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Enthusiastic Portrayal of 3D Bioprinting in the Media: Ethical side effects.

Abstract: There has been a surge in mass media reports extolling the potential for using three-dimensional printing of biomaterials (3D bioprinting) to treat a wide range of clinical conditions. Given that mass media is recognised as one of the most important sources of health and medical information for the general public, especially prospective patients, we report and discuss the ethical consequences of coverage of 3D bioprinting in the media. First, we illustrate how positive mass media narratives of a similar biofabricated technology, namely the Macchiarini scaffold tracheas, which was involved in lethal experimental human trials, influenced potential patient perceptions. Second, we report and analyze the positively biased and enthusiastic portrayal of 3D bioprinting in mass media. Third, we examine the lack of regulation and absence of discussion about risks associated with bioprinting technology. Fourth, we explore how media misunderstanding is dangerously misleading the narrative about the technology.

Keys words: 3D Printing, Bioprinting, Experimental trial, Human trial, Informed consent, Media, Prospective Participants, Positive Narrative, Risk of Harms. .

INTRODUCTION

There has been a recent surge in research on three-dimensional printing (3D printing),¹ especially for applications in medicine.² When looking more closely at how 3D printing may have the potential to impact some treatments, we observe that printing technology has been portrayed in the media as successfully fulfilling multiple medical purposes from custom-made, biodegradable, life-saving bronchial implants to orthopaedic, patient-specific transplants.³

As printing technology evolved to incorporate different materials, including living cells, into the printing process,⁴ the new field of ‘three-dimensional printing of biomaterials’ (3D bioprinting) was born. For the purposes of this work, we are distinguishing *biomedical applications* of 3D printing not involving live cells from *3D bioprinting*.⁵ The former incorporates 3D printing of surgical tools, implantable or wearable prostheses made from traditional materials. The latter, in contrast, refers to 3D printing of bioinks that include living cells (typically stem cell lines), and usually also include biocompatible scaffolds for growing these cells

¹ E.L. Neely. The Risks of Revolution: Ethical Dilemmas in 3D Printing from a US Perspective. *Sci Eng Ethics* 2016; 22: 1285-1297.

² G.G. Wallace, et al. 2014. *3D Bioprinting: Printing Parts for Bodies* ARC Centre of Excellence for Electromaterials Science: 153.

³ D.A. Zopf, et al. Bioresorbable airway splint created with a three-dimensional printer. *N Engl J Med* 2013; 368: 2043-2045; DukeHealth.org. 2015. *3-D printed Bone Implant Saves Woman's Leg*. DukeHealth. Available at <https://www.dukehealth.org/blog/3-d-printed-bone-implant-saves-womans-leg> [Accessed 19 Sept 2016]; R.J. Morrison, et al. Mitigation of Tracheobronchomalacia with 3D-printed Personalized Medical Devices in Pediatric Patients. *Sci Transl Med* 2015; 7: 285ra264-285ra264; R.J. Morrison, et al. Regulatory Considerations in the Design and Manufacturing of Implantable 3D-Printed Medical Devices. *Clin Transl Sci* 2015; 8: 594-600.

⁴ S.V. Murphy & A. Atala. 3D Bioprinting of Tissues and Organs. *Nature Biotechnol* 2014; 32: 773-785.

⁵ F Gilbert et al. Print Me an Organ? Ethical and Regulatory Issues Emerging from 3D Bioprinting in Medicine. *Sci Eng Ethics*. 2017 Feb 9. doi: 10.1007/s11948-017-9874-6

into tissues, which may be used to improve understanding of tissue functioning, for *in vitro* testing of drugs, or for implantation into patients. We define ‘bioink’ as *an ink that includes biological materials engineered to convey living cells through a printing process for fabricating biological constructs*.⁶ Bioink is being used as a tool for tissues engineering, including neural engineering work to create potential treatment.⁷

Reports involving 3D bioprinting have increased in the scientific literature with an increasing number of laboratories and hospitals adopting the technology in various research and medical settings.⁸ A search we conducted of resources listed through PubMed using the term ‘3D bioprinting’ showed a rapid expansion in the number of English language publications, especially in 2015 and 2016 (See Figures 1a and 1b). In the current academic literature, 3D bioprinting is being portrayed as addressing various needs for 1) biological tissue for a large range of applications,⁹ (2) patient-specific drug dosage,¹⁰ 3) customized prosthetics,¹¹ and 4) medical education purposes.¹² The number of patents for 3D-bioprinting-related technologies has followed a similar trajectory of expansion since 2015 (see Figures 1c and 1d).

⁶ Ibid.

⁷ J. L. Bourke, et al. Three-dimensional neural cultures produce networks that mimic native brain activity. *Journal of Tissue Engineering and Regenerative Medicine*. DOI: 10.1002/term.2508

⁸ B.C. Gross, et al. Evaluation of 3D Printing and its Potential Impact on Biotechnology and the Chemical Sciences. *Anal Chem* 2014; 86: 3240-3253.

⁹ Murphy & Atala, op. cit. note 4; K. Jakab, et al. Tissue Engineering by Self-assembly and Bio-printing of Living Cells. *Biofabrication* 2010; 2: 022001; F. Marga, et al. Toward Engineering Functional Organ Modules by Additive Manufacturing. *Biofabrication* 2012; 4: 022001.

¹⁰ I. Urgan, et al. Three-dimensional Drug Printing: A Structured Review. *J Am Pharm Assoc* 2013; 53: 136-144; FDA.gov. 2015. *SPRITAM*. FDA, Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207958s000lbl.pdf [Accessed 19 Sept 2016].

¹¹ C. Schubert, et al. Innovations in 3D Printing: a 3D Overview from Optics to Organs. *Br J Ophthalmol* 2014; 98: 159-161.

¹² J.A. Gillis & S.F. Morris. Three-dimensional Printing of Perforator Vascular Anatomy. *Plast Reconstr Surg* 2014; 133: 80e-82e.

With the rise in scientific publications related to 3D bioprinting and patent applications, there is a corresponding increased coverage of this technology in English-speaking media. A media search through FACTIVE Database to December 31, 2016 yielded 1734 articles on 3D bioprinting (See Figure 2). A sharp increase of media reporting of 3D bioprinting occurred from 2014 to 2015 (See Figure 2), with even further increases in 2016. This trend is similar to increases in PubMed-indexed scientific publications and World Intellectual Property Organization-indexed patents.

Mass media is identified among the most important sources of health information for the general public.¹³ Popular media can bias public perceptions of risk related to diseases.¹⁴ Some studies have shown that members of the general public and patients try to educate themselves about potential treatments from uncritical sources, such as television and the internet, leading to inflated hopes.^{15 16} A recent study has shown that patients prefer learning about treatments from iPads than from doctors when discussing their surgery.¹⁷ These studies indicate that mass media influences patient education, comprehension, and understanding of health issues. In that respect, content and stereotypes disseminated through mass media influence prospective patients' hopes and expectations. In particular, studies have demonstrated that positive portrayals of a novel technology in the media indirectly

¹³ G. Schwitzer, et al. What Are the Roles and Responsibilities of the Media in Disseminating Health Information? *PLoS Med* 2005; 2: e215.

