Bioethics™
Life, Politics, Economics
Edited by Joanna Zylinska
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Introduction: Bioethical Mutations in the Age of Capital

Bioethics is a serious business, in every sense of the word. A sub-domain of philosophy which deals with issues concerning life and health, it has to arbitrate not only over practical matters regarding patient care and medical experiments, but also over the very ontology of ‘life’: its manufacturing, patenting and redefinition in and by the biotech industry. Since bioethics functions as a node in the complex nexus of social, political and economic forces, it is perhaps not surprising that technocapitalism does not want to leave it just to philosophers. Instead, it mobilises a whole army of experts: morality salespeople, ethics technicians, value mathematicians, to help us decide on the price of life. Consequently, bioethics increasingly abandons its more
daring ambitions and responsibilities — such as exploring the metaphysics of life or the politics of everyday survival — to serve instead as just a ‘technical discourse about values clarification and choice’ (Haraway, 2007: 109). Its methods of working are thus principally procedural, akin to ‘facts and hypothesis testing’ in science (Haraway, 2007: 109). Feminist thinker Donna Haraway points out that medical ethics ‘is now a literal industry, funded directly by the new developments in technoscience. Ethics experts have become an indispensable part of the apparatus of technoscience-production’ (2007: 109). To put it crudely, bioethics’ role is often to get biotech corporations off the hook — although, of course, it has the potential to be much more than that. Indeed, in its engagement with life in both a metaphysical and material sense, bioethics is conceivably one of the most exciting areas of philosophical interrogation and artistic experimentation today.

Designed as a supplement to my 2009 book, *Bioethics in the Age of New Media* — which explores and experiments with some alternatives within and for bioethics — this living book, *Bioethics™: Life, Politics, Economics*, is to act as a warning against the foreclosure of the aforementioned potential by casting light on the increasing marketisation of both life and bioethics under late capitalism. Performed as a form of ‘mutation’, the introduction presented here outlines an academic-artistic method for *reading and writing as genetic recombination*, which can perhaps be seen as a biotech-era take on Roland Barthes’ *From Work to Text*. The text below is thus a product of the cross-fertilisation of all the sources that feature in the *Bioethics™* book: between one and four sentences have
been taken from each article and spliced to form a unified whole. The structure of individual sentences has been retained most of the time, and indication has been given whenever sentences have been split. No foreign material has been added to the mix. Phenotypically resembling a standard academic essay, yet referenced in a less conventional way by a series of direct links (although a full page of Attributions is also available here), the text below is an experiment in textual and conceptual hybridisation. Its main function is to foreground the questions of crossing over, intellectual property, political economy and the ethics and politics of academic research that are the topic of this particular living book, and of the Living Books project as a whole -- but it may also of course develop a life of its own...

Today, the pharmaceutical industry has settled comfortably into its place as the most profitable business in America. The media hoopla surrounding the sequencing of Watson’s genome has already had some commentators worrying that genome sequencing could become the next must-have for the rich and privileged.... However, beyond the publicity, it is only a matter of time until genome sequencing will be affordable for most people. Once it becomes commonplace, it will generate an enormous quantity of sequence data from a wide range of humans that could benefit biomedical research and drug development. More importantly, a ‘thousand-dollar genome’ could become an important tool to realize personalized medicine: perfectly tailoring diagnostics and treatments to a patient’s genetic make-up. (T)he emergence of an autonomous health industry establishes a potential structural problem for capitalism: insofar as the growth
of the health industry depends on ‘people becoming more sick,’ its growth seems to be in tension with the growth of other sectors of the economy. The solution to this structural problem is the creation of ‘surplus health,’ or that ‘proportion of health unnecessary for maintaining one’s capacity as a worker’... Preventive medicine is especially well suited for the creation of surplus health, for by enabling the diagnostic identification, and pharmaceutical management, of ‘risk factors’ for diseases, rather than simply the diseases themselves, it becomes possible to expand markets for diagnostics and medication, without at the same time reducing an individual’s capacity for labor.

Over the past half-century, American doctors have begun to use the tools of medicine not merely to make sick people better but to make well people better than well. But does making small normal children bigger also make them better? That is the fundamental and simplistic question underpinning the use of GH (growth hormone) in ‘idiopathic’ short stature. Just when it seemed that eugenics could not return to the forefront of the social arena, it appears once again, although its spectacle has been modified to suit the times. Eugenics, at least on the surface, is only implicitly attached to issues of race improvement or gene pool cleansing. Now it hides under the authority of medical progress and the decoding of nature.

The pharmaceutical industry influences psychiatrists to prescribe psychoactive drugs even for categories of patients in whom the drugs have not been found safe and effective. What should be of greatest concern for Americans is the astonishing rise in the diagnosis and treatment of mental illness in children, sometimes as young as two years old. These children are often treated
with drugs that were never approved by the FDA for use in this age group and have serious side effects.... Ten percent of ten-year-old boys now take daily stimulants for ADHD -- ‘attention deficit/hyperactivity disorder’ -- and 500,000 children take antipsychotic drugs. (I)ndustry uses ghostwriters to insert marketing messages into articles published in medical journals. (O)pen-ended activities such as ‘unrestricted’ research grants, ‘educational’ grants, membership in speakers’ bureaus and advisory panels, consultancies, and stock-holding could be of greater concern, through an insidious blurring of professional boundaries and obligations. There is evidence that these types of ties are common among specialist physicians.

The true purpose of a drug trial is not always obvious. Medical trials are not always conducted to test the drug -- sometimes it’s to seed the market. (R)esearch on humans has become a commercial enterprise. Most clinical trials have moved from academic settings to specialized contract research organizations (CROs), which contract with the pharmaceutical and biotechnology industries. Reports suggest finder’s fees ranging between $2,000 and $5,000 per patient are common, although it is not always easy to distinguish the reward for the recruitment of patients from remuneration for clinical activities that are part of the research. Few would argue that patients in trials should be treated as commodities, but patients have become de facto market products, while ‘market controls’ are neither clear nor sufficiently stringent.

In North America today..., where medical research happily converges with consumer capitalism, even bioethicists believe that the market ultimately works for justice. Ethical issues are a growing concern for
companies, in the wake of a series of corporate governance scandals and the accompanying sharp decline in societal and investor trust in firms. Some companies have responded to these concerns by creating internal ethics programs. (E)thics is an asset that firms can trade upon. Firms are considering ethics as central not only to their research activities and the dissemination of their products to consumers, but also to the reputation and branding of the company itself. (M)anufacturers were reported to demonstrate awareness of existing regulations and engage in strategic behaviors to work around them (e.g., by giving employees lectures about the regulatory environment that were understood to be a smokescreen) or to mask their violations of the law (e.g., by encouraging employees to not enter off-label marketing calls in their logs).

How do we resolve moral and bioethical issues provoked by ‘patenting life’? When do these issues concern the technology itself, such as concerns over stem cell research, and when do they concern the grant or ownership of exclusive patent rights over isolated chemical structures such as nucleotide sequences? (S)ynthetic biology presents a particularly revealing example of a difficulty that the law has frequently faced over the last 30 years -- the assimilation of a new technology into the conceptual limits posed by existing intellectual property rights. Historically, the signal achievement of bioethics was its development of practices, procedures and principles calibrated to specific problems (protection of human subjects in research, issues of justice, the need for bureaucratic norms for health care, etc.). The founders of both American and European bioethics were keenly aware that this calibration of a mode of ethics and problems,
in turn, entailed the construction of specific new venues (e.g. IRBs (Institutional Review Boards, aka independent research committees)), distinct modes of collaboration (e.g. advisory government commissions), and particular types of inquiry (e.g. the rise of bioethics as a discipline). ... it seems not only appropriate -- but scientifically and ethically mandatory -- to consider in what ways these bioethical practices and venues remain adequate to current conditions, and in what way they require augmentation.

Bioethics today has to deal not just with questions of the transformation of life on a biological level -- via genomics, DNA sequencing, cloning, and so forth -- but also with life situated in a broader political context, through questions of the financing of the biotechnological industry, of the database management of the immigration and asylum systems, of the normativity of cosmetic surgery, of national and cellular surveillance, of biocitizenship, etc. (Also, today, the global life expectancy gap is the widest in human history, with a disparity of nearly five decades. The division of the world into organ buyers and sellers is a medical, social, and moral tragedy of immense and not yet fully recognized proportions. Our reluctance to address the issue of whether our body (or parts thereof) is in fact property has resulted in ambiguous organ donation frameworks. Many of the concerns raised ... regarding the directed donation of organs hinge on the question whether transplantable organs should be considered personal property or a societal resource. (M)any proponents of a commercialization of organ procurement state that there is nothing wrong with commodification. Premising Locke’s idea that everyone is the rightful owner of his person and faculties, especially some liberals derive a specific conception of
‘self-ownership’ which entails that ‘each person is free to do with his body whatever he chooses so long as he does not cause or threaten any harm to non-consenting others’. Since most people tend to associate ownership with the right to alienation, this conception also encompasses the freedom to sell parts of one’s body. This line of thought seems to presuppose that the self can act as an autonomous authority disposing over its body like over some kind of property.

(The) preeminence of autonomy as an ethical value within bioethics is deeply related to the increasing commoditization of medicine in developed countries. For the more that medical practices are justified by reference to patient choice, the more that patients will be viewed as ‘clients’ and health care professionals perceived as ‘service providers’. This model of patient as ‘client’, which is prevalent in the United States of America and some parts of the western world, assumes affluence and power: the (literate) patient has to be capable of understanding and rationally weighing his/her options -- possibly even in disagreement with the physician -- and be in a position to pay in exchange for services chosen. The challenge facing bioethics in resource-poor settings is not then to mislead people with unrealistic promises of autonomy that very few people can indeed achieve, but to articulate moral principles and societal values that are oriented around the promotion of equitable access to care and which broaden the goals of medicine and public health.

(Critical artists, whose art work has been exhibited in thematic shows about biotech, are ‘fig leaves’. Vested interests require an appearance of actual debate concerning these technologies’ developments. The stage has been prepared for the next phase of the
implementation of such technologies. Is there a continuity between the ways of looking which are fetishized in laboratories, the complacent viewing of art appreciators and the voyeuristic thrill of surveillance TV as low-brow entertainment? Are the subjects of study also the objects of desire? Or, are they subjects of ridicule and objects for control’s sake? ... Is it possible that reflections on being a person trying to retain what it means to be human while under the observation of the whole of society has any redeeming social value or is it just a currently accepted form of pornography?

References


Articles
The selection of articles included in the pdf version of the Bioethics™ book is limited to fully open-access texts. The pdf version hence differs from the online ‘living’ version of the book.

The Business of Bioethics

Jocelyn E. Mackie, Andrew D. Taylor, David L. Finegold, Abdallah S. Daar, Peter A. Singer
Lessons on Ethical Decision Making from the Bioscience Industry

Carlos Novas
What Is the Bioscience Industry Doing to Address the Ethical Issues It Faces?

Ezekiel J Emanuel, Trudo Lemmens, Carl Elliott
Should Society Allow Research Ethics Boards to Be Run As For-Profit Enterprises?

The Commercialization of Medical Research and Patient Care

T Lemmens, PB Miller
Regulating the Market in Human Research Participants

Aaron S. Kesselheim, Michelle M. Mello, David M. Studdert
Strategies and Practices in Off-Label Marketing of Pharmaceuticals: A Retrospective Analysis of Whistleblower Complaints

Adriane J. Fugh-Berman
The Haunting of Medical Journals: How Ghostwriting Sold “HRT”

David Henry
Doctors and Drug Companies: Still Cozy after All These Years

**Biomanufacturing and Biopatenting**

Arti Rai, James Boyle  
*Synthetic Biology: Caught between Property Rights, the Public Domain, and the Commons*

Joanna Zylinska  
*Playing God, Playing Adam: The Politics and Ethics of Enhancement*

**The Body as Property, Commodity and Gift**

Tarif Bakdash, Nancy Scheper-Hughes  
*Is It Ethical for Patients with Renal Disease to Purchase Kidneys from the World's Poor?*

Mark Schweda, Silke Schicktanz  
*The "spare parts person"? Conceptions of the Human Body and Their Implications for Public Attitudes towards Organ Donation and Organ Sale*

**Global Health Inc.**

Kammerle Schneider, Laurie Garrett  
*The End of the Era of Generosity? Global Health amid Economic Crisis*

Jacquineau Azétsop, Stuart Rennie  
*Principlism, Medical Individualism, and Health Promotion in Resource-poor Countries: Can Autonomy-based Bioethics Promote Social Justice and Population Health?*

Stuart Rennie, Bavon Mupenda  
*Living Apart Together: Reflections on Bioethics, Global Inequality and Social Justice*
Lessons on Ethical Decision Making from the Bioscience Industry

Jocelyn E. Mackie, Andrew D. Taylor, David L. Finegold, Abdallah S. Daar, Peter A. Singer

Ethical issues are a growing concern for companies, in the wake of a series of corporate governance scandals and the accompanying sharp decline in societal and investor trust in firms. Some companies have responded to these concerns by creating internal ethics programs. In the aerospace sector, for example, companies have focused these efforts on ensuring compliance with government regulations, while in the energy sector, ethics initiatives have concentrated on environmental issues and corporate and social responsibility [1].

Companies in pharmaceutical, biotech, and bioagricultural industries must not only comply with a wide array of government regulations and balance the profit motive with social responsibility, but also must deal with the complex array of ethical issues raised by doing business in the biosciences. These complex issues include the production and sale of genetically modified foods; gene therapy experiments and embryonic stem cell research to produce new therapies; animal testing for pharmaceuticals; drug pricing at home and in developing countries; the potential misuse of personal genetic information; how to appropriately commercialize and profit from genetic and biological samples; and the creation of transgenic animals for drug production.

Although a theoretical debate rages about whether bioethicists should consult to industry [2,3], no one has systematically examined from the standpoint of bioscience companies themselves how they address these ethical issues and why they do so. In understanding the complex relationship between bioethics and industry, there is a need to obtain

The Policy Forum allows health policy makers around the world to discuss challenges and opportunities for improving health care in their societies.

Ethical issues are a growing concern for companies.

with top managers and executives at 13 bioscience companies to learn about bioindustry ethics from their perspective (see Table 1 for a list and description of the 13 companies). Of the 13 companies, the majority can be classified as biotechnology companies, engaged in developing medical products, tools, and bioagricultural or industrial products. We also chose to include some companies for comparison that are part of the biotech value chain: a few pharmaceutical companies that often partner with biotechnology firms, and a contract research organization that is a supplier to biotech firms; thus, we use the term bioscience rather than biotech. We invited 19 companies to take part in the project, and 13 agreed (four pharmaceutical, one biotech, and one bioagricultural company declined).

The companies were not approached because they were representative of the bioscience industry, but rather because we knew they had implemented interesting and varied mechanisms to address ethical decision making from which we felt the rest of the industry could learn. In our selection, we were also looking for variety in company size, type, and location. The individual company case studies have been published as a book, *BioIndustry Ethics* [4], and each case provides a detailed examination of the company, the ethical issues it faces, and the mechanisms the company is using to address these issues.

What was not covered in the book (and is reported in this article) are the

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Abbreviation: EAB, Ethics Advisory Board

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How Are Bioscience Companies Addressing Bioethics?

Our study revealed a variety of mechanisms that are presently being used by bioscience companies to address ethical issues. These mechanisms offer insight and provide ideas on how other bioscience companies could implement mechanisms in their firms to address their own ethical issues. The specific mechanisms fall into five mutually reinforcing approaches (Box 2). All of our findings represent a snapshot of what these companies were doing to address bioindustry ethics at the time of our interviews.

Approach Two: External Expertise

External ethics consultant. Several of the companies used external consultants at various stages in their development to provide ethics education or expertise that was missing internally. For Sciona, which was still in its start-up phase, an external ethics consultant was its primary ethics mechanism. Sciona’s consultant helped the company navigate the ethical issues associated with its business of providing genetic-based health and diet information. The consultant reviewed marketing material to make sure it was ethically appropriate for the audience and encouraged the company to re-think its direct-to-consumer sales approach and to engage in a dialogue with the United Kingdom Human Genetics Commission.

Ethics advisory boards. Ethics Advisory Boards (EABs) were used as the primary mechanism by two of the medium-sized companies, PharmaSNPs (this company was acquired and no longer exists, and as a result, the company name has been anonymized) and Affymetrix, as a...
A mechanism to provide independent guidance and advice on ethical issues the companies faced. The EABs were composed of outside members representing the fields of medicine, law, religion, and ethics—and at one of the companies, lay members of the general public. The members would meet on a regular basis and would discuss, debate, and provide actionable guidance on specific issues. An Affymetrix EAB member explained one of the roles of the EAB: “We hold space, a focus and a safe place for [the company] to have non-core business discussions. To ask questions like: ‘Is there anything wrong with this deal?’ or ‘How far should we go to be ethical?’ We help them clarify why a certain activity is acceptable and why other choices are not.”

**Approach Three: Internal Ethics Mechanisms**

**Hiring practices focused on ethics.** Some companies in our study are now putting weight on candidates’ values, in addition to their past performance and technical expertise, when making hiring decisions. Six of the companies in this study include interview questions during the hiring process that aim to assess how the potential employee’s values align with the ethical values of the company. For example, employees from both Millennium and Maxim explained that technical skills and experience are now combined with the candidate’s behavioral and ethical fit when assessing the candidate’s merits.

**Employee performance evaluations.** A key driver of employee behaviour in any organization is the types of behaviours that are rewarded and promoted by upper management. One

### Table 1. Description of Study Companies

<table>
<thead>
<tr>
<th>Company</th>
<th>Approximate Number of Employees</th>
<th>Year Founded</th>
<th>Public/Private</th>
<th>Location of Headquarters</th>
<th>Company Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin Genetics</td>
<td>8–22</td>
<td>1986</td>
<td>Public</td>
<td>Waltham, Massachusetts, United States of America</td>
<td>A nutrigenomics company focused on performing clinical trials that examine the impact of genes on nutrition.</td>
</tr>
<tr>
<td>Sciona</td>
<td>10</td>
<td>2001</td>
<td>Private</td>
<td>United Kingdom (recently relocated to Boulder, Colorado, United States of America)</td>
<td>A small, personalized health-care company focused on nutrigenomics (genetic testing based on nutrition).</td>
</tr>
<tr>
<td>TGN Biotech</td>
<td>20</td>
<td>2000</td>
<td>Private</td>
<td>Quebec City, Quebec, Canada</td>
<td>A start-up biotech company focused on transgenic technology to produce recombinant therapeutic proteins in the seminal fluid of transgenic hogs.</td>
</tr>
<tr>
<td>Pipeline Biotech</td>
<td>20</td>
<td>1999</td>
<td>Private</td>
<td>Denmark</td>
<td>A small contract research organization specializing in animal testing.</td>
</tr>
<tr>
<td>PharmaSNPs*</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>A genomics firm that was focused on identifying genetic linkages with major diseases. The company has been acquired and now operates as a subsidiary of a larger firm.</td>
</tr>
<tr>
<td>Maxim Pharmaceuticals</td>
<td>150</td>
<td>1993</td>
<td>Public</td>
<td>San Diego, California, United States of America</td>
<td>A company developing a range of therapeutics based on naturally occurring histamines.</td>
</tr>
<tr>
<td>Diversa</td>
<td>280</td>
<td>1994</td>
<td>Public</td>
<td>San Diego, California, United States of America</td>
<td>A company developing products from genetic and biological resources found in biodiversity.</td>
</tr>
<tr>
<td>Affymetrix</td>
<td>900</td>
<td>1991</td>
<td>Public</td>
<td>Santa Clara, California, United States of America</td>
<td>A pioneering company in the development of gene chips.</td>
</tr>
<tr>
<td>Genzyme</td>
<td>6,500</td>
<td>1981</td>
<td>Public</td>
<td>Cambridge, Massachusetts, United States of America</td>
<td>The world’s fourth largest biotech company and a leader in the development of ultra-orphan drugs for rare genetic disorders.</td>
</tr>
<tr>
<td>Millennium Pharmaceuticals</td>
<td>13,700</td>
<td>1993</td>
<td>Public</td>
<td>Cambridge, Massachusetts, United States of America</td>
<td>A biopharmaceutical company with a broad drug development platform.</td>
</tr>
<tr>
<td>Monsanto</td>
<td>13,700</td>
<td>1901</td>
<td>Public</td>
<td>St. Louis, Missouri, United States of America</td>
<td>A leading multinational agricultural biotechnology company that produces genetically modified seeds, herbicides, and a bovine growth hormone.</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>18,700</td>
<td>1923, 1925</td>
<td>Public</td>
<td>Copenhagen, Denmark</td>
<td>A large Danish biopharmaceutical company focused on diabetes care. Other product focuses include homeostasis management, human growth therapy, and hormone replacement therapy.</td>
</tr>
<tr>
<td>Merck</td>
<td>60,000</td>
<td>1887</td>
<td>Public</td>
<td>Whitehouse Station, Massachusetts, United States of America</td>
<td>One of the world’s largest research-driven pharmaceutical companies, with products for the treatment of cancer, HIV/AIDS, baldness, asthma, seasonal allergies, osteoarthritis, heart disease, stroke, and more.</td>
</tr>
</tbody>
</table>

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*Asterisk indicates pseudonym for company. Details on size and location not revealed to protect the firm’s identity. The information in this table was correct at the time of the study. In our analysis, the companies are divided into small, medium, and large based on employee numbers. The smaller companies at the time of the interviews had fewer than 30 employees, the medium between 30 and 999, and the larger over 1,000.*

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medium-sized and three large-sized companies that were interviewed have incorporated ethics into employee performance reviews. For example, a Merck interviewee explained that the intention when designing a performance system is to not create incentives that encourage employees to bend the rules. The employee said: “We try not to put people in situations where they have to ‘make a number’ so that they won’t be tempted to give a $10,000 research grant to a doctor just to make a sale and meet that number.”

**Ethics education and forums for ethics discussion.** The majority of the medium- and large-sized companies we interviewed have developed formal ethics education sessions on topics such as research ethics and informed consent. Several of these firms have also introduced less formal forums for ethics discussion, where employees can voice concerns and have questions answered. At Monsanto, these are called “town hall meetings.” Millennium used popular film screenings—e.g., Gattaca and Inherit the Wind—facilitated by an outside ethics expert to draw out issues for ethics debates among employees. Millennium, Genzyme, and Merck have also implemented an Ethics Helpline that employees can call anonymously to get guidance about ethical issues.

**Ethical reinforcement techniques.** All of the companies we interviewed use techniques to reinforce ethics within the company, although these techniques tend to be more formally organized in the larger firms. Some try to remind employees of the importance of ethics by defining core values as part of the company’s culture (such as Genzyme’s “Putting the Patient First” approach), and some provide oral and visual reinforcements (by printing them on placards around the company buildings or on employees’ mouse pads, as at Millennium). Ethical guidelines in areas such as clinical trials and sales and marketing of pharmaceuticals were given during training and then reinforced with oral and visual reminders. For these techniques to be effective and to have an impact on the ethical conduct of employees,
our interviewees explained that they need to be continually and consistently reinforced by management.

**Approach Four: External Ethics Engagement**

**Ethics mechanisms with partners and suppliers.** Of the 13 companies, seven, spanning all sizes, have extended their ethics approach to their business partners—to share the benefits created by these companies and/or to try to ensure that their partners also follow high ethical standards. The primary bioindustry ethics mechanism used by Diversa, for example, is the benefit-sharing partnerships they have developed with countries that are involved with the collection of biological samples. Instead of secretly taking genetic material from these countries, referred to as “biopiracy,” Diversa forms partnerships—with, for example, a national park—to collect and process samples. In return, the company provides its partner with some up-front funding and training, along with a royalty percentage on any discoveries that originate from the samples.

Novo Nordisk has extended its Triple Bottom Line approach beyond the company to include its suppliers, who must fill out a social/environmental survey to assess whether they are following the same social and environmental norms to which Novo Nordisk ascribes. If a supplier is found to be violating some of these norms, Novo Nordisk will work with them to improve their standards.

**Transparent engagement mechanisms with stakeholders.** Companies of all sizes in our study (seven of the 13) are engaging with external stakeholders on ethical issues, although this seemed to become more of a necessity as firms became larger and higher-profile. These stakeholders include local communities, nongovernmental organizations, governments, interest groups, and consumers. One example is Novo Nordisk’s invitations to animal welfare activist groups to tour its labs and to discuss potential solutions to their differences. Explained one Novo Nordisk VP: “It was successful because of the openness and because we weren’t seeking consensus. What we were seeking was to understand each other and to look for areas of commonality... However, some companies think that the dialogue is sufficient. But it’s not. It requires action and responsiveness. There has to be a tangible outcome.”

Another example of listening to stakeholders and acting on stakeholder concerns includes TGN Biotech’s efforts to engage citizens of a community in which the company planned to build a pig farm. They held an information night to educate the community about their science and to answer their questions. Interviewees explained that if the community had decided that it did not want the company to build the genetically modified pig farm in their community, the company was committed to finding another location.

**Transparency of science.** Some of the fear in society about new science and technology stems from a perception that companies develop their science and technology secretly and do not share negative results. The Vioxx incident with Merck, which occurred after our study, demonstrates the importance of transparency. According to our findings, this is one area where companies are presently struggling to find a balance between protecting important patent and research information and the need to be transparent in a manner that will meet public satisfaction. One mechanism to address this issue was highlighted by the Director of Clinical Reporting at Novo Nordisk, who reported that the company tries its best to publish academic papers on every study to the greatest extent possible—regardless of whether the study shows negative or positive results.

**Influencing industry standards and regulations.** A majority of the companies we studied were engaged in discussions with regulators and industry bodies to encourage the ethical adoption of new science and technology. Some of the smaller firms were working to devise the best method of regulation for an emerging science as demonstrated by Interleukin and Sciona (nutrigenomics) and TGN Biotech (transgenesis to make therapeutic proteins). Others were working with industry groups to encourage the use of high ethical standards in areas of genetic information privacy (as done by Affymetrix), animal testing (Pipeline Biotech), and human rights standards (Novo Nordisk).

**Strategic philanthropy.** Philanthropic and drug donation programs are a way for companies to give back to, and engage with, society. The latter strategy tends to be limited to the larger firms that have reached profitability, while smaller firms donate employee time and expertise to address societal needs. Merck has created a nonprofit foundation that has invested hundreds of millions of dollars in public–private partnerships to help build infrastructure and deliver needed drugs in Africa and South America to address HIV/AIDS, and for other health crises, such as river blindness. Another example is Novo Nordisk’s World Diabetes Foundation, which supports partnerships and initiatives around the world that help build health infrastructure and health-care capacity in these countries. Novo Nordisk works with local organizations and governments to learn what is needed from the developing country’s perspective.
Our findings in the area of ethics evaluation demonstrate a need for future development and research. For bioscience companies who are more familiar with tangible and quantitative outcomes (with respect to share price, market share, and scientific data and results), it is challenging to devise a method to evaluate something as intangible as ethics. Employee surveys, public opinion polls, share price, and product acceptance levels were some of the measurement approaches suggested during our interviews. Although many of the companies studied are not evaluating the effectiveness of their ethics mechanisms, it was very clear that companies feel that evaluating their ethics approaches in order to learn from their successes and failures is a vital component of any bioindustry ethics initiative.

Limitations of Our Approach
The objective of this paper is to highlight specific mechanisms used by companies to address their ethical issues. However, we recognize that the views of senior management of bioscience companies are not the only relevant perspectives on these issues. We feel that one important next step would be to engage the opinions of other key players, such as nongovernmental organizations, governments, academics, and the general public.

Another limitation of a study such as this is the risk of social desirability bias. This occurs when the research participant expresses a viewpoint that he or she thinks the interviewer wants to hear rather than what he or she truly believes. Although management opinions were given in this research study, the mechanisms described in this article are not opinions but rather a description of mechanisms being used by the companies—and, thus, they are less subject to bias. At each company, the descriptions of the mechanisms were given by more than one interviewee, and in most cases, we had documents supporting the fact that these mechanisms do occur as described. We recognize these limitations, but feel that because the people we interviewed are closest to the phenomenon, they represent a legitimate viewpoint and a highly logical entry point for empirical research into why and how bioscience companies address ethical issues.

Conclusion
Our study uncovered five interrelated approaches, each with several mechanisms to address bioindustry ethics. Based on our findings, a company of any size can start with strong ethical leadership and seek external ethics expertise early on. Internal ethics mechanisms and external ethics engagement mechanisms are other approaches that a bioscience company of any size can implement. As demonstrated by the larger companies in our study, companies can also develop ethics evaluation and reporting mechanisms that aim to keep the company on track and encourage management to monitor the outcomes of their ethical decision making. The mechanisms reported in this article demonstrate ideas for ways in which management in the bioscience industry can begin to address the complex ethical issues facing their companies.

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References
What Is the Bioscience Industry Doing to Address the Ethical Issues It Faces?

Carlos Novas

Corporations are increasingly expected to behave ethically and to make their operations as transparent as possible. This is especially the case for the bioscience industry (biotechnology and pharmaceutical firms). These firms deal with a commodity like no other: our health and well-being. They also engage in research that manipulates the basic building blocks of life and challenges common understandings of the boundaries between humans and animals, the treatment of disease versus the enhancement of healthy lives [1], and when life begins or ends. To address these complex challenges, bioscience corporations have begun to implement a range of practices to address the ethical questions that their operations pose. In a new Policy Forum article published in PLoS Medicine, Jocelyn Mackie and colleagues describe the variety of mechanisms that bioscience firms have put in place to address the ethical issues confronting them [2].

The Methodology

Based on more than 100 interviews with executives and senior managers from 13 firms, the authors sought to find out what these professionals had to say about what their companies are doing to promote ethical behaviour. To date, there has been relatively little empirical research on this topic. As such, it is a timely piece.

The authors draw upon a larger study, in which detailed case studies were developed for each firm, including the ethical challenges that the firms faced and the mechanisms used to address them. The firms selected for analysis were chosen because they were known to be developing innovative approaches to dealing with ethical issues. They were further selected to represent the diversity of this industrial sector and to account for variations in firm size and location. In the paper, the authors seek to draw comparatively upon the case studies they developed to highlight the range and variety of mechanisms adopted by firms to address ethical issues.

Approaches Used by Firms to Encourage Ethical Behaviour

Based on the analysis presented, firms of all sizes and in different market niches are using a variety of approaches to encourage ethical behaviour. First of all, executives are promoting ethics as part of a firm’s core values. There is also evidence of specialisation: larger firms are able to create dedicated departments, while smaller firms are incorporating ethics into the responsibilities of senior managers.

The companies studied have further retooled their organisational structures with ethics in mind: ethics shaped their hiring and staff performance evaluations, employees in some firms were given ethics training, and visual and oral reminders were being used in the workplace to reinforce an organisation’s commitment to its ethical values. In instances where internal expertise was lacking, external consultants were brought in or independent ethics advisory boards were created to provide guidance and advice. Regardless of size, most of the firms studied were engaging with a range of stakeholders—whether it be reshaping their relationships with suppliers to maintain high ethical standards, consulting with a local community, inviting activists to visit laboratory facilities, or launching corporate philanthropy programmes in Africa. Lastly, firms are beginning to develop measures for evaluating and reporting their ethical behaviour.

The Implications

This study demonstrates that (at least for a selective range of firms in the bioscience industry) some corporations have started to believe that the types of relationships they have with patients, carers, families, physicians, activists, partners, suppliers, regulators, and the public are an essential element of corporate financial and social viability. Considering that some of the firms studied do not seem to have any products on the market, current and anticipated ethical concerns are shaping their corporate practices and bottom lines in the here and now.

This paper also provides evidence of how ethical decision making is not an entirely abstract philosophical exercise: ethics has to be embedded in a range of social practices and relationships that need to be continually cultivated and reinforced if they are to be effective.

Lastly, it can be extrapolated that ethics is an asset that firms can trade upon. Firms are considering ethics as transparent as possible.

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The Perspectives section is for experts to discuss the clinical practice or public health implications of a published article that is freely available online.
as central not only to their research activities and the dissemination of their products to consumers, but also to the reputation and branding of the company itself. Of course, ethics, like any other asset, has multiple values. Ethics can be used by firms not only to shape their decisions, but to aid corporate public relations campaigns. No doubt, the multifaceted character of corporate ethics programmes can lead to outbreaks of scepticism amongst bioethicists and the public.

Unresolved Questions
A question that was left unresolved by the authors was how effective these mechanisms have been at accomplishing their objectives. Whilst firms may not yet be evaluating the actual impact of these mechanisms, it is imperative for bioethicists studying these mechanisms to discuss their relative merits and disadvantages. Better yet would be an evaluation of how ethical these companies actually are. In a similar vein, we need to know more about how and to what extent the mechanisms adopted by firms influenced their research, investment, or marketing decisions. Finding out about such influence will require further empirical analysis and a willingness on the part of executives in the bioscience industry to let researchers not only interview them but also observe what goes on in their boardrooms. This type of transparency would facilitate the investigation of what kinds of problems do and do not get defined as being ethical and the organisational processes that shape firm behaviour. Lastly, it is important to emphasise that firms, like individuals, do not live in isolation. We need to pay greater attention to the broader political, economic, and social context that has encouraged firms to develop mechanisms to address ethical issues, as well as the role of industry organisations and professional associations in facilitating the uptake and dissemination of these mechanisms.

It will be important to study bioscience firms as they start to incorporate ethics into their organisational practices and into the very products they develop through their research decisions. To date, this subject area has not been extensively explored by bioethicists. As more aspects of our health and illness are embraced by the bioscience industry, the ethical issues surrounding industry’s actions will become an area that is ripe for analysis.

The Relationship between Ethicists and Corporations
A question that this paper opens up for further analysis and debate, given that firms are starting to integrate ethics into their organisational practices, is how and through what forms bioethicists should relate to corporations. At the present time, there seem to be two dominant forms. One form appeals to the values long cherished in academe: independence, critical scholarship, credibility, and integrity [3,4]. The other form appeals to the values to be gained by consulting for industry: corporate or policy relevance, alongside honoraria, salaries, and grants [5]. Presently, bioethics seems to be at an impasse over what form to adopt.

Perhaps the lessons to be learned come from the bioscience industry itself. As firms have started to reformulate their organisational forms and modes of conduct in relation to changing socioeconomic circumstances, perhaps it is an opportune moment for bioethicists to rethink the subjects they choose to study and how bioethics engages with its various stakeholders. Just as scientists have created new theories and techniques to investigate the phenomena of life, bioethicists need to develop new concepts and tools for proposing how we should individually and collectively relate to one another in a manner that is capable of dealing with the dilemmas that will be posed by the provision of health in the 21st century.

References
Back to the debate: An important mechanism for protecting human research participants is the prior approval of a clinical study by a research ethics board, known in the United States as an institutional review board (IRB). Traditionally, IRBs have been run by volunteer committees of scientists and clinicians working in the academic medical centers where the studies they review are being carried out. However, for-profit organizations are increasingly being hired to conduct ethics reviews. Proponents of for-profit IRBs argue that these IRBs are just as capable as academic IRBs at providing high-quality ethics reviews. Critics argue that for-profit IRBs have a conflict of interest because they generate their income from clients who have a direct financial interest in obtaining approval.

Ezekiel J. Emanuel’s Viewpoint: Let’s Dump the Outdated Ideology of “For-Profit Bad, Not-for-Profit Good”

It is commonly thought that for-profit companies are necessarily worse than not-for-profit organizations doing similar activities. According to this thinking, for-profit companies are heartless, place profits over people, quality, or integrity, and are inherently exploitative. For-profit prisons must be worse than state-run prisons; for-profit health plans are worse than not-for-profit health plans; and surely for-profit auto manufacturers are worse than not-for-profit car makers.

This is a quaint notion. In prisons, we care about security and the respectful treatment and rehabilitation of the prisoners; in health plans we care about the quality of health care delivered to patients and the overall health of the people. Profit status is a tax designation, not a quality indicator. At best, profit status is a crude approximation—a proxy measure—for what we really care about: security and rehabilitation, or quality health care. What we should really focus on then is not the ideology of profit status but these substantive outcome data.

The same is true for IRBs. What we should focus on is not their tax status but the data regarding their quality. Are the IRBs evaluating protocols according to the ethical standards for clinical research? Are they ensuring that researchers are using reliable and valid scientific methods and selecting research participants fairly? Are the risks and benefits of the research reasonable? Does the informed consent document lucidly inform the patient without voluminous, superfluous, or distracting details? In addition, we want the IRB to carefully monitor the implementation of the protocol, especially monitoring for adverse events.

Why might we think that for-profit IRBs do these functions poorly? Perhaps being for-profit, they need to woo business, and so they are less independent of their clients, less inclined to be critical, and more inclined to overlook ethical problems. But these potential difficulties are not unique to for-profit IRBs. Researchers who sit on not-for-profit, academic IRBs are evaluating their colleagues’ research protocols, so these IRB members also have ties that may compromise their independence and critical evaluations. Furthermore, many academics tend to view IRB service as an uncompensated burden, which is not conducive to careful review work. Academic medical centers and their researchers also have their own financial interests in getting research protocols passed. They get money—as well as access to new drugs and prestige—for conducting the research. Many not-for-profit IRBs are also charging drug and device companies for review of their research protocols, and their rates are comparable to the rates charged by for-profit IRBs.

The crucial question is whether an IRB, regardless of its tax status, is performing at a high level of quality. Unfortunately, there are no validated quality indicators for IRB function, and no head-to-head comparison has been made of the performance of for-profit and not-for-profit IRBs. However, to evaluate the quality of IRB function we have some approximate indicators such as regulatory compliance, substantive outcome data, and so they are less independent of their clients, less inclined to be critical, and more inclined to overlook ethical problems.

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Abbreviations: CRO, contract research organizations; FDA, US Food and Drug Administration; IRB, institutional review board; OHRP, Office for Human Research Protections; WIRB, Western Institutional Review Board

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accreditation, knowledge sharing, and internal quality assurance practices.

In recent years the US’s Office for Human Research Protections (OHRP) has suspended, at least temporarily, the research being conducted at a number of major medical centers—including Johns Hopkins, Duke University, Rush University, University of Colorado, and University of Rochester. Furthermore, unexpected deaths in research participants that have captured the public eye have occurred at some of these same institutions—Johns Hopkins and University of Rochester—as well as at the University of Pennsylvania and Case Western Reserve University. The suspension of research by OHRP and the unexpected death of relatively healthy research participants are not perfect indicators of poor studies or poor IRB performance, but neither can they be dismissed as irrelevant. All of these prominent cases have occurred at not-for-profit academic institutions.

The first IRBs to receive “full accreditation”—the highest level of accreditation awarded by the Association for the Accreditation of Human Research Protection Programs—were one for-profit IRB, Western Institutional Review Board (WIRB), and one not-for-profit IRB, University of Iowa. And so it continued: of the first eight organizations to receive full accreditation, four were for-profit IRBs.

At least 26 academic institutions outsource all or part of their protocol review to for-profit IRBs. And in recent years, the OHRP has called upon WIRB to re-review protocols and revamp the IRB processes and procedures at not-for-profit academic institutions where the OHRP had temporarily suspended research. Calling upon WIRB constitutes a vote of confidence by federal regulators that at least this one for-profit entity provides high-quality IRB review, and has something to teach the not-for-profit academic centers about institutionalizing quality IRB review.

Furthermore, OHRP has never suspended a for-profit IRB. And, the US Food and Drug Administration (FDA) has issued only one warning letter to a for-profit IRB compared to hundreds to IRBs at not-for-profit institutions.

For-profit IRBs have made contributions to the common good. For example, WIRB has established a program allowing IRB administrators from developing countries in Latin America, Southeast Asia, South Asia, and other places to visit their location for six months of training in running an IRB. So far, 24 fellows have been trained. How many not-for-profit IRBs have established programs to improve protocol review either in the US or other countries using their own money—not grants from the National Institutes of Health?

Making a distinction about the quality and merits of IRBs based on tax status is an antiquated piece of ideology reminiscent of Orwell’s Animal Farm—“for-profit bad, not-for-profit good.” The distinction obscures what we should care about and directly measure—the quality of IRB review of protocols and the monitoring of the safety of research participants. There are absolutely no data showing that either independence of reviewers or quality outcomes are correlated with an IRB’s profit status, and there is some real evidence in the regulatory actions and accreditation that the quality of for-profits is as good as or better than many of their not-for-profit academic counterparts. Since we are supposed to be researchers and driven by data not emotion, let’s give up the crude ideology and stick to the data.

Trudo Lemmens and Carl Elliot’s Viewpoint: Commercial IRBs Have a Fundamental Conflict of Interest

Like it or not, research on humans has become a commercial enterprise. Most clinical trials have moved from academic settings to specialized contract research organizations (CROs), which contract with the pharmaceutical and biotechnology industries. Whereas 63% of clinical trials were still being undertaken in academic settings in 1994, a mere 26% of such trials remained there in 2004 [1].

It is widely recognized that the commercialization of medical research creates serious conflicts of interest [2–5]. What is often overlooked is that IRB review, which is often expected to provide protection against such conflicts, has also become commercialized. Some industry-funded trials are reviewed by in-house IRBs set up and funded by pharmaceutical companies or CROs themselves; others are reviewed by commercial, for-profit IRBs [6]. Of course, commercial IRBs are not an entirely new phenomenon. The oldest and most successful IRB, WIRB, has been in business since 1968. What is new about commercial IRBs is their extraordinary reach. According to its founder, WIRB is now responsible for the review of more than half of all new drug submissions to the FDA [7]. Several universities and hospitals also outsource ethics review to commercial IRBs.

