Ethical Issues in Bioprinting 2022

Prof. Steven S. Saliterman
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http://saliterman.umn.edu/

Prof. Angela Panoskaltsis-Mortari's BMEn 5361, 3D Bioprinting

Uses of Bioprinting

- Biopharmaceutical Research and Development
  - In-vivo and in-vitro models
- Disease modeling generally
  - Organoids
  - Organ-on-a-chip and body-on-a-chip systems
- Solid organs and other tissue replacement.
- Prosthetics and other implants.
- Models for pre-surgical training.

Ethical Considerations

- Purpose
  - Replacing diseased tissues and organisms – how about for enhancement?
- Source of Cells
  - Embryonic stem cells – how about combined with animal cells?
- The use of an instrument to manipulate human nature.
  - Eugenics & cloning? New species?
- Information and consent.
  - Public need to know, privacy and human subjects in experimentation.
- Safety
  - Unknown risk/benefit ratio vs established therapy.
- Justice and access.
  - Affordability; availability, commodification (parts as commodity).

Patuzzo S, Goracci G, Gasperini L, Ciliberti R. 3D Bioprinting Technology: Scientific Aspects and Ethical Issues. *Science and Engineering Ethics*. 2018;24(2):335-348.

Safety Concerns…

- Biomaterials derived from non-human organisms, such as gelatin (from porcine skin) or alginate (from seaweed), may induce immunological responses, introduce pathogens. [22]
- Use of living stem cells in any bioprinting therapy, even cells derived from the patient, carries risks, including tumor formation, immunological reactions, the unpredictable behavior of the cells, and long-term health effects yet unknown.[24]
- Transient *forces* in 3D bioprinting may direct stem cells towards an undesired lineage.[22]
- 3D bioprinting process often requires curing to convert liquid bioink into a more solid form. The effects of such exposure may cause DNA damage,[25] which may not be apparent initially.[4]
- Biodegradation may lead to cytotoxicity, clotting, inefficient excretion resulting in a buildup of toxins in the body, and migration of by-products.[26]

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Gupta N, Agarwal S. Three-Dimensional Bioprinting: Role in Craniomaxillary Surgery Ethics and Future. *Journal of Craniofacial Surgery*. 2020;31(4):1114-1116.

- Development of authentic bioinks, which can mimic the complex and diverse composition of various tissues is not easy.
- Quality control is problematic if the only reliable test for functionality is implantation.
- If the organ is successful in one person it does not guarantee functionality in other person[22] as each organ/tissue is customized.
- Procedures need to be cost-efficient, so that they can be utilized by people from all financial strata.

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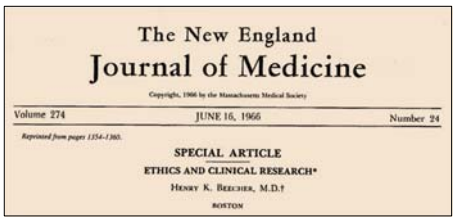
Gupta N, Agarwal S. Three-Dimensional Bioprinting: Role in Craniomaxillary Surgery Ethics and Future. *Journal of Craniofacial Surgery*. 2020;31(4):1114-1116.

Ethical Practices



The New England
Journal of Medicine

Volume 274 JUNE 16, 1966 Number 24

SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

HENRY K. BEECHER, M.D.†

BOSTON

Laid the foundation for current guidelines on informed consent and human experimentation.

Prof. Steven S. Saliterman

Aswar, U.M. *Ethical Principles: Nuremberg code, declaration of Helsinki and Belmonte Report* , Sinhgad Institutes, 9/17/2013

Thought Leaders…

- In a letter to the editor of *Lancet* in 1990, Arthur Caplan a University of Minnesota Ethicist stated:
  - "Ethicists have offered opinions about the morality of research proposals and generally support bodies such as institutional review boards to oversee clinical research.
  - The primary hindrance to controlled clinical trials in the USA today is not the regulations that emerged in the 1970s. Nor is it the rantings of ethicists about the immorality of such trials.
  - The morality of randomized trials is being questioned by patient advocacy groups and by many pharmaceutical and device companies."

