## Chapter 32

# Overview of Ethical Issues in Nanomedicine

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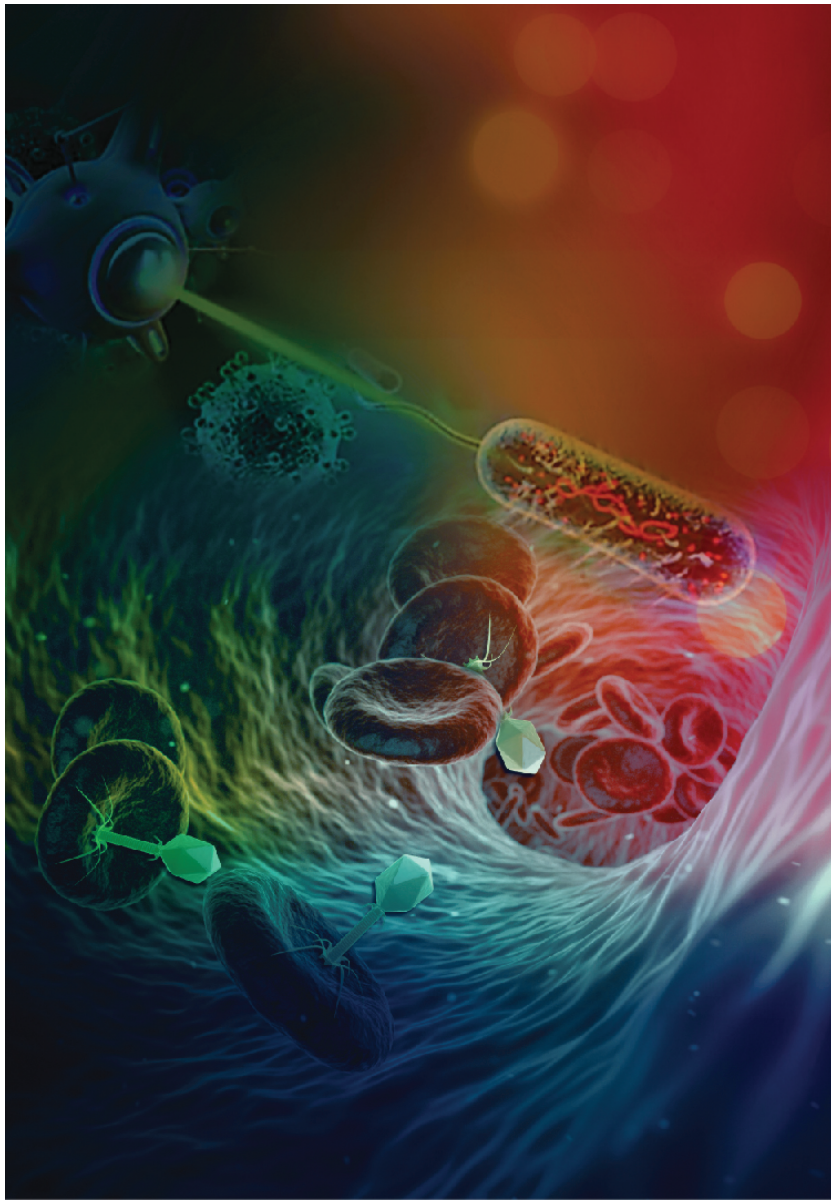

## 32.1 Introductory Overview

The air is thick with news of nanotechnology[1] breakthroughs, and there is no shortage of excitement and hype when it comes to anything "nano." Optimists tout nano as an enabling technology, a sort of next industrial revolution that could enhance the wealth and health of nations. Pessimists, on the other hand, take a cautionary position, preaching a go-slow approach and pointing to gaps in scientific information on health risks, general failure on the part of regulatory agencies to formulate clear guidelines, and issuance of numerous patents of dubious scope.[2] They highlight that nano is burdened with inflated expectations and hype. Whatever your stance, nano has already permeated virtually every sector of the global economy, with potential applications consistently inching their way into the marketplace.

