. The risk level assigned to each technology depends on a number of static or dynamic risk factors (e.g. maintenance requirement, equipment function).		
C	Lexa	2004	In our field a dramatic example is the end of pneumoencephelography with the introduction of computed tomography scanner, This a		

			striking example of reltively rapid replacement. […] Schumpeter termed this latter phenomena "creative destruction", and it is part and parcel of the most successful and significant effort of entrepereneur. Sometimes that destruction does not occur if two technologies are fairly robust.	
C	Boyle	2005	[…] research impact can be measured with the rate of citations by other researcher obtained by bibliometric database or commercialization outputs was developed by collecting the relative citation impact data for eight health and medical reserach fields in a group of developed countries, number of patents, number of licenses executed, amount of gross income from licenses, number of start-up companies.	
C	Editorial review	2008	[…] unless the innovation is not what it's cracked up to be and does not really produce better care or outcomes.	
C	Karim	2009	Innovation is generally considered to be the creation of new resources by the firm. In this paper, innovation is observed at the product level and is radical, representing internal entry (i.e., not via acquisition) into new product markets. Incremental innovations, namely changes within existing product lines.	Innovation literature has addressed how new resource combinations or similar resources combined in new ways (i.e., recombination) may result in innovation. […] Stemming from Schumpeter's concept of creative destruction, architectural innovation refers to new links between components within product architectures. Other scholars have theorized about the characteristics of knowledge affecting resource recombination and innovation, as well as knowledge itself (comprised of information and know-how) being a recombined resource that leads to market opportunities.
C	Atluri	2011	Decreased pain, more rapid return to work, reduced blood loss and length of hospitalization have been associated with technological advances leading to minimally invasive surgery. The improvements in visualization and rotational freedom may be difficult to justify in face of the added cost.	
C	Suter	2011	Medical device innovation continues […] Most are designed to improve durability, and their manufacturers cite laboratory studies showing reductions in wear.	Innovations are typically accompanied by cost increases, and devices providing small, incremental clinical benefits may be less likely to offer good value for any additional investment.

Table 2 (*continued*)

Classification	First author	Year	Definition 1	Definition 2	Definition 3
C	Chandra	2011	Authors propose implicitly a way to measure innovation in terms of economic impact.		
C	Gosset	2012	To be adopted, the new solution needs to save time in clinics to allow more patients to be treated or the new concept needs to reduce the cost by shifting the responsibility from an expensive staff member to a more affordable one.	In isolation, most ideas look worthy to pursue.[…] Established protocols of care or the way the medical staff organizes itself may leave no room to introduce an alternate test or a new treatment. […] thoroughly understand the business landscape that the new solution will be entering and derives revenue estimates for a company launching the new solution.	

A = Definitions based on the source and boundary conditions of the innovative process; B = Definitions based on the degree of discontinuity; C = Definitions based on innovation's impact and consequence.

of new elements are often beyond the control of involved actors [74].

In terms of regulation of healthcare markets, commonly justified on the basis of well-known market failures, [75] Lambooij et al. [52] found evidence that decisions by healthcare professionals on which innovation to adopt is embedded in a context that is influenced and shaped by the availability of resources on macro level and concluded that setting the level of resources available, as well as defining the rules of the game, deeply affects the choices of both physicians and companies. Smith and Sfekas [45] discuss instead the negative consequences of imposing financial restrictions on the producer-user relationship, generally applied to reduce the conflict of interest based on information asymmetries between physicians and decision-makers.

