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FROM THE EDITOR

Innovating Nanoethics

Linda Jiang and Kim A. Carmichael, MD

In the past decade, innovation in nanotechnology has led to rapid advances in the development of novel pharmaceuticals and imaging and diagnostic devices. Nanomedicine, a rapidly advancing subfield of nanotechnology that combines the basic and medical sciences, involves the use of nanoscale materials for the diagnosis, monitoring, prevention, and treatment of disease.¹ Indeed, nanomedicine has revolutionized how we think about diagnosis and treatment of disease at the atomic, molecular, and macromolecular level. Advances in nanodrugs, nanoimaging, theranostics, and other nanoproducts are expected to transform the practice of medicine.²

Nanotechnology has received significant attention and funding in recent years. Global funding for emerging nanotechnology reached \$18.5 billion in 2012, with US corporations investing \$4 billion in research and development.³ The National Institutes of Health also spent more than \$350 million annually between 2014 and 2018 on nanotechnology research.⁴ Global sales of nanomedicine products were estimated at \$138.8 billion in 2016,⁵ and the value of nanodrugs expected to be developed by 2019 is estimated at \$178 billion.⁶

The particular properties of nanomedicines make them superior to their traditional counterparts. Due to their size, composition, and design, nanodrugs have advantages over conventional medicines such as improved pharmacokinetics, increased tissue selectivity, and enhanced efficacy. However, despite these benefits, nanomedicine faces numerous developmental challenges due to high costs, indeterminate standards and regulations, and unknown biological interactions, effects, and toxicities.^{7,8}

This special issue of the *AMA Journal of Ethics* explores potential ethical, legal, regulatory, and policy challenges in the United States inherent in the development, regulation, and clinical application of nanomedicine.

Nanomedicine raises particular ethical challenges regarding respect for patient autonomy and beneficence. In her commentary on a case of 16-year-old with schizophrenia who resists use of a digital pill to track his compliance, Constance E. George explores the interests of the patient and parents and the benefits and risks of prescribing the medication. She argues that the adolescent's assent to the digital pill can best be gained through [shared decision making](#). Similarly examining the ethical dilemmas

of prescribing digital pills for patients with psychoses, Tahir Rahman argues that such medications can exacerbate delusional symptoms and [erode the therapeutic trust](#) between the physician and the patient. In addition, Nancy M. P. King and Christine E. Bishop examine the role of the physician in helping patients understand the unknowns of [nanomedicine-based clinical trials](#), arguing that physicians should draw upon their knowledge of the disease's typical progression, the patient's unique clinical situation, the clinical trial, and the characteristics of nanomedicines to promote reasonable expectations about the risks and benefits of trial enrollment and to facilitate discussions about goals of care. The striving of both patients and physicians toward a [common goal](#) is represented in an abstract painting by Madeleine Schachter.

In recent years, leaders in medical education have called for widespread reform in medical education to prepare students to practice medicine—with all its anticipated technological advances—in the 21st century. Given the enormous research support for and vast potential of nanotechnology, how should nanomedicine content (eg, the size and scale of nanotechnology, mechanisms of nanodrug delivery, interactions of nanomaterials with biological systems, nanodiagnosics, and nanoethics) be integrated into the medical school curricula? Should nanomedicine be a stand-alone course or part of other courses? What pedagogical approaches should be used in teaching this content? Joel C. Sunshine and Amy S. Paller review the importance of nanotechnology in medicine and discuss ways that medical educators can introduce concepts of nanotechnology, nanotoxicology, and nanoethics into the [medical school curriculum](#).

Regulation of nanotechnology remains controversial, as we lack clear frameworks for the use, disposal, and recycling of nanomaterials. Certain nanomaterials are known to cause harm to humans and the environment.⁹⁻¹¹ Although the Food and Drug Administration (FDA) has been regulating products containing nanotechnology for years, nanoscale products challenge existing [regulatory frameworks](#) and legal paradigms, as examined by Jordan Paradise. The regulation of nanowaste is difficult to address for several reasons. First, nanowaste is not visible to the naked eye, so it is difficult to track and monitor. Nanoparticles—and, by extension, nanowaste—do not behave like their bulk materials counterparts: nanomaterials are generally more chemically reactive due to their larger surface area-to-mass ratio. Predicting how nanoparticles would react under different environmental conditions has remained difficult. In addition, risks of toxicity and other hazards of nanowaste are not well understood.¹² David B. Resnik argues that, in order to minimize risks, policymakers should take [reasonable precautions](#) by using the best available evidence and existing laws to regulate engineered nanomaterials and by supporting additional research to assess their risks. These and other precautions can help to mitigate and manage the potential public health and environmental risks of nanomaterials without sacrificing their medical, social, and economic benefits.

Health monitoring has become ever more ubiquitous with the advent of the smart watches, activity trackers, and health monitoring mobile apps. An increasing number of

employers have implemented corporate wellness programs that provide workers with wearables or health apps to monitor their health, productivity, and well-being. Nanotechnology enables the development of more powerful monitoring devices with improved functional monitoring. Although such wellness programs provide potential win-win benefits to both employers and employees by promoting better employee health, they raise ethical and legal concerns. Gary E. Marchant argues that [workplace monitoring programs](#) can only succeed and be sustained when workers find them to be acceptable and transparent, and he discusses 5 best practices to ensure nano-enabled worker monitoring programs are acceptable and effective.

This special issue of the *AMA Journal of Ethics* aims to foster discussion among members of the medical community on the ethical complexities inherent in the development, disposal, regulation, and clinical application of nanomedicines. Physicians have a key role to play in such discussions, which will shape future legislation, national health policy, and their patients' health care.

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CASE AND COMMENTARY

Should a Psychiatrist Prescribe a Nanodrug to Help Parents Monitor a Teen's Adherence?

Constance E. George, MD, MA

Abstract

This case explores ethical questions about tracking medication adherence in a 16-year-old patient with schizophrenia. Relevant stakeholders are the teen, the parents, and society. How those stakeholders' interests should be considered is explored here in the context of the psychiatrist's professional care management responsibilities and the burdens each stakeholder must bear over the course of the patient's care.

Case

Dr S is a child psychiatrist who has been seeing BR, now age 16, for about 2 years. BR has been diagnosed with schizophrenia. Given the stress at home, BR has been forgetting to take prescribed medication and has suffered a psychotic episode that required him to be forcibly sedated and hospitalized for 10 days. Dr S considers prescribing BR a nanodrug that can monitor whether (but not necessarily exactly when) BR has ingested the medication. This would help Dr S's staff monitor BR's adherence to the medication and help prevent acute exacerbations, particularly psychotic episodes. BR's parents support this plan for nanopill-assisted surveillance of their son's medication compliance. However, BR is reluctant, stating, "I want to take the medicine, but I don't want to be monitored." BR clarifies that his usual treatments have worked well for him in the past, and he promises to keep taking his medication. BR's parents are adamant that he be prescribed the nanodrug and reiterate that BR has been forgetful and distracted lately and needs the reminders that the wearable patch, which contains a sensor that detects signals from the nanodrug, would trigger. Amidst this disagreement, Dr S is unsure about how to proceed.

Commentary

Aripiprazole, the active ingredient in the nanodrug described in the case, works via a digital health feedback system (DHFS). A patient swallows the drug, and then a nanosensor in the pill is activated by the patient's stomach acid, triggering release of an antipsychotic used to treat mental illness.¹ The sensor sends a signal to a patch worn on a patient's torso; the patch logs the date and time of ingestion and communicates this information to a smartphone app, usually within 2 hours. The patch also logs daily activity (steps) and time spent at rest (sleeping and reclining), which is sent to a

smartphone app. When registered users (caregivers, family members, or others invited—that is, authorized—by the patient) login to an application (app), this data is displayed on a dashboard and can be viewed, along with a patient’s daily rating of her mood and her subjective experience of rest.

Why develop this technology? What is its purpose? What is its promise? There is a high prevalence of low adherence to treatment among adolescents with chronic health conditions.^{2,3} Mental health disorders affect approximately 25% of children and adolescents worldwide,⁴ and early intervention is essential in improving outcomes for this group. Adolescent-onset [schizophrenia](#) is less common than adult-onset schizophrenia and phenotypically more severe.⁵ This severity entails comparatively greater compromise of social and occupational function. The purpose and promise of DHFSs is to promote better adherence to medications among adolescents, thus translating into better outcomes for these patients.

Ethical issues raised by this case are discussed here within the framework of a risk-benefit analysis. The benefits involve the promise. The question of risks, however, is primary in the ethical analysis of this DHFS, particularly given that its benefit as an adherence tool is not established. The basis for Food and Drug Administration (FDA) approval relied on the safety and usability of the device and the bioequivalence of the active ingredient, aripiprazole, whose efficacy was previously established.⁶

Promise of Benefit

Poor adherence to medications among adolescents with any chronic health condition is associated with poor outcomes, including increased complications, increased mortality, and increased utilization of health services.⁷ In contrast, getting care early improves outcomes.⁸ Part of that treatment includes use of antipsychotics.

Adolescents have adopted communication technology as a part of their everyday lives. The technology required in implementing the DHFS—an app—would not be unfamiliar to them.⁹ In addition, participants in the initial studies of aripiprazole with sensor reported the system was relatively easy to use.¹⁰ A survey published in the *JMIR Mental Health* in 2015 found that young adults, ages 18-35, with first-episode psychosis were comfortable with receiving information digitally and more than half had a positive view of receiving reminders to take medication by text or email.¹¹ Combined with DHFS’s ease of use and the prevalence of and familiarity with communication technology, this receptiveness to reminders could confer on DHFS a unique advantage in improving self-management skills in adolescents such as BR. Unfortunately, there is currently a dearth of evidence that these apps improve adherence to prescribed medications.¹²

BR is, at first glance, a perfect candidate for a DHFS. His stated reason for noncompliance is forgetting, and forgetfulness in adolescents is a known barrier to

adherence.^{4,9} The idea of an applied technology that could [improve adherence](#) in this population is compelling.

