

Responsible healthcare innovation: anticipatory governance of nanodiagnostics for theranostics medicine

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Theranostics signals the integrated application of molecular diagnostics, therapeutic treatment and patient response monitoring. Such integration has hitherto neglected another crucial dimension: coproduction of theranostic scientific knowledge, novel technological development and broader sociopolitical systems whose boundaries are highly porous. Nanodiagnostics applications to theranostics are one of the most contested and potentially volatile postgenomics innovation trajectories as they build on past and current tensions and promises surrounding both nanotechnology and personalized medicine. Recent science policy research suggests that beneficial outcomes of innovations do not simply flow from the generation of scientific knowledge and technological capability in a linear or automatic fashion. Thus, attempts to offset public concerns about controversial emerging technologies by expert risk assurances can be unproductive. Anticipation provides a more robust basis for governance that supports genuine healthcare progress. This article presents a synthesis of novel policy approaches that directly inform theranostics medicine and the future(s) of postgenomics healthcare.

KEYWORDS: anticipatory governance • engagement • ethics • innovation policy • nanodiagnostics • nanotechnology • responsible innovation • risk and uncertainty • sociotechnical integration • theranostics medicine

For over a decade, government literature, policy makers and a wide variety of stakeholders have touted the transformational potential of nanotechnology to contribute to a broad range of sectors, with nanomedicine frequently topping the lists of ‘dramatic breakthroughs’ [1]. Many organizations (both governmental and nongovernmental, national and international) have produced research programs and road maps to actively pursue the realization of nanomedicine [2,3,201–205]. One of the central areas of nanomedicine is nanodiagnostics, which is increasingly associated with theranostics [4]. Similar to personalized medicine, with which theranostics is often identified [5], the term can have a range of meanings. Here, the authors use it to denote systems that integrate molecular diagnostics, therapeutic treatment and patient response monitoring. Theranostics proponents envision a host of radical improvements in healthcare delivery, including increased efficacy and safety, patient empowerment and economic benefits. Others

note that these visions and goals raise persistent societal and policy issues and introduce some new ones. Recent science policy research suggests, however, that beneficial outcomes do not simply flow from the generation of scientific knowledge and technological capability in a linear or automatic fashion. It also suggests that public controversies and stakeholder concerns over emerging technologies cannot simply be offset by expert risk assurances. Accordingly, novel policy approaches that emphasize anticipating the ‘complex integration of scientific advances with technological, behavioral, social and cultural shifts’, especially when these shifts are not only disruptive but potentially volatile, provide a more robust basis for governance that supports genuine progress in healthcare [6].

After reviewing emerging nanodiagnostic research areas and applications, the authors sketch out three innovative visions for future theranostic systems. The paper then considers some of the potentially disruptive uncertainties

surrounding such innovations, focusing on societal and ethical issues often associated with them. It concludes with a discussion of anticipatory governance, which proposes integrating ongoing dialogue and reflection about these and other uncertainties into research and innovation activities themselves, in an effort to enhance the social responsiveness of the processes that give rise to technological emergence.

Nanodiagnosics research aspirations

When a physician evaluates the condition of a patient, diagnosis is at present largely based on macroscopic observations and the patient's own report. Even many of the more advanced tools at the physician's disposal are macroscopic visualization tools (CT scans, PET scans, and so on). The common blood tests performed to determine concentrations of specific analytes (cholesterol, glucose, electrolytes, and so on) provide useful molecular perspectives, but they are not particularly information rich measurements, given the detailed biochemical and genetic observations that are increasingly possible. As in the case of blood pressure or temperature, most of these measurements tell the physician about the overall status of the body. The prospect of personalizing medicine, determining who will respond to what drug and ultimately tailoring drugs and treatments for specific individuals, will entail a much more detailed understanding of personal biochemistry. It has long been recognized that much of the biomedically relevant differences between individuals and between specific types of conditions (e.g., different types of breast cancer) may be reflected at the molecular level [7]. The information content of the following changes manifests itself at the nanoscale: changes in protein-protein interactions; differences in the number, composition and functional associations of specific receptors in cell membranes; and changes in cell-surface interactions with the immune system [8]. This implies an increasing role for sensor systems with the ability to read this kind of information, and such systems will invariably require nanostructured parts.