Definitions based on the degree of discontinuity

Based on the level of discontinuity observed, innovation can be classified as radical or incremental [28]. More specifically, Iserson and Chiasson [62] note that innovation in medicine falls into two broad categories: evolutionary and revolutionary. Building on known scientific theory and learned skills, evolutionary innovations pose few problems to physicians wishing to add them to their practice. Revolutionary developments are, in contrast, the "gee-whiz" breakthrough devices that change aspect of medical care. Semi-radical innovations represent a significant rather than a major improvement over existing technology [39]. In order to operationalize the measure of degree of discontinuity, patent citations' counts have been adopted. The advantage of patent citations' counts is that they allow both the identification of the pieces of knowledge that have been integrated in a new entity and, over time, the spaces of knowledge that the new entity has contributed to generate. For example, Chatterji et al. [59] used patent data to evaluate the cooperation between industry and physicians in medical innovative processes. However, measuring discontinuity using patent counts could play at best the role of proxy, [58] as they capture a limited amount of information throughout the innovation process. The subjective nature of the magnitude of innovation is initially recognized by Rogers and Shoemaker [30] who included individual perceptions in the definition of innovation as any product, idea or practice that is viewed as new by an individual or the adopting unit. In a similar way, Djellal and Gallouj [38] describe the concept of innovation in hospitals as multifaceted, with multiple dimensions falling in the realm of users' perceptions. The subjective facet of discontinuity de-objectifies the measurement of innovation and introduces the user as an endogenous element of innovation, instead of reducing its role to a mere component of the technology, technological complement or source of information about needs [70,71]. Users are characterized by a need, i.e. an unsolved problem, openness to new technologies, free space for creative thinking and access to interdisciplinary expertise [33,46]. Even though their role could be understood as limited to some phases of innovation, many studies have considered their contribution as a resource to the firm [42,47,48]. The role of users is explicitly addressed by Lettl [41,42] whose focus

is on users as promoters of creative search and inventors and (co)-developers of radical innovations. By examining the role of surgeons in developing robotic and computer assisted navigation systems, he observed that encountering the limits of conventional technologies motivated them to search for other, more workable solutions [42].

Definitions based on innovation's impact and consequences

When innovation in medical devices is identified by its impact on the intended outcome, the underlying definition is actually overlapping with its measurement. In fact, some authors focusing on the impact of innovation leave the definition implicit in the proposed measure. The impact on patient benefit is a common reference measure of innovation, often associated with costs [57,66]. As Trajtenberg states, [58] the necessary condition for a technical advance to be innovative was to generate additional consumer surplus in that field and time. What is a consumer surplus is rooted in microeconomic theory, [76] as Trajtenberg clearly states that the appropriate measure of surplus is welfare, as the "magnitude" of innovations equates the welfare gains they generate [58]. Cost-effectiveness is a convenient measure to simultaneously look at health outcomes and costs, and categories of innovation based on average cost-effectiveness have also been proposed [35]. Gullikson et al. suggest technology assessment as a tool for innovative medical technologies management that allows to control negative legal and economic consequences by assessing risk throughout the medical equipment lifecycle [40]. In 1996, Citron [61] suggested to measure innovations on the extent to which they meet and satisfy patients' needs, as some forms of clinical or patient-relevant indicator should be an essential component of innovation measurement [34]. Measuring impacts on relevant outcomes, such as better care, has been proposed as a necessary condition for rewarding innovators [67]. Under a service-delivery perspective, Boyle et al. [65] defined innovation as the ability of a new element to produce a variation in either the quality of healthcare or its costs. In this sense, the impact of innovation can fall outside the specific benefit to patients and users. Generally speaking, an innovation has usually an impact on interdependent technological systems, as well as on the society and social actors that are directly or indirectly influenced by the continuous need of advancing science and technology. The concept of "creative destruction", imported by Schumpeter from Marxist theory of capitalism, [77,78] can describe how the need for continuous advancement in scientific knowledge and technological progress negatively impact on the stability of pre-existing equilibria. Lexa [43] provided an example of creative destruction when discussing the case of the introduction of computer tomography scanners, at the expense of pneumo-encephalography. Other authors reshaped the concept in an organizational perspective [51,79]. They highlight that some innovations might have negative or unintended consequences mediated by the necessity of exposing firms to risky changes or by overlooking complementary element of the technological endowment of an organization.

Discussion

Our literature review shows that innovation in relation to medical devices has been defined in several ways, each focusing on specific traits of this multidimensional concept, often influenced by the perspective layer taken.

