A Portrait of Nanomedicine and Its Bioethical Implications

Rebecca M. Hall, Tong Sun, and Mauro Ferrari

Introduction

A Brief Overview of Nanotechnology and Nanomedicine

While the definitions employed by different governmental agencies and scientific societies differ somewhat, the term "nanotechnology" is generally understood to refer to the manufacturing, characterization, and use of man-made devices with dimensions on the order of 1-100 nanometers (1 nanometer [nm] = 1 billionth of a meter). Devices that comprise a fundamental functional element that is nanotechnological are also frequently comprised within nanotechnology, as are manufactured objects with dimensions less than one micrometer. The differences in definition lead to occasional paradoxes, such as the fact that the most widely used nanodrug (albumin nanoparticles of dimensions up to 300 nm, comprising the anticancer drug paclitaxel) is labeled a "nanopharmaceutical" by governments of European countries, Canada, and Australia, but it is not a nanotechnology for the U.S. Food and Drug Administration (FDA). It is also common in scientific domains to restrict the term "nanotechnology" to objects that possess special, "emerging" properties that only arise because of their nanoscale dimension. Our perspective has been further restrictive, requiring

Mauro Ferrari, Ph.D., *is the President and CEO of The Methodist Hospital Research Institute where he holds the Ernest Cockrell Jr. Distinguished Endowed Chair, and is President of the Alliance for NanoHealth in Houston. He received his Dottore in Mathematics from the Universita' di Padova, Italy, and his Ph.D. in Mechanical Engineering from the University of California, Berkeley. Dr. Ferrari also served as Special Expert on Nanotechnology at the National Cancer Institute in 2003-2005, providing leadership into the formulation, refinement, and approval of the NCI's Alliance for Nanotechnology in Cancer, currently the world's largest program in medical nanotechnology.* **Rebecca M. Hall, Ph.D.,** *is the Manager of Scientific Communications for The Methodist Hospital Research Institute and has 15 years of experience in cancer and regenerative medicine research. Dr. Hall received her Ph.D. in Immunology from Baylor College of Medicine and B.S. in Biochemistry from the University of Illinois at Urbana-Champaign. She is an Aspen Cancer Conference Fellow and received the Theodore T. Puck Award for Cancer Research for her work on molecular cancer diagnostics while Assistant Professor of Cell and Molecular Biology at Baylor College of Medicine.* **Tong Sun, M.S., M.B.A.,** *is the Director of Central Operations for The Methodist Hospital Research Institute. Mr. Sun received a M.S. in Biomedical Sciences from the University of Texas Graduate School of Biomedical Sciences at Houston and a M.B.A. from the McCombs School of Business at the University of Texas at Austin. He spent 10 years at the University of Texas M. D. Anderson Cancer Center, conducting research on oncogenes, protein kinases, and signal transduction of leukemia. He was the Director of Management Operations in the Department of Nanomedicine and Biomedical Engineering at the University of Texas Health Science Center at Houston prior to joining The Methodist Hospital Research Institute.*

that the experimental data pointing to the existence of the emerging property be accompanied by a constructive proof of the necessity of the emergence of these properties, based on basic principles.[1] "Medicine" is a field, and "medicines" are pharmaceutical products; similarly, "nanomedicine" is a field comprising medical applications of nanotechnology, while "nanomedicines" are pharmaceutical products that comprise an enabling nanotechnological component, often a carrier, or vector, for the drug itself.

Fundamental events in the establishment and development of nanotechnology include the discovery of carbon-60 molecules, termed fullerenes or buckyballs, for which Nobel Prizes in Chemistry were awarded to Richard Smalley, Robert Curl, and Harold Kroto in 1995. The term "nanotechnology" was first used by Norio Taniguchi in 1974,[2] though many consider Richard Feynman's "There is plenty of room at the bottom" address at the American Physical Society at Caltech in 1959 as the visionary moment, the veritable manifesto of nanotechnology.[3] Feynman envisioned the ability to construct machines and devices one-atom-at-a-time, in what is now referred to as "bottom-up" nanotechnology. Nobel Prizes in Physics were awarded in 1986 to Gerd Binnig and Harold Rohrer for scanning tunneling microscopy, a technology that affords the ability to pick up individual atoms and assemble them in desired arrangements on a surface, which therefore significantly enabled bottom-up nanotechnology. Most recently, the 2010 Nobel Prizes in Physics were awarded to Andre Geim and Konstantin Novoselov for the discovery and characterization of graphene, a form of carbon based on a bi-dimensional arrangement of its atoms on the nanoscale.[4] The writer Isaac Asimov is frequently credited with early visions of nanotechnology, but the word itself is never found in his writings, though it then became a very common term in more recent science fiction. In his book *Fantastic Voyage*, Asimov envisioned nanoscale and microscale submarine-like robots that would travel through the bloodstream with miniaturized humans at the helm.[5] The notion of shrinking people to molecular size is obviously not compatible with the laws of science. Unfortunately, designing miniature "nanorobots" with nanoscale versions of the transport and guidance systems of their larger counterparts is also scientifically untenable.[6] The most successful nanomedical implements to date are indeed nanoparticles for intravascular injection and preferential transport to desired targets within the body. However, these particles have no guidance system, and owe their ability to concentrate within tumors to the fact that cancer blood vessels are typically hyper-permeable, and to the molecular recognition and transport properties of some of its constituents, as reviewed below in greater detail. The word "nanotechnology" was introduced into general use several years after a broad spectrum of scientific and technological developments at the nanoscale had taken place, which called for a new, encompassing term that embraced them — as commonly happens in the sciences. These nanotechnology precursors include the whole fields of colloid science and ultrafine particles, reverse osmosis membranes, zeolites, liposomes, and submicron fluidic systems, among others.

The most pragmatically impactful vision for nanotechnology, in our opinion, is owed to legendary entrepreneur Gordon Moore, who in 1965 predicted that the computational power of microchips would grow linearly in time, and more specifically would double every 18 months.[7] It is almost miraculous that his prediction, now known as "Moore's Law," has been holding true for about 50 years, so that now our everyday pocket electronics have much more computational power than NASA had at its disposal when flying Armstrong and Aldrin to the Moon. To increase computational power, it is necessary to develop devices where the charge message brought by electrons reaches its destination in a shorter time. Electrons travel through materials with a given speed, thus the only solution to gain computational power is to reduce the sizes. Therefore, the necessary enabler for this dazzling, historical, deeply society-changing growth in computational power is the ability to manufacture microchip components that become increasingly smaller — that is, to move from chip microtechnology to chip nanotechnology. The word "microchip" is still used for reasons of convenience; however, basically all electronics employed today are based on chip components that have dimensions in the tens of nanometers — truly "nanochips." Nanoelectronics used to be a small, academic part of the field of electronics, until a decade ago. Nowadays, nanoelectronics dominate all domains of electronics. The approaches used to manufacture electronic chips start with silicon wafers, and create thousands of identical copies of the chips through a process of addition of layers and selective removals of parts thereof through a technique known as photolithography. Thus, this type of nano-manufacturing does not involve the manipulation of individual atoms, but rather the carving out of nano-components from larger structures. Techniques of this type are referred to as "top-down" nanotechnologies. It is estimated that more than 1000 products using nanotechnologies are commercially available, with a global market size of billions of U.S. dollars, and rapidly rising, even outside of electronics.[8] All of these products are based upon top-down nanotechnologies. Bottom-up approaches,

however, provide essential enablers for fundamental scientific research, and may emerge with practical applications of great importance in future times.

The debut of nanomedicine in the clinic occurred in the mid-90s, with the regulatory approval in the U.S. and Europe of two liposomally encapsulated drugs: the anticancer agent doxorubicin and the antifungal antibiotic amphoteracin B (also used largely in the oncological setting).[9] Liposomes are nanoscale particles that are formed of lipid molecules in a way that resembles the basic structure of the cell membrane. Upon injection into the bloodstream, they concentrate with some degree of preferential distribution in certain cancers, owing to the fact that the new (angiogenic) blood vessels that support the growth of cancer lesions are typically leaky, presenting architectural defects (fenestrations) that allow the passage of the liposomes from the blood stream into the tumor proper. This physical phenomenon, known as Enhanced Permeation and Retention,[10] allows the drug to be delivered in higher concentrations to the tumor, thus increasing its local efficacy and reducing the undesired side effects that arise when the anticancer drugs accumulate in healthy parts of the body. The first liposomal nanodrug, Doxil, was originally afforded expedited review as a reformulation of the approved drug doxorubicin, approved for Kaposi's sarcoma in 1995 in response to strong public outcries for medical treatments during the AIDS crisis.[11] Liposomal nanodrugs have gone on to secure approval for many other cancer types and are widely used in clinics worldwide to treat cancers of the breast, ovaries, central nervous system in children, and many others. Approximately 130 multi-agent clinical trials involving liposomal drugs together with other conventional agents are currently taking place.[12] The "passive targeting" EPR effect is at the foundation of all but two clinical nanoparticle therapies to date involving liposomes, or any other type of particles (two exceptions will be discussed shortly). Despite over 30 years of research, no therapies have ever been approved that have added to the nanoparticle carriers a molecular recognition agent such as an antibody, aptamer, or a peptide. However, several clinical trials assessing these "active targeting" strategies are currently ongoing.[13] If successful, these would usher in a new era for medicine, allowing for the biologically specific targeting of therapeutic compounds to cancers and other intended pathological sites. Specific targeting is expected to result in a dramatic increase in therapeutic efficacy, and a concurrent decrease in adverse side effects.