In terms of the patient-physician relationship, there is potential for benefit as well. A DHFS might offer a tangible way of discussing nonadherence, as the physician and patient could review mood, sleep, and activity as it relates to the medication. It is a tool that might, in real time, shed light on the reason for the patient's nonadherence—be it simply forgetting or related to side effects such as sedation, fatigue, nausea, or general ineffectiveness of the medication. It might enhance an interactive relationship between BR and his psychiatrist as they in concert make decisions about medication or behavior based on the additional information provided by the DHFS. It could also help the illness seem less mysterious and more manageable.^{3,13}

A DHFS might also relieve the anxiety of parents. It doesn't take much imagination to suspect that one source of stress in the household is BR's nonadherence. Assuming his parents are notified by text or email by the app that BR ingested his medication, the system might relieve their anxiety and BR's as well. It could put an end to daily inquiries into his medication compliance by his parents. It might become part of a positive reinforcement system rather than a negative one if, for example, BR is praised for adherence rather than repeatedly questioned in fear or expectation of nonadherence.

Risks

BR, however, is hesitant. He would like to keep taking the medication of his own accord without the aid of a DHFS. In this case, there is a conflict between the autonomy of the patient on the one hand and the parents' need to care for and protect their child. This conflict is consequential. Empirical research has demonstrated that, by 14 years of age, adolescents' cognitive capabilities and decisional competence are comparable to adults'.¹⁴ BR is 16 and developmentally should be well on his way to a substantial understanding of personal responsibility as a measure of independence and emotional maturity.¹⁵

Psychiatrists are obliged to recognize the individual patient's dignity, autonomy, and capacity for self-determination regardless of age.⁹ Does this adolescent have decision-making capacity? Does he understand the risks and benefits of accepting or [declining treatment](#) and the potential outcomes of alternative treatments, and is he able to provide a voluntary noncoerced decision? Based on the case vignette, BR expresses knowledge of his illness, an understanding of the necessity of medication given his illness, and an awareness of the positive effect of medication on his well-being. In fact, he wishes to keep taking the medication. Given this apparent decision-making capacity and his age, BR's assent to employ the DHFS is necessary if not sufficient for consent. (Unless emancipated, a minor must have consent from the parents to receive treatment.¹⁴) Assent to the DHFS has the potential to produce better patient

participation and compliance with treatment and to improve communication between physician and patient.

Although the psychiatrist and patient would both benefit from the patient's assent, if BR feels spied on, or forced or manipulated into accepting the DHFS by his parents and the physician despite his voiced objection, a confrontational triad might ensue with resentment and anger infiltrating all relationships, thus destroying a foundation of trust and foreboding therapeutic relationships in need of repair. If the DHFS system worsens the patient's paranoia, it could actively insert distrust and suspicion into these relationships as well. (Of note, one study thus far did not find that the system worsened adult patients' psychosis.¹⁰) Such a scenario is unlikely to improve the substantial familial stress mentioned in the case study.

The patient's stage of development presents another set of difficulties. BR is a budding adult with a serious chronic illness, and he might view the DHFS as reducing his status to that of an irresponsible child whose word is disregarded in favor of technological confirmation. In addition, using, refusing, or failing the system could lay the groundwork for shaming, a known harm.¹⁶ Related to shame is another known concern among teenagers: cyberbullying. A study assessing the attitudes and concerns of young people (ages 15 and 16) pertaining to the employment of mental health apps found that their concerns included loss of confidentiality and cyberbullying.¹⁷

The FDA is well aware of privacy issues as they pertain to new digital technologies in the medical field.

Medical devices, like other computer systems, can be vulnerable to security breaches, potentially impacting the safety and effectiveness of the device. This vulnerability increases as medical devices are increasingly connected to the Internet, hospital networks, and to other medical devices. All medical devices carry a certain amount of risk. The FDA allows devices to be marketed when there is a reasonable assurance that the benefits to patients outweigh the risks. While the increased use of wireless technology and software in medical devices also increases the risks of potential cybersecurity threats, these same features also improve health care and increase the ability of health care providers to treat patients.¹⁸

Is it prudent to offer a patient a device that stores another source of personal data in the digital cloud—a device that is walking around with the patient? Aripiprazole with sensor addresses security by encrypting the Bluetooth signal between the chip and the patch, excluding the chip's connecting directly to the internet, and excluding any GPS capability. It also has an automatic timeout function protecting the app from needless exposure. The app requires that the patient specifically authorize any shared information in order to protect his or her privacy, and that authorization could be revoked at any time.⁶ But bullies with malignant intent can certainly spy on a smart phone, and the protection of confidentiality here requires individual diligence on the part of the patient regarding his or her phone.

A Decision

Given the facts of the case above, how should Dr S proceed in the context of BR's wariness and his parents' demands? Is this DHFS the most necessary and least harmful intervention? Again, the technology was not approved based on studies of its effectiveness as an adherence tool, nor is it marketed as such.¹ For this reason, the bar for implementation is set high. The promise of better compliance is a known good and could translate into decreased stress at home, better communication between BR and his psychiatrist, and improved control of symptoms with likely improved outcomes. Risks of harm as described above include undermining of BR's autonomy, further conflicts between BR and his parents and his psychiatrist exacerbated by distrust, possible data breaches, possible shaming, and possible exposure to unknown harms by peers. The psychiatrist, therefore, must weigh these risks and benefits and convey them, in detail, to the patient and his family. Dr S knows that parents are essential to adherence to medications in adolescents, as is their supportive relationship at home with parents who are well versed in the illness and accepting of its presence.⁸ Dr S must make BR aware that everyone's goal is to help him direct himself toward a future he chooses, a future made more tangible with good medication compliance. In so doing, the psychiatrist can help divorce punishment from treatment options. Dr S must also make it known to the parents that fully informed assent by BR is required in order to protect his dignity, his autonomy, and his capacity for self-determination. The use of a DHFS should be and must be as a tool, not as a bat. Whether other interventions were implemented is not clear given the case description. Interventions such as supportive psychotherapy; watch, phone, or computer reminders; and peer support groups involve much less risk to patient privacy and must be explored with BR and his family prior to the use of a DHFS with the high risk-to-benefit ratio described. A collaborative relationship wherein all agree on a treatment course based on relevant risks and benefits has a much greater chance of success and utility.¹² Adolescent-onset schizophrenia is, at this time, a chronic illness that requires a great deal of resources and mental health interventions, a motivated patient, and support from parents. Enlisting BR in his treatment is essential, and obtaining his assent is crucial no matter the final decision.

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Editor's Note

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The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

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CASE AND COMMENTARY

How Should Physicians Help Patients Understand Unknowns of Nanoparticle-Based Medicines?

Nancy M. P. King, JD and Christine E. Bishop, MD, MA

Abstract

When a patient wants to enroll in a clinical trial to gain early access to an apparently promising but unproven intervention, her physician should clarify differences between participating in research and receiving treatment to help her avoid therapeutic misconception, make a thoughtful decision, and consider relevant clinical and ethical details. These include a patient's disease and treatment experiences, needs, interests, values, the design and phase of the trial, and the nature of the intervention being studied. When an unproven intervention is a nanodrug, a physician's role is especially difficult, because though nanomedicine might offer real benefits, it can also pose unexpected or even unprecedented harms. Thus, a physician should help a patient explore possible outcomes while promoting realism, countering hype, and preserving hope.

Case

Dr R, an oncologist treating AM, a 42-year-old woman with multiple myeloma, is currently considering AM's different treatment options, since her cancer is now refractory to many conventional treatment regimens. Among the new options is a nanodrug currently in clinical trials.¹ AM has learned about the "miracles" of nanotechnology through various Facebook pages and groups and Twitter accounts she's followed, and she is eager to get access to the trial drug. Dr R is aware of a general lack of knowledge among health care professionals about long-term side effects of nanodrugs,² particularly those still being investigated, so she has been carefully trying to learn about the risks and benefits of this drug and is preparing how to convey information about this drug trial to AM. (Potential benefits of the use of nanoparticles in cancer drug delivery are these: improved drug bioavailability, decreased dosing frequency, and reduced toxicity from chemotherapy.³ Common risks include diarrhea, nausea, and vomiting.⁴ Less common but more severe side effects include neutropenia, lymphopenia, thrombocytopenia, neutropenic fever, and neutropenic sepsis.⁴)

Dr R has learned in a recent article that nanomaterials have key differences from traditional drugs in their biochemical, electromagnetic, and optical properties. As a result,

there are many unknowns regarding their activity within the human body. For example, nanomaterials are of similar size to organelles found within the cell and could potentially interfere with crucial cellular functions, leading to cell damage and death.⁵ In addition, nanoparticles might be rapidly cleared by the immune system because they are similar in size to pathogens that the immune system has evolved to fight.⁵ Upon contact with biological fluids (eg, blood, mucosal secretions), nanoparticles can become coated with immunoglobulins, albumin, fibrinogen, and complement cascade proteins that can change their surface charge and properties as well as facilitate their clearance by the immune system.⁵ There are limited data on interactions between nanomaterials and proteins (eg, blood proteins such as albumin, clotting factors, complement cascade proteins, antibodies) and on how various physiological conditions affect the clearance and fate of nanomaterials. For example, it has been shown that physiological stress can stimulate overexpression of acute-phase proteins that can increase complement activation and macrophage phagocytosis of pathogens.⁵ Dr R also learns that the long-term effects on human physiological pathways of nanoparticles' differences in size and surface-to-volume ratio from traditional drugs are not known. She wonders how to go about the process of helping her patient make an informed decision about participation in a clinical trial involving a nanodrug.

Commentary

As the patient's primary clinical oncologist, Dr R has undertaken the important task of helping her patient, AM, decide whether to seek enrollment in a nanodrug clinical trial. Because Dr R is not an investigator or otherwise engaged in the research that interests her patient, her role is necessarily general; she can learn more about the investigational drug, examine information about the trial on ClinicalTrials.gov, and, later, review the consent form with AM and offer help with her decision. Dr R and AM have probably considered many options together when seeking the best available next treatment for AM's multiple myeloma, so this kind of informed decision-making discussion—a precursor to informed consent—should be familiar to them both, with an important twist: Dr R needs to inform her patient about the clinical and ethical differences between participating in research and receiving treatment in order to avoid therapeutic misconception and help AM make the best decision for herself under the circumstances.^{6,7}

Nanomedicine's Appeal

AM is excited about the promise of nanodrugs and hopes they will be more effective—and less harmful—at lower doses than the same drugs would be if administered in conventional larger particle sizes that have different surface-to-volume ratios. This is what patients want, but it is also exactly what has not been proven about nanodrugs that are being tested in clinical trials. When hopes dominate decision making for patients who become research participants, therapeutic misconception might be interfering with understanding.

