Beyond Human Subjects: Risk, Ethics, and Clinical Development of Nanomedicines

Jonathan Kimmelman

Introduction

Like all policies, contemporary human research policies are the product of their history. The scandals and traumas motivating their creation — the Nazi doctors trials, Tuskegee, the Milgram experiment on obedience — however different in their particulars, all share a common narrative: a scientist, pursuing valued social ends, runs roughshod over the personal interests of disadvantaged human subjects. From the Nuremberg code through the latest revisions of the Declaration of Helsinki, research ethics policies have sought to erect a sphere of protection around the latter.

As a consequence of this history, all major policies start with a well-rehearsed model of human investigations. Clinical research is viewed as an encounter between investigators and volunteers. The clinical investigator is given certain duties. The human volunteer has certain moral entitlements. What is ethically at stake in human investigations inheres in the nature and quality of the interactions between investigators and volunteers. These interactions involve an asymmetry because the investigator has privileged knowledge and influence. Because the investigator divides her loyalty between science and participant welfare (much less professional advancement), her activities in relation to the interaction are refereed by a third party: the institutional review board (IRB).

This "refereed transaction model" has served science and subjects well in stemming the kinds of abuses that motivated the emergence of formalized research ethics policy. However, various widely shared ethical concerns are accommodated poorly, if at all, by this model. These fall into two broad categories. The first concerns the externalized impact of private transactions: research acts implicate the interests of many other parties besides human volunteers. How should these interests be incorporated into decision making during the planning, conduct, and reporting of studies? Second and closely related is the aims of clinical investigation. The institution of research is directed toward a particular end — namely, the production of socially useful knowledge. As a consequence, concerns about research extend beyond the welfare of private individuals. How should the institutional aims of clinical investigation direct the course of individual human studies where the personal interests of volunteers are not implicated?

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Nanomedicine clinical research is not unique in exposing limitations in the refereed transaction model. Whether its challenges to this model are more pressing I leave to others. It does, however, reveal some limitations in the way research ethics confronts risk and knowledge value in novel research arenas. In what follows, I will use the case of gene transfer to preview how the prosecution of nanomedicines might present certain challenges for the standard transaction model of research ethics. I will further argue that effective and ethical translation of nanomedicines would be advanced by devising frameworks and policy structures that address these issues. I close by sketching some options for negotiating the ethical challenges in translation of nanomedicines.

There is another crucial way in which a transaction model of research does not necessarily capture the universe of salient ethical and policy concerns in human investigation. Transactions in market settings serve the ends of parties to the transaction. However, clinical investigation as an enterprise serves a higher order function whose existence is independent and prior to those of the transactors: the institution of research aims to supply health care systems, patients, providers, and payers with a steady stream of reliable information. There are various ways that this function can be subverted without affecting the personal welfare of volunteers. Consider publication bias or reporting fraud in studies involving little or no risk to volunteers. If researchers report positive studies but not negative ones, medical evidence consumers receive a distorted view of evidence supporting an intervention or diagnositic.[1] Future patients can be harmed if such distorted evidence grounds their care. However, if a study involved minimal risk and patients were told in advance that researches might not share findings with the broader community, it would have neither subjected patient-subjects to undue burden nor violated their autonomy.

A crucial task for ethical research systems is to devise structures and policies that prevent negative externalities in research (or at least, arrange for them to be absorbed by the transactors) and that protect and advance the institutional mission of research. Research ethics has some role to play in both shaping these systems, and also in incorporating such considerations into the evaluation of individual research protocols.

Externalities and Ends

I began by describing a model of research participation as a kind of private transaction. Researchers recruit participants, obtain and maintain informed consent, and collect information. Volunteers provide their consent, adhere to protocols, and submit to a series of manipulations and observations. Like many private transactions, research transactions affect parties that are not conducting the transaction. Economists call these effects "externalities." Some externalities are positive. An academic medical center might gain in status because it has hosted an important trial; trainees who helped conduct a study might carry newly acquired skills into the workforce; patient volunteers might have a positive experience in a trial, and transmit this to peers, who then enroll in other studies. Negative externalities also occur in medical research. Trials can deplete the supply of patients meeting eligibility criteria for investigation, thus rendering rival studies unable to meet recruitment targets; patients might experience serious adverse events, the costs of which are carried by a third-party payer; a community might learn that samples from their members were used in genetic studies without consent or consultation, leading the group to declare a moratorium on further population-based studies.