¹⁴ M.E. Young et al. Medicine in the Popular Press: The influence of the Media on Perceptions of Disease. *Plos One* 2008; 3(10): e3552.

¹⁵ L.J. Schneiderman. The Perils of Hope. *Camb Q Healthc Ethics* 2005; 14: 235-239; S.J. Diem, et al. Cardiopulmonary Resuscitation on Television. Miracles and Misinformation. *N Engl J Med* 1996; 334: 1578-1582.

¹⁶ C.K. Daugherty. The "cure" for cancer: Can the media report the hope without the hype? . *J Clin Oncol* 2002; 20: 3761-3764.

¹⁷ European Association of Urology. 2016. *Study Shows Patients Prefer iPads to Doctors when Discussing Surgery*. *ScienceDaily*. Available at <https://www.sciencedaily.com/releases/2016/03/160314085043.htm> [Accessed 19 Sept 2016].

affect patient consent to undergo treatment.¹⁸ Studies have also demonstrated that media coverage prompted prospective participants to contact their physician to enroll in phase I clinical trial.¹⁹ A study has shown that risks disclosed in informed consent have little impact on patients' decision to enroll in trial as their choice to participate has been determined long before.²⁰ Evidence gathered from all these studies suggest that media depiction of a specific technology can substantially impact the public, especially prospective patients.

How 3D bioprinting is portrayed in mass media is crucial in shaping public understanding of the technology's clinical application, especially for prospective patients prior to consenting to surgery. Beyond the hype, we report on and critically discuss the ethical implications of this increased coverage of 3D bioprinting in mass media – coverage that often appears to be biased and enthusiastic in its portrayal. We start by discussing how the positive depiction of a similar technology in the media, Macchiarini scaffold tracheas, influenced public and potential patient perceptions, despite the absence of sound evidence to support the clinical use of the technology; second, we report and analyze portrayal of 3D bioprinting in mass media; third, we examine the lack of regulation and absence of discussion about risks associated with the technology; and fourth, we explore how media misunderstanding is shaping the narrative about the technology in ways that may increase risk of harm.

¹⁸ E. Bell, et al. Hope and Patients' Expectations in Deep Brain Stimulation: Healthcare Providers' Perspectives and Approaches. *J Clin Ethics* 2010; 21: 112-124.

¹⁹ R. D. Pents et al. Study of the Media's Potential influence on prospective research participants' understanding of and motivations for participation in a high-profile phase I trial. *J Clin Oncol* 2002; 20(18): 3785-3791.

²⁰ H. Nakada et al. *Does informed consent function for decision making process? : patients' perspective and experiences of clinical trials in Japan*. 13th World Congress of Bioethics, IAB 2016

POSITIVE REPORTING OF BIOFABRICATION: 7 PATIENTS DEAD OUT OF 9 IMPLANTED.

The first biofabricated scaffold tracheas were experimentally implanted in nine patients between July 2011 and June 2014. Looking back at how mass media reported these biofabricated implants can offer some insight into the potential effects of current media coverage of 3D bioprinted therapies. In July 2011, Mr. Andemariam Beyene became the first patient to be implanted with a tailor-made stem-cell-seeded implant. The mass media reporting portrayed the intervention as a complete success and celebrated it as a medical breakthrough.²¹ As a consequence, Mr. Beyene became something of a local and international star patient. In the weeks and months following the intervention, Mr. Beyene gave interviews to news outlets and to TV and radio reporters from several major international media.²² A few months after implantation of the trachea, *The Lancet* published an article discussing its success, by indicating that Mr. Beyene had an ‘almost normal airway’, was free of infection, and was growing new tissue.²³ The media reports helped Dr. Macchiarini, the lead thoracic surgeon involved in the trial, to gain fame. As a result of Mr. Beyene’s story appearing in the global media, prospective patients began to request access to this experimental treatment. In an article published by *NPR* right after first positive media reports of Mr Beyene’s

²¹ M. Roberts. 2011. *Surgeons Carry Out First Synthetic Windpipe Transplant*. BBC Health. Available at <http://www.bbc.com/news/health-14047670> [Accessed 16 Sept 2016]; R. Knox. 2011. *Cancer Patient Gets First Totally Artificial Windpipe*. NPR. Available at <http://www.npr.org/sections/health-shots/2011/07/20/137701848/cancer-patient-gets-first-totally-artificial-windpipe> [Accessed 16 Sept 2016]; R. Flinn. 2011. *World’s First Laboratory-Grown Windpipe Transplanted*. Bloomberg. Available at <http://www.bloomberg.com/news/articles/2011-07-07/world-s-first-laboratory-grown-windpipe-is-transplanted-in-patient> [Accessed 16 Sept 2016].

²² Roberts, op. cit. note 20; Knox, op. cit. note 20; Flinn, op. cit. note 20; New Tang Dynasty (NTD) Television. 2011. *First Successful Transplant of Trachea Made of Stem Cells*. YouTube. Available at <https://www.youtube.com/watch?v=GyQWAIu0w> [Accessed 16 Sept 2016].

²³ P. Jungebluth, et al. Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. *Lancet* 2011; 378: 1997-2004.

intervention, Macchiarini declared: ‘I checked my inbox this morning, [...] and already had an email from a Boston surgeon who said, “We have patients who could benefit from this, are you interested in collaborating?”’.²⁴

In September 2012, *The New York Times* interviewed Macchiarini and Mr. Beyene, explaining how the life of the latter was saved by the intervention of the former: ‘Now, 15 months after the operation, Mr. Beyene, [...] is tumor-free and breathing normally.’ In this interview, Macchiarini indicated that patients implanted in Russia ‘ha[d] been discharged from the hospital and [we]re doing well’. This article noted that one American patient died, but it quickly stressed that ‘Dr. Macchiarini said that the implant had been functioning well’.²⁵ We argue that these are illustrations of how a positively-biased narrative influenced the media’s reporting about an experimental technology; particularly the use of the now famous thoracic surgeon’s comments and work at face value, without question.

However, the reality was far from positive for many implanted patients. An independent report and separate investigation requested by the Karolinska Institute, where some of the experimental work took place, raised alarming ethical violations, scientific misconduct, and fraud.²⁶ The biofabricated scaffold had not been first tested on animals; the patients’ conditions had not been not immediately life threatening therefore did not require immediate surgical intervention; no proper

²⁴ Knox, op. cit. note 20.

²⁵ H. Fountain. 2012. *A First: Organs Tailor-Made With Body’s Own Cells*. The New York Times. Available at http://www.nytimes.com/2012/09/16/health/research/scientists-make-progress-in-tailor-made-organs.html?_r=0 [Accessed 16 Sept 2016].