Nanomedicine research presents a complicated picture, however. Employing nanoparticles in health care appears to be a new approach, but, in fact, nanoparticles have been used in treatment and clinical research for some time. Nanoparticles are currently used in many settings, from over-the-counter products like sunscreen to virus-transgene combinations that are studied for their potential to treat genetic diseases. Their very small particle size causes nanodrugs to work differently from agents with larger-than-nano particle sizes; this difference could introduce new and potentially unknown risks of harm. At present, information about potential benefits and risks of harm from nanodrugs is limited because nanoparticles vary considerably in both composition and size.⁸ Moreover, there is no agreed-upon standard for determining which particle sizes should be given the “nano” label.⁸

However, the term *nanomedicine* carries a certain mystique, potentially reinforcing a public perception that nanomedicines, even when unproven, hold special promise. Having learned about nanomedicines through social media, AM seems to subscribe to this view; she hopes that the investigational nanodrug will be her miracle. Social media and public information can be wonderful tools for patients and patient advocates, but misinformation and exaggeration, even when based on genuine scientific excitement about a new biotechnology,^{7,9} could inflate expectations and potentially cause harm.

Nonetheless, when a patient like AM faces a life-limiting illness for which there are no further approved therapies, it is expectable and understandable that she might seek other potential means of prolonging her life. This search may be especially familiar to patients with multiple myeloma, whose survival time has lengthened in recent years as a result of earlier diagnosis and an expanding armamentarium of new treatments and research opportunities.¹⁰ However, patients like AM still face many side effects, setbacks, and recurrences¹¹ and thus can sometimes put themselves at considerable risk when pursuing new approved treatments or enrolling in clinical trials. Thus, as much as AM and Dr R both hope that AM can benefit, Dr R will need to explain that therapeutic benefit to patient-subjects is not the primary goal of clinical trials.^{6,7}

Supporting Patients’ Decision Making About Nanomedicine Research

It is essential for Dr R to emphasize that research is intended and designed to obtain knowledge to benefit future patients; she should discuss in general terms what that goal could mean for patients who are research participants. In this conversation, Dr R should lay out the framework of how an investigational medication should be considered within the overall clinical care plan for AM. A compassionate but clear discussion about research participation will enable Dr R to balance 3 factors: care for her patient within the context of their long-standing therapeutic relationship, maintenance of realistic hope, and an honest approach to AM’s prognosis. While this approach is always necessary when a clinician is considering referring a patient to learn about a clinical trial, Dr R has already determined that her patient’s situation might be more complex because of the

potentially unique characteristics of the investigational nanodrug and AM's excitement about its potential benefit for her.

Because Dr R is not one of the researchers, her discussion with AM about the goals of the research study, what to expect from the research consent process, and what she might experience as a study participant will be based on what she learns about the design of the study. Information about study design includes whether the research is at an early or more advanced stage, which is usually signaled by whether the primary goal of the study is (1) to find a safe and tolerable dose, (2) to determine whether the drug appears to work in a small number of participants, or (3) to compare it to approved and well-characterized treatments. Dr R will also need to learn about the investigational nanodrug itself—about how extensively it has been tested so far and what has been learned about it. If, as is likely, the nanodrug is being tested as an addition to standard therapies, AM's experience in the trial will be quite different from the experience of being in an [early trial](#) in which the drug is being given to humans for the first time and participants who enroll first receive smaller doses than participants who enroll later in order to test safety and find a maximum tolerated dose. If the drug has been determined safe in an early trial and is now being studied at the safe dose but AM does not meet the trial's inclusion criteria, she might even decide to seek access to the drug without enrolling in research by using the new federal "right to try" law,¹² which has its own promise and perils. In that case, Dr R would need to explore her own views about this form of expanded access, determine how to counsel AR, and decide whether to assist with her access request.¹³

Dr R can help prepare AM for the research consent process by discussing what AM has learned about and expects from nanomedications and what she herself has learned, stressing points of agreement and identifying points of divergence. She can help AM formulate general questions about the study and the investigational medication as well as about the risks of harm, potential benefits, and other implications of enrolling in the study. In the process of reviewing these themes, Dr R should directly address the concept of therapeutic misconception with AM. She must discuss with AM how hope for medical progress creates a temptation for investigators and clinicians to overstate the potential benefits and minimize the risks of harm associated with investigational medications, including nanodrugs. Heightened expectations about emerging biotechnologies are common, are strengthened by overoptimistic discussion in both traditional and social media, and can give rise to unrealistic hope by leading patients to view receiving unproven interventions in research as their best treatment options; this is the therapeutic misconception. Investigational nanodrugs might be particularly attractive for cancer patients like AM, whose previous treatment experience is often characterized by progress at the cost of significant side effects. Yet the possibility that investigational nanodrugs might be more effective and have fewer side effects at lower doses than approved drugs with larger particle sizes is precisely the reason to study these unproven

agents and to learn whether their potential is real. It is not a reason to seek treatment using them until more is known, especially because very small molecules can have paradoxical and unusual effects.^{9,14}

Therefore, Dr R must help AM understand that her hope can mistakenly encourage her to view clinical research as just like medical treatment. She should directly acknowledge AM's probable view that research participation could seem like her best option simply because all approved treatments have failed her.^{15,16} And she must remind her that novel interventions like nanomedicines need to be studied precisely because their potential benefits and risks of harm are uncertain and unknown. She must do so in a compassionate, balanced way, clearly explaining why the primary goal of research is not treatment, so that AM can make a decision based on her own goals and values and on reasonable expectations about study participation. This conversation is one aspect of working with AM to develop an ongoing clinical care plan for her as she potentially faces the end of her life.

Scenario Planning

One method that Dr R could use to help illustrate the role of clinical research to AM while providing concrete examples of her options for standard medical care is scenario planning.¹⁷ Using this method would help Dr R explain best-case and worst-case scenarios for her condition in general and for the protocol currently under consideration in particular so that together they can address in open, honest conversation what it could be like to be enrolled in a clinical trial involving nanomedicine at this stage of AM's disease. Scenario planning can also begin to illuminate the "if this, then that" situations that often unfold at the end stage of a disease and at the end of a person's life. For example, a best-case scenario that envisions AM's trial participation might address successful life prolongation while also considering the need to manage side effects and to face uncertainty about both the long-term effects of the investigational nanodrug and the potential for future disease recurrence. A worst-case scenario that envisions AM's trial participation might involve discussing a potential care plan addressing goals of care at the end of life in a supportive manner that would help to maintain AM's hope for improvement of her illness while ensuring that she knows she will not be abandoned if the investigational agent does not produce the miracle for which she hopes. Using scenario planning, Dr R can help AM re-examine her expectations about participation in the research study, prepare for the research decision-making process, and gain insight into the experience of being in a nanomedicine trial. She can also discuss AM's ongoing clinical care while she is enrolled in the trial and introduce the prospect of planning for potential progression of her disease regardless of whether she enrolls in the trial.

If and when more information about the trial is available—for example, if AM meets with a study team member and brings the consent form to Dr R so that they can discuss the trial in more detail—Dr R can use scenario planning to more clearly illustrate for AM

what it might be like to participate in the research based on the characteristics of the study and of the nanodrug. If the new drug is being studied as an addition to standard therapies, Dr R can review those therapies and discuss AM's previous (or probable) experiences with them. Dr R could explain many aspects of the trial in lay terms to help clarify what participation might entail on a daily or weekly basis, including details of administering the investigational agent, lab draw or assessment schedules, and any additional testing that AM might need to undergo as part of the protocol. They could then talk together about how participation might affect AM's daily life and health, ideally enabling a frank discussion about how AM would like to spend her remaining time.

Advice for Clinicians

Dr R's primary duty is to care for AM, and while AM might desire to participate in a research study, Dr R should remain mindful of the bigger picture of AM's care. It is not her role to encourage or discourage AM's participation in research. Instead, as a physician with a therapeutic relationship with AM, Dr R is uniquely equipped to combine AM's previous experiences during her illness journey with her own knowledge of AM's disease progression and her newly acquired knowledge of the study design and characteristics of this particular nanoagent. Dr R should support AM in decision making by (1) promoting reasonable expectations about study participation as she hopes for the best outcome that the study and the investigational agent can offer; (2) helping AM to think about her priorities and goals of care moving forward and to consider how participation in a nanomedicine study might affect those goals; and (3) caring for and about her, regardless of whether she enrolls in research, as she lives with—and faces dying with—her disease.

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CASE AND COMMENTARY

Should Trackable Pill Technologies Be Used to Facilitate Adherence Among Patients Without Insight?

Tahir Rahman, MD

Abstract

Aripiprazole tablets with sensor offer a new wireless trackable form of aripiprazole that represents a clear departure from existing drug delivery systems, routes, or formulations. This tracking technology raises concerns about the ethical treatment of patients with psychosis when it could introduce unintended treatment challenges. The use of “trackable” pills and other “smart” drugs or nanodrugs assumes renewed importance given that physicians are responsible for determining patients’ decision-making capacity. Psychiatrists are uniquely positioned in society to advocate on behalf of vulnerable patients with mental health disorders. The case presented here focuses on guidance for capacity determination and informed consent for such nanodrugs.

Case

Mr A is a 43-year-old patient with schizophrenia brought by police to the emergency department of an academic medical center. Police stated that he was making threats to harm himself while holding a knife. A neighbor noticed that he was pacing the street and responding to auditory hallucinations. In past psychotic episodes, he experienced similar auditory hallucinations and persecutory delusions of being tracked by government satellites. He believes that a “microprocessor” is imbedded in his right wrist, which he can feel “getting warmer” when the government “turns it on.” He has auditory hallucinations of male and female voices warning him to avoid people, especially on the streets, because they are “trying to harm me.” He has seriously injured himself in the past, cutting his wrist to try to remove the imagined microprocessor; this injury required extensive surgical repair of his tendons and vasculature.