This broader concept of innovation contrasts with the narrower viewpoint taken by payers when assessing drugs. If we look at currently available tools of grading innovation at major reimbursement agencies around Europe, we see that they are mainly related to pharmaceuticals and rely upon the concept of therapeutic added value. In terms of categorical scales, the Transparency Commission of the French Health National Authority (HAS) grades the medical benefit assessment (ASMR) in five levels of therapeutic benefit [8]. The additional benefit of pharmaceuticals is categorised in six levels by the Federal Joint Committee according to the German Act on the Reform of the Market for Medical Products (AMNOG) [9]. In Italy the National Drug Agency (AIFA) has introduced in 2007a scale of innovativeness based on the availability of therapeutic alternatives (e.g. no alternatives or absolute contraindication to patients sub-groups; patients who do not respond to existing alternatives; presence of alternatives for the same indication) and added therapeutic value (e.g. major effects on final or surrogate validated endpoints; partial benefits on surrogate endpoints; minor or temporary impacts on symptoms) [10]. By fulfilling the accepted definitions of innovative drug in these countries, the manufacturers gain specific advantages: in France the ASMR is taken into account during price negotiation; discounts over list prices for drugs covered by the German Social Health Insurance are partially driven by benefit assessment [80]; in Italy drugs with a major added value are allowed to bypass further locally appraisal steps [81]. When comparing the emerging definitions of innovation found in the literature for medical devices with the current systems adopted to value drug innovation by payers, the main conclusion is that the meanings suggested by the scientific literature go beyond the change in the health outcomes, or therapeutic value, usually adopted by payers when appraising pharmaceuticals. On top of measures of clinically meaningful benefit, innovation, certainly when referred to medical technologies, usually encompasses a number of additional interrelated dimensions and consequences at the level of user/consumer, single organizations or whole system that have largely been overlooked by innovation scales used so far. These relate to meeting patients' or users' preferences, creating organizational features to improve quality or efficiency in service delivery, or fostering the overall innovativeness of the system.

In terms of degree of discontinuity introduced by innovation, available frameworks set different thresholds of uncertain origins that are barely applicable to medical technologies. Whilst occasionally single breakthrough technologies produces significant health gains in the reference population, further refinements of the technology itself or its use have produced important cumulative impact and better outcomes than would have been achieved by the initial technology [82]. This is the case with left ventricular assistive devices [83] or new fenestrated or chimney

versions of the endovascular repair of aortic aneurysms. In addition, when considering the degree of innovation, payers look at it *ex post*, i.e. in terms of results reached, and often seek to confirm with real world data what has been found in clinical experiments. On the other hand, applied definitions of breakthrough innovation in the academic literature envisages an *ex ante* paradigm shift. Hence, uncertainty is a major contextual factor in emerging definitions. It has been listed as a prerequisite for radical innovations to become successful, [84] that is an alternative way of framing the risk and opportunity trade-off [54]. Otherwise, this is a consequence of the focus payers give to static allocative efficiency or an ever more restricted cost-containment approach, whereas other policy-makers may be heralds of a dynamic and systemic vision of innovation, provided that a breakthrough innovation will activate future incremental innovations.

Another important aspect emerging from the literature is the crucial role played by the health innovation system and relationships among its players. Several authors stressed the relevance of relationships among organizations and single individuals, with a particular focus on relationships between users/clinicians and the industry, and the crucial role played by target users, particularly lead users. The relationship between lead users and the industry is considered a crucial factor for the development of innovations that become a standard for the future. Therefore, initiatives aimed at strengthening the relationships between users of medical devices and the industry should be encouraged. These may include actions intended to strengthen ideas into products or technology transfer initiatives, but also informal interaction within activities aimed at promoting a new technology (e.g. conferences, joint publications) [85]. Sustained and continuous interaction may enhance unpredicted consequences of the innovation process, fluid participation to decisional processes is a known factor influencing the coupling between problems and solutions. In this respect, also relationships between the industry and policy-makers, i.e. regulators and payers, in the forms of early scientific advice or public consultation should also be encouraged. Open innovation systems' benefits have been described also in hightech medical device companies as they can more easily capture the multifaceted ideas of scientists, engineers, clinicians and indeed patients [37].