Medical practice is entering a new era also focused on the nanoscale, more specifically on the practice of "nanomedicine."[3] In fact, in the next decade, many areas within nanomedicine (nanoscale drug delivery systems, nanoimaging, theranostics, etc.) are believed to be a healthcare game-changer by offering patients access to precision medicine. The creation of nanodevices—such as nanobots capable of performing real-time therapeutic plus diagnostic functions *in vivo*—is the major long-term goal

[1]Nanotechnology is "the design, characterization, production, and application of structures, devices, and systems by controlled manipulation of size and shape at the nanometer scale (atomic, molecular, and macromolecular scale) that produces structures, devices, and systems with at least one novel/superior characteristic or property." See: Bawa, R. (2007). Patents and nanomedicine. *Nanomedicine (London)*, **2**(3), 351–374.

[2]Nanopatent filings and patent grants have continued unabated since the early 1980s. Universities and industry have jumped into the fray with a clear indication of patenting as much nano as they can grab. Often in this rush to patent anything and everything nano by "patent prospectors," nanopatents of dubious scope and validity are issued by patent offices around the world, thereby generating potential "patent thickets." Since the early 1990s, in light of inadequate search tools/commercial databases available to patent examiners at the US Patent & Trademark Office (PTO) along with an explosion of "prior art" in nanotech, patents of questionable validity and/or scope have dribbled out.

[3]Nanomedicine may be defined as the monitoring, repair, construction, and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures. Nanomedicine is, in a broad sense, the application of nanoscale technologies to the practice of medicine, namely, for diagnosis, prevention, and treatment of disease.

of nanodrug delivery and the Holy Grail of medicine. Advances in nanotherapeutics, miniaturization of analytical tools, improved computational and memory capabilities, advances in genome manipulation, advent of artificial intelligence, higher resolution microscopic and imaging technologies, and developments in remote communications will eventually cross new frontiers in the understanding and practice of medicine.

Nanomedicine is gradually blossoming into a robust industry. Clearly, rapid advances and product development are already in full swing as it continues to influence the pharmaceutical, device, and biotechnology industries [1–8]. The potential impact of nanomedicine on society could be huge [1–8]. Nanomedicine could drastically improve a patient's quality of life, reduce societal and economic costs associated with health care, offer early detection of pathologic conditions, reduce the severity of therapy, and result in improved clinical outcomes for the patient. Numerous companies are actively involved in nanomedicine research and development (R&D), with many nanomedicine-related products (mostly nanodrugs or nanomedicines)[4] already on the market or under development. The global nanomedicine market was reported to be worth $72.8 billion in 2011, $138 billion in 2016 and is predicted to be worth $350 billion by 2025 [9]. Yet, despite all of this R&D in nanomedicine, federal funding related to the research and educational programs on ethical issues has clearly lagged behind. It is critical that ethical, social, and regulatory aspects of nanomedicine be proactively addressed to minimize public backlash similar to that seen with other promising technologies, most notably, genetically modified foods and stem cell research. The public should be properly educated regarding the benefits and risks of nanomedicine. Transparency is essential for greater acceptance and support, and is critical for commercialization.

[4]A nanodrug is defined as *"a formulation, often colloidal, containing (1) therapeutic particles (nanoparticles) ranging in size from 1–1,000 nm; and (2) carrier(s) that is/are themselves the therapeutic (i.e., a conventional therapeutic agent is absent), or the therapeutic is directly coupled (functionalized, solubilized, entrapped, coated, etc.) to the carrier(s)."* See: Bawa, R. (2018). Current immune aspects of biologics and nanodrugs: An overview. In: Bawa, R., Szebeni, J., Webster, T. J., Audette, G. F., eds. *Immune Aspects of Biopharmaceuticals and Nanomedicines,* Pan Stanford Publishing, Singapore, chapter 1, pp. 1–82.

