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BIOTECHNOLOGY ENTREPRENEURSHIP AND ETHICS: PRINCIPLES, PARADIGMS, AND PRODUCTS

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Abstract: Biotechnology, whether in the context of new drugs derived from DNA and genetic technology, genetically modified food, or biologics making use of living cells, raises ethical concerns at a variety of different levels. At the research level, there is concern that the very nature of research is being subverted, rather than enhanced, by entrepreneurship. This area of ethical concern has intensified in the United States as a result of the conflicts of interests resulting from the growing alliance between University academia and private industry in the research enterprise. As we travel down the research path into development of a drug or technology, ethical questions arise with respect to protecting human subjects and society from danger and exploitation by researchers. As development gives way to marketing and dissemination of a new product, government regulators are pressed to get drugs and biologics through the regulatory pipeline into the market faster, walking an ethical tightrope between speed and safety. As new biotechnology products enter the market place, doctors and patients traverse yet another tightrope, that between unknown risk and the promise of benefit. And finally, patent protection is increasingly viewed as a unethical culprit in keeping prices high and depriving the global poor from lifesaving drugs and biologics. Bioethics has, to date, been largely a creation of Western research and medicine. As such it is wholly inadequate to respond to the cascade of ethical issues that flow from a vibrant biotechnology industry. And if biotechnology is in its infancy, as most believe, it is crucial that scientists, entrepreneurs and governments engage in dialogue about the ethical and societal questions raised on the road of scientific progress.

Keywords: Biotechnology; ethics; global health

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Introduction

Biotechnology, whether in the context of new drugs derived from DNA and genetic technology, genetically modified food, or biologics making use of living cells, raises ethical concerns at a variety of different levels. There is growing concern that the very nature of research is being subverted, rather than enhanced, by entrepreneurship. This area of ethical concern has intensified in the United States as a result of the conflicts of interests resulting from the growing alliance between University academia and private industry in the research enterprise. As we travel down the research path into development of a drug or technology, ethical questions arise with respect to protecting human subjects and society from danger and exploitation by researchers. As development gives way to marketing and dissemination of a new product, government regulators, such as the United States Food and Drug Administration (FDA), are pressed to get drugs and biologics through the regulatory pipeline into the market faster and are forced to walk an ethical tightrope between speed and safety. As new biotechnology products enter the market place, doctors and patients traverse yet another tightrope, that between unknown risk and the promise of benefit. And finally, we have growing attention paid to patent protection as a culprit in keeping prices high and depriving the global poor from lifesaving drugs and biologics.

Bioethics has, to date, been largely a creation of Western research and medical norms. As several scholars have noted, this is wholly inadequate to respond to the cascade of ethical issues that flow from a vibrant biotechnology industry. Moreover, it may not be particularly apt from a perspective of multiple cultures. And if biotechnology is in its infancy as most believe, it is crucial that scientists, entrepreneurs and governments – to name only a subset of the players – engage in dialogue about the ethical and societal questions raised on the road of scientific progress. This brief paper will consider some of the ethical challenges resulting from the brave new world of biotechnology and consider some ways of recasting ethical inquiry to better meet these challenges.

Principles-based Bioethics: An Overview

Modern bioethics grew out of the post WWII Nuremberg trials. The Nuremberg trials involved testimony that referred frequently to the "laws of humanity" and the "ethical principles" that are necessary to ensure human rights of the individual. The Nuremberg Code ushered in a code of ethics with respect to research that provides a construct for the protection of subjects involved in

medical research. This rights-based approach focuses on the duty of the researcher to provide full disclosure of risk and benefits of research and to obtain consent from the patient or subjects who will be used in the research. This approach gave rise to what is known as the principles-based approach to biomedical ethics, developed by ethicists Thomas Beauchamp and James Childress and initially spelt out in the 1979 Belmont Report which detailed guidelines for the protection of human subjects in medical research.