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Two exceptions to the EPR mode of action have a fundamental role in the history of nanomedicine, in that they introduce truly divergent paradigms. The first is a special type of particle (categorized as "nano" outside of the U.S.) consisting of the biological molecule albumin and comprising the anticancer drug paclitaxel.[14] Approved in 2005 in the U.S., and shortly thereafter in many other countries, this formulation has proven extremely beneficial in ovarian and breast cancer, is the subject of many clinical trials for other cancer types, and has a market size that is beginning to rival those of the most successful cancer drugs of any type. The paradigmatic switch of albumin nanoparticles for the field is that they not only are subject to EPR, but most importantly also take advantage of the molecular chaperoning and transport effect of albumin itself, which allows them to actively penetrate the vascular walls (although with limited or no tumor selectivity) and enter the tumor to deploy its therapeutic payload. These particles are the first ever to have received approval by the FDA with a Mode of Action (MoA) that explicitly cited its albumin-assisted mode of transport, rather than the molecular MoA of the drug. The second exception to the EPR dominance in nanomedicine is the use of locally administered, superparamagnetic iron oxide nanoparticles,

which received approval in Germany and the European Union in 2010 for the treatment of the uniformly deadly brain cancer, Glioblastoma Multiforme.[15] The particles are infused directly into the brain tumor with imaging guidance, and therefore EPR is immaterial, and the broad generality of the method in oncology may be limited. The paradigmatic innovation here resides in the fact that the "drug" is the nanoparticle itself, and the mode of action is not traditionally pharmacological, but is rather in the form of thermal ablation therapy: upon selective irradiation of the nanoparticle-infused tumors with magnetic energy, the particles heat up and destroy the surrounding cancer tissue. There are many different variations on the theme of thermal ablation by different forms of exogenous energy (e.g., mechanical, radiofrequency, optical, X-ray, etc.) assisted by different nanoparticles acting as signal-converting antennae. Some of these are in clinical trials while most are in the preclinical, proof-of-principle stage. Gold nanoshells[16] were the first example of optically activated nanothermal therapy and are now in early stage clinical trials. It is interesting to note that they were classified as devices by the FDA rather than as drugs or biological or combination products.

To date, it has been impossible to secure regulatory approval for molecularly targeted nanoparticle therapy. We believe that there is a deep underlying reason for this: any increase in localization selectivity that may follow from the biological recognition of molecules expressed preferentially in cancer is adversely counterbalanced by an increase in the difficulty of transport across the biological barriers that largely determine the fate of agents circulating in the blood stream. Nanoparticles that are decorated with molecular targeting agents such as cancer-specific antibodies become much larger, "stickier," immunogenic, and likely to be cleared by the trapping organs of the body such as the liver, spleen, and lungs, as well as other defensive mechanisms.[17] To address the sequence of biological barriers and deploy the therapeutic agents in a more selective fashion, we have developed multistage vectors (MSV), which are essentially nested nanoparticle systems with a primary "mothership" submicron-sized carrier.[18] We have demonstrated the superior properties of MSV for RNAi therapeutics of ovarian cancer,[19] nanothermal therapy of metastatic breast cancer,[20] and imaging contrast,[21] among others. We believe that multistage systems are a third generation of therapeutic carriers and will afford a general method of cancer therapy. On the other hand, some individual nanoparticles with targeting agents have secured major advances in clinical trials and may also provide specific opportunities for novel treatments. For instance, cyclodextrin nanoparticles with transferrin as a targeting moiety enabled the first-ever clinical trial of siRNA therapeutics.[22]

Applications of nanotechnology to medicine involve several platforms that are not nanoparticle therapy-based. For instance, nanomaterials offer advantages for cell cultures and the programming of differentiation of stem cells for applications in regenerative medicine.[23] Nanochannels can be used for time-release drug delivery from implants[24] and immunoisolation of cell transplants.[25] A broad variety of nanotechnologies has been demonstrated to have applications in laboratory medicine.[26] Several of these platforms will be considered below within the framework of the discussion of the ethical implications of nanomedicine.

Finally, some literature presentations of nanomedicine include the discussion of "nanotoxicology," or the possible adverse health effects of nanotechnologies. In this article, however, we will largely focus on nanotechnologies for medical applications only, though a brief discussion of the societal impact of other industrial nanotechnologies is presented in the next chapter.

Nanomedicine and Personalized Medicine

A fundamental reason why nanomedicine may be expected to acquire a central importance in health care, as has been the case for nanoelectronics in the communication industry, is that nanotechnology comprises a set of necessary enablers for personalized medicine therapeutics to become reality. The notion of "personalized medicine" refers to the ability to provide the right therapeutic treatment to any individual patient at any time point in the evolution of their disease. This may be based on genetic, proteomic, metabolic, and/or other individual signatures of a disease in the context of the patient history and other health indicators. In such a detailed situation, it becomes necessary to have tools that are very specific, controllable in time and space, and responsive to changes in therapeutic needs as the patient progresses though therapy. It is our contention that nanotechnology has the most potential to enable this kind of therapeutic regimen.

Perhaps in no other field of medicine the necessity of personalization is as clear as in cancer.[27] The extraordinary diversity of cancer presentations is the fundamental reason why the war on cancer has been less successful than desired. In metastatic disease, patients normally have multiple lesions with different molecular signatures and treatment responses. Unless therapy can be suitably "personalized," it is difficult to imagine that the war on cancer will ever be won. Personalization of therapy requires five fundamental achievements:

1. Prediction of individual patient response to therapy
2. Delivery to the right location
3. Delivery at the right time
4. Triggering of beneficial biological defenses and healing processes
5. Rapid and efficient monitoring of efficacy and adverse effects during treatment for real time tailoring as the disease changes in response to therapy

As previously mentioned, these five functions have the potential to be enabled by nanotechnological platforms.[28] For example, nanoparticle vectors can enable site-selective delivery of therapeutics. Nanochannel systems can be used to produce "nanoglands" that release drugs from implants to enable timed-release and triggering of beneficial responses. These systems are capable of timed-release in a metronomic or self-regulated fashion that mimics the corresponding functions of the immune and endocrine systems of the body.[29] The engagement of the body's healing processes and the ability to enhance these processes is at the very heart of regenerative medicine, and nanotechnology and nanomaterials have an essential role in providing stimulatory and protective scaffolds where stem cells can rebuild, repair, and regenerate dysfunctional and damaged tissue.[30] The monitoring of the efficacy of therapeutic regimens requires the querying of soluble molecular biomarkers, which can be associated with pathological conditions and their evolution under therapy. Be these of the proteomic type, or simply measures of metabolism or other biological processes, the tests required will be performed by sensors, proteomic capture surfaces, or in combination with particulate matters such as signal amplifiers, i.e., platforms that are inherently nanotechnological, and will be more and more so over time.[31] It is exactly because of its expected pervasiveness that an ethical inquiry into nanomedicine and its expected impact is essential at this point in time.

Current Nanomedicine and Bioethical Considerations

Twenty-five years after Taniguchi coined the term "nanotechnology," Congress began hearings on the creation of the National Nanotechnology Initiative. This program was widely supported and implemented the following year, with an announcement by President Clinton at Caltech in 2000.[32] The initiative was created to stimulate nanotechnology research with an infusion of almost $500 million for funding by the NSF, the Pentagon, the Energy Department, NASA, the Commerce Department, and the NIH.[33]

The need for oversight and regulation to ensure the safety of emerging applied nanotechnology is generally agreed upon, though the extent and nature of this oversight is hotly debated. As the technology has developed, the regulatory challenges have become clearer: defining biocompatibility, biodistribution, manufacturing standards and environmental protection regulations, regulatory classifications, and new regulatory pathways for approval of multifunctional nanotechnologies. The greatest challenges are in the creation of standards and manufacturing specifications for nanoparticles, materials, and devices.

As the pace of nanotechnology innovations accelerated, so did concern about the unknown impact of new technologies on the environment, human health, and society. To address the growing need to regulate applied nanotechnology, Congress began hearings on the societal impact of nanotechnology and considered the creation of the American Nanotechnology Preparedness Center in 2003.[34] At this time, "nanotechnology" was still in the process of being defined, a task that would continue for years and is still debated today.[35]

The ethical issues were also in the early stages of definition and included risk/benefit balance of potential harm from manufacturing mishaps, loss of control of the technology, economic disruption from technological progress, potential for negative environmental impact, economic barriers to consumer access to beneficial technology, and abuse of technology for nefarious purposes like bioterrorism and biowarfare.[36] In addition, Peter Singer cautioned us to carefully consider the equity of this technology on a global scale, taking care to consider the needs and applications of nanotechnology in developing countries.[37] While of great concern, these are not issues unique to nanotech-

nology, but are concerns we repeatedly face during the early and rapid development of any new technology.

That being said, the need for oversight and regulation to ensure the safety of emerging applied nanotechnology is generally agreed upon, though the extent and nature of this oversight is hotly debated.[38] As the technology has developed, the regulatory challenges have become clearer: defining biocompatibility, biodistribution, manufacturing standards and environmental protection regulations, regulatory classifications, and new regulatory pathways for approval of multifunctional nanotechnologies.[39] The greatest challenges are in the creation of standards and manufacturing specifications for nanoparticles, materials, and devices.