Given this backdrop, nanomedicine could be poised to add a profound and complex set of ethical questions for health care professionals. Once nano-based interventions are tested in clinical trials and given US Food and Drug Administration (FDA) approval, it becomes the domain of health care practitioners to use it for the improvement of human health and populations. However, for most physicians and patients, nanomedicine is still an entirely new arena for preventive and diagnostic interventions and curative therapies that will require continuing education, and a heightened awareness of the risks and benefits. We will focus primarily on issues that are likely to emerge once nanomedicine moves out of the preclinical and clinical stages of research and development. In other words, our discussions here will be limited to nanomedicine products as they enter the market and find medical applications in diagnosis, prevention, and treatment.

Nanomedicine raises fundamental questions, such as what is it to be human, how human disease is defined, and how treating disease is approached. Just as with the era of genetics and molecular biology, physicians will have to reconceptualize how they think about the diseases they treat, the means they have to treat them, and the meaning of the phrase "do no harm."

Yet, nanomedicine is not a medical specialty or a single class of medical interventions that can easily be analyzed from an ethical perspective. As discussed earlier, it includes a wide range of technologies that can be applied to medical devices, materials, procedures, and treatment modalities. The simplest way to distinguish categories of nanomedical interventions is to differentiate "diagnostic nanomedicine" from "therapeutic nanomedicine." Diagnostic nanomedicine can include a wide range of interventions, from monitoring changes in blood chemistry, alterations in DNA, or tissue aberrations. It has been postulated that in the near future, clinicians and health care workers at the bedside or in the clinic will be capable of scanning a patient's entire genome in a few minutes and draw remarkably accurate conclusions pertaining to disease potential and corresponding therapies. Therapeutic nanomedicine includes a wide range of interventions—from nanopharmacology to nanobased medical devices, such as nanobots[5]

[5]Certain therapeutics submitted to the FDA for regulatory approval are combination products, which consist of two or more regulated components (drug, biologic or device) that are physically, chemically or otherwise combined/mixed to produce a single entity. In such cases, the FDA determines the "primary mode of action (PMOA)"

or nanodrugs to nanomaterials used for bone grafts or other body implants.

Just as different ethical issues exist for preventive medicine versus curative or therapeutic medicine, there exist very different kinds of ethical issues that arise out of diagnostic nanomedicine versus therapeutic nanomedicine. Interventions based on nanotechnologies likely will resurrect old questions about human enhancement, human dignity, and justice that have been asked many times before in the context of pharmaceutic research, stem cell research, artificial life, and gene therapy.

Much of what was discussed or "hyped" in the past two decades as the future of nanomedicine, however, has yet to occur.[6] Therefore, it is difficult for ethicists to predict in advance of the arrival of actual technologies what kinds of issues might arise out of nanomedicine. Yet, on the basis of other kinds of biomedical technologies that have affected health care, it is possible to conjecture what some of the perennial ethical issues and novel ethical problems will be. Therefore, this chapter outlines a range of potential ethical issues for preventive and therapeutic nanomedicine that may occur as these nanotechnologies move from the laboratory to the clinic. Specific focus is on the ethical question of enhancement versus therapy, the risk for and benefits

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of the product, which is defined as "the single mode of action of a combination product that provides the most important therapeutic action." This process is frequently imprecise because it is not always possible to elucidate a combination product's PMOA. In future, novel "multifunctional/multicomponent" nanobots will be engineered that incorporate both a drug and diagnostic (so called "theranostic"). As these combination products seek regulatory approval, they are sure to present additional challenges for the FDA because the agency's current PMOA regulatory paradigm may prove ineffective.

[6]Nanomedicine's potential benefits are often overstated or inferred to be very close to application when clear bottlenecks to commercial translation exist. Academia, startups and companies are all guilty as they continue to offer inflated promises or exaggerate potential downstream applications based on early-stage preclinical discoveries. Such "spin" or "fake medical news" does great disservice to all stakeholders; it not only pollutes the medical literature but quashes public support for nanomedicine translational activities. This issue is quite serious and often emanates from eminent academic labs perched at distinguished universities or from established industry players. Another common phenomenon observed by us is that many have desperately tagged or thrown around the "nano" prefix to suit their own motives, whether it is for research funding, patent approval, raising venture capital, or running for office.

of nanotechnologies in health care, changing understanding of human disease, and privacy and confidentiality.