²⁶ S. Heckscher, et al. 2016. *Karolinska Institutet and the Macchiarini case. Summary in English and Swedish*. Karolinska Institute. Available at http://ki.se/sites/default/files/karolinska_institutet_and_the_macchiarini_case_summary_in_english_and_swedish.pdf [Accessed 16 Sept 2016]; Karolinska Institute. 2016. *The Macchiarini Case: Investigation of the Synthetic Trachea Transplantations at Karolinska University Hospital*. Karolinska Institute. Available at [http://www.sll.se/Global/Verksamhet/H%C3%A4lsa%20och%20v%C3%A5rd/Nyhet%20bilaga/The%20Macchiarini%20Case%20Summary%20\(eng\).pdf](http://www.sll.se/Global/Verksamhet/H%C3%A4lsa%20och%20v%C3%A5rd/Nyhet%20bilaga/The%20Macchiarini%20Case%20Summary%20(eng).pdf) [Accessed 16 Sept 2016].

informed consent process was followed; and the overall conclusion was that ‘there was not an adequate scientific foundation for a human transplant of a synthetic trachea seeded with bone marrow cells, combined with the application of growth-stimulating drugs’.²⁷ Mr. Beyene’s condition, as with cases of other patients implanted with the biofabricated scaffold, was far from what was described in both scientific and mass media. Following the transplant of the trachea, he suffered from repeated infections, and his trachea needed to be held open by a series of stents.²⁸ In January 2014, Mr. Beyene died. His autopsy revealed that the synthetic trachea had come loose. According to the Swedish public service broadcaster *SVT* and the *BBC*, seven out of nine patients implanted in different countries with the same technology died.²⁹ This experimental trial has become the ‘biggest scandal’ in Swedish medicine while tarnishing some Nobel Prize committee members involved in the decision to allow the experimental treatment to proceed.³⁰ The Swedish Medical Products Agency subsequently filed a police report against Karolinska University Hospital for violating the Medicinal Products Act, and the Health and Social Care Inspectorate filed a police report against the hospital for violating the Ethical Review Act.³¹ Currently, a public prosecutor in Stockholm is investigating the three operations that took place at Karolinska University Hospital, and it will decide ‘whether to press charges equivalent to manslaughter and grievous bodily harm’.³²

²⁷ Ibid.

²⁸ L. Schneider. 2016. *Macchiarini’s Patients, the Real Situation. For Better Science* Wordpress. Available at <https://forbetterscience.wordpress.com/2016/05/07/> [Accessed 16 Sept 2016].

²⁹ W. Kremer. 2016. *Paolo Macchiarini: A Surgeon’s Downfall*. BBC World Service. Available at <http://www.bbc.com/news/magazine-37311038> [Accessed 16 Sept 2016].

³⁰ Heckscher, et al, op. cit. note 25; Karolinska Institute, op. cit. note 25; T.M. Andrews. 2016. ‘*Biggest Scandal*’ in Swedish Medicine Leaves Two People Dead and Tarnishes Nobel Prize. National Post. Available at <http://news.nationalpost.com/news/world/biggest-scandal-in-swedish-medicine-leaves-two-people-dead-and-tarnishes-nobel-prize> [Accessed 2016 sept 16].

³¹ Heckscher, et al, op. cit. note 25; Karolinska Institute, op. cit. note 25.

³² Kremer, op. cit. note 28.

By using the Macchiarini case as an example, we want to highlight that positive reporting can directly impact prospective patients and can contribute to the continuation of experimental trials that are unsafe. The case is characterized by the fact that mass media depictions were dominated by very positive patient stories, description of the technology as a revolution, and overly-positive reporting of the experimental outcomes. In addition, there were very few critical reports or reporting on ethical and safety concerns; and when criticisms did surface, they were initially refuted or ignored by the Karolinska University Hospital. A result of the positive narrative through media reports, some patients may have sought a treatment that proved to be dangerous. As mention above, some doctors directly solicited Macchiarini to enrol their patients. Given the similarity between biofabrication of the synthetic tracheas and 3D bioprinting for implants, is there evidence that the media portrayal of the latter repeats the mistakes and biases of the former? Research on 3D printed custom-made, biodegradable, bronchial implants has already advanced,³³ so coverage and reporting of 3D bioprinting might create the conditions for another case similar to the Macchiarini case in 3D bioprinting, unless the positive media portrayals are balanced with critical assessment of existing evidence.³⁴

PORTRAYAL OF 3D BIOPRINTING IN MASS MEDIA

³³ Zopf, et al., op. cit. note 3; Morrison, et al., op. cit. note 3(a); Morrison, et al., op. cit. note 3(b).

³⁴ In addition to being reported in a biased manner in the media. Macchiarini's experimental surgery violated a number of Swedish regulations and should never have been allowed to proceed; independent of the favourable media coverage. Nonetheless, the media played a key role in promoting the trial and creating conditions that made it easy to overlook the ethical defects of the trial, given the high profile the media gave Macchiarini. We acknowledge the anonymous reviewer for this clarification.

We analyzed English language media coverage of 3D bioprinting technology to understand how its mass media coverage could potentially shape patients' hopes and beliefs about potential resulting treatments. A search through the FACTIVE Database until June 15, 2016 yielded 1734 (1311 relevant) articles on 3D bioprinting (See Figure 2). FACTIVE is a database developed by DowJones as a business research and information tool that collects content from newspapers, journals, magazines, blogs, images and other electronic coverage. We used the search term *((("3D" or "3-D" or "three dimensional" or "three-dimensional") AND ("bioprinting" or "bioprinted" or "bioprint")))* to select articles. An independent researcher assessed the articles for relevance, which were then coded systemically. Articles focusing on an issue unrelated to bioprinting, articles providing only minimal original content, or articles presented in a format that could not be coded were discarded (287 articles were deemed irrelevant). Coding of articles was based on an in-depth assessment of relevant content. Coding established: (A) source of articles (publications, web news, blogs, Dow Jones, noticeboards); (B) title and dates; and determined whether the articles (C) refer to a patient life-changing story; (D) portray bioprinting in an positive manner (unbalanced depiction in favor of benefits of the technology, with no supporting evidence, using positive language and terminology);³⁵ (E) mention risk, safety, and ethical concerns; (F) allude to printing organs; and/or (G) describe bioprinting as a revolution.

In our search, we observed that more than 86.7% of articles portrayed 3D bioprinting positively (Figure 3); 32.7% of articles alluded to the possibility of printing organs in the near future and 7.08% of articles described 3D bioprinting as revolutionary. In addition, these positive reports frequently conflated the preliminary experimental data with demonstrated clinical effectiveness and safety.

³⁵ C.H. Vinkers, et al. Use of Positive and Negative Words in Scientific PubMed Abstracts Between 1974 and 2014: Retrospective Analysis. *BMJ* 2015; 351.