Currently, there is a major push toward discovering and validating biomarkers [9–11]. These are specific molecules or complexes, either in blood or tissue, that are altered in form or concentration in a way that correlates with disease. Such biomarkers are read by their association with other specific molecules or complexes (typically antibodies) that have complementary nanoscale structures. A technical challenge with this approach is that single biomarkers, or even small panels of biomarkers, still lack the information content to interpret the level of heterogeneity that complex diseases such as cancer present. One cannot distinguish between more than four things with two bits of information. Thus, ultimately, a sensor system must have a level of resolution that at least matches the complexity of the information to be read. An analogy can be drawn between a light level detector, such as one might use to set the speed on a camera, and a 10-megapixel charge coupled device (CCD) system. Both measure light, but the CCD camera measures an image. The key thing about information in an image is that the measurements between elements are correlated, in that case in space. The future of diagnosis and theranostics, and the real utility of nanotechnology in this area, is expected to be in the

generation of high-resolution information where many different elements are brought together to create a correlated molecular 'picture' of a patient's biochemical status related to health.

Emerging applications

Nanoscale science and engineering not only greatly enables the advance of molecular diagnostics, it also allows a substantial decrease in the size of devices and systems. Accordingly, current research and development in nanomedicine focuses on engineering devices that are capable of imaging for either diagnosis or monitoring purposes and that are capable of targeted drug delivery. Increasingly, some research contributes to the development of devices that combine two or all three of these functions, in theory allowing clinicians to not only diagnose a disease, but also to deliver targeted therapy and to monitor its effects.

For example, one diagnostic device that has attracted attention because of its possible future capacity to deliver targeted therapy is the 'nanopill' [12,13,206] (for an animation, see [207]). This ingestible pill contains nanowires that are able to identify mutations in methylated DNA strands indicating the presence of a tumor in the colon. The result is communicated to a mobile phone, whether owned by the physician or by the patient. Thus, diagnosis could take place almost anywhere, in what would seem to be a patient-friendly manner. In theory, such devices as these could also contain a drug, which could in turn be released at the location of the tumor.

Emerging theranostic instruments also include sensitive imaging techniques, which are able to produce an image of diseases at an early stage, that support targeted therapy. In the field of nuclear medicine, radionuclides (or radioisotopes), which produce an ionizing radiation, are being investigated for their capacity to detect cancer at a very early stage and to provide immediate and accurately targeted treatment. The same vector molecule could thus possess a dual capacity, by exchanging the imaging and the therapeutic radionuclides, in turn making it possible both to select patients in need of early treatment and to provide immediate treatment [14].

In the area of infectious diseases, the term 'theranostics' refers to molecular tools that have been developed for the diagnosis of respiratory infections, which are a significant cause of death among young children as well as people of old age. Multiplex PCR assay, for example, enables the simultaneous detection of a wide range of viral and bacterial agents involved in respiratory infections. Currently available tests allow the detection of 12–23 pathogens, including viruses and bacteria [15]. These techniques allow quicker tests for more disease-causing bacteria and viruses at the same time, which allows physicians to choose appropriate treatments. Such molecular tools are also developed for home use, such as point-of-care (POC) rapid immunological tests. These tests are mostly envisioned for highly industrialized countries, but they could also be useful for the detection of HIV infections, tuberculosis and malaria in developing countries [16].

Other devices have been developed for treating chronic diseases, for instance, the lithium chip. This chip is an example of the so-called 'lab-on-a-chip', which allows POC testing for people

who suffer from a bipolar disorder and use lithium as medicine. POC testing refers to medical testing at home or in a professional setting without the mediation of a (physical) laboratory, and it provides immediate results. With the lithium chip patients would not have to go to the hospital four or five times a year to check their lithium level, but are able to do it themselves [17] (for an animation, see [208]).