## 32.2 Understanding Human Disease

Diagnostic nanotechnologies eventually will be able to detect and characterize individual cells, subtle molecular changes in DNA, and even minor changes in blood chemistry—scenarios that will likely cause pause and reconsideration of what it means to be a "healthy person" versus a "person who has a disease." In a "nanoworld," we might have to reconsider how to diagnose someone who has, say, cancer. Is the presence of a genetic mutation known to have a predisposition for causing cancer in a single cell a diagnosis? Or is it simply a risk factor? How many cells from the body must be of a cancerous nature for it to be defined as cancer? 1? 50? 1000? The answers to these questions are difficult because no one currently knows exactly how to define, diagnose, or detect disease with this level of sensitivity. Eventually, disease may be able to be detected in this way, but it is important to remember that the development of such diagnostic technologies will require reconceptualizing understanding of disease. Obviously, this will have a significant impact on health care professionals and patients.

The key is that if the slightest abnormality can be discovered, one must ask whether such information will have clinical relevance from a diagnostic, therapeutic, or prognostic point of view. If such knowledge does have clinical relevance, then it seems reasonable to develop technologies, assays, or mechanisms that could detect diseases at their earliest stages with the hope that this early detection would result in fewer side effects, less aggressive treatments, superior patient compliance, and better survival rates.

There may be some cases, however, where more information is simply too much information [10]. Such heightened awareness simply could result in anxious patients and worried family members. One must, therefore, think carefully about which diseases and conditions it would be appropriate to apply such nanotechnologies to so that those interventions are helpful, rather than creating a burden, unnecessary concern, or risk for patients

and others. Therefore, the balance of information processed and disseminated versus benefit to society and individual health is a significant consideration for the ethics of nanotech-based diagnostic technologies [10].

## 32.3 Enhancement versus Therapy

A related distinction for judging the morality of a medical procedure or treatment is whether or not it is regarded as therapeutic or enhancing—a subjective determination that is coupled with the determination of whether or not such action results in a normal or abnormal individual. A little analysis, however, reveals these distinctions to be unavailing because both enhancement and therapy are based on the relative concept of "normal" [11]. Most novel medical technologies that are employed for diagnosis, prevention, or treatment of diseases can also be used to enhance the function of the human body or mind. The traditional distinction between therapy and enhancement lies in the fact that therapy is concerned with maintaining, repairing, or restoring bodily parts or functions that a patient previously had or used. Enhancement, however, is concerned with the creation or improvement of bodily parts or functions that were absent, undamaged, or previously malfunctioning. Using this subjective distinction, the implantation of a nanoscale device that emulates the function of a congenitally absent organ paradoxically would be enhancing rather than therapeutic.

As to this question, a frank prohibition pragmatically is unworkable. There are simply too many potential benefits that nanoscale medical devices offer and policing their use will only be effective when society has reliable methods to detect violations. Rather, the practice of nanomedicine must be governed by a nanomedical ethic that maps the classical principles onto a transhuman and posthuman reality. Of these, the principle of "justice" in access to nanomedical procedures and entitlement to nanomedical treatment likely will be the most contentious. In this context, issues relating to unfair competition, socioeconomic inequality, discrimination, and bias will arise and need to be addressed. At the level of civilization, a morality must be crafted

that honors an unprecedented expansion in the meaning of human being and militates against any eugenics agenda.