Mr A’s mental status exam revealed an alert, fearful, and minimally cooperative male with poor hygiene, disorganized speech, paranoid delusions, bizarre abstraction, poor insight, impaired judgment, and tactile hallucinations of a microprocessor in his wrist. He was involuntarily admitted to a psychiatric unit due to psychosis and imminent risk of serious self-harm.

Records of prior inpatient care reveal that Mr A tends to improve dramatically after brief hospitalizations and administration of antipsychotics, and on his last admission he was stabilized with oral aripiprazole. Currently, his admission status is involuntary, but Mr A is willing to take medications. His admitting resident psychiatrist contemplates using aripiprazole trackable pill technology to aid Mr A's treatment adherence. Other members of the treatment team raise concerns about its use for this patient—specifically, whether using it would create unintended harms and undermine his trust in them, given the nature of Mr A's self-harm history as it relates to the imagined device in his body.

Commentary

Antipsychotics have gained broad approval for mental disorders ranging from schizophrenia to major depression, bipolar disorder, and autism spectrum disorder. Various formulations have been developed including oral disintegrating tablets, oral solutions, short-acting intramuscular injections, and long-acting injectable formulations.¹ The recent introduction of wireless technology to track patient information such as compliance is a clear departure from existing drug delivery systems, routes, or formulations. For example, aripiprazole is available as a tablet containing an ingestible sensor. A patch is worn on the skin of the abdomen that tracks and records medication compliance.²⁻⁴ After swallowing the pill, a patient can track ingestion and activity level data as well as self-reported mood and quality of rest on a smart phone app. The patient can elect to share the collected data with others, including a clinician. Clinicians who have access to the information can be alerted about a patient's noncompliance with the medication. Currently, aripiprazole tablets with sensors have not been shown to improve patient compliance.^{3,4} Similar drugs are being explored and are referred to as "smart" drugs, nanodrugs, digital drugs, or electronic drugs. Although the technology might prove to be a significant medical advance, it could also introduce unintended harm (eg, increased distress) in some patients, such as Mr A. Specifically, it would be critical for Mr A's team to assess whether Mr A would be at increased **risk for self-harm**, distrust of psychiatric services, and increased emotional distress if he were prescribed a "trackable" pill and to determine whether he has decision-making capacity to consent to the medication. A critical ethical question is this: Which criteria should be used to assess whether and when this drug is appropriate for patients who don't have insight or decision-making capacity?

Ethics and Nanodrug Prescribing

Clinicians often struggle with improving treatment adherence in patients with psychosis who lack insight and decision-making capacity, so trackable nanodrugs, even though not proven to improve compliance, are worth considering. At the same time, guidelines are lacking to help clinicians determine which patients are appropriate for trackable nanodrug prescribing. The introduction of an actual tracking device in a patient who suffers from delusions of an imagined tracking device, like Mr A, raises specific ethical concerns. Clinicians have widely accepted the premise that confronting delusions is

countertherapeutic.⁵ The introduction of trackable pill technology could similarly introduce unintended harms. Paul Appelbaum has argued that “with paranoid patients often worried about being monitored or tracked, giving them a pill that does exactly that is an odd approach to treatment.”⁴ The fear of invasion of privacy might discourage some patients from being compliant with their medical care and thus foster distrust of all psychiatric services.^{2,4} A good therapeutic relationship (often with family, friends, or a guardian involved) is critical to the patient’s engaging in ongoing psychiatric services.

The use of trackable pill technology to improve compliance deserves further scrutiny, as continued reliance on informal, physician determinations of decision-making capacity remain a standard practice. Most patients are not yet accustomed to the idea of ingesting a trackable pill. Therefore, explanation of the intervention must be incorporated into the informed consent process, assuming the patient has decision-making capacity. Since patients may have concerns about the collected data being stored on a device, clinicians might have to answer questions regarding potential breaches of confidentiality. They will also have to contend with clinical implications of acquiring patient treatment compliance data and justifying decisions based on such information. Below is a practical guide to aid clinicians in appropriate use of this technology.

Criteria for Appropriate Nanodrug Use

First, it should be determined whether the patient has [decision-making capacity](#) with regard to antipsychotic medications. The usual criteria for determining decision-making capacity include “factual understanding of the issues,” “appreciation of the situation and its consequences,” and “rational manipulation of information.”⁶ In most situations, the goal is to facilitate patient autonomy once insight is restored. If poor insight is present (but the patient does not necessarily lack decision-making capacity), a second decision must be made about whether more intrusive and paternalistic methods such as pill counts or changing the formulation to a long-acting injectable antipsychotic might be warranted.^{7,8} Trackable pills might be considered after careful review of a patient’s unique disorder and symptoms. For example, trackable pills might not be appropriate for patients who feel threatened and might therefore carry out actions, including harm to self or others, designed to prevent realization of their fears driven by persecutory delusions.⁹ If trackable pills are deemed clinically and ethically appropriate, a sliding-scale approach can be used to determine decision-making capacity based on the risk-benefit ratio of the trackable pills (ie, if trackable pills are deemed a low-risk, high-benefit treatment, a patient who refuses the treatment would be held to a higher standard than one who accepts it).⁶ Finally, if the patient consents to trackable pills, any treatment modifications based on the data collected should be made transparent to the patient. For instance, if the clinician later wishes to hospitalize the patient or to abandon the trackable pill treatment in favor of a long-acting injectable antipsychotic, the patient should be able to consent or refuse.

Applying the Criteria to the Case

After rapport was established with Mr A, the above steps were applied to his case. Although he desired to be treated with antipsychotics, his ability to rationally consider the benefits and risks of taking a trackable pill was deemed to be poor. For this reason—and because the trackable pill was determined to be a poor choice for him given his delusions of surveillance and the possibility that it could lead to his further distrust of the treatment team—he was not given information about the new trackable pill. Instead, it was recommended to him and his family that more established antipsychotic and psychotherapeutic treatment options be utilized. He ultimately did choose to consent to a long-acting injectable formulation of aripiprazole. It could be argued that, with proper [informed consent](#), Mr A might benefit from the new trackable pill technology once he is stabilized with standard aripiprazole tablets. However, given his multiple admissions for psychotic exacerbations and the paucity of data on treatment efficacy of trackable pills in patients with schizophrenia, the team decided against this option because Mr A might experience further exacerbations of his symptoms, increased mental suffering, distrust of psychiatric services, and an increased risk of self-harm.

Conclusion

New technologies that offer patients with mental illness alleviation from suffering are certainly desirable. Psychiatrists have a uniquely entrusted position in society that obligates them to be advocates for patients with mental disorders.^{10,11} Although trackable and other nanotechnologies represent medical breakthroughs for treatment of many diseases, they could have unintended implications and thus their use must be carefully considered in the individual case. The guidelines discussed here offer an approach to determining whether trackable pill technology should be used in cases in which a patient might have poor insight and persecutory delusions.

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MEDICAL EDUCATION

Which Nanobasics Should Be Taught in Medical Schools?

Joel C. Sunshine, MD, PhD and Amy S. Paller, MD, MSci

Abstract

The progressive growth in nanotechnology approaches to diagnostics and therapeutics, especially for cancer, necessitates training physicians in nanoethics. This article explains why it is critical for medical education to include instruction in nanotechnology, nanomedicine, nanotoxicology, and nanoethics and suggests basic concepts educators can use to infuse curricula with this content.

Introduction

As it continues to evolve to meet the needs of the next generation of clinicians, medical education should incorporate new interventions and diagnostics, among them nanotechnology applications. Nanotechnology is a science built on fundamental changes in material properties because of unique chemical, physical, mechanical, and optical properties that occur when particle size falls into the nanorange. The nanoscale ranges from 1 to 100 nm, as that is the size at which many of the special properties particular to the nanoscale arise, although most unique properties arise below 30 nm.¹ However, the entire 1 to 999 nm range is sometimes included under the heading of nanotechnology. Optical properties of some materials (eg, the fluorescence signature of quantum dots and the color of nanogold) are determined simply by the size of the nanoparticles, not by the choice of material.² At this scale, surface chemistry and charge dramatically increase bioimaging and biosensing capabilities.^{3,4} In addition, nanoparticle size, shape, and surface charge can dictate how nanoparticles are processed and signals are amplified in the body.⁵⁻⁹

Although nanotechnology has brought together the fields of materials science, engineering, and medicine in the development of diagnostic and treatment options in medicine and surgery,¹⁰ nanomedicine and nanotechnology have not been included in recent influential publications on medical education reform such as the Association of American Medical College and the Howard Hughes Medical Institute's "Scientific Foundations For Future Physicians."¹¹ However, it is imperative that the next generation of physicians understand these developments so that they can be better prepared to provide consultation to scientists about potential applications, integrate nanotechnology-based therapeutic choices into

practice, and respond to ethical challenges.¹² This article explains why it is critical for medical education to include instruction in nanotechnology, nanomedicine, nanotoxicology, and nanoethics and suggests basic concepts educators can use to infuse curricula with this content.