Envisioned theranostic systems

A suite of long-term visions are either explicitly or implicitly helping to mobilize and guide research investments, research conduct, research evaluation, patient advocacy, business, administrative, regulatory and other innovation choices. In the following sections, the authors develop and present three such visions.

Nanotechnology & user-centric medicine

Comparisons from one technological domain to another can be deceptively simple and even misleading. In making comparisons to the Internet, for instance, it is especially challenging to avoid incorrect assumptions about 'digital democracy' [18]. That being said, it is increasingly easy to imagine digitalizing and remotely administering, monitoring and adjusting diagnostic and treatment operations. Thus, it makes sense to contemplate what the rapid development and widespread use of Internet and communication technologies could suggest for future healthcare delivery. The 'digital revolution' is frequently celebrated for transforming one-way information banks, in which well-defined sources of information (experts, companies and publishers) provided and controlled access to information, into more user-centric knowledge systems. What would more decentralized medical knowledge and practice entail?

Currently, medical data structures in industrialized nations are determined by healthcare institutions and are hierarchical, at least locally. There is very little interconnection, no opportunity for organic growth and the user is largely passive, providing information to the system only in formal ways (filling out forms, having a specific kind of test or examination by an expert, and so on). Within this approach, both the collection of data and the decision making process are very expensive and the data structures created are very limited and unconnected, constraining their utility.

Currently, there are a number of efforts underway to standardize information structures and more closely connect healthcare institutions to each other (electronic medical records). These efforts seek to facilitate the use of existing databases, although not necessarily at the scale seen in Internet-based information systems.

It is also possible to envision an internet-based medical system capable of collecting and analyzing data on a massive scale, comprehensive in its scope. Such a system could enable possibilities for more dynamic information flows and for nontraditional participation in healthcare delivery. For instance, the user rather than the provider could become not only the primary source of data but a central driving force defining the structure and evolution of healthcare information. A combination of technological and institutional evolutions could conceivably allow users, with or without formal intervention by medical institutions, to become

more active participants in theranostic networks. Sensing devices such as the nanopill could provide the means for collecting medically relevant information from users outside of the medical establishment and for transferring such information to and from medical data networks, theoretically enabling users to, in turn, effect change based on this information.

This scenario raises a suite of challenging sociotechnical considerations, such as how comprehensive, expensive and invasive data collection may be. It also assumes that healthcare institutions and experts would be willing to cede more control to users, yet without placing the patient at further risk. Conversely, healthcare providers could delegate increased 'agency' to technological systems and computational machines, which would themselves recommend or even initiate interventions based on complex, data-intensive and biopolitical algorithms. In the longer term, the ability to monitor and modulate human biochemistry could evolve to a point where medical intervention was based on new purposes, such as being designed to maintain health rather than cure disease.

Emerging data collection technologies

While standard physiological measurements (temperature, blood oxygen, heart rate, and so on) are relatively easy to make, some argue that they are in and of themselves not rich enough sources of information to comprehensively and sensitively monitor human health. Such information becomes more available at the nano or molecular scale. Usually, measurement at these scales involves placing molecules in locations on surfaces and looking at their interaction with complex mixtures such as blood. Currently, read-out is via secondary interactions (e.g., binding of an antibody) but ultimately, the sensor molecules themselves could become devices that generate their own signal.

There are large numbers of biochemical measurements of specific compounds that either have been, or are being, developed that are thought to be connected to disease progression. The majority of these so-called biomarkers are not very well suited for health monitoring as they require either milliliters of blood (much more than can be removed painlessly), are not comprehensive, use tissues that are hard to sample, are not accurate enough for early detection, or are expensive and time consuming to perform.