Most agree that because of these regulatory challenges, one of our primary challenges is defining nanotechnology from a regulatory standpoint.[40] The nanotechnology applications that have been the focus of regulatory studies to date are often simple composition materials with size-dependent properties such as carbon nanotubes. However, more sophisticated and complex nanomaterials are on the horizon and require flexibility in our regulatory framework to address their assessment when the time comes.[41] Maynard argues that we should not define nanotechnology too tightly or as a unique class of materials based solely on size, but instead be guided by a list of about ten adaptive triggers for regulation based on shape, porosity, surface area, and chemistry with standard quantitative parameters around each that define how much of a change is tolerable before the regulatory process is initiated.[42] In addition, consideration of the application of a nanomaterial is critical for defining the regulatory context of the technology.[43]

Biodistribution and toxicity issues comprise a second area that is a critical area in need of definition and standardization. Previously clearly defined toxicity properties for a material are often rendered irrelevant when the same material is reduced to the nanoscale, which radically alters surface area and often imparts new properties to the material that make it behave differently in the body.[44] Carbon nanotubes are a good example of these challenges; carbon is a nontoxic material with an acquired property of toxicity that is size- and shape-dependent.[45] Defining the toxic potential of materials is essential information to underpin safety regulations for nanomaterial manufacturing and oversight in the market and clinic.[46]

Despite the early understanding of these challenges, these same challenges and regulatory issues continue to be a major issue in the field as discussed in detail in the Institute of Medicine Nanotechnology and Oncology Workshop Summary of 2011.[47] The lack of progress on this front calls for more attention to these hurdles, with a major conclusion from the workshop being that consensus on definitions and standards within the field, and collaboration between researchers and regulatory agencies on policy, was essential to move forward.[48] As these policies are developed, we are cautioned to consider lessons from past regulatory challenges, suggesting that we emphasize post-market monitoring, multi-agency monitoring, public input, adaptability, clarity of regulatory goals, and provision of adequate review panel expertise and other resources required for accurate assessment of technologies.[49]

Continuing research is needed to develop standard tools for imaging, tracking, and classification of nanoparticles. With these tools and standards in place, the stage is set for universal risk/benefit analysis, and mathematic/computer-guided design of nanoparticles for clinical applications.[50] In this way, we can approach the development of nanotechnology proactively, minimizing regulatory delays and protecting public health. At the same time, we can maximize the potential for advancement of the field with comparative data and the realization of innovations in medicine that come from technologies with this kind of revolutionary potential.[51]

In our laboratory, we approach medical research in a translational fashion, that is, with a dominant focus on bringing innovation to the clinic. Thus, the ethical framework we employ parallels the canons of medical ethics, which comprise four classical, fundamental principles: Beneficence, Non-Maleficence, Respect, and Justice. These are not competing principles, nor do they have a priority ranking among themselves. Rather, they need to be integrated and balanced within any decision-making process, in keeping with the ethical framework of the medical provider or researcher and those impacted by the medical decision. In what follows, we will discuss these four ethical considerations as they apply to nanomedical platforms.

Beneficence

The principle of Beneficence involves the necessity of providing the greatest good to society. In the absence of the balancing function of the other three principles, Beneficence merges with utilitarianism and suffers from the risks associated with subjective definitions of "good." Historically, differing perspectives on societal good have given rise to clear benefits, but also to medical horrors such as eugenics, which had its fundamental roots in pre-war Germany and the United States.[52] To place the need for Beneficence into perspective, it may be helpful to bear in mind that a person dies from cancer every minute in the U.S., every three in Europe, and about every fourteen in the world.[53]

These numbers have not changed significantly over the years. Cancer is the leading cause of death in the U.S. for people aged 85 and younger.[54] Nanomedicine can contribute toward Beneficence in the manners discussed above, i.e., by providing methods for more refined personalized treatments and reducing adverse side effects.

Molecular sensors and biomarker nanotechnologies can help screen populations for the occurrence of disease and yield opportunities to detect disease at early stages when treatment has the greatest likelihood to succeed. The very notion of risk assessment based on individual gene signatures is tightly linked to nanotechnology: gene sequencing technologies such as "microarrays" and "DNA chips" were initially developed in the early 1980s, when the fundamental manufacturing technology they were based on (i.e., photolithography, exactly the same as in the microelectronic industry) was only able to produce on-chip testing domains 50-100 microns, and thus the terms "microarray" and "microchip" were introduced.[55] The manufacturing platforms have evolved to control feature sizes on chips to tens of nanometers, and while the "micro" terminology has remained the same, the reality is that nanotechnology now dominates electronics. In parallel, biomolecular "nanochips" now have the ability to address much more complex problems than the sequencing of the human genome, such as the deconvolution of the proteome, metabolome, transcriptome, and other collections of biological molecules. Definition of these "omes" will expand our ability to assess the health and risk of acquiring a disease from our current capabilities — the domain of genes and probabilities, largely disconnected from the dynamic nature of life and interactions with the environment — to a much more global, accurate, and dynamic monitoring of health and disease risk for an individual in real time. From the perspective of Beneficence, then, it may be concluded that nanomedicine offers substantial opportunities for transformational improvements in health care. No novel issues or categories of ethical analysis appear to be required for nanomedicine, with respect to Beneficence: the same classes of considerations and approaches apply to any other form of innovation in medical research.

Non-Maleficence

The principle of Non-Maleficence echoes the Hippocratic tenet, "First, Do No Harm." It is certainly the case that nanomedicines and nanotechnology-based devices can have unintended adverse effects in patients, as discussed in more detail later in this section. This is the case for all medical interventions, and the balance of risks and benefits must always be taken into consideration. The primary purpose of regulatory agencies such as the FDA and their counterparts in other countries is exactly the examination of safety of drugs and medical devices, and it is carried out in a largely successful manner. It must be recognized, however, that the notion of complete safety is not only unrealistic, but also directly contrary to the efficacy of medical interventions:[56] a surgeon with a dull scalpel will be unable to accurately excise diseased tissues, yet a sharp scalpel may cause collateral harm in the process of surgery. Likewise, cancer chemotherapeutics used throughout history are among the most toxic substances on earth, and it is precisely their ability to effectively kill proliferating cells that renders them suitable for their medical uses; however, many "normal" and necessary cell types that proliferate and reproduce in the body at any given time are also killed by this therapy, not only those that form cancers.

Regulatory agencies in several countries have been successful at examining classes of nanomedicines and nanomedical devices, and their findings have authorized the clinical uses of the above-summarized classes of nanomedical products. No new general categories of examination, no new tests, no new protocols of analysis have been mandated for the regulatory approval of nanomedical products. These nanomedical products are classified in the traditional categories of devices, drugs, biological, and combination products, and follow exactly the same approval pathway as all entities in these classes. To date, judging from the

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actions of the regulatory bodies, there appears not to have been any need to introduce novel forms of toxicity analysis for nanomedical products. Actually, it is interesting to note that both major classes of clinically available nanodrugs have essentially received their regulatory approval based on their ability to provide equal or greater medical benefit to patients, while *reducing* adverse side effects for the same amount of active pharmaceutical ingredient.[57] The potent traditional chemotherapeutic agent doxorubicin has several side effects dose-limiting toxicities, especially related to heart damage. However, its nanopharmaceutical version (doxorubicin encapsulated within liposomes of approximately 100-150 nm diameter) dramatically reduces cardiotoxicity, and was initially approved on this basis in 1994, at the height of the AIDS crisis, for the treatment of Kaposi's sarcoma.[58] Liposomal doxorubicin, however, suffers sometimes from two other adverse side effects, including the so called "hand and foot syndrome," which may have been masked by the cardiac toxicities presenting first in doxorubicin-treated patients.[59] Secondly, patients sometimes experience pseudo allergy reactions (CARPA) due to complement activation by the liposomes, which can be minimized with pretreatment regimens. The potent conventional chemotherapeutic drug paclitaxel, which is widely used, for instance, for breast and ovarian cancer, in its current clinical formulation requires an additive that is extremely proinflammatory. Thus, patients receiving treatment must be co-treated with steroidal anti-inflammatory medications, which are simultaneously beneficial, but highly damaging substances themselves. It is actually the steroids that are the dose-limiting factor in these taxane treatments. A primary benefit in the introduction of paclitaxel containing nanoparticles of albumin, now among the most widely used anticancer drugs, was the fact that the inflammatory additives were not needed in the formulation. Based on this, larger amount of paclitaxel can be administered, without the limitations imposed by the use of steroids.

More generally, the objective of anticancer nanoparticle formulations, their very raison-d'etre, is to increase the concentration of the drugs they carry at the tumor site while reducing the amount dispersed in the healthy parts of the body. This conceptual design seeks to reduce adverse side effects while increasing efficacy (i.e., improving the "therapeutic index"). In the clinical trials that lead to the approvals of these nanodrugs, no deaths or major adverse events were attributed to the nanoparticles themselves. Of course, nanoparticles can potentially be damaging and toxic to patients. The strategy we recommend, and have always used in our primary investigations, is to always use nanoparticles that are fully degraded in the body, in a period of time that is well characterized (typically on the order of days to a few weeks), and with known, harmless degradation byproducts, which already exist in the body in much larger concentrations, and for which the metabolic pathways are satisfactorily understood. Materials that have these properties to an extent sufficient to warrant their clinical use include albumin and other proteins, certain lipids, meso- or nano-porous silicon (which degrade into orthosilicic acid), and certain biodegradable polymers (poly-lactic and poly-glycolic acids, and their copolymers). Novel nanotherapeutics that require non-degradable or partially degradable particles such as those comprising iron oxide, or gold nanoshells or fullerenes and carbon nanotubes may also be medically acceptable, if they can be excreted in a complete and sufficiently rapid manner. Again here it is helpful to recognize the medical context: non-degradable nanoparticles may be used for the thermal ablation of cancer, and may reside safely where they were infused for long periods of time, perhaps for the duration of the life of the patient, as routinely happens for macroscopic objects such as surgical clips or orthopedic implants. While no evidence suggests that they will be harmful long term (i.e., 20-30 years), it remains possible that the ill effects of these particles may be incompletely understood and could pose a risk for the safety of the patient as they age. Yet the question remains: do these concerns prohibit the use the nanoparticle-assisted nanothermal therapy in patients with uniformly lethal disease and a very short life expectancy? Diseases conferring a 6-9 month median survival time from diagnosis are particularly relevant in this context, such as glioblastoma multiforme, pancreatic adenocarcinoma, and hepatocellular carcinoma. It is perhaps not a coincidence that iron oxide nanoparticle-assisted thermal ablation therapy was first approved for glioblastoma multiforme.[60]