## 32.4 Risk versus Benefit

Another important concern for nanomedicine is the need to balance the potentially significant benefits of nanomedical interventions with their potential risks. In the area of therapeutic nanomedicine, for example, it is clear that nanotechnologies will continue to allow chemical compounds, therapeutics, or drugs to be more bioavailable, less toxic, and targeted to specific tissues and even sub-cellular structures. Therefore, these compounds will be needed at lower doses and have fewer side effects in the patient. One likely risk of nanomedicine, however, is that these drugs will receive FDA approval and be on the market long before the long-term risks are conclusive. Nanomedicines have the potential to cross the blood–brain barrier or enter cells easily; therefore, it is a concern that the retention of these molecules in the body may cause long-term or unintentional harm to healthy tissues. Because long-term follow-up data exist for only a handful of nanomedicines, it is important that patients be informed that these drugs may present long-term consequences. Although this is not altogether different from the long-term risks associated with exposure to chemotherapeutic or radiologic agents, it is an important risk factor that must be disclosed to patients taking nanomedicines or any kind of intervention involving nanoparticles or nanomaterials. A similar argument could be extended to nano-nutraceuticals or nano-cosmetics, categories whose definitions may overlap with nanomedicines. In fact, both nano-nutraceuticals or nano-cosmetics may present greater risk in some cases given that neither are subjected to any FDA premarket regulatory approval prior to commercialization.

## 32.5 Privacy and Confidentiality

Another important ethical issue relates to the protection and maintenance of health information in the era of nanomedicine. Nanotechnologies will make possible the collection of an enormous amount of individual cellular/subcellular level surveillance data

of the human body. Nanomedical technology is expected to miniaturize implantable devices so that they function at the subcellular or synaptic level with the ability to monitor or collect data regarding cellular activities and biochemical events within organs, tissues, or individual cells. One application of this technology would be to include a means by which that information could be transmitted remotely.

If and when such technologies are made possible via nanotechnology, a key ethical question arises: Can the health information infrastructure handle, collect, process, and analyze real-time ongoing electronic health data in a secure manner? With healthcare institutions slow to adopt electronic medical record systems and accommodate increasingly large medical files across institutions and time periods, it is of concern that massive amounts of health information is being generated without efficient systems in place to effectively utilize it or that adequate security measures are in place. Clearly, ensuring privacy and confidentiality in such systems would be of utmost importance. Systems without adequate safeguards present serious ethical problems.

## 32.6 Future Perspectives

Given that nanomedicine is an emerging and evolving arena, it is difficult to precisely predict how ethical issues related to nanomedicine will evolve in the next decade. Nevertheless, ethical considerations will continue to play a significant role in the development and use of nanotechnologic interventions in medicine and healthcare. Initially, some of the important ethical concerns have focused on risk assessment and environmental management. However, in the future, novel ethical issues and unforeseen dilemmas are likely to arise as the field advances further and intercepts other areas of biomedical research, including artificial intelligence, genomics, precision medicine, bioinformatics, and brain science. As with other biomedical and life science advances before it, nanomedicine will face significant challenges as it moves from the lab to the clinic. Along the way, ethical questions regarding social justice, privacy, confidentiality, long-term risks

and benefits, and human enhancement are certain to arise. Health care providers must be ready to answer such ethical questions for themselves and be able to address those questions for their patients. Ultimately, it seems likely that nanomedicine will usher in a new area in health care where pharmaceuticals will be more effective, specific, targeted, and less toxic, where disease monitoring will be done on a highly sensitive and specific level, where injections, surgical procedures and a host of other interventions will be made less painful, less toxic, and with fewer side effects than their current versions. It is important to ensure, however, that these advances in medical care do not come at the expense of fairness, safety, transparency, or basic understanding of what it means to be a healthy human being. Ultimately, public and political interest for regulations needs to be carefully balanced with the interests of scientists and businesses for uninhibited science and technological progress. Hype or excitement about nanomedicine should not obscure its important ethical and societal implications. Nanomedicine's future appears brightest if it can be ensured that it also will be a future where such ethical issues are timely, accurately, and transparently addressed via involvement and cooperation of all stakeholders. This will also ensure that the public's desire for novel nanomedical products, investment from venture communities, and big pharma's interest in nanomedicine are not quenched.

## Disclosure and Conflicts of Interest

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