For example, in 2011, an article first published by *Agence France-Presse* and widely disseminated, claimed that Prof. Anthony Atala had ‘printed’ a human kidney using a machine that eliminates the need for donors for organ transplants during a Technology, Entertainment and Design (TED) talk.³⁶ Wake Forest University where Atala is affiliated issued a press release the following day that discredited the *Agence France-Presse* report, stating “Reports in the media that Dr. Anthony Atala printed a real kidney at the TED conference in Long Beach, Calif., are completely inaccurate.”³⁷ Subsequently, the video of the TED talk also included a disclaimer saying ‘These printed kidney structures are early prototypes that are being studied experimentally and are years away from functional and clinical use’.³⁸ Nonetheless, the positive *Agence France-Presse* report had already reached a wide audience who are likely to have accepted the earlier report uncritically. This example illustrates that across a range of media outlets, it is very difficult for researchers to ‘control’ what is disseminated in mass media ‘news’.

We found that 1.22% of mass media reports in our sample included descriptions of how bioprinting has changed patients’ lives. Although this number is low, it is surprising to find such an association being made between a patient’s story and bioprinting, *given that no clinical trials incorporating 3D-printed cells have been scientifically reported*. In that respect, the media disseminates misleading news, which leads to confusion about the current availability of 3D bioprinting as a clinical treatment. For example, a news article discussing how a 3D-printed nose

³⁶ K. Yandell. 2013. *Organs on Demand*. The Scientist. Available at <http://www.the-scientist.com/?articles.view/articleNo/37270/title/Organs-on-Demand/> [Accessed 13 Aug 2016].

³⁷ K. Richardson. 2011. *Media Reports on Kidney Printing Inaccurate*. Wake Forest University. Available at <https://web.archive.org/web/20110310061956/http://www.wfubmc.edu/Research/WFIRM/Media-Reports-on-Kidney-Printing-Inaccurate.htm/> [Accessed 16 April 2017].

³⁸ Ted.com. 2011. *Anthony Atala: Printing a Human Kidney*. Ted. Available at https://www.ted.com/talks/anthony_atala_printing_a_human_kidney?language=en [Accessed 13 Aug 2016].

was successfully implanted on a boy (Dalan) by a New York clinic named Dagan MD, states: ‘As a direct result of Dagan’s innovative 3-d bioprinting technology, Dalan’s face, skull, nose and most importantly, his confidence have been restored’. In addition, the phrase ‘3-d bioprinting technology’ is hyperlinked to the website of Dagan MD.³⁹ These illustrate a conflation between traditional 3D printing technology, used in this case used as a surgical model to help reconstruct the cartilaginous parts of the boy’s nose with donor cartilage, with 3D bioprinting, which concerns the implantation of printed biomaterials and living cells.⁴⁰ The potential danger here is that readers could attribute an operation’s success to ‘3d bioprinting’, believing that it is a mature, clinically available technology, when it is currently not. This conflation has the potential to cloud the judgement of patients or prospective participants in future clinical trials. In contrast to the Macchiarini case, the number of reports that refer to life-changing outcomes are modest, but again, *given the technology has not been used yet in humans, it is concerning to see that several news articles have already referred to its use in humans.* We believe that

³⁹ This might lead some people to think that Dagan MD indeed offers 3d bioprinting-based surgeries and that this innovative “3-d bioprinting technology” is what actually led to the success of the operation; when in fact, they did not print any cells and just utilised traditional fabrication techniques. Prweb.com. 2016. *3D Printing Used to Give a New Nose to a Badly Burned Young Boy*. Prweb. Available at

<http://www.prweb.com/releases/2015/12/prweb13120518.htm> [Accessed 2016 Sept 17].

⁴⁰ Another alarming example is the 2013 Associated Press article entitled ‘3D printing of airway tube helps save U.S. baby’, which was widely distributed through new services, positively reported the story of the treatment of baby Kaiba as a life-saving intervention while portraying surgeons as heroes. See The Associated Press. 2013. *3D printing of airway tube helps save U.S. baby*. CBC News. Available at

<http://www.cbc.ca/news/health/3d-printing-of-airway-tube-helps-save-u-s-baby-1.1347835> [Accessed 3 Sept 2016]. While this article does not use the term *bioprinting* (therefore not included in our result-sample), the implant was ‘made from biodegradable polyester’;

nevertheless, it is another clear illustration of some confusions about the actual usage of 3D printing in medicine. See The Associated Press, op. cit. note 38. The implanted trachea was not 3D printed. Rather, it was cast from a 3D printed mould. See Zopf, et al., op. cit. note 3. In another instance, in an article published in the New Yorker, entitled ‘Print Thyself. How 3-D printing is revolutionizing medicine’, the author positively described several successful medical applications of 3D printing, which have changed or saved the life of some patients, then introduced bioprinting by using the idea that ‘as scientists make more concerted efforts to grow organs in the lab, the question is no longer whether they will succeed but how’. See J. Groopman. 2014. *PRINT THYSELF 2014. How 3-D printing is revolutionizing medicine*. The New Yorker. Available at <http://www.newyorker.com/magazine/2014/11/24/print-thyself> [Accessed 19 Sept 2016]. These examples illustrate of positive narrative can increase hope and expectation from prospective patients.

this way of reporting the technology could generate a similar news-driven narrative to the Macchiarini case, should a team succeed in testing bioprinting in humans.

An in-depth search of articles through our coding revealed that little attention has been given to potential safety problems or other risks associated with 3D bioprinting. Overall, we found that only 2.44 % of media reports mentioned potential ‘safety, risk and ethics issues’ in relation to clinical applications for 3D bioprinting. It must be stressed that this 2.44 % included any article referring to plausible ‘safety, risk and ethics issues’, despite the fact that most of these accounts were limited to a few words of caution in an otherwise disproportionately positive representation.

This enthusiastic depiction of 3D bioprinting, combined with a lack of coverage of safety and ethical concerns, could be attributed to the lack of discussion of such issues in academic journals (Figure 4). A search of PubMed, Embase, and Web of Science resulted in 799 publications on 3D bioprinting until March 31, 2017, only 30 (3.75%) of which mentioned ethics and/or safety in the title and/or abstract (Fig. 4a). Not surprisingly, the majority of articles discussing bioprinting in scientific journals are focusing on basic technical aspects of the technology. Most of them did not primarily address its clinical applications, explaining the low percentage of articles that discuss potential ethical issues or highlight safety concerns. It is concerning nonetheless that these aspects of bioprinting are rarely raised in either scientific or bioethics journals. Surprisingly, the top 30 bioethics journals (based on International Scientific Indexing and Google Scholar metrics) have not really contributed to ethical discussion on bioprinting despite the growing coverage of bioprinting in scientific journals, as shown by only one article mentioning ‘bioprinting’ in any of these journals even though there were 119 articles on bioengineering in the same time period (Fig. 4b). Following these observations, 3D

bioprinting may have gained popularity in public opinion and clinical practice before robust academic discussions and evaluation of relevant safety, efficacy, and ethical concerns have taken place.