Another possible cause of unintended harm may arise from unintended distributions of the vectored drug in the body, such as to a body compartment where the naked drug typically does not concentrate as much. Of course, these are the occurrences that are studied in great detail in preclinical studies in animal models, and normally become evident in the early stages of clinical trials. On this topic, there seems to have been some major misunderstandings in the "nanotoxicology" literature, where this concern is sometimes presented as caused by the 'smallness of nanoparticles, that allows them to reach otherwise inaccessible parts of the body.' This is indeed a gross misunderstanding: small as they are, nanoparticles are literally millions of times larger than the drug molecules they carry and

are readily blocked by the compartmental biological barriers of the body.[61] The very reason why small molecule drugs have been the dominant force of the conventional pharmaceutical industry to date is that these molecules are so small that they can exit the blood stream and permeate almost any location in the body (and that is also why they create such adverse side effects). Nanoparticles do not have anywhere near comparable ease of permeation.

A related health care consideration in the realm of Non-Maleficence is the consideration of the adverse environmental effects of nanoparticles and nanotechnologies from non-medical industries. Concerns about the toxicity of nano-artifacts are reasonably heightened by the increasing number of industrial products being launched in many different markets, including sporting equipment, paints, textiles, sunscreens, and many others. It is estimated that over 1,000 different nanotechnology-containing products are currently present in the market.[62] Our article focuses on medical nanotechnologies and not with the health effects of non-medical nanotechnologies, which are treated elsewhere in this symposium. However, it may be appropriate to point out that all medical products are screened for safety, and rigorous methods are enforced for their distribution, handling, and disposition. This is obviously not the case for non-medical industries; the safety of all commercial products, nano- and non-nano, is effectively governed by the dynamics of other regulatory agencies, our legal system, and its emphasis on personal injury litigation. In the absence of pre-market safety testing, the *a priori* concerns about the safety of non-medical nanoparticle-containing products may well be justified, though fortunately, no death or serious injury to anyone has been attributed to any of these nanotechnologies to date. Recently, a whole field of investigative endeavor has emerged, which focuses on studying the potential adverse effects of industrial nanoparticles. While these studies may yield useful insights into novel forms of toxicity that pertain to nanoscale objects only, we hold the opinion that the field of "nanotoxicology" will not reach full maturity until suitable scientific standards are developed and validated. The currently available data are largely a collection of observations in convenient cell cultures and animal models, without quantitation, and without a demonstrated link to human safety. For preclinical research involving animal models, it is expected that these models recapitulate forms of human physiology and disease in a scientifically demonstrable fashion. Nanotoxicology might benefit from the application of similar standards of scientific rigor, which are regularly applied in the regulatory setting, and in expert toxicology laboratories,[63] but are often forgotten in the scientific literature.

Drug delivery approaches involving nanoparticles essentially predicate their success in enhancing therapy upon their ability to favorably negotiate the biological barriers that comprise a defensive system of the body.[64] It is then clear, though a chilling thought, that the same nanoparticle systems could be weaponized and used as agents of biological warfare or bioterrorism, and potentially mediate mass destruction. For instance, nanoparticles could be used to change the modality of infection of certain viruses, from blood contact-only to nanopathogens that are effective through inhalation or oral ingestion. To achieve this potentially devastating effect, it would suffice to package the virus into a carrier that enhances its bioavailability (concentration in the blood stream). Nanocarriers are available to transport viruses across biological barriers, such as the intestinal epithelium when administered orally, or via the lung alveolar macrophages if inhaled. Thus, for instance, a hemorrhagic virus that causes only limited damage because its infection can only be transmitted by direct contact with blood or biological fluids, could be intentionally spread to large populations through the air, or by contaminating food supplies. The technology required for this weaponization is relatively simple, and since terrorists are not required to secure FDA approval or OSHA standards, it could be manufactured by adapting methods published in the scientific literature on drug delivery for larger-scale production. Faced with the terrifying thought that one's research in medical technology could be used by others for these nefarious purposes, researchers may consider the ethical implications of their work in the context of Non-Maleficence and be faced with a limited cadre of options. They may stop research altogether, thus infringing dramatically on the ethical responsibilities arising from the principle of Beneficence. Or, they may continue research and warn all of the possible risks of weaponization of their research in the open literature. This second option poses the risk of drawing the attention of adverse parties and terrorists. One option is to continue medical research and inform only the "good people," but of course this requires the highly subjective judgment of "good," and a level of information control that would impede research and development. The simplest approach, and perhaps a frequent one, is simply to ignore these uncomfortable thoughts and continue on with one's research. In our laboratory, we have decided to only focus on research and development of drug delivery systems for intravenous injection and subcutaneous implantation. The risk of these

The ethical questions on how to deal with the possible weaponization of medical nanotechnologies by adverse parties extend beyond the domain of the concerns of individual scientists. Nations that subscribe to treaties that ban biological warfare research may not want to study such weaponized nano-virus systems, but must nevertheless consider their responsibility in ensuring the protection of their citizens.

becoming biological weapons is extremely low as they do not facilitate mass distribution.

The ethical questions on how to deal with the possible weaponization of medical nanotechnologies by adverse parties extend beyond the domain of the concerns of individual scientists. Nations that subscribe to treaties that ban biological warfare research may not want to study such weaponized nano-virus systems, but must nevertheless consider their responsibility in ensuring the protection of their citizens. However, it is generally impossible to build a protective system against a threat that is not well understood. Frightening as these thoughts may be, they are certainly not the first occurrence of ethical considerations concerning the crossover of beneficial science into weapon systems that may be used for nefarious purposes. One is immediately reminded of The Manhattan Project, the Atomic Energy Act of 1946, and the formation of the Atomic Energy Commission. The example of atomic energy and nuclear weapons stands prominently in the history of the ethical debate on dual-use research and development.[65] A more recent example is the discovery of a highly contagious version of the H5N1 virus by Ron Fouchier that unleashed a media frenzy over the potential weaponization of the virus and intense international scrutiny that delayed publication of the work until the ultimate conclusion that the response was a overaction to a misunderstanding of the research.[66] Far from being just limited to nanomedicine and the nuclear industry, these ethical issues are more the norm than the exception in new fields of science and certainly pertain to biotechnology,[67] materials science,[68] and many other fields of science throughout history.

These considerations of the potential violent uses of medical technologies bring about a broader category: that of the unintended consequences of one's research. The science fiction literature abounds in cataclysmic visions brought about by self-replicating, "swarming" nanosystems that take over the Earth, resulting from some killing mechanism with the exquisitely biological capability to reproduce.[69] While these ideas are clearly fictional, there have been conceptual breakthroughs in the synergistic combination of engineering artifacts at the nanoscale with biological nano-components. For instance, the molecular rotary domain of the F1-ATPase enzyme was connected with a silicon micromachined "propeller,"[70] to generate a biohybrid engine that is capable of harvesting energy and generating motion in biological environments. Scientifically exciting as these developments may be, they are simplistic in comparison to the science fiction version and certainly do not enable the production of a "killer nanomachine." In the face of the reality of the science, the very thought of these "swarm systems" appears impossible on the nanoscale.

To close the discussion of Non-Maleficence, the urgent need to identify interventions for medical tragedies such as cancer is again brought to the forefront of this analysis. It may be argued that any unnecessary, avoidable delays in the implementation of solutions to problems that take enormous tolls in suffering and loss of life constitute maleficence. Certainly, identical considerations are relevant to fields beyond nanomedicine; however, one must consider the delays in the safe and effective clinical implementation of novel nanotherapeutic agents that is due to a set of avoidable inefficiencies. These include:

- delays in scientific progress, brought about by the inertial resistance of the academic establishment to emerging multi-disciplinary fields such as nanomedicine;
- delays in the formulation of a proper and effective regulatory framework (though the proactive initiatives of the FDA in nanomedicine are laudable, having started with considerable energy and vision in 2003 in partnership with the National Cancer Institute); and
- the inertial resistance of the large pharmaceutical and medical technologies industries, which is reminiscent of the slow response of the chemical pharmaceutical industries to the advent of biotechnology and biopharmaceuticals about 30 years ago.

The provision of health care is strongly guided by the dynamics of reimbursement protocols and the educa-

tion and preferences of the medical care providers. Thus, attention to these aspects is equally necessary in order to bring safe and effective nanomedicines to the clinic. Finally, and most importantly, no transformational advance should be brought into the community-at-large without suitable opportunities for everyone to participate in the discourse and affect the path of its deployment. Ethical considerations are the foundations of healthy progress, and must be openly participatory in their undertaking. We therefore consider the publication of this volume on the ethics of nanotechnology and nanomedicine very timely and necessary for all stakeholders in the public, research, health care, industry, government, legal, and regulatory communities to participate in and expedite the building of consensus on this subject.

Respect

From our perspective, the principle of Respect is comprised of four major categories: the classical notion of Autonomy, and then informed consent, privacy, and performance enhancement.