The Importance of Nanotechnology to Medicine

While its use is still early, nanotechnology promises to revolutionize medical care. The number of nanotechnology-based drugs, devices, and diagnostics clinically available and in clinical trials is growing rapidly. Many of the early applications of nanotechnology have been in the field of drug delivery and have allowed for new agents with improved pharmacologic or pharmacodynamics profiles. Underlying these advances is the enhanced permeability and retention effect (EPR) in solid tumors, which allows for the passive or active accumulation of nanoformulated drugs at the site of solid tumors at higher levels than in the rest of the body.¹³ Major clinical examples of such drugs include US Food and Drug Administration (FDA)-approved cancer nanochemotherapeutics such as nanoparticle albumin-bound paclitaxel,¹⁴ liposomal doxorubicin,¹⁵ liposomal daunorubicin,¹⁶ liposomal daunorubicin-cytarabine,¹⁶ and liposomal vincristine.¹⁷ Emerging applications of nanotechnology for treating cancer include more targeted approaches, stimuli-responsive delivery agents, combinatorial approaches, gene therapeutics, and immunotherapies.¹⁸⁻²¹ Additionally, there are hundreds of new technologies in preclinical development.²²

Early incorporation of nanotechnology into medicine has primarily involved drug delivery, which has been criticized for simply extending patent protection on blockbuster medications that are close to losing patent protection rather than truly offering paradigm-shifting improvements in patient care.²³ Most first-to-market nanotechnologies, however, show improved pharmacologic or pharmacodynamic profiles,²⁴⁻²⁶ making for more convenient medication dosing and potentially better safety profiles. The increased ease of use and reduced dosing frequency of nanodrugs can enhance patient experience and adherence and potentially reduce drug-related toxicity. However, studies have not yet shown improved survival with nanodrugs compared to unmodified, carrier-free parent drugs.²²

Beyond chemotherapeutics, nanoparticle formulations have shown potential for delivery of a wide spectrum of therapeutic agents that otherwise do not have “druggable” characteristics. Examples include nucleic acids and targeted inhibitors that are either in early phase clinical trials or just starting to reach the clinic to treat cancer, amyloidosis, and—as vaccines—to prevent infectious disease.²⁷⁻³⁰ Patisiran, an siRNA encapsulated in a lipid nanoparticle formulation, was recently FDA-approved for treatment of transthyretin-mediated familial amyloidosis polyneuropathy (FAP).³¹ Phase I clinical trials are underway for using lipid

nanoparticles for delivery of mRNA as a vaccine for cytomegalovirus,³² as a vaccine for cancer,³³ and as an intratumoral injectable for cancer.^{34,35} Additionally, otherwise toxic drugs have been formulated as nanoparticles to mitigate the associated side effect profile while maintaining or improving efficacy. For example, there are multiple clinical trials with an encochelated form of amphotericin B for treatment of mucocutaneous candidiasis³⁶ and resistant vulvovaginal candidiasis³⁷ and planned trials for antifungal prophylaxis in chemotherapy patients³⁸ and for treatment of cryptococcal infection.³⁹

Nanotechnology has other medical applications. It has been used to develop devices such as nanoporous drug-eluting stents,⁴⁰ nanofluidics for advanced lab-on-a-chip design,⁴¹ and clinical assay systems, including a nanogold-based system for rapid detection and identification of infectious pathogens.⁴²⁻⁴⁶ Major strides have been made in the development of next-generation nanovaccines with benefits ranging from longer sustained release of antigens or adjuvants to better tissue penetration and improved cross-presentation for activation of multiple T-cell subsets.⁴⁷ For example, development of a single-shot polio vaccine using nanotechnology may allow for improved vaccination strategies in Third World settings.⁴⁸ Combined imaging and therapeutic agents (termed *theranostics*) have been developed to co-deliver imaging and therapeutic agents, such as photothermal therapy.^{49,50} In dermatology, nanotechnology has been used in diverse topical applications, among them improved sunscreens (nanoparticulate zinc and titanium dioxide), antiseptics (nanosilver, chlorhexidine), and follicular targeting (eg, nanoparticle delivery of retinoids for acne), and nanoconjugates have been shown in preclinical studies to be novel topical therapeutics for diabetic wound healing,⁵¹ scar identification,⁵² and psoriasis.^{53,54}

Ethical Considerations in Nanomedicine

With the development of this new technology also come new ethical considerations. The majority of ethical concerns raised about nanomedicine are not novel or specific to nanotechnology in particular.⁵⁵ However, due to the greater uncertainty of nanotoxicity compared to the toxicity of more traditional medications, nanotechnology clinical trials theoretically have a higher risk for participants. This increased risk has implications for informed consent in clinical trials.⁵⁶⁻⁶⁰ For example, the occurrence of side effects may be delayed, given that some nanotechnology platforms, such as nanogold, can accumulate in tissues and persist longer than traditional medicines.⁶¹ As a result, some side effects might not be captured during the trial itself or even during the first few years of postapproval long-term safety monitoring. Although clinical trials are often powered to detect strong early negative safety signals, years of experience with medications is required before clinicians can fully understand the long-term effects of exposure.

Some have argued that the additional theoretical risks of nanotechnology have been underrecognized and that insufficient regulatory attention has been paid to these [nanotoxicity risks](#).⁶² These additional risks may be at least partly ameliorated through the use of biodegradable nanotechnology platforms, which by design do not persist long term and accumulate in tissues.⁶³ Generally, the FDA has articulated a belief that standard [regulatory protocols](#), sound science, thorough product characterization, and its own flexible and responsive regulatory oversight is sufficient for nanomedicine applications.^{64,65}

As with much of new technology, nanomedicine is often quite expensive, and when covered by insurance plans, the cost is passed on to all covered patients via higher insurance premiums. That cost leads to concerns that nanotechnology and its applications will serve to further [compromise global equality](#) in access to health care,⁶⁶ and it raises questions about the ethics of new formulations and patent exclusivity extensions.

Changing Medical Education to Keep Pace With Nanotechnology

Given the growing prevalence of nanotechnologies in medicine and their concomitant ethical risks, it is important for students to have an introduction to nanotechnology during their medical education. Multiple approaches could be envisioned to optimally integrate nanotechnology content into the medical school curriculum. Nanotechnology could be a stand-alone course that covers the fundamental scientific principles of physiochemical behavior at the nanoscale and the application of nanotechnology to imaging, drug design, and specific clinical disciplines, in addition to nanotoxicology and the risks of nanomedicine.⁶⁷

A problem-based approach in a stand-alone course is well suited to an in-depth discussion of nanotechnology and its implications. For example, the pros and cons of using liposomal formulations of doxorubicin (vs free drug alone) could introduce a discussion of the benefits of nanomedicine as well as the ethics of drug pricing, patent protection windows, and the incentive structures that exist for pharmaceutical development. Additionally, problem-based coursework offers a way to discuss nanopharmacology and to consider other potential agents, formulation requirements, and future targeting capabilities. This approach might allow for a holistic view of nanotechnology and its applications.

Instruction in nanotechnology could be infused into courses in clinical pharmacology, pathology, immunology, and oncology. Clinical pharmacology coursework could include the size and scale of nanotechnology, unique properties of nanomaterials, targeted delivery systems, mechanisms of nanodrug delivery, and the interaction of nanomaterials with the host. Pathology coursework could include nanodiagnosics, nanotoxicology, and nanoethics. Immunology and infectious

disease coursework could include the immune response to vaccination and nanoparticle-based cancer vaccines.⁴⁷ Immunology coursework could also be modified to reflect the cross talk between nanotechnology, materials science, and innate immunity. For example, instruction on immunologic foreign body responses could highlight the way that nanotechnology applications and implantable devices have been designed to prevent the normal biological response of protein binding, opsonization, and phagocytosis, thereby reducing clearance of therapeutics. Ethics courses might review nanotoxicology, potential side effects in patients of nanotherapy, possible risks to the environment, and cost-benefit analyses. Ideally, coursework on nanotechnology would involve collaborative discussion between medical specialists, bioethicists, and researchers involved in developing these technologies or translating them into the clinic.

Conclusions

Rapid developments in nanotechnology have begun to enter the clinic and are poised to make a major impact. Nanotechnology is a multidisciplinary field, making it amenable to multiple points of entry into medical curricula, including coursework on pharmacology, pathology, immunology, and oncology. Medical education will need to meet the challenge of integrating nanomedicine, nanotoxicology, and nanoethics into the current curriculum to ensure that future physicians are prepared for a nanotechnology future.

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HEALTH LAW

Regulating Nanomedicine at the Food and Drug Administration

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Abstract

The US Food and Drug Administration (FDA) oversees safety and efficacy of a broad spectrum of medical products (ie, drugs, biologics, and devices) under the auspices of federal legislation and agency regulations and policy. Complex and emerging nanoscale products challenge this regulatory framework and illuminate its shortcomings for combination products that integrate multiple mechanisms of therapeutic action. This article surveys current FDA regulatory structures and nanotechnology-specific guidance, discusses relevant nanomedicine products, and identifies regulatory challenges.

Regulatory Demands of Nanotechnology

Nanotechnology is research and technology development on the nanoscale (traditionally 100 nanometers (nm) or less, or one billionth of a meter) at which particles have novel properties and functions because of their size.¹ At this size, materials exhibit quantum effects, impacting fluorescence, conductivity, magnetic permeability, melting point, and reactivity.¹ The ability to control atoms and molecules at the nanoscale has significantly advanced medical science and catalyzed the field of nanomedicine, defined by the National Institutes of Health as a “highly specific medical intervention at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerve.”² Nanomedicine also includes nanotechnology applications for “diagnosis, monitoring, and control of biological systems.”³

Cutting-edge nanomedicine applications often integrate chemical, mechanical, and biological properties to enable and enhance detection, diagnostic capabilities, and therapeutic modes of action. In the near future, it will be possible for a single nanomedicine product, once deployed in a patient’s body, to be programmed to target specific organs and tissues, create images, measure vital signs, diagnose in real time, and subsequently provide tailored therapeutics.

The US Food and Drug Administration (FDA), as a gatekeeper of health care products, plays a vital role in assessing nanomedicine products. However, its decades-old classifications to distinguish products for purposes of review and approval prove challenging for nanomedicine products due to their novel characteristics and cross-

category features. In addition, nanoscale particles and materials have different risk profiles given their decreased size, increased biological activity, and unique properties. These risk profiles, which are largely unknown, create novel [legal and ethical challenges](#) for clinical trials, patient use, and public health.

Traditional Regulatory Approaches

The FDA is tasked with protecting public health and promoting innovations and striking a balance between the two when evaluating products generated by science and emerging technologies. The FDA regulates products under 2 primary statutes: the Food, Drug, and Cosmetic Act (FDCA), which addresses chemically synthesized drugs as well as devices; and the Public Health Service Act (PHSA), which addresses biologically derived therapeutic products.⁴ The FDA must characterize products under definitions provided by Congress in both the FDCA and the PHSA. Fundamentally, these definitions and supplemental FDA policies distinguish among 3 product areas based on whether the product has a chemical mode of action (drug), a mechanical mode of action (device), or a biological source. The Table provides statutory definitions for each of the 3 product domains. Nanotechnology products span all 3 regulated domains, and many products' mechanisms of action span 2 or more of these domains.