We acknowledge potential limitations of this study whilst gauging its findings. First and foremost, we relied on published academic publications. Although other sources, such as policy briefs or magazines, may provide alternative definitions of innovation, the body of knowledge developed by the scientific community through peer-reviewed publications around the topic may be considered as an unbiased and expert source for the purpose of our study. We did not perform a formal quality appraisal of included papers in this systematic review because of the aim of this study (i.e. identifying definitions of innovation and not evaluating healthcare interventions). Also, we did not perform a systematic search for current available scales for innovation. We described and referred to evaluation frameworks in place at main public healthcare agencies in Europe, which, to the best of our knowledge, represent the most advanced attempts for grading innovation in health products.

Conclusion

Overall, our review found that innovation for medical devices has an important multidimensional and perceptive facet that should not be limited to therapeutic added value under the healthcare policy-makers perspective.

Policy-makers play an important role in the process of innovation since they intervene in different phases, and with multiple consequences, in the market relationships between innovators, producers, users and patients. The presence of regulation and policy in healthcare markets is generally justified on the basis of the relevance of market failures. Policy-makers are, therefore, expected to correct the negative consequences on outcomes, equity and sustainability that a free healthcare market would inevitably imply. In other words, policy-makers set the boundary conditions of the market by determining the rules of interaction between healthcare actors and by selecting the sample of services and goods that can be made available. According to the system, they also set payment and reimbursement conditions. Under a static efficiency perspective, the role of policy-makers is exogenous with respect to the process innovation. However, with respect to dynamic efficiency, a trade-off may emerge between ensuring a static beneficial equilibrium and giving sufficient incentives to market actors to constantly improve goods and services available in healthcare. Whilst *ex-ante* industrial policies aiming at supporting innovation and research cover different fields, direct incentives to sustain healthcare applications may still be useful. The responsibility of tight constraints and regulation goes, therefore, beyond the short-term need of ensuring sustainability to the system and information caveats on therapeutic added value at market launch. It impacts companies' ability to innovate by two mechanisms. First, tight regulation and constraints reduce the expected returns of innovation, by raising the minimum expected incremental contribution of a new product or service. Second, it increases the costs of innovation by limiting the potential synergies between demand and supply. In the long run, this situation may rebound on the sustainability conditions of the healthcare systems as artificial shrinks of net returns from innovation, an undesirable consequence that professionals at any level should try to prevent.

Author statements

Funding

This study was funded by the Drugs and Medical Devices Directorate at the Italian Department of Health. The publication of study results was not contingent on the funder's approval or censorship of the manuscript. The authors have no additional direct or indirect financial relationships with the sponsor.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

Not required.

Acknowledgment

This study was funded by the Drugs and Medical Devices Directorate at the Italian Department of Health under a program of research (n. VI) on the management of innovation and medical devices within the healthcare system. We thank the anonymous reviewers for the useful comments provided to improve the manuscript. Any errors or oversights are ours alone.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hlpt.2015.10.005.