Contemporary Ethical Discussions…

TOPICAL REVIEW

Ethical considerations in the translation of regenerative biofabrication technologies into clinic and society

I A Otto[1,2], C C Breugem[3], J Malda[1,2] and A L Bredenoord[4]

[1] Department of Orthopaedics, University Medical Center Utrecht, Utrecht, The Netherlands
[2] Department of Plastic and Reconstructive Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[3] Department of Equine Sciences, Faculty of Veterinary Science, Utrecht University, Utrecht, The Netherlands
[4] Department of Medical Humanities, Julius Center, University Medical Center Utrecht, Utrecht, The Netherlands

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Keywords: biofabrication, bioprinting, regenerative medicine, ethics, bioethics, translation

Otto, I. A., C. C. Breugem, J. Malda, and A. L. Bredenoord. "Ethical Considerations in the Translation of Regenerative Biofabrication Technologies into Clinic and Society." [In English]. *Biofabrication* 8, no. 4 (Dec 2016): 7.

Sci Eng Ethics (2018) 24:335–348
https://doi.org/10.1007/s11948-017-9918-y

REVIEW PAPER

3D Bioprinting Technology: Scientific Aspects and Ethical Issues

Sara Patuzzo[1] · Giada Goracci[2] · Luca Gasperini[3,4] · Rosagemma Ciliberti[5]

Abstract The scientific development of 3D bioprinting is rapidly advancing. This innovative technology involves many ethical and regulatory issues, including theoretical, source, transplantation and enhancement, animal welfare, economic, safety and information arguments. 3D bioprinting technology requires an adequate bioethical debate in order to develop regulations in the interest both of public health and the development of research. This paper aims to initiate and promote ethical debate. The authors examine scientific aspects of 3D bioprinting technology and explore related ethical issues, with special regard to the protection of individual rights and transparency of research. In common with all new biotechnologies, 3D bioprinting technology involves both opportunities and risks. Consequently, several scientific and ethical issues need to be addressed. A bioethical debate should be carefully increased through a multidisciplinary approach among experts and also among the public.

PERSPECTIVE

Bioethical and Legal Issues in 3D Bioprinting

Anastasia Kirillova[1,*,†], Stanislav Bushev[2,†], Aydar Abubakirov[1], Gennady Sukikh[1]

[1]National Medical Research Center for Obstetrics, Gynecology and Perinatology Named After Academician V.I. Kulakov of the Ministry of Healthcare of Russian Federation, Moscow, 117513, Russia
[2]Department of Philosophy, Lomonosov Moscow State University, Moscow, 119991, Russia
[†]These authors contributed equally to this work.

Abstract: Bioethical and legal issues of three-dimensional (3D) bioprinting as the emerging field of biotechnology have not yet been widely discussed among bioethicists around the world, including Russia. The scope of 3D bioprinting includes not only the issues of the advanced technologies of human tissues and organs printing but also raises a whole layer of interdisciplinary problems of modern science, technology, bioethics, and philosophy. This article addresses the ethical and legal issues of bioprinting of artificial human organs.

Keywords: Three-dimensional printing, Bioethics, Ethical issues, Regulatory concerns, Artificial ovary, Oncofertility

[*]**Corresponding Author:** Anastasia Kirillova, National Medical Research Center for Obstetrics, Gynecology and Perinatology Named After Academician V.I. Kulakov of the Ministry of Healthcare of Russian Federation, Moscow, 117513, Russia; stasia.kozyreva@gmail.com

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Role of Bioethics…

- "In translational medicine, dynamic interactions between scientists, clinicians, ethicists, patients, and other members of society are instrumental in enabling effective scientific progress."[1]
- "Ethics is sometimes regarded as a brake on science, yet in our perspective, ethics provides moral guidance and the incentive to continuously refocus on the scientific direction and its impact."[2]