LACK OF REGULATION AND ABSENCE OF DISCUSSION REGARDING RISK OF HARMS

There are currently substantial regulatory uncertainties regarding 3D bioprinting.⁴¹ For instance, in the US, the Federal Drug Administration (FDA) does not address the use or incorporation of biological, cellular, or tissue-based products in 3D printing. According to the FDA's recent *Technical Considerations for Additive Manufactured Devices*, biological, cellular or tissue-based products manufactured using 3D printing technology 'may necessitate additional regulatory and manufacturing process considerations and/or different regulatory pathways'.⁴² Current FDA guidelines refer to the Center for Biologics Evaluation and Research (CBER) for assessment of the 3D printing pertaining to products containing biologics, cells or tissues. However, the CBER does not specifically address 3D bioprinting or provide guidance: at least, its search engine revealed no entry. This regulatory silence follows a public workshop hosted by the FDA in 2014, which investigated the fundamental regulatory issues arising from 3D printing technology.⁴³ Although the workshop discussed the regulation of biomedical

⁴¹ Gilbert, et al., *op. cit.* note 5

⁴² FDA.gov. 2016. *Technical Considerations for Additive Manufactured Devices. Draft Guidance for Industry and Food and Drug Administration Staff*. FDA. Available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm499809.pdf> [Accessed 19 Sept 2016].

⁴³ FDA.gov. 2014. *Public Workshop - Additive Manufacturing of Medical Devices: An Interactive Discussion on the Technical Considerations of 3D Printing*. FDA. Available at <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm397324.htm> [Accessed 16 Sept 2016]; GPO.gov. 2014. *Additive Manufacturing of Medical Devices: An Interactive Discussion on the Technical Considerations of 3-D Printing*. GPO. Available at <https://www.gpo.gov/fdsys/pkg/FR-2014-05-19/html/2014-11513.htm> [Accessed 20 Sept 2016].

applications of 3D printing (including aspects of quality control as manufacturing moves from the factory to the bedside), bioprinting of live cells was judged beyond its scope and that the unique risks of bioprinting were not specifically addressed.⁴⁴ Meanwhile, some industry analysts have anticipated that the rapid development of 3D bioprinters could spark calls to ban the technology for human tissue use.⁴⁵

3D Bioprinting is a promising medical innovation, but it is not free of safety and ethical concerns.⁴⁶ The clinical application of 3D bioprinting is largely untested, which may have many risks of harm associated with it. These include risks associated with the implantation of scaffold materials, the implantation of stem cells, development of teratomas, and the dislodgement and migration of implanted materials or cells.⁴⁷ These risks are compounded by the fact that the implantation may be irreversible.

The 3D bioprinting process involves artificial or naturally-derived biomaterials used in the form of a 'bio-ink' medium for carrying the cells during printing, and encapsulating them in a 3D matrix after deposition. The implantation of any bioprinted material into the body carries with it some risk of rejection by the host, leading to inflammation. Biomaterials derived from non-human organisms may carry the additional risk of introducing pathogens.⁴⁸ Furthermore, degradation of the biomaterial carries further risks including the cytotoxicity of degraded by-

⁴⁴ FDA.gov. 2014. *Food and Drug Administration (FDA) Public Workshop Additive Manufacturing Of Medical Devices: An Interactive Discussion on Medical Considerations of 3D Printing*. FDA. Available at <http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM425399.pdf> [Accessed 19 Sept 2016].

⁴⁵ Gartner.com. 2014. *Gartner Says Uses of 3D Printing Will Ignite Major Debate on Ethics and Regulation*. Gartner. Available at <http://www.gartner.com/newsroom/id/2658315> [Accessed 20 Sept 2016].

⁴⁶ **AUTHOR op. cit. note 2; AUTHOR. reference 3.**

⁴⁷ H. Hentze, et al. Cell Therapy and the Safety of Embryonic Stem Cell-Derived Grafts. *Trends Biotechnol* 2007; 25: 24-32.

⁴⁸ R.B. de Vries, et al. Ethical Aspects of Tissue Engineering: A Review. *Tissue Eng Part B Rev* 2008; 14: 367-375.

products, clotting, inefficient excretion, and migration of by-products causing disruption of another organ.⁴⁹

Bioprinting often involves printing stem cells, which also carries risks.⁵⁰ In the case of autologous induced pluripotent stem cells (IPS) (cells derived from the fat or bone marrow of the patient being treated), there is no risk of rejection.

Nevertheless, there is the additional risk of stem cells differentiating along an undesired lineage or even to a teratoma.⁵¹ As a form of personalized medicine, these risks may depend on the patient's unique genetic profile. As such, even if safety is demonstrated for one human, the results may not be generalizable to others in the population.

Because of these inherent risks, 3D bioprinting may require additional considerations that do not fit neatly into the extant medical device approval processes. One danger is that bioprinted organs and therapies could become commercially available before the risks and efficacy are adequately assessed.⁵² The situation is analogous to the rise in stem cell therapies being offered by unscrupulous clinicians outside any regulatory framework.⁵³ The enthusiastic portrayal of 3D bioprinting in the media may fuel a demand for these technologies before they are rigorously tested.

⁴⁹ B. Ratner, et al. 2004. *Biomaterials Science, an Introduction to Materials in Medicine*. 2nd edn. California, USA: Academic Press: 864.

⁵⁰ S.-S. Yoo. 3D-Printed Biological Organs: Medical Potential and Patenting Opportunity. *Expert Opin Ther Pat* 2015; 25: 507-511.

⁵¹ Hentze, et al., op. cit. note 46.

⁵² M. Varkey & A. Atala. Organ Bioprinting: A Closer Look at Ethics and Policies. *Wake Forest J.L. & Pol'y* 2015; 5: 275-298.

⁵³ M. Munsie & I. Hyun. A Question of Ethics: Selling Autologous Stem Cell Therapies Flaunts Professional Standards. *Stem Cell Res* 2014; 13: 647-653.

Even though there are risks of significant harms associated with clinical use of 3D bioprinted materials, little of this has been discussed in the literature (see Figure 4). Given the therapeutic potential and risks of harm associated with 3D bioprinted therapies, there is a pressing need for an assessment of the ethical challenges posed by these technologies for protecting human participants in clinical trials, particularly at the formative stages of clinical evaluation, and ultimately, for clinical patients. Such critical risk should be discussed, or at least mentioned in both academic and popular media.

Conflations, Confusions, and Responsibility

As discussed earlier, positive reports of 3D bioprinting application frequently conflated the preliminary experimental data with demonstrated clinical effectiveness and safety. One of the reasons for concern about the Macchiarini case was the potential for patients to confuse the positive reporting of the preliminary trial information with reporting on a proven treatment.⁵⁴ This misperception that 3D bioprinting is clinically available is likely reinforced by a confusion with other successful applications of 3D printing in medicine, such as 3D-printed metals in orthopaedic surgery. Despite both involving a 3D printing process, the 3D printing of metals and 3D bioprinting are vastly different technologies with very different clinical applications. 3D printing of metals, acrylics, and polymers has been used to replace bone including ribcage,⁵⁵ heel,⁵⁶ and in craniofacial reconstruction, for

⁵⁴ Karolinska Institute, op. cit. note 25.