A crucial task for ethical research systems, then, is to devise structures and policies that prevent negative externalities in research (or at least, arrange for them to be absorbed by the transactors) and that protect and advance the institutional mission of research. Research ethics has some role to play in both shaping these systems, and also in incorporating such considerations into the evaluation of individual research protocols.

Neither of these two limitations to the transaction model is entirely overlooked by research ethics policies. The World Medical Association includes a paragraph in the Declaration of Helsinki urging researchers to consider risks other than those directed at research subjects: "appropriate caution must be exercised in the conduct of research, which may affect the environment...."[2] (for a description of the origin of this statement, see the World Medical Association[3]). The

second edition of Canada's Tricouncil Policy warns IRBs to vet phase IV trials to ensure they do not entail "inappropriate utilization of public resources (e.g., diagnostic services and medical imaging."[4] The National Commission reportedly considered seven principles for the Belmont Report, one of which was "minimize consequential harm to others" (to streamline their message, they dropped this).[5] And of course, documents like the Belmont Report view the institutional mission of research as producing "benefit to society in the form of knowledge to be gained."[6] Yet policy formulations offered in these documents address negative externalized impacts of research, or threats to institutional ends of human investigation independent of risk posed to subjects by protocols, in a way that is either lacking or inconsistent with stated principles.

Gene Transfer and Nanomedicine

Having provided this background, I now turn to novel therapeutic development focusing on two realms: (1) gene transfer (which provides an observable record of two decades) and (2) nanomedicine (as of this writing, a new arena). The analysis that follows builds on the premise that one can use the former to learn something about the latter. There are obvious differences between the two fields. But commonalities that motivate the analogy are many. Both involve novel interventions with uncertain properties and risk profiles. Both are surrounded by high levels of expectation in patient communities — alloyed with public sensitivities. Both involve compositionally complex and multicomponent interventions. Both are characterized by competitive and private firm-driven innovation environments. Each involves a high degree of scientific and medical interdisciplinarity.

The regulatory environment surrounding each area was (for gene transfer) and is (for nanomedicine) unsettled; platform technologies do not fit squarely into pre-existing regulatory or administrative categories. As well, norms surrounding design, techniques, reporting, and interpretation were (and are) unsettled in each. If, indeed, gene transfer is prologue, then perhaps nanomedicine can look to issues and policies in gene transfer as guides.

For instance, the Common Rule language on IRB review functions states "the IRB shall determine that… risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result…. The IRB should not consider possible long-range effects of applying knowledge gained in the research."[7] The Belmont Report's listing of six considerations that should guide "assessment of the justifiability of research"[8] centers on risks and burdens to volunteers, rather than downstream consumers of medical evidence. Some argue that the principles articulated in the Belmont Report are broad enough to encompass some of the kinds of externalized impacts described above.[9] Though it is possible that ethics committees and others may take it upon themselves to address third-party risks or the value of studies apart from their burden for subjects, there is no language in either the Common Rule nor in the Belmont Report that clearly urges them to do so. There may very well be practical or policy reasons for directing IRBs to focus on the personal interests of volunteers. However, this begs the question of where and to whom policies should delegate responsibilities for addressing externalized impacts and threats to the research enterprise.

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Novel Therapeutic Strategies and Bystanders

An obvious externalized issue for both gene transfer and nanomedicine is risk to third parties. Many gene transfer protocols involve genetically modified viral vectors. Viral vectors can present risks not only to study volunteers, but also to workers and to personal contacts of study volunteers via shedding. I have previously called these "bystander risks."[10] For example, many gene transfer protocols use lentiviral vectors. A needle-stick injury in the course of handling could cause seroconversion, thus confounding a worker's future HIV tests. Numerous gene transfer studies have documented viral shedding from volunteers (for a recent review, see Schenk-Braat et al.[11]). To date, bystander harm in gene transfer seems to have been

theoretic: in 20 years of trials, no major incidents of bystander harm have been reported. However, there have been instances where gene transfer vectors were transmitted to workers.[12]

Some nanomedicines are believed to present risk of inadvertent exposure of workers during production, administration, and monitoring (see, for example, Murashov[13]). After delivery to patient-volunteers, residues of medical products will be excreted and/or discarded, thus exposing family members, the environment, and/or other individuals.