The Belmont Report established three principles for medical research: respect for persons, beneficence, and justice. In subsequent years, Beauchamp and Childress and others have further developed and embellished the principles, applying them to a host of research and clinical controversies. The principles-based framework embraces four fundamental principles. First is the principle of respect for autonomy. In health care, respect for autonomy is exemplified by the concept of informed consent, which requires full disclosure of material information, comprehension of nature, risks and benefits, and voluntary agreement by the patient or subject to engage in the proposed intervention. Privacy and confidentiality are integral to respect for autonomy. Coercion, duress, or other external constraints are contrary to respect for autonomy.

The second and third principles are the complementary notions of beneficence and non-maleficence. The former requires that benefits to both the individual and society at large be maximized relative to harms. The latter is captured by the mantra of medicine: " above all, do no harm." In essence, these two principles require a careful, impartial and well-reasoned risk/benefit assessment. Applications of these two principles are context dependent. For example, in research, the principle of nonmaleficence is not emphasized, and the risk/benefit analysis assessing beneficence is preeminent.

The final principle is the multi-faceted principle of justice. One aspect of this principle is distributive justice which addresses the knotty question of fairly allocating society's benefits and burdens. Justice and fairness will vary with context. For example, the selection of research subjects presents one set of justice issues. How should the burdens and benefits of medical research be allocated? Fair may mean equal in some cases such as democratic voting or entitlement to a universal package of health care benefits. Alternatively "fair" may mean equitable — such as the graduated income tax. Distributive justice is the proverbial bone of contention in virtually all questions of health care financing and policy. Procedural justice speaks to the achievement of a fair or unbiased result through adherence to well-ordered, consistent procedures.

In the United States legal system, procedural due process strives to provide this type of justice. Finally, compensatory justice attempts to remedy or redress past wrongs. In the common law, for instance, tort law is one means by which compensatory justice is achieved.

Some of the difficulty with the principles-based approach to biomedical ethics is that it focuses on the individual subject or patient –this of course is problematic in cultures where the relevant unit is not the individual, but the family or the community. For example, even in the United States, our Native American population believes that the relevant unit is the tribe, not the individual. Moreover, principles-based ethics does not translate well to issues of organizational ethics, business ethics and the overarching ethical issues created by controversial biotechnology products.

But the principles do provide a starting point from which to look at biotechnology from the bench to the marketplace —beginning with the clinical research phase. The principles-based approach has translated into well-developed law and policy that provides a construct for the protection of the human subject involved in research. In the research context, respect for persons encompasses both recognition of personal dignity and autonomy. Recognition of personal dignity speaks to the issue of confidentiality and respect for the privacy of the human subject. Inherent in the concept of autonomy is the need for the subject's understanding and comprehension of the risks and benefits of the research intervention. In the case of someone with diminished autonomy, such as a child or incapacitated vulnerable adult, special protections are necessary and indeed have been provided for in the law. Beneficence requires the researcher to maximize the anticipated benefits while minimizing the possible risks of harm. This is often an elusive goal as the anticipated benefit to the subject may be non-existent and the risk of harm, especially in the early phases of research, unknown and indeed unknowable. Finally, researchers must seek to distribute the benefits and burdens of research as fairly and equitably as possible.

In the US, the parameters of research ethics are now codified in federal regulations as well as the common law standard of care. Under the federal regulations, research must meet prescribed standards with respect to methods of subject recruitment and evaluation of the risks and benefits for the research subject. Typically this is monitored by an Institutional Review Board (IRB) or Human Subjects Committee that is primarily focused on the safeguarding of human subjects. Federal law requires that all research that is funded or

sponsored by federal dollars must be approved by the IRB before it is undertaken. In addition, most universities and medical research centers require that all research, regardless of funding source, comply with federal human subjects requirements.

In addition to the federal regulatory regime, there is also a well-developed body of medical malpractice case law supporting the doctrine of informed consent. Fully informed consent requires that the patient be apprised of and comprehend any information that would be "material" in making a decision to undergo or forego the proposed intervention, be it experimental or standard accepted treatment. Although standards vary somewhat from jurisdiction to jurisdiction, the trend in informed consent is toward ever greater disclosure of risks and information. In recent years, what is deemed to be "material" may extend beyond the particulars of the actual medical intervention and incorporate numerous other issues: conflict of interest and financial incentives, outcome statistics, and physician competence and experience.