⁵⁵ CSIRO. 2015. *Cancer Patient Receives 3D Printed Ribs in World First Surgery*. CSIRO. Available at <http://www.csiro.au/en/News/News-releases/2015/Cancer-patient-receives-3D-printed-ribs-in-world-first-surgery> [Accessed 16 Sept 2016].

⁵⁶ CSIRO. 2014. *CSIRO Produces 3D Heel in World First Surgery*. CSIRO. Available at <http://www.csiro.au/en/News/News-releases/2014/3D-Heel-In-World-First-Surgery> [Accessed 16 Sept 2016].

which it is approved by the US Food and Drug Administration.⁵⁷ These successes build upon the longstanding paradigm of replacing bone with metal to restore function (for example, the artificial hip was developed in the 1940s), and piggyback on metal printing technologies developed over two decades for the aviation industry. 3D bioprinting, on the other hand, has seen very few clinical applications in humans to date. The task of printing living cells and tissues is much more challenging than printing metal, and the technology is relatively immature. As seen above, there is a danger of the media conflating these recent advances in 3D printing in medicine with the 3D *bioprinting* of living cells, which remains at a basic research stage. We would recommend that mass media reports should use the term ‘3D bioprinting’ to refer exclusively to the structured printing of live cells in three dimensions rather than the printing of a single layer of cells or the 3D printing of inert medical devices. Doing so would reduce the likely ambiguity and potentially misleading findings; consequently putting prospective patients in a better position to understand differences among these technologies.

How potential risks of harms are integrated into research publications about 3D bioprinting may influence how the findings are reported in mass media, as well as how prospective and vulnerable patients may interpret positive reports.

Expectations that are unrealistically positive, for example, those that suggest that safe, functional 3D printed organs will be clinically available in the near future, can lead patients to seek out potentially dangerous or futile interventions, or cause distress when they realize that these treatments are not yet available. Surely, responsibility for both accurate reporting and anticipating the potential consequences of biased reporting are among the editorial duties of both scientific

⁵⁷ BioArchitects. 2015. *BioArchitects Gets FDA Approval for a Pioneer 3D Printed Titanium Cranial Plate*. Available at <http://bioarchitects.com/bioarchitects-gets-fda-approval-for-a-pioneer-3d-printed-titanium-cranial-plate/> [Accessed 16 Sept 2016].

and mass media publishers, as well as of researchers and journalists. Without this, it would seem impossible to build a scientifically engaged public—one that is critically alert to the distorting effects of biased reporting.⁵⁸

Sadly, the use of positive language to report on novel technologies is common in the medical literature: for instance, a study by Vinkers and colleagues showed an increase of 880% in using positive wording in scientific journals over the last 4 decades.⁵⁹ The positive reporting of academic research is characterized in medicine by a tendency for negative findings to be underreported; which illustrates a phenomenon of ‘publication bias’.⁶⁰ Exposed to potential scientific reporting bias, journalists and their editors should nuance and dissect plausible biases, consequently not directly relaying enthusiastic content to large audience.

The positive portrayal of advances in 3D bioprinting in the mass media may misrepresent or obscure relevant ethical and safety concerns. In the absence of coverage addressing these concerns, readers of mass media reports are likely to conclude that 3D bioprinting is safe, effective, and ethically uncontroversial. This relative neglect of safety and ethical issues could lead the public to believe that authorities have already given regulatory approval for the clinical use of 3D bioprinting.⁶¹ This, in turn, can contribute indirectly to public acceptance of premature experimental treatments, raising patients’ hopes in a manner that threatens the integrity of their informed consent to participate in experimental trials. We believe that disseminating selectively positive 3D bioprinting findings in the media may increase the risk of understating of risks of harm for those potential

⁵⁸ AUTHOR, op. cit. note 45.

⁵⁹ Vinkers, et al., op. cit. note 34.

⁶⁰ I. Brassington, The ethics of reporting all the results of clinical trials. *Br Med Bull* 2017. 121 (1): 19-29.

⁶¹ AUTHOR reference 4.

patients who are considering participation in experimental trials of this technology. An optimistic depiction in the popular media can be far more influential on patient decisions than some of the austere and subtle explanations found in specialized medical or ethics journals.

Because of the importance and influence of published reports in shaping decisions relevant to the welfare of many individuals, researchers, scientists, journalists and editors can be understood to have role-related duties: including the duty of accurate reporting, backed by evidence; the duty to disseminate research findings (whether positive or negative findings); and a degree of responsibility for the effects of what is reported. Together these may be thought of as elements required for excellence in reporting.⁶² Any decision to publish content involves a decision-making process that should conform to a standard inspired by a model of excellence. Failure to meet this standard can be seen as a failure of responsibility on the part of the researcher, journalist, editor or publisher.

CONCLUSION: SHARED SCIENTIFIC AND JOURNALISTIC RESPONSIBILITY

Based on a review of academic and mass media portrayals of the clinical applications of 3D bioprinting, we have established that reporting of this technology is increasing and that overall, most reports in mass media are enthusiastic and overly sanguine with very limited attention paid to ethical and safety issues. Dissemination in the medical literature of findings that are only positive, which biases in favor of the technology, also means that there is little

⁶² S.L. Borden & C. Tew. The Role of Journalist and the Performance of Journalism: Ethical Lessons From “Fake” News (Seriously). *Journal of Mass Media Ethics Exploring Questions of Media Morality* 2007; 22: 300-314.

informed and accurate basis upon which to properly inform prospective research participants and patients of the risks of harm associated with this technology. While acknowledging the scientific advances made in 3D bioprinting, editors' and publishers' responsibilities must also include fair representation as an over-riding aim in reporting, while seeking to engage the public. Scientists must 'ensure that studies report facts and not fantasy'.⁶³ Doing so requires a commitment to accurate reporting on the science as well as critical discussion of the ethical and safety issues associated with novel scientific discoveries. Through this, the public would be able to view scientific innovations more objectively and make well-informed decisions should they decide to participate in research or seek treatments involving these novel technologies.

Positive reporting of 3D bioprinting is correlated with a conflation of innovations in 3D printing in medicine (i.e. orthopaedics) with the 3D bioprinting of living cells. In order to reduce misleading information being given to prospective patients, we recommend journalists and academic journals to reserve the term '3D bioprinting' to report on the structured printing of live cells in three dimensions rather than the 3D printing of inert medical devices or cell monolayers. As a result, prospective patients are less likely to be confused about available treatments.

The Macchiarini case has shown that positive media reports of a novel technology may ignore safety issues while indirectly promoting a risky treatment to prospective patients and their relatives. It has also taught us that when positive claims are scientifically supported by publication in top scientific journals, this gives additional credibility which is less likely to be questioned. It is not surprising that prospective patients accept the positive reports when even experts can fall for

⁶³ T.C. Sudhof. Truth in Science Publishing: A Personal Perspective. *PLoS Biol* 2016; 14: e1002547.

it. Reports of 3D bioprinting in mass media appear to follow a similar path: they often do not address the safety risks and ethical issues raised by the technology while depicting it as almost ready to be offered as a clinical treatment.