As discussed below, policies like the Common Rule make no provisions for bystander protections; other mechanisms, like occupational and/or institutional biosafety policies, do not currently address interests of nonsubjects who might be harmed by exposure to nanomedicines in trials.

Novel Therapeutic Strategies and Collaborators

The integrity of a research field is another externalized liability in cutting edge research. New research areas are often fragile endeavors. They must recruit sponsors, institutional supporters, investigators, and trainees. Since, by definition, novel arenas for medical innovation must coalesce before they produce decisive evidence of clinical utility, the stability of these coalitions depends on the status of members within the arena.

Whether deserved or not, gene transfer quickly developed an unfavorable reputation after a series of setbacks and publicized events. The most publicized was the death of a relatively healthy volunteer, Jesse Gelsinger, in a 1999 gene transfer protocol at the University of Pennsylvania. This occurred before the field had achieved major clinical successes. Various observers believe the University of Pennsylvania episode triggered more costly regulation, as well as a withdrawal of public and institutional support.[14]

Nanotechnology currently enjoys public support in the U.S.[15] However, nanomedicines have also received their share controversy, and they confront somewhat greater skepticism in Europe. Likely, the same kinds of pressures that threatened the integrity of the gene transfer research enterprise are also present in nanomedicine. These include strong professional and financial incentives for initiating trials (and reporting breakthroughs).

Various actors in research ethics — investigators, IRBs, and others — have responsibilities for addressing such potential externalized effects of research on sustained scientific collaboration.[16] For instance, there may be instances where the welfare interests of patient-volunteers are adequately secured, and yet a protocol presents a major liability for the broader scientific endeavor because it rests on an impoverished scientific foundation. This might occur where motivated and informed patients are willing to take a chance on a novel intervention that is believed to be safe, but where there is very little basis to believe the intervention will show activity, and where testing is unlikely to substantially advance understanding about nanomedicines. However, no language in the Common Rule, or in the Belmont Report, safeguards the integrity of a scientific enterprise. These policies also lack language to motivate studies that enhance the scientific quality of studies apart from their impact on patient-volunteers.

Novel Therapeutic Strategies and Ends

Clinical translation involves a large collaborative endeavor. Research actors join this collaboration pursuing different private interests. For instance, investigators conduct research pursuing ends like career advancement; patient-volunteers generally enter trials pursuing treatment; nonprofits support research in search of cures; and industry funds research to pursue commercial opportunities. As previously noted, however, this collaborative endeavor has an emergent, institutional purpose: the production of information that can inform further research, as well as health care decision-making. There are several ways that novel research arenas encounter challenges in attaining this overarching goal.

One is poor coordination. Formation of robust theories and generalized insights requires coordination of many different research actors. Different research actors have to address priority questions in an orchestrated manner. They must collect data and report it in a way that other actors can use. Dispersed information must be accessible, and it must be amenable to aggregation. Such coordination can only occur when research actors have incentives to align their practices along community norms.

Research areas that are mature, or that use common methodologies, often have established mechanisms and norms of coordination (consider cancer clinical research, which has norms for assessing disease response[17] and toxicity[18]). However, novel research areas contend with uncertainty about such issues as which variables to measure, which assays or reagents to use, and what findings to report (and how to report them). This coordination problem impairs the ability of new research areas to discharge their institutional mission. Arguably, it also presents problems for risk/benefit in trials since the value of accrued knowledge is related to the ability to assimilate findings within a larger body of theory and knowledge.