On the other hand, there are several sources of information that can be accessed from very small quantities of blood and that appear to be comprehensive in their diagnostic capability and highly correlated with health and disease. One involves measurements of specific nucleic acids that can be extracted from the blood that are involved in the response to disease. Most commonly, this involves extraction of RNA from white blood cells [19–21] or the detection of miRNA [22]. A set of such nucleic acids can be amplified very specifically and provide a response profile. Metabolite levels represent another comprehensive set of biochemicals that are indicative of health [23,24]. Both of these approaches present technical trade-offs for health monitoring. RNA is difficult to extract reproducibly, but can be readily amplified, while many of the important metabolites are fairly stable, but cannot be amplified. Another class of molecules that contain rich information about health status is circulating antibodies. They have the advantage

of amplifying naturally and specifically when a new antigen is presented and as long as they are in blood, they are very stable to store, handle and transport. A number of different biomarkers have been developed based on so-called 'auto-antibodies' [25]. However, a significantly large number of these would appear to be necessary as a basis to facilitate comprehensive health monitoring.

Monitoring health, rather than testing for a specific disease, arguably requires a very different mindset and the development of new technologies, more or less, from the ground up with this goal in mind. One platform that has been created for this purpose is called immunosignaturing [26–32]. The concept here is very different from standard biomarker technologies. Instead of looking for one or a small number of markers, the platform assays the total profile of circulating antibodies. The device and protocol are very simple. The platform consists of an ordered array of thousands of peptides on a surface. A drop of blood is diluted and incubated with the peptide surface. Less than a microliter of blood is required per assay and that sample can be obtained from a drop of blood dried on a piece of filter paper and sent through the mail. The pattern of antibody binding is recorded and analyzed. There is another very important difference between this and the use of specific biomarkers; none of the peptides on the surface represent real antigens. Thus, there is no preprogrammed correspondence between a particular peptide and a particular disease. The peptide sequences are simply chosen to cover as much of the diversity of antigen sequence space as possible with a limited number of peptides (currently, the arrays used are sequences generated by a random number generator). Any change in the immune system gives rise to a signal.

Recent advances in both batch peptide synthesis and printing as well as *in situ* peptide array synthesis have opened the door to scalable production of peptide arrays at very low cost. The ability to draw small quantities of blood painlessly and send samples through the mail allows, and may even encourage, the user to participate outside of the clinical setting. While still in an early phase, this kind of technology suggests a more direct link between the molecular makeup of an individual and large-scale data collection and analysis in the more decentralized medium of the Internet. When linked to outcomes (medical records, information mined from emails and social networking, and interactions with avatar medical programs), the potential is huge for the creation of a dynamic database for the monitoring of health and diagnosis of disease. Essentially, this becomes a clinical trial with millions of participants [33,34]. Models exist for how such a system could work in terms of web interactions (e.g., [209]).

Theragnostics coupled to personalized medicine

One of the most actively pursued aspects of biomarker technology is the development of specific biomarkers to predict efficacy and safety of a drug for a particular patient [35,36]. One type of biomarker already in use is the identification of specific genetic alleles, such as for breast cancer [37]. This type of screening is expected to depend more and more on the availability of individual DNA sequences. While the speed and cost of DNA sequencing has been decreasing for years, and there are already

consumer-based companies that provide both DNA sequences for individuals and identification of potentially important alleles [210], nanotechnology is likely to play an increasingly important role in such screening. Roche recently licensed a nanopore-based sequencing technology from Arizona State University (AZ, USA) [211] that involves threading a single molecule of DNA through a carbon nanotube that has a specific detector – a set of molecules that undergoes specific base-pairing with the bases that make up DNA and creating a corresponding electrical signal [38,39]. This technique could be extremely rapid and cost effective.

Going beyond the 'hard wired' DNA sequence of an individual, again the immune system may well hold clues into predicting the safety and efficacy of drugs. The same types of technologies described above for assaying white blood cells and circulating antibodies may also allow the differentiation of responders from nonresponders.