Yet commercial IRBs have a fundamental conflict of interest [5,8–11]. They are in a client–provider business relationship with the commercial entities whose studies they review. Because commercial IRBs generate their income from clients with a direct financial interest in obtaining approval, they are affected by the very problem they are expected to curtail. The financial interests involved are huge. Pharmaceutical companies pay CROs for their speed and efficiency. Clinical trials are a crucial step in the drug development process. Any delay in approval by an IRB affects the sponsor’s profit margins.

The countries that have allowed these private IRBs to flourish have also failed to regulate them carefully. Neither the US nor Canada has placed any serious restrictions on the establishment of new IRBs. Although an IRB registry has recently been set up for federally funded research in the US, and although the FDA and Health Canada sporadically inspect IRBs involved in the review of clinical trials, they do not have formal registration and approval processes for IRBs. Anyone who can bring together five people, including a community representative, a physician, a lawyer, and an “ethicist,” can set up shop and start competing for business.

Moreover, regulations in those countries fail to prevent CROs from selecting the IRB least likely to reject the trial or delay approval by imposing too many restrictions. If one IRB is too stringent, they can simply go to the one next door.

Free market advocates will argue that the research industry has an interest in promoting quality IRB review. In theory, sound ethical review could prevent lawsuits, and commercial IRBs could use ethical review as a marketing tool. In fact, however, commercial IRBs market their speed and efficiency, and lawsuits are still relatively rare. Most are settled out of court, with the records sealed from public view. Moreover, the costs of these lawsuits pale in comparison with the profit gained by bringing a new drug faster to market. For
multinational pharmaceutical companies, litigation is a manageable cost of doing business.

Commercial IRBs fill a regulatory vacuum in countries that lack a governmentally organized system of ethics review. Yet, as Bloomberg Markets reported, several commercial IRBs have approved and been involved in overseeing controversial research practices. SFBC International, the largest CRO in the United States, has recruited undocumented immigrants to a converted motel in Miami and paid them to enroll in trials overseen by an unlicensed medical director [7]. Some of SFBC International’s clinical trials were approved by a now-dismantled commercial IRB owned by the wife of an SFBC International vice president [7]. To oversee the research conducted at the Fabre Research Clinic, the clinic’s owner founded a private IRB that had his business partner and lawyer as members. The clinic was eventually shut down by the FDA after an investigation into the death of a research subject more than ten years after the agency first flagged several serious research irregularities [12]. In another article, Bloomberg Markets reported that a Canadian affiliate of SFBC International, Montreal’s Anapharm, is currently being investigated by the Canadian drug regulatory authorities after several human research participants were infected with tuberculosis. Research participants had been submitted to basic medical screening, according to the report, but not to any specific tests for tuberculosis, even though the trial involved an immunosuppressant drug [13].

In 1999, Swiss authorities were alerted that a CRO in the Canton Basel was recruiting individuals from Eastern Europe and asylum seekers as research participants for Swiss clinical trials. An investigation conducted by a special working group for the drug regulatory agency revealed troubling consent procedures, such as consent forms being in languages the trial participants did not understand. The principal investigator for the clinical trials, who combined the position of CRO director with that of local director of the commercial IRB that approved the research, was not licensed to practice medicine [14].

At a time when commercial interests threaten the safety of research participants and the integrity of medical research, it is remarkable that North American regulatory agencies have not seen any problem with entrusting the rights and well-being of human research participants to a lightly regulated commercial enterprise. In the wake of the Swiss scandal, the authorities in Basel introduced new regulations requiring registration and regulatory approval of IRBs. IRBs also received exclusive jurisdiction, making it impossible to shop for the most lenient IRB. These new regulations, under which no commercial IRBs were approved, were upheld by the Swiss Supreme Court. The court argued that research ethics committees fulfill a public function with a direct mandate from the state [15,16]. It is time for regulatory authorities in Canada and the US to follow suit. The protection of research participants is a critically important public mandate, and it merits a truly independent regulatory structure.

**Emmanuel’s Response to Lemmens and Elliot’s Viewpoint**

I agree with Lemmens and Elliot that “the protection of research subjects is a critically important public mandate, and it merits a truly independent regulatory structure.” That is where the agreement ends.

Lemmens and Elliot claim that “commercial IRBs have a fundamental conflict of interest.” But IRBs at academic medical centers have even greater conflicts of interest [17]. Both commercial and academic IRBs have a financial conflict of interest, especially since increasingly academic IRBs are charging competitive prices for their services, making them indistinguishable from commercial IRBs. Academic IRBs have the additional conflict that the researchers being reviewed are colleagues of the IRB members. And they have yet a further conflict since the institution wants and needs the commercial research in order to gain access to new drugs and devices to enhance its reputation as innovative.

Lemmens and Elliot conflate CROs and commercial IRBs, trying to tar the reputation of commercial IRBs with unsavory practices of CROs. Furthermore, when all the hyperbole is ignored, these authors base all their objections on just three anecdotes, rather than on rigorous scientific data. That the owners/operators of SFBC, Fabre Research Clinic, and a research center in Switzerland have been accused of unscrupulous practices hardly constitutes an indictment of all commercial IRBs. Using similar logic one might indict all not-for-profit IRBs because of the documented poor performance of academic IRBs that have to be suspended at Johns Hopkins, Duke University, University of Colorado, University of Rochester, etc.

Lemmens and Elliot marshal absolutely no scientific data to show that any of the major commercial IRBs in the US—including WIRB, Schulman, Chesapeake, Essex, and Copernicus—are performing poorly. The authors cite no studies, for example, to show that the quality of the reviews by these IRBs is poor or that these IRBs have approved unethical studies. I do not know whether these IRBs are all good, but if Lemmens and Elliot’s broad indictment leveled against all commercial IRBs is valid, they surely should provide data about the poor quality of the major commercial IRBs, since these account for the majority of reviews done in the commercial sector. Otherwise, the charges appear to be good headlines, but are baseless.

Finally, despite their rhetoric, Lemmens and Elliot do not actually call for the prohibition of commercial IRBs. They want more regulatory oversight. Yet, I am unaware of their having delineated a comprehensive proposal describing such an oversight system. With Wood and Grady, I have proposed a system of regional ethics organizations that would review and monitor research protocols, educate researchers on the ethics of human research, and develop policies in controversial areas, such as paying participants [18]. Such organizations would completely eliminate conflicts of interest, financial and otherwise, between the reviewing organizations and researchers. Maybe this is something Lemmens and Elliot can agree with? If not, let’s hear their positive proposal for a “truly independent regulatory structure.”

**Lemmens and Elliott’s Response to Emanuel’s Viewpoint**

Not too long ago, an article on the protection of sick and vulnerable research participants that compared the funding of IRBs to the funding of for-profit jails would have been read
as satire. In North America today, however, where medical research happily converges with consumer capitalism, even bioethicists believe that the market ultimately works for justice. Do we need to point out that the problem with the consumerist model for protecting research participants is not, as Emanuel suggests, its “tax status”? The problem is that commercial IRBs are paid in full by the very companies conducting the research. What is more, those companies are free to shop around for any IRB whose reviews they find congenial. Research participants who are worried that they may face death or injury in a study sponsored by a pharmaceutical company are unlikely to feel more secure knowing that their safety has been entrusted to a panel of paid experts whose financial livelihood depends on a company paycheck.

Acknowledging that no good data exist to compare commercial and university IRBs, Emanuel nevertheless exhorts us to “stick to the data” anyway, recommending the example of WIRB, a commercial IRB that earned $20 million in 2004, and whose president was Emanuel’s research collaborator (as he acknowledges in his competing interests statement). Yet part of the data he omits from his enthusiastic recommendation comes from Bloomberg Markets, which reported in December that WIRB “oversaw tests in California and Georgia in the 1990s for which doctors were criminally charged and jailed for lying to the FDA and endangering the lives of trial participants. No action was taken against WIRB” (p. 37 of [7]). The same report revealed that WIRB had settled a lawsuit after it approved a placebo-controlled trial for a Genentech psoriasis drug in which a patient was severely injured, that it had drawn criticism from the FDA in inspection visits, and that on one occasion, when reviewing protocols for Johns Hopkins University, it reversed a previous decision under pressure from a clinical sponsor, using a panel dominated by alternate members.

It is rarely, if ever, possible to know whether financial incentives have improperly influenced a member of an IRB. This uncertainty is the reason for rules about conflicts of interest—to prevent people from being placed in situations where they are likely to be improperly influenced. We agree with Emanuel that academic IRBs are marred by many of the same problems facing for-profit IRBs, including conflicts of interest [6,19]. But the problems of academic IRBs do not make those of for-profit IRBs disappear. The proper solution is to clean up the conflicts of interest, not to institute a replacement in which such conflicts are built right into the system.

References
Regulating the Market in Human Research Participants

Trudo Lemmens*, Paul B. Miller

In the past couple of years, several investigations by the Office of the Inspector General (OIG) of the US Department of Health and Human Services (DHHS) have drawn attention to the use of recruitment incentives in research. In 2003, Toronto’s Globe and Mail reported that the pharmaceutical company Biovail became the subject of an investigation because it paid $1,000 per patient to American physicians who managed to renew prescriptions of its new drug Cardizem LA for at least 11 patients. The company argued that the payments were a reward for data gathering for post-marketing research.

The practice of paying research participants is inadequately regulated. [1]. Less successful physicians received only $250 per patient. In 2005, the OIG started an inquiry into payments made by Advanced Neuromodulation Systems to physicians who implanted a pain-management device in their patients for a five-day trial [2]. According to the Wall Street Journal, those who managed to implant the device in at least five of their patients received $1,000 for “data collection and management of the trial process.”

Although the OIG has not yet released results of either investigation, it previously documented in 2000 that a family medical practice, because it paid $1,000 per patient to those who managed to implant the device, became the subject of an investigation by the Office of the Inspector General (OIG) of the US Department of Health and Human Services; IRB, institutional review board; OIG, Office of the Inspector General.

Recruitment incentives are thus a crucial challenge, partly filled this void.

Recruitment Incentives in Context

The increasing prevalence of recruitment incentives is directly related to growing competition between research sponsors. More pharmaceutical clinical trials are being undertaken than ever before. US statistics indicate industry investment of increasing magnitude in clinical trials. As of 1999, more than 450 heart, cancer, and stroke drugs were under development in the US, and a further 191 were under development for Alzheimer disease, arthritis, and depression [10]. Pre-clinical trials are also on the rise. In 1998, there were 3,278 drugs in pre-clinical testing in the US, an increase of 26.8% from 1995 [3].

Similar trends are evident elsewhere. Health Canada has indicated that it reviewed “over 800” applications for approval to proceed with clinical trials in 1998, and that it has witnessed an average 20% annual increase in clinical trials conducted in Canada [11]. These trends partly explain heightened demand for research participants. Another contributing factor is the trend toward larger trials. According to the OIG, clinical trials supporting new drug approval applications averaged 4,237 participants in 1995, an increase of 2,916 in one decade [3].

Speed of testing is as crucial as recruiting sufficient numbers of patients. Thomas Bodenheimer mentions, without providing a source, that a single day’s delay in getting a drug to market costs $1.3 million [12]. Claims associated with costs of drug development merit careful scrutiny since they are often used as a rhetorical tool to argue for faster approval times or to justify the high price of pharmaceuticals. However, it is fair to presume that delays have financial repercussions. At a 2003 conference, Neil Maresky, vice president of scientific affairs at Wyeth, stated that problems in patient recruitment are “the biggest delaying factor in clinical trials” [14]. Patient recruitment is thus a crucial challenge.
one that industry is attempting to address through use of financial incentives.

**Payments to Health-Care Professionals**

Industry research sponsors are increasingly paying finder’s fees to health-care professionals to encourage them to recruit patients. Finder’s fees can be defined as payments to physicians, nurses, or other health-care professionals for the mere recruitment of research participants. Reports suggest finder’s fees ranging between $2,000 and $5,000 per patient are common [15], although it is not always easy to distinguish the reward for the recruitment of patients from remuneration for clinical activities that are part of the research.

These incentives may partly explain the increasing involvement of community-based physicians in clinical research. Between 1988 and 1998, the number of community-based physicians participating in research in the US increased by 60% [16]. Sponsors target community-based physicians because their patient bases are seen as an untapped reserve of potential research participants. Academic researchers, in turn, now feel they must compete with community-based physicians for recruitment incentives, either for personal gain or to pay researchers’ salaries.

Direct payments to researchers, often with bonuses for fast recruitment, are not the only tools of the trade. Sponsors may offer other incentives, including authorship priority, paid consulting work, and further research sponsorship [12,17]. For this reason, we use the wider term “recruitment incentive” rather than “finder’s fee” to discuss the general ethical and legal issues associated with various practices used to entice physicians into recruiting patients.

**Concerns Raised by Recruitment Incentives**

**Interference with physicians’ judgment.** A general concern is that recruitment incentives will encourage physicians to act contrary to their fiduciary obligations to their patients. The prospect of considerable fees for referrals may interfere with the judgment of physicians trusted by patients to act in their best interests.

A related concern is potential interference with consent processes. Fraudulent behavior can be dealt with under criminal law [18]. But other forms of influence are likely to be more subtle and therefore harder to control. Researchers who know that enrollment of an additional patient will bring a $20,000 bonus may be tempted to find a way to convince that patient of the “advantages” of participation.

**Patient safety.** Safety is another important concern: financial interests associated with the recruitment of patients may encourage researchers to disrespect inclusion and exclusion criteria, putting patients at risk.

Misconduct at a VA (Veterans Affairs) hospital in Albany, New York, highlights this concern [19,20]. Federal officials launched a criminal investigation against two researchers involved in a cancer study at the hospital in which at least five patients died [21,22]. An inspection report by the US Food and Drug Administration (FDA) concluded that patients’ medical records were altered in at least five experimental drug studies, enabling veterans to be enrolled in studies for which they were either too sick or too healthy to qualify [23]. The hospital reportedly received a fee of $5,000 for each patient enrolled [23], and some individual investigators are reported to have received undisclosed recruitment incentives [19]. The junior researcher pled guilty to criminally negligent homicide as well as fraud and was sentenced to six years in prison [24]. The senior researcher was not charged, but the FDA initiated disqualification proceedings against him on September 22, 2004 [25]. As of June 5, 2006, the case was still open (confirmed in a phone call to the FDA’s Division of Scientific Investigations on June 5, 2006). Safety concerns may be amplified with the involvement of community-based physicians, who may lack experience in research, who may be overburdened, and who work more in isolation, perhaps making it harder to critically evaluate and discuss research benefits and risks with other professionals.

**Erosion of public trust in clinical research.** More general concerns relate to the public interest in clinical science. In a competitive environment, commercial sponsors enjoy significant control over research. Careful selection of patients and development of research methodology, combined with selective publication, may lead to the approval of minimally effective and potentially harmful drugs. A host of recent controversies indicate how pharmaceutical sponsors have engaged in the selective publication of results, the manipulation of data, the use of ghost authors, and, allegedly, the fraudulent promotion of off-label prescription, on the basis of questionable research [26]. Erosion of scientific integrity risks the health of future patients and places undue burden on publicly funded health care. Further, recruitment incentives are implicated in the distortion of research agendas and priorities [27]. Researchers who conduct publicly funded research may encounter difficulties recruiting patients because they cannot offer significant recruitment incentives. As a result, valuable research may be neglected for research of sometimes questionable scientific importance and clinical value.

**Existing Controls on Recruitment Incentives**

Few would argue that patients in trials should be treated as commodities, but patients have become de facto market products, while “market controls” are neither clear nor sufficiently stringent. Various organizations have taken a stand against certain recruitment practices. The American Medical Association’s Council on Ethical and Judicial Affairs stated unequivocally in one opinion that “offering or accepting payment for referring patients to research studies (finder’s fees) is unethical” [28]. In a report on finder’s fees, the council clarifies the basis for its recommendation, and seems to widen its ambit. It states that “any kind of compensation in return for the referral of patients” is unethical [29]. An earlier general opinion on conflicts of interest indicates, however, that remuneration that is “commensurate with the efforts of the researcher on behalf of the company” is acceptable [30].

The Canadian Medical Association has issued a statement on relations with the pharmaceutical industry that...
refers to finder’s fees [31]. But it fails to clearly prohibit them or to mandate their disclosure, and essentially diverts the issue to institutional review boards (IRBs). Several academic institutions offer more direct guidance, expressly prohibiting finder’s fees [32–37]. But since most clinical drug trials now take place outside of academic institutions, such guidance has little impact on the practice. It is also not clear whether academic institutions have thorough control over the research practices in their institutions, even when they have such policies in place.

IRBs are currently neither sufficiently regulated nor independent.

Physicians should, however, be aware that legal and regulatory sanctions may be imposed on them for accepting recruitment incentives. Significant private liability may arise. If physicians purposefully misinform or fail to adequately inform patients of their financial interests, they expose themselves to tort liability for battery or negligence. Moore v. Regents of the University of California [38] suggests that non-disclosure of financial interests by a physician can give rise to a cause of action for breach of fiduciary duty, although a more recent Florida District Court rejected the argument that physicians have to disclose financial interests [39].

Other serious legal consequences, including criminal charges, are also possible [40]. Most US states [41] and some Canadian provinces [42] have statutory frameworks on professional misconduct, with provisions that could apply to research activities. The US federal “anti-kickback statute” also makes it a felony to induce referral of patients covered by federal health-care programs [43]. These statutes generally prohibit the offer or acceptance of rewards for referring patients to health-care providers or facilities. The general terms in which such statutory provisions are constructed suggests that they could readily be applied to sanction the offer or receipt of a broad range of recruitment incentives used in clinical research [40]. The California Business and Professions Code, for example, prohibits the “receipt, or acceptance…of any rebate, refund, commission…or other consideration…as compensation or inducement for referring patients, clients, or customers to any person” [44].

In the US, regulatory authorities have also laid charges under the federal False Claims Act in cases where financial interests were not disclosed to granting agencies, and where researchers violated regulations, compliance with which was a condition for funding [45]. In Canada, significant case law has expanded the potential scope of application of general Criminal Code fraud provisions [46]. Canadian physicians who fail to disclose financial interests in referrals or other forms of advice to patients expose themselves to possible criminal prosecution for fraud, and when the patient’s treatment suffers as a result [40].

Recruitment Incentives and Regulatory Reform

The problems raised by finder’s fees cannot be resolved by focusing exclusively on sanctioning the individuals who may accept them. They ought to be addressed as part of a broader institutional and regulatory reform effort designed to address weaknesses in research governance.

Such reforms ought to include specific institutional and regulatory guidance on broad conflict-of-interest issues. Strict but narrow rules on finder’s fees may fail to protect participants from the influence of conflicts arising from other arrangements that are harder to detect and control. Several organizations have come up with sensible recommendations to strengthen conflict-of-interest rules. A task force of the Association of American Medical Colleges issued two important reports on investigator [47] and institutional [48] conflicts of interest. The task force strongly recommends that institutions separate the financial management of research from their conduct and oversight, and, further, that they establish independent conflict-of-interest committees. With regard to individuals, it recommends that institutions introduce a rebuttable presumption that individuals holding a significant financial interest in a study may not participate in its conduct.

The DHHS has also recommended the establishment of specialized institutional conflict-of-interest committees in a guidance document: “Financial Relationships and Interests in Research Involving Human Subjects” [49]. If the recommendations of the Association of American Medical Colleges and the DHHS are acted upon, they may go a long way to address concerns about conflicts of interest within academic institutions. However, it is unlikely that the adoption and enforcement of more stringent institutional policies will alone satisfactorily address concerns generated by recruitment incentives.

Regulatory agencies and institutions rely too much on IRBs to evaluate and control conflicts of interest. While the development of specialized conflict-of-interest committees within academic institutions would add a layer of more focused protection, IRBs would presumably still play the central role in protecting research participants from the ill effects of conflicts of interest. Unfortunately, while IRB review can deal with small-scale, specific conflict-of-interest issues, IRBs themselves are currently neither sufficiently regulated nor independent to fulfill their important function.

Various reports clearly indicate that the IRB system is currently facing considerable challenges [50–52]. One of the core problems with regard to IRB review of conflicts of interest is the significant conflicts faced by IRBs themselves. While IRBs have an important public-policy mandate (protection of human research participants), they are deficient with respect to some basic principles of administrative law [53]. Academic IRBs often lack independence or suffer the perception of bias because of the interests of their host institutions in the approval of research. The increasing reliance of academic institutions on private sponsors augments concerns about direct or indirect institutional pressure on IRBs. Many contract research organizations have set up internal IRBs, which suffer from similar conflicts of interest. Further, for most clinical trials involving community-based physicians, commercial IRBs are employed. The legitimacy of the review provided by these IRBs is undermined by an inherent conflict of interest, given that they are paid to
make a decision that has an immediate impact on the financial interests of their clients [53,54]. Improvement of the IRB system, for example through the establishment of IRBs with a strong governmentally controlled mandate and exclusive jurisdiction [53], is a logical first step in dealing with problems relating to the increased commercialization of medical research.

There are, however, other solutions that are more radical and simpler. One option is to establish an independent national institute for drug testing, to ensure the reliability of the data supporting drug approval [55,56]. Drug companies seeking to have a drug approved would submit the drug for testing to the institute, which would then negotiate a research protocol with the sponsor. The research would be contracted out to a qualified independent drug-assessment center, which would negotiate contractual terms and matters of data publication with the institute. Other proposals include the establishment of a three-pronged independent drug regulatory authority that would not only control clinical trials and post-marketing studies more directly, but also control drug promotion and publicity [57].

Proposals such as these would do much to safeguard the independence of research. They could also provide a check on competition for research participants. Strict guidelines on recruitment of, and payments to, patients could be established for these drug assessment centers, and clinical trials could be better coordinated. The number of industry-driven exploratory trials—often aimed at coming up with “good data” to support applications and marketing—would also likely decrease. More rigorous review of the merit of trials, and the resulting decrease in their number, could also help alleviate industry concerns. Centralization of patient recruitment and reduction in recruitment competition might make it easier to recruit patients for valuable research, thus also reducing pre-approval time windows. Since these proposals require a thorough overhaul of current drug-regulation structures, and since they will not occur tomorrow, it is important that regulatory and professional agencies immediately investigate other measures, including those recommended above.

Conclusion

We note one problem raised by our proposals. They do not address the problem of jurisdiction shopping. Strengthened regulatory structures in North America have resulted in clinical trials being moved even more often to middle- or low-income countries, where recruitment and other research-related costs are cheaper, where regulations either do not exist or may not be adequately enforced, and where research participants are even more vulnerable [58]. These developments are a real cause for concern. Our recommendations for a more stringent regulatory review in the North American context will hopefully inspire others to look at strengthening the national regulatory regimes in other countries and at developing and enforcing international standards for recruitment in clinical trials.

Acknowledgments

This article draws upon a longer paper by the same authors [40], and on a slightly revised version of this longer paper, published in [59].

References

Strategies and Practices in Off-Label Marketing of Pharmaceuticals: A Retrospective Analysis of Whistleblower Complaints

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Abstract

Background: Despite regulatory restrictions, off-label marketing of pharmaceutical products has been common in the US. However, the scope of off-label marketing remains poorly characterized. We developed a typology for the strategies and practices that constitute off-label marketing.

Methods and Findings: We obtained unsealed whistleblower complaints against pharmaceutical companies filed in US federal fraud cases that contained allegations of off-label marketing (January 1996–October 2010) and conducted structured reviews of them. We coded and analyzed the strategic goals of each off-label marketing scheme and the practices used to achieve those goals, as reported by the whistleblowers. We identified 41 complaints arising from 18 unique cases for our analytic sample (leading to US$7.9 billion in recoveries). The off-label marketing schemes described in the complaints had three non–mutually exclusive goals: expansions to unapproved diseases (35/41, 85%), unapproved disease subtypes (22/41, 54%), and unapproved drug doses (14/41, 34%). Manufacturers were alleged to have pursued these goals using four non–mutually exclusive types of marketing practices: prescriber-related (41/41, 100%), business-related (37/41, 90%), payer-related (23/41, 56%), and consumer-related (18/41, 44%). Prescriber-related practices, the centerpiece of company strategies, included self-serving presentations of the literature (31/41, 76%), free samples (8/41, 20%), direct financial incentives to physicians (35/41, 85%), and teaching (22/41, 54%) and research activities (8/41, 20%).

Conclusions: Off-label marketing practices appear to extend to many areas of the health care system. Unfortunately, the most common alleged off-label marketing practices also appear to be the most difficult to control through external regulatory approaches.

Please see later in the article for the Editors’ Summary.


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Competing Interests: ASK reports consulting for the Alosa Foundation, a nonprofit organization that runs the Independent Drug Information Service and is not affiliated in any way with any pharmaceutical company. From 2008–2009, ASK served as an expert witness for the state of Texas in a lawsuit against Merck related to improper promotion of rofecoxib (Vioxx). From 2007–2008, ASK helped develop an educational program to encourage evidence-based prescribing, with funding from a grant derived from the settlement of a fraud case regarding improper promotion of gabapentin (Neurontin).

Abbreviations: DOJ, US Department of Justice; FDA, US Food and Drug Administration

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Introduction

In the US, a setting dominated by aggressive advertising of prescription drugs to patients and physicians, off-label marketing has been a controversial subject area. Physicians are permitted to prescribe drugs “off-label”—that is, for purposes and patient populations outside of those formally approved by the US Food and Drug Administration (FDA). However, the FDA prohibits pharmaceutical companies from engaging in direct promotion of those unapproved uses [1]. The rationale is that such marketing can lead to widespread uses of a drug that are not based on evidence of efficacy and safety, expose patients to uncertain benefits and the prospect of adverse effects, and undermine incentives for manufacturers to conduct clinical trials necessary to achieve FDA approval for new uses [2–5].

Despite regulatory restrictions on off-label marketing, the practice appears to have flourished [6,7]. In 2009, Pfizer paid US$2.3 billion to settle allegations that it marketed its drugs illegally to physicians—the largest federal health care fraud settlement in US history [8]. In 2010, at least six other manufacturers settled charges pertaining to off-label marketing, and more were under investigation [9–15]. The widely publicized litigation over the anti-inflammatory drug rofecoxib (Vioxx) also exposed marketing practices, such as seeding trials and ghost-writing of medical journal articles, that could promote off-label uses [16,17]. What is known about off-label marketing practices comes largely in this form—namely, episodic reporting of high-profile prosecutions in the popular media [18–20], or personal testimony or congressional investigations arising from these same cases [21,22]. There has been no systematic collection and analysis of these cases, which makes it difficult to identify larger themes and draw conclusions about the favored tactics.

An accumulating number of these cases over the last decade makes such an analysis feasible. Moreover, the data available to conduct this type of analysis are remarkably rich because virtually all of the major cases have been instigated by “whistleblowers” whose complaints provide detailed, firsthand knowledge of the practices at issue [23]. Because off-label marketing activities are secretive and difficult to detect and examine through other means [24], reports from these insiders provide a uniquely illuminating perspective on the range and nature of practices pursued.

We analyzed whistleblower-initiated legal complaints filed in off-label marketing cases over the last 15 y to shed more light on this widely discussed but poorly understood challenge for health regulation. We aimed to create a typology for understanding these cases and a coherent thematic model for mapping pharmaceutical companies’ fraudulent promotional behaviors and strategies. Improved understanding in this area has the potential to contribute to the development of strategies for better detection and enforcement.

Methods

Design Overview

The primary data for this study consisted of complaints filed by whistleblowers in “qui tam” cases brought under the US federal False Claims Act (FCA). In brief, the FCA prohibits the submission of false claims to the government for reimbursement. Private citizens who notice potential violations of the FCA can file a sealed complaint in federal court; those who do nearly always retain a personal attorney to represent them and help them write their complaint. The allegations in the complaint are then investigated by the US Department of Justice (DOJ)-Civil Division, which, depending on the strength of the evidence, may elect to intervene and take over the enforcement action, essentially inserting the government as the lead party in the case. At this point, the original whistleblower’s complaint is usually unsealed. Multiple complaints may be filed against the same company, but the DOJ intervenes only on the first complaint brought to its attention or subsequent complaints that provide new information (other nonintervened complaints against the same company are usually dismissed and remain sealed). Because of this screening process and the clout of the DOJ, nearly all complaints in which the DOJ intervenes lead to a settlement or judgment against the defendant company. This study focused on cases against pharmaceutical manufacturers for off-label marketing of prescription drugs in which the DOJ intervened.

Setting and Participants

Officials in the DOJ-Civil Division provided us with a full list of pharmaceutical-related federal qui tam cases in which the DOJ intervened and that were settled between January 1996 and 2005. We updated the list to include all DOJ-intervened cases through October 2010 by conducting a search of DOJ press releases [25] and electronic media reports in Lexis-Nexis. We cross-checked the final list with data compiled by Taxpayers Against Fraud, a nongovernmental organization that tracks federal fraud actions. We then obtained the unsealed complaints in these cases from the DOJ, on-line searches of archives of US federal court filings [26], and direct approaches to lawyers involved in the litigation.

Complaints are written documents that generally consist of a summary of the allegations, a description of the whistleblower(s) and defendants, and a detailed account of the allegations and the evidence supporting them. They may be amended during the course of the investigation. We used the most recent versions of the whistleblower-filed complaints available and accessible at the extraction date (6 November 2010). We searched the summaries of the allegations to determine which made allegations about unlawful off-label marketing by the defendant company; 41 complaints in 18 cases did. These complaints formed our analytical sample. Copies of the complaints can be found at http://www.drugenei.org/education/primarydocs.php.

Qualitative Analysis

We designed a structured instrument for abstracting information from the complaints. An initial typology was generated using a standard coding methodology [27,28]. Two investigators (ASK and DMS) acting independently conducted a preliminary review of 20% of the complaints. After comparing and discussing results of these reviews, we identified two major descriptive domains for further analysis: the strategic goal of the off-label marketing scheme and the specific practices manufacturers used to achieve that goal. We also identified categories and subcategories within each of those domains. One of us (ASK) then read each complaint and coded the details provided into the prespecified categories and subcategories in each domain.

It is important to note that the range of off-label marketing strategies and behaviors we identified and report below are drawn from across the sample of cases as a whole; no manufacturer was accused of all of them.

Results

A total of 41 complaints arose from 55 whistleblowers (Table 1). At the time of the alleged fraud, the whistleblowers worked as pharmaceutical sales representatives (39/55, 71%), sales or accounting managers (11/55, 20%), and unaffiliated physicians (5/55, 9%). The cases were brought against 18 manufacturers,
including both large companies with diverse drug portfolios (e.g., Pfizer, Eli Lilly) and smaller companies selling a relatively narrow range of products (e.g., Orphan Medical, Medicis). At the time of analysis, settlements had occurred in 16 of the 18 cases and totaled US$7.9 billion in damages.

### Off-Label Marketing Strategies

According to the complaints, manufacturers aimed to increase use of their products through off-label marketing schemes in three non–mutually exclusive ways. They sought to expand uses to different disease entities, to variations on the approved indication, and to alternatives to the approved dosing schedule (Table 2).

#### Expansion to unapproved disease entities.

The most prevalent strategy involved expanding use on the basis of diagnosis—that is, seeking off-label uses for disease entities distinct from those approved by the FDA (35/41, 85%). For example, gabapentin (Neurontin), approved as adjunctive treatment for certain types of epilepsy, was also allegedly promoted as therapy for patients with psychiatric disease such as bipolar disorder or depression [29]. Another case involved Pfizer’s alleged promotion of sildenafil (Viagra) to treat low libido and to “restore and increase orgasmic sensations” in women [30].

In many examples of this marketing strategy, the drug was promoted for treatment of similar symptoms across disease classes (17/35, 49%). For example, modafinil (Provigil), initially approved for narcolepsy-related sleepiness, was allegedly promoted for many types of sleepiness in non-narcoleptic patients [32]. Another

### Table 1. Pharmaceutical fraud cases related to off-label marketing, January 1996–October 2010.

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Complaints</th>
<th>Complainants</th>
<th>Drug(s)</th>
<th>Case Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parke-Davis/Warner-Lambert</td>
<td>1</td>
<td>Medical marketing liaison</td>
<td>Gabapentin (Neurontin)</td>
<td>Settled in 2004 (US$430 million)</td>
</tr>
<tr>
<td>Serono</td>
<td>3</td>
<td>Sales representatives, marketing managers, unaffiliated nonprofit organization</td>
<td>Somatropin (Serostim)</td>
<td>Settled in 2005 (US$704 million)</td>
</tr>
<tr>
<td>InterMune</td>
<td>1</td>
<td>Sales representative</td>
<td>Interferon gamma 1b (Actimmune)</td>
<td>Settled in 2006 (US$37 million)</td>
</tr>
<tr>
<td>Bristol Myers-Squibb</td>
<td>1</td>
<td>Business manager</td>
<td>Pravastatin (Pravachol), Metformin (Glucophage), others</td>
<td>Settled in 2007 (US$515 million)</td>
</tr>
<tr>
<td>Cell Therapeutics</td>
<td>1</td>
<td>Sales representative</td>
<td>Arsenic trioxide (Trisenox)</td>
<td>Settled in 2007 (US$11 million)</td>
</tr>
<tr>
<td>Orphan Medical</td>
<td>1</td>
<td>Sales representative</td>
<td>Sodium oxybate (Xyrem)</td>
<td>Settled in 2007 (US$20 million)</td>
</tr>
<tr>
<td>Medicis</td>
<td>1</td>
<td>Sales representatives</td>
<td>Ciclopirox gel (Loprox)</td>
<td>Settled in 2007 (US$10 million)</td>
</tr>
<tr>
<td>Cephalon</td>
<td>4</td>
<td>Sales representatives, sales manager, unaffiliated physician</td>
<td>Modafinil (Provigil), Tiagabine (Gabitril), Fentanyl buccal (Actiq)</td>
<td>Settled in 2008 (US$425 million)</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>4</td>
<td>Sales representatives</td>
<td>Olanzapine (Zyprexa), others</td>
<td>Settled in 2009 (US$1.4 billion)</td>
</tr>
<tr>
<td>Pfizer</td>
<td>8</td>
<td>Sales representatives, sales managers, unaffiliated physician</td>
<td>Valdecoxib (Bextra), Ziprasidone (Geodon), Pregabaline (Lyrica), others</td>
<td>Settled in 2009 (US$2.3 billion)</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>1</td>
<td>Sales representative</td>
<td>Quetiapine (Seroquel)</td>
<td>Settled in 2010 (US$520 million)</td>
</tr>
<tr>
<td>Ortho-McNeil-Janssen</td>
<td>2</td>
<td>Sales representatives, unaffiliated physician</td>
<td>Topiramate (Topamax)</td>
<td>Settled in 2010 (US$81 million)</td>
</tr>
<tr>
<td>Novartis</td>
<td>1</td>
<td>Marketing managers</td>
<td>Tobramycin (TOBI)</td>
<td>Settled in 2010 (US$72.5 million)</td>
</tr>
<tr>
<td>Forest</td>
<td>2</td>
<td>Sales representative, unaffiliated physician</td>
<td>Citalopram (Celexa) and Escitalopram (Lexapro)</td>
<td>Settled in 2010 (US$313 million)</td>
</tr>
<tr>
<td>Allergan</td>
<td>3</td>
<td>Sales representative, managers, unaffiliated physician</td>
<td>OnabotulinumtoxinA (Botox)</td>
<td>Settled in 2010 (US$600 million)</td>
</tr>
<tr>
<td>Novartis</td>
<td>4</td>
<td>Sales representatives</td>
<td>Oxcarbazepine (Trileptal), others</td>
<td>Settled in 2010 (US$422.5 million)</td>
</tr>
<tr>
<td>Scios</td>
<td>2</td>
<td>Sales directors</td>
<td>Nesiritide (Natrecor)</td>
<td>Complaints unsealed (2009)</td>
</tr>
<tr>
<td>Wyeth</td>
<td>1</td>
<td>Sales representatives</td>
<td>Sirolimus (Rapamune)</td>
<td>Complaints unsealed (2010)</td>
</tr>
<tr>
<td><strong>41</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>US$7.9 billion</strong></td>
</tr>
</tbody>
</table>
example related to the anti-inflammatory drug valdecoxib (Bextra), which was approved for a limited number of pain-related indications and then allegedly promoted by Pfizer for pain relief more broadly [33].

**Expansion to unapproved indications.** The second most common strategy for off-label promotion was to expand the product’s use to different variations of the same condition (22/41, 54%). In some cases, the off-label disease was closely related to the approved one—for example, when a product was specifically approved for a severe manifestation of a condition but then promoted for milder forms. In the case of nesiritide (Natrecor), the drug was approved for “acutely decompensated heart failure” and was allegedly promoted in patients with chronic stable heart failure as a preventative measure [34]. Although both groups of patients had heart failure, they were quite different manifestations of the disease.

One prominent subcategory of this type of off-label promotion focused on patient subgroups different from those contemplated in the FDA approval (10/22, 45%). For example, ciclopirox gel (Loprox) was approved for fungal dermatoses in patients over age 10, but allegedly promoted by its manufacturer to manage diaper-related fungal dermatitis in babies [35]. In some of the antidepressant drugs in our sample, the product was approved for adult use, but allegedly promoted to pediatricians and family practice physicians specifically for young patients who demonstrated signs of depression [30,36]. In the case of citalopram (Celexa), studies that had shown dangers with using the drug in pediatric populations were allegedly withheld from physicians as part of the marketing campaign [36].

**Expansion to unapproved dosing strategies.** The final, and least common, variety of off-label expansion was off-label prescribing based on different dosing regimens than that approved by the FDA (14/41, 34%). Typically, manufacturers promoted higher doses to enhance revenues by encouraging sale of more units of the product. For example, the manufacturer of oxcarbazepine (Trileptal) allegedly promoted use of the antiepileptic drug “as monotherapy for seizures using extremely high dosages” [37]. By contrast, the manufacturer of sirolimus (Rapamune), which was approved for transplant patients in combination with cyclosporine and corticosteroids, allegedly trained its staff to encourage its use in combination with “any drug or combination of drugs that a physician could be convinced to prescribe” to enhance its market possibilities [38].

### Table 2. Frequency of off-label marketing strategies and practices reported in whistleblower complaints.

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>n/N, Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Off-label marketing strategies</strong></td>
<td></td>
</tr>
<tr>
<td>Expansion to different disease entity</td>
<td>35/41, 85%</td>
</tr>
<tr>
<td>Similar symptoms, different disease</td>
<td>17/35, 49%</td>
</tr>
<tr>
<td>Expansion to variation of approved indication</td>
<td>22/41, 54%</td>
</tr>
<tr>
<td>Different patient subgroup</td>
<td>10/22, 45%</td>
</tr>
<tr>
<td>Expansion to variation of approved dosing schedule</td>
<td>14/41, 34%</td>
</tr>
<tr>
<td><strong>Off-label marketing practices</strong></td>
<td></td>
</tr>
<tr>
<td>Prescriber-related</td>
<td>41/41, 100%</td>
</tr>
<tr>
<td>Direct financial incentives</td>
<td>35/41, 85%</td>
</tr>
<tr>
<td>Distorted presentation of supporting evidence</td>
<td>31/41, 76%</td>
</tr>
<tr>
<td>Influence on continuing medical education programs</td>
<td>22/41, 54%</td>
</tr>
<tr>
<td>Influence on peer-reviewed literature, including ghost-writing</td>
<td>20/41, 49%</td>
</tr>
<tr>
<td>Recruitment as clinical trial investigators</td>
<td>8/41, 20%</td>
</tr>
<tr>
<td>Free samples</td>
<td>8/41, 20%</td>
</tr>
<tr>
<td>Internal practices</td>
<td>37/41, 90%</td>
</tr>
<tr>
<td>Intramural meetings</td>
<td>27/37, 73%</td>
</tr>
<tr>
<td>Internal documents, brochures</td>
<td>17/37, 46%</td>
</tr>
<tr>
<td>Use of company-based physicians and scientists</td>
<td>19/37, 51%</td>
</tr>
<tr>
<td>Cloaking strategies</td>
<td>25/37, 68%</td>
</tr>
<tr>
<td>Sham warnings from legal counsel</td>
<td>16/25, 64%</td>
</tr>
<tr>
<td>Direct orders to conceal activities</td>
<td>12/25, 48%</td>
</tr>
<tr>
<td>Financial incentives to employees</td>
<td>15/37, 41%</td>
</tr>
<tr>
<td>Payer-related</td>
<td>23/41, 56%</td>
</tr>
<tr>
<td>Discussions with prescribers about how to ensure reimbursement</td>
<td>18/23, 78%</td>
</tr>
<tr>
<td>Development of billing systems that circumvent restrictions</td>
<td>13/18, 72%</td>
</tr>
<tr>
<td>Falsification of billing codes</td>
<td>11/18, 61%</td>
</tr>
<tr>
<td>Direct approaches to payers to ensure presence on formulary</td>
<td>8/23, 35%</td>
</tr>
<tr>
<td>Consumer-related</td>
<td>18/41, 44%</td>
</tr>
<tr>
<td>Direct identification of/approaches to consumers through physician office or pharmacy</td>
<td>10/18, 56%</td>
</tr>
<tr>
<td>Funding of consumer organizations</td>
<td>3/18, 17%</td>
</tr>
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doi:10.1371/journal.pmed.1000431.t002
Off-Label Marketing Practices

The marketing practices manufacturers allegedly employed to achieve these strategic goals for off-label use fell into four non-mutually exclusive categories: internal practices, payer-related practices, prescriber-related practices, and consumer-related practices. We defined internal practices as incentives and other aspects of the employment environment at the defendant manufacturer that encouraged employees to promote off-label uses. Payer-related practices were strategies aimed at encouraging insurers to pay for off-label prescriptions. Prescriber-related and consumer-related practices involved direct promotion of off-label drug use to prescription writers and consumers, respectively.