Table. Food and Drug Administration Product Definition Overview

Product Domain	Definition
Drug	Generally, a drug is any chemically synthesized product intended for use in the "diagnosis, cure, mitigation, treatment, or prevention of disease"; products "intended to affect the structure or any function of the body"; and components. ^a New drugs are those "not generally recognized" by qualified experts "as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof" ^b and must undergo clinical trials as a requirement for approval.
Biologic	A biological product is a product that is "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein ... or analogous product ... applicable to the prevention, treatment, or cure of a disease or condition of human beings." ^c
Device	A medical device is a product that is not a drug, meaning that it does not act through chemical action and is not dependent upon metabolism to achieve its primary intended purpose. Medical devices are "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease ... or ... intended to affect the structure or any function of the body." ^d
<p>^a Quotation from United States Code.⁵ ^b Quotation from United States Code.⁶ ^c Quotation from United States Code.⁷ ^d Quotation from United States Code.⁸</p>	

The approval process for both new drugs and biological products is subject to 3 phases of clinical trials. Each phase includes laboratory and manufacturing controls; protections for human subjects; review and approval procedures; and requirements for labeling, adverse event disclosure, reporting and tracking, and [postmarket surveillance](#), including ongoing assessment to ensure safety and efficacy using a risk-benefit approach tailored to a product's intended use.^{4,9} Products developed to address an unmet health need or to treat a serious or life-threatening disease may qualify for abbreviated review and approval under breakthrough therapy status and other accelerated mechanisms.¹⁰ There are also abbreviated routes to market for drugs and biologics through the generic¹¹ and biosimilar¹² pathways based on comparisons to reference innovator products already approved by the FDA. These routes to market do not require full-scale clinical trials but only a showing of bioequivalence (for generics) and biosimilarity (for biosimilars).

Based on level of risk, devices enter the market in 1 of 2 ways: a premarket approval (PMA) process or a premarket notification (PMN) process. Like the new drug and biologic approval process, the PMA process for [high-risk devices](#) deemed potentially life saving and life supporting involves clinical trials tailored to a device's perceived risk classification and may involve specific safeguards to protect research subjects and demonstrate safety and efficacy.¹³ The PMN process, otherwise known as a "clearance" process for lower-risk devices, requires an applicant to demonstrate that a device is substantially equivalent to a device already on the market with the same or similar technological characteristics and intended use.¹⁴ Laboratory and manufacturing controls and requirements for labeling, tracking and adverse event reporting, and postmarket surveillance and ongoing assessment also apply to devices. The Government Accountability Office estimated that between 2003 and 2007, almost one-third of medical devices entered the market through the PMN clearance process, 67% were exempt from premarket review, and 1% were subject to the PMA process.¹⁴ Currently, the FDA requires first-in-kind devices, which hold promise to play a diagnostic or imaging role via a drug or biologic, to undergo market entry through the PMA process.¹⁵

Combination Product Regulatory Approach

The FDA's Office of Combination Products (OCP) assesses emerging technologies at the interface of the 3 product domains.¹⁶ A combination product is one containing a drug and a device; a drug and a biologic; a device and a biologic; or all 3 types of products. A combination product is categorized and reviewed according to its primary mode of action, which is the mode of action by which the product achieves its primary therapeutic effect—whether chemical, biological, or mechanical.¹⁷ Once the primary mode of action is determined, the FDA evaluates the product according to applicable statutory and regulatory requirements. For example, if the product's primary mode of action is chemical, the FDA will apply drug requirements. The FDA can also adjust or combine regulatory requirements to address novel issues arising with combination products.

The combination product process has been subject to criticism for its shortcomings in classifying products that integrate chemical, biological, and mechanical elements; for a general lack of transparency; and for inconsistency in applying and making decisions about the requirements.¹⁸ Notably, the 21st Century Cures Act, enacted in December 2016, contains provisions for transparency and consistency in FDA procedures for classifying and evaluating combination products and for the conduct of collaborative product assessment.¹⁹ While not changing the FDCA in substance, the act served to nudge the agency on these issues. The FDA routinely classifies nanotechnology-derived products as combination products, assigning a primary regulatory route (ie, drug, device, or biologic) and supplementing with ad hoc requirements as necessary to assure safety and efficacy.

Nanomedicine Landscape

Nanoscale research reveals that, as particle size decreases, surface area increases along with the biological activity of particles.²⁰ The unique physical properties of nanoparticles hold promise for surmounting some of the most difficult barriers to therapeutic and diagnostic efficacy. Nanoscale properties involving optical absorbance, fluorescence, and electrical and magnetic conductivity enable targeted localization, visualization, and treatment of cancerous tumors, for example.¹ Nanoscale properties involving pharmacokinetics, biodistribution, and cell permeability assist in precision drug formulation and in getting the correct drug load to an exact location faster.^{1,21} Nanoparticles' ability to interact directly with biological systems within the body increases the efficacy of myriad health applications.¹⁸

Review and approval of drugs, biologics, and devices in the nanorealm is ongoing, with many nanoproducts designated as combination products. For example, the FDA has approved nanoformulations of paclitaxel and doxorubicin as new cancer drugs, a nanoformulation of sirolimus (an immunosuppressant), and a nanoformulation of estradiol topical emulsion.²² The first approved nanodrug, the liposomal formulation of doxorubicin, consists of a nanoscale closed vesicle for drug delivery.²³ These vesicles can also be composed of polymers, creating polymersomes that create a steric barrier and confer stealth properties to the drug carrier.²³ Device nanoproducts that have entered the market through the PMN clearance process include a tissue reinforcement and hernia repair device (constructed with a nanoscale covalent-bonded titanium coating, imparting increased flexibility), a bone graft substitute (using betatricalcium phosphate nanoparticles that aggregate into 3-dimensional scaffolds with increased surface area for enhanced resorption), and a tissue-sealing and hemostasis system for laparoscopic and open surgery (using enhanced fluorescence properties of nanoparticles).²⁴ A nanoformulation of the hepatitis A vaccine was also approved as a biologic.²²

The FDA has published several nanotechnology-specific guidance documents instructing industry on agency policy.^{25,26} Topics include whether an FDA-regulated product involves

an application of nanotechnology, drug and biological products that contain nanomaterials, and safety of nanomaterials in cosmetics and food products.²⁶ Acknowledging that nanotechnology “poses questions regarding the adequacy and application of our regulatory authorities,” the FDA’s Nanotechnology Task Force, assembled in August 2006 at the direction of the FDA commissioner, was asked to determine appropriate regulatory approaches and to identify and recommend mechanisms to address knowledge gaps.²⁷ In July 2007, the task force concluded that nanoscale products did not warrant novel regulatory frameworks and thus were subject to traditional legal frameworks, including the combination product mechanism.²⁷ Nanotechnology combination products were named by the task force as necessitating further exploration—specifically, whether employing the combination product approach to determine the regulatory pathway to market as a drug, medical device, or biological product was appropriate. The report states:

The very nature of nanoscale materials—their dynamic quality as the size of nanoscale features change, for example, and their potential for diverse applications—could permit development of highly integrated combinations of drugs, biological products, and/or devices, having multiple types of uses, such as combined diagnostic and therapeutic intended uses. As a consequence, the adequacy of the current paradigm for selecting regulatory pathways for ‘combination products’ should be assessed to ensure predictable determinations of the most appropriate pathway for such highly integrated combination products.²⁷

Subsequently, the FDA published 2 guidance documents on nanotechnology in the context of medical products. One outlines considerations for industry when determining whether a product involves an application of nanotechnology, which indicates the need for sponsors to communicate nanotechnology status to the FDA as part of the product review process.²⁸ The other discusses a nanotechnology risk-based framework, specific requirements for conduct of nonclinical and clinical trials, manufacturing quality and controls, and special environmental considerations for drug and biologic products containing nanomaterials.²⁹

Future Challenges

The FDA continues to use a case-by-case approach for evaluating nanotechnology products, applying the combination product framework to determine the type of product and resulting regulatory requirements. There are persistent pleas from medical, scientific, and legal experts such as the National Academy of Medicine (formerly the Institute of Medicine) to fix inconsistent and inadequate drug, biologic, and device classifications as well as the combination product framework itself.¹⁴ Concomitant with the debate about whether existing regulatory structures and processes are adequate, broader questions have emerged regarding inherent risks of nanotechnology and products containing nanoparticles. Areas of concern include nanoparticle toxicity and human health impacts of exposure, especially effects of various exposure routes and routes of administration,³⁰ unintended effects of nanoparticles’ ability to cross the blood-brain barrier, and long-term effects of nanoparticles.³¹

The FDA faces numerous challenges as nanomedicine progresses, and 3 core challenges stand out. The first is the adequacy of the regulatory framework itself; nanomedicine highlights the rigidity of product domains that dictate product approval requirements. At the nanoscale, decades-old definitions of chemical and mechanical action may not be suitable to characterize products with novel mechanisms of action and properties. For the purpose of evaluating such products, traditional definitional distinctions and accompanying legal requirements for review, approval, and postmarket surveillance and assessment may not be ideal. Current regulatory structures and processes may work for existing products, but the increasing complexity of nanotechnology and its convergence with other fields (eg, neurotechnologies and genetics) will likely strain their limits. Ongoing deliberations, stakeholder input, and agency policy must assess whether and to what extent current regulations are adaptable to newly emerging nanomedicine products or whether implementation of new frameworks is necessary to ensure safety and efficacy.

A second challenge has to do with the potential for [novel risks](#), which raise questions about traditional safety and efficacy requirements' appropriateness. Questions persist about whether nanoscale properties alter established risk-benefit measures and assessments of clinical trials and research protocols; whether and when abbreviated review of nanomedicine products is appropriate; and whether and when postmarket assessments should be tailored to address nano-specific toxicology and exposure concerns. As nanotechnology advances, particularly in the realm of human health, ample attention to scientific developments should also be paid to characterizing, assessing, and reporting adverse events. As part of the National Nanotechnology Initiative and other federal agency collaborations, large-scale research efforts are underway to characterize nanoscale materials and quantify their impact for purposes of developing toxicological assessment and testing tools.³² Information obtained from this research should be integrated into FDA review and approval processes as appropriate.

A third challenge has to do with whether labeling of nanomedicine products for consumers is sufficient to inform them that products contain nanotechnology or nanomaterials. This is not to say that explicit labeling should be a requirement; however, the FDA must contemplate whether increased patient and consumer education and consumer engagement is warranted and whether FDA policy on labeling requirements for nanoproducts responds well to public sentiment and the public's health literacy needs. For these efforts to succeed—similar to consumer awareness campaigns and advocacy efforts in the realm of genetically modified food and biotechnology—positive perceptions and understanding of applications is essential.