1. van Delden J JMand Bredenoord AL 2015 Future challenges for bioethics: regenerative medicine Global Bioethics: What for? edGSolinis (Paris: UNESCO Publishing) pp 137–41

2. Otto, I. A., C. C. Breugem, J. Malda, and A. L. Bredenoord. "Ethical Considerations in the Translation of Regenerative Biofabrication Technologies into Clinic and Society." [In English]. *Biofabrication* 8, no. 4 (Dec 2016): 7.

Bioethical Considerations…

- Positive ethical consequences, for example, creating alternatives to animal testing (e.g. drug testing), filling a therapeutic need for minors and avoiding species boundary crossing.
- There is a need for disease and drug testing models.
- 3D bioprinting remains an untested clinical paradigm and is based on the use of living cells placed into a human body; there are risks including teratoma and cancer, dislodgement and migrations of implant.

Vermeulen, Niki et al. "3d Bioprint Me: A Socioethical View of Bioprinting Human Organs and Tissues." *J med Ethics* 43 (2017): 7.

Technology

- In 2006, Shinya Yamanaka described successful reprogramming of human somatic cells into a pluripotent state that was similar to embryonic stem cells (ESC) in both its phenotype and transcriptome.
- Researchers may now pursue the more recently developed *"Induced Pluripotent Stem Cell" (iPSC)* technologies, or collect multipotent stem cells (adult/somatic stem cells) for producing pluripotent stem cells for 3D tissue engineering *in order to bypass the destruction of human embryos*.

Li, P., and A. Faulkner. "3d Bioprinting Regulations: A UK/EU Perspective." *European Journal of Risk Regulation* 8, no. 2 (Jun 2017): 441-47.

Anderson, C. W., et al. "Stem Cells in Cardiovascular Medicine: The Road to Regenerative Therapies." *Current Cardiology Reports* 19, no. 4 (Apr 2017).

CRISPER & Gene Drive

- Clustered Irregular Interspaced Short Palendromic Repeats.
- *Gene drive* – process by which mutations or corrections in genetic code can be "driven" through subsequent populations. Approaching 100% vs Mendelian inheritance of 50%.
- Changes in organisms with longer lifespans take longer to occur; and conversely, short lived organisms like insects may see rapid changes
  - The addressing Zika infected populations of mosquitos with Zika-resistant gene with guide RNA and Cas protein.
- Somatic gene editing vs. editing the germline.
- *Moderate intuitionism* and *Anticipatory Ethics* are approaches ethicists take to study these technologies.

Nestor MW, Wilson RL. Beyond Mendelian Genetics: Anticipatory Biomedical Ethics and Policy Implications for the Use of CRISPR Together with Gene Drive in Humans. *Journal of Bioethical Inquiry*. 2020;17(1):133-144.

Safety

Int J Med Sci 2018, Vol. 15 36

IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

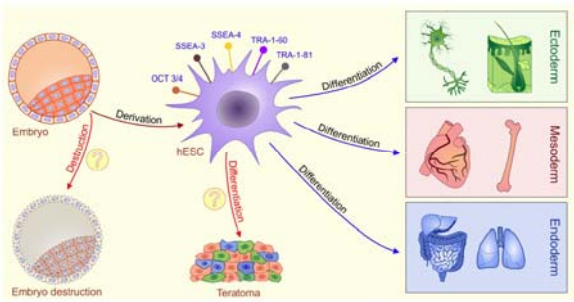
2018; 15(1): 36-45. doi: 10.7150/ijms.21066