Prescriber-related practices. All of the complaints we analyzed detailed off-label promotion to prescribers; this was generally the centerpiece of the whistleblowers’ complaints. Though manufacturers are not supposed to discuss off-label uses unless a physician inquires, many were accused of either floating that rule or designing their representatives’ presentations in such a way as to guarantee that discussion would inevitably lead to off-label uses.

According to the complaints, off-label use was frequently encouraged through self-serving presentations of the scientific literature through which physicians were given false or unbalanced study data supporting the unapproved use (31/41, 76%). A common example was selective presentation of favorable studies, where dangers from the off-label uses allegedly being promoted were not mentioned [39]. Other examples included presenting one drug as being superior to another when no head-to-head studies had been conducted [40] and characterizing reports of individual cases or poorly designed studies as definitive evidence supporting an off-label use [41].

A number of whistleblowers alleged that free samples had been provided (8/41, 20%) as a way to promote off-label use. The whistleblowers in this group reported that these samples were intended to encourage physicians to use a product on the basis of convenience, even though it might not be approved for a certain use. In addition, many described how free samples were intended to introduce unapproved patient populations to the manufacturer’s product with the intention of stimulating their continued use.

Complaints alleged that manufacturers also encouraged off-label use through direct financial incentives to physicians. Lavish gifts or honoraria were mentioned in most complaints (35/41, 85%), with many whistleblowers reporting strategies to target these gifts to physicians who were high off-label prescribers (18/41, 44%). In some cases, physicians might be invited to serve in focus groups or as consultants to the manufacturer, although it was alleged that the association was intended not to obtain expert advice, but to provide money to prescribers to positively reinforce off-label use (15/41, 37%).

Finally, off-label use was encouraged among prescribers through teaching and research activities. In over half the cases, Continuing Medical Education (CME) seminars were organized with speakers known to promote off-label uses (22/41, 54%). In a few cases, whistleblowers reported that CME activities were organized by shell corporations to impart an appearance of scientific neutrality [34]. Nearly half of whistleblowers also alleged that manufacturers sought to promote off-label drug use through journal publications (20/41, 49%). These practices included falsely reporting outcomes from patients in manufacturer-sponsored studies [42] and publishing “ghostwritten” articles supporting an unapproved use written by the manufacturer under the name of a respected scientist [43]. Finally, a minority of whistleblowers alleged that manufacturers recruited physicians to conduct clinical trials for them with the intent of encouraging off-label use (“seeding trials”), rather than for any useful scientific or information-gathering reasons (8/41, 20%).

Internal practices. Thirty-seven of the whistleblower complaints (90%) detailed particular internal manufacturer practices intended to bolster the off-label marketing (two of the four complaints where these were not mentioned were filed solely by whistleblowers positioned outside the companies). All of the practices described were reported to be company-wide, rather than the work of an individual manager or group of managers. In 73% (27/37) of these cases, the off-label marketing strategy was implemented through intramural meetings and seminars in which marketing practices were discussed; in 46% (17/37) of them, it was also implemented through development of brochures and other materials for dissemination; in 51% (19/37), employees other than the sales representatives, such as internal physicians and scientists, were involved.

Many of the complaints describing internal practices (25/37, 68%) pointed to specific efforts by drug manufacturers to conceal off-label marketing activities. Some described warnings from legal teams to avoid off-label marketing (16/25, 64%). These were generally understood by employees as providing “plausible deniability” to the company [33], and were widely undermined through strategies such as verbal orders diverging from what was declared in their company policies [31]. For example, one whistleblower reported that his company purposefully designed “do not detail” labels on materials related to off-label uses that could easily be removed by a sales representative [30]. A third of complaints included reports of direct orders to conceal, such as “cleaning” internal reports and memoranda of all mentions of off-label marketing (12/25, 48%).

The complaints frequently described use of financial incentives for employees to engage in off-label marketing. Forty-one percent (15/37) of the reports of internal strategies described incentives or other aspects of employees’ compensation plans that were directly tied to effectively implementing an off-label prescription strategy. In one case involving a drug approved by the FDA for a rare indication, a whistleblower reported that the company imposed sales quotas on representatives that could only be met through expanding use beyond the limited approved indication [31]. Other examples included internal sales “contest” for employees who could demonstrate greatest compliance with marketing programs encouraging off-label use [44] and direct payments to encourage them not to report off-label marketing practices [35].

Payer-related practices. Payer-related promotional practices were reported in just over half of the complaints (23/41, 56%) and fell into two categories: discussions with payers about ways to ensure insurance reimbursement for their off-label prescriptions (18/23, 78%) and direct discussions with payers themselves (8/23, 35%) (three complaints described both). The reports of discussions with payers in complaints described efforts to educate them about how to manage the billing system to ensure that off-label prescriptions were reimbursed, including advice on ways to bypass insurers’ restrictions on prescriptions of the product (13/18, 72%). For example, one whistleblower reported being taught to overcome a requirement that patients receive a trial of a competitor’s drug first by instructing physicians to issue two different prescriptions at the same time: one for the competitor’s drug that the patient could ignore, the other for the company’s drug [45]. The other strategy commonly reported was to encourage providers to falsify billing codes (11/18, 61%).

Seven complaints reported that manufacturers interacted with payers to encourage off-label drug use by ensuring drugs were on a formulary for off-label uses (four reports) or developing organizational protocols that included the off-label use (four reports; one
cards, and bus tokens’ as inducements to seek out prescriptions of company provided indigent patients with ‘gift certificates, phone company [47]. In a third case, the whistleblowers alleged that the were developed by a marketing firm linked to the defendant were intended to promote off-label use of the product, but which management organizations in exchange for their support of the next step was bringing those patients eligible for an off-label use through payments to nonprofit, consumer-focused disease included promotion of consumer demand for off-label uses by conducting chart reviews in physicians’ offices. The next step was bringing those patients eligible for an off-label use to the physician’s attention, thereby fusing a consumer-focused practice with a prescriber-focused one. Other practices intended to directly encourage off-label use among consumers allegedly promotion of consumer demand for off-label uses through payments to nonprofit, consumer-focused disease management organizations in exchange for their support of the off-label use [43]. Another complaint described on-line resources presented by a “noncommercial public interest organization” that were intended to promote off-label use of the product, but which were developed by a marketing firm linked to the defendant company [47]. In a third case, the whistleblowers alleged that the company provided indigent patients with “gift certificates, phone cards, and bus tokens” as inducements to seek out prescriptions of a drug for an off-label purpose [48].

Discussion

Through a comprehensive review of whistleblower complaints, to our knowledge the first of its kind, we found descriptions of a range of marketing practices related to off-label promotion of prescription drugs. All of the strategies and behaviors we outlined were alleged by whistleblowers with special knowledge of company practices, although none of the complaints was subject to full trial and evaluation by a judge or jury. The study provides a basic empirical snapshot of the extent to which each of these strategies and practices have been employed, at least among cases exposed in qui tam litigation.

Our findings show that off-label marketing practices have a broad reach. Similar behaviors and strategies were linked to manufacturers of varying sizes across drugs in virtually all therapeutic classes; they extended to many aspects of the health care system; they affected a multitude of players (prescribers, pharmacists, disease advocacy groups, CME organizations, consumers); and were pursued through virtually every facet of physician-industry relationships (paid consultancies, preceptorships, and collaboration in clinical trials and research publications). The alleged tactics in our analytic sample ranged from subtly encouraging physicians to ask for information about off-label uses to providing strong financial rewards for encouraging off-label uses; they also included targeting multiple links in the prescription production chain, from company scientists and sales representatives to prescribers.

Some of the practices we identified have been highlighted in anecdotal reports and are relatively well known. Others have received little or no attention, such as pharmaceutical marketing representatives working directly with physicians and their office managers to circumvent reimbursement restrictions set by government payers and other insurers. Nearly a quarter of the whistleblowers alleged that pharmaceutical sales representatives were given access to patients’ confidential medical records at physicians’ offices for the purposes of trolling for prospective targets for illegal direct-to-consumer promotion of off-label uses. Despite the remarkable prevalence of this practice among the complaints we analyzed, media coverage has tended to center on other, more institutionally focused aspects of fraud.

New regulatory strategies, both public and private, aimed in part at preventing off-label marketing, have proliferated in recent years. Medical journals have changed their authorship standards to foil ghostwriting [49]; following the example of several states, the federal health care reform legislation requires disclosure of pharmaceutical industry payments to physicians [50]; the leading pharmaceutical manufacturers’ association, PhRMA, has adopted a Code of Ethics that prohibits certain types of gifts [31]; and a handful of academic medical centers have restricted or prohibited visits by pharmaceutical sales representatives [32]. Our findings support the need for these measures to combat gifts to physicians, which we identified as the single most prevalent modality of off-label promotion reported by whistleblowers.

However, our results also suggest that additional steps will likely be necessary to curb off-label marketing. For example, interventions seeking to insulate physician education from industry influence have largely been limited to programs in which the manufacturer controls the content, but the reports in this study suggest that even so-called “unrestricted” educational grants from industry may be deployed to effect off-label marketing. A better policy solution would be fully independent programs of continuing medical education, an approach that has received limited support in a few states and has been proposed (but not enacted) in US Congress. Another potential solution is a central repository, independent from any physician or health care organization, where manufacturers can donate money that is then distributed for educational purposes.

Some experts have suggested that fraudulent off-label marketing might be prevented through more substantial fines for manufacturers under investigation or other penalties for company managers [53]. Criminal prosecutions of executives are rare [54], but the DOJ has signaled increasing interest in using this approach [53]. While seeking to fortify deterrence through such tactics might address some behaviors, our findings suggest that some common off-label marketing practices may be difficult to control through external regulatory approaches because of their deep-seated nature. Whistleblowers in most of the cases we reviewed reported that private conversations between sales representatives and prescribers were a leading strategy for off-label promotion. The opportunity to prompt and answer physicians’ questions about off-label uses, address their individual concerns, and provide a digest of empirical evidence that can be slanted as needed likely makes these conversations a particularly effective form of marketing. The fact that so many of the communications are oral and take place in private offices makes them very difficult for regulators to monitor and sanction. It is impossible to conceive of how anyone other than a company insider or a physician could bring many of these marketing practices to light (indeed, this underlines the distinctive strength of our data source). The move by a few prominent academic medical centers to ban sales representatives from the premises is a bold and powerful one, but it has not, as yet, been followed by many hospitals or physician practices.

Changes in the PhRMA Code are a positive sign that the industry is responsive to public concerns about inappropriate marketing practices. In some news reports, manufacturers have described new corporate cultures that avowedly reject the illegal tactics described in the whistleblower complaints [55]. However, in many of the cases we studied, manufacturers were reported to demonstrate awareness of existing regulations and engage in strategic behaviors to work around them (e.g., by giving employees lectures about the regulatory environment that were understood to...
be a smokescreen) or to mask their violations of the law (e.g., by encouraging employees to not enter off-label marketing calls in their logs).

Our approach has limitations. First, although the DOJ conducted thorough investigations of each complaint in the study sample, the settled cases concluded without a full trial, which would have included formal fact-finding by a judge or jury. Thus, some allegations may be false and, for nearly all complaints, internal company documents that might have corroborated the complainants’ specific reports remained confidential. Second, our analyses were conducted mainly at the complaint level, but none of the 18 cases involved more than one complaint (the DOJ permits multiple complaints when each brings new information to bear on the case); the clustering of complaints in some cases may have inflated the reported prevalence of certain behaviors. Third, most whistleblowers were US-based sales representatives with a particular field of vision in relation to their companies’ off-label marketing practices. It is possible that other behaviors and strategies exist that the whistleblower did not observe and the government investigations did bring to light. Our reliance on the text of the complaints means that we would have missed these. Finally, the complaints were composed to support claims of fraud under certain specific legislation, including the False Claims Act.

Conclusion
Off-label marketing has been ubiquitous in the health care system and features some behaviors and strategies that may be resistant to external regulatory approaches. Our findings suggest that no regulatory strategy will be complete and effective without physicians themselves serving as a bulwark against off-label promotion. Aside from sales representatives and other company insiders, who play important roles as whistleblowers, physicians are alone in having a full view of many of the most insidious forms of illegal marketing outlined in the complaints we reviewed. As physicians’ understanding of these practices and the consequences of inappropriate off-label promotion for public health evolves, so may their enthusiasm for shutting them down.

Acknowledgments
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Author Contributions
ICMJE criteria for authorship read and met: ASK MMM DMS. Agree with the manuscript’s results and conclusions: ASK MMM DMS. Designed the experiments/the study: ASK DMS. Analyzed the data: ASK MMM DMS. Collected data/did experiments for the study: ASK DMS. Wrote the first draft of the paper: ASK. Contributed to the writing of the paper: ASK MMM DMS. Contributed to the design of the study: MMM.

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15. Sandberg B (2009) Health care fraud investigations bedevil Pharma industry: if you're not under investigation, it's only because you're recently settled. Pink Sheet 71: 21–24.

Off-Label Marketing of Pharmaceuticals

April 2011 | Volume 8 | Issue 4 | e1000431
Editors’ Summary

Background. Before a pharmaceutical company can market a new prescription drug in the US, the drug has to go through a long approval process. After extensive studies in the laboratory and in animals, the pharmaceutical company must test the drug’s safety and efficacy in a series of clinical trials in which groups of patients with specific diseases are given the drug according to strict protocols. The results of these trials are reviewed by Federal Drug Administration (FDA, the body that regulates drugs in the US) and, when the FDA is satisfied that the drug is safe and effective for the conditions in which it is tested, it approves the drug for sale. An important part of the approval process is the creation of the “drug label,” a detailed report that specifies the exact diseases and patient groups in which the drug can be used and the approved doses of the drug.

Why Was This Study Done? Physicians can, however, legally use FDA-approved drugs “off-label.” That is, they can prescribe drugs for a different disease, in a different group of patients, or at a different dose to that specified in the drug’s label. However, because drugs’ manufacturers stand to benefit financially from off-label use through increased drugs sales, the FDA prohibits them from directly promoting unapproved uses. The fear is that such marketing would encourage the widespread use of drugs in settings where their efficacy and safety have not been rigorously tested, exposing patients to uncertain benefits and possible adverse effects. Despite the regulatory restrictions, off-label marketing seems to be common. In 2010, for example, at least six pharmaceutical companies settled US government investigations into alleged off-label marketing programs. Unfortunately, the tactics used by pharmaceutical companies for off-label marketing have been poorly understood in the medical community, in part because pharmaceutical industry insiders (“whistleblowers”) are the only ones who can present in-depth knowledge of these tactics. In recent years, as more whistleblowers have come forward to allege off-label marketing, developing a more complete picture of the practice is now possible. In this study, the researchers attempt to systematically classify the strategies and practices used in off-label marketing by examining complaints filed by whistleblowers in federal enforcement actions where off-label marketing by pharmaceutical companies has been alleged.

What Did the Researchers Do and Find? In their analysis of 41 whistleblower complaints relating to 18 alleged cases of off-label marketing in federal fraud cases unsealed between January 1996 and October 2010, the researchers identified three non–mutually exclusive goals of off-label marketing schemes. The commonest goal (85% of cases) was expansion of drug use to unapproved diseases (for example, gabapentin, which is approved for the treatment of specific types of epilepsy, was allegedly promoted as a therapy for patients with psychiatric diseases such as depression). The other goals were expansion to unapproved disease subtypes (for example, some antidepressant drugs approved for adults were allegedly promoted to pediatricians for use in children) and expansion to unapproved drug dosing strategies, typically higher doses. The researchers also identified four non–mutually exclusive types of marketing practices designed to achieve these goals. All of the whistleblowers alleged prescriber-related practices (including providing financial incentives and free samples to physicians), and most alleged internal practices intended to bolster off-label marketing, such as sales quotas that could only be met if the manufacturer’s sales representatives promoted off-label drug use. Payer-related practices (for example, discussions with prescribers about ways to ensure insurance reimbursement for off-label prescriptions) and consumer-related practices (most commonly, the review of confidential patient charts to identify consumers who could be off-label users) were also alleged.

What Do These Findings Mean? These findings suggest that off-labeling marketing practices extend to many parts of the health care delivery system. Because these practices were alleged by whistleblowers and were not the subject of testimony in a full trial, some of the practices identified by the researchers were not confirmed. Conversely, because most of the whistleblowers were US-based sales representatives, there may be other goals and strategies that this study has not identified. Nevertheless, these findings provide a useful snapshot of off-label marketing strategies and practices allegedly employed in the US over the past 15 years, which can now be used to develop new regulatory strategies aimed at effective oversight of off-label marketing. Importantly, however, these findings suggest that no regulatory strategy will be complete and effective unless physicians themselves fully understand the range of off-label marketing practices and their consequences for public health and act as a bulwark against continued efforts to engage in off-label promotion.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1000431.

- The US Food and Drug Administration provides detailed information about drug approval in the US for consumers and for health professionals; its Bad Ad Program aims to educate health care providers about the role they can play in ensuring that prescription drug advertising and promotion is truthful and not misleading.
- The American Cancer Society has a page about off-label drug use.
- Wikipedia has pages on prescription drugs, on pharmaceutical marketing, and on off-label drug use (note that Wikipedia is a free online encyclopedia that anyone can edit; available in several languages).
- Taxpayers Against Fraud is a nonprofit organization dedicated to helping whistleblowers, and it presents up-to-date information about False Claims Act cases.
- The Government Accountability Project is a nonprofit organization that seeks to promote corporate and government accountability by protecting whistleblowers, advancing occupational free speech, and empowering citizen activists.
- Healthy Skepticism is an international nonprofit membership association that aims to improve health by reducing harm from misleading health information.
The Haunting of Medical Journals: How Ghostwriting Sold “HRT”

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Introduction

In recent litigation against Wyeth, more than 14,000 plaintiffs brought claims related to the development of breast cancer while taking the menopausal hormone therapy Prempro (conjugated equine estrogens [CEE]s) and medroxyprogesterone acetate [MPA]). Some 1500 documents revealed in the litigation provide unprecedented insights into how pharmaceutical companies promote drugs, including the use of vendors to produce ghostwritten manuscripts and therto them into medical journals. These documents became public when PLoS Medicine and The New York Times intervened in the litigation. Both intervenors successfully argued that ghostwriting undermines public health and that documents proving the practice should be unsealed.

In this Policy Forum article, I use these documents, which are available through PLoS at http://dx.doi.org/doi:10.1371/journal.pmed.1000335, to show how industry uses ghostwriters to insert marketing messages into articles published in medical journals. As a paid expert witness, I had access to these documents during the litigation but I have received no payment for researching or writing this Policy Forum.

Hormone Therapy History

In 1942, Premarin (CEE) became the first FDA-approved treatment for hot flashes. Promotional efforts implied that estrogen could preserve youth and health. By the early 1970s, physicians, under the mistaken impression that menopause was an endocrine disease similar to hypothyroidism, were prescribing estrogen to millions of asymptomatic women. In 1975, an eight-fold increase in endometrial cancer was linked to estrogen use, and estrogen sales decreased [1].

After adding a progestin pill to counteract estrogen-induced endometrial cancer, hormone “replacement” therapy (HRT; now properly termed menopausal hormone therapy, or HT) became popular in the 1990s. Through the 1990s, HT was touted to prevent cardiovascular disease, osteoporosis, Alzheimer’s disease, colon cancer, tooth loss, and macular degeneration [1]. Prempro, which combined CEE and the progestin Provera (medroxyprogesterone acetate), was approved in the U.S. in 1995. In 1998, the Heart and Estrogen/progestin Replacement Study (HERS), a randomized controlled trial (RCT) in women with cardiovascular disease, found no benefit of HT for preventing cardiovascular events [2]. In 2002, the Women’s Health Initiative (WHI), a large RCT in healthy women, demonstrated conclusively that HT failed to prevent cardiovascular disease, increased the risk of breast cancer and stroke, and reduced fracture risk [3, 4]. Later analyses revealed that HT increased the risk of dementia [5] and incontinence [6].

Today, despite definitive scientific data to the contrary, many gynecologists still believe that the benefits of HT outweigh the risks in asymptomatic women [1, 7–8]. This non-evidence–based perception may be the result of decades of carefully orchestrated corporate influence on medical literature.

Publication Planning

Publication planning is the process by which pharmaceutical, biotech, and medical device companies produce and release articles in medical journals and posters at meetings to establish key marketing messages [9, 10]. Some companies employ writers and publication planners, and most hire medical education and communication companies (MECCs) to create publications. Academic physicians are invited by these MECCs to “author” prewritten articles [11, 12]. It is unknown how many academics participate, or how many articles in peer-reviewed medical journals are ghostwritten, but there is concern that the practice may be extensive.

Between 1996 (when Premarin was marketed) and 2004, Wyeth worked with several MECCs, but most closely with DesignWrite, to promote the Premarin family of products. DesignWrite offers comprehensive services to pharmaceutical companies and has helped to promote topiramate, epoietin alfa, etanercept, and many other drugs [13]. Indeed, according to DesignWrite’s website, over 12 years DesignWrite “… planned, created, and/or managed hundreds of advisory boards, a thousand abstracts and posters, 500 clinical papers, over 10,000 speakers’ bureau programs, over 200 satellite symposia, 60

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Abbreviations: CEE, conjugated equine estrogens; CVD, cardiovascular disease; ERT, estrogen replacement therapy; FDA, U.S. Food and Drug Administration; HERS, Heart and Estrogen/progestin Replacement Study; HT, menopausal hormone therapy; HRT, hormone replacement therapy; MECC, medical education and communication company; MPA, medroxyprogesterone acetate; RCT, randomized controlled trial; SERM, selective estrogen receptor modulator; WHI, Women’s Health Initiative
* E-mail: ajf29@georgetown.edu
Provenance: Not commissioned; externally peer reviewed.
Summary Points

- Some 1500 documents revealed in litigation provide unprecedented insights into how pharmaceutical companies promote drugs, including the use of vendors to produce ghostwritten manuscripts and place them into medical journals.
- Dozens of ghostwritten reviews and commentaries published in medical journals and supplements were used to promote unproven benefits and downplay harms of menopausal hormone therapy (HT), and to cast raloxifene and other competing therapies in a negative light.
- Specifically, the pharmaceutical company Wyeth used ghostwritten articles to mitigate the perceived risks of breast cancer associated with HT, to defend the unsupported cardiovascular “benefits” of HT, and to promote off-label, unproven uses of HT such as the prevention of dementia, Parkinson’s disease, vision problems, and wrinkles.
- Given the growing evidence that ghostwriting has been used to promote HT and other highly promoted drugs, the medical profession must take steps to ensure that prescribers renounce participation in ghostwriting, and to ensure that unscrupulous relationships between industry and academia are avoided rather than courted.

International programs, dozens of websites, and a broad array of ancillary printed and electronic materials” [14].

In its communications with Wyeth, DesignWrite noted that “Research shows high clinician reliance on journal articles for credible product information.” In addition to “full-length review articles,” DesignWrite recommended that the publication plan for Premarin products should include mini-reviews, case reports, editorials, letters, and comments [15]. These short pieces could be published quickly, DesignWrite noted, so were an efficient “means of placing important information about the therapeutic profile of an agent into the hands of influential physicians …” [15]. DesignWrite also explained that it would help Wyeth decide what data to present, recruit “authors,” choose journals, create abstracts and posters for medical meetings, and “Position the product appropriately to influence prescribers” [15].

During its work with Wyeth, DesignWrite wrote the first drafts of articles and submitted them to Wyeth. DesignWrite then incorporated Wyeth’s comments into a second draft, and sent the company-approved draft to the “author,” whose comments, if any, were incorporated into the third draft. DesignWrite then assisted in submitting the paper to a journal [15]. There is no evidence that authors were paid for authoring articles. Throughout the documents referred to in this Policy Forum, “writer” refers to the ghostwriter, and “author” refers to the person whose name appeared on the published article [16].

Between 1997 and 2003, DesignWrite’s output for Wyeth on the Premarin family of products included “over 50 peer-reviewed publications, more than 50 scientific abstracts and posters, journal supplements, internal white papers, slide kits, and symposia…” [17]. Primary publications (articles that report clinical trials) ghostwritten by DesignWrite included four manuscripts on the HOPE trials of low-dose Prempro [18,19] for which DesignWrite was paid US$25,000 each [20]. Secondary publications (articles that follow clinical trial reports and contain “subsequent analyses, and reviews of the drug and its field of use” [10]) included 20 review articles that DesignWrite was assigned to write in 1997 [21] for $20,000 each [22], a price that later rose to $25,000 [23]. Abstract production cost $4,000. [24] DesignWrite charged $10,000 for editing manuscripts and $2,000 for editing abstracts “written by author or other agency” [24].

As part of its publication planning, Wyeth’s Marketing Department convened monthly meetings to discuss publication strategies [25], draft outlines [26,27], and sometimes adjust the overall publication plan. In 2002, for example, Wyeth management “charged the Publication Committee with increasing the number of positive HRT/Premarin-related publications. They have asked us to publish at least 1 study per month” [28].

Unregulated Marketing through Medical Journals

It is illegal for pharmaceutical companies to promote a marketed drug for off-label use, i.e., for uses other than those approved by the U.S. Food and Drug Administration (FDA) or equivalent national agencies. Articles in medical journals, newsletters, and magazines, however, are not considered promotional. As an industry article states, “Peer-reviewed publications offer pharma companies shelter from often-stormy regulatory waters. FDA views published articles as protected commercial speech so doesn’t regulate their content” [29].

In the absence of data (or in the presence of data adverse to marketing goals), review articles in medical journals are crucial vehicles for encouraging off-label uses, promoting unproven benefits, and for downplaying harms. Narrative reviews summarize and analyze prevailing literature and often offer clinical recommendations [30]. Commentaries and other opinion pieces are also highly valued because they provide clinical direction, and are usually not peer-reviewed. Presentations at medical meetings are important for the same reason [30].

As Table 1 shows, DesignWrite helped to produce numerous ghostwritten reviews and commentaries, including articles designed to promote the off-label use of Prempro for preventing Alzheimer’s disease, Parkinson’s disease, age-related macular degeneration, and wrinkles. The scope of these articles is summarized in Box 1. The DesignWrite documents avoid discussing off-label marketing, but noted that reviews can “Disseminate messages that fill the gaps not addressed by current studies” [31]. Another document noted that the “Strategic Publications Team” should “Identify data gaps” and “Fill the gap with review papers” [32].

In addition, clinical trial reports were sometimes modified for marketing purposes. For example, Wyeth apparently wanted the metabolic effects of a Premarin/trimedostone combination removed from the lead publication on this product. A 2003 DesignWrite email to James H. Pickar, a physician employed by Wyeth, noted the marketing team’s concerns: “… it is highly desirable for them to not have the metabolic data included in the lead paper, as this would cause labeling problems, making the lead paper unusable for promotional purposes” [33].

Managing “Authors” and Journals

An important part of DesignWrite’s work for Wyeth was to manage “authors” and journals. There is evidence in unsealed DesignWrite documents that although some authors signed off on ghostwritten articles, others insisted on
Table 1. Examples of ghostwritten reviews and commentaries*.

<table>
<thead>
<tr>
<th>Article</th>
<th>Messages From Published Article</th>
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<tr>
<td>Creasman WT. Is There an Association between Hormone Replacement Therapy and Breast Cancer? J Women's Health 1996; 7(10)</td>
<td>“In aggregate, these data fail to provide definitive evidence that the use of postmenopausal HRT is associated with an increased incidence of breast cancer.”</td>
</tr>
<tr>
<td>Nachtigall LE. Sex Hormone-Binding Globulin and Breast Cancer Risk Primary Care Update for Ob/Gyns 1999; 6 (2):39-45.</td>
<td>“Extensive epidemiologic studies provide conflicting evidence as to whether ERT significantly impacts the risk of breast cancer in postmenopausal women…”</td>
</tr>
<tr>
<td>Eden J. Progestins and breast cancer. Am J Obstet Gynecol. 2003 May;188(5):1123-31.</td>
<td>“…studies have clearly demonstrated that prior or current HRT use results in a paradoxically improved survival for patients with breast cancer.”</td>
</tr>
<tr>
<td>Cefalu T. The Use of Hormone Replacement Therapy in Postmenopausal Women with Type 2 Diabetes. J Women's Health 2001; 10 (3):241-255</td>
<td>“Although a possible risk has been shown in long-term users, a causal relationship between ERT/HRT and breast cancer remains controversial.”</td>
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Promoting Unproven, Off-Label Uses

<table>
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<tr>
<th>Article</th>
<th>Messages From Published Article</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fillit, M. The Role of Hormone Replacement Therapy in the Prevention of Alzheimer Disease. Arch Intern Med. 2002;162(17):1934-42.</td>
<td>“At present, most observational evidence, which is supported by neurobiological research findings on the action of estrogen, indicates that ERT/HRT mitigates the degeneration that may lead to AD. The lack of evidence of a role of estrogen in the treatment of AD suggests that ERT/HRT should be initiated as early as possible after menopause, before the onset or the progression of the disease.”</td>
</tr>
<tr>
<td>Birge SJ. Practical Strategies for the Diagnosis and Treatment of Alzheimer's Disease. Clinical Geriatrics 1999;7(4):56-74.</td>
<td>“Estimates of the annual cost of AD per individual range from $34,000 to $47,000, with the annual overall cost to society estimated at $67 billion.”</td>
</tr>
<tr>
<td>Shulman L. Is there a Connection Between Estrogen and Parkinson’s Disease? Parkinsonism Relat Disord. 2002;8(5):289-95</td>
<td>“Increasing evidence suggests that estrogens may protect the nigrostriatal dopaminergic pathway affected in Parkinson’s disease (PD).”</td>
</tr>
<tr>
<td>Sherwin BB. Mild Cognitive Impairment: Potential Pharmacological Treatment Options. J Am Geriatr Soc. 2000;48(4):431-41.</td>
<td>“Estrogens, in particular, deserves more attention because its cognitive-enhancing properties, which have been verified by several controlled clinical trials, are complemented by its potential for preventing cardiovascular disease and osteoporosis and for reducing the risk of colorectal cancer and all-cause mortality in postmenopausal women.”</td>
</tr>
<tr>
<td>Brincat M, Baron Y, Galea R. Estrogens and the Skin. Climacteric 2005;8(2):110-23.</td>
<td>“Estrogen treatment in postmenopausal women has been repeatedly shown to increase collagen content, dermal thickness, and elasticity. … Physiologic studies on estrogen and wound healing suggest that HRT may play a beneficial role in cutaneous injury repair; however, molecular studies have yet to articulate the mechanisms.”</td>
</tr>
<tr>
<td>Snow KK, Seddon JM. Age-Related Eye Diseases: Impact of Hormone Replacement Therapy and Other Risk Factors. Int J Fertil Womens Med. 2000 Sep-Oct;45(5):301-13</td>
<td>“Evidence suggests that among women, long-term exposure to endogenous estrogens or replacement estrogens may reduce the risk of AMD and cataracts. … The potential value of this therapy in reducing visual impairment among women deserves increased attention.”</td>
</tr>
<tr>
<td>Freedman, MA. Quality of Life and Menopause: The Role of Estrogen. J Women’s Health 2002;11(8):703-718.</td>
<td>“Less attention has been paid to the menopausal symptoms that can impair the quality of life of menopausal women, such as hot flushes, sleep disorders, sexual dysfunction, and alterations in mood … Evidence supporting the effectiveness of ERT/HRT in the treatment of symptoms affecting quality of life is growing and supports the use of ERT/HRT during menopause.”</td>
</tr>
<tr>
<td>Bachman G, Leiblum S. The Impact of Hormones on Menopausal Sexuality: a Literature Review. Menopause 2004;11 (1): 120-130.</td>
<td>“Estrogen deficiency initially accounts for altered bleeding and diminished vaginal lubrication. Continual estrogen loss often leads to numerous signs and symptoms, including changes in the vascular and urogenital systems. Alterations in mood, sleep, and cognitive functioning are common as well. These changes may contribute to lower self-esteem, poorer self-image, and diminished sexual responsiveness and sexual desire.”</td>
</tr>
<tr>
<td>Cefalu T. (above)</td>
<td>“The potential in a diabetic population for improved insulin and glucose metabolism, as well as reduced risk of CVD, with the use of ERT/HRT has been shown in several prospective studies.”</td>
</tr>
<tr>
<td>Gallagher JC.</td>
<td>“The beneficial effects of estrogen on the prevention of osteoporosis are likely to carry over to improved dental health in women.”</td>
</tr>
</tbody>
</table>

Competitive Messaging

<table>
<thead>
<tr>
<th>Article</th>
<th>Messages From Published Article</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warren M. A Comparative Review of the Risks and Benefits of Hormone Replacement Therapy Regimens. Am J Obstet Gynecol. 2004 Apr;190(4):1141-67</td>
<td>“Overall, these data indicate that the benefit/risk analysis that was reported in the Women's Health Initiative can be generalized to all postmenopausal hormone replacement therapy products.”</td>
</tr>
</tbody>
</table>
Mitigating Perceived Risks of Breast Cancer


“HRT, the current standard of care, has the advantage of long-term epidemiologic data that indicate that the benefits of therapy clearly outweigh the risks. In contrast, the riskbenefit of the emerging SERMs needs to be better defined and evaluated.”

The clinical use of SERMs has yet to demonstrate beneficial effects shown with HRT on all-cause mortality, colon cancer, and central nervous system function (i.e., reduced risk of Alzheimer’s disease, improve cognition)."


“At present, each potential adverse event needs to be weighed against potential benefits in the decision to undergo SERM treatment…”

“The development of future generations of SERMs that improve upon the current therapies is eagerly anticipated.”


[Regarding non-pharmacological interventions]: “Although anecdotal reports have suggested that some of these strategies may provide relief, few patients seem to benefit from these interventions.”

[Regarding SERMs]: “the utility of these drugs is restricted by frequent side effects.”


“Generic conjugated estrogens have been manufactured; however, the therapeutic equivalence of these generic products to CEE cannot be ensured…”


“I’ve seen quite a bit of confusion regarding the substitutability of certain drugs, most recently between Premarin (conjugated estrogen tablets, USP) and Cenestin (synthetic conjugated estrogens, A1),” says Ronald Maddox, Dean of the Campbell University School of Pharmacy. “The FDA determined that these two drugs are not therapeutically equivalent and, therefore, has not listed the products with a therapeutic equivalence code.”

Defending Cardiovascular Benefits


“Remarkable consistency among epidemiologic studies supports a cardioprotective role of ERT.”

“The biologic evidence for a role of estrogen to prevent CVD is compelling. Concerns regarding potential adverse effects among susceptible women and the lack of confirmatory data from randomized trials make general recommendation [sic] difficult to make.”


“The use of HT was associated with higher baseline levels of CRP but no change in IL-6 in either the case or the control group. However, the use of HT was less important than the actual baseline values of CRP and IL-6 in predicting cardiovascular risk.”


“…the HERS trial had certain methodological pitfalls, including insufficient statistical power, a high crossover rate between treatment arms, and other medications effect. Second, the early increment in coronary event rates might have been precipitated by procoagulant effects of HRT and a susceptible cohort… The controversy occasioned by the HERS trial can be resolved only through sufficiently powered, randomized controlled trials.”

Positioning Low-dose Therapy


“The potential for fewer side-effects with low-dose formulations may play an important role in enhancing patient acceptance and continuance of ERT/HRT. Lower doses may also reduce patients’ concerns about cancer.”

Maddox RW. The Efficacy and Safety of Low-dose Hormone Therapy. US Pharmacist 2004 (June).

“The recent approval by the FDA of the new oral LD [low-dose]-ET/HT formulations… represents an important advance in menopausal management and osteoporosis prevention. The dosage of ethinyl estradiol in low-dose oral contraceptives is… four to seven times greater than that in SD [standard-dose]-HT, or six to 14 times greater than that in LD-ET/HT.”

*For documentation of ghostwriting, see Table S2.

doi:10.1371/journal.pmed.1000335.t001

ing, an author’s request “to shorten the Early Bone Loss paper…and prepare it for a practical audience…” was discussed [40]. The consensus was that this was acceptable as long as the message remained that “HRT is the most cost-effective therapy for preventing bone loss contributing to their articles. One co-author seemed puzzled by the concept that she was to author, but not write, an article [34]: “From what you have written, I would be more of an ‘editor’ rather than the major writer—that is, you guys would be writing the versions—with me ‘altering, editing, etc.? Is that correct?” This query was in response to an e-mail from Karen Mittleman (a DesignWrite employee who supervised medical writers) that stated: “The beauty of this process is that we become your postdocs! … We provide you with an outline that you review and suggest changes to. We then develop a draft from the final outline. You have complete editorial control of the paper, but we provide you with the materials to review/critique.” [34].

After receiving a draft, this co-author (Leiblum) noted that the outline contained “…many factual errors and mis-information (sic), as well as over-emphasis on the hormonal contributions to post-menopausal sexuality as opposed to the interpersonal contributions” [33]. She did not agree to authorship until her numerous changes [36] were incorporated [37]. To appease another author, a writer was told by DesignWrite that the author’s “…own additions will probably have to stay no matter what” [38]. This author later unsuccessfully attempted to credit the ghostwriter as a coauthor[39].

In general, authors’ revisions were permitted if marketing messages were not compromised. For example, at a 2002 Strategic Publications Development Meeting, an author’s request “to shorten the Early Bone Loss paper…and prepare it for a practical audience…” was discussed [40]. The consensus was that this was acceptable as long as the message remained that “HRT is the most cost-effective therapy for preventing bone loss.
for women entering menopause due to its other benefits and low cost” [40].

Furthermore, when one author submitted a manuscript “unilaterally” to a journal, an attempt was made by DesignWrite to reassert control: “We have provided him with an updated draft of the manuscript and he will try to incorporate these revisions in the paper where possible…” [41].

The trivial role authors were expected to play is demonstrated by DesignWrite’s reference to planned reviews as “opinion leader–endorsed” [42]. Furthermore, authors were considered interchangeable; one document states, “I moved Dr. Creasman as an author to the patient ed piece (with Blackwood, Weiss, & Speroff) and left Horwitz and Boman on the basic science manuscript” [43], although Horwitz’s name does not appear on the published article.

Finally, in response to a question about whether previously commissioned papers could be reused, Gerald Burr of Wyeth wrote: “You can’t just put another name on the article, but you can plagiarize the way we did when we wrote papers in college. What you need to do is give your potential authors Karen’s version of the article before the author modified it. Then have your authors modify it for publication under their name. Wyeth owns Karen’s draft, not the final publication” [44]. Burr supplied five drafts [45] but asked that Karen Mittleman be notified of any reuse of them. Wyeth’s and DesignWrite’s ghostwriters also managed journals by responding to editor and reviewer comments [46,47]. Ghostwriters argued for retention of specific marketing messages, sometimes scolding reviewers under the guise of defending peer-review. Responses to one presumably unfavorable review included: “The review of the current paper is not the appropriate place to criticize the methodological flaws of published papers”; and “The reviewer’s suggestion to revise the statement on page 8 “…absence of a definitive causal relationship between exogenous postmenopausal ERT [estrogen replacement therapy] and breast cancer risk is not justified. This interpretation is well documented” [46].

In one case, a ghostwriter asked the author for assistance in preparing a response: “…If you have any thoughts about how we might reply to this reviewer’s comment, please let us know.” The author provided a slide to the writer: “the enclosed powerpoint could serve as a figure to summarize how this all hangs together… it obviously needs ‘cleaning up.’” [48].

**Messaging**

Clinical trials, reviews, case reports, letters, and other publications are used by pharmaceutical companies to convey specific marketing messages. Besides extolling the benefits of a specific drug, marketing messages may emphasize the prevalence or severity of targeted conditions, promote unproven uses, deride competing therapies, or reassure clinicians that adverse effects are rare, manageable, or not specific to a targeted therapy.

Even though a 1997 DesignWrite proposal admitted that “HRT continues to be a drug in search of a disease” [49], my examination of the available documents indicates that the lack of evidence regarding the prevention and treatment of cardiovascular disease, dementia, and other diseases proved no deterrent to Wyeth/DesignWrite’s promulgation of numerous marketing messages positioning HT as a panacea. A message strategy listed under “Value of Estrogen Therapy (or Bundle of Benefits)” in DesignWrite’s 1997 publication plan was “Define the serious nature of menopause-related illness and demonstrate the clinical benefits of instituting hormone replacement therapy in the treatment of multiple disorders including cardiovascular, osteoporosis, vasomotor, Alzheimer’s, and colon cancer” [15].