Gene transfer faced daunting challenges with coordination. Early on, a review of NIH investment in gene transfer research warned of problems coordinating intramural research programs.[19] Following the above-mentioned volunteer death, researchers and regulators were unable to pool prior studies using similar vectors and estimate risk because various trials used different techniques for measuring vector dosage.[20] It took another five years for the field to develop and validate a reference standard for the vector used in the University of Pennsylvania study. Reference standards for other vectors also took many years to develop and stabilize. Because research ethics – and structures like IRBs in particular — tend to focus on review of individual studies, it offers few mechanisms for promoting coordination and knowledge synthesis.

Nanomedicine confronts many similar challenges.[21] Protocols for manufacturing, purifying, and characterizing interventions must be described in sufficient detail to support independent replication.[22] Nomenclatures need to be developed so that different research teams can communicate and exchange materials.[23] Databases for housing large datasets need to be created and used.[24] These databases require ontologies for annotation.[25] Common assays for characterizing toxicity need to be developed.

Nanomedicine, Translation, and Protecting Others

How might the nanomedicine clinical translation arena address externalities and ends issues discussed above? One option would be to leave these issues to other actors. Environmental or public health impacts of nanomedicines, for example, could be left to occupational safety or environmental authorities. Coordination issues might be left to individual scientists. However, at least in the early years of nanomedicine clinical translation, leaving these issues to others is hardly a solution. For example, contemporary occupational and environmental regulations are unlikely, at the point of trial initiation, to be well suited to protecting workers or the environment. Safety regulations, which are currently mass-based, would need to be modified to suit nanomaterials because their toxicities are exerted through properties like surface area.[26] However, regulation and policy take a long time to change. Investigators and IRBs should therefore prepare for shouldering moral responsibility for environmental and worker safety.

There might nevertheless be straightforward ways for IRBs to incorporate consideration of ends and externalities. IRBs might ask investigators about assay validity, or generalizability where nonstandard assays are used. They can refuse protocols that, while presenting reasonable risks to informed volunteers, are unlikely to deliver much knowledge value due to flimsy supporting evidence. IRBs can ask investigators about their plans for trial reporting, and whether studies will be prospectively registered.

A second, more demanding option would be to expand the mandate of IRBs (and investigators) to address ends and externalities. As mentioned, concerns like welfare of bystanders or integrity of research fields do not fall within the current mandate of investigators and IRBs. Policies might be modified to capture these considerations. For example, IRBs might be asked to consider informed consent provisions for identifiable bystanders; they might be asked to weigh knowledge value independent of risk to subjects.[27] However, investigators and IRBs have finite cognitive and material budgets. Unless additional resources are provided, absorbing broader moral mandates could erode the ability of IRBs and investigators to protect the welfare interests of volunteers. A variation of the "expand the mandate" approach would be for granting agencies, professional societies, and journals to establish policies that better advance causes of bystander welfare, integrity and coordination. Journals, for example, might promote enhancement by requiring use of standardized reporting of agent properties, doses, and bystander safety issues.

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tors about their plans for trial reporting, and whether studies will be prospectively registered.

More ambitious still is the creation of new institutions and mechanisms. Gene transfer provides several models. With respect to bystander interests, Institutional Biosafety Committees (IBCs) review protocols for protection of workers and the environment. The function of IBCs might be expanded to capture nanomedicines that are not already captured under current policies. However, the IBC model has limitations. Their ethical remit is highly circumscribed. IBCs do not evaluate risk/benefit,[28] or procedures for disclosure of risk to bystanders where risks are nonminimal and bystanders are individually identifiable. Some commentators argue that, in such circumstances, bystanders should be informed (there are no clear reasons why exposures to toxic agents ought to be conditioned on informed consent when exposures are intentional, but not when they are foreseen but unintentional).[29] Another concern about IBCs is that their operations are opaque to members of the public whose welfare is implicated.[30]

Another institutional innovation in gene transfer is the Office of Biotechnology Activities (OBA), which resides within the National Institutes of Health. OBA oversees several programs. One is the organization of occasional safety conferences; another is the centralization of public adverse event reports. Probably the most visible OBA function is centralized review of gene transfer trial protocols through the Recombinant DNA Advisory Committee (RAC). Many commentators have examined the ethical function of centralized review,[31] and some have explored whether the RAC model might be extended to nanomedicine.[32] These commentaries have generally understood central review as providing extra muscle for protecting human subjects. I agree that centralized review enhances subject protection where protocols are complex and involve novel interventions. However, centralized review should be considered for other functions of equal if not greater importance. Protecting the integrity of nascent research areas and coordinating dispersed and competitive research actors are two such functions. Space limitations prevent further elaboration of this view.