Informed consent is truly a matter of Respect for individuals, regardless of their degree of education, their sophistication, skills, and intellectual capabilities. With the increasing complexity of medicine, including nanotechnology-based approaches, it becomes more challenging to provide information about treatment and validate the degree of understanding by patients in order to make informed consent meaningful. Without a true understanding, obtaining a signature on a piece of paper is largely perfunctory.

Nanomedicine can provide the enhancement of performance in many ways. For instance, performance-enhancing substances can be administered in a target or time-released, self-regulated fashion from intravascularly injected vectors, or subcutaneous implants acting as "nanoglands." These can be envisioned to stimulate responses upon need, going beyond the capabilities of the "normal" individual. Among the questions that arise in this context is the definition of "normal" at the individual level, which of course is required to differentiate medical therapy from performance enhancement. Obviously, "normal" is not an absolute category. The "normal" ability to run long distances among certain Kenyan populations, for example, might be much greater than the world averages, and probably greater than any possible comparison group. If a slower-than-average runner in that Kenyan group implanted a running-aid nanocapsule, then would that be considered a therapy against a "running disability," or a performance enhancement? Does the answer change if one considers the same treatment for someone in a different population? While adding a degree of greater potential efficacy and technological sophistication, nanomedicine does not create novel categories of ethical concerns with respect to performance enhancement. Caffeinated substance, energy drinks, steroids for athletes, erectile dysfunction medications used in the absence of erectile pathologies, and plastic surgeries for the non-disfigured present largely analogous ethical queries. Of course, with the increase in cost that may be associated with novel approaches to performance enhancement, it is reasonable also to ask what, if any, costs should be carried by society as opposed to the individual, if there is a "right" to performance enhancement, and what levels of risk are legitimately acceptable in the medical practice of providing enhancement.

A dominant aspect of rubric under Respect is Autonomy. Control over one's own medical treatment is a statement of respect for the sovereign authority of an individual over his/her own body and fate. Many prior studies have discussed the impact of genomic medicine on Autonomy.[71] By providing the scientific basis for assessing the likelihood of the developing diseases, genetic screening on one side affords the ability to try to prevent, treat more effectively, or manage these. On the other hand, it poses many substantial ethical questions. Who, if anyone other than the individual, is entitled to learn about one's genetic predispositions to disease? What are the roles and right of the family, the employer, the insurance company, and the government? In the social arena, does a spouse-to-be have the right to learn about predispositions to illness of the person s/he is about to marry? Whether the information is provided directly or through consent of the individual, what are its ethically acceptable uses? Can a genetics-based risk profile be used to deny employment or insurance coverage, or to set its price? We do pay premiums on insurance, in different domains, if we are at higher risk of adverse events, and pre-existing conditions have historically been the base for denial of coverage. Returning to the medical insurance arena, where is the line that demarcates the "pre-existing condition" that can be grounds for denial of coverage, or its premium pricing? Cancer typically takes 5-15 years to develop into a clinically detectable disease. The progress toward the malignant, and ultimately deadly, metastatic phenotype normally requires multiple stages of cellular transformation, triggered by environmental insults or simply adverse random mutations. So, at what point is a cancer a cancer? We do not know, and possibly never will, which of the intermediate stages in the progression to the clinically detectable malignant cellular phenotype is a point-of-no-return, with commitment to a malignancy that cannot be treated by the individual's own

immune defenses, *at the particular point in time and environmental circumstances that the individual is in*. The distinction between "pre-existing condition" and genetic inclination is largely arbitrary and scientifically indefensible. Along the same lines of argument, the distinction between therapy and prevention is a blurry artifact, a resounding statement of our medical ignorance. Sharp distinctions are not scientifically warranted, though they are pragmatically convenient in some cases.

A better approach perhaps would be that of introducing a metric — the notion of a stochastic "distance" between a state of health and a recognized state of disease. This is a conceptual transition that is already happening as our scientific frame of reference transitions from genomics to "multi-omics." The analyses of collections of molecular families, such as proteomics, transcriptomics, metabolomics, lipidomics, and many others, provide a more comprehensive analysis of personal health. Nanotechnology is critical for these "omics" and therefore enables more comprehensive molecular profiling of individuals. These other areas are intrinsically more complex problems than "simple" genomic sequencing. This may well be recognized by considering three facts that make proteomics the ultimate needle-in-the-haystack problem. First, there is at least a 50-1 ratio of proteins to genes. Second, the protein concentration in blood and biological fluids varies by as much as 10 orders of magnitude. Third, no amplification techniques exist, such as PCR for protein analysis. The technology platforms that are required to handle challenges like this are by necessity of a nano-scale nature. An illustrative metaphor to visualize the necessity of going beyond genomics is that the genes are the cards one is dealt while the protein and other molecular portraits are the images of the card game, play-by-play, fully dynamic and interactive.

Nanotechnology will afford us the ability to transition from the fixed probability analysis of genomic medicine to a more comprehensive profile of health, disease risk, and responses to therapy for an individual. With this, the ethical questions that pertain to genomic medicine are current matters of debate and also considerations for nanotechnology.[72] What uses can be allowed for this information? An argument against applying a tax or similar measure that uses societal pressure to affect behavioral changes (e.g., discourage smoking, drinking alcohol, or eating high-fat diets) is that it infringes on the freedom of individuals who can manage these behaviors without causing harm to themselves, or others. What happens when we have enough information to discern between those who can balance behaviors and those who cannot? Or those who respond positively or negatively to the same stimulus such as cigarettes, alcohol, high-fat diets, etc., and we can positively predict their responses using "-omic" measures enabled by nanotechnology? Not long ago syphilis testing was required in many states to obtain a marriage license. The requirement disappeared over time, largely because of the availability of treatment, and not on ethical grounds. Is there any difference between requiring testing for syphilis, and requiring a full genomic profile, with a map of probability for many diseases? Is it the right of a spouse-to-be to know that the person he or she is about to marry has a 70% likelihood of dying of glioblastoma before age 40? Is it the right of an employer to know the same about someone they are about to spend years and resources training for a pivotal position? Can employment be then denied based on "distance to disease"?

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These are ethical concerns that resemble those of genomics, but perhaps in a much heightened form because of the potential breadth of information that may be enabled by nanotechnology. In the domain of Autonomy with respect to therapeutic choices, there is also a qualitative but perhaps not quantitative parallel between "-omic" nanomedicine and genetics. Molecularly targeted drugs are extremely efficacious and often curative of otherwise untreatable diseases, but their efficacy is limited to a small fraction of the population with a nominally identical cancer. For instance, a patient with a HER2/neu positive breast cancer typically respond well to Herceptin treatment.[73] However, only 5-15% of all breast cancer patients have HER2 positive disease, and not all of these respond equally

well, some not at all. One underlying reason is that the HER2 overexpression is not a matter of black or white; it is a graded, quantitative metric, and the response is also influenced by other factors such as immune status and unknown factors. The question then is: what is the right ethical approach to deciding who gets the molecularly targeted drug? These are typically very expensive, and there is no guarantee of their efficacy. Should the patient be entitled to request the treatment, though there is only a 10% likelihood that it will work for them? Does it make any difference if the patients pays for it themselves, or it is covered by their private insurance or the government? Does it make any difference if it is the doctor who recommends the treatment on the grounds that there is nothing else that can be done, even though the prognosis is not good? What efficacy probability value justifies treatment? How is that number decided upon, and by whom? Do factors such as age, overall health status, value to society, criminal record, wealth, employment, marriage status, age, number of dependents, military service, or others factors enter the life-or-death algorithm? If these are to be governmental decisions, then it may be reasonable for some to resort to a utilitarian algorithm — that is, to invest resources in a manner that ensures the greatest good for the population as a whole. But then, is the individual autonomy not violated *de facto*? If it is a collective governance body that decides who gets what treatment, is there not a risk that there will be a funneling of resources toward preferred segments of the population, thus effectively creating a "cast of ubermensch"? And then again, how is this different, if at all, from the current state of affairs, where life expectancy in some regions of the world exceeds 70 years, while in others it hovers around 40 years? The advent of nanomedicine will heighten our awareness of these classes of concerns, even if they clearly pertain to all domains of medicine.

At this point of the analysis, the transition into the category of Justice is natural. This pertains to the notion that equitable access to health care should be provided to all. Of course, that has never happened in history, but with the growth of medical sophistication, the health care inequalities are growing at an unprecedented pace. Two generations ago, a blood cancer in a child would have also uniformly meant a death sentence, no matter what the location, wealth, and societal importance of the family of the child. Fortunately, great progress has been made in the treatment of childhood leukemias, but just as unfortunately, only a small portion of the world population has access to the required drugs. So, a child will die unless born into a fortunate family and in a fortunate location. Similarly, death by cervical cancer has decreased dramatically in the wealthier part of the world, where it appears to be on its way to virtually disappearing.[74] This fortunate development is due to the pervasive use of cytological tests (the time-honored Papanicolau smear), new drugs, and vaccines against the general cancer causative pathogen, the Human Papilloma Virus. On the other hand, the most prevalent cause of cancer death in women in many African regions is still cervical cancer.[75] The main reasons for this concern are cost and access. The new drugs and vaccines are typically not available in this part of the world, or are too costly. Pap smears must be administered with regularity by physicians, but medical providers are frequently not available in sufficient numbers, especially in remote areas. Pap smears must be analyzed by cytology laboratories with suitable equipment and trained personnel, and both of these are also scarce resources.