A more long-term scenario is that of using the kinds of information that the comprehensive immunosignaturing systems provide to actually create personalized drugs for specific individuals. For example, in patients with autoimmune diseases specific circulating antibodies sometimes trigger the undesired immune response [40]. By identifying peptides or peptide analogues on an immunosignaturing array that specifically bind to those circulating antibodies and block their ability to initiate autoimmunity, custom drugs could potentially be created. Such an approach raises many questions about how to ensure safety and what kinds of regulatory standards would be appropriate in creating such reagents [41]; but conceptually, the idea of using chemically diverse libraries to both recognize the molecular agents of change in a disease state and then to use that same information to directly create new molecular recognition elements that modify those agents would provide the ultimate in personalized medicine.

Societal & ethical issues

Such aspirations as these, and advances in the knowledge and practice that they depend on, are not without uncertainties. Just as the advent of personalized medicine would require a much more detailed understanding of personal biochemistry and genetics, it would also necessitate restructuring established healthcare policy institutions in order to deal with complex societal considerations. The theranostic systems envisioned above are, for instance, potentially disruptive and for a number of stakeholders and current healthcare delivery practices, and they trigger a host of potential societal, ethical and policy issues – for individual patients, current institutional arrangements and public well-being in general. In the case of nanodiagnostics, there has been some dedicated attention to such issues [42], but they are usually part of broader reflections on nanomedicine [43–48,212]. As some authors have argued, many of the challenges raised by nanomedicine are largely variations of, by now, more familiar medical ethics issues, which demand reflections on themes such as privacy, informed consent, risks and distributive justice. Next to these general issues, however, it is worthwhile to consider more specifically how devices for nanodiagnostics or theranostics may shape patient-clinician responsibilities, the design of medical organizations, conceptions

of health and disease and even the very purpose that medicine is supposed to serve in society.

Privacy

Real-time monitoring and diagnosing anytime, anywhere poses potentially serious privacy issues – especially if information is exchanged over the Internet. Information technologies connected to sensors, which communicate and exchange information through wireless networks, raise possibilities for questionable use and abuse of private information. It may also drive public debates about health/privacy trade-offs, particularly where public health and security may be concerned. Diagnostic devices that communicate results by wireless technology could make personal information widely available. Third party access to this personal information could have both insurance (e.g., genetic or biochemical discrimination) and personal consequences that may be challenging to resolve [49,50].

Equity

As for other applications of nanotechnology, the question has been raised whether (the development of) nanodiagnostics and/or theranostics is distributed in a just way. On a global scale, the development of nanotechnology takes place in the wealthier parts of the world, resulting in what is often called a ‘nano divide’. This leads to two types of distributive justice issues. First, those countries most in need of good healthcare may not be able to afford nanodiagnostics. Second, developments in nanodiagnostics and theranostics may be biased towards diseases quite common in the western world, leaving important, and perhaps more urgent, diseases (e.g., infectious disease) unaddressed [46,213]. Several authors have called for active policies at the national and international level to counteract these potential injustices [43,212].

Equity issues are also possible on a national scale, either because of similar dynamics playing out locally and regionally, or because ‘orphan populations’ are generated for whom existing treatments are ineffective or too risky due to unique genetic dispositions.

Safety

The potential and often unknown risk of nanomaterials, in particular nanoparticles, used for diagnostic purposes is the most consistently mentioned topic of concern in the ethical literature. Risk concerns may relate to the health and safety of patients as well as medical professionals, but also to the environment [44]. Risks can arise because of the toxicity of a specific nanomaterial, but also from the combination of nanotechnology and biomaterials, for example in gene therapy [46]. Like some other materials, nanomaterials can translocate from the exposure site to other parts of the body and may even cross cell membranes and the blood–brain barrier [51,52]. Opinions differ as to the question whether current regulation of medical drugs and devices suffices to ensure the risks are anticipated and dealt with in a responsible manner. Some plead for more stringent regulation [46], whereas others argue that current regulation suffices [50]. The lack of accurate information about the (long-term) risks of nanomaterials also makes it difficult to provide patients and research subjects the information that

they need to be able to give their informed consent [53] (see ‘Moral autonomy’ section below). This may complicate the voluntary participation in research involving nanomaterials, as well as the (legal) protection of research subjects and patients.