Conclusion

This article began by describing the model of research ethics embedded within traditional policies. These policies center on three actors: the investigator, the volunteer, and the IRB. The alternative model of research ethics suggested here includes an expanded and networked series of moral agents and actors. The traditional actors of research ethics have a role to play in protecting and advancing the interests of other research stakeholders.

Ultimately, however, addressing moral concerns beyond the personal interests of human subject will require delegating some responsibilities to other actors, like medical journals or research societies. Nanomedicine is relatively immature; its institutions and practices are a work in progress. The task for actors in this field is to build structures and frameworks that efficiently address the issues canvassed above. The task for ethicists working in this area is to give these actors a reason and incentive for doing so.

Note

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References

1. There is limited language in research ethics policies that would condemn publication bias. For example, trial registration rules under FDAAA pertain only to clinical trials at phase 2 and above, and obligatory reporting pertains only to trials within a licensed indication; the Common Rule does not address publication. Paragraph 30 of Declaration of Helsinki urges publication of all results.
2. World Medical Association, "Declaration of Helsinki," *World Medical Journal* 54, no. 4 (2008): 122-25.
3. K. Myllymäki, Revising the Declaration of Helsinki: An Insiders' View," in A. Frewer and U. Schmidt, eds., *History and Theory of Human Experimentation: The Declaration of Helsinki and Modern Medical Ethics* (Stuttgart: Franz Steiner Verlag, 2007).
4. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, "Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans," December 2010.
5. A. R. Jonsen, "On the Origins and Future of the Belmont Report," in J. F. Childress, E. M. Meslin, and H. T. Shapiro, eds., *Belmont Revisited: Ethical Principles for Research with Human Subjects* (Washington, D.C.: Georgetown University Press, 2005).
6. The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research," edited by Department of Health, Education and Welfare, 1979.
7. U.S. Department of Health & Human Services, "Code of Federal Regulations: Title 45 - Public Welfare - Part 46 - Protection of Human Subjects, 45 CFR 46," 2009.
8. See the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, *supra* note 6.
9. D. B. Resnik and R. R. Sharp, "Protecting Third Parties in Human Subjects Research," *IRB* 28, no. 4 (July-August, 2006): 1-7.