Nanotechnology can help address all three of these problems. Investigators have developed optical imaging instrumentation (an "optical colposcope") that can be used even by minimally trained operators to examine the cervical surface during an ambulatory visit.[76] During the examination, the existence and exact location of a local malignancy or precancerous lesion can be readily visualized, without pathology services. Two basic detection modes can be envisioned for such a device: one in which the optical properties of the tissue itself can be used for the diagnosis, and one in which a nanoparticulate contrast agent with biological recognition properties is used. In either case, the diagnosis is immediate, and may not require an attending physician. The next step along this development trajectory is to incorporate therapeutic modalities into the same instrument. These could be light-activated thermal ablation or the infusion of a therapeutic agent. While the current diagnostic, therapeutic, and preventive modalities for cervical cancers may be preferred over this system when available, the novel methodology probably would save many lives and greatly reduce the burden of suffering in areas where care is currently not available. This example illustrates a very innovative and potentially beneficial paradigm for the development of nanomedicine from the perspective of the principle of Justice[77] — that is, to focus on developing nanotechnologies and nanomedical platforms that are designed with the purpose of reducing health care disparities. In contrast, even in the most benign of contemporary approaches to bridging costly innovation and Justice, the norm is that industry first develops a new drug or device, which is invariably priced very much out of the reach of most health care systems in the world. This is then accompanied by the donation of sometimes large provisions of the new drug or device to underprivileged populations. We believe that

the direct development of low-cost systems that take into account the reality of the circumstances that lead to the health care disparities is a superior approach to enhancing Justice, for nanotechnology and medicine in general.

Even in the wealthiest regions of the world, the cost of novel medicines and medical devices are frequently prohibitive, and access to them is limited to the most privileged or denied for all because they are too costly to bring to market. Nanomedicines comprising an active "conventional" pharmaceutical agent, such as doxorubicin and paclitaxel, plus a vectoring nanoparticle, are typically more expensive per dose or per unit mass of the active agent than the naked drug by itself. This may be a misleading observation, however, if it is related to the cost of manufacturing of the drugs; the price points for the pharmaceutical and medical device industries are governed by market dynamics, and only in minimal part by the cost of manufacturing. Profit margins for the pharmaceutical industry on patented drugs are very high, which is partially justified by high costs of research and development, which requires experienced personnel, stable and technologically advanced infrastructure, equipment maintenance, experienced management, and culture of innovation. Be that as it may, in the pharmaceutical world, the profits overwhelm in magnitude the manufacturing expenditures. Thus, the higher costs of the clinically available nanodrugs may be attributed more to the fact that they are "newer" and more effective than their pharmaceutical principles alone, with the added manufacturing costs playing a minor role. The first-ever cost effectiveness analysis, directly comparing conventional cancer drugs and nanotherapies was recently presented.[78] This analysis concluded that while nanodrugs are more expensive per treatment, the reduction of costs associated with the treatment of side effects and the additional health benefits induced by the nanodrugs make them overall a less costly option than conventional treatment on the basis of a Quality-of Life-Years adjusted analysis.

Conclusions

Nanotechnology offers extraordinary opportunities for medical advances, especially as a set of enabling platforms for personalized medicine. The environmental risks from medical nanotechnologies nanotech are very modest. It appears that current regulatory approaches to nanomedical innovations are adequate, as demonstrated by the fact that the first nanomedicines were approved for clinical use about 20 years ago, and there are multiple classes of nanodrugs currently in broad clinical use, especially in oncology, with no recall or major adverse events to date. Proper attention must be given to potential concerns over the environmental implication of large-scale uses of industrial nanotechnologies, where there are no premarket safety screens. It is, however, comforting that no death or major injury have been attributed to nanotechnology to date. Risks associated with military and terrorist uses of nanotechnology and nanomedicine are speculative at this point, but may be substantial in the future. Nanotech-enabled personalized medicine poses ethical questions of autonomy and privacy, and there is a potential risk that nanomedicines might be available only to privileged societies, at least initially. On the positive side, nanotechnology offers yet largely unexplored opportunities for medical advances specifically directed at underprivileged populations with the intent to reduce health care disparities. With the evolution of more sophisticated nanomedical platforms, the boundaries between medicine and performance enhancement may become more blurred. In this respect, and in all respects explored in the field, the ethical questions posed by nanomedicine are the identical counterparts of questions that have arisen in multiple other domains of medicine and medical research: no new categories of bioethical thoughts have emerged to date. In this article, we have analyzed the current state and prospects of nanomedicine from the perspective of the four principle of medical ethics: Beneficence, Non-Maleficence, Respect, and Justice. Our conclusion is that the greatest risk in nanomedicine at this time may well be in not taking advantage of its full potential for the benefit of society.

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References

1. T. Theis, D. Parr, P. Binks, J. Ying, K. E. Drexler, E. Schepers, K. Mullis, C. Bai , J. J. Boland, R. Langer, P. Dobson, C. N. Rao, and M. Ferrari, "Nan'o.tech.nol'o.gy n.," *Nature Nanotechnology* 1, no. 1 (2006): 8-10.
2. N. Taniguchi, "On the Basic Concept of 'Nano-Technology'," in *Proceedings of the International Conference of Production Engineering*, Tokyo, Part II, Japan Society of Precision Engineering, 1974.
3. R. P. Feynman, "There's Plenty of Room at the Bottom," *Engineering and Science* (1960): 22-36, *available at* <calteches.library.caltech.edu/47/2/1960Bottom.pdf> (last visited October 25, 2012).
4. *The Nobel Prize in Physics 2010*, Nobel Prize website, *available at* <http://www.nobelprize.org/nobel_prizes/physics/laureates/2010/> (last visited October 25, 2012).