Despite well-developed standards, regulations and case law, lapses in human subjects protection remains an ever-present hazard. This has been exemplified by a series of high profile research ethics scandals in the US – the Jesse Gelsinger case in which a research subject in a gene therapy experiment died and it was alleged that the researchers' financial interest in the vector influenced them to prematurely engage in the clinical trial that resulted in Mr. Gelsinger's death. This case focused on the conflict of interest in genetic research – an area that is full of new ethical concerns that revolve around the perception that genetics is worthy of careful and perhaps even increased protections for subjects, patients, families and populations.

Ethics, Conflicts of Interest, and the "Cooperative" Model of Clinical Research

Ethical issues get considerably more complex as the research emerges from the laboratory and enters the realm of clinical testing as would be the case, for example with a new biotechnology product or genetic "designer" drug or a genetic testing methodology. It is at this stage that conflict of interest on the part of the researchers may become part of the equation. This is largely as a result of the thriving and ever more present collaboration between University academia and private pharmaceutical industry.

In the United States, collaboration has been fostered by legislation that leverages

federal investments in research while simultaneously providing incentives to researchers and their universities. These laws, the Stevenson-Wydler Technology Act (1980), the Bayh-Dole Act (1980), and the Federal Technology Transfer Act (1986), provide the opportunity for both the research university/ institution as well as the researcher to share in the ownership and profits of the ultimate commercial product. The goal was to move scientific advancements from the research laboratory into the marketplace so that benefits of science could be translated into population health benefit.

These technology transfer statutes have proven to be major boons to research universities as well as to private laboratories. This phenomenon has been particularly marked in the biotechnology industry which is dominated by small firms that often engage in a complex web of collaborations with research universities. Beset with decreasing allocations from state legislatures and increasing operational costs, research universities have found income from technology transfer a veritable lifesaver. The dollar gains realized by universities from the shift to the "cooperative model" have been substantial. In 1980, royalty payments to universities totaled a modest one million dollars; by 1994 nonprofit universities netted over $265 million in royalty payments. Research universities are increasingly party to many entrepreneurial agreements which provide them with steady streams of opportunity and dollars. By the year 2000, the Atlantic Monthly Magazine, focused its cover story on "The Kept University" and decried the decline of disinterested inquiry in favor of commercially sponsored research.

In the context of clinical research, the most troubling and fundamental conflicts of interest arise when the research scientist is also a treating physician conducting the clinical trial. In such cases, this double role creates an ever-present actual or perceived conflict of interest. The researcher/physician is subject to conflicting loyalties — the classical duty of care to the patient/ subject and the simultaneous loyalty and fiduciary duty to the research enterprise—in which he may have an equity interest or other potential downstream gain. The fear is that the lure of profit will corrupt scientific integrity and prompt researchers to withhold or minimize the risks of the trial. This fear is rational. Growing numbers of researchers report personal financial ties to industry sponsors. These ties are diverse and nuanced, ranging from short-term commitments to attend a single meeting or provide one-time consulting to more substantive commitments as long-term members of advisory boards and holding stock in the company. The International Committee of

Medical Journal Editors (ICMJE) has identified the most common and troubling of financial conflicts, citing employment, consultancies, stock ownership, honoraria, and expert witness work, either on the part of the research scientist or an immediate family member. There is reason for concern that, even in more mundane areas of research than genetics and biotechnology, there is skewing of study design, research results and study as a result of industry financial support.

From a conflict of interest perspective, biotechnology and genetics have embraced the "cooperative" model of research in which the university researchers are often engaged with private industry for funding of bench and clinical research. One study of 800 biotechnology faculty members revealed that 47 percent serve as consultants to industry, over 25 percent received industry sponsored grants, and 8 percent had an equity interest in their industry sponsor. Another study analyzing 789 articles in medical journals found that 34 percent of the authors had a financial interest in the subject matter they were studying and writing about. The question arises as to whether the university-based researcher is furthering science, or rather, furthering the aims and development of the private company's products and interests. The line between the two is likely to be blurred and neither the university, the researcher, nor the private industry companies are credible arbiters for clarification.