Review

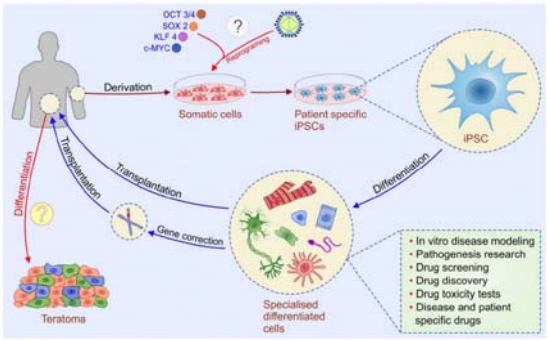
Ethical and Safety Issues of Stem Cell-Based Therapy

Vladislav Volarevic[1,2], Bojana Simovic Markovic[3], Marina Gazdic[2], Ana Volarevic[4], Nemanja Jovicic[5], Nebojsa Arsenijevic[1], Lyle Armstrong[6], Valentin Djonov[5], Majlinda Lako[6] and Miodrag Stojkovic[2]

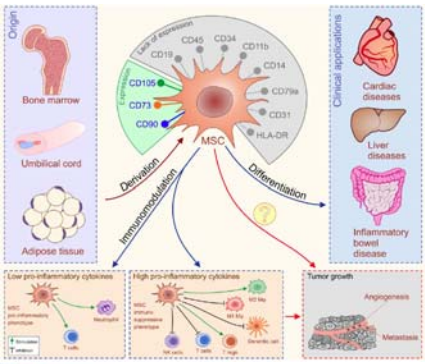
Received: 2017.06.28; Accepted: 2017.10.11; Published: 2018.01.01



Volarevic V, Markovic BS, Gazdic M, et al. Ethical and Safety Issues of Stem Cell-Based Therapy. *Int J Med Sci.* 2018;15(1):36-45. doi:10.7150/ijms.21666



Volarevic V, Markovic BS, Gazdic M, et al. Ethical and Safety Issues of Stem Cell-Based Therapy. *Int J Med Sci.* 2018;15(1):36-45. doi:10.7150/ijms.21666



Volarevic V, Markovic BS, Gazdic M, et al. Ethical and Safety Issues of Stem Cell-Based Therapy. *Int J Med Sci.* 2018;15(1):36-45. doi:10.7150/ijms.21666

Integrity

Scientists call for halt in stem-cell trial over alleged fabricated data

By CAROLYN Y. JOHNSON
Washington Post

Days after Harvard Medical School said it found extensive falsified or fabricated data from the laboratory of a prominent heart researcher, doctors and scientists are urging a halt to a medical trial based in part on his work. They say that sick people should not be subjected to the risks of an experiment whose underlying science has been called into question.

In the ongoing, taxpayer-funded trial, cardiac stem cells are injected into the hearts of people with heart failure, in the hopes that those cells — alone or in combination with others — will improve heart function.

The regenerative effects of those cells were first reported by an influential but controversial scientist, Piero Anversa, whose work has been thrown into doubt. Harvard disclosed a yearslong investigation had identified "falsified and/or fabricated data" in 31 papers from his laboratory, without specifying which publications were affected. Last year, the Harvard-affiliated Brigham and Women's Hospital, where Anversa worked until 2010, reached a $10 million settlement with the Justice Department to resolve allegations that fraudulent data had been used by Anversa's laboratory in grant applications for federal funding.

Last week, the New England Journal of Medicine retracted one paper and flagged two others with an "expression of concern" intended "to indicate that the data presented in the articles named above may not be reliable." The journal said it is waiting for more information on the two papers.

New York Medical College, where Anversa previously worked, said that "serious concerns" have been raised about a 29-year-old study. It said an investigation is underway.

New York Times

Dr. Piero Anversa, in his home in Manhattan this month, stands by his work.

Anversa is not directly involved in the heart failure trial, which is being run by a national clinical trial network supported by $61 million in federal funds. But given the turmoil and uncertainty over the work that helped lay the foundation of the trial, outside researchers called for a pause and careful examination of whether it should proceed. The trial carries inherent risks, because it requires an invasive biopsy that can cause serious complications.