Scientization

Nanotechnology enables diagnostics to focus on the level of molecules and cell, often in real time and *in vivo*. It tends to redefine disease in molecular terms; disease is equated with deviations in molecular processes in the body [48–54,211]. This conceptualization of disease implies an enlargement of the difference between the subjective experience of ‘illness’ by patients (or people without complaints) on the one hand and the objectively diagnosed ‘disease’ on the other. This growing separation between ‘illness’ and ‘disease’ may invite patients to distrust their personal experience [55,56], which in turn may elicit more hypochondriac fears. Moreover, the boundary between what is normal and what is pathological may become increasingly difficult to determine [54,57]. As health and disease are changing concepts, it is already sometimes hard to draw the line between a ‘therapy’ that takes away the disease and interventions that extend the length of human lives beyond what we consider ‘normal’ right now, thus expanding present notions of what it means to lead a human life [58,59]. Finally, the scientization of health can be seen as a step towards treating and transforming ‘the self itself’ through medical biotechnology – which raises questions of (biopolitical) power and subjectivity [60].

Medicalization

Nanomedicine’s ambition to realize a more reliable and earlier detection of disease, presupposes that disease processes are like cascades, starting as a little stream, but gradually widening into a bigger and, if not stopped, ultimately uncontrollable water flow [56]. Early detection is thought to enable early intervention, thus countering the disease process when it is still possible to do so, and maybe even prevent complaints. However, criticism against early detection in general is also applicable to nanodiagnostics aiming at early detection. First of all, the underlying disease model may be false or at least too simple. Early molecular changes need not necessarily lead to complaints, morbidity or mortality later on. This means that early detection risks overtreatment and unnecessary medicalization. Moreover, early detection of a disease does not mean that it can be treated; in this case, early detection just means knowing earlier that one has an untreatable disease [55,56,61,62]. In both treatable and untreatable cases, early detection may induce serious anxiety and stress in patients [57] and again raises questions of identity, power and biopolitics [60].

Knowledge/health disconnect

While prevention and early treatment of disease are generally considered two important goals of medicine, it is not always clear what these goals demand [63]. In combination with the molecularization of the disease process mentioned above, it has been argued that the wealth of data on molecular processes may be difficult to interpret, even for medical professionals. What exactly do specific

results mean and when do they justify action? On the one hand, there is the risk of (ironically, since the data is meant to be more information rich) not having enough of the right data to comprehensively determine an individual's state of health and need for an intervention. For instance, a real-time picture of the body's functional status does not necessarily provide sufficient information to act on, in the absence of medical history and anamnesis [48]. On the other hand, there is a risk of data overload, whether psychologically for the patient, or computationally in terms of pulling out justifiably actionable information patterns [57].

Patient responsibilities

When nanodiagnosics is combined with an information system on personal health, for example analyzing and communicating the results of sensing implants, the individual may become more involved in interpreting and taking action on the basis of the data produced. When sufficient data about personal bodily functioning are available, one may even individualize the boundary between normal and abnormal [55,56] and make individual patients more responsible to manage their own sense of health. Taking responsibility for one's own health resonates well with current calls for patient empowerment: healthcare politicians and governments might hope that active patients will manage self-care better, thereby easing the economic constraints on the healthcare sector [64–66]. On the other hand, some philosophers question what the effects of such shifts in the responsibilities of patients would be in terms of 'good life ethics'. This includes changes in morality regarding the value of 'health' in cultural conceptions of what constitutes the good life, the motivation of individuals to act and interact in order to preserve or realize health, and the habits that individuals accordingly develop [67].