**Defending Cardiovascular Benefits**

Soon after HERS found no evidence for cardiovascular benefit for HT, numerous articles attacking the trial appeared in the medical literature. A 2001 article authored by Thorneycroft [50] states: “The results of HERS do not contradict the weight of epidemiologic study findings showing a primary protective CVD effect in longer-term HRT users. Indeed, because of possible serious flaws in the study, a protective benefit of HRT for secondary CVD prevention cannot be ruled out.” Some articles were ghostwritten (see Table S1). For example, a 2000 article authored by Mosca [51] states, “Remarkable consistency among epidemiologic studies supports a cardioprotective role of ERT.”

**Saving One’s Skin and Self-Esteem**

After the WHI lay to rest the concept that HT prevented cardiovascular disease, stroke, and Alzheimer’s, marketing messages shifted to unproven lifestyle benefits (see Table 1). Messages in the 2003 publication plan included: “the importance of quality-of-life issues that are improved with postmenopausal HT use” and “…the benefits of postmenopausal HT on skin and sexual health” [52]. Ghostwritten articles supporting this message included a 2005 article by Brincat [53] that states, “Estrogen treatment in postmenopausal women has been repeatedly shown to increase collagen content, dermal thickness, and elasticity.” A 2004 article by Bachman and Leiblum states, “Continual estrogen loss often leads to numerous signs and symptoms, including changes in the vascular and urogenital systems. Alterations in mood, sleep, and cognitive functioning are common as well. These changes may contribute to lower self-esteem, poorer self-image, and diminished sexual responsiveness and sexual desire” [54].

**Questioning Breast Cancer Risk**

Many ghostwritten articles dispute the link between HT and breast cancer, or imply, falsely, that breast cancers associated with HT are less aggressive (see Tables 1 and 2, and Box 2). Some articles were built around a single message, including a 2003 paper by Eden [55]. Notes from a publication planning meet-
ing held in 2000 read: “...John Eden was suggested as the author of a breast cancer paper questioning the role of progestins as a causative factor” [56]. Discussion points the ghostwriter was told to put in the paper included “why progestins may not be responsible for the incidence of breast cancer in hormone replacement therapy (HRT) users” [57]. The published article states, “…results from epidemiologic studies are inconsistent and mechanistic studies have not provided a physiologic foundation to implicate progestin in the pathogenesis of breast cancer” [35]. Battling Competitors

Ghostwritten articles also raise questions about the safety of competing drugs and the efficacy of generics (see Table 1). For example, negative messages were developed for raloxifene, a selective estrogen receptor modulator (SERM) used to treat Postmenopausal Hormone Therapy and Breast Cancer: A Review for Clinicians.

**Table 2. Relationship between planned messages and final text in the supplement**

<table>
<thead>
<tr>
<th>Article</th>
<th>Planned Messages [80]</th>
<th>Excerpts From Published Article [109]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speroff L. a Inconsistency in Epidemiologic Findings on Postmenopausal Hormone Therapy and Breast Cancer</td>
<td>“Recent studies suggest the possibility of a slightly increased risk of breast cancer associated with long-term use of postmenopausal hormone therapy.” “However, the results from the many epidemiologic studies on this relationship are not consistent or uniform, and taken together, fail to provide definitive evidence of causality.” “Discussion of results of recent studies, pointing out strengths and weaknesses, as well as both null and positive findings of a relationship between HRT and breast cancer detection.” “Mortality data, detection bias, more treatable tumors”</td>
<td>“…more than half of the studies conducted in the past 25 years found either no difference in risk or a decreased risk of breast cancer with ERT/HRT use.” “…if there is an increased risk of breast cancer associated with the use of ERT/HRT, this risk must be small.” “These recent studies continue the pattern of inconsistency in research on this topic…” “Even studies that detect an increased risk of breast cancer in hormone users suggest, paradoxically, a better outcome.” “In the absence of results from large, randomized clinical trials, clinicians can help patients to understand that current research findings on breast cancer risk and long-term use of ERT/HRT are inconclusive, no studies find an increased risk with short-term use, and women who use postmenopausal hormones have lower mortality rates.”</td>
</tr>
<tr>
<td>DiSaia PJ. b A Rationale for Estrogen Use in Breast Cancer Survivors [originally Estrogen use after breast cancer]</td>
<td>“Rationale for estrogen use in breast cancer survivors (esp., number of women)” “Review evidence from naturally-occurring situations with estrogen exposure and breast cancer (pregnancy during or after breast cancer, HRT use, OC use)” “Use of estrogen by women who have had breast cancer does not appear to increase risk of recurrence”</td>
<td>“Numerous studies have reported better survival rates for women using HRT at the time of breast cancer diagnosis compared with those for nonusers.” “Observational studies suggest that postmenopausal hormone therapy after breast cancer diagnosis does not negatively affect breast cancer recurrence or survival.” “Breast cancer prognosis is not negatively affected by exposure to increased estrogen levels during or after pregnancy or by exposure to exogenous estrogens around the time of diagnosis.” “…exposure to estrogen around the time of breast cancer diagnosis and the use of ERT/HRT in breast cancer survivors do not negatively impact patient outcomes.”</td>
</tr>
<tr>
<td>Commonly Asked Questions About Postmenopausal Hormone Therapy and Breast Health [originally Patient Education Handout]</td>
<td>“Inform patients that many studies do not show an increased risk.” “give clear information about how many more women will get breast cancer if reported risk are [sic] accurate.” “compare risk of breast cancer from postmenopausal hormone therapy with everyday risks.” “emphasize significant health risks for postmenopausal women (cardiovascular diseases)” “Connect HRT to OCs and the comfort level that many women have with OCs”</td>
<td>“Close to 60 research studies have compared breast cancer risk in women who use HRT and in women who do not. Most of these studies found no increased risk of breast cancer with HRT use.” “Researchers have consistently found no increase in breast cancer risk with short-term use of HRT. Studies on long-term use, however, have reported conflicting results, which means that more studies are needed.” “Researchers have consistently found that HRT use does not increase breast cancer risk in women with a family history of breast cancer.” “However, there is no evidence that HRT use affects breast cancer detection.” “Studies have found that breast cancer patients using HRT at the time they were diagnosed tend to have smaller tumors that are less aggressive and are detected at a more favorable stage than are tumors of nonusers.” “…estrogen and progesterone, are the same hormones found in birth control pills, only at much lower doses (less than 1/10th the dose).” “Use of HRT also protects bone health and may decrease a woman’s risk of developing colon cancer, Alzheimer’s disease, heart disease, and macular degeneration (a condition associated with aging that may cause loss of vision).”</td>
</tr>
</tbody>
</table>

All documentation of ghostwriting is taken from Szaller J. Wyeth’s hormone therapies & ghostwritten medical literature (unpublished manuscript), with permission. 

“DWRITE076512; DWRITE078370; Janas_010408 at 483:11–485:13.


dDraft outline DWRITE078512; DWRITE078370; Janas_010408 at 483:11–485:13.

doi:10.1371/journal.pmed.1000335.t002
Box 2. Planned Messages and the Final Text in the Supplement
Postmenopausal Hormone Therapy and Breast Health: A Review for Clinicians

Articles in this supplement, which also included a patient education handout,
- Cast doubt on the link between HT and breast cancer
- Questioned whether HT-induced changes in mammographic density were related to increased breast cancer risk
- Implied that use of estrogen after breast cancer was safe
- Promoted the concept that HT-associated breast cancers were less aggressive cancers

Table 2 details how the numerous planned messages included in the Outline for this supplement [109] were incorporated into the published articles [80] by providing relevant quotations from both sources.

Initiative can be generalized to all postmenopausal hormone replacement therapy products” [63].

Table 1 lists other examples of marketing messages included in ghostwritten reviews. In addition, Tables 3 and S1 summarize planned and published marketing messages in ghostwritten articles for clinical trials of low-dose Prempro and of Premarin with trimestestone, respectively. Wyeth ceased development of this latter combination in 2003 [64]. It is important to note that the Tables provided as supporting evidence for this Policy Forum article only list articles for which extensive documentation of ghostwriting exists within publicly available documents. These articles and their authors may represent only the tip of the iceberg.

Supplements

Another way that pharmaceutical companies spread their marketing messages is through supplements—separately bound publications carrying a medical journal’s name that are often industry-sponsored and rarely peer-reviewed. In DesignWrite’s words: “The value of journal supplements is that it allows you to better tailor your marketing message since it is a manufacturer-sponsored publication form. Additionally, reprints of supplements may be purchased and distributed widely among health care professionals via sales representatives…” [65].

Perhaps because meeting proceedings lend credibility to supplements, Wyeth/DesignWrite held an “Expert Forum on Breast Cancer Health” in April 2001 in Philadelphia [66] to develop materials for a CME supplement [67]. Wyeth/DesignWrite invited speakers [68], assigned topics [67,69], provided participants with a “reading packet” [70], and an agenda [71,72] that listed the topics the speakers should address. These topics seemed designed to reassure clinicians that breast cancer risk with HT was extremely low and that breast cancers in women on HT were easily treated. The “key messages to be derived from those talks” [69,71] aimed to “diminish the negative perceptions” [15] regarding HT and included: “The evidence that use of ERT and/or HRT increases risk for breast cancer is weak”, “MPA does not increase risk of breast cancer”, and “Women who have had breast cancer may gain benefits from ERT/HRT” [71], DesignWrite prepared drafts of the supplement articles based on the speaker’s slide presentations [73,74] and submitted them to the journal Women’s Health in Primary Care [75]. DesignWrite responded to comments from the University of Wisconsin [76] (the CME accreditor) and two reviewers from the journal [76–78], one of whom subsequently authored a ghostwritten article for Wyeth/DesignWrite [79] (see Table 1). DesignWrite also asked Jeff Solomon of Wyeth’s marketing department to provide “comments or suggestions” to reviewers’ comments [76].

Better Breast Cancers

The resulting supplement, Postmenopausal Hormone Therapy and Breast Health: A Review for Clinicians [80], included unsupported claims that HT decreased mortality and had multiple health benefits, but its predominant marketing message appears to be the mitigation of concerns that HT causes breast cancer (Box 2 and Table 2). Speroff declares in one article, “…if there is an increased risk of breast cancer associated with the use of ERT/HRT, this risk must be small”, Fiorica states in another article, “…there is no evidence that ERT/HRT-induced changes in breast density, which are rapidly reversible upon cessation of hormone therapy, increase breast cancer risk”, states Fiorica in another article. A breast cancer diagnosis was, apparently, no reason to cease use. DiSaia states, “Observational studies suggest that postmenopausal hormone therapy after breast cancer diagnosis does not negatively affect breast cancer recurrence or survival.” Similarly, Fiorica states: “Women who use ERT/HRT after breast cancer diagnosis may also have more favorable outcomes compared with nonusers” [80].

Commenting on drafts of the supplement’s introduction, Jamie Durocher of Wyeth Marketing [81,82] suggested: “So that physicians are open to reading the supplement, I think certain revisions are necessary to unobtrusively acknowledge...
the conflict of recent years (without being negative)" [80–83]. Regarding the patient handout, Durocher noted: "...[any risk of cancer is perceived as too much] it may be helpful to also mention in the first answer that women on HRT who do develop cancer have a less virulent cancer and a better outlook for recovery..." [84].

<table>
<thead>
<tr>
<th>Article</th>
<th>Planned “Potential Key Messages” [20]</th>
<th>Messages From Published Article</th>
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<tbody>
<tr>
<td>Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH. a</td>
<td>&quot;This paper will serve as the lead paper and contain the entire list of HOPE trial investigators. The suggestions contained in this paper for treatment strategies will be reiterated in each of the four publications.&quot;</td>
<td>&quot;In summary, the Women’s Hope trial demonstrated the efficacy of CEE 0.45 combined with either 1.5 or 2.5 mg of MPA per day and of CEE 0.3/MPA 1.5 for vasomotor symptom relief and improvement in VMI in postmenopausal women. Confirmation of the efficacy of these lower doses of estrogen and progesterin expands the number of options for women considering HRT. Lower doses of CEE and CEE/MPA appear to be as effective as the most commonly prescribed doses and should be considered as initial treatment options for a majority of women. These lower-dose combinations may allow more patients to obtain the proven preventive benefits of long-term HRT.&quot; Note: Acknowledges the “editorial assistance provided by Bernadette Janas, Ph.D.”</td>
</tr>
<tr>
<td>Pickar JH, Yeh I-T, Wheeler JE, Cunnane MF, Speroff L. a</td>
<td>&quot;Both the 0.45/1.5 and 0.3/1.5 doses demonstrate similar efficacy with respect to endometrial safety. A hyperplasia rate of 0.23% (1 case) was reported for both groups. For women in the Prempro 2.5 group, no cases of endometrial hyperplasia were observed.”</td>
<td>&quot;The incidence of endometrial hyperplasia was significantly lower (P&lt;.001) for the groups treated with CEE/MPA than with the comparable dose of CEE alone, with the exception of the lowest dose (CEE 0.3/MPA 1.5 mg), which did not reach statistical significance in the consensus analysis.&quot;</td>
</tr>
<tr>
<td>Archer DF, Dorin M, Lewis V Schneider DL, Pickar JH. a</td>
<td>&quot;When compared to Prempro 2.5, the 0.45/1.5 HRT dose results in an improved rate of amenorrhea, particularly in the early cycles.&quot;</td>
<td>&quot;The increased rates of amenorrhea that we observed in women treated with lower doses of CEE and MPA compared with those taking the most commonly prescribed CEE/MPA regimen provide strong evidence that lower-dose HRT reduces vaginal bleeding.&quot;</td>
</tr>
<tr>
<td>Lobo RA, Bush T, Carr BR, Pickar JH. a</td>
<td>&quot;When compared to Prempro 2.5, the 0.45/1.5 HRT dose results in similar increases in HDL-cholesterol and similar decreases in LDL-cholesterol. Carbohydrate metabolism was not adversely affected by either treatment.”</td>
<td>&quot;In summary, this study indicates that lower doses of CEE and CEE/MPA induce favorable changes in lipoproteins and modest changes in carbohydrate metabolism and hemostatic factors.”</td>
</tr>
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</table>

All documentation of ghostwriting is taken from Szaller J. Wyeth’s hormone therapies & ghostwritten medical literature (unpublished manuscript), with permission. aDELCA004-001404 and DELCA004-001405.  
DELCA004-001404 and DELCA004-001405; MARTN010-003367; MARTN010-003371; MARTN010-003512 and MARTN010-003513; PCSAR001-000769.  
DELCA032-028548 and DELCA032-028549.  
doi:10.1371/journal.pmed.1000335.t003

**Table 3. Planned and published messages in the ghostwritten HOPE trials of low-dose Prempro.**

Promotion via Exam

- **The CME test accompanying the supplement reinforced its marketing messages.** For example, based on the text, the answer to the test question, “One of the most consistent findings from research on postmenopausal hormone therapy and breast cancer risk is that:” is most likely to be “ERT/HRT use is associated with a decrease in all-cause mortality”. The most likely answer to the question, “Use of ERT/HRT has traditionally been avoided in breast cancer survivors because of:” is “the unsubstantiated hypothesis that hormone therapy will activate dormant malignant cells” [80]. The CME accreditor...
claims that it has no records of the correct
physicians [87] with regular and "Gyne-

The supplement was mailed to 128,000
supplement, and CME accreditation [86].

Primary Care

Women's Health in Primary Care

this supplement are those of the authors,
ions expressed in the articles that appear in
from Wyeth-Ayerst Pharmaceuticals" [80]
…by an unrestricted educational grant
[86] and distributed the supplement to

queries [90–94].

employed by Wyeth to respond to physician
Liaisons—physicians or pharmacologists
were to be distributed to Medical Science
ments also indicate that the supplement and
Journal articles were mailed or delivered via
drugs reps to doctors. DesignWrite docu-
ments also indicate that the supplement and
at least seven other ghostwritten publications
were to be distributed to Medical Science
Liaisons—physicians or pharmacologists
employed by Wyeth to respond to physician
queries [90–94].

Discussion

Marketing messages in credible journals have almost certainly contributed to wide-
spread use of HT among millions of women who had no medical indication for the drug.
Journal articles were mailed or delivered via drug reps to doctors. DesignWrite docu-
ments also indicate that the supplement and at least seven other ghostwritten publications
were to be distributed to Medical Science Liaisons—physicians or pharmacologists
employed by Wyeth to respond to physician queries [90–94].

Ghostwriting has been documented for
drugs other than Prempro. For example, Forest Laboratories' 2004 marketing plan
for Lexapro (escitalopram) [95], stated: "Bylined articles will allow us to fold
Lexapro messages into articles on depres-
sion, anxiety and comorbidity developed by (or ghostwritten for) thought leaders"
[96]. Ghostwriting has also been docu-
dented in the promotion of Paxil (parox-
etine) [97–100], "Fen-phen" (fenfluramine
and phentermine) [101], Neurontin (ga-
bapentin) [102], Viocox (rofecoxib) [103],
and Zoloft (sertraline) [104].

Industry-funded marketing messages
may infest articles in every medical
journal. Although the prevalence of pro-
fected or accepted invitations to sign
ghostwritten articles is unknown, the
practice may be common. Several recent
examples of academic physicians receiving
invitations to affix their names to pre-
written articles have been documented
[11,105–106]. Acceptance of ghostwriting,
euphemistically termed "editorial assis-
tance," may be so widespread that it is
considered normal. This could explain
why several authors of ghostwritten arti-
cles have defended their involvement
[107,108].

Medicine, as a profession, must take
responsibility for this situation. Naïvete is
no longer an excuse. Perhaps physician-
investigators should create and uphold a
standard where relationships with industry
are regarded as unsavory rather than
sought after. Academic institutions and
medical journals should take a hard line
on ghostwriting. Patient care will benefit if
physicians draw together as a profession to
denormalize relationships with industry
and avoid the role of corporate pawns in
the future.

Supporting Information

Table S1 Planned marketing messages consistent with published text in clinical
trials of estrogen and trimenogestone.
Found at: doi:10.1371/journal.pmed.1000335.s001 (0.08 MB DOC)

Table S2 Examples of ghostwritten re-
views and commentaries.
Found at: doi:10.1371/journal.pmed.1000335.s002 (0.07 MB DOC)

Acknowledgments

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Doctors and Drug Companies: Still Cozy after All These Years

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The relationships between doctors and drug companies are controversial and have long been scrutinized by researchers, ethicists, professional bodies, and legislators [1]. In recent years, growing concerns about these ties, and allegations of some corrupt practices, have engendered a large amount of coverage in the media and professional journals [2–4].

In my experience, the main concerns about close ties between companies and doctors are that 1) they lead to inappropriate prescribing that can harm patients; 2) they create divided loyalties for doctors between the health system, their patients, and manufacturing companies, which is a conflict of commitment as well as a conflict of interest; 3) they lead to use of unnecessary and expensive medications with consequent costs falling on health care systems and patients; 4) they may lead to medicalisation of human variation, i.e., “disease-mongering”; and 5) they diminish the professional standing of doctors in the eyes of the public and governments, which leads to a reduced ability to advocate for the health of patients, for the public, and on behalf of the profession.

In response to community concerns, legislators have tried to improve the transparency of the relationships between doctors and drug companies—for example, the recently passed Physicians Payments Sunshine Act in the United States, and mandatory disclosure requirements for companies in Australia [5,6]. These require public reporting of certain types of industry-sponsored activities; in Australia, this includes the nature of the sponsored meetings, the venues, any hospitality provided, and overall costs [6].

In response to widely voiced concerns, professional bodies around the world have tightened their codes of conduct, and the state of Massachusetts passed legislation banning gifts from drug and device manufacturers [7–9]. Drug companies are trying to reduce some of their more egregious activities, such as provision of lavish gifts and entertainment, and overly generous travel support. Recent revisions to the Code of Practice of the Pharmaceutical Research and Manufacturers of America specifically prohibit these activities [8]. Such activities have long been the focus of those who have questioned the relationships between doctors and drug companies. They have also been the main target of the legislative responses in the US and Australia. But, open-ended activities such as “unrestricted” research grants, “educational” grants, membership in speakers’ bureaus and advisory panels, consultancies, and stock-holding could be of greater concern, through an insidious blurring of professional boundaries and obligations [10]. There is evidence that these types of ties are common among specialist physicians [11].

Underlying all of these concerns is a belief that close ties between doctors and pharmaceutical companies have been shown to create the negative effects noted at the start of this article. It is fair to ask whether the evidence underpinning these beliefs. The paper by Geoffrey Spurling and colleagues in the October 2010 issue of PLoS Medicine addresses the question of whether drug company information has an impact on doctors’ prescribing [12]. This publication is timely and important. It is a substantial update to previous work—38 of the 58 studies that were included did not feature in previous reviews. Spurling and colleagues highlight some important points. It was not possible to obtain confident summary quantitative estimates of the effects of industry activities, and they ended up expressing the overall results by doing “head counts”. The majority of studies found either an undesired effect on prescribing quality or costs, or found no effect. The lack of a quantitative summary measure is not
surprising, but is regrettable, as the overview of numbers of studies rather than their results takes no account of the effect size, the sample size, or the quality of individual studies. However, the authors made an assessment of the methodological rigor of the studies included in their review. They concluded, not surprisingly, that it was low. There was a heavy reliance on cross-sectional studies and time series analyses, which are susceptible to a range of biases and order effects. There were only two randomised trials, and these were not relevant as they did not test the interventions generally used in the field by pharmaceutical manufacturers.

Spurling and colleagues made a solid assessment of the methodological quality of this literature and addressed two additional concerns—publication bias and outcome reporting bias. The former is the well-known tendency for authors to submit only positive studies for publication. Publication bias seems more common in the case of low quality non-randomised studies, the type reviewed here [13]. This is acknowledged by the authors. Tests for publication bias include funnel plot asymmetry, which requires an estimate of effect size and precision for each study, and is not possible with this literature. The authors seem to argue against their results being subject to outcome reporting bias. This has been identified as the tendency for studies to be published, but for authors to report preferentially those outcomes that changed significantly with the intervention [14]. The authors of this review found that significant associations between exposure to industry promotion and changes to measures of prescribing were more common in studies that reported a single unit of analyses than those that reported multiple units of analyses. They argue against reporting bias, but one possible explanation of their results is that the authors were selective about reporting their units of analyses, being more likely to do this when they found significant associations.

But does any of this matter? Sometimes we are forced to draw conclusions and take actions even when the supporting evidence is of a low level, as it is here. When assessing a body of evidence for harm we have to consider a number of factors, including the magnitude of the effect and the quality of the research behind the claims. But there are other dimensions, including the potential benefits of the activities and the availability of alternatives (in this case other sources of information on new pharmaceutical products). These questions, normally applied to treatments, may sit uncomfortably in a political economy where private companies have the right, indeed the obligation, to market their products effectively to health professionals.

But if industry promotional activities influence the treatments that patients receive, we should ask for evidence of benefit. If that benefit is better knowledge and more effective and safer use of medications, and commercial promotion is better at doing this than publicly funded drug information, we should be prepared to tolerate some adverse effects. If the benefits are slight, or absent, then we should have a low tolerance for any adverse effects. Spurling and colleagues may have difficulty demonstrating a strong evidentiary base for claims of harm from industry promotion, but they have done an effective job of excluding any important benefit from this relationship [13].

So why don’t governments, all of whom struggle with the costs of new drugs, make greater efforts to provide unbiased prescribing information to doctors? Activity is patchy. For instance, the Australian government makes a modest but admirable attempt through funding the National Prescribing Service, and in England there is a National Prescribing Centre (NPC) with “NPC associates” in Primary Care Trusts [15,16]. By contrast, where I live, in Ontario, Canada, neither the national nor the provincial government makes any general effort to inform doctors, or to modify prescribing practices. The pharmaceutical industry may still hold the medical profession in a warm embrace, but they don’t seem to be at serious risk of being jilted in favor of other suitors.

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Novel artificial genetic systems with twelve bases instead of four [1]. Bacteria that can be programmed to take photographs [2] or form visible patterns [3]. Cells that can count the number of times they divide [4]. A live polio virus “created from scratch using mail-order segments of DNA and a viral genome map that is freely available on the Internet” [5]. These are some of the remarkable, and occasionally disturbing, fruits of “synthetic biology,” the attempt to construct life starting at the genetic level. In terms of their scale and ambition, these efforts go beyond traditional recombinant DNA technology. Rather than simply transferring a pre-existing gene from one species to another, synthetic biologists aim to make biology a true engineering discipline. In the same way that electrical engineers rely on standard capacitors and resistors, or computer programmers rely on modular blocks of code, synthetic biologists wish to create an array of modular biological parts that can be readily synthesized and mixed together in different combinations. The Massachusetts Institute of Technology (MIT) has a Registry of Standard Biological Parts that supports this goal by indexing biological parts that have been built, and offering assembly services to construct new parts, devices, and systems [6]. Systems, devices, parts, and DNA represent descending levels of complexity—systems consist of devices, and devices consist of parts composed of DNA. The idea behind a registry of parts is that these parts can, and should, be recombined in different ways to produce many different types of devices and systems. Although the registry currently contains physical DNA, its developers believe that, as DNA synthesis technology becomes increasingly inexpensive [7], the registry will be composed largely of information and specifications that can be executed in synthesizers just as semiconductor chip designs are executed by fabrication firms.

Synthetic biology has already produced important results, including more accurate AIDS tests and the possibility of unlimited supplies of previously scarce drugs for malaria [8]. Proponents hope to use synthetic organisms to produce not only medically relevant chemicals but also industrial materials, including biofuels such as hydrogen and ethanol [9]. At the same time, synthetic biology has engendered numerous policy concerns. From its inception, commentators have raised issues ranging from bioethical and environmental worries to fears of bioterrorism—indeed, the US Central Intelligence Agency released a report in 2003 called “The Darker Bioweapons Future” that explicitly referred to the dangers posed by the possibility of genetically engineered viruses [10]. There is, however, one area that has been largely unexplored until this point—the relationship of synthetic biology to intellectual property law. Two key issues deserve further attention. First, synthetic biology presents a particularly revealing example of a difficulty that the law has frequently faced over the last 30 years—the assimilation of a new technology into the conceptual limits posed by existing intellectual property rights. There is reason to fear that tendencies in the way that US law has handled software on the one hand and biotechnology on the other could come together in a “perfect storm” that would impede the potential of the technology. Second, synthetic biology raises with remarkable clarity an issue that has seemed of only theoretical interest until now—the tension between different methods of creating “openness.” On the one hand, one standard mechanism for creating openness has involved putting material in the public domain, outside the world of property. On the other, synthetic biology researchers may want to use intellectual property rights to create a “commons,” just as developers of free and open source software use the leverage of software copyrights to impose requirements of openness on future programmers, requirements greater than those attaching to a public domain work. But synthetic biology, unlike software, is not necessarily protected by copyright. Should we rethink the boundary lines between intellectual property and the public domain as a result?

The Perfect Storm: Flawed Biotech Law Meets Flawed Software Law?

Intellectual property law in the US has already had difficulty incorporating the revolutionary technologies from which synthetic biology draws inspiration—biotechnology and computers. US patent law requires that inventions be...
“nonobvious” to the ordinary scientist working in the area. Yet, in the area of biotechnology, years after methods for cloning genes have become routine and widely known, the US Court of Appeals for the Federal Circuit continues to treat the gene products of such methods as patentable [11]. By the Federal Circuit’s reasoning, what matters is not whether a practicing biologist would find a particular invention obvious, but rather per se rules about nonobviousness developed for chemical inventions in the mid-20th century [12].

While biotechnology has mainly posed difficulties for patent law, computers have posed both copyright and patent problems. Copyright covers original works of expression, explicitly excluding works that are functional. Patent law requires functionality; however, it had traditionally been understood to exclude formulas and algorithms. Thus, software—a machine made of words, a set of algorithmic formulas and algorithms. Thus, software—a machine made of words, a set of algorithmic instructions devoted to a particular function—seemed to fit neither the copyright nor the patent box. It was too functional for copyright, too close to a collection of algorithms and ideas for patent. What’s more, certain economic aspects of software, including its high propensity to display “network effects” (increased utility based on increased numbers of users) led scholars to believe that both copyright and patent were ill-suited to encourage innovation without discouraging competition. Several sui generis, or custom-made, intellectual property regimes were proposed as an alternative.

As a result of statements by the US Congress and actions by the courts, software ended up being covered by both copyright and patent in this country—a result that most scholars thought was far from ideal. Court refusals to allow patent examiners to use unwritten information to determine whether a particular patent application is obvious [13] may also have a disproportionate impact on computer-related inventions. Because much knowledge in the field of computer technology is not written down in journal articles, it may be hard for a patent examiner to find specific written references testifying to information that is generally known. Additionally, many scholars have argued that the Federal Circuit allows unduly broad patents to issue in the area of software [14].

The specter of broad patents has already reared its head in the field of synthetic biology. Consider patent 6,774,222, issued by the US Patent and Trademark Office on August 10, 2004 [15]. The patent, issued to the US Department of Health and Human Services (HHS), is entitled “Molecular Computing Elements, Gates and Flip-Flops.” This patent covers using the combination of nucleic-acid binding proteins and nucleic acids to set up data storage as well as logic gates that perform basic Boolean algebra. As the patent document notes, the invention could be used not only for computation but also for complex (“digital”) control of gene expression. The broadest claim does not limit itself to any particular set of nucleic-acid binding proteins or nucleic acids. Moreover, the claim uses language that would cover not only the “parts” that performed the Boolean algebra but also any device and system that contained these parts. Such a patent would seem effectively to patent the basic functions of computing when implemented by one likely genetic means. Would such a foundational patent hold up in court?

Given the low nonobviousness threshold that the Federal Circuit has set in the area of biotechnology, there is some possibility that the court would apply a similarly low threshold here. The Federal Circuit’s reluctance to allow unwritten knowledge to be used in determining nonobviousness may also impose a low threshold. Thus, even if, at the time the HHS invention was made, individuals working in the field knew that many computing functions could readily be performed using DNA-based “genetic switches,” this unwritten knowledge might not be factored into the nonobviousness determination. Notably, the HHS patent is not unique in its breadth [16,17].

Considerable historical evidence, including evidence from virtually every important industry of the 20th century, suggests that broad patents on foundational research can slow growth in the industry [18]. In the area of computer hardware, the specter of broad patents loomed large in the US until government action forced licensing of the AT&T transistor patent as well as patents obtained by Texas Instruments and Fairchild Instruments on integrated circuits. Fortunately, software was already a robust industry before broad software patents became available. Biotechnology’s foundational technologies—monoclonal antibodies and recombinant techniques—either were not patented or were made available widely at reasonable cost. Synthetic biology may be coming of age under different circumstances, at the juncture of two technologies with which the law is already struggling.

To be sure, to the extent that foundational patents are held by universities or government institutions, they may not be asserted aggressively so as to block research. However, in addition to the problem of broad foundational patents, there is the possibility of a plethora of narrower patents (some of which may fall within the scope of the foundational patents). For example, scientists at Boston University have filed patents that claim the use of DNA to produce specific gene regulation mechanisms such as a multi-state oscillator [19–21]. MIT and the company Sangamo have patents on various types of DNA binding proteins. At least in the area of information technology, there is evidence that patent thickets [22] or “anti-commons” [23] create difficulties for subsequent researchers above and beyond those created by foundational patents. (The situation in biotechnology is less clear; compare [24] and [25].) This is because many products in information technology represent combinations of dozens, if not hundreds, of patented parts. Not only does a crowded patent landscape create the possibility of “hold up” by a previously unknown patent holder who emerges only after others have invested large sums of money in the area of the patented invention, but to the extent that patent rights holders rely upon reach-through royalties to secure revenue, standard economic theory predicts that product output by the improver will be suboptimal. Moreover, while firms that work in information technology have sometimes succeeded in pooling patents, particularly patents around industry standards, such efforts have also been stymied by failure on the part of participating firms to disclose relevant patents [26]. In any event, because synthetic biology encompasses
A Synthetic Biology Commons?

These intellectual property concerns have not gone unnoticed. The MIT scientists involved with the Registry of Standard Biological Parts are sufficiently concerned that they have created the BioBricks Foundation, which might serve to coordinate a synthetic biology “commons.” The idea of a synthetic biology commons draws inspiration, in part, from the prominence of the open source software model as an alternative to proprietary software. Unlike proprietary software developers, open source software producers make their source code freely available for improvement, modification, and redistribution. Certain types of open source licenses also have a “commons-expanding” aspect: these “copyleft” licenses not only make source code freely available, but they also require those who distribute improvements to the source code to make the improvements available on the same terms (see [27], which discusses GNU General Public License and other “copyleft” licenses). Copylefted software relies heavily on the existence of property rights—specifically, copyright in the source code. Because of this copyright, users of the copylefted software necessarily use it subject to the terms of the license.

Synthetic biologists might argue that strings of DNA bases are comparable to source code and that DNA strings could therefore also be covered by copyright. However, software itself fits poorly into copyright’s categories. The US Congress indicated a desire that software be covered by copyright, but left it to the courts to work out the method of doing so. As developed by the courts, copyright protection in software is thin—for example, source code is generally protected against verbatim copying. But even with source code, if the code is entirely dictated by functional concerns or has become an industry standard, it may not be protected by copyright at all.

Where does this leave synthetic biology? There are two major obstacles to establishing copyright. First, unlike software, the products of synthetic biology are not discussed as copyrightable subject matter in the US copyright statute. Thus, a court that wished to find that material copyrightable would have to do so by analogy. Second, even if courts were willing to make such an analogy, there are the internal restrictions of US copyright law, which does not cover functional articles or methods of operation, and requires expressive choices. As a matter of legal doctrine, the answer to whether an expressive choice had been made might depend upon the type of synthetic biology involved. For example, the construction of DNA sequences using base pairs that do not exist in nature might allow significant room for expressive choice. Such DNA sequences might be protected by copyright, at least against verbatim copying. However, most synthetic biologists working today, including those at MIT, are working within the confines of the existing genetic code. This code constrains the expressive choices that they make, making copyright protection less likely.

Thus, in the case of synthetic biology, the ability to invoke copyright is by no means clear. An obvious alternative is patents. One example of a patent-based commons is that created by the group Biological Innovation for an Open Society (BIOS). BIOS is using patent protection on a few key plant gene transfer technologies to force licensees to put improvements to those technologies into the commons [28]. Although some have suggested that the BIOS approach could raise concerns about antitrust and patent misuse [29], the concern should be relatively small given BIOS’s mission to expand the commons and the relatively permissive, rule-of-reason-based approach taken by contemporary US antitrust law. The more pressing problem for projects like the MIT Registry of Standard Biological Parts—which contains more than 2,000 standardized parts—is expense. A single patent can cost tens of thousands of dollars to secure.

Of course, to the extent that a few broad patents—like the HHS patent noted above—might effectively cover many of the parts in the registry, the patent option becomes more plausible. In this scenario, the registry would essentially be exploiting flaws in the current patent system for commons-expanding purposes. The difficulty would be to identify an area of inventive territory that was quite broad but nonetheless not suggested either by prior broad patents or by information already in the public domain.

Alternatively, the registry might try to attract statements of non-assertion by other patentees, on the model of recent statements by IBM, Sun Microsystems, and other firms, that they will not assert their patents against anyone working on open source software. Indeed, the fact that many synthetic biology patents are currently held by academic and government institutions may make such statements of assertion a real possibility. To the extent that institutions with synthetic biology patents vowed not to assert their patents against academic researchers, such a move would be a salutary development and a comfort to those working on the registry. Non-assertion statements are not, however, a property right. In order to secure a property right, the owners of the MIT registry would need a license with explicit permission to sublicense. Moreover, patents licensed to the registry would have to cover, at least in some fashion, parts that were important for maintaining and expanding the commons.

Another alternative for securing an expanding commons might rely on some kind of contract, such as a “clickwrap” license over the BioBricks Foundation data. This contractual alternative does not require an underlying property right. Instead, the contract simply imposes conditions as part of the price of access. One problem with such contracts is that they bind only those who receive the technology from the entity imposing the terms. Attempts to prevent leakage to those not bound by the terms of the contract can require strict restrictions on information dissemination. For example, for some time the publicly funded International HapMap Project (a database of human genetic variation) used a clickwrap license. This license required users of single nucleotide polymorphism data to refrain from combining it with their own proprietary single nucleotide polymorphism data in order to seek product patents on haplotypes (collections of single nucleotide polymorphisms). In order to prevent leakage of the data outside the confines of this clickwrap license, to those who
would then have no obligation to the HapMap commons, the license required those who sought the data to refrain from disseminating it to anyone who had not signed on to the license. Conventional publication of the data was not possible. This condition is no longer imposed because it is believed that the database has reached a sufficient density to be self-sustaining and to defeat subsequent patent claims. But the old requirements indicate one of the difficulties of the clickwrap approach; the comparative weakness of the contractual restraints paradoxically requires extremely broad restrictions on dissemination.

Finally, legislative proposals might create sui generis property rights mechanisms for protecting BioBricks Foundation data. Indeed, the European Union currently has sui generis protection of data. The evidence suggests, however, that strong property rights protection is likely to hinder rather than promote innovation [30]. A recent draft of the proposed “Treaty on Access to Knowledge” offers an alternative sui generis approach: under this approach, member countries would adopt legislation protecting “qualifying open databases” from patents on certain types of improvements for a specified period of time (Article 5-6 of [31]). Various commentators affiliated with the Access to Knowledge proposal have also suggested the possibility of “social patents” legislation: under this approach, a type of patent right could be secured at low or no cost, but it could not be used for exclusionary commercial purposes. Although these sui generis alternatives are quite intriguing, and certainly an improvement over ordinary property rights in databases, securing new legislation is a difficult, uncertain, and slow route. Table 1 summarizes the advantages and disadvantages of a sui generis strategy as well as other strategies.

We close with one overarching observation. Copyleft licenses, which lead to the formation of an ever-expanding commons, have worked well—even brilliantly—in the software context. These licenses have produced well-functioning code, and they have also constrained the threat posed by copyright and patent, particularly when such intellectual property could be attached to an incipient industry standard. Would they work as well in synthetic biology? There is reason for some caution. Intellectual property rights are relatively unimportant as incentives at any stage in the production of copyleft software. They are important mainly for the leverage they give to the licensor. But synthetic biology might be different. Though the uses of synthetic biology are by no means limited to biomedicine, at the end of some biological chains of innovation will lie the expensive development and commercialization of a drug. While taking a drug all the way through clinical trials mandated by the US Food and Drug Administration may not cost as much as drug companies claim, it does cost hundreds of millions of dollars. Whether patent rights are the best incentive mechanism for purposes of eliciting pharmaceutical R&D is not a question we can address here. Suffice it to say that our current system of financing pharmaceutical innovation relies heavily on these rights. There is no direct equivalent in the world of free software. If a copyleft condition—however drafted and imposed—did attach to some of synthetic biology’s parts, care would have to be taken in the design of the system, lest the result be to make it impossible for that technology to be developed into a patented therapy. The BIOS licenses, which restrict the copyleft condition to improvements on the enabling technology and do not constrain patenting on transgenic plant products, provide an interesting model. But the distinction between enabling technology and product may be easier to make in a situation like that faced by BIOS, where the enabling technology in question has a relatively clear innovation trajectory, both in terms of improvement to the technology itself and in terms of production of end products.

In the meantime, the decision, already implemented, of the MIT Registry of Standard Biological Parts to place its parts into the public domain certainly provides important protection against the threat of patents clogging innovation in the synthetic biology space. Placing parts into the public domain not only makes the parts patentable, but it undermines the possibility of patents on trivial improvements. In the end, a public domain strategy comparable to that employed by the public Human Genome Project may not be ideal, but it is certainly a good start. ■

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PLAYING GOD, PLAYING ADAM:
THE POLITICS AND ETHICS OF ENHANCEMENT

Joanna Zylinska

Why enhancement?

The question of enhancement occupies a prominent place in current bioethical debates. This is evident not only in the publication of volumes such as Liberal Eugenics: A Defence of Human Enhancement by Nicholas Agar (2004), Enhancing Evolution: The Ethical Case for Making Better People by John Harris (2007), or Julian Savulescu and Nick Bostrom’s edited collection Enhancing Humans (2009), but also in the setting up of a number of interdisciplinary groups and workshops on the subject: e.g. the Enhancement Technologies Group at McGill University, first led by Carl Elliott and then by Margaret Lock in the late 1990s; or the Arts and Humanities Research Council workshop on Human Enhancement Technologies held at the Royal College of Art in February 2008.¹ The issues of enhancement also feature increasingly in wider public debates about ‘our human future’ and the direction of its transformation. Mobilising, unsurprisingly perhaps, experts and non-experts alike, the problem of enhancement is usually articulated via two sets of questions: moral questions over its permissibility, extent and direction; and technical questions over the feasibility of different forms of regenerative and synthetic alterations to human bodies and minds. My article postulates that none of the dominant positions on enhancement within the field of bioethics is entirely satisfactory due to the limited, monadic, pre-technological and non-cultural conception of the human that is adopted in these models. Enhancement therefore becomes for me an entry point into a broader interrogation of the limitations of liberal moral and political philosophy, with its particular set of assumptions about human and nonhuman subjectivity, capitalism and ‘life itself’, when applied to bioethics.
Critically engaging with both opponents of enhancement (Jürgen Habermas) and its advocates (John Harris, Nicholas Agar, Nick Bostrom, Ronald Dworkin), I also want to take some steps towards outlining a non-normative ethics of enhancement that sees its human and non-human subjects as always already enhanced, and hence dependent, relational and co-evolving with technology. This latter position will not be used to justify the ‘anything goes’ approach to biological or technical intervention into the human or animal body, but rather to outline a more responsible engagement with enhancement. As such this article will constitute a modest attempt to start thinking about bioethics differently, beyond the more established liberal framework which takes a singular and fixed moral entity – a patient, a foetus, a guinea pig – as the object of its enquiry. My focus is thus not on how much we can or should enhance, and by what means. Instead, my argument is guided by the following two questions:

(1) What kind of ethical framework would we need to adopt if we were to concede that enhancement is inherent, rather than external, to human existence?