Outside scientists have said the scientific underpinnings of the trial must be weighed against the risks of medical research. One patient died early in the trial when the heart was perforated while cells were being harvested to create stem cells, highlighting the inherent risks.

"I think that the trial should be halted, and they should have an external review," said Darryl Davis, a cardiologist at the University of Ottawa Heart Institute studying how to regenerate heart tissue. "The Anversa data comprised part of the rationale for that trial, and I think we have to understand better what those cells actually can do before we subject the patients to the risk of having an invasive procedure."

Anversa's laboratory did the foundational work in this field and provided cells for a previous clinical trial that is cited as part of the supporting evidence for the current trial. However, the National Heart, Lung and Blood Institute does not consider the trial to be based on Anversa's work, according to Dennis Burton, director of the Basic and Early Translational Research program at the institute.

Burton said that the trial is instead based on an idea that grew out of Anversa's original work — that the cells secrete various molecules that help regenerate muscle tissue, although he said it was "not a well-characterized effect at the moment."

"Multiple preclinical studies have demonstrated improvement in cardiac function, and advanced heart failure patients really have no treatment options and have poor survival," Burton said. There is "compelling need for new therapies that can improve quality of life in these patients. I think the feeling is this trial has the potential to provide such an option."

He said that a board that monitors patient safety in clinical trials would now be tasked with evaluating the information related to the 31 retractions requested by Harvard, and that patients would be informed of the board's recommendations.

Anversa's lawyer said his client stands by the scientific findings in his papers and that Anversa only learned from the Harvard investigation that a longtime colleague who left his lab in 2013 had improperly altered images. Anversa says that, in many cases, those images can be replaced with correct images, and the results will still stand, his lawyer said.

Star Tribune, Minneapolis, MN, October 30, 2018.
Photo – RetractionWatch.com

He Jiankui
(pronounced HEH JEE'-an-qway)

Chinese scientist who produced genetically altered babies sentenced to 3 years in jail

By Dennis Normile, Dec. 30, 2019 , 8:15 AM

He Jiankui, the Chinese researcher who stunned the world last year by announcing he had helped produce genetically edited babies, has been found guilty of conducting "illegal medical practices" and sentenced to 3 years in prison.

A court in Shenzhen found that He and two collaborators forged ethical review documents and misled doctors into unknowingly implanting gene-edited embryos into two women, according to Xinhua, China's state-run press agency. One mother gave birth to twin girls in November 2018; it has not been made clear when the third baby was born. The court ruled that the three defendants had deliberately violated national regulations on biomedical research and medical ethics, and rashly applied gene-editing technology to human reproductive medicine.

…"He had defied government bans and conducted the research in the pursuit of personal fame and gain."

The CRISPR Journal, Vol. 2, No. 1 | Retraction Notice

Retraction of: Draft Ethical Principles for Therapeutic Assisted Reproductive Technologies by He, J *et al.*, *CRISPR J* 2018; fast track. DOI: 10.1089/crispr.2018.0051

Published Online: 21 Feb 2019 | https://doi.org/10.1089/crispr.2018.0051.retract

View article | Tools | Share

"Retraction of: Draft Ethical Principles for Therapeutic Assisted Reproductive Technologies by He, J et al., CRISPR J 2018; fast track. DOI: 10.1089/crispr.2018.0051." The CRISPR Journal, 2(1), p. 65

In the article, He and colleagues outlined five general principles to be followed when performing human gene editing, summarized as follows: mercy for families in need, only for serious disease never vanity, respect a child's autonomy, genes do not define you, and everyone deserves freedom from genetic disease.

He et al. failed to disclose their conflict of intertest.

Corporate Fraud…

Theranos founder Elizabeth Holmes has been convicted of defrauding investors after a months-long landmark trial in California.