We believe that in order to avoid a new Macchiarini case, media reports of biofabrication, in particular 3D bioprinting involving human testing, must be subject to more critical reporting in scientific publications and mass media. First, as Südhof has advocated, although authors of misleading conclusions should be held accountable for misrepresenting their research, editors and reviewers should also be held accountable for failing to challenge unfounded claims.⁶⁴ In light of the Macchiarini case, journals should be careful in reviewing studies that are based on studies involving very small numbers of participants or have a short follow-up period (e.g. Macchiarini's first few success stories), regardless of how novel the technology may seem to be or how dramatic its potential applications could be. The statistical and scientific validity of small and short studies are limited and should be treated as such when published. Conclusions drawn should be careful not to create an impression that a particular novel technology is completely safe and highly efficacious. Hopefully, these steps would lead to more modest claims being reported in scientific journals and could deflate the hyped mass media reports. Second, we believe funds should be available through independent bodies to promote and encourage media to act as the watchdogs of biofabrication science, specifically those involving human testing. This would keep track of the editorial responsibilities of both scientific and mass media publishers; consequently helping to build a scientifically engaged public—one that is critically alert to the distorting effects of biased reporting. Third, researchers themselves should take an active role in drafting (or at least approving) press releases to main agencies about the

⁶⁴ Ibid.

technology, rather than leaving it to a public relations team. Scientists should take responsibility for their role in the media machine, as they are providing the quotations and the authority that can often buttress hyped stories. Medical scientists, especially those working on research translation, have a particular responsibility to ensure that scientific publications of their work are not misleading or open to exaggeration. Researchers, scientists, journalists and editors have a duty to ensure that dissemination of research findings is accurate, based on sound evidence. Scientists must be aware of and bear some responsibility for the impact of their claims when promoting their work, be it to the academic and medical community or to the general public.

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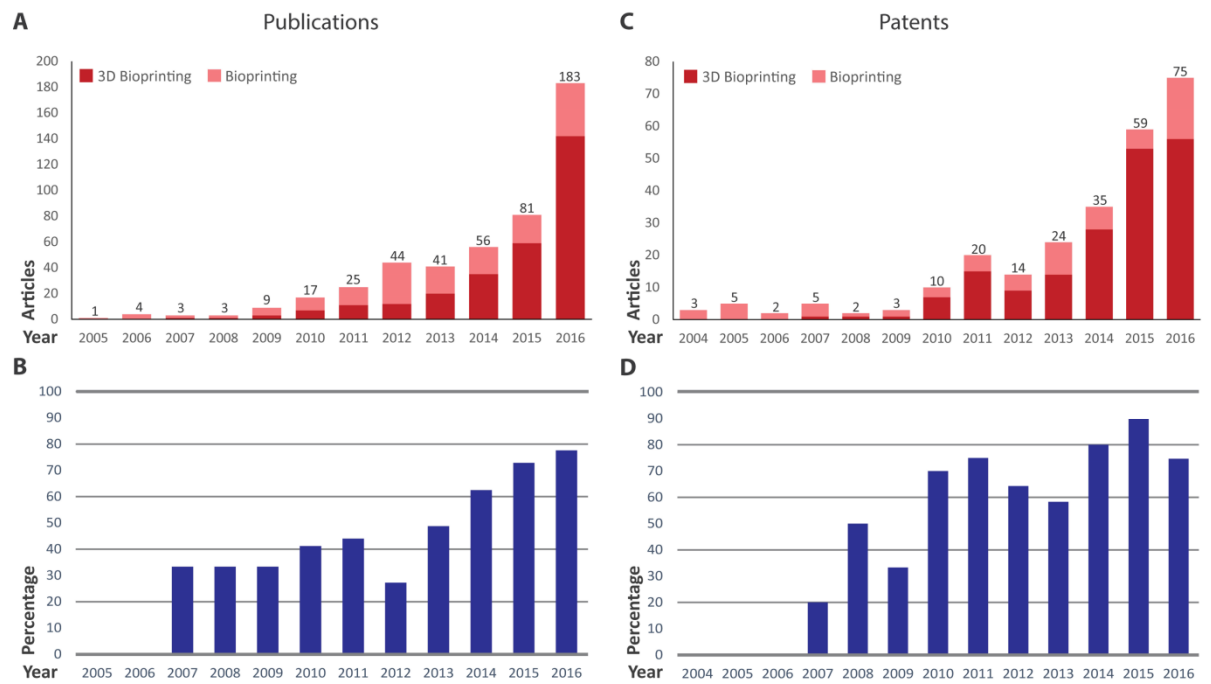


Figure 1. Increase in PubMed-indexed papers (A) and WIPO-indexed patent applications (C) on bioprinting over the years. Along with the increase in bioprinting papers and patent applications is a comparable increase in the percentage of papers (B) and patents (D) using '3D' in conjunction with 'bioprinting'. For instance, in 2016, more than 77% of articles in 'Bioprinting' discuss '3D bioprinting' (B). The search terms *bioprinting* and *3D bioprinting* were used to search for articles and patents published until December 31, 2016.