(2) Even if enhancement as such is inherent to humans, are all kinds of enhancements to our bodies and minds equally desirable from a cultural and political standpoint?

‘For’ or ‘against’ enhancement?

Few moral philosophers, scientists or even media experts would advocate a tout court rejection of human enhancement. Indeed, the term itself covers such a complex network of procedures – from inoculations and cosmetic surgery, through to height enhancement and engineering new kinds of human functions such as flight (Miah 2008) – that it is difficult to imagine anyone being ‘against enhancement’ per se. Some efforts to eliminate the ambiguity of this term involve positing enhancement as an intervention into human corporeal or psychic integrity, one that is negatively contrasted against ‘therapy’. The latter is then presented as focused on reducing or even eliminating human suffering, while enhancement is characterised in terms of ‘added value’ or even gratuitousness. This rather crude distinction obviously entails making a number of assumptions not only about what it means to live a good life but also about ideas of ‘life’, ‘nature’, ‘goodness’ and ‘necessity’. The moral question about enhancement is thus also, inevitably, cultural and
political: it is a question about the moral values one holds dear, but also about the socio-political context through which these values are shaped, tested and contested.

Jürgen Habermas, for example, positions the human as uniquely singular, autonomous and bearing ‘the right to an unmanipulated genetic heritage’ (2003, 25). In *The Future of Human Nature*, Habermas draws on Kierkegaard to present the idea of the human as existing outside, but also somehow above, his environment. Pulling himself out of ‘the anonymous, scattered life that is breathlessly disintegrating into fragments’, the human achieves transparency, moral agency and freedom precisely via this separation from the biological (6). In Habermas’s ethical framework life seemingly has to be disavowed for the moral agency of the human to emerge. Even though he acknowledges that we are born as biologically ‘unfinished’, it is only in mutual exchanges with other humans that our autonomy and subjectivity are ultimately confirmed (34). Habermas is therefore deeply suspicious about any technical developments aimed at enhancing our biological makeup. For him, such developments can at best be seen as the work of rhetorical hubris; at worst, as threats to our ‘organic disposition’. Habermas writes:

> Bodies stuffed with prostheses to boost performance, or the intelligence of angels available on hard drives, are fantastic images. They dissolve boundaries and break connections that in our everyday actions have up to now seemed to be of an almost transcendental necessity. There is fusion of the organically grown with the technologically made, on the one hand, and separation of the productivity of the human mind from live subjectivity, on the other hand. Whether these speculations are manifestations of a feverish imagination or serious predictions, an expression of displaced eschatological needs or a new variety of science-fiction science, I refer to them only as examples of an instrumentalization of human nature initiating a change in the ethical self-understanding of persons who live in the mode of self-determination and responsible action. (41-42; emphasis added)

For Habermas, any form of interaction with non-human others, or, more broadly, with the forces of the environment that produce and reproduce life, amounts to instrumentalisation because it leads to the dissolution of our autonomy and moral agency. The philosopher
perceives the distinction between ‘the naturally grown’ and ‘the made’ as ‘categorical’ (42). Enhancement is therefore a potential ontological and moral pitfall, although Habermas is careful to distinguish between human ‘development’ via socialisation, which is both necessary and morally right, and technical or synthetic enhancement, which is always potentially dangerous and hence morally suspect.

Yet British bioethicist John Harris argues that no one has so far provided a systematic and intellectually satisfactory account of the relevant moral differences between biotechnological interventions on the one hand, and medical and social ones on the other. He also doubts whether such an account can actually be provided. Harris admits that there are ‘moral differences between different sorts of interventions... But these are not mirrored by the distinctions, such as they are, between therapy and enhancement nor between the normal and natural on the one hand and the artificial and unusual on the other’ (2007, 125-6). It is precisely around ways of determining the stability of the distinction between the natural and the artificial, or the organic and the technological, that many debates regarding the permissibility of enhancement pivot. Some philosophers, such as Habermas, oppose most forms of enhancement due to the ‘dedifferentiation’ effect it allegedly exerts on what is seen as a natural and inviolable distinction between categories. Others, such as Harris, reject such criticism on the basis of the existent continuity they perceive between enhancement and therapy as well as between different forms of social and technological enhancement throughout human history.

Playing God, playing Adam

Harris himself is one of the most vocal supporters of enhancement. In Enhancing Evolution: The Ethical Case for Making Better People, he goes so far as to present the need for enhancement as a universal ‘moral imperative’. Interestingly, Harris has a very clear sense what this ‘enhancement’ actually means: it will lead quite simply to the creation of ‘better people’. These people will be more intelligent, more beautiful, but also ‘longer-lived, stronger, happier, smarter, fairer (in the aesthetic and in the ethical sense of that term)’ – in other words, ‘more of everything we want to be’ (2007, 2, 5, 8). However, Harris seems to turn a blind eye to the socio-cultural circumstances of his technologically enhanced moral subjects. By merely focusing on the expansion, through technological means, of
the already agreed on ‘good’ human characteristics, he ends up reaffirming their humanism. While I am in agreement with Harris that there is no need for a moral panic over enhancement since ‘many of us are already enhanced’, there is little realisation in his argument that the allegedly objective human qualities he presents as desirable – beauty, fairness and so on - are actually cultural values, underpinned by numerous assumptions and judgments. What is more, the issue of equal opportunity, which is the guiding force behind his project, cannot be resolved merely on a philosophical level as he proposes it without addressing the broader question of politics and its alleged progressivism. Yet Harris seems to take the latter for granted: he believes that the ‘good’ of enhancement enjoyed by the ‘early adopters’ will then spread into whole populations. He does not spend too much time reflecting on the logic of capitalism in which, arguably, a certain sense of inequality is imbedded. To think that technological enhancement as such will magically solve the issue of inequality is not particularly innovative – various technolibertarians have had similar thoughts about the automobile or the internet – but it is politically reductive and hence rather naïve.

An interesting critique of the categorical distinctions between, and assumptions about, nature and technology is provided by another supporter of enhancement, Ronald Dworkin, even though his argument ultimately runs into problems similar to those encountered by Harris. In a chapter entitled ‘Playing God: Genes, Clones, and Luck’ from his *Sovereign Virtue*, Dworkin takes to task those critics of genetic engineering and cloning who resort to what he calls ‘derivative values’: i.e. values that are parasitic on the interests of particular people. It is not so much people’s rejection of, or revulsion at, genetic transformation he disapproves of as their lack of (self)transparency over which values they actually defend in their moral positions. And yet, even though most users of the ‘playing God’ rhetorical device dress their moral revulsion in the ‘heated and logically inappropriate language’ that allegedly shows their reliance on derivative, self-interested values, their position is in fact shaped by an adherence to deeper, or what Dworkin calls ‘detached’, values – values that are intrinsic to the object itself (2000, 443). (Dworkin has much more sympathy for the second position, at least as far as the constitution of a credible moral argument goes.) He writes:

> it is deeply unclear what the injunction [not to play God] really means – unclear what playing God is, and what, exactly, is wrong with it. It can’t mean that it is always wrong
for human beings to attempt to resist natural catastrophes, or to improve upon the hand that nature has dealt them. People do that – always have done that – all the time. What is the difference, after all, between inventing penicillin and using engineered and cloned genes to cure even more terrifying diseases than penicillin cures? (443)

Dworkin goes on to interpret the act of reaching for the ‘playing God’ trope as a manifestation of the emergent moral instability over distinctions between categories – such as those between nature and technoscience, between the given and the made, and, most fundamentally, between chance and choice. He actually shows understanding for this kind of psychological reaction – ‘we are entitled to worry that our settled convictions will, in large numbers, be undermined’ (446), he states - even if he does not find this kind of anxiety satisfactory on a philosophical level. So, even though Dworkin does acknowledge that ‘Playing God is playing with fire’, he insists that play with fire we must because ‘that is what we mortals have done since Prometheus, the patron saint of dangerous discoveries’ (446). It is precisely this injunction towards invention and change, coupled with the warning that any such intervention always threatens to upset the existent world order, that Dworkin borrows from the Promethean myth.

There seems to be something both hubristic and tragic in Dworkin’s story about this human imperative to go beyond the limits of the familiar in order to reach for the unknown – a myth that comes to us not just from the Greeks but also in the Biblical story of Adam and Eve. In upsetting God, man becomes Prometheus - a Titan famous for disobeying the omnipotent and omniscient Zeus. But he is also called to act like Adam, a Biblical rebel who has eaten from the tree of knowledge, ‘because the alternative is cowardice in the face of the unknown’ (446). As we can see, Dworkin’s essay is full of intriguing rhetorical slippages between different religious traditions and their deities – i.e. between the Judeo-Christian God, the king of gods and ruler of the Mount Olympus Zeus and the Greek Titan Prometheus. Even though the ontological structure of the world and its beings may be changing in the age of biotechnologies, Dworkin reconfirms its moral framework, with the capital G ‘God’ becoming for him a metaphor for a particular, temporarily stabilised natural and moral order, while the lower case ‘god’ stands for a symbol of rebellion against this order. There are limitations to this blasphemous bravery though. Dworkin admits to being aware of the dangers which genetic engineering and other technological transformations
allegedly pose, and hence issues a moral admonition against ‘losing our grip on what is wrong’ (446). What he therefore ends up proposing by drawing on all these different religious myths of rebellion is familiar human-centred liberalism. He terms this stance ‘ethical individualism’ and dresses it up as heroism and adventurousness – i.e. a willingness to take on God, although one that should not be exercised too lightly. Significantly, enhancement for Dworkin does not fundamentally alter the biological make-up or the ontological position of the human species. Indeed, the moral imperative for him lies in the injunction to maintain this very distinctness of the human, in spite of any genetic kinship or overlap with other living or even machinic entities that may be opened up by scientific investigation and experimentation.

As in Habermas’s case, Dworkin’s ‘human’ seemingly exists outside the complex biological and political nexus of forces and influences. Due to his or her unique position as both a species and a moral being, the human can raise him- or herself above the world in order to exercise judgement over it as well as ensure his or her own successful functioning, or living a ‘successful life’, in an ‘objective’ way. Dworkin insists nevertheless that ‘one person – the person whose life it is – has a special responsibility for each life, and that in virtue of that special responsibility he or she has a right to make the fundamental decisions that define, for him, what a successful life would be’ (449). We can hear an echo of Harris’s ‘flourishing’ in Dworkin’s notion of ‘living a successful life’ – an allegedly neutral concept which is rooted in the rather odd coupling of the biological idea of growth and the atemporal, humanist idea of spiritual progress. The overt depoliticisation of ‘success’ in Dworkin does not therefore mean that the concept itself is free from any political connotations. Dworkin himself makes it clear that his ethical fundamentalism is a theory of ‘political morality’ which is egalitarian but also liberal, ‘because it will insist that government must leave people finally free to make decisions that set the parameters of success for their own lives for themselves’ (449). It is not only Adam the Biblical Rebel that Dworkin wants us to play: we must also become Adam Smith.

In his defence of making enhancement initially available only for the wealthy, who will then pass the benefits on to the rest of the population, Dworkin’s moral framework is clearly underpinned by the liberal economic model in which rational self-interest and competition are seen as goods in themselves. The exercise of this rational self-interest by the select few – in our particular case,
doctors, genetic engineers, global biotech companies, rich clients – is supposed to lead eventually to the economic prosperity and well-being, or ‘success’, of all. Waving Adam Smith’s invisible hand of the market at any objections against the accumulation of enhancement as well as against the emergent normativity to which such a model of the distribution of enhancement will inevitably lead, Dworkin admits, somewhat impatiently, that ‘the unfairness ... is already part of our lives’ (434). This is not to say he does not care about injustice. But any solution he may propose will be rooted in a monadic, individualistic, liberal moral and political framework. The problem with the bioethics rooted in ethical individualism, however, as noted by Timothy Campbell in his introduction to Roberto Esposito’s Bías, is that it ends up being rather non-ethical because it exerts too many a priori constraints on bios: i.e. on life in its political configuration. Campbell writes: ‘Dworkin’s perspective on life is disastrous for any affirmative biopolitics .... [I]n such a scheme, ethic individualism quickly becomes the norm that transcends life; it is a norm of life that limits life to the confines of an individual subject and individual body; in this it operates, as it has traditionally done, to immunize the community and modernity itself, from the immanence of impersonal, singular life’ (2008, xxxvii-xxxviii).

Yet monadic ethical individualism of this kind underpins the majority of bioethical theories developed in Western moral philosophy. In this respect Dworkin’s position is actually quite similar to that espoused by Habermas, who in The Future of Human Nature is deeply critical of the ‘explosive alliance of Darwinism and free trade ideology’ (2003, 21), but stops short of analysing the political and economic aspects of the current bio-technological transformations. Instead, he all too quickly takes recourse to firm but unexamined notions such as ‘human freedom’, ‘dignity’ and ‘nature’, and to the belief in the naturalness and linearity of evolution. Even Peter Singer, one of the most radical and controversial thinkers of bioethics today, resorts to the very same monadic model of the human in outlining his ethical theory. While in his book Rethinking Life and Death: The Collapse of Our Traditional Ethics, Singer takes significant steps towards radicalising the humanist bioethics by shifting the boundaries of who counts as a ‘person’ - an ape or possibly a dolphin may, while an anencephalic baby does not – the individual person still serves as a cornerstone of his bioethical theory. For Habermas, Harris, Dworkin and Singer, then - who all take different positions on enhancement - the moral agent and the object of bioethical enquiry are defined as individual self-enclosed entities which are extricated from the networks of
social relations and political circumstances, as well as from the material and discursive conditions of their own emergence.

In religious as well as secular versions of many bioethical theories, bioethics clearly conjures up the idea of a freethinking neoliberal subject, both as someone who is in charge of making a decision and as someone regarding whom a decision regarding life and death is to be made. Enhanced persons are merely ‘stretched persons’ – both in a literal sense and on a metaphorical level, with Singer adjusting his notion of moral agency by stretching the boundaries of who counts as ‘human’ but not questioning the notion as such. But any bioethics that relies on the firm idea and material distinctness of its subjects, and that develops firm moral positions in advance and then applies them to specific cases, may be difficult to retain if the self-enclosure of ‘the person’ which is its prerequisite turns out to be both a philosophical and a biological fiction. A number of examples which stretch or enhance individual personhood in totally unpredictable ways, perhaps even beyond the point at which calling them ‘human’ is still applicable, could be evoked here. If we take into account the radical opening of the boundaries of the human body and life – through prosthetic enhancements such as corneal implants or gene therapy, programs such as the Human Genome Project and the redefinition of death through the notion of being ‘brain dead’ - the presumed humanism of what I call here, for reasons of brevity, ‘traditional bioethics’, as espoused by both critics and supporters of enhancement, is indeed found wanting (see Zylinska 2009, 3-34). Catherine Mills argues that ‘the “epistemic” shift wrought by new technologies can be seen as an opportunity and invitation to re-imagine our ontologies of ourselves as ethical agents in such a way that rational individuality is no longer seen as the primary modality of being ethical’ (2008, 43). In what follows I will argue that it is precisely in re-imagining the conceptual and material boundaries of ethical subjects that any attempt to outline an alternative ethics of enhancement must lie.

**Human, transhuman, nonhuman**

Not every attempt at the ontological re-imagining of the human via new technologies creates such potential for an ethical opening, though. For example, Nick Bostrom’s ‘transhumanism’ ends up reinforcing the humanist framework it purports to transcend. In his ‘Letter to Utopia’, Bostrom observes, not without chagrin, that ‘We are built for mundane functionality, not lasting bliss’ (2008). In
order to achieve the latter he advocates enhancement as a panacea for the natural processes of illness and ageing, all with a view to achieving ‘a higher life’. Steeped in what sounds like a bizarre mixture of Christian transcendentalism and new age spiritualism, Bostrom gives the following advice: ‘In the attic of your mind, reserve a drawer for the notion of a higher state of being, and in the furnace of your heart keep at least one aspiring ember alive’ (2008).

In recommending the construction of enhanced – better, smarter – brains, he adopts a linear idea of human progress and a quantitative understanding of value, culture and art, which clearly does not need any further investigation because all rational beings will already share it. Transhuman enhancement for Bostrom is thus merely a process of the multiplication of what is self-evidently ‘good’ in the human.5

It is however possible to put forward a different framework for understanding enhancement, one which is rooted in the ontological conception of the human as **always already enhanced**. Such a framework can offer a more immersive and less normative entry point for debates on bioethics. The account of our being-human as being-technological, or even perhaps becoming-technological, also raises questions for many of the philosophical positions that present ‘human enhancement’ as a desirable good, something the human does not yet have but should reach for in order to ensure his survival, optimum functioning and competitiveness on a biological and social level. Indeed, what distinguishes the bioethical standpoint I want to defend in the latter part of this article from those espoused not only by critics of enhancement but also its supporters, is that this ‘we-are-already-enhanced’ position is based on the acknowledgement of our inherent ‘technological condition’: i.e. our co-emergence and co-evolution with technology. This is not to say that singular instances of enhancement cannot be subject to a critique. But if we accept ‘originary technicity’ as the intrinsic condition of humanity – although I realise this may be a very big ‘if’ for some – then the very articulation of the debate on enhancement in terms of being ‘for’ or ‘against’ it will need repositioning. Simply being ‘for’ or ‘against’ enhancement will become an impossible position to sustain.

A more fundamental reconceptualisation of ‘enhancement’ is therefore needed, I suggest, one that goes beyond its everyday understanding as a mere extension or external attachment. Drawing on the philosophy of **tekhnē** as elaborated by the French philosopher Bernard Stiegler, as well as experiential developments in the area of digital technologies and biotechnologies, I want to suggest we need
to rethink the mainstream understanding of technology as a tool that can be applied to discrete entities, and consider instead mutual co-constitution between the entity that gets designated as ‘the human’ and what we call ‘technology’. Significantly, in the Greek word tekhnē one can still hear echoes of technique, craft, skill and art, with what we translate into English as ‘technology’ being originally understood as a creative process of poiēsis, i.e. bringing-forth, rather than just an instrumental application of a tool (see Weber 1996 and Poster 2001). In *Technics and Time*, Stiegler goes back to this now occluded meaning of tekhnē – rendered as ‘technics’ by his English-language translator - in an effort to trace a different history of technological development and thus re-tell and re-imagine the history of ‘technics’.

**Playing Prometheus**

Stiegler’s excursion into the past is not only etymological. In his search for alternative narratives about technology and evolution, he draws on the paleontological theories of André Leroi-Gourhan as well as Greek myths. Stiegler also revisits the myth of Prometheus on this journey, but he does so in a different manner from Dworkin. For the latter Prometheus is just one of a series of mythical god-like figures portrayed as embodying some very human characteristics: individualism, adventurousness, bravery, curiosity. For Stiegler, however, an attempt to play Prometheus is not just about making ‘dangerous discoveries’ or about playing with dangerous objects – fire, weaponry - but rather about being prepared to radically challenge the established ontological and epistemological order in which man is positioned as a self-contained being, fully present to himself. The myth of Prometheus serves for Stiegler as a reminder of man’s technical being, whereby technology is what brings man forth and is fully active in the process of hominisation, rather than just functioning as an external agent that can be picked up, appended and then discarded at will. According to him, man’s drive towards exteriorisation, towards tools, fire and other prostheses – towards tekhnē, in other words – is due to a technical tendency which already exists in the older, zoological dynamic. It is due to this inherent tendency that the (not-yet) human stands up and reaches for what is not in him. It is also through visual and conceptual reflexivity - seeing himself in the blade of the flint, memorizing the use of the tool - that he emerges as always already related to, and connected with, the alterity that is not part of him. ‘For to make use of his hands, no longer to have paws, is to manipulate - and what hands
manipulate are tools and instruments. The hand is the hand only insofar as it allows access to art, to artifice, and to *tekhnē,* writes Stiegler (1998, 113). The human is thus always already prosthetic, whereby relationality and dependence on ‘the outside’ are the condition of his emergence and existence in the world. It is precisely in this altered understanding of what we could term ‘technology as originary and inevitable enhancement’ that a potential for a new theory of bioethics lies, I want to suggest.

Before we consider in more detail what the parameters of this new bioethics might be, I would like to spend a little time looking at Stiegler’s engagement with Prometheus. In *Technics and Time, 1* and an interview included in the film *The Ister* he provides a careful exposition of the Platonic dialogue *Protagoras,* which narrates the story of the creation of living yet mortal beings, including man, and the role that two Greek gods, Prometheus and Epimetheus, played in this process. Epimetheus – a god that Stiegler presents to us as rather absent-minded and not particularly clever – takes it upon himself to furnish all newly created earthly creatures with ‘qualities’. So he distributes strength to the lion, speed to the gazelle and hardness to the turtle and its shell, making ‘*his whole distribution on a principle of compensation, being careful by these devices that no species should be destroyed*’ (187, emphasis in original). By the time he gets to man, however, Epimetheus discovers he has run out of qualities, leaving man unprovided for - ‘naked, unshod, unbedded, and unarmed’ (187). This is the moment when Prometheus comes to the rescue by offering to steal from Hephaestus and Athena the gift of skill in the arts, coupled with fire – ‘for without fire there was no means ... for anyone to possess or use this skill’. In other words, Prometheus gives man *tekhnē,* while simultaneously completing the creation of man as a technological being - a being that has the power to create but that also needs to rely on external elements to fully realise his being. Thanks to this newly gained ‘art’, writes Plato, ‘men soon discovered articulate speech [*phonen]* and names [*onomata]*, and invented houses and clothes and shoes and bedding and got food from the earth’ (quoted in Stiegler 1998, 188).

Through his re-reading of the myth of Prometheus and Epimetheus Stiegler provides an alternative story about technology, nature and the human. But he does more than that: he also proposes a different framework for the human’s self-understanding in the technical world. If we want to grasp the question of technics the way it presents itself to us in the 21st century, he claims, we must return to the Greeks because they posed the problem of the human-
technology relation very precisely, within their own tragic, religious terms. The historical expedition Stiegler embarks on has therefore contemporary resonances – not just because Greek philosophy still shapes a number of our ideas regarding ethics and politics but also because in that particular myth the Greeks managed to articulate the dramas, tensions and anxieties of ‘human becoming’ in a world that was constantly evolving. It is in a dynamic, connected model of the world that Stiegler locates the possibility of developing a less hysterical and more responsible understanding of tekhnē. What is however significant about the current moment – and by current Stiegler refers to the modern period inaugurated by the Industrial Revolution of the late 18th/early 19th century - is the speed of technological development. It has increased exponentially over the last two centuries, getting out of sync with the speed of the development of other areas of life: social, cultural, spiritual, legal, etc. This acceleration of the technological development, evident in the emergence of machinic production, railway networks, computation, cybernetics and, last but not least, globalisation, has serious consequences for the philosophical order which has been in place since Plato and the Greeks. It is precisely this order that has allowed for the emergence of the hegemonic consensus in modernity which maintains that technics has no ontological sense, that it is only an artifice which must be separated from Being (The Ister, 2004). So, even though we have always been enhanced, that is to say, technological, a radical change has occurred over the last hundred years or so, with the speed of technological transformation and intensity of technical production constantly increasing and getting ahead of the development of other spheres of life.

The bioethics of (inevitable) enhancement

Indeed, there is something tragic about this emergence of man as a technical being who is equipped with no pre-defined qualities, only with what is simultaneously a skill and an injunction to be technical – to build, bring-forth, create. Stiegler explains that a ‘pros-thesis is what is placed in front, that is, what is outside, outside what it is placed in front of. However, if what is outside constitutes the very being of what it lies outside of, then this being is outside itself. The being of humankind is to be outside itself. In order to make up for the fault of Epimetheus, Prometheus gives humans the present of putting them outside themselves’ (1998, 193, emphasis in original). And yet, even though he has a way of getting outside of himself, as well as a constitutive need to reach for prostheses, the human has no
way of being with others. Since he lacks inherent political wisdom [sophia], there is nothing to stop him producing weapons rather than utensils, to prevent him from making war rather than love. The question of enhancement – of the network of which we are part but which is over-encompassing us - is therefore not only an ontological question but also a political one. It is a question of how a lacking, externally-dependent fragile mortal is to live together with other mortals in a constantly evolving universe, without inflicting upon them, upon himself or upon the world ‘as such’ any unnecessary and untimely conflict, violence and death. It is in the very open-endedness of this question that the nature and timeliness of Greek tragedy lies. As Stiegler puts it, ‘the tragic is experienced in terms of (the astonishment that there is) technicity’ (185).

Stiegler’s work is interesting in our search for an alternative narrative about enhancement because it highlights a certain deconstructive logic at work in the dynamic relation between technology and the human, a logic that ultimately disables many of the traditional positions on enhancement and ends up undermining the way the debate on enhancement has been set up so far. There is also something unique about the way in which the story of the human as a technical being is told in his early work, which is why I am focusing on this, by now quite well known, account in my piece. Simply put, in Technics and Time, 1, Stiegler seems much more aware he is telling us a story. He goes back to a number of established oral and written texts not so much with an intention of informing his readers what the world is like (a far more dangerous, and, one might argue, hubristically naive desire, which he nevertheless cannot resist in the further volumes of Technics and Time), but rather with a preparedness to reflect on and think through some of the stories that others have told about the origin of the human: Greek myths, paleontological theories, earlier philosophical accounts. The same stories – including the key narrative about the fault of Epimetheus - are then reframed via another narratological form, i.e. the interview with the philosopher included in the video-essay The Ister. This very act of conscious reiterative story-telling is significant here. The stories about the origin of the human we are told join a long line of technical prostheses such as flint stones and other ‘memory devices’ that have played an active role in the very process of the constitution of the human. (This latter observation will become significant in the context of my own efforts to take some steps towards proposing an alternative bioethics – a bioethics which, inevitably, will also have a narratological character. In other words, it will be a story about how humans should live with other animate and non-animate beings, in a
dynamically interwoven world, and it will be based on the dismantling of the dominant set of narratives about enhancement that shape the debate on this issue in the biomedical and social fields.)

In the pre-Platonic, pre-metaphysical times which the myth of Prometheus and Epimetheus deals with - a myth which Stiegler retells for us - this tragedy is exacerbated by the fact that there is no possibility of redemption from this condition of openness man exists in, other than through the inevitable finality of death. Arguably, similar anxieties are reflected in contemporary debates over ethical dilemmas regarding technological enhancements conducted by experts and non-experts alike in Western, secular, post-metaphysical societies, with hysteria and moral panic frequently serving as strategies to contain and foreclose this Greek-like sense of tragic open-endedness. The post-metaphysical position with regard to notions such as God, soul and eternity is often rerouted via the metaphysical distinction between tekhnē and phusis, i.e. technology and nature, with the latter being positioned as originary, pure and therefore needing protection against the former. Contemporary ecological discourse or the organic food movement are just two examples of how politically significant issues are frequently discussed in philosophically suspect and uncritically conservative terms.

Yet an interesting breach is created in this theory of originary technicity as outlined by Stiegler, a theory which may perhaps be described - not necessarily in a derogatory manner – as ‘softly determinist’. Drawing inspiration from the work of Emmanuel Levinas and his notion of ethics as primordial openness to, and responsibility for, the alterity of the other, we can perhaps go as far as to suggest that this primordial originary technicity is also an ethical condition. If, as Stiegler has it, ‘The being of humankind is to be outside itself’, the always already technical human is a human that is inevitably, prior to and perhaps even against his ‘will’ – engaged with an alterity. Being in the world therefore amounts to being ‘in difference’, which is also – for Levinas, as much as for Stiegler - being ‘in time’: i.e. having an awareness and a (partial) memory of what was before and an anticipation of what is to come (see Levinas 1969, 224, 235; Stiegler 1998, 13-16). The idea of the originary self-sufficient, total man, living in the state of nature is exposed here as nothing more than a myth, whereby the state of nature stands ‘precisely [for] the absence of relation’ (Stiegler 1998, 128). As such, it marks the impossibility of the human (and also of
tool use, art, language, and time), as well as of ethics. Originary technicity can thus be understood as a condition of openness to what is not part of the human, of having to depend on alterity—be it in the form of gods, other humans, fire or utensils—to fully realise one’s being. But this imperative to get outside of oneself and to be technical, i.e. to bring things forth, to create, is perhaps also an ethical injunction to create well, even if not a condition of ethical behaviour. A prosthesis is therefore also an ethical ‘prop’.

The condition for ethics is thus constituted before the human—and it is in this sense that ethics for Levinas is primordial and that it precedes being. Yet there exists absolutely no guarantee that the human will respond to this ethical condition responsibly, rather than ignorantly or violently. Indeed, because of Epimetheus’s act of forgetting, the human has no ‘qualities’ that will ensure a particular execution of his relationality with others. But it is in the fact that there is relationality, that the human emerges only in relation with what is outside of him or her, that foundations for a new non-normative ethics of inevitable enhancement lie. This non-normative ethics of inevitable enhancement will not therefore prejudge once and for all whether enhancement per se is good or bad, or even whether particular enhancements as later-time additions or alterations to the fully constituted human, foetus or animal are desirable or not. However, even though the moral subject is positioned as always already enhanced and relational, this does not mean that any interventions to its corporeal or genetic make-up will be seen as unproblematic. The ethical task that emerges here consists in knowing how to differentiate, or, in other words, how to use prostheses well. The taking up of an ethical task involves carrying out the creative work of technics, learning from the connectivities and alterities, while resisting the temptation to rely on singular selfhood as the ultimate arbitrator of this goodness. The ethics of inevitable enhancement is thus also an ethics of infinite responsibility, whereby recognising that we are always already enhanced is another way of saying that we are indebted to (not always human) alterity, that we are always already ‘other’.

Outlining a whole new paradigm for bioethics is naturally beyond the scope of this article. However, we have hopefully arrived at what can be described as a different entry point for bioethical enquiry. We also have to bear it in mind that outlining such an alternative paradigm once and for all is actually impossible if we take into account the question of responsibility that is never entirely mine, and that imposes itself on me from outside, in a myriad singular
ways. The framework of originary technicity in which the human emerges only through his or her prostheses brings to our attention the fact that ‘my child’, ‘my genome’ and ‘my foetus’ – concepts that structure many traditional debates within bioethics - never belong just to ‘me’. Instead, they exist as part of a complex network of attachments, dependencies and kinship relations that require a more immersed and hence inevitably limited or even indebted starting point for any ethical consideration – which is also, at the same time, an ethical sensation. The recognition of our own incompleteness and dependency can help us develop a more responsible politics, one that does not position the individual with his fully transparent wishes and desires as its cornerstone but that rather looks at his or her indebtedness to both animate and inanimate alterity.

The bad conscience of bioethics

To sum up, what serves as an ultimate stumbling block for debates on enhancement within traditional moral philosophy is its understanding of the ontological status of technology. For the advocates of enhancement such as Harris, Dworkin or Bostrom, ‘humans’ and ‘technology’ are two separate entities. Even if Harris does acknowledge that enhancement ‘has been part of human history from our first beginnings’ (2007, 16) or that ‘[s]helter, learning and teaching, tool using, body decoration, clothing, gathering and hunting, cooking, storing, co-operation, cultivation, animal taming and domestication, funding, social living, language, and education are all enhancement techniques or technologies’ (13), or even if Dworkin does state that people have always tried ‘to improve upon the hand that nature has dealt them’ (2000, 43), a certain linearity of progression from ‘nature’ to ‘culture’ is assumed in all of these accounts, as is the understanding of technology as artifice, ornament and cultivation, that is, as a sequence of discrete objects and actions. One might be tempted to suggest that this originary interlocking of the human and technology is nevertheless implied by Harris et al. Yet none of the advocates of enhancement discussed in this article seriously consider the radical consequences of this implication, i.e. the fact that it creates fundamental problems for continuing to position singular, monadic subjects, such as individual human beings or singular animals, as cornerstones - both agents and objects - of bioethics. In other words, to acknowledge that human beings do not exist apart from cultures, which include technologies, is not yet the same things as to consider the full radicalism of the deconstructive critique of the human/humanist
subject. Deconstructive thinking, as argued by Timothy Clark, ‘upsets received concepts of the human and the technological by affirming their mutual constitutive relation or, paradoxically, their constitutive disjunction. ... The identity of humanity is a differential relation between the human and technics, supplements and prostheses’ (2000, 247). From this perspective, one which posits humans as always already enhanced, it becomes impossible to think about enhancement as a (bio)technical intervention enacted on a singular, skin-bound human, in the way the moral philosophers referred to in the first part of this article have tended to approach it. Indeed, I would go so far as to suggest that the debate on the ethics of enhancement cannot actually continue in its current form once we have followed the logical implications of adopting such a differential model of human identity.

However, even if we have ‘always’ been enhanced, biotechnologies and digital media are increasingly challenging in new ways our established ideas of what it means to be human and live a human life. Consequently, they command from philosophers and non-philosophers alike a transformation of the recognised moral frameworks through which we understand life, as well as a rethinking of who the moral subject is in the current conjuncture. What is different about the current temporality, then, is that in the biodigital age this tentatively differentiated human needs to respond to an expanded scope of obligations, beyond those exerted by singular human others. Bioethics today has to deal not just with questions of the transformation of life on a biological level – via genomics, DNA sequencing, cloning, and so forth – but also with life situated in a broader political context, through questions of the financing of the biotechnological industry, of the database management of the immigration and asylum systems, of the normativity of cosmetic surgery, of national and cellular surveillance, of biocitizenship, etc. Amidst those complex processes of technological co-emergence, the human is presented with a unique ethical task: that of having to make decisions, always in an uncertain terrain, about life, in all its different incarnations and enactments.

We should therefore bear in mind that the deconstructive mode of thinking about the human as always already technical does not mean doing away with the category of the human altogether, or with the responsibility that those who deem themselves human carry. The decision-making processes of ‘us, humans’ (aware as we need to be of the historical and cultural baggage this term carries, and of the temporary and fragile nature of any such identification), are
important in any situation when issues of life and its multiple transformations are at stake. Involvement in these processes does not have to amount to the celebration of human superiority though: it should rather be seen as a practical mobilisation of the human skills, however compromised and imperfect, of critical reflexivity and practical intervention. Now, the question of whether ‘animals’ or ‘machines’ should also engage in such ethical processes is irrelevant, even if we recognize that the features and behaviours that used to be seen as uniquely human have recently been identified across the species barrier. It is irrelevant because this responsibility only ever refers to ‘me’: a temporarily stabilised singular human who emerges in-relation-with technology.

Going beyond the monist, acultural solipsism of humanist moral philosophy which is rooted in the political principle of liberalism, the ethics of inevitable enhancement does not relieve us of the responsibility of having to transform what I described earlier as ethical sensations into workable pragmatic solutions to issues of human and non-human life, in all its different permutations. It thus provides a stepping stone to the work of bioethics committees, policy making bodies, research councils – all those organisations, such as the Nuffield Council on Bioethics in the UK or the US-based President’s Council on Bioethics, that are engaged on a daily basis in making bioethics work. But we should also recognise that what most established organisations and projects that have bioethics in their title are involved in is precisely the work of ‘politics’. It is the necessary but perhaps misnamed work of decision-making within a particular organisational context, frequently at a state level, that most of them are primarily involved in. To do this work well, and not to default on our human lack of sophia, all these organisations need an ethical supplement. So, rather than call for the radical reform or even abolishment of many of the traditional bioethics bodies in my attempt to draw some pointers towards thinking bioethics otherwise, my ethical proposal is much more modest.

The ethics of inevitable enhancement I have attempted to sketch here thus becomes a supplement to both morality and politics. Rather than as a set of guidelines on whether to enhance and by how much, it can be seen as a prior demand on those of us who call ourselves human to respond to the alterity of the world critically and responsibly, without taking recourse all too quickly to pre-decided half-truths, opinions, beliefs and political strategies. Significantly, this kind of bioethics cannot be implemented once and for all. It will therefore not become a practical tool for resolving specific moral
dilemmas over life and death, nor will it be able to be instantiated in any single ‘example’. (Any such example would inevitably take over and colonise the need for open-ended critical work of bioethics by becoming a measuring stick against which other bioethical cases and dilemmas could be compared.) My interest in proposing this kind of critical-creative work of bioethics lies first of all with my aspiration to shift the parameters of the conventional bioethical debate - from an individualistic problem-based moral paradigm in which rules can be rationally and strategically worked out on the basis of a previously agreed principle, to a broader political context in which individual decisions are always involved in complex relations of power, economy, and ideology. This non-normative ethics of inevitable enhancement can thus perhaps be taken as a pre-condition of ‘responsible biopolitics’ that is the task of many bioethics committees, panels and policy-making bodies. But it must also become – if need be – the bad conscience of dominant bioethics.

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1 It is my participation in the RCA workshop on enhancement that provided inspiration for writing this piece. I am grateful to Prof. Sandra Kemp for inviting me to attend it.

2 While my recent book, *Bioethics in the Age of New Media* (2009), was already an attempt to test the limitations of what I termed ‘traditional bioethics’ in the context of recent transformations to our concepts and bodies facilitated by new media technologies, this article is a continuation of my earlier efforts to think bioethics otherwise, while also attempting to serve as a stand-alone intervention into what seems to be one of the key debates within the established field of bioethics today.

3 The discourse of human enhancement – from Habermas through to Bostrom and Stiegler – displays a curious gender bias. While we have to take into account different conventions of writing in German, French and English with regard to the use or non-use of gender-specific pronouns, and the different translators’ decisions as to their rendering, I cannot help but notice a strange similarity between the gender-specific language of the philosophy of enhancement and the similar bias revealed in the ‘enhancement emails’ that our mailboxes get flooded with on a day-to-day basis. The comic awkwardness, with its intriguing gender and sexual assumptions, of those emails provides an unintended, Dada-like commentary on the enhancement debate. (‘Your Husk will be so big that you can use it on submarine like periscope!’ or ‘If your wife became cold, light the fire in her again with female enhancers’ - to
cite just two of the most recent spam messages found in my inbox.) While I have attempted to avoid replicating here the gender bias of much of traditional bioethical writings, I have sometimes retained the use of ‘he’ when referring to the person of either gender if the context of the worked cited clearly made that assumption.

Incidentally, variations on the notion of ‘flourishing’ - in the form of ‘growth’, ‘emergence’ or ‘creation’ - can be found not only in proponents of liberal humanism but also in authors of more interconnected and less monadic models of the world, such as Canguilhem, Bergson, Spinoza and Deleuze. Indeed, in the work of the latter philosophers it can be sometimes difficult to separate the biology-inspired descriptiveness of their concepts from those very concepts’ socio-political normativity, especially if life’s alleged force and inclination for movement, mutation, and growth is being used by various readers of these philosophers to justify all sorts of ‘developments’ – from human enhancement to market growth and globalisation.

In an earlier piece titled ‘Human Genetic Enhancements: A Transhumanist Perspective’, Bostrom’s floral prose reveals a number of seriously unquestioned hypotheses and assumptions regarding the idea and nature of the human. He writes:

We can imagine beings that reach a much greater level of personal development and maturity than current human beings do, because they have the opportunity to live for hundreds or thousands of years with full bodily and psychic vigor. We can conceive of beings that are much smarter than us, that can read books in seconds, that are much more brilliant philosophers than we are, that can create artworks, which, even if we could understand them only on the most superficial level, would strike us as wonderful masterpieces. We can imagine love that is stronger, purer, and more secure than any human being has yet harbored. Our everyday intuitions about values are constrained by the narrowness of our experience and the limitations of our powers of imagination. We should leave room in our thinking for the possibility that as we develop greater capacities, we shall come to discover values that will strike us as being of a far higher order than those we can realize as un-enhanced biological humans beings. (2003)

It has to be acknowledged that Stiegler’s work runs against some of the very same ‘humanist’ limitations that we have identified in the
writings of Harris et al. This is evident in the way he re-introduces a number of problematic anthropological distinctions such as those between culture and nature, or human and animal, into his argument presented in Technics and Time.

7 ‘Post-metaphysics’ is of course not the only philosophical standpoint that shapes debates on bioethics in the West. Even in those societies which are more explicitly secular, such as the British one, religious frameworks and ideas also feature in the bioethical debate, although these frameworks are of less interest to me in this particular article. Fernando Cascais writes that ‘Whereas in the United States the distinction between “bioethics” in general and “religious bioethics” (“Christian bioethics”, “Jewish bioethics”, etc.) is clear, the latter expressing the distinct positions of various confessional morals, in Europe, especially in the South, the straight and plain impoundment of bioethics by religious morals is notorious … (2003, 29)’.