These financial conflicts of interest are an unintended, albeit predictable, outcome of technology transfer policy. However, financial conflicts are not the only problem. The increasingly entrepreneurial approach to science has produced a change in the culture of biomedical research. The zeal to protect intellectual property discourages the free and open exchange of information that is so fundamental to intellectual discourse and scientific advancement. Such non-financial conflicts and "conflicts of commitment" are at least as, if not more, deleterious than the financial conflicts.

Many universities have instituted renewed polices to address conflict of interest. This has been fueled by government agencies, such as the FDA and the Office of Human Research Protections, as well as by a growing interest on the part of patient rights activists. The latter advocate mandatory, enforced disclosure of both investigator and institutional conducts before the patient or subject begins the research trial. There are increasing questions as to whether or not disclosure, even an expanded level of disclosure, is sufficient to adequately protect human subjects. Disclosure is but one of the models for managing conflict of interest. It is criticized for being susceptible to loopholes and inconsistency.

Increasingly, it is being viewed as "too cheap and easy" a method for addressing conflicts. The other model is that of prohibition — a zero tolerance of financial conflict of interest. This was recently adopted at the NIH as a consequence of the problems that they have experienced. The prohibition model is criticized as having a chilling effect on research and development of new therapies and treatment. Several leaders in medicine support a prohibition policy. They argue that disclosure merely 'passes the buck" to the hapless subject/patient who is ill equipped to assess its importance in the equation of impending care.

In justifying prohibition, adherents note that university-based investigators should be held to a higher standard than researchers working in commercial venues, because of their role in training and mentoring the next generation of scientists. This movement toward prohibition is gaining favor. Advocates argue that the only way to solve conflict is to remove it completely by refusing to allow researchers to have a financial stake in the therapies they are researching.

Complicating any strategy to thwart conflict of interest is the patent and intellectual property regimes. As a result of the technology transfer laws, universities and researchers aggressively seek to patent their discoveries as early as possible. This preserves their competitive edge in the market of tomorrow and validates them as the inventor of the new technology. However, patenting simultaneously forecloses access to scientific information by other researchers working in the field, possibly also foreclosing follow-on discoveries that would benefit humankind. Licensing fees, even if affordable to the secondary follow-on researcher, will likely increase the overall costs of the downstream product. The concern is that patents could arguably retard new discoveries, rather than facilitate them. This is of particular concern in biotechnology and genetic research in which patents may secure and essentially "close off" information and discoveries that are vital stepping stones to the next generation of discovery.

Genetics and Biotechnology: Challenges for the Future

Questions of ethics and conflicts of interest are increased manifold in biotechnology and particularly in genetics research. In tinkering with genetic material, research scientists and clinicians are crossing new, more intimate treatment frontiers, and coming perilously close to species boundaries. In the course of decoding the genome, research reveals not only information about the individual human subject, but often about their family and population

subgroup. These ancillary subjects may not only be unwitting, but unwilling participants in the research enterprise.

Genetics research, in particular, presents challenges to the concept of the individual human subject. Much of research ethics focuses on the individual subject — the individual subject's right to autonomy, the individual subject's right to voluntarily agree to assume the risks, the individual subject's right to privacy and expectation of confidentiality. But, in fact, much of genetic research hinges not on one individual, but on their extended family disease pedigree and its epidemiologic significance.

Although pedigree studies and epidemiologic identification of disease related genes present threats to privacy and potential breaches of confidentiality, the potential harms to subjects are psychosocial and personal in nature. While these harms are significant and largely unbalanced by any subject benefit, they do not impose physical danger or injury upon the subjects. But that does not mean that they should be immune from ethical concern and consideration.