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STATE OF THE ART AND SCIENCE

What Are Best Practices for Ethical Use of Nanosensors for Worker Surveillance?

Gary E. Marchant, PhD, JD, MPP

Abstract

Many employers now offer workers wearable or implantable devices that can monitor their health, productivity, and wellness. Nanotechnology enables even more powerful and functional monitoring capacity for these devices. A history of workplace monitoring programs suggests that, despite nanosensors' potential benefits to employers and employees, they can only be successful and sustainable when a company's motivations for offering them are acceptable and transparent to workers. This article describes 5 best practices for motivating nano-enabled worker monitoring programs that are acceptable, effective, and ethical.

Workplace Nanoethics

Workplace applications of nanotechnology to date have primarily raised concerns about the exposure of workers in manufacturing and other jobs to potentially hazardous nanoparticle dusts.¹ However, as nanotechnology becomes more integrated into an ever-wider range and diversity of products, other occupational issues are starting to arise. One such issue is the use of nano-enabled electronic and microfluidic technologies to create powerful and miniature connected sensors that can be used for a variety of communication, monitoring, and surveillance functions. This paper addresses the ethical, legal, and policy implications of using nanosensors in mobile health (mHealth) products such as nano-enabled wearables, implants, and tattoos to monitor the activity, productivity, health, and wellness of employees. Workplace nanosensor applications have significant potential for win-win benefits by promoting the health, wellness, and productivity of workers, but they also raise profound ethical questions about employee privacy, security, and autonomy that must be carefully negotiated and managed. Accordingly, this paper suggests best practices for implementing nanotechnologies.

Workplace Nanotechnology and mHealth Products

New mHealth products such as wearables, implants, and tattoos that collect data on a person's activities, environment, location, performance, productivity, health, and other parameters have been enabled by nanotechnology.² The small size and novel properties of nanomaterials afford electrochemical sensors and biosensors that can monitor specific exposures, movements, and interactions.³ The result has been the development

of wireless intelligent devices that are tiny, portable, low cost and battery free; capable of communicating with smart phones and other connected devices; and equipped with sensors that can detect and signal specific chemicals, physiological changes, motions, and environmental conditions.^{4,5} Materials with these capabilities are sometimes referred to as “programmable nanomaterials.”⁶ These products can consist of wearable wristbands such as Fitbit or Apple Watch,⁷ sensors built into clothing or equipment,⁸ tattoo sensors applied to a person’s skin that can monitor physiological and chemical parameters in real time,⁹ and even some radio-frequency identification or memory chips that are placed under a person’s skin and provide a permanent built-in identification and communication device.^{2,10} Nano-enabled wearables and implants have the potential to help improve worker productivity, health, and wellness by monitoring for adverse exposures and early disease indicators, [incentivizing exercise](#) and other healthy behaviors, and tracking performance and productivity parameters.

Such applications can theoretically benefit both the employer and the employee. Employers are looking to such technologies to try to stem rising employee health care costs as well as to reduce employee absences and health impairments that affect job performance.¹¹ Employees seek information and incentives to be healthier and more productive.^{12,13} Nanosensors could potentially enable employers and employees to cooperate in undertaking advanced technology-based monitoring to achieve these mutual goals, which Ajunwa et al have referred to as “participatory surveillance.”¹⁴

However, technology-based workplace [surveillance programs](#) of the past have often been designed and administered in ways that are perceived by many workers as being too intrusive and heavy handed and as benefiting employers at the expense of employees and, for these reasons, have often been unpopular with workers.¹⁴ In some cases, these programs are implemented in ways that intrude upon workers’ privacy both inside and outside the workplace (eg, by constantly tracking their location) and restrict employee liberties, while workers’ perception of being constantly monitored by technology generates unnecessary stress and pressure.¹⁴ Unsurprisingly, many existing employer wellness programs have been found to provide modest if any benefits to either workers or employers in terms of decreased health expenditures, improved health behaviors, or increased productivity.¹⁵

The following section provides some best practices to avoid the types of pitfalls typical of technology-based workplace surveillance programs and to encourage a true partnership between employers and employees, which will be critical to the success of workplace nano-enabled mHealth programs.

Best Practices for Legal and Ethical Use

In the United States, there are relatively few—and, at best—weak federal and state legal protections for workers from technological surveillance in the workplace.¹⁴ This lack

of legal protections is exacerbated by the declining role of trade unions in most industries as a force to advocate for worker rights (including privacy rights) as well as the growing number of “at will” employment contract states in which employees can be fired for any reason, giving employers greater coercive powers over their employees, including through surveillance.¹⁴ Yet, the history of surveillance efforts that are imposed on workers without employee approval demonstrate that such unilaterally imposed surveillance requirements often backfire by reducing employee morale, increasing worker turnover, and incentivizing workers to find ways to “beat the system.”¹⁴

As nano-enabled mHealth devices increase the potential power and intrusiveness of worker monitoring programs, it is critical that employers implement such programs in cooperation with workers as that is the only way to realize in practice the significant benefits to employers and employees that are possible from such efforts. The following best practices, derived from an extensive literature on bioethics, employee management, technology acceptance, risk management, and practical experience with worker surveillance programs,^{2,14,16-22} can best ensure that nano-enabled mHealth applications can be a win-win for both workers and their employers.

1. *Voluntary, not mandatory, participation.* A key element of successful, cooperative worker monitoring programs is that a worker chooses to voluntarily employ the surveillance technology used in the program. Any program in which worker monitoring devices are mandated or coerced is likely to cause employee resentment and undermine the acceptability and success of the program. For example, West Virginia recently tried to mandate that all state public school teachers download a monitoring app and use a Fitbit wearable that connects to the app—or face penalties. Responses to this mandatory program were so overwhelming and strong by teachers and supporters that the state quickly made participation voluntary.²³
2. *Transparent data use.* Data collected by nanosensor wearables and implants from workers could be immense, and uses to which those data are applied are highly variable. To ensure workers’ trust and cooperation in the program, employers should only use data collected from workers for disclosed purposes. This restriction also means that identified, individual data will not be provided to third parties without a worker’s approval; data that is shared must be anonymized and aggregated. Moreover, employers should ensure that employees have access to their data and to the analyses done on that data; such disclosures will build workers’ trust and participation in—and capacity to benefit from—the program.
3. *Validated technologies.* Employers should offer only mHealth products with demonstrated validity for measuring parameters of interest. Inaccurate

mHealth data is ineffective at best and might even be harmful if it provides erroneous incentives or leads to incorrect health or performance conclusions. There have already been complaints and lawsuits alleging that some commercially popular wearable health trackers provide inconsistent and inaccurate results.²⁴

4. *Data collection limited to the workplace.* Nano-enabled wearables and implants might continue to be worn by a worker and potentially continue to collect data outside the workplace during nonworking hours. There have been instances of employees trying to disable such devices for nonwork times and even being disciplined or fired for such actions.²⁵ Worker data collected outside of working hours is less relevant to workplace performance and productivity and therefore should not be made available to employers, although employees should be given the option to access and use data generated by the technology for their own self-improvement and wellness.
5. *Secure storage.* Any time data is collected, it is vulnerable to being hacked and stolen via cyberattacks. Such attacks would likely undermine worker confidence in nanosensor mHealth programs and thus undermine their effectiveness. Employers can do 2 things to enhance the security of data collected in such programs. First, they should ensure that both the sensors on a worker and the data storage location have the best feasible cybersecurity protection. Second, employers should only keep data for as long as actively needed to fulfill the objectives for which it was collected; data that needs to be stored for longer periods in order to track long-term trends should be permanently deidentified to minimize potential for sensitive worker data to be hacked.

While such nonbinding principles have the weakness of being unenforceable, employers can benefit from implementing the best practices suggested here to achieve more sustainable and acceptable monitoring programs. The experience implementing such best practices can help build norms that can eventually be enacted into binding legal requirements.^{26,27}

Partnering With Workers for Sustainable mHealth Solutions

Nanosensors have the potential to greatly enhance the utility of wearable and implanted wearables and implants. Monitoring programs that use such sensors could provide significant benefits to both workers and their employers, creating a win-win scenario by improving worker health, wellness, and productivity. However, to be successful and sustainable, such monitoring programs must be voluntary and acceptable to workers. Employers therefore share a common interest with their workers in ensuring that

workplace surveillance programs are conducted in a fair, transparent, and ethical manner. As a recent analysis of wellness programs by Ajunwa et al concluded,

By committing to the well-settled ethical principles of informed consent, accountability, and fair use of personal health information data, wellness programs can safely navigate the ethical quagmires associated with the collection of sensitive personal health information from employees.... [and] employers may have a better chance at realizing the healthcare cost reductions that is their primary objective without undue disadvantages to the employee.²²

The 5 best practices described above can help ensure that such programs will be acceptable and beneficial to their workers and therefore of value to both employers and employees.

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POLICY FORUM

How Should Engineered Nanomaterials Be Regulated for Public and Environmental Health?

David B. Resnik, JD, PhD

Abstract

A central ethical and policy issue regarding minimizing and managing risks of engineered nanomaterials (ENMs) is whether existing legal frameworks sufficiently protect public health and the environment. This article argues that policymakers should (1) use existing laws to regulate ENMs and the best available evidence to inform appropriate levels of regulation and (2) support additional research on risks of ENMs. Were they to do so, public health and environmental risks of ENMs could be minimized and managed without sacrificing their potential clinical, social, and economic benefits.