8 Ethics, for Levinas, is not something imposed from outside or above; instead, ethics is inevitable. An ethical event occurs in every encounter with difference, with the ‘face’ and discourse of the other that addresses me and makes me both responsible and accountable (even if I ultimately decide to turn my back on this difference or even annihilate it). I am thus always already a hostage of the other, of his/her ethical demand. As Levinas himself puts it in a poetic but also somewhat menacing way, our subjectivity ‘does not have time to choose the Good and thus is penetrated with its rays unbeknownst to itself’ because the Good ‘has chosen me before I have chosen it’ (1998, 11). It is through this encounter that I become aware of my place in the world, of my corporeal boundaries, of the language that comes to me as a gift. But it is also through this encounter that I may become a murderer, a destroyer of the difference that threatens my ‘place in the sun’ (even if I manage to persuade myself or others that this murder is ‘only’ an act of retaliation, that it is part of a ‘just war’, or that the other hates me and thus needs to be excluded from my world). For an introduction to Levinas’s philosophy of alterity, see his essay, ‘The Trace of the Other’ (1986).

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Background to the debate: In many countries, the number of patients waiting for a kidney transplant is increasing. But there is a widespread and serious shortage of kidneys for transplantation, a shortage that can lead to suffering and death. One approach to tackling the shortage is for a patient with renal disease to buy a kidney from a living donor, who is often in a developing country, a sale that could—in theory at least—help to lift the donor out of poverty. Such kidney sales are almost universally illegal. Proponents of kidney sales argue that since the practice is widespread, it would be safer to formally regulate it, and that society should respect people’s autonomous control over their bodies. Critics express concern about the potential for exploitation and coercion of the poor, and about the psychological and physical after-effects on the donors of this illegal kidney trade.

Selling one’s own kidney would be better than enduring the horrors of poverty.

What would you do if you had to choose between selling your kidney and letting your children starve? I have come to believe that selling one’s own kidney would be better than enduring the horrors of poverty. Living below the poverty line on less than a dollar per day makes it hard for parents to feed their children, let alone to clothe them, and organ sales offer a way out of destitution.

After returning to Syria from the United States, I learned about a man who had sold one of his kidneys to help lift his family out of poverty and pay for his children’s education. The Arabic news Web site Al-Arabiya (http://www.alarabiya.net) told the story of a young man living in the United Arab Emirates who wanted to sell his kidney in order to help his family of two wives and six children living at their grandparent’s home. The Tribune, India reported that a 42-year-old Nepalese man named Man Dhoj Tamang sold one of his kidneys to pay off his debts and buy a piece of land [1].

Having trained and taught in North America for almost 14 years, my initial reaction to these reports was that such organ sales were immoral. I was aware that many medical societies and health-care organizations took the position that selling organs is unethical. For example, the Ethics Committee of the Transplantation Society advises transplant surgeons that: “No transplant surgeon/team shall be involved directly or indirectly in the buying or selling of organs/tissues or in any transplant activity aimed at commercial gain to himself/herself or an associated hospital or institute” [2]. The World Health Organization and the International Congress on Transplantation in Developing Countries have also condemned the selling of organs, arguing that it is a coercive practice that exploits the poor [3–5].

But then I remembered my own experience of poverty, standing in long lines to buy a few oranges or a little bread, having to live without electricity and running water, and sleeping on the floor with roaches crawling over my face. And then it struck me that poverty itself is a kind of coercion. None of the decisions that any poor person makes are made on the basis of free will—instead, these decisions are all dependent on the person’s dire financial situation.

Tarif Bakdash’s Viewpoint: Poor People Should Have the Right to Exercise Their Autonomy by Selling Their Organs

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The PLoS Medicine Debate discusses important but controversial issues in clinical practice, public health policy, or health in general.
We live in a world of startling inequities: of the 10.8 million children under age five who die each year, 10 million (more than 92 percent) live in the lower-income countries [6]. Millions of the world’s poorest people have no access to clean water, and no opportunities to educate themselves or their children. It is no wonder that some of these people sell their organs to have a glimpse of a better life. The argument that we should protect the poor from being exploited by banning them from selling their organs is a myth. The poor are always exploited from the day they are born, and in all avenues of life. The only thing of value left for some of them is their bodies.

It is surely a kind of hypocrisy and arrogance on the part of the rich world to reject the right of poor people to exercise their autonomy when it comes to selling their organs. Is it ethically justifiable to deprive the world’s poorest people of the chance for a better life? The decision to sell one’s organs is never taken lightly—it is often an act of great altruism driven by the desire to create a better life for one’s family.

Abdallah Daar, Director of the Program in Applied Ethics and Biotechnology at the University of Toronto, has argued that the position taken by the Ethics Committee of the Transplantation Society “has been totally useless in stopping the increase of the buying and selling of organs” [7]. Unfortunately, those who currently sell their organs risk major complications because the surgery is often done under sub-standard conditions. It would be good medical practice for the buying and selling of organs to be taken out of the black market and become regulated. Instead of banning organ sales, I would add my voice to the growing number of commentators that argue that the sale of organs should be legalized and regulated [8–10]. Janet Radcliffe-Richards and colleagues have argued that “all the evidence we have shows that there is much more scope for exploitation and abuse when a supply of desperately wanted goods is made illegal” [10]. And the best way, they say, to avoid coercion and exploitation of the poor in organ sales would be to ensure “regulation and perhaps a central purchasing system, to provide screening, counselling, reliable payment, insurance, and financial advice.”

Of course we must address the underlying root causes of poverty, so that people are never forced to have to sell their bodily organs. But until we solve the problems of social, political, educational, and economical underdevelopment we need to face reality by legalizing and regulating organ sales in the developing world.

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Nancy Scheper-Hughes’ Viewpoint: Dividing the World into Organ Buyers and Sellers Is a Medical, Social, and Moral Tragedy

The late Michael Friedlaender, a transplant nephrologist at Hadassah Hospital in Jerusalem, was initially “adamant that organ trading was wrong and would lead to terrible crimes” [11], but he later changed his position. He described how 300 of his patients, Jews and Arabs, traveled abroad for illegal kidney transplants from paid living donors. Although a few of these patients fell seriously ill and one died as a result of their illicit “black market” transplant, most fared as well or better than those transplanted safely at home with a cadaver kidney. Friedlaender joined several respected medical colleagues and prominent bioethicists in supporting proposed legislation in Israel to govern regulated kidney sales [12]. Their refusal to condemn the kidney trade helped pave the way for a global kidney trade that harmed as well as healed people and that engendered new antagonisms toward Israel as a global leader in “transplant tourism.” In August 2006, the Jerusalem district court instructed HMOs to pay kidney donors U$14,000 to cover their expenses, essentially legalizing sales [13].

The philosopher Janet Radcliffe-Richards and her colleagues also called for a regulated market in organ sales: “If a living donor can do without an organ,” they said, “why shouldn’t the donor profit and medical science benefit?” [10].

When it comes to organ sales, the ethical conflict between the principles of non-malfeasance (“do no harm”) and beneficence (the moral duty to perform good acts) is being resolved via the market principle: those able to broker or buy a human organ should be allowed to do so. Paying for a kidney “donation” is often described as a “win–win” situation beneficial to both parties [10]. Patient autonomy has become the final arbiter of medical values. Social justice and notions of the good society hardly figure in these discussions. Virtue in suffering and grace in dying can only appear as patently absurd.

But the transformation of a person into a “life” that must be prolonged or saved at any cost has turned human life into the ultimate commodity fetish. The absolute value of a single human life saved or prolonged at any cost ends all ethical inquiry and erases any possibility of a global social ethic. Meanwhile, the traffic in kidneys reduces the human content of all the lives it touches.

The arguments for “regulation” as opposed to prohibition have some merit, but are out of touch with the social and medical realities in many developing countries. Often institutions in these countries created to “monitor” organ harvesting and distribution are weak, dysfunctional, corrupt, or compromised by the impunity of the organ brokers, and by outlaw surgeons willing to violate the first premise of classical medical bioethics: above all, do no harm.

The results of the few available studies of the effects of nephrectomy on kidney sellers in India [14] and Iran [15,16] are clear. Even under attempts (as in Iran) to regulate and control systems of “compensated gift giving” by the Ministry of Health, the outcomes are troubling. Paid donors are not followed and some who encounter subsequent medical problems are turned away. Our research among hundreds of kidney sellers in Moldova, Romania, Turkey, the Philippines, and Brazil has shown that many suffer post-operatively from chronic pain, social isolation, stigma, and severe psychological problems [17]. Their economic conditions decline following the sale due to negative perceptions and self-perceptions of kidney sellers as weak and disabled individuals. The feelings of disappointment, anger, resentment, and even

Putting a market price on body parts exploits the desperation of the poor.
seething hatred by kidney sellers toward the surgeons and the recipients of their organs suggest that the practice engenders deep social pathologies. These outcomes have been found in countries where kidney selling is illegal as well as in Iran, where kidney selling is legal and regulated.

Organs Watch, an independent, university-based human rights and research project, has provided assistance to kidney sellers in Moldova, Brazil, and the Philippines, including diagnostic exams and sonograms. These revealed that many organ sellers face a range of post-operative complications and medical problems, including hypertension and kidney insufficiency, without access to adequate medical care or medications (http://sunsite.berkeley.edu/biotech/ organswatch/pages/research.html). Kidney sellers find themselves unemployed because they are unable to sustain the demands of heavy agricultural or construction work, the only labor available to men with their skills. Kidney sellers are often alienated from their families and coworkers, excommunicated from their churches, and excluded from marriage. The children and spouses of kidney sellers are subject to cruel taunts (“Your father is a one-kidney!”) and ridicule.

In our studies, male kidney sellers suffered from exclusion by potential employers and coworkers, and by girlfriends and wives who labeled them as “weak,” “inadequate,” or mutilated. “No young woman in the village will marry a man with the tell-tale scar of a kidney seller,” a village elder in Mingir, Moldova, told me. Even in the United States, kidney donors have died or become comatose as a result of donation [18]. In the context of for-profit transplant tourism, nephrectomy is a risky procedure [19].

The violence associated with kidney selling gives reason to pause.

Bioethical arguments supporting the right to sell an organ are based on Euro-American notions of contract and individual “choice.” But the social and economic contexts make the “choice” to sell a kidney in an urban slum of Calcutta, or in a Brazilian favela or Philippine shantytown, anything but a “free” and “autonomous” one. Consent is problematic with “the executioner”—whether on death row or at the door of the slum resident—looking over one’s shoulder. Putting a market price on body parts—even a fair one—exploits the desperation of the poor, turning their suffering into a medical opportunity. Asking the law to negotiate a fair price for a live human kidney goes against everything that contract theory stands for. When concepts such as individual agency and autonomy are invoked in defending the “right” to sell an organ, medical anthropologists suggest that certain “living” things are not alienable or proper candidates for commodification. The problems multiply when the buyers and sellers are unrelated. In this situation, the sellers are likely to be extremely poor and trapped in life-threatening environments facing everyday risks to their survival, including exposure to urban violence, transportation- and work-related accidents, and infectious diseases that could compromise their single kidney. And when that ultimate “spare part” fails, kidney sellers often have no access to dialysis, let alone to organ transplantation. Moldova, which inadvertently supplied a great many desperate kidney sellers to affluent transplant tourists in Turkey, South Africa, and the United States, is today one of Europe’s poorest nations. The country has only one public transplant unit and no capacity to guarantee dialysis to all those who may require it, least of all to rural men who fall into the hands of ruthless international kidney brokers.

Wouldn’t a regulated system be better than the current state of racketeering in human kidneys? Perhaps, but how can a national government set a price on a healthy, but destitute, human being’s body part without compromising essential democratic and ethical principles that guarantee the equal value of all human lives? Any national regulatory system would have to compete with global black markets that establish the value of human organs based on consumer-oriented prejudices. In today’s kidney market, Asian kidneys are “worth less” than Middle Eastern kidneys and American kidneys worth more than European ones. The circulation of kidneys transcends national borders, and international markets will coexist and compete aggressively with any national, regulated systems. Surgeons whose primary responsibility is to provide care should not be advocates of paid self-mutilation by anonymous strangers even in the interest of saving lives.

Ethical solutions to the chronic scarcity of human organs are not always palatable to the public, but must be considered. Foremost among these are systems of educated, informed “presumed consent,” in which all citizens are assumed to be organ donors at brain death unless they have officially stipulated their refusal beforehand. This practice, which is widespread in parts of Europe, preserves the value of organ transplantation as a social good in which no one is included or excluded on the basis of their ability to pay. While many individuals have benefited from the ability to get the organs they need through illegal circuits, the violence associated with kidney selling gives reason to pause. The division of the world into organ buyers and sellers is a medical, social, and moral tragedy of immense and not yet fully recognized proportions.

References
The "spare parts person"? Conceptions of the human body and their implications for public attitudes towards organ donation and organ sale

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Abstract

Background: The increasing debate on financial incentives for organ donation raises concerns about a "commodification of the human body". Philosophical-ethical stances on this development depend on assumptions concerning the body and how people think about it. In our qualitative empirical study we analyze public attitudes towards organ donation in their specific relation to conceptions of the human body in four European countries (Cyprus, Germany, the Netherlands and Sweden). This approach aims at a more context-sensitive picture of what "commodification of the body" can mean in concrete clinical decisions concerning organ donation.

Results: We find that moral intuitions concerning organ donation are rooted in various conceptions of the human body and its relation to the self: a) the body as a mechanical object owned by the self, b) the body as a part of a higher order embodying the self, and c) the body as a hierarchy of organs constitutive of the self.

Conclusion: The language of commodification is much too simple to capture what is at stake in everyday life intuitions about organ donation and organ sale. We discuss how the plurality of underlying body-self conceptions can be taken into account in the ethical debate, pointing out consequences for an anthropologically informed approach and for a liberal perspective.

Introduction

In September 1999, visitors to the internet auction website eBay were presented with an unconventional offer: A human kidney, praised as "fully functional" in the accompanying advertisement text. Bidding for the organ began at $25,000 and soon reached $5,750,100, but since organ trafficking constitutes a criminal offence under the US-National Organ Transplants Act, eBay stopped the auction as soon as it was informed. Nevertheless, the case attracted broad media attention and aroused considerable public debate [1-3].

The incident could easily be dismissed as just another bizarre internet episode, and was in any case probably a hoax [4]. In two respects, however, it appears to be quite characteristic of certain tendencies in contemporary society [5]: First, it seems to represent a general trend of commercialization affecting more and more areas of personal life and social relationships, now even encroaching upon the human body and turning it into a commodity (indeed, real offers of human kidneys are still easy to find on the internet) [6]. And secondly, the crossing of this last, "physical" border obviously provokes a culturally deeply-
rooted unease among the general public in most western countries.

Subsumed under the catchphrase "commodification of the human body", the critical reflection of this development constitutes an important issue in current bioethics, most prominently in the debates about market models for blood, tissue and organ procurement [7,8]. However, while the commodification debate seems to touch upon very strong intuitions about the nature of the body and its moral implications, these intuitions are often not easy to explain and to translate into rational, intersubjectively convincing bioethical arguments [9]. In the spirit of empirically-informed ethics [10], one step in this direction could be to take into account the general public and explore their views and attitudes in order to achieve a more context-sensitive picture of the positions and arguments occurring.

Against this background, we want to empirically investigate the conceptions of the human body involved in the public debate and their role in public attitudes towards organ transplantation: How are the body and its parts perceived and conceptualized and what are the implications for the evaluation of different modes of organ procurement from altruistic donation to profit-oriented sale? We start with a theoretical overview of body conceptions in recent ethical and political discussions about the commercialization of organ donation. In the methodological section, we give a short description of our own research methods. Our analysis is based on socio-empirical material from focus group discussions on transplantation medicine made up of lay people and patients in four European countries (Cyprus, Germany, the Netherlands, and Sweden) [11]. We examine three different body conceptions brought forward by the participants and their argumentative use, showing that the language of commodification is much too simple to capture what is at stake in everyday life intuitions about organ sale. In the discussion, we revisit the theoretical level in the light of our empirical findings and draw conclusions for the ethical and political debate on organ donation and its commercialization.

Background: The human body in the debate of organ donation and its commercialization

The commodification debate shows paradigmatically that an issue like organ donation and especially organ trade [12] not only concerns our explicit evaluative and normative standards, but also culturally deeply-rooted ideas concerning human nature and existence, personhood, personal identity and the body [13,14]. The concept of commodification [15] entails that an entity is viewed and treated as a commodity, that is, an instrumental object without subjectivity and intrinsic value which can be replaced by similar objects or money [16]. Therefore, commodification arguments for (or against) the commercialization of organ procurement obviously draw on some conception of the human body which specifies why it is (or is not) adequate to view and treat it this way.

In the Kantian tradition, for example, scholars usually assume that the body is an essential part of the person as such and that persons generally have dignity, that is, incomparable value, and represent an end in themselves. Kantian philosophers therefore conclude that it would be wrong to use parts of our bodies "as a means only" [17] or even sell them because this would infringe upon our moral status as persons [18]. And especially in Marxist social philosophy, criticizing the adverse impacts of universal commodification in modern capitalistic society in terms of "commodity fetishism" and "alienation" has a long tradition. In analogy to Marx's considerations about the commodification of labor power, markets for body parts are deemed problematic because of their exploitative nature and dehumanizing effects on individuals and societies ([19], p. 3f.). On the other hand, many proponents of a commercialization of organ procurement [20] state that there is nothing wrong with commodification. Premising Locke's idea that everyone is the rightful owner of his person and faculties, especially some liberals derive a specific conception of "self-ownership" which entails that "each person is free to do with his body whatever he chooses so long as he does not cause or threaten any harm to non-consenting others" ([21], p. 40). Since most people tend to associate ownership with the right to alienation, this conception also encompasses the freedom to sell parts of one's body [22]. This line of thought seems to presuppose that the self can act as an autonomous authority disposing over its body like over some kind of property [23].

Thus, on both sides of the debate, addressing the question as to whether commodification of the body and its parts is justifiable apparently entails certain basic assumptions regarding what the body means for the self and the person as such [24]. In order to give an overview of these assumptions and systematize their role in the debate, Joralemon and Cox ([25], p. 28) have introduced a conceptual matrix. According to them, the spectrum of possible standpoints can be roughly structured along two axes: (a) a variety of approaches to organ acquisition resting on different degrees of voluntariness which range from altruistic donation with prior consent on the one end of the scale over several stages of external motivation by financial incentives to coercion via conscription on the other; and (b) a scale of conceptions of the self and its relation to the body which range from the monistic idea of the body as identical with the self on the one hand to a dualistic notion of the body as a piece of property of the detached self on the other. According to this scheme, for example, donation on
the basis of a narrow consent solution is the result of a voluntary and purely altruistic (that is: supererogatory) choice and presupposes a monistic idea of the body as equatable with the self. On the other side of the spectrum are inter-vivos sale of organs. They are located in the less voluntary/more dualistic quadrant because potential donors are supposed to be coerced to do something they would not otherwise do on the basis of a body-as-property paradigm.

Clearly, these interrelations between body conceptions, conceptions of commodity and the human being are in need of further investigation – not only from a philosophical point of view, but also on the level of empirically informed ethics. Otherwise, the dynamics of individual and social decisions taking place in concrete situations cannot be adequately addressed [26].

**Methods**

In the light of the academic commodification debate, our research is interested in the conceptions of the human body which actually underlie public attitudes towards organ donation in Europe. This research interest aims at a deeper understanding of public opinions by exploring their ideational and motivational backgrounds, that is, the subjective meanings they express and the cultural web of ideas and values they are embedded in. Given the specific direction of this interest and the lack of precedent research, methodological standards and systematic knowledge in this field, we used qualitative methods to gain access to this symbolic dimension.

**Composition of samples**

In qualitative socio-empirical research, focus groups, and social decisions taking place in concrete situations cannot be adequately addressed [26].

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The selection of countries was guided by an attempt to obtain a rough cross-section of the variety of national regulatory and organizational frameworks of organ transplantation in Europe. Of course the findings of qualitative studies are not representative for a country or even Europe as a whole. But an inter-European comparison allows for building hypotheses about public moralities by abstracting from specific national or religious backgrounds.

Two focus groups with 8–10 participants per group were set up in each country. One consisted of lay people and one of affected persons. The latter were patients who had had a transplant, were waiting for a transplant or had refused transplantation, along with relatives of such patients. In total, 66 European citizens took part, 34 men and 32 women. The participants were recruited using different strategies such as the distribution of flyers, online and print advertisements or the snowball method. The affected people were approached more directly with the support of medical centers, self-help groups and patients' organizations. The overall number of responses was in Germany 85, in the Netherlands 71 and in Sweden 34 (for Cyprus, no figures on overall response are available).

The composition of the groups was intended to achieve a gender balance and to be as heterogeneous as possible in regard to age and educational level. In regard to religion, however, the composition often mirrored the respective national situation; thus, in the Cypriot groups, all participants were of the Christian Orthodox faith, whereas the Swedish groups showed a dominance of Protestants. A degree of religiosity could not be given.

**Method of data collection and analysis**

In all countries, the group discussions were moderated by two facilitators and followed the same semi-structured method of data collection and analysis.
questionnaire. The questionnaire contained a) a future scenario of unlimited organ replacement, b) questions about a hypothetical case of a proxy decision for a brain-dead relative and open questions about c) attitudes towards post-mortem and living donation, and d) public policy. It was designed to initiate discussion and kick-off a discursive dynamic through which participants would be incited to bring in their positions and explicate underlying world views and value systems.

All discussions (lasting for 1.5 – 2 hours) were recorded and transcribed, the transcripts made anonymous and translated into English. The speaker codes used only provide information about gender (Mr./Ms.) and group membership (aff/lay: affected person/lay person); the country is also indicated: CYP: Cyprus, GER: Germany, NED: Netherlands, SWE: Sweden. The coding process (= assigning thematic categories to text passages) of the material was conducted by two researchers in parallel with Atlas.ti® scientific software. The coding was compared and differences were adjusted. This approach reduced subjective bias. Since we were mainly interested in moral positions and cultural values, we followed a hermeneutic-analytical procedure common in social science based on a combination of qualitative content analysis [29] and Grounded Theory [30]: Interpretive concepts were applied to structure the material along our general research questions, but they were also developed inductively to identify main lines of argument. The eight FGs’ transcripts were treated as one broad sample in which we compared inter-individual arguments to justify or reject specific positions. The final step of our analysis was the identification of main lines of argument by working out a qualitative typology of ideas and values lying behind them.

Results
Although a full commercialization of organ procurement is rejected throughout all focus groups, the language of commodification, instrumentalization and exploitation seems to be densely interwoven with many argumentative threads of the discussion. Several participants refer to organ extraction as “harvesting” [Mr. N., NED_lay], “disemboweling” [Mr. M., GER_lay] or as taking out of “spare parts” [Ms. C., SWE_lay]. This imagery hints at the relevance which background conceptions of self and body already have for attitudes towards organ transplantation in general and not only for the commercialization of organ procurement in particular. Thus, the agricultural image of a field which is harvested might tend to elicit different answers to the question as to what should be permitted than the mechanistic imagery of the body as some piece of machinery with replaceable parts might suggest [31]. In the following section, the main types of images and conceptions of self and body which appeared in our focus groups will be described and explored with respect to their interdependence with attitudes towards organ donation as such and the commercialization of organ procurement in particular.

"Just like cars": the body as private property
Many participants in all focus groups attach great importance to the idea of personal autonomy. For most of them, this idea also comprises bodily self-determination in the sense that one has the right to freely dispose of one’s own body. In the context of organ transplantation, this right plays a crucial role when it comes to decision-making processes. Thus, a Dutch speaker would “start from the point that I have 100% self-determination over my own body” [Mr. N., NED_lay]. And a speaker from Cyprus declares: “What I will do with my body is my own business.” [Mr. A., CYP_lay]

On closer examination, two different conceptions of bodily self-determination seem to present themselves. The first one is premised on the idea that no other person may make any claims with respect to one's own body or is allowed to interfere with one’s decisions concerning it. In the group discussions, this “defensive” aspect of bodily self-determination is stressed when it comes to the question as to whether individuals have any responsibility or obligation to donate, be it towards the family or society at large. In these contexts, bodily self-determination is widely and vehemently postulated as “the right to refuse” [Ms. Q., NED_lay] donation, or, as these Swedish speakers put it: "[T]hey do not have the right to take my organs if I do not want them to." [Mr. B., SWE_aff] "No, it must happen by free will." [Ms. W., SWE_aff]

However, the mere absence of third parties’ claims to my body or its parts does not necessarily imply that I myself am entitled to freely dispose of it as I wish. After all, there may still be limits to my bodily self-determination based on religious or “philosophical” considerations (see below). Thus, a German speaker who vehemently stresses the right to refuse donation also states: “I have problems with transplantations anyway because I believe ... that we can’t prolong life artificially and just for kicks, or replace or manipulate it, because life as such ... has another sense than immortality” [Mr. U., GER_lay]. In this respect, the second conception of bodily self-determination goes much farther, the postulate being that one has an unrestricted right to actively do with one's body whatever one likes. In the focus groups, this “empowering” aspect of free choice and self-development in view of one's body primarily comes into play when future technological scenarios such as enhancement or infinite organ replacement are discussed and assessed:

[...] as long as it remains your own choice – referring to what you said about getting new livers again and
again while your mind wears away – as long as it remains your own choice whether you get a new liver or not then in my opinion there is no problem. When at a certain point you say: well, I am seventy years old, all this is not necessary for me, let me just await my own time, then isn’t that just fine? [...] But if somebody else DOES choose to lengthen his life with new organs again and again, I think it is up to him.” [Ms. R., NED_lay]

In the group discussions, the idea of bodily self-determination is frequently addressed in terms of ownership. The notion "that [...] my body belongs to me" [Mr. I., GER_lay] appears to be deeply rooted in everyday intuition because it is often presented as a consensual and nearly self-evident point requiring no further justification, as a Dutch speaker’s argument against obligatory donation shows. As he says: “Everybody owns his own... has the right to dispose of his own body... It’s my body.” [Mr. N, NED_lay]

This idea of bodily self-determination in terms of ownership seems to bring the human body in line with other pieces of private property. On closer inspection, however, the application of this ownership paradigm does not necessarily imply approval of commercialization in the sense of making money with one’s body or its parts. On the contrary, money often seems to be perceived as a factor which has the potential to impede self-determination by corrupting persons and distorting their own proper will, that way inducing them to do things they would not do otherwise. Thus, the autonomy and authenticity of decisions concerning the body can be called into doubt when financial motives are involved since this is seen as "something different than voluntary registration" [Ms. D., NED_aff]. Against the background of similar considerations, German participants discussing the obligatory psychological test in the case of living donation even compare financial incentives with other constraints on the freedom of decision such as psychological pressure in the family context.

On the other hand, arguments for bodily self-determination do show a certain affinity to a particular kind of body conception. Thus, especially when discussing the pros and cons of a future scenario in which self-preservation through infinite organ replacement becomes technically feasible, the participants frequently employ images from the sphere of handicraft or engineering which suggest analogies with the reparation of machinery in order to address and articulate their position: “It actually will be just like cars: Well, gosh, the radiator is broken or won’t live long: out with it, put a new one in.” [Mr. N., NED_lay]

Such descriptions of the human body within the framework of a mechanistic paradigm show a certain tendency towards accentuating aspects of functionality and performance when describing the body and its parts. These aspects are usually also described in terms of mechanistic and technological images such as automobiles, comparing organ transplantation to “fixing a car” [Ms. E., CYP_aff]. Such is the case in this statement made by a participant from the Netherlands:

“I have got ‘Mercedes’-lungs. I had an argument with my physician: I want ‘Mercedes’-lungs, or else I want to die. I mean it, I really said it like this. I have got ‘Mercedes’-lungs, I don’t want a ‘Lada’. And then it was: Mrs. V. – I have got ‘Mercedes’-lungs for you. Let’s say it like this...” [Ms. V., NED_aff].

This mechanistic focus on functionality and performance seems to correspond to a tendency to relativize all other aspects of the body and thus to regard it like a mere "commodity". Hence, in discussing the provenance of a donor organ, some participants almost exclusively discuss the functional capabilities of the organ, explicitly denying that any other features (artificial/organic, human/non-human, living/dead, male/female) play any role. Moreover, from this perspective, organs are bereft of any symbolic meaning and do not have any significance for the person, the sentiment being that "only the mind can change somebody, the parts do not change a human being." [Ms. O., CYP_lay]

This disregard of all aspects except for functionality and performance certainly plays no small role in the fact that mechanistic body conceptions generally tend to promote quite a positive and optimistic attitude towards the technological possibilities of modern biomedicine, as is expressed in this statement from the Swedish group:

“So, one should probably not have an altogether negative attitude towards this [an overall replacement of organs]. Since it can easily become, as we said, like science fiction, let us replace this, let us replace ...that. Just like when you take your car to the garage, it is coughing and such, yes, let us replace that and fix that and then you are off again.” [Mr. B., SWE_aff]

"The human being is not a car": the body as part of a larger order

On the other hand, some lay people and patients in all four European countries also point out several limitations to autonomy and the free disposal of one’s own body. One of these limitations arises from the belief that the body is not merely a piece of machinery with replaceable components, but an organic entity with its own intrinsic structure and dynamics which resist external interventions.

“But a human being is not a car.” [Mr. F., NED_lay]

“No. That's right. It's being loaded just as heavy, but it is not a car.” [Mr. N., NED_lay] "And what do you
mean by that?" [Moderator] "Well, a car: that is material, it doesn't talk back, though it does wear out too... but well, a human being is just something really different, a lot more sensitive too... well, how do you express that. It is not a thing, it is... well." [Mr. F., NED_lay]

In contrast to aforementioned mechanistic ideas, this more organicistic conception is rarely ever articulated in a direct and positive manner. This means that instead of explaining their conception of the body by means of explicit terms or images, the respective speakers often tend to address it indirectly, that is, by negating and rejecting mechanistic descriptions. Nevertheless, these conceptions of the body seem to have important implications for peoples' views and attitudes. They often correspond to a reluctant, skeptical stance towards science and the conviction that there are moral limits to technological possibilities. Especially when moral directives cannot be derived from the principle of self-determination, e.g. in the case of proxy decisions for deceased relatives, the conception of the holistic or organic nature of the human being and its body is brought to bear as a moral orientation which even has the potential to override relatives' presumptions:

"Well, if there is no decision, I mean it is clear that nothing should be taken out. I mean this is crystal clear. Because a human being as such is not a spare parts store. Well, for me, this wouldn't be ethically acceptable at all." [Mr. U., GER_lay]

This sense that certain limits are given can be related to the idea that nature itself has some sort of intrinsic, self-contained order that sets limits to all human interventions. In part, this notion is based on the religious image of nature as divine creation. Thus, under the premise that the human being was created by God and embodies divine will, one Dutch speaker interprets the body in a teleological manner as "a creation with a goal" [Mr. F., NED_lay].

On the other hand, the insistence on limits which is associated with organicist views is sometimes embedded in the non-religious idea of a natural order of things, which imposes certain limits on human action and invests human life with certain aims. This conviction often manifests itself when speakers refer to nature or natural entities like the body in a moral line of argument or qualify interventions in moral terms, calling them "natural" or "unnatural."

Such underlying notions of a natural order are sometimes accompanied by the conviction that one has the responsibility to leave the body as it is and instead adapt one's own behavior or way of life to the conditions set by one's natural bodily constitution. Thus, the aforementioned German speaker continues, saying that "I have no right to change my body in a way that I change parts there. Well, if it no longer functions, I will have to find a way to deal with the consequences of that, that is to say to deal with it without operation" [Mr. U., GER_lay]. And a participant from the Dutch group seems to proceed from the idea of a divine natural teleology in which everything that occurs has a function:

"I think you have been created for good reason, with two kidneys." [Mr. F., NED_lay] "You have a kind of back-up inside." [Mr. N., NED_lay] "Yes." [Mr. F., NED_lay] "You shouldn't start fiddling with people in this respect. See, those things are there, you are born like that and they have a function. Why do you have two, why not one?" [Mr. Y., NED_lay]

In this line of thought, the body is often perceived less as a passive, irresponsible object which is separate from the self than as something more or less congruent with the person as such. One way to conceptualize this monistic intuition of an embodied self is to speak of the body as an instance with its own inherent "authority" or "wisdom" which can influence a person's attitudes, behaviors and lifestyles:

"I guess there are also signs somehow from your body, that, in a way you can't continue your life-style or something like that ... No idea, if you smoke. Someday you'll get, everything doesn't look like it should be anymore or so. I think all these things are hints and challenges, which will help you in a way to find out what to change, and that you can change it, and that it needs to be done." [Ms. G., GER_lay]

Such monistic conceptions can have a great impact when it comes to attitudes towards organ donation. Thus, they seem to promote the idea that (a part of) the donor lives on in the body of the recipient via organ transplantation. As this affected speaker from Cyprus explains, if body and soul are – more or less – congruent, then a transfer of physical parts can appear as a transfer of portions of one person to another:

"I would know that a part of my child would breathe and live in another body and I would have a part of my child in life. Apart from saving a life, a part of child, either an eye or a kidney or whatever, would be alive." [Ms. E., CYP_aff]

The notion that (a part of) the donor lives on in the recipient via organ transplantation makes it difficult to view or treat organs as fungible commodities. Thus, many speakers speculate as to whether attributes of the donor "may be transferred to somebody psychosomatically and change a person." [Mr. H., CYP_aff] Although such considerations
are often articulated in a slightly facetious manner, they still play a major role in discussions, especially for the affected people. Attributes which are considered to be potentially transferable are e.g. character traits, preferences or aversions, talents or even hobbies:

"I would like to say something I read in a newspaper seven years ago in Canada. A woman received a kidney from a deceased donor. When she went home she wanted to have a beer and a hamburger everyday at lunch time, something that she never did in her life. Thus, she wanted to find out who the donor was. She discovered and the donor used to do this everyday at lunch time..." [Mr. K., CYP_aff] "So, these things are transferred." [Mr. H., CYP_aff]

"The brain makes us special": meaningful organs

The aforementioned complexes of self and body conceptions do not constitute two distinct, monolithic blocks. There are contradictions within the camps and floating boundaries between them. Thus, within the dualistic framework of the property paradigm, the brain often receives a specific status. It is identified as the physical basis of a person's mind, its anchorage in the body, so to speak, and thus the locus of personal identity. In this perspective, the brain consequently marks a logical and technical limit of bodily self-determination since it accommodates the self itself: the subject of self-determination.

"There is one single organ that of course cannot be replaced - that's the brain. That's what makes us special. If we did replace it, in reality we actually wouldn't replace the brain, rather we would give the brain a different body. Since it is the brain that makes you a personality. Other than that I'm in favor of replacing all organs as soon as this can be done technically, biologically." [Mr. S., GER_aff]

Interestingly, one Dutch participant also holds that the genitals should be excepted from transplantation because he regards them as relevant for personal identity, as well, due to progenitory considerations:

"I think there are two organs that certainly shouldn't be transplanted and those are the brains and the genitals. Because I think they do influence who you are. Brains definitely, I think that you become a wholly different person. Namely the other person. They can not do it [now], but if they could. And with the genitals – you do not beget your own children, but someone else's, suppose you would undergo a transplant as a man. So that's ... not even allowed." [Mr. T., NED_aff]

Eventually, in one Cypriot group, a discussion about the status of the eyes evolved, indicating that some participants also consider them as relevant to personal identity. In this context, the special status of the eyes is not based on their visibility, alone; they are rather described as a kind of gateway to the person's inner self:

"Ms. X. has said something earlier. That is, "I think it is better if the eyes of the child live..." [Moderator] "Not only the eyes. But the issue of eyes has impressed me because I had heard about such a case in the past." [Ms. X., CYP_lay] "Would it be remarkable because we see the eyes whereas we don't see the liver or the kidney?" [Moderator] "You see the person through the eyes" [Ms. O., CYP_lay].

The view that the brain has an exceptional status has significant consequences for an evaluation of organ transplantation in at least two respects. First of all, it establishes certain reasons for accepting the occurrence of brain death as marking the death of a person as such. If personal identity is an exclusively spiritual phenomenon which is based on brain functions but detached from the rest of the body, an irreversible breakdown of brain functions simultaneously marks the death of the person as a whole, leaving only a "living body":

"I think that the body may be still alive but to me this person would be dead... perhaps I may not say that he/she is dead, perhaps I would say that the body lives and therefore I would kill it by myself in order to take the organs and give them to somebody else... because the body lives. But in this case I would perhaps say that "yes, I have no problem" because I would give life to other people. Perhaps I would take life by myself but I would give it to other people because I would know that it was over." [Mr. L., CYP_lay]

Secondly, on the basis of the notion that the brain has a particular status, several speakers, especially in the groups of lay people, also strictly reject any speculations about the possibility of transmitting personality or personal characteristics through transplantation of other organs, since "[p]ersonality does not come with the heart." [Ms. P., SWE_lay]:

"But it is a technical organ, I mean, someone's hobbies don't reside in his kidney. Perhaps it resides in your brains, but my kidneys don't indicate that I love sport. At the utmost they have been influenced by that, that perhaps they are in better shape, but that implies only their technical state. And that could perfectly fit in someone else's body." [Ms. Z., NED_lay]

A transplant receiver from the Dutch group who declares that he is "not so sensitive to what I will disrespectfully call "ghost stories"" (i.e. personality-transmission narratives) even offers an alternative, exclusively naturalistic explanation referring to
"...the physical phenomenon that a tissue has a certain dependence on a certain substance, you know your 'tostis', and that the desire comes with that. ..." [Mr. J., NED_aff]

Interestingly, in the course of the discussion, the selfsame patient also states that his down-to-earth naturalism might be a coping strategy to avoid emotional stress. This stress could be induced by thinking about "his" organ donor and "to protect myself from that, also because I’m afraid I would get too carried away" [Mr. J., NED_aff].

Discussion
Throughout all group discussions, we actually found a great number of references to cultural images and conceptions of self and body. On our level of analysis we could not detect any national differences. Three main positions seem to present themselves in all four European countries: On the one hand, arguments in favor of maximum bodily self-determination are often articulated in terms of ownership of the body. In this context, body conceptions which address the body as some kind of machine composed of single elements which can be replaced by functional equivalents are particularly prominent. In contrast, limits to bodily self-determination are often expressed against the background of a more or less articulate notion that human beings and the human body belong to some higher realm, be it that of divine creation or of a natural order of things. Finally, there are arguments which accentuate specific organs, mainly the brain, but also the genitals and the eyes, thus implying more differentiated conceptions of bodily self-determination and unavailability.

These findings show certain similarities to the results of previous studies [32]. However, the body-self conceptions we found apparently do not possess the character of explicit positions based on articulate arguments; on the contrary, they seem to operate as background notions that are deeply rooted in particular cultural customs and traditions [33]. Moreover, their connections to peoples’ attitudes towards organ donation and its commercialization are far more complex and difficult to trace than the scheme of Joralemon and Cox suggests [25]. Thus, although the participants frequently refer to the notion of ownership when talking about the human body, this does not necessarily imply that they consider the body as some piece of private property available for commerce. On the contrary, the concept of ownership often rather seems to serve as a metaphor for autonomy and bodily self-determination, principles which can as well imply a rejection of commercialization. In this respect, the idea of self-ownership seems to be at least ambivalent [34]. Moreover, claiming one’s right to bodily self-determination can serve as a basis for rejecting third parties’ claims to one’s body and organs as well as for justifying extensive use of the technological possibilities of transplantation medicine. Those who held that limits are placed on bodily self-determination, on the other hand, often based their arguments on convictions which refer to natural order or divine creation. These conceptions, however, can be used to reject organ transplantation or commodification as unnatural or against god’s will, but also prepare the ground for the idea that a person has no exclusive rights over her own body. Finally, there is evidence of certain "organocentric" conceptions of the body which identify particular organs as central to personal identity. Such organs may demarcate a definite limit to any technical modification, transplantation, or commercialization, the notion being that these practices would affect the personhood and self-understanding of both, donors and receivers. But their identification seems to depend on socio-cultural and bio-philosophical background assumptions which are embedded in culturally and historically variable contexts (see table 1).

Conclusion
Although more and broader representative research on these topics would be necessary and valuable, our sample allows conclusions that could inform applied ethics and constitute hypotheses for further sociological and anthropological research. Thus, the way we found lay people and patients to think about the body and organ donation may correspond with some of the academic philosophical and anthropological positions on commodification described above. But in contrast to academic authors’ restriction to (or preference for) one single paradigm, we observe a plurality of different body conceptions among the public which are interwoven with their attitudes towards transplantation medicine in rather complex ways.