5. I. Asimov, *Fantastic Voyage: A Novel* (Boston, Houghton Mifflin, 1966).
6. R. Baum, "Nanotechnology: Drexler and Smalley Make the Case for and against 'Molecular Assemblers,'" *Chemical & Engineering News* (American Chemical Society), 81, no. 48 (2003): 37–42, *available at* <http://pubs.acs.org/cen/coverstory/8148/8148counterpoint.html> (last visited October 26, 2012).
7. G. E. Moore, "Cramming More Components onto Integrated Circuits," *Electronics* 38, no. 8 (1965), *available at* <ftp://download.intel.com/museum/Moores_Law/Articles-Press_Releases/Gordon_Moore_1965_Article.pdf> (last visited October 26, 2012).
8. BCC Research Market Forecasting, *Nanotechnology: A Realistic Market Assessment. 2010*, NAN031D, *available at* <http://www.bccresearch.com/report/NAN031D.html> www.bccresearch.com/report/NAN031D.html> (last visited October 26, 2012).
9. M. Ferrari, "Cancer Nanotechnology: Opportunities & Challenges," *Nature Reviews in Cancer* 5, no. 3 (2005): 161-171; M. Ferrari, "Frontiers in Cancer Nanomedicine: Directing Mass Transport through Biological Barriers," *Trends in Biotechnology* 28, no. 4 (2010): 181-188. C. Salvador-Morales, P. M. Valencia, A. B. Thakkar, E. W. Swanson and R. Langer, "Recent Developments in Multifunctional Hybrid Nanoparticles: Opportunities and Challenges in Cancer Therapy," *Frontiers in Bioscience* (Elite Ed.) 4, no. 4 (2012): 529-545; R. Langer, "Drug Delivery and Targeting," *Nature* 392, no. 6679, Supp. (1998): 5–10.
10. J. Fang, H. Nakamura, and H. Maeda, "The EPR Effect: Unique Features of Tumor Blood Vessels for Drug Delivery, Factors Involved, and Limitations and Augmentation of the Effect," *Advanced Drug Delivery Reviews* 63, no. 3 (2011): 136-151; H. Maeda, J. Wu, T. Sawa, Y. Matsumura, and K. Hori, "Tumor Vascular Permeability and the EPR Effect in Macromolecular Therapeutics: A Review," *Journal of Controlled Release* 65, no. 1-2 (2000): 271-284.
11. Y. C. Barenholz, "Doxil® - The First FDA-Approved Nano-Drug: Lessons Learned," *Journal of Controlled Release*, March, 29, 2012, *available at* <http://www.ncbi.nlm.nih.gov/pubmed/22484195> (last visited October 26, 2012); P. McGee, "Delivering on Nano's Promise," *Drug Discovery & Development Magazine* 9, no. 10 (2006): 12-18.
12. Clinicaltrials.gov, Bethesda (MD): National Library of Medicine (US), *available at* <http://www.clinicaltrials.gov/ct2/results?term=liposome&recr=Open&no_unk=Y> (last visited October 26, 2012).
13. M. E. Davis, J. E. Zuckerman, C. H. Choi, D. Seligson, A. Tolcher, C. A. Alabi, Y. Yen, J. D. Heidel, and A. Ribas, "Evidence of RNAi in Humans from Systemically Administered siRNA via Targeted Nanoparticles," *Nature* 464, no. 7291 (2010): 1067-1070; Calando Pharmaceuticals, "Safety Study of CALAA-01 to Treat Solid Tumor Cancers," in ClinicalTrials.gov, Bethesda (MD): National Library of Medicine (U.S.), NLM Identifier: NCT00689065, *available at* <http://www.clinicaltrials.gov/ct2/show/NCT00689065> (last visited October 26, 2012); BIND Biosciences, "A Study of BIND-014 Given to Patients with Advanced or Metastatic Cancer," in ClinicalTrials.gov, Bethesda (MD): National Library of Medicine (US), NLM Identifier: NCT01300533, *available at* <http://www.clinicaltrials.gov/ct2/show/NCT01300533> (last visited October 26, 2012).
14. P. Vishnu and V. Roy, "Nab-Paclitaxel: A Novel Formulation of Taxane for Treatment of Breast Cancer," *Womens Health* (London) 6, no. 4 (2010): 495-506.
15. K. Maier-Hauff, F. Ulrich, D. Nestler, H. Niehoff, P. Wust, B. Thiesen, H. Orawa, V. Budach, and A. Jordan, "Efficacy and Safety of Intratumoral Thermotherapy Using Magnetic Iron-Oxide Nanoparticles Combined with External Beam Radiotherapy on Patients with Recurrent Glioblastoma Multiforme," *Journal of Neurooncology* 103, no. 2 (2011): 317-324.
16. M. Hu, J. Chen, Z. Y. Li, L. Au, G. V. Hartland, X. Li, M. Marquez, and Y. Xia, "Gold Nanostructures: Engineering Their Plasmonic Properties for Biomedical Applications," *Chemical Society Reviews* 35, no. 11 (2006): 1084-1094; L. R. Hirsch, R. J. Stafford, J. A. Bankson, S. R. Sershen, B. Rivera, R. E. Price, J. D. Hazle, N. J. Halas, and J. L. West, "Nanoshell-Mediated Near-Infrared Thermal Therapy of Tumors under Magnetic Resonance Guidance," *Proceedings of the National Academy of Sciences of the United States of America* 100, no. 23 (2003): 13549-13554.
17. See Ferrari (2010), *supra* note 9.
18. E. Tasciotti, X. Liu, R. Bhavane, K. Plant, A. D. Leonard, B. K. Price, M. M. Cheng, P. Decuzzi, J. M. Tour, F. Robertson, and M. Ferrari, "Mesoporous Silicon Particles as a Multistage Delivery System for Imaging and Therapeutic Applications," *Nature Nanotechnology* 3, no. 3 (2008): 151-157.
19. T. Tanaka, L. S. Mangala, P. E. Vivas-Mejia, R. Nieves-Alicea, A. P. Mann, E. Mora, H. D. Han, M. M. Shahzad, X. Liu, R. Bhavane, J. Gu, J. R. Fakhoury, C. Chiappini, C. Lu, K. Matsuo, B. Godin, R. L. Stone, A. M. Nick, G. Lopez-Berestein, A. K. Sood, and M. Ferrari, "Sustained Small Interfering RNA Delivery by Mesoporous Silicon Particles," *Cancer Research* 70, no. 9 (2010): 3687-3696.
20. H. Shen, J. You, G. Zhang, A. Ziemys, Q. Li, L. Bai, X. Deng, D. R. Erm, X. Liu, C. Li, and M. Ferrari, "Cooperative, Nanoparticle-Enabled Thermal Therapy of Breast Cancer," *Advanced Healthcare Materials* 1, no. 1 (2012): 84-89.
21. J. S. Ananta, B. Godin, R. Sethi, L. Moriggi, X. Liu, S. E. Serda, R. Krishnamurthy, R. Muthupillai, R. D. Bolskar, L. Helm, M. Ferrari, L. J. Wilson, and P. Decuzzi, "Geometrical Confinement of Gadolinium-Based Contrast Agents in Nanoporous Particles Enhances T1 Contrast," *Nature Nanotechnology* 5, no. 11 (2010): 815-821.
22. See Davis, *supra* note 13.
23. S. Prakash, A. Khan, and A. Paul, "Nanoscaffold Based Stem Cell Regeneration Therapy: Recent Advancement and Future Potential," *Expert Opinion on Biological Therapy* 10, no. 12 (2010): 1649-1661; A. Dolatshahi-Pirouz, M. Nikkhah, K. Kolind, M. R. Dokmeci, and A. Khademhosseini, "Micro- and Nanoengineering Approaches to Control Stem Cell-Biomaterial Interactions," *Journal of Functional Biomaterials* 2, no. 3 (2011): 88-106; A. Mata, L. Palmer, E. Tejeda-Montes, and S. I. Stupp, "Design of Biomolecules for Nanoengineered Biomaterials for Regenerative Medicine," *Methods in Molecular Biology* 811(2012): 39-49.
24. T. A. Desai, D. J. Hansford, L. Kulinsky, A. H. Nashat, G. Ras, J. Tu, Y. Wang, M. Zhang, and M. Ferrari, "Nanopore Technology for Biomedical Applications," *Biomedical Microdevices* 2, no. 1 (1999): 11-40; D. Fine, A. Grattoni, E. Zabre, F. Hussein, M. Ferrari, and X. Liu, "A Low-Voltage Electrokinetic Nanochannel Drug Delivery System," *Lab on a Chip* 11, no. 15 (2011): 2526-2534; D. Fine, A. Grattoni, S. Hosali, A. Ziemys, E. De Rosa, J. Gill, R. Medema, L. Hudson, M. Kojic, M. Milosevic, L. Brousseau Iii, R. Goodall, M. Ferrari, and X. Liu, "A Robust Nanofluidic Membrane with Tunable Zero-Order Release for Implantable Dose Specific Drug Delivery," *Lab on a Chip* 10, no. 22 (2010): 3074-3083; A. Grattoni, H. Shen, D. Fine, A. Ziemys, J. S. Gill, L. Hudson, S.Hosali, R. Goodall, X. Liu, and M. Ferrari, "Nanochannel Technology for Constant Delivery of Chemotherapeutics: Beyond Metronomic Administration," *Pharmaceutical Research* 28, no. 2 (2011): 292-300.
25. T. A. Desai, W. H. Chu, G. Rasi, P. Sinibaldi-Vallebona, E. Guarino, and M. Ferrari, "Microfabricated Biocapsules Provide Short-Term Immunoisolation of Insulinoma Xenografts," *Biomedical Microdevices* 1, no. 2 (1999): 131-138; T. A. Desai, W. H. Chu, J.K. Tu, G. M. Beattie, A. Hayek, and M. Ferrari, "Microfabricated Immunoisolating Biocapsules," *Iotechnology and Bioengineering* 57, no. 1 (1988): 118-120.
26. A. Bouamrani, Y. Hu, E. Tasciotti, L. Li, C. Chiappini, X. Liu, and M. Ferrari, "Mesoporous Silica Chips for Selective Enrichment and Stabilization of Low Molecular Weight Proteome," *Proteomics* 10, no. 3 (2010): 496-505; H. D. Hill and C. A. Mirkin, "The Bio-Barcode Assay for the Detection of Protein and Nucleic Acid Targets Using DTT-Induced Ligand Exchange," *Nature Protocols* 1, no. 1 (2006): 324-336; D. G. Georganopoulou, L. Chang, J. M. Nam, C. S. Thaxton, E. J. Mufson, W. L.

Klein, and C. A. Mirkin, "Nanoparticle-Based Detection in Cerebral Spinal Fluid of a Soluble Pathogenic Biomarker for Alzheimer's Disease," *Proceedings of the National Academy of Sciences of the United States of America* 102, no. 7 (2005): 2273-2276; R. Fan, O. Vermesh, A. Srivastava, B. K. Yen, L. Qin, H. Ahmad, G. A. Kwong, C. C. Liu, J. Gould, L. Hood, and J. R. Heath, "Integrated Barcode Chips for Rapid, Multiplexed Analysis of Proteins in Microliter Quantities of Blood," *Nature Biotechnology* 26, no. 12 (2008): 1373-1378; L. Qin, O. Vermesh, Q. Shi, and J. R. Heath, "Self-Powered Microfluidic Chips for Multiplexed Protein Assays from Whole Blood," *Lab on a Chip* 9, no. 14 (2009): 2016-2020; T. P. Burg, M. Godin, S. M. Knudsen, W. Shen, G. Carlson, J. S. Foster, K. Babcock, and S. R. Manalis, "Weighing of Biomolecules, Single Cells and Single Nanoparticles in Fluid," *Nature* 446, no. 7139 (2007): 1066-1069; Y. Hu, A. Bouamrani, E. Tasciotti, L. Li, X. Liu, and M. Ferrari, "Tailoring of the Nanotexture of Mesoporous Silica Films and Their Functionalized Derivatives for Selectively Harvesting Low Molecular Weight Protein," *ACS Nano* 4, no. 1 (2010): 439-451.