References

[1] Aronson JK. Something new every day: defining innovation and innovativeness in drug therapy. J Ambul Care Manag 2008;31(1):65–8.
[2] Immelt JR. The Innovation Imperative 2004. Available from: ⟨http://www.ge.com/files/usa/company/news/cornell_transcript.pdf⟩.
[3] Huang H, Xu C. Institutions, Innovations, and Growth.
[4] Fagerberg J. Schumpeter and the revival of evolutionary economics: an appraisal of the literature.
[5] Nelson R, Winter S. An evolutionary theory of economic change. United States: Belknap Press; 1982.
[6] Lundvall BA. National systems of innovation: towards a theory of innovation and interactive learning. London: Pinter; 1992.
[7] Aronson JK, Ferner RE, Hughes DA. Defining rewardable innovation in drug therapy. Nat. Rev. Drug Discov 2012;11(4):253–4.
[8] Bouvenot G. The benefit provided by new medicinal products in 2005-2006–the viewpoint of the French National Authority for Health. Therapie 2007;62(5):387–91.
[9] Ruof J, Schwartz FW, Schulenburg JM, Dintsios CM. Early benefit assessment (EBA) in Germany: analysing decisions 18 months after introducing the new AMNOG legislation. The European journal of health economics: HEPAC: health economics in prevention and care. 2013.
[10] AIFA. Criteri per l'attribuzione del grado di innovazione terapeutica dei nuovi farmaci ed elementi per l'integrazione del dossier per l'ammissione alla rimborsabilità 2010 2010 [cited 2014 November]. Available from: ⟨http://www.agenziafarmaco.gov.it/allegati/documento_integrale.pdf⟩.
[11] Webb DJ. Value-based medicine pricing: NICE work? Lancet 2011;377(9777):1552–3.
[12] Ferner RE, Hughes DA, Aronson JK. NICE and new: appraising innovation. BMJ Clin Res Ed 2010;340:b5493.
[13] International Society of Drug Bulletins. ISDB Declaration on therapeutic advance in the use of medicines 2001 [cited 2014 November]. Available from: ⟨http://www.icf.uab.es/informacion/boletines/ISDB/ISDB.pdf⟩.
[14] Adami S, Ciampalini S, Dell'Aera M, Di Turi R, Ferrarese A, Messori A, et al. Defining innovations of therapeutic interventions: a position paper by the Italian Society of Hospital Pharmacists. Int J Clin Pharm 2012;34(2):259–62.
[15] Europe M. The European Medtech industry in figures 2013. Available from: ⟨http://www.medtecheurope.org/⟩.
[16] Kirisits A, Redekop WK. The economic evaluation of medical devices: challenges ahead. Appl Health Econ Health Policy 2013;11(1):15–26.
[17] Drummond M, Griffin A, Tarricone R. Economic evaluation for devices and drugs-same or different? Value Health: J Int Soc Pharmacoecon Outcomes Res 2009;12(4):402–4.
[18] Taylor RS, Iglesias CP. Assessing the clinical and cost-effectiveness of medical devices and drugs: are they that different? Value Health: J Int Soc Pharmacoecon Outcomes Res 2009;12(4):404–6.
[19] Gonzalez FM, Finch AP, Armeni P, Boscolo PR, Tarricone R. Comparative effectiveness of Mitraclip plus medical therapy versus medical therapy alone in high-risk surgical patients: a comprehensive review. Expert Rev Med Devices 2015;12(4):471–85.
[20] Council of the European Union. Proposal for a Regulation of the European Parliament and of the Council on medical devices and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009. 2012.
[21] The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0 ed2011.
[22] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ Clin Res Ed 2011;343:d5928.
[23] Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013;13:117.
[24] The Oxford Handbook of Innovation Management. New York, NY, United States of America: Oxford University Press, 2014.
[25] Cyert RM, March JG. A behavioral theory of the firm. NJ: Englewood Cliffs; 2.
[26] Schumpeter JA, Fels R. Business cycles. Cambridge, Massachusetts: Cambridge Univ Press; 1939.
[27] Dosi G. Technological paradigms and technological trajectories: a suggested interpretation of the determinants and directions of technical change. Res Policy 1982;11(3):147–62.
[28] Dunlap-Hinkler D, Kotabe M, Mudambi R. A story of breakthrough versus incremental innovation: corporate entrepreneurship in the global pharmaceutical industry. Strateg Entrepreneurship J 2010;4(2):106–27.
[29] McDade SR, Oliva TA, Pirsch JA. The organizational adoption of high-technology products "for use": effects of size, preferences, and radicalness of impact. Ind Mark Manag 2002;31(5):441–56.
[30] Rogers EM, Shoemaker FF. Diffusion of innovation: a cross-cultural approach. New York, 1983.
[31] Anderson P, Tushman ML. Technological discontinuities and dominant designs: a cyclical model of technological change. Adm Sci Q 1990;35(4):604–33.
[32] Abernathy WJ, Utterback JM. Patterns of innovation in technology. Technol Rev 1978;80(7):40–7.
[33] Ahn MJ, York AS, Rizova P. Pathways to biomedical tipping points: vertical, horizontal or other? J Comm Biotechnol 2010;16:224–38.
[34] Atluri P, Woo YJ. Minimally invasive robotic mitral valve surgery. Expert Rev Med Devices 2011;8(1):115–20.
[35] Amitabh Chandra, Jonathan Skinner. Technology growth and expenditure growth in health care. J Econ Liter 2012;50(3):645–80.
[36] Consoli D, Mina A. An evolutionary perspective on health innovation systems. J Evolut Econ 2009;19:297–319.
[37] Davey SM, Brennan M, Meenan BJ, McAdam R. Innovation in the medical device sector: an open business model approach for high-tech small firms. Technol Anal Strateg Manag 2011;23:807–24.