Against this backdrop, we conclude that the language of commodification is much too simple to capture what is at stake in everyday life intuitions about organ donation and organ sale. Those who base their evaluation of commercialization in organ procurement on a (pro or con) stance to commodification should be aware of the variety of ideas regarding the human body. This is necessary in order to reflect the anthropological assumptions implicit in their own arguments and their prevalence on a socio-political level (for the public and those who would be motivated to donate or sell their organs). Whether there is any intersubjectively graspable way of ever proving the adequacy or plausibility of a particular conception of the human body is doubtful, however. Therefore, the more interesting question is how bioethical discourse and political practices confront the plurality of body-self conceptions in the public as a given reality. We see at least two basic possibilities:

On the one hand, one could defend an "anthropologically informed" position, arguing that the body has a particular
constitution which makes it either resist or suit commodification. This position would take on a certain expertocratic air since it would seem to claim definitive objective insights into the nature of human beings and their corporeal existence. Besides the epistemological question of how such insights could be gained and justified in the first place, it would be interesting to see how this approach would handle or "sublate" recent plurality. How, for example, would it deal with uninformed, ignorant or disinterested lay people who simply insist on having their own views on body and self? Given the fact that in modern, liberal democracies not superior insights, but the will of the majority determines (within the limits of constitutional rights and democratic procedures) the legitimacy of political decisions, there seems to be no way of imposing certain body conceptions on those who simply do not accept them. Thus, when it comes to ethical recommendations and political consultation, anthropological approaches will have to find a way to incorporate public attitudes and psychological images as well as socio-cultural conceptions of the body instead of simply insisting on the superiority of particular expert theories.

On the other hand, one could take a liberal approach and try to get rid of all substantial anthropological or metaphysical assumptions from the very start in order to approximate a "neutral" framework for the peaceful coexistence of a plurality of worldviews. In this spirit of tolerance, however, one must be all the more aware of some liberal thinkers' affinity to Lockean self-ownership and the distinct world view of modern science which imply and promote particular mechanistic conceptions of nature, the self and the body [23]. To this end, a liberal position might have to abandon the pretense that they take an agnostic perspective on the body and refrain from addressing existential questions, engaging – instead – in an explicit discussion on the plurality of existing conceptions of the body. This way, liberal ideology would not demand exclusion of the body from public discourse, but rather explicit admission, acknowledgement and protection of the plurality of ideas which are attached to it, e.g. through the development of legal regulations which are not based on any fixed body-related conceptions.

The sketched heuristic distinction between the "anthropologically informed" approach and the liberal approach should not be confused with other prominent classifications such as the one of "bioconservatism" versus "transhumanism" in the debate on human enhancement [35]. Our distinction is located on a more general level insofar as it refers to bioethical and political approaches towards the plurality of body conceptions while "bioconservatism" and "transhumanism" rather stand for two specific positions within this plurality. Hence, in the perspective of our distinction, both positions can be advanced in an "anthropologically informed" as well as in a liberal manner, depending on their way of dealing with plurality. Thus, the "transhumanist" stance that "current human nature is improvable through the use of applied science and other rational methods" ([35], p. 202) rather seems to express an "anthropologically informed" approach because it obviously claims insights into the existence and qualities of human nature. And the "bioconservative" counter position can definitely represent a liberal approach as long as it does not rely on a particular conception of human nature, but rather mirrors respect for actual "bioconservative" consensus among the general public.

Another prominent bioethical and political debate in which the capacities of both, "anthropologically informed" approaches as well as liberal approaches, are challenged, evolves around the problem of death in the context of modern biomedicine. On the one hand, a conception of death, explicit or not, is of central importance for many fields of biomedical practice, from organ procurement policies to the withdrawal of life sustaining treatment. On the other hand, however, it is widely agreed that death is not simply an objective scientific fact that can be determined by means of empirical research. Understandings of death are always embedded in cultural, religious or metaphysical views. Nowadays, there actually exists a wide plurality of such world views which can lead to quite different conceptions of death [36]. In this situation, the State of New Jersey's law on brain death [37], as well as more recent legislation in Japan [38] seem to point towards a liberal strategy which allows the individual to choose a definition of death for him or herself. From an anthropologically informed point of view, however, it can be questioned whether this really constitutes a satisfactory solution. After all, assuming (and be it just for the sake of the argument) that there is one definite answer to the question of death, a contravening practice would simply amount to an instance of killing, although perhaps at the request of the person killed.

Against this background, the two approaches could possibly rather be understood in the sense of two diametrical, but at the same time complementary and mutually corrective perspectives. Both seem to be needed for an adequate consideration of plurality in bioethical and political debates touching upon body conceptions. The liberal perspective, on the one hand, makes us aware of the wide range of individual ideas regarding the body in modern pluralistic societies, thus preventing us from naively taking our own intuitive views as self evident facts. And the "anthropologically informed" perspective, on the other hand, provokes us to really take each of these conceptions seriously, respect their claims for validity and consider their ideational and normative implications as well as their social consequences – rather than just content our-
selves with comfortable illusions of indifferent coexistence or a superficial “anything goes”.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
Both authors have contributed equally to the article.

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References
Commentary

The end of the era of generosity? Global health amid economic crisis

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Abstract

In the past decade donor commitments to health have increased by 200 percent. Correspondingly, there has been a swell of new players in the global health landscape. The unprecedented, global response to a single disease, HIV/AIDS, has been responsible for a substantial portion of this boon. Numerous health success have followed this windfall of funding and attention, yet the food, fuel, and economic crises of 2008 have shown the vulnerabilities of health and development initiatives focused on short term wins and reliant on a constant flow of foreign funding. For too long, the international community has responded to global health and development challenges with emergency solutions that often reflect the donor’s priorities, values, and political leanings, rather than funding durable health systems that can withstand crises. Progress towards achieving the Millennium Development Goals has stalled in many countries. Disease specific initiatives have weakened health systems and limited efforts to improve maternal and child health. As we enter this era of scarce resources, there is a need to return to the foundations of the Alma Ata Declaration signed thirty years ago with the goal of providing universal access to primary healthcare. The global health community must now objectively evaluate how we can most effectively respond to the crises of 2008 and take advantage of this moment of extraordinary attention for global health and translate it into long term, sustainable health improvements for all.

Introduction

Over the past eight years global health has taken center stage in an era of historic generosity as the wealthy world has committed substantial resources to tackle poverty and disease in developing countries. Between 2000 and 2006, estimated donor commitments for global health increased by 200 percent – from $15 billion to $45 billion [1]. Correspondingly, there has been a massive swell in the number of nonprofit organizations (NGOs), faith based groups, and private actors contributing to this boon.

Remarkable achievements have followed this windfall of funding and attention, including numbers of lives saved, children vaccinated, people placed on HIV/AIDS medication, institutional improvements, and rising commitment by developing countries themselves, to the public goods needs of their people. But the economic, food, and fuel crises of 2008 threaten to erase these achievements, pushing those peoples of the world that saw hope on their horizons back into dire poverty, disease, and despair. Will rising food costs, economic uncertainty, and an increased focus on problems within their own borders erode the
wealthy world’s commitment to poverty eradication and global health as we enter an era of scarce resources?

Past is prelude
Thirty years ago, in the midst of the Cold War, representatives from 134 World Health Organization (WHO) member states gathered in the former Soviet Republic city of Alma-Ata. East and west, north and south convened to discuss how to provide essential public health goods and access to healthcare for the world’s poorest. More historic than the gathering of communist and capitalist nations, was the recognition by all parties of health as a key determinant of development rather than an outcome of medical interventions. On September 12, 1978 the Alma-Ata Declaration was born, stating that primary health care "based on practical, scientifically sound, and socially acceptable methods and technology made universally acceptable through people's full participation," [2] was key to meeting the goal of providing health care for all by the year 2000. In the past three decades progress has been made. A baby born in Alma-Ata in 1978 had a 7.3 percent risk of dying before his or her fifth birthday. The risk for a baby born today, in what is now Almaty, Kazakhstan, is now only 2.9 percent and this reduction mirrors the average worldwide reduction in child mortality over the last thirty years [3]. Yet today, the landscape of global health is drastically different from that of three decades ago. The effects of globalization, spread of infectious diseases, rapid urbanization, and increasing disparities between rich and poor have, by necessity, shifted the world’s focus from meeting the goal of access to universal primary health care to finding emergency, stopgap solutions to ease the suffering caused by high mortality crises, such as HIV/AIDS and humanitarian disasters.

The emergence of HIV/AIDS fundamentally transformed the way in which the world engaged global health. It shook world leaders out of a long period of a smug belief that microbes would be conquered as a corollary of rising economic growth. It also awoke the average citizen to the gross disparities in access to health that exist between rich and poor countries, mobilizing remarkable numbers of wealthy world citizens to take action on behalf of people living both great cultural and physical distances from themselves. The political zeal and advocacy efforts generated by the AIDS pandemic pushed health to the top of the international development agenda. The fight against HIV/AIDS rallied tremendous political and financial support for global health, while at the same time, moving investments in health from infrastructure: clinics, roads, clean water, sanitation, medical supplies, and the training and management of skilled medical personnel, to funding disease specific initiatives with emergency, short term targets, and often unsustainable results.

Building on success
Over the past decade, there has been a massive increase in new global health players. Private foundations, such as the Bill and Melinda Gates Foundation, innovative global funds, such as the GAVI Alliance and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), and engaged corporate actors have transformed the landscape of global health with their access to substantive funding streams and ability to respond more rapidly to the perceived needs on the ground. In addition to these multilateral initiatives, the United States, under the Bush Administration, made an unprecedented bilateral commitment to HIV/AIDS in 2003 under the President's Emergency Plan For AIDS Relief (PEPFAR) and to malaria as part of the President's Malaria Initiative (PMI). The excitement generated by new global health players and monies has mobilized the citizenry of wealthy countries – whether buying a red iPod as part of the RED campaign to support HIV/AIDS efforts, or wearing a white bracelet to raise awareness of issues of global poverty in the ONE campaign – the average rich world citizen is engaged in global health like never before.

Since 2000, great achievements have been made. By October 2008, the GFATM had dispersed $6.4 billion worth of grants for country-designed programs in a mechanism that is both without precedent, and empirically successful in achieving its targets some 80 percent of the time [4]. PEPFAR had, by March 31, 2008, started 1.73 million people on antiretroviral treatment for HIV infection, and provided antiretroviral prophylaxis for more than one million pregnant women to prevent infant in utero infection [5]. The combined donor, GFATM, and United Nations (UN) efforts to tackle malaria had, by the end of 2008, pushed down deaths due to malaria by fifty percent in key African and Asian countries, in large part due to dispersal of pesticide-treated mosquito nets and insecticide spraying campaigns [6].
2008 has been a historic year for global health. In June, the U.S. Congress passed the PEPFAR reauthorization act with nearly unanimous support, raising the U.S. commitment to treating and preventing HIV/AIDS and Malaria, and Tuberculosis infections in fifteen target countries to an astounding $48 billion over the course of the next five years [7]. In September, the UN, in partnership with a variety of governments and NGOs, launched the Global Malaria Action Plan – aimed at eradicating Malaria worldwide by 2015 [8]. The effort has received a $3 billion dollar boost from a dozen organizations, led by the World Bank and the Bill and Melinda Gates Foundation [9].

Yet, despite large investments, audacious goals, and widespread attention and support for global health, 2008 has also been a year that has brought into question the sustainability and durability of many of these efforts. The economic, food, and fuel crises of 2008 have shown the vulnerabilities of health systems reliant on a constant flow of foreign funding. For too long, the international community has responded to global health and development challenges with emergency, short term solutions that often reflect the donor’s priorities, values and political leanings, rather than funding durable health systems that can withstand crises.

In October 2008, the World Bank President, Robert Zoellick, warned, "While people in the developed world are focused on the financial crisis, many forget that a human crisis is rapidly unfolding in developing countries. It is pushing poor people to the brink of survival," where the number of malnourished people globally will grow by forty-four million, to 967 million in 2008, as several countries experienced double-digit food inflation [10].

The food crisis has shown how unprepared health authorities often are to changes in the broader environment. In the past year, the cost of wheat has risen by 130 percent, rice by 120 percent, with corn and soy prices not far behind. As a result, millions of people are starving and at least 100 million more people will be pushed further into poverty [11]. The International Fund for Agricultural has estimated that the number of food-insecure people in the world will rise by sixteen million for every percentage increase in the prices of staple goods [12]. We have only begun to witness the impact of hedge fund trading in New York on the lives of some two billion people living in poverty. Instead of investing in long term agricultural development schemes, the majority of donor funding over the past decade has focused on providing emergency food aid to countries on the brink of widespread famine. We have jumped from one emergency band-aid solution to the next, instead of focusing on the structural causes of food insecurity.

2008 also marks the midway point for achievement of the MDGs [13]. In September, the Office of the UN Secretary General concluded that both funding and program development were falling far short of those needed to reach the 2015 MDGs, and at least six of the eight targets were on course to fail. MDG 5 – maternal survival – has not shown significant improvement and no region is on track to achieve the goal at current rates [13]. The target of MDG 1 – to reduce the proportion of people who suffer from extreme poverty and hunger – is in reverse. Well before the impact of the financial meltdown was felt, donor support had declined. Aid dropped 8.4 percent in 2007, after a 4.7 percent drop in 2006. The Group of 8 industrialized nations pledged in 2005 to donate more than $25 billion to Africa by 2010, but just $4 billion has actually been delivered [14].

International institutions and governments heavily reliant on steady inflow of foreign donor funding are now frantically trying to resolve how to continue the operations of their health programs, as wealthy nations are paying hundreds of billions to rescue the world’s financial industry. Undoubtedly, the economic crisis will crimp humanitarian aid, and international efforts to fight disease and alleviate poverty. Philanthropic giving from governments, foundations, and corporations is expected to sharply decline as the world tightens its belt and heads into a global recession. "It is not clear what the current financial crisis will mean for low income and emerging economies, but many predictions are highly pessimistic. Margaret Chan, Director General of the WHO, warned in a statement. "In the face of a global recession, fiscal pressures in affluent countries may prompt cuts to official development assistance” [15].

As evidenced over the past thirty years, increased commitments to global health do not automatically equate to sustainable changes in health in individual countries, especially among the poorest of poor. Although health indicators have improved among some groups, we have seen increases in gaps in health outcomes among women, children, and marginalized populations, across regions and within countries. In poor rural areas of western China, the maternal mortality ratio is four times that of urban areas and double that of rural areas in eastern China [16]. Despite the great efforts of many organizations, life expectancy has barely budged in these populations.

Today, the global life expectancy gap is the widest in human history, with a disparity of nearly five decades. Each day around 28,000 children under five die from largely preventable causes and every minute of every day a woman dies of pregnancy-related complications. Recent UN data on maternal mortality show that a woman living...
in Afghanistan or Sierra Leone has a one in eight chance of dying in pregnancy or childbirth. This compares with a one in 4,800 risk for a woman in the United States, and a more than one in 17,400 risk for a mother in Sweden [17]. This logarithmic differential in maternal survival represents the most striking, even egregious, health disparity in the twenty-first century world.

The special challenge of HIV
Increased focus on the urgent management of specific diseases has weakened the ability of health systems to respond to crises. To respond to the AIDS epidemic, the share of global health aid devoted to HIV/AIDS more than doubled between 2000 and 2004 – reflecting the global response to an important need, yet, the share devoted to primary care dropped by almost half during the same time period [18]. Enhancing one program, at the apparent cost to another, merely shifted the face of catastrophe from one health paradigm, to another.

With increased funding, the world has made progress towards the goal of universal access to HIV/AIDS treatment. The number of people on antiretroviral therapy (ARVs) has increased from two per cent to twenty-eight per cent in the last four years [19]. For international donors, making a commitment to provide treatment comes with great responsibility and an ever-increasing price tag. As the number of people infected grows, the number of people that require second line, more expensive, drugs swells. But treatment alone will not end the AIDS pandemic. For every HIV+ individual that went on ARVs in 2006, six more people contracted the virus [20,21].

The current focus on ARVs risks creating a medicine-dominated response to HIV/AIDS, and diverting attention and funds away from the more fundamental political, social, and economic determinants of poverty and the spread of infectious disease. Many current initiatives are trying to build dams – pharmaceutical dams to hold back the pandemic – but behind those dams the number of newly infected keeps rising, threatening to overflow and drown these efforts.

In many of the countries hardest hit by the pandemic, a large portion of their funding for AIDS medications come from outside donors. For example, in Mozambique, 98 percent of all funding for the country's HIV/AIDS programs comes from outside donors: 78 percent of it is from the U.S. PEPFAR program. Similarly, Uganda is 95 percent dependent on external donors for financing of its HIV/AIDS programs: 73 percent of outside support is from the U.S. PEPFAR program [22]. In both of these cases the nation's extraordinary dependence on external support begs questions about the efforts' sustainability, and country ownership and control. Were the U.S. to suddenly cease underwriting these programs, AIDS patients would die by the thousands for lack of life-extending treatment. As we enter an economic downturn, the sustainability of emergency initiatives, such as PEPFAR, that are 100 percent dependent on a never ending supply of donor dollars, are called into question [23].

Moral hazard amid complexity
Instead of making things simpler and more efficient on the ground, in many cases, the rapid increase in funding and number of global health players has made the mechanisms for delivering aid even more complex. At the developing country level, where these activities are targeted, hundreds of foreign entities are competing for the attention of local governments, civil society interest, and the desperately short supply of trained healthcare workers. Ministers of Health in recipient countries say that their days are over burdened by long lines of NGOs and bilateral program contractors, each demanding their attention. In Mozambique, for example, there are fifty distinct donors funding health and development programming in the country. Of these, nineteen are providing foreign aid directly to the government through budgetary support while the majority provides aid through their own individualized mechanisms or agreements which each require their own monitoring and reporting requirements from recipients [24].

Further exacerbating the difficulties of responding to the health needs of the world’s poorest is the current state of health systems and capacity in the many developing countries. Decades of neglect, coupled with austerity programs imposed by the International Monetary Fund in the 1980s and 1990s, have rendered hospitals, clinics, laboratories and health care workers dangerously deficient. According to the WHO’s World Health Report 2006, there is a shortage of more than four million health care workers in 57 developing countries [25]. Compounding the problem, local healthcare workers often grow so exasperated and demoralized by their dysfunctional health systems that they apply for higher paying jobs abroad, thus accelerating a ‘brain drain’ at home. One quarter of physicians and one in 20 nurses trained in Africa currently work in the 30 industrialized countries in the Organization for Economic Cooperation and Development (OECD) [26]. There is also an internal brain drain within countries as healthcare workers leave public hospitals and health centers lured by more lucrative jobs in clinics run by foreign NGOs, bilateral donors, and faith-based organizations. In Ethiopia, contract staff hired to help implement disease specific programs earned salaries three times greater than regular government health employees [27] and in Malawi, one hospital reported that 88 of its nurses left within an eighteen month period to take better paying jobs in NGOs programs [28].

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A moral path forward

Progress towards achieving the MDGs has slowed in many countries. Disease specific initiatives have weakened health systems and limited efforts to improve maternal and child health and our ability to respond to new health and development crises. The threats posed by newly emerging infectious diseases, climate change, urbanization, and the rise of chronic diseases threatens to erase many of the gains we have achieved. Thirty years on, the concept of providing primary health care for all offers a possible roadmap to attain the MDGs by 2015 and create sustainable, long term investments in health. It is heartening to see that global health leaders have recognized the urgent need to create greater coherence among health initiatives and organizations, and focus funding and attention on basic health system investments to save millions of people every year that now perish needlessly from preventable diseases and find new tools to save still more lives.

Given the scale of the world’s healthcare workers deficit, no progress can be made in the creation of universal primary care systems if models continue to be doctor-based. Even if the world committed today to the most massive medical training exercise in history, the deficit would not be overcome for more than two generations. Only a substantial commitment to building genuinely viable health infrastructures centered on community based workforces, coupled with local profit incentive systems, and global scale supply and inventory management can create primary health systems that can prevent hundreds of millions of deaths due to childbirth complications, pediatric diarrheal diseases, infectious diseases, and the newly emerging chronic diseases of diabetes, heart disease, and cancer.

The crises of 2008 have brought together committed government officials, UN agency leaders, NGOs, faith-based groups, and corporate actors to collectively think about new ways to break out of patterns of charitable giving and move towards real sustainable investments in health utilizing the wealth of resources and technical expertise available both on the ground and within international agencies. A number of promising initiatives, commitments, and programs are beginning to emerge in an effort to improve global health funding efficacy through longer term commitments, more coordinated accountability measures, and inner-agency collaboration mechanisms.

Within the UN system, efforts are underway to improve relations between health-focused UN agencies, and large global initiatives, including, the GAVI Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the Bill & Melinda Gates Foundation. Calling itself the H-8 (health-8: WHO, UNICEF, UNAIDS, UNFPA, World Bank, GFATM, GAVI, and Gates), this alliance has set its top management tiers to the task of talking to one another on a regular basis to clarify the core responsibilities of each agency, and bring coherence and alignment to their activities. Recently, the GAVI Alliance announced that it will increase its funding for strengthening health systems to US$800 million [29]. The WHO dedicated its State of the World Health Report 2008 to a renewed focus on the commitments made in Alma Ata to provide universal primary health care for all [30].

Multiple donor countries have embarked upon new initiatives to make aid more effective. The Norwegian government has recently created the Global Campaign for the Health MDGs and committed to funding one billion dollars over the next ten years towards meeting the goals of reducing child mortality, improving maternal health, and combating HIV/AIDS, malaria and other infectious diseases [31]. In September 2007, a consortium of wealthy governments and private donors announced the creation of the International Health Partnership (IHP) [32]. The IHP seeks to redesign the relationship between donors and recipient nations, to improve transparency, accountability, and cooperation in the programs executed by typically rival agencies. If the IHP succeeds, country governments will have more control over what foreign entities do within their borders, and, in return, will commit to improving all aspects of strategic planning, civil society engagement, and financial processing. The IHP promises longer term financial commitments – up to a full decade – in exchange for commitments from recipients to accountability for every dollar spent at the country level. The goal is respond more efficiently to the immediate needs of developing countries, including health infrastructures, clean water and sanitation systems, health human resources training and support, and microfinance schemes that set realistic long term goals for individual and community development [33].

As a global health community, we must stand back and objectively evaluate how we can most effectively respond to the crises of 2008 and take advantage of this moment of extraordinary attention for global health and translate it into long term, sustainable health improvements for all. On the donor side, existing commitments to global health must be upheld despite economic uncertainty. As President Bush described at a recent White House Summit, "During times of economic crisis, some may be tempted to turn inward – focusing on our problems here at home, while ignoring our interests around the world. This would be a serious mistake" [34].

Times of economic crisis necessitate a strategic evaluation of how to make each dollar, yen, or euro spent on health
and development initiatives more efficient and sustainable. In an effort to make funding more impactful, donors should not put health programs – whether vertical, horizontal or diagonal – in competition with one another. For recipient countries the greatest challenges are in management: juggling precious human resources, external funds and programs, rural versus urban needs, and donor demands. The management balancing act is hard enough on a day to day basis, but must expand to encompass health infrastructure and private sector growth that function on decades long timetables. Achieving such long range strategic targets will require sustained commitment from national leaders, donors, NGOs, and private philanthropies, especially in difficult economic times.

Three decades ago, a previous momentum to put health in the forefront of the development agenda and provide access to health for all was followed by a series of economic disasters – soaring oil prices, debt crisis, multiple economic depressions, and stagflation. The international response to these crises was to enact a series of economic relief strategies that pushed developing countries further into debt and shifted their budgets away from social spending for health, education, welfare, and local infrastructure. The world became distracted from the goal of providing access to health for all, and entrenched in finding emergency, stopgap solutions, instead of tackling the larger structural determinants of poverty and disease.

In this time of financial catastrophe, the onus sits squarely on the shoulders of global health advocates living in the wealthy nations: push your governments and philanthropic institutions to not only maintain their technical and financial commitments to the poor nations of the world, but actually increase the scale of investment to reflect the rising costs of doing good in a troubled world. It is conceivable that 2008 will mark the beginning of the end of the Era of Generosity. But it is equally probable that the economic crisis will usher in a bold new era of investment in the public goods of poor and emerging market nations worldwide. Successful navigation of these turbulent waters will require a shift from the morality of "charity," to that of "change." With "charity" comes dependency and, frankly, a demeaning imbalance of power. If global health advocates seize this moment to move all priorities towards lasting change, and sustainable improvements in life expectancy and human survival, the Era of Generosity could well morph into the progressive turning point, when peoples long locked into desperate poverty and disease started on the road towards permanent transformation.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
Both authors (KS and LG) wrote and revised the manuscript. Both authors read and approved the final manuscript.

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References


Principlism, medical individualism, and health promotion in resource-poor countries: can autonomy-based bioethics promote social justice and population health?

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Abstract

Through its adoption of the biomedical model of disease which promotes medical individualism and its reliance on the individual-based anthropology, mainstream bioethics has predominantly focused on respect for autonomy in the clinical setting and respect for person in the research site, emphasizing self-determination and freedom of choice. However, the emphasis on the individual has often led to moral vacuum, exaggeration of human agency, and a thin (liberal?) conception of justice. Applied to resource-poor countries and communities within developed countries, autonomy-based bioethics fails to address the root causes of diseases and public health crises with which individuals or communities are confronted. A sociological explanation of disease causation is needed to broaden principles of biomedical ethics and provides a renewed understanding of disease, freedom, medical practice, patient-physician relationship, risk and benefit of research and treatment, research priorities, and health policy.

Introduction

Respect for autonomy or respect for persons has tended to be the leading principle of biomedical ethics or research ethics, respectively. This principle historically has its roots in the liberal moral and political tradition of the Enlightenment in Western Europe. Within this tradition, the ethical justification of actions or practices strongly depends on the free decisions of individuals, i.e. an action or practice can only be ethically justified when undertaken without any coercive influence and entered by free and informed agreement. While there have always been disagreements on the details, all theories of autonomy agree on two essential conditions: the first is liberty, specifying the independence from controlling influences; the second is agency, referring to the capacity for intentional action[1]. Used in clinical ethics, autonomy functions primarily to examine decision-making in health care and serves to identify actions that are protected by the rules of informed consent, informed refusal, truth telling, and confidentiality[1]. Autonomy-based approaches are strongly expressed in Tom Beauchamp and James Childress’s classic text Principles of Biomedical Ethics for clinical bioethics and, for research ethics, the influential Belmont Report[1,2].

Many criticisms of autonomy-based bioethics have appeared over the past thirty years from a number of different angles, such as feminism, casuistry, disability rights, multiculturalism, cultural studies, and ethnography. In this article, we take a different approach by exploring what we will call the ‘medical individualism’ that autonomy-based bioethics largely assumes, and by raising questions about the relevance and impact of autonomy-based bioethics in developing countries (and communities within developed equitable ones), especially in light of initiatives to ‘build capacity’ in research sites and to ensure access to healthcare in resource-poor settings. This paper argues that the medical individualism underlying autonomy-based bioethics renders the latter incapable of addressing some of the most pressing bioethical issues in resource-poor settings, which have to do with social justice. The first section of this paper considers some of the limitations of principlism. The second section examines the inability of this approach...
to address social justice concerns in resource-poor countries. Finally, the third section attempts to offer an alternative approach by exploring the contribution of the sociological model of disease causation to research ethics, health justice and health policy.

A brief anatomy of autonomy-based bioethics

One of the major defenders of the centrality of autonomy in bioethics, the British medical ethicist and pediatrician, Raanan Gillon argues that respect for autonomy should hold a primary place among the four principles of biomedical ethics[3]. Other proponents of autonomy, Beauchamp and Childress, define autonomy as a form of personal liberty of action where the individual determines his or her own course of action in accordance with a plan chosen by himself or herself[1]. In application to clinical medicine, respect for autonomy dictates that patients with decision-making ability have a right to voice their medical treatment preferences, and physicians have the concomitant duty to respect those preferences[4]. Like Beauchamp and Childress, Gillon embraces a Millian understanding of autonomy, understanding it as deliberated self rule; the ability and tendency to think for oneself, to make decisions for oneself about the way one wishes to lead one’s life based on that thinking, and then to enact those decisions—is what makes morality—any sort of morality—possible[3]. Given its supreme ethical importance, autonomy is not merely a value to be respected, but a virtue or trait that ought to be actively developed, nurtured and promoted.

According to Gillon, other ethical principles (beneficence, non-maleficence, and justice) presuppose (and can be reduced to) respect for autonomy. Beneficence and non-maleficence toward autonomous moral agents presuppose respect for the autonomy of these agents even when they choose to refuse medical interventions which are life-saving. Gillon also takes an autonomy-centered approach to justice, arguing that responding to people’s needs justly will require respect for those people’s autonomous views, including autonomous rejection of offers to meet their needs; and, more importantly, because providing for people’s needs requires resources, including other people’s resources[3]. To conclude his praise for autonomy, Gillon writes that respect for autonomy contingently builds in a prima facie moral requirement to respect both individual and cultural moral variability[3]. While it is true that not all autonomy-based approaches in bioethics take the explicit and extreme form expressed by Gillon, autonomy continues to be treated implicitly as a primary value in many controversial clinical and research debates, from end of life issues (such as the Terri Shiavo case) to questions of exploitation of research subjects in international health research. When ethical principles conflict, it is often thought that the conflict can be resolved in an ideally impartial way by asking, for example, what the patient wants (or would have wanted) or whether the research subject really understood and freely consented to the procedures described in the research protocol. In this way, the multifarious values involved in the practice of medicine and biomedical research tend to be reduced to the principle of respect for persons, itself narrowly understood as respect for autonomy. Furthermore, the preeminence of autonomy as an ethical value within bioethics is deeply related to the increasing commoditization of medicine in developed countries. For the more that medical practices are justified by reference to patient choice, the more that patients will be viewed as ‘clients’ and health care professionals perceived as ‘service providers’. This model of patient as ‘client’, which is prevalent in the United States of America and some parts of the western world, assumes affluence and power: the (literate) patient has to be capable of understanding and rationally weighing his/her options—possibly even in disagreement with the physician—and be in a position to pay in exchange for services chosen.

Autonomy, exaggeration of human agency, and ethical pluralism

An autonomy-based ethics places the responsibility for medical decision-making largely in the hands of the patient. This raises the descriptive question of whether this conception accurately depicts how clinical decisions are actually made, as well as the normative question about whether such a conception of responsibility should (or should not) function as a universal ideal. In regard to the descriptive issue, patients in resource-poor settings are often not concerned with their ability to determine and shape the course of care. Their arrival at the local health center is the outcome of a long family discussion that led to the collection of money. Sometimes, the patient arrives at the dispensary when the disease has reached its critical stage because the cost of care is too high. The primary expectation of both patient and family is to get the medicine or undergo a medical procedure they need and go back to their workplace. Spending time at the hospital means loss of earnings for them and their families or the diminishment of financial resources. When people can barely afford the cost of care or satisfy the nutritional requirements for a good recovery, the ethics of medical encounter should be understood differently and expressed in different terms than patient choice. Instead of developing a highly-organized medical bureaucracy that cares for the enforcement of patients’ rights and protects medical professionals from accusations of malpractice, it would be more helpful to develop new sets of values that guide medical practice and promote patient participation in the healing relationship. The framing of these values
may encourage and foster a non-confrontational relationship between health professionals and patients in the clinical setting, and include social challenges that influence health in the bioethics agenda. The role of bioethics will then consist in identifying social values and laws that may guide clinical work, restore the social dimension of medicine, connect the macro-determinants of health to medical practice and health system delivery, avoid the fragmentation of healthcare, and advocate for good health policies.

The challenge facing bioethics in resource-poor settings is not then to mislead people with unrealistic promises of autonomy that very few people can indeed achieve, but to articulate moral principles and societal values that are oriented around the promotion of equitable access to care and which broaden the goals of medicine and public health. The goals of medicine cannot be confined to the alleviation of suffering within the clinical setting. Medicine needs to be concerned with the determinants of good and bad health outside the clinical context in order to contribute to evidence-based clinical and public health interventions and education. The major bioethical questions prevalent in resource-poor countries do not essentially revolve around the provision of informed consent at the individual level, but rather around the burning social questions of access to care, commodification and quality of medical care, the relationship between income disparities and health inequalities, the impact of poverty and underdevelopment on population health, priorities in biomedical research, and impacts of gender discrimination on women's health[5,6].

Once the focus is shifted away from the individualistic ‘patient as client’ paradigm, the social problems connected with the domination of medicine by market forces become apparent. If the goal of medicine is to restore health functioning, bioethics should avoid adopting a conception of autonomy that can be used to justify the domination of healthcare delivery by market forces alone and (wittingly or unwittingly) legitimizing health care systems that exclude the needy sick because the latter are unable to pay (or co-pay) for services or afford hefty medical insurance premiums. Even those bioethicists who promote market-driven medicine based on a libertarian anthropology[7,8] ought to carefully articulate alternative ethical values for health care and biomedical research, if they not to be lured into a ‘self-defeating’ conception of medicine. As an example of the latter tendency, Robert Sade considers medicine as a market commodity and understands medical practice as sets of skills that physicians are entitled to sell on the marketplace to make as much money as possible. Even the cries of the destitute sick or government regulatory function cannot restrict the physicians’ appetite for greater financial reward. Sade’s anthropology and approach to medicine is based on the assumption that individuals have the right to select the values that they deem necessary to sustain one’s own life. They are also entitled to exercise their judgment to take the best course of action to achieve chosen values. Finally, they have the right to dispose of those values, once gained, in any way one chooses, without coercion by other men[7]. Similarly, Tristram Engelhardt protects human freedom to the point of ignoring the fact that the concern that we have for each other makes life in society possible. For him, as long as freedom functions as a side constraint, and as long as the moral community is based on respect for freedom and not force, individual persons will have the possibility of holding entitlements[8], Engelhardt’s suggestion is paradoxical because, in trying to protect freedom of individuals to use their resources to access health care and other goods, he does not ensure that those with few resources have the freedom to obtain health care. Realistically, a genuine affirmation of autonomy cannot result in action informed or motivated by the desire to avoid being a responsible member of one’s moral community[9]. Here, responsibility means that one should not exploit others by using autonomy as a warrant to market-driven medicine or profit-seeking attitudes. Once medicine is understood as a commoditized product like any other, those who cannot afford services are merely unfortunate consumers. In this way, a strong emphasis on autonomy can contribute to a culture in which healing and health promotion are no longer at the center of clinical practice and biomedical research.

One can hardly refute the fact that complex social and economic forces have placed patient autonomy at the center of medical ethics, and thereby undermined the age-old ethic of physician beneficence[10]. This change is sustained by waning trust in the traditional patient-physician relationship. With the control of medicine by the forces of the market, patients have become consumers of a market commodity called medical care. As a result of this change, the clinical relationship between the patient and physician begins to be seen as a contract and not as a covenant of care as it was in the past. Autonomy-based bioethics has a tendency to distort the relationship between individuals and the world. On the one hand, it exaggerates the power and range of individual agency; furthermore, it underestimates the impact of society, culture and environment, both on individual decision-making and on health. If persons are regarded as atomistic, certain defensive notions of individualistic rights-based autonomy prevail. If a relational construction of personal identity is employed instead, then respect for autonomy becomes part of a wider morality of relationship and care[1]. ‘Atomistic autonomy’ is divisive and lacks social rootedness while relational autonomy brings about trust and communality. The second
version of autonomy, which reveals our true self in society, presents the possibility of placing trust and partnership at the center of the patient-physician relationship. With such an understanding of personhood, bioethics can better balance its concerns over choices and actions with those of relationship and responsibility. A more plausible philosophical anthropology would conceive individuals as entangled in the world, both capable of acting on it and subject to being affected by it.

Reflection on the notion of disease, both infectious and chronic, can contribute to a more plausible philosophical anthropology for bioethics. Infectious diseases question our understanding of autonomous agency in two important ways. First, as both a victim and a vector, a patient cannot be simply seen as a rational agent who has the final ethical word on his own decisions. Both vulnerability to infection and threat of transmission to others should shape our understanding of patient agency. Second, the concept of choice that shapes our conception of agency in bioethics can no longer be understood in isolation from society. Risk of acquiring and transmitting infectious diseases reflects the patient’s interconnectedness with others and the biological environment, an interconnectedness which is always there even when infectious disease is not present[11]. Although the values and desires of the patient obviously need to be considered, the ideal of the autonomous agent will remain a fiction unless the social context of the patient’s vulnerability is also considered. For other reasons, chronic disease also challenges our understanding of autonomy, especially when the patient finds it hard to manage his or her chronic condition. Family or friends stand as important resources for decision-making and long-term daily care for chronic diseases. We should then recognize that the family and community, which may play an important role in patient care, are part of the resource needed by the patient to exercise agency[12]. More and more, it is becoming obvious that the promotion of patients’ agency requires serious consideration of patients’ best interests in a broader way. Against the backdrop of contemporary institutional medicine, family solidarity is more important than ever to help maintain patient’s dignity and agency throughout stressful time[13]. Exclusion of family and relatives from decision-making on account of respect for individual autonomy does not necessarily serve patients’ best interest. Furthermore, primary care, because of its focus on treatment and prevention of chronic and infectious diseases, is the domain of medicine that goes beyond techno-medical solutions to consider patients as persons with their stories, relationships, and social environment in which they live. Consequently, primary care should essentially rely on socially-grounded values rather than on desocialized principles[14].

Family and social relationships are important in the context of clinical medicine. However, we cannot underestimate the importance of individual freedom. We simply reject strong claims that do not have any social rootedness. It would be almost unsound and socially untrue to radically endorse autonomy to the detriment of an ethic of responsibility and socially-based care because they are mutually interdependent, and a complete account of medicine’s moral axis requires that they be integrated. This reorientation is crucial for reasserting the ethos of clinical medicine, whose fundamental mandate remains the care of others[10].

Autonomy ethics and the ‘moral vacuum’
For Immanuel Kant, respect for persons never refers to the freedom to be left alone. Kant’s understanding of respect for autonomy provides the ground for the categorical imperative, which he formulated in five different ways. The third formulation, “act so that you treat humanity whether in your own person or in that of another, always as an end and never as means only”[15] cannot be reduced to the respect for autonomy often found in the bioethics literature. The view of autonomy commonly found among individuals and in some of the bioethics literature in North America or Western culture is more in tune with John Stuart Mill’s formulation of liberty: do not intrude on the freedom of any person by an invasion foreign to his or her own wishes and values. When Kant talks about autonomy, he does not imply that one should act according to one’s own desires, unconstrained by a balanced consideration of one’s situation as a being-among-others[9]. Instead, he refers to the dignity of humans who are capable of making for themselves and others universal law. Hence, autonomy, rightly construed… results in action informed and motivated by the desire to be responsible member of one’s moral community (the ground of one’s being-among-others)[9]. Kantian autonomy is tied the moral agent’s search for the truth and respectable conduct. The autonomous subject does not act in accordance to his or her primary inclination. Kantian autonomy is applied to actions performed when the will is freed from any selfish determination. When humans treat each other as ends and never as means merely, there arises a systematic union of rational beings under common objective laws. Physician and patient, each with their own needs, desires, capabilities, must find those principles that allow them to coalesce into a helping alliance to achieve a common goal.

Contemporary readings often accept a Millian version of autonomy that is associated with self-seeking attitudes. This approach to respect for autonomy refers to the capacity to act on needs, wants, or wishes; a capacity shared by many creatures. Since the person’s action is informed by instrumental reasoning, it constrains the
scope of reason so that it is subject to any desire or disposition that one happens to endorse at the time one acts[9]. Focusing essentially on individual choices sets up a false and pernicious opposition between persons and the community to which they belong. It is reasonable, on both conceptual and empirical grounds, to suppose that individuals acquire their values through engagement with a concrete moral tradition, rather than through a private and self-directed process. Instead of providing ethical decision-making with an objective and rational process, the obsession with individual autonomy tends to create what McCormick calls a ‘moral vacuum’, i.e. the disappearance of the network of shared and established goods and values that make the choices of individuals right or wrong, moral or immoral[16].

**Balancing autonomy and community in ethical decision-making**

It is hard to undermine the influence of social, cultural and environmental factors on moral decision making. We have to take these factors into account in order to fully appreciate the moral dilemmas and health challenges in settings and traditions where individualism does not prevail. Writing from their Jewish background, Barth-Rogers and Jotkowitz note that within Jewish tradition, the idea of unlimited human autonomy is not a defining value; Judaism deems the intrinsic human value of each individual’s life to take precedence over patient autonomy[12]. Similarly, the Confucian culture from East Asia understands the person not only as a rational, autonomous being but also as a relational and altruistic entity whose self-actualization involves participating in and promoting the welfare of fellow persons[4]. In the same line of thought, African traditions present a view of the human person that is essentially relational; it is within the social network that the individual lives and acts as a free person. The Jewish, Confucian, and African cultures convey an understanding of the human person and society which is different from individualism operative in some cultures.

This is where the shortcomings of Gillon’s autonomy-centered conception of bioethics become the most obvious. Gillon does not reject the view that particular cultures should be respected, instead he theorizes that the *prima facie* nature of autonomy requires that both the individual and cultural moral variability be respected [3]. But this sense of respect for culture does not adequately reflect the social rootedness of the human person. Despite making ‘concessions’ to culture, Gillon continues to view societal relationships, determinants and influences to be peripheral to human reason and, because of the danger of ethical relativism, something to be transcended by a universal ethic. Hence, the four principles (with autonomy as supreme among them) can account for all our moral worries and being applied straightforwardly to all situations and contexts[17]. Gillon contends that any other moral principle or value can be explained by one or some combination of the four principles. In fact, however, Gillon’s quest for a universal discourse is nothing more than the promotion of one approach to ethics among others, one which reflects specific cultural assumptions concerning individual choice and future-oriented action that are associated with class position and social opportunities and foreign to the lived reality of the poor, the marginalized, and people of color in a multicultural society like the United States[18]. Any attempt to universalize an ethnic particularity fails the test of respect for pluralism in bioethics and in our ever-globalizing world.