27. M. K. Brenner, "Personalized Medicine: Words That Mean Just What You Choose?" *Molecular Therapy* 20, no. 2 (2012): 241-242; J. H. Sakamoto, A. L. van de Ven, B. Godin, E. Blanco, S. E. Serda, A. Grattoni, A. Ziemys, A. Bouamrani, T. Hu, S. I. Ranganathan, E. De Rosa, J. O. Martinez, C. A. Smid, R. M. Buchanan, S. Y. Lee, S. Srinivasan, M. Landry, A. Meyn, E. Tasciotti, X. Liu, P. Decuzzi, and M. Ferrari, "Enabling Individualized Therapy through Nanotechnology," *Pharmacology Research* 62, no. 2 (2010): 57-89.
28. *Id.* (Sakamoto et al.).
29. See Desai et al., Fine et al. (2010 & 2011), and Grattoni et al., *supra* note 24.
30. See Prakash et al., Dolatshahi-Pirouz et al., and Mata et al., *supra* note 23.
31. See Bouamrani et al., *supra* note 26; Sakamoto et al., *supra* note 27.
32. W. J. Clinton, "President Clinton's Address to Caltech on Science and Technology," remarks by the President at Science and technology Event, California Institute of Technology, Pasadena, CA, 2002.
33. D. Malakoff, "A Clinton Initiative in a Science of Smallness," *New York Times*, January 21, 2000, *available at* <http://www.nytimes.com/library/tech/00/01/biztech/articles/21chip.html> (last visited October 30, 2012).
34. D. Malakoff, "Nanotechnology Research: Congress Wants Studies of Nanotech's 'Dark Side,'" *Science* 301, no. 5629 (2003): 27.
35. See Theis et al., *supra* note 1; C. Peterson, *Testimony at the Committee on Science, U.S. House of Representatives Hearing to Examine the Societal Implications of Nanotechnology and Consider H.R. 766*, The Nanotechnology Research and Development Act of 2003 (April 9, 2003); Institute of Medicine, *Nanotechnology and Oncology: Workshop Summary* (Washington, D.C.: The National Academies Press, 2011).
36. See Theis et al., *supra* note 1; *id.* (Peterson); (Institute of Medicine).
37. F. Salamanca-Buentello, D. L. Persad, E. B. Court, D. K. Martin, A. S. Daar, and P. A. Singer, "Nanotechnology and the Developing World," *PLoS Medicine* 2, no. 5 (2005): e97.
38. M. Ferrari, "Session 5: Nanotechnology, Medicine, and Ethics," testimony at the President's Council on Bioethics, June 7, 2007, *available at* <http://bioethics.georgetown.edu/pcbe/transcripts/june07/session5.html> (last visited October 30, 2012); M. Ferrari, "Cancer Nanotechnology: Opportunities & Challenges," *Nature* 5, no. 3 (2005): 161-171; W. R. Sanhai, J. H. Sakamoto, R. Canady, and M. Ferrari, "Seven Challenges for Nanomedicine," *Nature Nanotechnology* 3, no. 5 (2008): 242-244; see Theis et al., *supra* note 1; Peterson, *supra* note 35; Institute of Medicine, *supra* note 35; A. D. Maynard, "Don't Define Nanomaterials," *Nature* 475, no. 7354 (2011): 31; A. D. Maynard, D. B. Warheit, and M. A. Philbert, "The New Toxicology of Sophisticated Materials: Nanotoxicology and Beyond," *Toxicological Sciences* 120, Supp. 1 (2011): S109-S129; A. D. Maynard, "Session 4: Nanotechnology: Benefits and Risks," The President's Council on Bioethics, June 29, 2007, *available at* <http://bioethics.georgetown.edu/pcbe/transcripts/june07/session4.html> (last visited October 30, 2012).
39. *Id.* (Ferrari); Sanhai et al., *supra* note 38.
40. See Theis et al., *supra* note 1; Peterson, *supra* note 35; Institute of Medicine, *supra* note 35; Maynard et al. (*Nature*), *supra* note 38; Maynard et al. (*Toxicological Sciences*), *supra* note 38; Maynard (The President's Council on Bioethics), *supra* note 38.
41. See Maynard (*Nature*), *supra* note 38; Maynard (*Toxicological Sciences*), *supra* note 38.
42. See Maynard (*Nature*), *supra* note 38.
43. See Maynard (President's Council on Bioethics), *supra* note 38.
44. A. Nel, T. Xia, L. Mädler, and N. Li, "Toxic Potential of Materials at the Nanolevel," *Science* 311, no. 5761 (2006): 622-627; F. Zhao, Y. Zhao, Y. Liu, X. Chang, C. Chen, and Y. Zhao, "Cellular Uptake, Intracellular Trafficking, and Cytotoxicity of Nanomaterials," *Small* 7, no. 10 (2011): 1322-1337.
45. Y. Zhao, G. Xing, and Z. Chai, "Nanotoxicology: Are Carbon Nanotubes Safe?" *Nature Nanotechnology* 3, no. 4 (2008): 191-192.
46. See Ferrari (President's Council on Bioethics), *supra* note 38; Maynard (*Toxicological Sciences*), *supra* note 38.
47. See Institute of Medicine, *supra* note 35.
48. *Id.*
49. 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.
50. See Maynard (*Nature*), *supra* note 38.
51. M. Ferrari, M. A. Philibert, and W. R. Sanhai, "Nanomedicine and Society," *Clinical Pharmacology & Therapeutics* 85, no. 5 (2009): 466-467.
52. E. Black, *War Against the Weak* (New York: Four Walls Eight Windows, 2003); R. N. Proctor, *Racial Hygeine: Medicine Under the Nazis* (Cambridge: Harvard University Press, 1988).
53. J. Ferlay, H. R. Shin, F. Bray, D. Forman, C. Mathers, and D. M. Parkin, "GLOBOCAN 2008," v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10, Lyon, France: International Agency for Research on Cancer, 2010, *available at* <http://globocan.iarc.fr> (last visited October 31, 2012; for statistics cited, search under "Online Analysis" link).
54. National Center for Health Statistics, "Deaths: Final Data for 2009," at table 9, National Vital Statistics Reports, Volume 60, Number 03, 117 pp. (PHS) 2012-1120, *available at* <http://www.cdc.gov/nchs/products/nvsr.htm> (last visited November 6, 2012).
55. S. P. Fodor, J. L. Read, M. C. Pirrung, L. Stryer, A. T. Lu, and D. Solas, "Light-Directed, Spatially Addressable Parallel Chemical Synthesis," *Science* 251, no. 4995 (1991): 767-773.
56. See Maynard (President's Council on Bioethics), *supra* note 38.
57. See Ferrari (2005 and 2010), Salvador-Morales, and Langer, *supra* note 9; Maier-Hauff, *supra* note 15.
58. See Barenholz, *supra* note 11.
59. *Id.*
60. See Maier-Hauff, *supra* note 15.
61. See Ferrari (2010), *supra* note 9.
62. D. Rejeski, "Comments of Consumers Union of United States, Inc. to the U.S. Consumer Product Safety Commission on 'Agenda, Priorities and Strategic Plan FY 2011,'" Panel 1, Consumer Product Safety Comissions: Public Hearing Commission Agenda, Priorities and Strategic Plan for FY2011, Bethesda, MD, August 25, 2009, *available at* <http://www.cpsc.gov/library/foia/foia09/pubcom/2011priorities.pdf> (last visited October 31, 2012).
63. See Nel and Zhao, *supra* note 44; Zhao et al., *supra* note 45.
64. See Ferrari (2010), *supra* note 9.
65. R. Rhodes, *The Making of the Atomic Bomb* (New York: Simon & Schuster, 1987).
66. M. Specter, "The Deadliest Virus," *The New Yorker*, March 12, 2012, at 32; M. Enserink, "Scientists Brace for Media Storm

around Controversial Flu Studies," *ScienceInsider*, November 23, 2011; M. Enserink, "Free to Speak, Kawaoka Reveals Flu Details While Fouchier Stays Mum," *ScienceInsider*, April 3, 2012; M. Enserink, "One of Two Hotly Debated H5N1 Papers Finally Published," *Science Now*, May 2, 2012; M. Imai, T. Watanabe, M. Hatta, S. C. Das, M. Ozawa, K. Shinya, G. Zhong, A. Hanson, H. Katsura, S. Watanabe, C. Li, E. Kawakami, S. Yamada, M. Kiso, Y. Suzuki, E. A. Maher, G. Neumann, and Y. Kawaoka, "Experimental Adaptation of an Influenza H5 HA Confers Respiratory Droplet Transmission to a Reassortant H5 HA/H1N1 Virus in Ferrets," *Nature* 486, no. 7403 (2012): 420-428.

67. Committee on Opportunities in Biotechnology for Future Army Applications, Board on Army Science and Technology, Division on Engineering and Physical Sciences, National Research Council, *Opportunities in Biotechnology for Future Army Applications* (Washington, D.C.: The National Academies Press, 2001): at 11-15.
68. National Materials Advisory Board and Board on Army Science and Technology, Division on Engineering and Physical Sciences, National Research Council, *Opportunities in Protection Materials Science and Technology for Future Army Applications* (Washington, D.C.: The National Academies Press, 2011): at 11-15.
69. M. Crichton, *Prey* (New York: HarperCollins, 2002).
70. R. K. Soong, G. D. Bachand, H. P. Neves, A. G. Olkhovets, H. G. Craighead, and C. D. Montemagno, "Powering an Inorganic Nanodevice with a Biomolecular Motor," *Science* 290, no. 5496 (2000): 1555-1558.
71. Institute of Medicine's Committee on Genomics and the Public's Health in the 21st Century and L. M. Hernandez, ed., "Implications of Genomics for Public Health: Workshop Summary," in *The National Academies Collection: Reports Funded by National Institutes of Health* (Washington, D.C.: National Academies Press, 2005).
72. *Id.*
73. C. G. Murphy and M. Fornier, "HER2-Positive Breast Cancer: Beyond Trastuzumab," *Oncology* (Williston Park) 24, no. 5 (2010): 410-415.
74. See Ferlay et al., *supra* note 53.
75. *Id.*; L. Denny, "Cervical Cancer Treatment in Africa," *Current Opinion in Oncology* 23, no. 5 (2011): 469-474.
76. M. Cardenas-Turanzas, J. A. Freeberg, J. L. Benedet, E. N. Atkinson, D. D. Cox, R. Richards-Kortum, C. MacAulay, M. Follen, and S. B. Cantor, "The Clinical Effectiveness of Optical Spectroscopy for the In Vivo Diagnosis of Cervical Intraepithelial Neoplasia: Where Are We?" *Gynecologic Oncology* 107, Supp. 1 (2007): S138-S146; R. Richards-Kortum, *Biomedical Engineering for Global Health* (Cambridge, U.K.: Cambridge University Press, 2010).
77. See Ferrari et al., *supra* note 51.
78. R. Bosetti, *Cost Effectiveness of Cancer Nanotechnology*, Dissertation, D/2012/2451/8 (Belgium: Hasselt University, 2012).