BBC News January 4, 2022

Prosecutors said Holmes knowingly lied about technology she said could detect diseases with a few drops of blood. Jurors found Holmes guilty of conspiracy to commit fraud against investors and three charges of wire fraud. She denied the charges, which carry a maximum prison term of 20 years each.

Holmes was able to raise more than $900m from billionaires such as media magnate Rupert Murdoch and tech mogul Larry Ellison. The firm promised it would revolutionize the healthcare industry with a test that could detect conditions such as cancer and diabetes with only a few drops of blood.

But these claims began to unravel in 2015 after a Wall Street Journal investigation reported that its core blood-testing technology did not work.

Holmes was not taken into custody, with no date confirmed yet for sentencing and a further hearing scheduled next week.

Our Responsibilities

- Protecting personal data.
- Avoid inappropriately extending the human lifespan.
- Avoid inappropriate cosmetic use.
- Managing public expectations.
- Avoiding scientific research exploitation.
- Recognizing conflict of interests of the experts.
- Maintaining transparency of the entire process.
- Making it affordable.
- Meeting supply and demand of human or non-human animal transplants.

Organ Transplantation

Organ donation and transplantation can save lives

Every 9 minutes, someone is added to the national transplant waiting list.

On average, 95 transplants take place each day in the U.S.

One organ donor can save eight lives. Sign up to be a donor in your state.

DHHS Organ Procurement and Transplantation Network. https://optn.transplant.hrsa.gov/. November 2020

Transplants by Organ Type 2018 vs 2019...

Liver	↑ 7.8%	2019: 8,896	2018: 8,250
Heart	↑ 4.2%	2019: 3,552	2018: 3,408
Lung	↑ 7.3%	2019: 2,714	2018: 2,530
Pancreas	↓ 25.5%	2019: 143	2018: 192

Prof. Steven S. Saliterman

UNOS (United Network for Organ Sharing)
https://unos.org/data/transplant-trends/. November 2020

Kidney-pancreas	↑ 4.4%	2019: 872	2018: 835
Intestine	↓ 22.1%	2019: 81	2018: 104
Heart-lung	↑ 40.6%	2019: 45	2018: 32
Vascular composite allograft	↑ 36.4%	2019: 15	2018: 11

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UNOS (United Network for Organ Sharing)
https://unos.org/data/transplant-trends/. November 2020

Transplant	Total Estimated Number of Transplants	Estimated Billed Charges
Single Organ/Tissue		
Bone Marrow - Allogenic	9,950	$1,071,700
Bone Marrow - Autologous	14,745	471,600
Cornea	53,065	32,500
Heart	3,499	1,664,800
Intestine	38	1,240,700
Kidney	21,963	442,500
Liver	8,219	878,400
Lung - Single	821	929,600
Lung - Double	2,011	1,295,900
Pancreas	126	408,800

Multiple Organ		
Heart-Lung	35	2,637,200
Intestine with Other Organs	58	1,662,900
Kidney-Heart	238	2,644,600
Kidney-Pancreas	900	713,800
Liver-Kidney	807	1,355,100
Other Multi-Organ	79	2,185,800

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Bentley, TS, N.J. Ortner. Milliman Research Report, 2020

Emerging Concerns

VOL. 36:1 SPRING 2020 ETHICS & MEDICINE

GREY MATTERS

CEREBRAL ORGANOIDS AND THE THRESHOLD OF CONSCIOUSNESS

WILLIAM P. CHESHIRE, JR., MD

We cannot confidently conclude that cerebral organoids will forever continue to have no consciousness. – Sawai et al.[1]

Brain Research

...cal issues related to brain organoid research

BMJ

Cerebral organoids and consciousness: how far are we willing to go?

Andrea Lavazza,[1] Marcello Massimini[2]

Creating Sentient Organoids…

- *Brain organoids* – self organized cellular structures that evolve to form brain tissue.
- Considerations:
  - Research oversight,
  - Procurement and donor consent translational delivery,
  - Animal research,
  - **Organoid consciousness and moral status.**

Hyun I, Scharf-Deering JC, Lunshof JE. Ethical issues related to brain organoid research. *Brain Research*. 2020;1732.