In resource-poor countries where medical paternalism prevails on account of patient beneficence and shared responsibility for health promotion[19], the necessity to create the conditions that improve, for example, patient-physician communication in ways that favor patient agency needs to be acknowledged. Very often, the physician does not even tell the patient what is going on with his or her health. However, the one-sided view of the human person which prevails in autonomy-based bioethics should not be adopted as a model to correct paternalism; a more fruitful alternative would be a combination between a community- and tradition-oriented view and autonomy that conceives decision-making as guided by important human values such as partnership, trust and solidarity, in addition to autonomy. This view would acknowledge the embedded and relational nature of human choices, behavior, ways of expressing emotions and feelings, patterns of thinking, and conceptions of disease and healing.

**Autonomy, biomedical individualism, and social justice**

Some criticisms of autonomy-centered bioethics have been purely conceptual. Others have emerged from reflections on its limitations in dealing with collective macro-problems including social, sanitary and environmental problems that mark everyday life in poor countries. Autonomy-based bioethics fails to engage the lived worlds of diversely constituted and situated social groups, particularly those that are marginalized[18]. Similarly, in clinical medicine, broad issues such as the common good, distributive justice and the spirituality of the patient are ignored for the sake of the primacy of secular business concerns. To guide clinical practice, laws have been developed to reduce risk for malpractice and protect patients. However, emphasis placed on the principle of autonomy has led to an excessive control of clinical practice by judicial institutions. Consequently, this obsession with the law has led to the elimination of a wide range of moral concerns from public consideration[16]. To emphasize this point, McCormick criticizes
clinical ethics for being preoccupied with cost control that focuses narrowly on matters of financial efficiency, thus exiling the more basic ethical questions (ends of medicine, the meaning of life, death, illness and health) [16]. Furthermore, any public health intervention that adopts the biomedical model fails to address issues of wider social injustices that are responsible for health-related vulnerability and risk.

**Autonomy ethics and medical individualism**

The biomedical model is premised on individualism, because it adopts an abstract view of the body and mind of an individual person from a liberal model of economy and politics[20]. In this model, individuals choose health behaviors. Thus, poor health is largely due to exposures to health risks that the individuals have decided not to avoid. This approach to health risks disregards the role of social structures in structuring the array of risk factors that individuals are supposed to avoid[18], and fails to explain how social inequalities can be embodied in poor-health outcomes[21]. Thus, autonomy-focused bioethics, rather than presenting an objective perspective, deprives itself of theoretical tools to adequately address non-pathological causes of ill-health. Similarly, in research sites, much effort is often invested in securing the informed consent of individual participants while often ignoring the broader issues of justice in places where research takes place[22]. Consequently, the absolutization of autonomy with the unreal and distorted picture of the person helps explain why so much bioethical writing is concerned with procedures that protect choice, rather than more substantive issues, with consent itself rather than what is consented to[16]. This tendency to make the social causes of poor health (and the broader ethical problems related to health improvement) invisible can even be seen among those working in public health to the extent that they subscribe to the biomedical model[20].

**Biomedical model and the social gradient in health**

Health differentials between individuals cannot be explained simply by their health behavior or lifestyles, but also by their social position and economic status, the social networks to which they belong, and the levels of education that provide them with the means to avoid health risks, deal with adversity, and have access to life-protecting information. The pervasiveness of the social gradient in health remains even when well-designed public health interventions are implemented. Even when these public health interventions may reduce health risks and mortality, they do not eliminate the social gradient because individuals in the lower socioeconomic groups take less advantage of health interventions than those who are better off.

When we compare the health statistics between poor and rich within countries or between countries, the differentials are striking. HIV/AIDS statistics provide us with striking examples of the impacts of socioeconomic status on risk differentials and chances of survival between groups within countries and between countries. Even in developed countries, the geography of HIV/AIDS challenges us to investigate the social causes of its distribution. Risks and survival differentials prompt us to consider a view that places political-economic critiques of global resource distributions, and criticism based on the higher and qualitatively different disease burdens in poor countries within a common framework of international and internal socio-economic structure [23]. At the local level, income inequality in poor countries affects health and can be an indicator of life expectancy[24,25]. Poverty affects individuals’ ability to have access to goods which are instrumental for well-being. At the country level, poverty limits government’s ability to found social programs and provide people with basic social goods such as safe drinking water, electricity, good public health coverage, healthcare institutions, schools, social services, and economic opportunities. These structural causes are steady and they include access to basic resources that can be used to avoid all sorts of health risks or reduce the negatives outcomes of diseases when they occur[26].

Most public health interventions focus on individual risk factors and behavior. To lessen vulnerability and risk, health professionals will need to address income differences between individuals and population groups. Otherwise, they will only address the symptoms and not the root-causes of poor health. As public health practitioners and other health professions ‘resocialize’ their conceptions of health and disease, bioethicists should join and inform their efforts. A sociological approach to disease can increase the social relevance of bioethics because it provides an acute perception of disease etiology and pathology that includes the social and material conditions in which people live.

**Sociological model and autonomy-based bioethics**

To underscore the difference between Western and non-Western conception of illness, Bowman writes that most non-Western cultures tend to perceive illness in a much broader and far less tangible manner. Illness is often viewed as being linked to social, spiritual, and environmental determinants[27]. The sociological model of disease explanation shares some important connections with many non-Western cultures in which disease representation and explanation is not primarily understood in biomedical terms, but in social ones. Autonomy-based bioethics is premised on the view that disease is located in the individual. The focus on the individual person often reduces the scope of justice in clinical medicine and health research to an equal
treatment of individuals involved and a fair distribution of available resources and burden regardless of people's social status, age, race, gender or religion. In the clinics, for example, justice requires that patients whose circumstances are the same deserve the same level and quality of care.

Conversely, the sociological model perceives the disease as an integrated social-physiological process which includes the person's relation to the environment. In addition to its bio-physiological dimension, a disease is a relational phenomenon; as a subjective and socially-constructed reality, a disease develops out of the omnipresence of symptoms and bodily feelings in everyday life. The sociological model allows us to develop a socially-relevant approach to health justice, a new set of principles that may guide research as well as an approach to health policy based on the features of the site where research is done. Thus, this model points to the fact that there are two reminders of our embeddedness in the world relevant to bioethics: first, biological embeddedness and infectious disease and second, social embeddedness, particularly (but not exclusively) in contexts where people are obviously dependent on one another and traditional behavior and customs are strong.

Contribution of medical sociology: Sociological model and social justice

The current formulation of ethical principles as they are applied to medical research in poor countries is inappropriate for capturing some crucial implications of medical research since they ignore the roots of health crises with which these countries are confronted[28]. Analyzing the health crises in African countries in the late 1980s, the Cameroonian sociologist Jean-Marc Ela argues that disease and malnutrition never exist by themselves; rather they come from a system characterized by violence, by a pattern of impoverishment of the majority, and by the monopoly by a minority of the means to live with dignity[29]. Health interventions should not merely address the symptoms of a disease-producing society, but also its structures. Social structures not only shape distribution of disease across population, but they also determine societal and individual responses to suffering. When the major determinants of health are far from being addressed by a conceptual framework that prioritizes individual problems and morality, there is a need to call its relevance into question. The high rates of infectious diseases in poor countries are linked to poor living conditions and structural problems. These primary sources of exposure and vulnerability to health hazards should necessarily be considered in any attempt to develop bioethical standards for research or any bioethical agenda. The poverty that permeates all spheres of society should be studied because poverty never exists in isolation from societal influences, but rather is integrally a product of the inner workings of each society's political economy. Minimizing the contribution of poverty to the production of disease and disability in poor countries makes suffering invisible and limits our understanding of the etiology of disease.

Medical sociology scrutinizes patterns of diseases and pathways through which social inequalities are embodied in individual vulnerabilities and major epidemics. Thus, the model of disease causation that comes from sociological investigations challenges us to move beyond the clinics or research sites to broaden the scope of justice. Similarly, the prevalence of infectious diseases in resource-poor countries challenges the way justice is understood in research sites. If we consider the patient as a potential victim and vector, we need to shift our gaze from the healthcare that might be most desirable for the individual patient to broader social concerns and the worldview distribution of care that might enable all to achieve opportunities over a reasonable life span[11]. The extension of care to all not only aims at serving individual needs for care, but more importantly it addresses infectious diseases as a threat to population health. Opting out from an intervention of this kind would simply mean that the individual remains a threat to the entire population[3].

The sociological explanation of disease incorporates a distinctive view of etiology, prevention, pathology, treatment, and justice. This approach to disease explanation tacitly promotes a conception of responsibility for infection or disease causation which is not only individual. This approach questions the uses of individualism as methodology and framework for analyzing disease occurrence, and thus criticizes the one-sidedness of the anthropology that sustains the biomedical model.

Sociological model and justice in current biomedical research

Documents such as the Declaration of Helsinki issued by the World Medical Association and the International ethical guidelines for biomedical research involving human subjects (CIOMS) as well as the work of the National Council on Bioethics in 2002 and that of the National Bioethics Advisory Commission (NBAC) in 2001 all take material poverty as the main reason for developing bioethical standards that apply to medical research conducted in poor countries. Surprisingly, the bioethics standards they promote hardly reflect the physical, social, and cultural environment of poor countries. This is another important area for revision[28].

Given the substantial differences in individual exposure to health risks and the availability of health protective resources as well as differences in the disease burden and mortality and morbidity at the population level, it is clear that illness in poor countries can be
better understood using a ‘social causation of illness’ perspective. The principles of respect for persons, beneficence, and justice that shape the Belmont Report are all built on the biomedical model. The principle of respect for persons reinforces individual agency and protection in the research setting by ensuring that participants are properly informed about the research or the course of care that will be taken to restore normal functioning. The principle of beneficence extends the latter by insisting that research protocols should maximize potential benefits and minimize harm. Finally, the principle of justice ensures that those with diminished autonomy are protected and that participants share in the benefits of the research. Agency, benefit, participation, risk, and vulnerability are all understood from the standpoint of the individually-focused disease management whether in the clinical setting or the research site. To be of broader global significance, ethical principles of biomedical research should be responsive to the context of poverty and social inequities, since these structural factors can lead to increased vulnerability and exploitation. For example, the incapacity of poor people to satisfy their basic needs can lead to increased participation in clinical trials without true understanding of risk and benefit at least in part due to financial incentives. Thus, even if these people ‘consent’ to participation in a trial, is that decision truly autonomous? Is it then clear that ‘research protections’ cannot be ensured solely through the use of the consent form and the provision of information to the subject. A formal provision of consent by the research subject can simply mask the misery that inhibits his or her ability to consent freely.

Similarly, what counts as ‘benefits’ can be tied to different levels of poverty and disease burden in different resource-poor countries. Ethical principles and guidelines that oversee biomedical research can be defined in terms of public good rather than merely as an improvement in individual health status because public good and social policy transcend the framework of individual-based ethics [28]. In resource-poor countries, death-rates are high and infectious diseases contribute significantly to the burden of disease—as opposed to richer countries, where cardiovascular disease and cancer are the leading causes of mortality—the difference in exposure, health risk, mortality, and morbidity between poor and rich countries challenges us to develop a new approach to the concept of benefit in biomedical research. We need to think of ‘benefits’ as running to the whole community in which research takes place, and not just to single research subjects. Therefore, the availability of and access to modern health services is a substantial issue for evaluating the impact of biomedical research benefits in poor countries since the outcomes of health initiatives are largely determined by some structural arrangements that transcend the benefits of research subjects. These arrangements are based upon national and international patterns of control over society’s resources.

Current ethical guidelines continue to be inappropriate because they do not address the international context of exploitation within which research is done. People’s health status cannot be separated from the capitalist system of resource distribution and exchanges which favors the rich countries or high socioeconomic groups and reinforces the impoverishment of the poor ones. The economic exploitation that prevails in the capitalist system shapes the global and local distribution of resources and diseases as well as the health risks and vulnerability of those who live on the margins of the global market. The concepts of ‘benefit’ and ‘justice’ have been inadequately extended to biomedical research in poor countries because the possibility of exploiting the underprivileged is more complex than an exploitative relationship with vulnerable populations in developed countries, where at least the rule of law and the respect due to every citizen have already been institutionalized. Furthermore, the number of research studies conducted in poor countries is increasing because regulatory measures are often less strict; this situation may facilitate the exploitation of the poor, non-respect for basic ethical standards, and unlimited search for benefit.

Bioethics scholarship that focuses on the sociological model considers local as well as global issues of social inequality, because this model is premised on the intimate connection that exists between social inequality and health inequality. The distribution of illness is likely to reflect the geography of inequality. A social approach to bioethics emphasizes distributive justice and benefits at both the population and individual level. Three important principles flow from this analysis. The first one can be called principle of public benefits (community-based approach to benefits); it is a context-based principle which derives from factors that contribute to ill-health and vulnerability to preventable diseases in poor countries. It states that risks, benefits, and equity can no longer be defined in terms of individual health, but also in relation to the international, national and local contexts[23]. Such a principle challenges the individualistic understanding of benefits in places where exploitation and inequality are at the center of research. Consequently, a community-based understanding of benefits calls for a large-scale distribution of the benefits of research as an important requirement of justice. This principle is relevant for political and socioeconomic critiques of the ethics of carrying on research in poor countries, given well-established patterns of exploitation and oppression of the underprivileged. Reliance on the sociological model brings out the fact that the health conditions under study originate in socioeconomic conditions that need to be treated to have an impact on the health status of research participants[28]. Thus, the notion
of population or community-based benefits is related to that of health as a public good which is, in turn, linked to the global-capitalistic system that significantly contributes to the health conditions found in poor countries.

The second principle, the principle of social justice, is rooted in a broad approach to justice that places poor health at the center of public and research policy and seeks to correct systemic injustices. This principle is related to the principle of public benefit since it states that the distribution of benefits should take into account the poverty of local healthcare systems and people’s disempowerment as a function of social structures[23]. Here, the challenge is that the distribution of benefits should address the root-causes of poor health and not only its symptoms. The third principle underscores the need for building local capacity. This principle states that building capacity to promote healthcare sustainability will have a lasting effect on people’s health. This principle emphasizes the need for building local capacity and improving human capital to reduce the burden of preventable diseases. For example, research on AIDS vaccine often uses existing facilities or new ones built by funding agencies to conduct research or administrate the vaccine on trial. Building capacity may involve researchers and funding agencies improving the training of local medical professionals and reinforcing existing facilities to reduce the burden of disease; and, if a new medical facility has been built for the research study, local communities can still use it even after the research project comes to an end.

To avoid exploiting the underprivileged and reinforcing an existing system of oppression, the distribution of benefits should be determined by the context within which diseases occur, the state of the healthcare system, and available resources. Therefore, research institutions and their financial sponsors are morally obligated to contribute to the development of a healthcare system and the improvement of human resources that can benefit the whole population. Carrying on research in impoverished parts of the world where people have been enduring a systemic marginalization would not be ethical if our understanding of benefit will not address the root causes of poor health. Thus, it is no longer enough to avoid not doing harm; addressing health challenges that prevail in the research site is consistent with a broader view of justice[28].

**Sociological model, bioethics, and health policy**

An autonomy-centered ethics places the burden of prevention and access to healthcare on the moral agent. In doing so, it frames disease within a model that limits political intervention in the health domain strictly to biomedical solutions or behavior change. This leads to the perpetuation of the social status quo within which risks for poor health are greater, and lends legitimacy to the social forces that increase health risks. This failure to promote social justice contrasts with John Lynch’s understanding of public health intervention. Lynch believes that elements of the social fabric should shape the conception, framework, and implementation of public health intervention. Discussing the influence of socioeconomic status on behavioral and psychosocial risk factors for cardiovascular disease, he argues that the public health community should consider the potential for a broad array of social, educational, and economic policies as effective public health interventions to reduce the unequal distribution of risk factors and the unequal burden of disease[30]. Similarly, bioethicists need to study health-promoting effects of structural interventions to determine which ones are ethically acceptable and justified. Such a move requires bioethicists to look at broad issues of social equity and advocate for a shift in public policymaking.

In a population-based study examining the associations between socioeconomic status measures (education, income, and occupation) reflecting different stages of the lifespan of 2674 middle-aged Finnish men, health behaviors, and psychosocial characteristics in adulthood, Lynch et al. conclude that: understanding that adult health behavior and psychosocial health orientations are associated with socioeconomic conditions throughout the lifespan implies that efforts to reduce socioeconomic inequalities in health must recognize that economic policy is public health policy[31]. The sociological model within which Lynch’s understanding of public health intervention is built challenges us to advocate for a shift in policymaking mindset because health is not a sphere of justice which is separate from other aspects of human life. Since disease is a social process, a policy vision that focuses on the individual and individual risk factors fails to promote social justice and to address structural elements that create conditions favorable to the production of disease. Hence, we need to move from healthcare policy to health policy, or rather, a healthcare policy that is responsive to facts explaining why (certain) people with (certain) diseases from (certain) communities require medical care. Health policy should embrace healthcare policies but include considerations regarding welfare, work, occupational, economic development, employment, and educational policies.

**Conclusion**

Sociologists and social epidemiologists challenge bioethicists, especially those working in developing countries, to be socially and culturally relevant. The sociological theory of disease explanation starts with a concrete analysis of the social setting within which illness occurs or research is carried on. Since societal factors shape patterns of mortality and morbidity, principles of biomedical and research ethics need to be framed within the
context of the social inequalities that shape vulnerability to illness. Aligning bioethics to perspectives, concerns and information in the fields of public health, health policy and medical sociology could vastly improve its global significance. Thus, bioethicists should be challenged to develop a philosophical anthropology that goes beyond radical affirmations of the individuality to acknowledge both the communal and the individual dimension of the human person.

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JA originated the article, did the research and wrote a first rough draft of the manuscript. SR read the first version and contributed editorial and critical suggestions. After the first peer-review, JA made substantial revisions to the earlier draft in close collaboration with SR. They have both read and approved the final version of the manuscript.

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Commentary

Living apart together: reflections on bioethics, global inequality and social justice
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Abstract

Significant inequalities in health between and within countries have been measured over the past decades. Although these inequalities, as well as attempts to improve sub-standard health, raise profound issues of social justice and the right to health, those working in the field of bioethics have historically tended to devote greater attention to ethical issues raised by new, cutting-edge biotechnologies such as life-support cessation, genomics, stem cell research or face transplantation. This suggests that bioethics research and scholarship may revolve around issues that, while fascinating and important, currently affect only a small minority of the world’s population. In this article, we examine the accusation that bioethics is largely dominated by Anglophone and industrialized world interests, and explore what kinds of positive contributions a ‘bioethics from below’ (as Paul Farmer calls it) can make to the field of bioethics in general. As our guide in this exploration, we make use of some experiences and lessons learned in our collaborative bioethics project in the Democratic Republic of Congo, Building Bioethics Capacity and Justice in Health. We conclude that while there is some evidence of increased attention to bioethical challenges in developing countries, this development should be further cultivated, because it could help expand the horizons of the field and enhance its social relevance wherever it is practiced.

Introduction: bioethics and inequality in health

There are vast differences in health between low-income, middle-income and high income countries around the world, as well as significant differences in health within these countries. Epidemiologists, health economists and health policy makers typically express global health inequalities in the form of differences between country health (and health proxy) indicators such as life-expectancy, maternal and child mortality, and average per capita income. For example, there is more than a 2-fold difference in life expectancy between the top three countries (Japan, 82.3 years; Hong Kong, China, 81.9 years; Iceland, 81.5 years) and the bottom three (Zambia, 40.5; Sierra Leone, 40.7; Zimbabwe, 40.9) [1]. In terms of child mortality (one year and younger), commonly considered an indicator of country health or development, the worst affected countries have rates more than 90 times higher than those least affected. In regard to maternal mortality, the lifetime risk of pregnancy-related death in Malawi is 1 in 7, as compared with 1 in 2800 in industrialized nations[2]. As is well known, income is inversely related to infant mortality and a host of other health indicators. There is a 400-fold increase between average per capital income among the richest and poorest countries, and
although average income overall in the world has increased in the past few decades, the differences at the outer ends of the global income index have been widening significantly[3,4]. In addition, research has indicated that not only does absolute poverty have a strongly negative impact on health, but the greater the disparity between rich and poor in a given society, the worse the health of the ‘less fortunate’ in such societies tends to be. Inequality, as Norman Daniels puts it, is bad for your health [5,6].

Given the importance of health as a human value, and the traditional aspiration of bioethics to articulate universal principles, one might predict that ethical issues related to these appalling global disparities would feature very prominently in bioethics scholarship and research. However, some commentators claim that (a) mainstream bioethics research and scholarship is marked by excessive attention on bioethical issues largely affecting the world’s more affluent countries and (b) that in the light of global realities, the predominantly ‘first-world’ agenda of bioethics should change. Leigh Turner, for example, writes that many of the questions that bioethicists address (such as face transplantation, cessation of life-support, or prenatal genetic diagnosis) are only intelligible in the contexts of wealthy developed nations, and these topics appear ‘trivial’ when compared to the kinds of health issues faced by people in impoverished, developing countries. Unless bioethics broadens its agenda, Turner writes, it risks becoming a form of entertainment[7,8]. In a similar vein, Paul Farmer writes that mainstream bioethics has largely been focused on issues of personal autonomy in regard to new developments in biotechnology, rather than the problems of social justice arising from the growing (health) gap between the world’s rich and poor communities[9]. Steven Miles writes that the ‘soul of bioethics’ has been rendered unhealthy partly by its tendency to engage more with issues of assisted reproduction and gene therapy than with the growing number of medically uninsured in America, minority and migrant health, the links between health and human rights, or the political and economic barriers preventing developing countries from gaining greater access to essential medicines[10].

Does bioethics, as a field of research and scholarship, concentrate too much on ‘problems of affluence’ while neglecting the bioethical problems prevalent in resource-poor settings? And if so, should the agenda of bioethics be broadened, and in what ways? In attempting to answer the first question, it should be noted that there is currently little empirical data on what topics are studied by bioethicists or trends in bioethics scholarship over time. Borry et. al. [11,12] have studied authorship of bioethics publications, and have concluded that peer-reviewed bioethics journals describing themselves as ‘international’ largely publish articles by authors from Anglophone developed countries, particularly the United States, United Kingdom, Australia and Canada. However, as Borry et. al. admit, these findings do not in themselves show that the content of bioethics research and scholarship is biased towards the concerns, interests and perspectives of more affluent nations, though it is plausible that the social, cultural and class origins of bioethicists might significantly affect topic selection and directions of scholarship and research. In a recent study of trends in bioethics topics by Cohen et. al[13], the authors suggest that ‘favored subject matter’ in bioethics varies significantly over time due to legal controversies, discussion saturation and epidemiological importance. One striking finding of this study was that the number of publications on ‘AIDS and ethics’ rose from 16 during the period 1980–84 to a peak of 793 in the period 1990–94, and then sharply declined to 197 between 2000 and 2004. As the authors note, the interest in this topic among bioethicists in this case is strongly related to the epidemiology of HIV/AIDS in the United States. With increased public health surveillance and prevention efforts, the advent of (and access to) effective anti-retroviral treatment and the virtual disappearance of mother-to-child transmission of HIV through prenatal testing policies, the prevalence of HIV/AIDS dropped dramatically in the early 1990’s, and the interest of bioethicists in the topic of AIDS and ethics seems to have declined with it. However, during this same period there were many millions of new HIV infections and AIDS-related deaths worldwide, with widespread and devastating economic, political and social effects. This suggests that HIV/AIDS was of significant interest and concern to the mainstream bioethics community when it significantly threatened the developed world, but is a considerably less compelling bioethics topic when HIV/AIDS affects poorer countries elsewhere.

The plausibility of ‘first-world bias’ in bioethics is further strengthened by relatively easily accessible data regarding the agencies who fund the bulk of bioethics research, the location of the vast majority of bioethics centers or publishing houses of bioethical journals[14]. It is probably safe to claim that most bioethicists originate from and/or work in developed countries. On the other hand, there is currently no firm data on origins, education or location of bioethicists, and the issue is further complicated by the fact that those who deal with ethical issues arising from health research, policy or practice may not self-identify as ‘bioethicists’ or publish their work in mainstream bioethics journals. In summary, while there is some credible evidence in favor of a current ‘first-world bias’ in bioethics, more empirical research should be conducted to evaluate the claims of bias and parochialism that continue to be made.
Indeed, there are signs that current global situation regarding bioethics is more complex than is sometimes depicted in ‘first-world bias’ claims. For example, in the past decade, there has been a sharp increase in the number of sophisticated biomedical institutions established in India, partly a response to the demand for medical tourism and the economic incentive to host large-scale clinical trials. Researchers and physicians working in these institutions are increasingly faced with standard ‘first-world’ bioethics issues such as cessation of life-support and death criteria in view of organ transplantation. In pockets of even the poorest countries, such bioethics issues are not trivial, and are likely to increase in relevance as the health standards of developing countries rise. The situation is similar with the bioethical issues surrounding assisted reproductive technologies as these become more accessible in resource-poor settings[15]. To further complicate the picture, controversial biomedical research on mother-to-child HIV transmission in Africa and Asia during the 1990’s raised the profile of bioethics issues in developing countries in a number of important ways. The controversy increased attention on the issue of the appropriateness of placebo controlled trials in general when conducting clinical trials in poor countries, the content and role of international declarations protecting research participants, and the meaning of exploitation in the context of international research. The controversy was also the likely origin of the Nuffield Council on Bioethics’ report The Ethics of Research Related to Healthcare in Developing Countries (2001), the Wellcome Trust’s initiative to fund bioethics research in developing countries (started in 2002), and the International Research Ethics Education and Curriculum Development Awards offered by the Fogarty International Center at the National Institutes of Health (launched in 2000), which is responsible for training health professionals in bioethics and research ethics relevant to developing world contexts at 18 institutions worldwide. The European and Developing Countries Clinical Trials Partnership (EDCTP) has offered funds for establishing ethics review committees and bioethics educational programs in sub-Saharan Africa. Developing World Bioethics, a peer-reviewed journal launched in 2001, is devoted entirely to bioethics issues relevant to resource-poor settings and has become an important target journal for those working in this field. There is increasing talk of African[16-18], Muslim[19,20] or Buddhist[21,22] bioethics, and predictably, renewed challenges to the idea of universal bioethics principles applicable to all cultural contexts [23-25].

In short, while developed world topics, institutions and authors still tend to be predominant, the global bioethics landscape is slowly changing. What then are some key concerns that tend to be marginalized within the mainstream bioethics community but are more prominent in developing world contexts? We will explore this question through the prism of a collaborative bioethics program we have helped establish in Kinshasa, Democratic Republic of Congo.

**Centre Interdisciplinaire de Bioéthique pour L’Afrique Francophone (CIBAF) at the Kinshasa School of Public Health**

The Democratic Republic of Congo (DRC) covers the largest geographical area (> 900,000 miles) and has the largest population (approximately 63 million) of all Francophone African countries, and is the second largest French-speaking country in the world. Its capital city, Kinshasa, is estimated to have a population of 8.9 million, making it the second largest city in sub-Saharan Africa, and the third largest city on the African continent after Lagos and Cairo. This former Belgian colony is economically and politically crucial to the sub-Saharan African region, but is only slowly recovering from decades of political oppression and mismanagement, violent civil conflict, and economic exploitation of its natural resources. The legacy has left many essential sectors, particularly education and medicine, in a state of disarray[26].

In 2004, the University of North Carolina-Chapel Hill, the University of Louvain (Belgium) and the Kinshasa School of Public Health applied for what was then called an International Bioethics Education and Career Development Award from the Fogarty International Center at the National Institutes of Health. The stated main purposes of the grant are (a) to improve the quality of international research ethics training (i.e. develop courses on bioethics and research ethics issues affecting resource-poor countries) and (b) to support advanced training of health care and other professionals from resource-poor countries, in order to improve ethical review of biomedical or public health research conducted in such settings. In our application for this grant, we proposed to train a small core of Congolese scholars in Belgium and/or the United States, who would establish and manage a center for bioethics at the Kinshasa School of Public Health on their return to the DRC. The center, later named the Centre Interdisciplinaire de Bioéthique pour L’Afrique Francophone (CIBAF) was conceived as a place for research ethics and bioethics research, scholarship, education and consultation, focusing in particular on ethical issues faced in biomedicine and public health research, policy and practice in sub-Saharan Francophone Africa. The Fogarty project we proposed, entitled ‘Strengthening Bioethics Capacity and Justice in Health’, was approved for initial funding in 2004 and renewed funding in 2008.

Why strengthen bioethics and research ethics capacity in the DRC, given its troubled social, economic and political context? There have been some sharp criticisms of Fogarty...
bioethics projects and similar programs, namely that bioethics training of professionals from developing countries constitutes 'ideological transfer' of Western values, and the hidden agenda of the program is to facilitate US federally funded biomedical and public health research in resource-poor countries [27]. In our experience, these criticisms have limited application and relevance. 'Ideological transfer' tends to fade in the face of local values, realities and practical constraints, and we have managed to ensure that medical ethics and public health ethics – not just research ethics – retain a prominent role within CIBAF activities. For us, the bottom line is that – often in the face of tremendous challenges – medicine, public health interventions and biomedical research are conducted in Francophone African countries, complex ethical issues regularly arise from them, and explicit discussion of these issues is still rare in medical, in popular media, among NGOs or in local communities and other stakeholders. CIBAF takes a social justice perspective on these issues, befitting a context where the sub-standard health of the vast majority is clearly linked to man-made historical, social, cultural, economic and political forces. In the DR Congo, it is clear that many local bioethics and research ethics issues are ultimately rooted in unjust forms of inequality, and this consideration undermines any possibility for local bioethics to remain 'politically neutral'. Bioethical reflection on the problems stemming from health inequalities, including efforts to overcome them, is itself a form of political commentary.

Ethical challenges raised by the struggle to improve health in resource-poor countries
In order to offer some examples of these ethical challenges, it is first important to ask: what are some of the most important ways of reducing global health inequalities? In what follows, we will briefly discuss what we see as prominent ethical challenges in five important and interrelated approaches to reducing global inequalities by improving health in resource-poor countries: (1) global health research, (2) implementation of tested health interventions, (3) changing of health policies, (4) strengthening of health care infrastructure, and (5) tackling upstream forces impacting on health.

Global health research
The general goal of clinical and public health research is to produce new, reliable information which could be used to improve the health conditions of individuals and/or populations. Prevention of mother-to-child HIV transmission research in the 1990's vividly demonstrated how pursuit of this worthwhile goal can raise ethical controversies in low-income countries[28,29]. The University of North Carolina at Chapel Hill and the Kinshasa School of Public Health currently conduct operational research on effective and appropriate provision of anti-retroviral treatment to HIV-positive persons in Kinshasa. Operational research – sometimes called implementation research – is considered a crucial preliminary stage in the process of integrating health interventions effectively and sustainably into health systems[30]. However, when the researchers wanted to involve HIV-positive minors (less than 18 years old) in their study, they ran into an ethical and regulatory quandary. On the one hand, local physicians informed the research team that minors are rarely told their HIV status by their parents or doctors. On the other hand, US regulations state that Institutional Review Boards have the discretion to require assent from minors when they participate in research. How could meaningful assent be obtained from minor participants – some of whom were already in their early and mid-teens – for HIV-related research without thereby disclosing their HIV-status to them? And is assent considered culturally appropriate by parents, guardians and local health care providers? How does the concept of assent – originating in the idea of the children's rights – relate to local conceptions of the relationship between parents and children in the context of medical decision-making? The involvement of HIV-positive children and adolescents in this operational research study would be undoubtedly beneficial for the participants, since those who need it would be provided with treatment known to be effective and to which only a small minority of children (or adults) currently have access in the Democratic Republic of Congo. While involving HIV-positive children in this research raises problems from an ethical and regulatory perspective, not involving them would be akin to the withholding of known effective treatment.

In response to this problem, qualitative research on issues surrounding pediatric assent and disclosure in HIV-related research was conducted among parents, guardians, physicians and young HIV-positive adults. The results of this research are or will be published elsewhere [31,32], but the main findings were that most youth interviewed believed minors participating in HIV-related research should be informed of their HIV-positive status, while parents/caregivers had varied perspectives on if and when HIV status should be disclosed to minors during research participation. The age of the youth influenced parents'/caregivers' responses, and disclosure to adolescents was more frequently supported than disclosure to children. Several parents/caregivers suggested that minors should never be told their HIV-positive status when participating in HIV-related research regardless of their age. The implications of these results for policy-making on pediatric assent and disclosure in HIV-related research and clinical practice were discussed in a workshop among a number of local stakeholders, including members of CIBAF, the Ministry of Health, the National AIDS Control Program and local health NGOs. In the case of the ongoing operational...
research, it was decided while assent should not be a requirement for the children's involvement in the research, disclosure of HIV status should be regarded as an ultimate goal for all HIV-positive youth (particularly as they become sexually active), and a gradual and individualized process of disclosure should be initiated for each child involving parents, physicians and psychosocial assistants. Our point here is not so much to weigh in on this particular case, but to give a taste of the kinds of scientific, cultural and ethical controversies that are part and parcel of health research in low-income countries. Of all ways of reducing global health inequalities, health research receives the most bioethical attention[33].

Implementation of tested interventions

The fact that many health interventions, already shown to be effective, have not been implemented in many low-income countries is itself a matter of (longstanding) serious ethical concern[34]. Millions of deaths and disabilities in these countries occur due to conditions we already know how to prevent or treat. But when one tries to buck this trend, new ethical challenges emerge. For example, there have recently been global initiatives (such as PEPFAR and the Global Fund) to increase access to AIDS treatment in low-income countries. Programs funded by such initiatives typically offer a package of services to those living with HIV/AIDS and (sometimes) their close family members. There are two major ethical challenges. First, the rollout of greater access is gradual, and this means that there is not enough treatment and services for all those who stand to benefit from it. In short, treatment and services in the short term have to be rationed, with the ethical choices that rationing involves[35-37]. Second, when an HIV-positive person and his/her family receive treatment and services, this may only reach the tip of the iceberg. HIV/AIDS is one – and perhaps not the most pressing – of the health-related needs of the program's beneficiaries. HIV-positive persons in low-income countries are vulnerable in many ways: they may suffer from other health conditions for which there is no local or affordable treatment, like cancer or mental illness; their homes may be destroyed by natural disasters or civil strife; they may be children orphaned from their dead parents, or have to take care of such children; and they may have more regular access to antiretroviral treatment than they do to the food that helps them absorb it. Anecdotal reports of AIDS patients selling their drugs to buy other medications for their family members or for food indicate that there may be differences in perception about health-related needs and priorities on the part of global initiatives and local communities. Programs with the goal of reducing global health inequality by providing antiretroviral treatment must decide to what extent they can (or are allowed by their funders to) tackle these other needs. Such decisions regarding 'ancillary care' in biomedical research always have ethical dimensions and implications[38-40]. In Kinshasa, the members of CIBAF have established a monthly ethics session with local research teams, and problems of ancillary care responsibilities are highly prominent in these discussions.

Changing health policies

Health policies, in general, aim to promote health by legislating approaches to health prevention, treatment and care. The general assumption is that health policies are not just words on paper, but can have a real impact – especially when integrated into institutional procedures and/or backed by the force of law – on how health interventions are implemented in the real world. Health policies may have a stronger or weaker evidence base, or more or less appropriate in a given context, but that they can have an impact on health is hard to seriously doubt. Altering health policies is therefore another important means of reducing global health inequalities, though again, such changes can raise a network of ethical concerns and challenges. For example, take recent changes in HIV testing policy. For decades, voluntary testing and counseling (VCT) was the model for HIV testing policy around the world. According to the policy as initially promoted, VCT centers should be established that offer intensive pre- and post-HIV test counseling for those who come to these centers to learn about their HIV-status. This policy, stressing individual choice and confidentiality of results, was quite different from past policies regarding other serious infectious diseases, and was likely shaped by the fact that HIV first emerged among stigmatized populations (gay men and injection drug users) who, because there were no effective drugs yet, could not be treated once diagnosed with HIV. With roughly 90% of HIV positive persons in sub-Saharan Africa unaware of their HIV-status, and increasing access to antiretroviral treatment, the World Health Organization and the Centers for Disease Control and Prevention now promote what they call 'provider-initiated' HIV testing policies. One such policy is 'opt-out' HIV testing, whereby patients at clinics and hospitals are told by staff that they will be tested for HIV unless they explicitly decline testing. While the policy has the worthwhile goal of increasing the numbers of persons with knowledge of their HIV status, there are ethical concerns when the policy is promoted in low-income countries, such as the DRC. For example, it is unclear to what extent patients (particularly women) in these countries are capable of declining testing or whether the existence of an 'opt-out' testing policy will lead people to avoid health clinics[41,42]. The weighing of the burdens and benefits of 'provider initiated' testing is also more complicated when those tested are not guaranteed access to HIV treatment[43]. As studies are conducted on the impact of the new HIV testing policies, and treatment access increases, at least some of these ethical concerns may be identified.
and addressed[44-46]. Again, the point here is not to argue for or against new changes in HIV testing policy, but simply to indicate how changes in health policy trigger complex ethical challenges in low-resource settings that bioethicists, together with other stakeholders involved in the improvement of health in developing countries, must reckon with.

**Strengthening health care infrastructure**

Raising the standards of medical care in low-income countries would go some way in reducing global health inequalities. That health care services in some low-income countries are less than adequate is well-known, and there is growing acknowledgement that it is important to strengthen local health infrastructure, in terms of medical materials and supplies, organization and records-keeping, as well as human resources. In regard to the latter, there is a phenomenon one might call the ‘brain-drain capacity-building conundrum.’ On the one hand, low-income countries (particularly sub-Saharan Africa) have the lowest nurse-patient and doctor-patient ratios in the world, and therefore there is a great and urgent need for capacity-building of health care professionals in these countries. On the other hand, those training at institutions in low-income countries are increasingly being lured by employment opportunities in more affluent countries, whose demand for health care professionals is increasing as their population ages. For example, out of an estimated 4000 nurses in active service in Malawi in 2005, 453 nurses who had been trained in Malawi were reported to be working in developed countries (mostly United Kingdom), representing 11.3% of the number of the active nurse workforce at the time[47].

There is additionally the internal brain drain, i.e. health professionals abandoning the public health sector for more lucrative and career-enhancing positions in the private health sector, foreign-funded health research projects or medical positions within non-governmental organizations. There is an ethical conflict between an individual’s right to seek better occupational circumstances for him- or herself and responsibilities towards patients and supportive institutions in his/her country of origin and training. Given this conundrum, those attempting to build capacity among health professionals in low-income countries (including our own efforts in the DRC) must ensure that they are not contributing to the brain drain and making a bad situation even worse. The ‘push’, ‘pull’ and ‘grab’ factors driving the brain drain[48,49], however, must also be tackled at another level, factors having to do with economic conditions in a global market, government policy and international relations.

**Tackling upstream factors**

Debates about globalization have entered the domain of public health with the acknowledgment that forces, trans-
ily members and clinicians at an individual level. High-technology interventions also have a prominent profile in bioethics discussions, and there is something of a bioethics fashion cycle as ethical reflections on newest inventions (e.g. stem cell research, enhancement technologies, facial transplants, gene transfer therapy) replace those that have become less-than-fresh (e.g. dialysis, IVF, life-support). Bioethics also tends to align itself with whatever topics are currently considered scientifically fundable; unsurprisingly, many bioethicists have made the choice of pursuing the ethics of stem cell research, genomics or bioterrorism during the last decade. The focus of bioethicists on novel technologies may be non-accidentally related to the potential market value of such technologies and the interests of public and private funding institutions, which may set money aside to study their ethical implications. This is not to say that such issues are unimportant. The point here is that the objection to the very idea of priority-setting in bioethics is moot when there is already a social and partly market-based de facto process of priority-setting in place.

The question is whether it is desirable, or even ethically justified, for bioethics to continue to reflect something like a ‘90/10’ gap, i.e. a situation where 90% of discussions on bioethics in the literature and the popular media may revolve around issues affecting 10% of the world’s population. This situation, as mentioned before, seems to be slowly changing and these changes should be encouraged. But it is important to point out that the preoccupations of mainstream bioethics may not even be representative of the range of possible issues within developed countries themselves. Bioethical questions related to urban poverty, drug use, immigration, occupational hazards in the workplace or environmental injustice make only rare appearances in peer-reviewed bioethics journals, course syllabi, and conferences. These areas of scholarship – tightly linked to issues of social justice – may fall below the radar of many bioethicists due to the social, class and racial barriers between many practitioners of bioethics and affected communities. Commonalities exist between bioethical challenges familiar in the low-income countries and those in underserved or marginalized communities within more affluent nations, arising from historical inequities, limited access to health care, racial discrimination, and gender violence. For this reason, greater attention to ethical issues arising from biomedical research, clinical practice and public health interventions ‘far away’ might have a positive effect on bioethics ‘closer to home’, potentially expanding the horizons of the field and enhancing its social relevance.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
SR wrote a first rough draft of the manuscript. BM read the first version and made editorial suggestions. After the first peer-review, SR made substantial revisions to the earlier version in close collaboration with BM. They have both read and approved the final version of the manuscript.

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