10. J. Kimmelman, "Medical Research, Risk, and Bystanders," *IRB* 27, no. 4 (2005): 1-6.
11. E. A. Schenk-Braat, M. M. van Mierlo, G. Wagemaker, C. H. Bangma, and L. C. Kaptein, "An Inventory of Shedding Data from Clinical Gene Therapy Trials," *Journal of Gene Medicine* 9, no. 10 (October 2007): 910-921.
12. A. Tarantola, D. Abiteboul, and A. Rachline, "Infection Risks Following Accidental Exposure to Blood or Body Fluids in Health Care Workers: A Review of Pathogens Transmitted in Published Cases," *American Journal of Infection Control* 34, no. 6 (2006): 367-375; P. J. Openshaw, W. H. Alwan, A. H. Cherrie, and F. M. Record, "Accidental Infection of Laboratory Worker with Recombinant Vaccinia Virus," *The Lancet* 338, no. 8764 (1991): 459.
13. V. Murashov, "Occupational Exposure to Nanomedical Applications," *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology* 1, no. 2 (2009): 203-213.
14. J. Kimmelman, *Lost in Translation: The Ethics and Policy of Human Gene Transfer* (New York: Cambridge University Press, 2009).
15. M. Siegrist, C. Keller, H. Kastenholz, S. Frey, and A. Wiek, "Laypeople's and Experts' Perception of Nanotechnology Hazards," *Risk Analysis* 27, no. 1 (2007): 59-69.
16. A. J. London, J. Kimmelman, and M. E. Emborg, "Research Ethics: Beyond Access vs. Protection in Trials of Innovative Therapies," *Science* 328, no. 5980 (2010): 829-30.
17. P. Therasse, S. G. Arbuck, E. A. Eisenhauer, J. Wanders, R. S. Kaplan, L. Rubinstein, J. Verweij, M. Van Glabbeke, A. T. van Oosterom, M. C. Christian, and S. G. Gwyther, "New Guidelines to Evaluate the Response to Treatment in Solid Tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada," *Journal of the National Cancer Institute* 92, no. 3 (2000): 205-216.
18. U.S. Department of Health & Human Services, National Institutes of Health, and National Cancer Institute, "Common Terminology Criteria for Adverse Events (C.T.C.A.E.), Version 4.03," June 14, 2010.
19. S. H. Orkin and A. G. Motulsky, "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy," edited by National Institutes of Health - Office of Biotechnology Activities, 1995.
20. See Kimmelman, *supra* note 10.
21. D. G. Thomas, F. Klaessig, S. L. Harper, M. Fritts, M. D. Hoover, S. Gaheen, T. H. Stokes, R. Reznik-Zellen, E. T. Freund, J. D. Klemm, D. S. Paik, and N. A. Baker, "Informatics and Standards for Nanomedicine Technology," *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology* 3, no. 5 (2011): 511-532; M. Gaumet, A. Vargas, R. Gurny, and F. Delie, "Nanoparticles for Drug Delivery: The Need for Precision in Reporting Particle Size Parameters," *European Journal of Pharmaceutics and Biopharmaceutics* 69, no. 1 (2008): 1-9.
22. European Medicines Agency, Human Medicines Development and Evaluation, *1st International Workshop on Nanomedicines 2010 Summary Report*, *available at* <http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500098380.pdf> (last visited November 13, 2012).
23. R. Bawa and S. Johnson, "Emerging Issues in Nanomedicine and Ethics," in F. Allhoff and P. Lin, eds., *Nanotechnology & Society: Current and Emerging Ethical Issues* (City of publication?: Springer Science + Business Media, 2009): at 207-223.
24. See Thomas et al., *supra* note 21.
25. D. G. Thomas, R. V. Pappu, and N. A. Baker, "Nanoparticle Ontology for Cancer Nanotechnology Research," *Journal of Biomedical Informatics* 44, no. 1 (February 2011): 59-74; V. Maojo, F. Martin-Sanchez, C. Kulikowski, A. Rodriguez-Paton, and M. Fritts, "Nanoinformatics and DNA-Based Computing: Catalyzing Nanomedicine," *Pediatrics Research* 67, no. 5 (May 2010): 481-489.
26. A. Baun and S. F. Hansen, "Environmental Challenges for Nanomedicine," *Nanomedicine (London)* 3, no. 5 (2008): 605-608.
27. See Kimmelman, *supra* note 10.
28. J. Kimmelman, "Missing the Forest: Further Thoughts on the Ethics of Bystander Risk in Medical Research," *Cambridge Quarterly of Healthcare Ethics* 16, no. 4 (Fall 2007): 483-490.
29. K. S. Aultman, E. D. Walker, F. Gifford, D. W. Severson, C. B. Beard, and T. W. Scott, "Research Ethics: Managing Risks of Arthropod Vector Research," *Science* 288, no. 5475 (2000): 2321-2322.
30. See Kimmelman, *supra* note 10, *supra* note 28.
31. N. M. King, "RAC Oversight of Gene Transfer Research: A Model Worth Extending?" *Journal of Law, Medicine & Ethics* 30, no. 3 (2002): 381-389; C. Levine, R. Faden, C. Grady, D. Hammerschmidt, L. Eckenwiler, and J. Sugarman, "'Special Scrutiny': A Targeted Form of Research Protocol Review," *Annals of Internal Medicine* 140, no. 3 (2004): 220-223.
32. J. Paradise, S. M. Wolf, J. Kuzma, A. Kuzhabekova, A. W. Tisdale, E. Kokkoli, and G. Ramachandran, "Developing U.S. Oversight Strategies for Nanobiotechnology: Learning from Past Oversight Experiences," *Journal of Law, Medicine & Ethics* 37, no. 4 (2009): 688-705.