[38] Djellal F, Gallouj F. Mapping innovation dynamics in hospitals. Res Policy 2005;34:817–35.
[39] Ghodeswar BM, Vaidyanathan J. Organisational adoption of medical technology in healthcare sector. J Serv Res 2007;7:57–81.
[40] Gullikson ML, David Y, Blair CA. The role of quantifiable risk factors in a medical technology management program, 1996.
[41] Letti C, Hienerth C, Gemuenden HG. Exploring how lead users develop radical innovation: opportunity recognition and exploitation in the field of medical equipment technology. IEEE Trans Eng Manag 2008;55:219–33.
[42] Lettl C. User involvement competence for radical innovation. J Eng Technol Manag 2007;24:53–75.
[43] Lexa FJ. Med Entrepreneurism: Curr Oppor Am 2004;1:762–8.
[44] Morlacchi P, Nelson RR. How medical practice evolves: learning to treat failing hearts with an implantable device. Res Policy 2011;40:511–25.
[45] Smith SW, Sfekas A. How much do physician-entrepreneurs contribute to new medical devices? Med. Care 2013;51:461–7.
[46] Weigel S. Medical technology's source of innovation. Eur Plan Stud 2011;19:43–61.
[47] Xu S, Avorn J, Kesselheim AS. Origins of medical innovation. Case Coron Artery Stents 2012;5:743–9.
[48] Chatterji AK, Fabrizio K. How do product users influence corporate invention? Org Sci 2012;23:971–87.
[49] Galbrun J, Kijima KJ. Fostering innovation in medical technology with hierarchy theory: narratives on emergent clinical solutions. Syst Res Behav Sci 2010;27(5):523–36.
[50] Graham SJH, Merges RP, Samuelson P, Sichelman T. High Technology Entrepreneurs And The Patent System: Results Of The 2008 Berkeley Patent Survey Berkeley Technology Law Journal. 2009;24:1255–327.
[51] Karim S. Business unit reorganization and innovation in new product markets. Manag Sci 2009;55(7):1237–54.
[52] Lambooij MS, Engelfriet P, Westert GP. Diffusion of innovations in health care: does the structural context determine its direction? 2010;26:415–20.
[53] Littell CL. Innovation in medical technology: reading the indicators. Health Aff (Project Hope) 1994;13(3):226–35.
[54] Moosmayer DC, Koehn A. The moderating role of managers'uncertainty avoidance values on the performance impact of radical and incremental innovation. Int J Bus Res 2011;11:6.
[55] Pullen A, de Weerd-Nederhof PC, Groen AJ, Fisscher OAM. SME. Network characteristics vs. product innovativeness: how to achieve high innovation performance. Creativity Innov Manag 2012;21:130–46.
[56] Reitsma AM, Moreno JD. Ethics of innovative surgery: US surgeons' definitions, knowledge, and attitudes. J Am Coll Surg 2005;200:103–10.
[57] Suter LG, Paltiel AD, Rome BN, Solomon DH, Golovaty I, Gerlovin H, et al. Medical device innovation-Is "better" good enough? United States: Massachussetts Medical Society (860 Winter Street, Waltham MA 02451-1413, United States); 2011 [cited 365 (Suter) Yale School of Medicine, New Haven, CT, United States]. 16:[1464-6]. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMp1109285, ⟨http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2011580418⟩.
[58] Trajtenberg M. The welfare analysis of product innovations, with an application to computed tomography scanners. J Polit Econ 1989;97:444.
[59] Chatterji AK, Fabrizio KR, Mitchell W, Schulman KA. Physician-industry cooperation in the medical device industry. Health Aff 2008;27(6):1532–43.
[60] Anderson G, Steinberg E, Heyssel R. The pivotal role of the academic health center. Health Aff 1994;13:146–58.