Ethics & Regulation…

Sci Eng Ethics (2018) 24:73–91
https://doi.org/10.1007/s11948-017-9874-6

ORIGINAL PAPER

Print Me an Organ? Ethical and Regulatory Issues Emerging from 3D Bioprinting in Medicine

Frederic Gilbert[1,2] · Cathal D. O'Connell[2,3] · Tajanka Mladenovska[2,4] · Susan Dodds[1,2,5]

Received: 12 October 2016 / Accepted: 11 January 2017 / Published online: 9 February 2017
© Springer Science+Business Media Dordrecht 2017

- Is there a limit to what should be bioprinted in medicine?
- How do we examine risks of significant harm associated with testing 3D constructs.
- Clinical trial paradigms.
- Ethical questions of irreversibility, loss of treatment opportunity and replicability.
- Need for of a specific framework for regulation and testing.

Gilbert F, O'Connell, C.D., Mladenovska, T. et al. Print Me an Organ? Ethical and Regulatory Issues Emerging from 3D Bioprinting in Medicine. *Sci Eng Ethics* 2018;24(1).

Ethics and the Media…

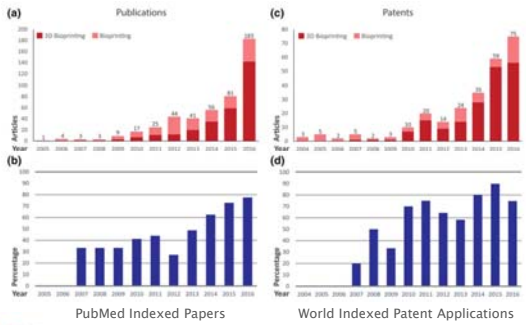
ORIGINAL ARTICLE

WILEY bioethics

Enthusiastic portrayal of 3D bioprinting in the media: Ethical side effects

Frederic Gilbert | John Noel M. Viana | Cathal D. O'Connell | Susan Dodds

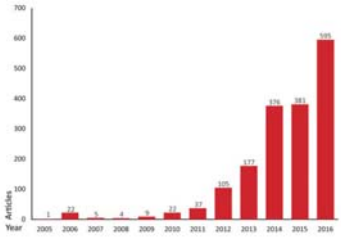
Abstract



PubMed Indexed Papers World Indexed Patent Applications

Gilbert F, Viana JNM, O'Connell CD, Dodd S. Enthusiastic portrayal of 3D bioprinting in the media: Ethical side effects. *Bioethics*. 2018;32(2):94–102.

- Mass media is an important source of health information for the public.
- English articles indexed by Factiva related to 3D bioprinting:



Gilbert F, Viana JNM, O'Connell CD, Dodd S. Enthusiastic portrayal of 3D bioprinting in the media: Ethical side effects. *Bioethics*. 2018;32(2):94–102.

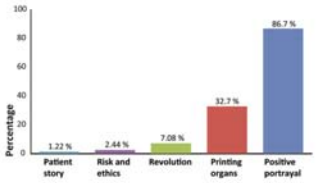


FIGURE 3 Overall percentage of Factiva-indexed articles until June 15, 2016 that discuss risks and ethical issues on 3D bioprinting, report a patient life-changing story, allude to organ printing, have an overall positive portrayal of 3D bioprinting, and/or describe 3D bioprinting as a revolutionary 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 [Colour figure can be viewed at wileyonlinelibrary.com]

Summary

- Uses of Bioprinting
- Ethical issues
  - Safety
- Ethical Practices
  - Thought leaders
  - Induced Pleuripotential Stem Cells (IPSC)
  - Integrity
- Our Responsibility
  - Transplants
- Emerging Concerns
  - Brain Tissue
  - Regulations
  - Media/Press Coverage