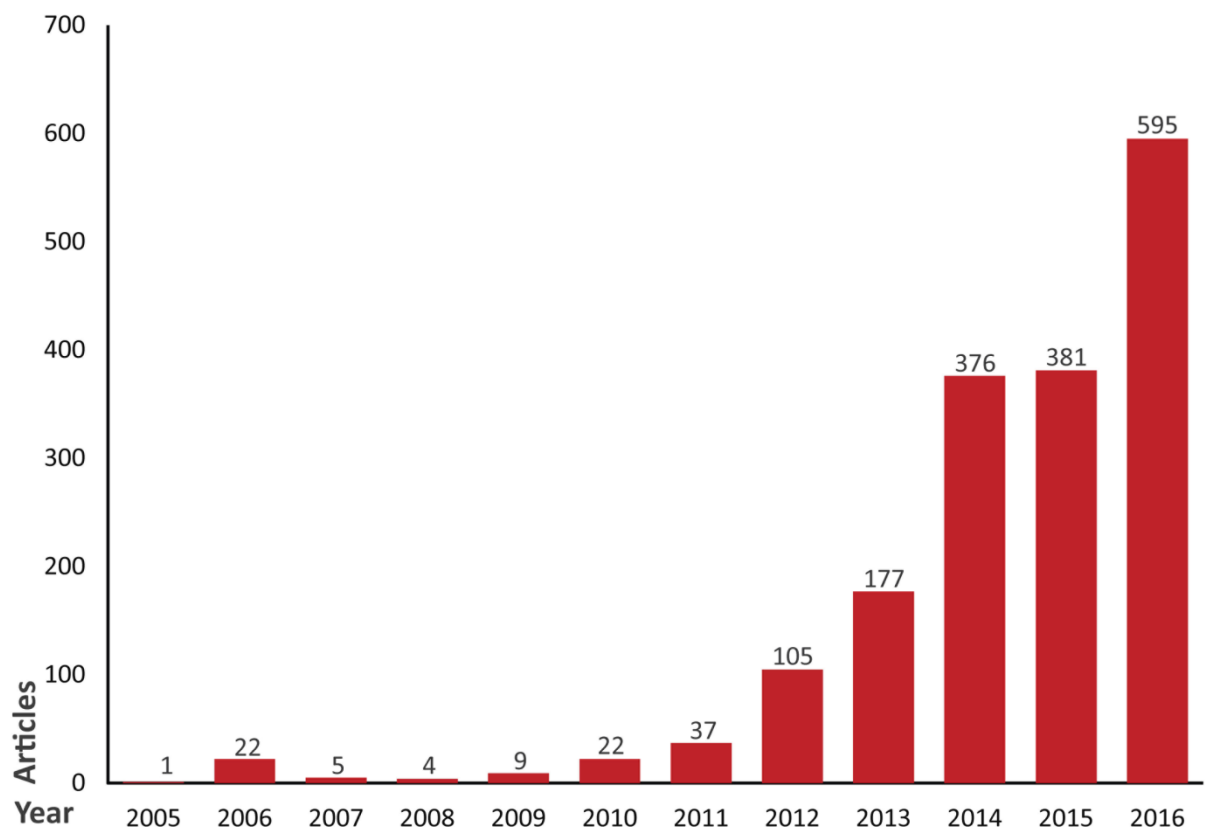


Figure 2. Number of English articles indexed by Factiva until December 31, 2016. The search term *("3D" or "3-D" or "three dimensional" or "three-dimensional") and ("bioprinting" or "bioprinted" or "bioprint")* was used, and blogs and notice boards were included in the search. Duplicate entries were excluded from the count.

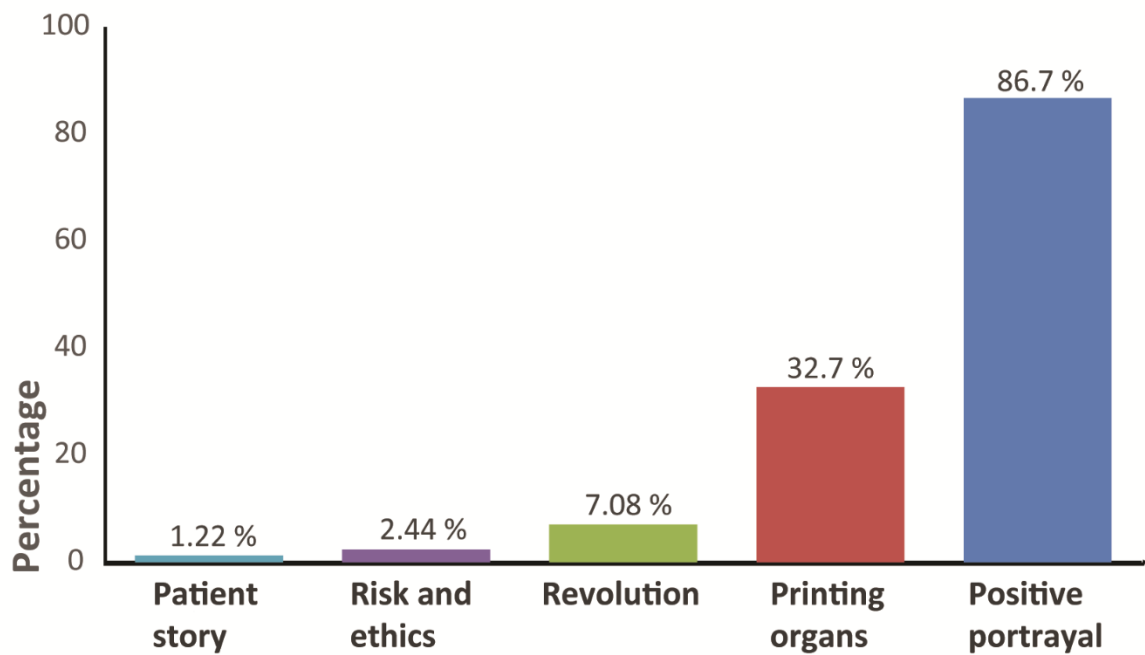
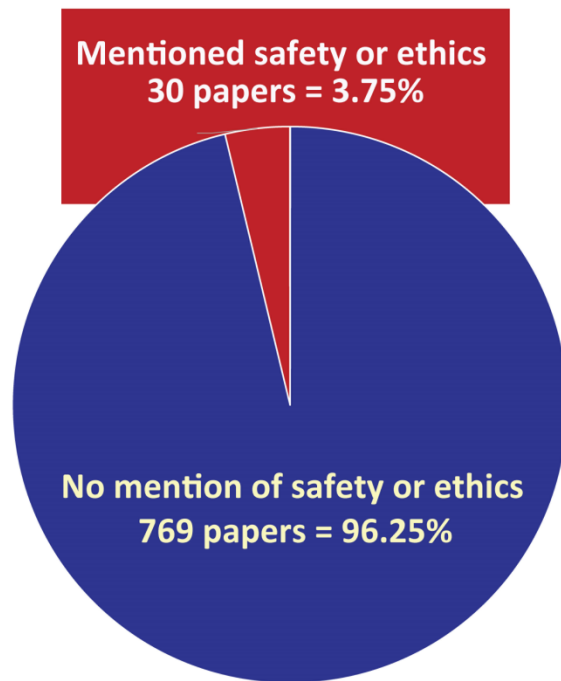


Figure 3. Overall percentage of Factiva-indexed articles until June 15, 2016 that discuss risks and ethical issues on 3D bioprinting, report a patient life-changing story, allude to organ printing, have an overall positive portrayal of 3D bioprinting, and/or describe 3D bioprinting as a revolutionary technology. The search term *("3D" or "3-D" or "three dimensional" or "three-dimensional") and ("bioprinting" or "bioprinted" or "bioprint")* was used, and irrelevant results were filtered out manually.

A 799 3D bioprinting papers**B****1**

Bioprinting article

Top 30 Bioethics journals

Bioengineering articles

119

Figure 4. (A) Percentage of publications that discuss safety and ethical issues associated with 3D bioprinting. The search terms *((("3D" OR "3-D" OR "three dimensional" OR "three-dimensional") AND ("bioprinting" OR "bioprinted")) and ((("3D" OR "3-D" OR "three dimensional" OR "three-dimensional") AND ("bioprinting" OR "bioprinted")) AND ("ethics" OR "ethical" OR "safe" OR "safety"))* were used to determine the total number of publications and the percentage that mentions safety and ethics, respectively. Publications until March 31, 2017 were obtained from PubMed, Embase, and Web of Science and were filtered for duplicates using EndNote X7. **(B)** Search results for articles on bioprinting and bioengineering in top bioethics journals. The top 30 bioethics journals were identified by their ranking in Thomson Reuters/ ISI and Google Scholar (based on h5 index), and the search terms *bioprinting* and *bioengineering* were used to determine the number of corresponding articles published until April 3, 2017.