[61] Citron P. Medical devices: factors adversely affecting innovation. J Biomed Mater Res 1996;32:1–2.
[62] Iserson KV, Chiasson PM. The ethics of applying new medical technologies. Semin Laparosc Surg 2002;9:222–9.
[63] Roberts EB.Technological innovation and medical devices. 2003.
[64] Morscher EW. Failures and successes in total hip replacement – why good ideas may not work. 2003;92:113–20.
[65] Boyle J, Maeder A, Bell J, John S, Scott R. Medical device research. Expert Rev Med Devices 2005;2:41–5.
[66] Gosset N, Lasch JG. Accelerating medical innovation at USC: realizing the dream of Alfred E. Mann. IEEE Pulse 2012;3(4):46–8.
[67] Buying New Technology. Health Affairs. 2008;27:1619.
[68] Pullen A, de Weerd-Nederhof PC, Groen AJ, Fisscher OAM. SME network characteristics vs. product innovativeness: how to achieve high innovation performance. Creativity Innov Manag 2012;21(2):130–46.
[69] Gelijns A, Rosenberg N. The dynamics of technological change in medicine. 1994;13:28–46.
[70] Von Hippel E. Lead users: a source of novel product concepts. Manag Sci 1986;32(7):791–805.
[71] Von Hippel E. Democratizing innovation: the evolving phenomenon of user innovation. Int J Innov Sci 2009;1(1):29–40.
[72] Camarillo DB, Krummel TM, Salisbury Jr JK. Robotic technology in surgery: past, present, and future. Am J Surg 2004;188(4A Suppl):2S–15S.
[73] de Ruijter V, Halvax P, Dallemagne B, Swanstrom L, Marescaux J, Perretta S.The Business Engineering Surgical Technologies (BEST) teaching method: incubating talents for surgical innovation. Surgical endoscopy. 2014.
[74] Cohen MD, March JG, Olsen JP. A garbage can model of organizational choice. Adm Sci Q 1972:1–25.
[75] Donaldson C, Gerard K, Mitton C, Jan S, Wiseman V. Economics of health care financing: the visible hand.2nd ed. Basingstoke: Hampshire: Palgrave Macmillan; 2004.
[76] Frank RH, Glass AJ. Microeconomics and behavior. New York: : McGraw-Hill; 1997.
[77] Schumpeter JA. Creative destruction. Capitalism, socialism and democracy. 1942.
[78] Schumpeter JA. The theory of economic development. an inquiry into profits, capital, credit, interest, and the business cycle. New Brunswick: NJ: London: Transaction Publishers; 1934.
[79] Henderson RM, Clark KB. Architectural innovation: the reconfiguration of existing product technologies and the failure of established firms. Adm Sci Q 1990:9–30.
[80] Jommi C, Dellamano L. Valutazione del beneficio incrementale e prezzo di cessione per i farmaci rimborsati: il caso dell'AMNOG tedesco. PharmacoEconomics Italian Research Articles 2013;15(Suppl):S25–33.
[81] Jommi C, Costa E, Michelon A, Pisacane M, Scroccaro G. Multitier drugs assessment in a decentralised health care system. The Italian case-study. Health Policy 2013;112(3):241–7.
[82] Henshall C, Schuller T. Health technology assessment, value-based decision making, and innovation. Int J Technol Assess Health Care 2013;29(4):353–9.
[83] Gelijns AC, Russo MJ, Hong KN, Brown LD, Ascheim DD, Moskowitz AJ. Dynamics of device innovation: implications for assessing value. Int J Technol Assess Health Care 2013;29(4):365–73.
[84] Ergeneli A, Gohar R, Temirbekova Z. Transformational leadership: its relationship to culture value dimensions. Int J Intercult Relat 2007;31(6):703–24.
[85] Tarricone R, Ferre' F, Torbica A, Drummond M. Generating appropriate clinical data for value assessment of medical devices: what role does regulation play? Expert Rev Pharmacoecon Outcomes Res 2014;14(5):707–18. Oct.