Moreover, as we look down the road, we see a realm of possibility that both intrigues and frightens us. One scholar has characterized biotechnology as being in the second of four obvious stages. The first stage was the preliminary research of the recombinant DNA era, where we first began to take apart and replicate DNA. This stage coincided with the late 1980s when biotechnology engaged venture capital, despite uncertain product potential. This first stage ebbed in the early 1990s as the biotech boom faded. In the wake of this first phase, the second stage commenced, fueled by the international Human Genome Project and the prospect of learning the genetic etiology of disease and, in time, devising treatments using biotechnology drugs, biologics and even somatic therapy. We are, quite obviously, firmly within this second phase at the present time. Down the line, however, there are two more stages postulated as waiting in the time-distant wings. In Stage 3, which will be in the mid 21st century, we will have gained the capacity to use somatic therapy to improve human capacity. This may go well beyond the Better Baby phenomenon heralded on the covers of popular magazines. For example, we may gain the capacity to withstand and flourish in the environment of another planet. In Stage 4, in the 22nd century, it is postulated that science will have the capacity to redesign the genome and *ergo* alter the species.

Even if these prophesies are more fiction than science, they provide a glimpse into the enlarging impact of biotechnology upon human life and increasing

scope of ethical issues in the future. Already weighty issues are presenting ethical challenges for researchers and policy-makers alike. They include those presented by genetically modified crops and biotechnology enhanced foodstuffs, predictive genetic tests and genetic "designer" drugs.

Genetically modified crops and biotechnology drugs to enhance yield, such as bovine somatotropin may have a negative impact on biodiversity and frustrate natural evolution at a molecular level. They may destroy the wild type norm and forever change the ecology. Moreover, the genetically modified new product may be unexpectedly susceptible to disease after displacing the wild type and result in extinction of the product or foodstuff. How will introduction of a genetically modified version change the natural evolution of the crop species? Is a crop species or the natural ecology something that should be accorded ethical standing and consideration? Similarly will the change in the natural evolution of the crop negatively affect or disadvantage populations in developing countries or non-dominant culture groups or peoples?

For example, recently, UN food aid to Guatemala included genetically modified "Starlink" corn that has not been approved for human consumption; this very corn had been removed from the US market as a result of high risk of allergic reaction. Moreover, the global effect of patenting is to benefit wealthy countries and regressively disadvantage developing countries – both in terms of access to the end-product and in participation in the research. One can easily argue that genetically modified organisms of all types present a level of uncertainty and danger that is unethical and immoral by that very fact.

A different, but equally troubling cascade of ethical concerns present with genetic susceptibility and predictability testing. In these cases, the proband or index patient is not the only affected party. Genetic information is at once the most – and least – personal information. How will this testing affect other family members, including future family members, who would perhaps not wish to know their genetic destiny? Genetic information has the power to impact family dynamics and foster intra-family stigmatization. It may have psychological effects on the family that are only just beginning to be appreciated. These include deleterious impacts on self-image, survivor guilt, and concepts of worthiness and marriageability. External to the family are issues of genetic discrimination in access to education, jobs, and other societal benefits. Will a "genetic underclass" be created? Moreover, what if the testing is informational only and there is no therapeutic opportunity or clinical utility. This is the case with many of the genetic tests currently available. What is the

opportunity cost vis-à-vis other health care interventions in a resource-limited society?

A third current example is genetic "designer" drugs. Such drugs offer individualized therapy tailored to the genetics of the disease or the individual ability to fight disease. Some of these drugs have already revolutionized the treatment of childhood cancers, offering a clear benefit to these critically ill children. However, as we consider designer drugs, the ethical propriety of devoting massive resources to benefit a few, rather than devoting the same resources to benefit many cannot be ignored. Suppose our designer drug will allow someone to escape the ravages of male-pattern baldness? Is that as compelling an aim as the designer drug that saves children with leukemia? Can we ethically justify devoting resources to male-pattern baldness, when those same resources could be used to address an issue more determinative of health? How will the development of designer drugs avoid ethnic and racial bias? Will they positively impact global health, or draw down resources to benefit the populations of the developed, industrialized nations?

Conclusion: Expanding the Ethical Paradigm

Clearly western "principles-based" bioethics is at present inadequate to fully address the issues arising in biotechnology and genetic research and innovation. The future will demand an ethical construct that is focused on the individual and more on populations. It will need to be more global and capable of addressing cultural diversity and pluralism. The new ethical paradigm will need to more firmly embrace social justice and consider the skewing of justice by politics and economics. It will need to address not only the rights of individuals and populations, but also ecologies. With respect to genetic modification, ethics and social justice requires risk evaluation with an orientation to the generations of the future.

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