Growth of Nanomaterial Use in Health Care

The nanotechnology industry has expanded rapidly since the 1990s as scientists, engineers, and technologists have developed useful applications of nanomaterials in manufacturing, transportation, communications, energy production, waste treatment, consumer products, and medicine.^{1,2} Nanomaterials are solid, liquid, or gaseous substances typically between 1 and 100 nm in diameter or length. They are larger than subatomic particles (eg, protons, electrons) but smaller than the smallest microscopic ones seen through a conventional light microscope (eg, red blood cells). Nanomaterials occur naturally (for example, in ash from forest fires or volcanic dust) and as the products of manufacturing processes, also known as engineered nanomaterials (ENMs). Because nanomaterials are so small, they are influenced by quantum mechanical effects and often have unique physical and chemical properties (such as melting point, fluorescence, electrical conductivity, magnetic permeability, and chemical reactivity) that can change as a function of size.^{1,2} Nanomaterials are often highly reactive because they have a large surface area-to-volume ratio and chemical reactions occur on surfaces. Chemical engineers can use this property to design nanomaterials that catalyze chemical reactions.¹

Nanomaterials have medical and industrial applications. For example, silver nanoparticles (ie, nanosilver) have antimicrobial properties that make them useful in wound dressings, stents, catheters, and bandages.³ Bioengineers have created nanogold shells containing chemotherapy drugs that deliver their payload only to cancer cells, thus

sparing the patient most of the adverse effects of the medication.⁴ Since gold nanoparticles accumulate in tumors, biomedical researchers have been able to develop tests that take advantage of nanogold's optical properties to detect the presence of cancer in the body. Chemists also have developed assays containing nanogold that can detect various types of proteins in blood and other body fluids.⁵ Carbon nanotubes—cylindrical carbon molecules that conduct electricity and heat—have been used as materials in batteries, capacitors, boat hulls, water filters, and sporting goods and as coatings and films in various industrial applications.⁶ Many commercial sunscreens contain titanium dioxide and zinc oxide nanoparticles to enhance protection from UV radiation.⁷ According to one estimate, the global market for products containing ENMs will be \$3 trillion by 2020.⁸

Assessing the Risks of ENMs

Although ENMs have many potential benefits for society, they also pose some risks to human health and the environment that are not well understood at this time.⁹⁻¹² Most of the information concerning the risks of ENMs has come from in vitro cell studies, in vivo animal experiments, or computer modelling of physical, chemical, and biological processes related to exposure to and distribution, excretion, aggregation, and toxicity of ENMs. For example, some types of carbon nanotubes can induce inflammation, pulmonary fibrosis, and genotoxicity when inhaled and are potential carcinogens.¹² Factory workers might inhale carbon nanotubes during manufacturing, and consumers might inhale them when handling materials, such as tennis rackets or frying pans, which have been coated with these materials. Other ENMs, including titanium dioxide and nickel, can induce immune responses.^{11,12} Nanosilver can cause oxidative stress and can have toxic effects on marine species if it enters aquatic environments.^{13,14} Overuse of nanosilver, especially in nonmedical applications, could lead to the development of antibiotic resistance.¹⁵ Although human and nonhuman species have been exposed to naturally occurring nanoparticles throughout geological time, there is some concern that ENMs could pose greater risks than naturally occurring nanoparticles because organisms have not had sufficient time to adapt to their unique properties.^{10,11} Also, some types of ENMs might persist in the environment longer than naturally occurring nanoparticles.⁵

Exposure to ENMs can occur in many ways. The most direct forms of exposure can happen when ENMs are used in medicines, cosmetics, foods, or consumer products. Exposure can also occur, however, when manufacturing, distributing, selling, disposing of, or recycling products containing ENMs.¹² Nanomaterial waste products (or nanowaste), which can enter the environment at various stages of manufacture, use, and disposal, are another source of exposure to ENMs. For example, ENMs could slough off from consumer products and enter the soil, air, or [water](#). ENMs used in medications could enter sewage systems via urination or defecation. ENMs could also leach out of landfills and enter waterways, such as rivers, lakes, or estuaries.¹⁶

Numerous factors make it difficult to assess the risks of ENMs. First, ENMs are characterized only by size (approximately 1 to 100 nm) and origin (eg, human) and are therefore highly heterogeneous. Risk assessment must therefore focus not on the risks of ENMs as a class but on the risks of particular types of ENMs.¹² Second, research has demonstrated that many types of ENMs can enter the bloodstream, translocate through the body, accumulate in organs or tissues, cross the blood-brain barrier, and penetrate the cell nucleus.^{11,12} Contact with ENMs via the skin, lungs, or mouth could therefore lead to immune reactions or toxicity beyond the site of exposure.^{10,11} Third, since the properties of ENMs can change in relation to size, the risks of ENMs can vary accordingly when they aggregate or disaggregate in the body.¹⁰⁻¹² For example, a type of ENM that poses a low risk at 1 nm might pose a greater risk when it accumulates in a tissue and reaches 50 nm in size. Fourth, it can be difficult to measure exposures to ENMs or track their movement in the environment due to lack of reliable biomarkers of exposure and other methods of detection.^{10,16} Fifth, the risks of nanomaterials can vary across species and among individuals within the same species. For example, an ENM that produces no adverse effects in laboratory mice can pose significant toxicity risks in humans or other species.⁵ Such heterogeneity poses regulatory challenges.

Regulating ENMs

The United States and many other developed nations have laws that can help to minimize and manage the public health and environmental risks of ENMs. For example, the [US Food and Drug Administration](#) has the statutory authority to regulate ENMs used in foods, drugs, biologics, medical devices, and cosmetics to protect the public from the toxic effects of ENMs.⁵ The [US Environmental Protection Agency](#) can regulate ENMs in the air and water, in solid and hazardous waste disposal sites, and in pesticides or other chemical products used in agriculture or industry.^{17,18} The US Occupational Safety and Health Administration has the authority to regulate exposure to ENMs in the workplace. States also have their own laws pertaining to public, occupational, and environmental health.^{17,18}

The central ethical and policy issue with respect to minimizing and managing the risks of ENMs is whether existing legal frameworks are sufficient to protect public health and the environment.^{17,18} Proponents of new regulations argue that ENMs are so different from existing substances and pose such far-reaching and poorly understood risks to public health and the environment that new forms of government oversight, such as regulations that address ENMs as a class, are needed.¹⁹ Nanowaste poses a particularly difficult problem for current legal frameworks because existing laws might not adequately account for the different ways that nanowaste can enter the environment.¹⁶ For example, existing laws might not address the risks of disposal of nanowaste from consumer goods (such as tennis rackets or sunscreens) or medical products (such as drugs or bandages). Opponents of new regulations argue that existing legal frameworks have been successfully applied to emerging technologies in the past (such as gene

therapy and genetically modified organisms), so there is no need for new regulations tailored to ENMs.²⁰ Opponents also point out that the heterogeneous nature of ENMs makes it difficult if not impossible to develop regulations for ENMs as a class.¹⁷

Policymakers who are developing and applying regulations to protect public and environmental health face the dilemma of underregulation vs overregulation.²¹ Underregulation occurs when regulations are not stringent or extensive enough to adequately protect public and environmental health. For example, one might argue that dietary supplements were underregulated in the United States prior to passage of dietary supplement legislation in the 1990s because existing legal frameworks did not adequately protect the public from the risks of these products.²¹ Overregulation, by contrast, occurs when regulations are more stringent or extensive than is required to adequately protect public and environmental health. Overregulation can have negative effects on consumer autonomy, industry, and the economy that are not offset by positive impacts on public health or the environment. For example, HIV/AIDS activists argued in the 1980s and 1990s that the stringent Food and Drug Administration regulations and policies pertaining to drug testing and approval were preventing patients from obtaining access to life-saving medications.²¹

The dilemma of overregulation vs underregulation looms large in the societal debate of how best to minimize and manage the risks of ENMs. On the one hand, creating new regulations tailored specifically to ENMs could lead to onerous policies that interfere with the medical and industrial applications of nanotechnology without yielding compensating societal benefits. For example, regulations that seek to prevent nanosilver from entering the environment might interfere with its medical uses. On the other hand, failing to adequately regulate ENMs could have significant, long-term adverse impacts on public health and the environment. For example, failing to address the problem of nanowaste could lead to accumulation of various ENMs in the environment.¹⁶ However, since evidence of the adverse effects of nanowaste is currently lacking, more research is needed to determine the appropriate level of regulation.

Taking Reasonable Precautions Concerning ENMs

Critics of the current regulatory framework have argued that the precautionary principle provides a useful way of addressing the overregulation vs underregulation dilemma concerning ENMs.²² Since the 1980s, the precautionary principle has played an important role in policy debates concerning climate change, chemical regulation, food safety, and other public health and environmental issues.¹⁷ Early versions of this principle held that precautionary measures should be taken to prevent serious harms even when the scientific evidence concerning those harms is uncertain or incomplete.²² Although early versions of the principle were criticized for supporting risk-averse policies that stifle technological innovation, newer versions of the principle recognize that precaution has social and economic costs that must also be considered.²³ According to a version of the

principle favored by many, including this author, policymakers should take reasonable precautions to prevent, minimize, or manage risks that are plausible and significant.¹⁶ A precaution is reasonable if it appropriately balances competing moral and social values, such as protecting public health and the environment, on the one hand, and promoting industry, agriculture, and the economy, on the other.¹⁷

One could argue that since the risks of ENMs—and strategies for minimizing them—are poorly understood at this point, policymakers should (1) use existing laws to regulate ENMs and the best available evidence to set regulation levels without creating new laws or an overarching system to regulate ENMs and (2) support additional research on the risks of ENMs.^{22,24} These and other precautions can offer a way to minimize and manage the public health and environmental risks of ENMs without sacrificing their potential medical, social, and economic benefits.

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ART OF MEDICINE

Journeys

Madeleine Schachter, JD

Abstract

This abstract painting represents how patients' experiences of darkness and doubt can be replaced by a sense of buoyancy and lightness. Color and movement convey a patient's sense of striving, aspiration, and optimism.

Figure. *Journeys*



Media

Acrylic on canvas.

Abstract arboreal images at the sides of the painting suggest patients' and their carers' seeming independence and separateness, each reaching and striving on their own. Both share common aspirations of healing, each traversing alone yet needing one another. The top of the image emerges from a murkier, darker chaos below; the possibility of hope is evinced in lighter, brighter colors. The curvature of earth tones at the lower right depicts a swarm of lurking doubt, the weight of decision making, and uncertainty about what might lie ahead along patients' and carers' journeys. Colors and paint layers become more ephemeral, in parallel, perhaps, with how a caregiving collaboration progresses. Density and depth of color and texture shift; metaphorically, that which was initially cumbersome lightens. Contrasts of light and dark convey movement, tilt, wisp, and froth, further signaling release from doubt, the evolution of certainty, a decision made, and the conviction in a path now taken.

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