Clinician responsibilities

The mirror image of the changing responsibility of patients is that of the changing roles of clinicians. While clinicians have traditionally been the primary agent responsible for diagnosing patients and proposing treatment on the basis of their expertise, patients' self-management could turn clinicians into advisors, coaches, guardians or the like for patients who are, in principle, enabled to diagnose and treat themselves. While this could effectively reduce the much-criticized paternalism of clinicians, it could also compound or introduce new tensions in the patient–provider relationship. As argued above, it also imposes more responsibility on nonexpert patients to be proactive, become more knowledgeable about the results that they get, inform themselves about treatment options and make decisions.

Moral autonomy

Nanodiagnosics and theranostics is criticized for challenging the institutionalized concept of informed consent that is meant to foster the autonomy of individuals (research subjects and patients) and protect them from abuse. It is questionable, however, whether it would continue to protect patients in a clinical context. As mentioned above, some of the nanodiagnostic devices would allow patients to diagnose themselves, which may lead to the

'automation of medical expertise', where diagnostics may take place without any exchange of information between patients and physicians [53]. Patients may be confronted with a diagnosis, while they are not aware of the relevant information that allows them to make an informed decision about the further steps they have to take. Furthermore, informed consent in clinical and research contexts may be even further complicated if new medical technologies require individuals to make a risk assessment in the absence of adequate information about nanorisks – a controversial area in itself. These ethical challenges to the process of informed consent also create challenges to existing legal and institutional policies that are bound-up with informed consent. Since the autonomy of research subjects and patients is considered a basic human right, it is questionable how it can be protected when so much is unknown about applications of nanomedicine [68,69].

In addition to enabling diagnostics to be performed anywhere, nanotechnology makes it possible to diagnose anytime. The small size and (anticipated) low costs of *in vivo* sensing devices offer opportunities for body-area networks, which in principle can measure bodily health parameters 24 h a day. This raises issues of reliability, responsibility and liability, in particular in case of errors or malfunctioning. Here, as above, much depends on the design of the diagnostic systems and the specific role assigned to patients, professionals and the device itself. The question of how permanent monitoring relates to the autonomy of users is fraught with ambiguity. On the one hand, providing data about real-time bodily functioning may enhance autonomy, if these data offer useful knowledge that may inform action. However, if the data are difficult to interpret, drive automated action, or no alternatives for action exist, continuous monitoring seriously limits autonomy. Limits to moral autonomy may also arise from the likelihood of strong social pressure to behave in a specific way, despite perceived risks, trade-offs or religious beliefs.

Theranostics could pose 'slippery slope' problems for autonomy, as the automatic follow-up of diagnostics or monitoring by treatment removes the opportunity to consider the desirability of treatment. Moreover, to the extent that theranostics reduces or even altogether removes human judgment and intervention, this will inevitably raise questions of assigning moral agency to technological systems and devices [47,50,213].

As this review of social and ethical issues shows, robust progress in healthcare based on the envisioned theranostics systems would require more than the integration of diagnostic, therapeutic and monitoring capabilities; it would also require confronting the complex and ambivalent social, cultural and institutional uncertainties associated with advances in postgenomics healthcare in ways that are responsive to the diverse values and varied concerns of numerous stakeholders.

Challenges for responsible development

As in other areas of nanotechnology, policy makers around the world are stressing the importance of supporting the 'responsible development of nanotechnology' [70–73]. American conceptions of 'responsible development', American and British notions of 'responsible innovation' [72,74] and the recent European idea of 'responsible

research and innovation' [73] imply new institutional arrangements that support multistakeholder interaction and enhanced expert decision-making. As such, they represent a relatively novel policy orientation that sees expert pronouncements and public education campaigns as inadequate responses to potential technological controversies. Rather, they suggest a shift away from top-down governmental approaches towards more distributed governance capacities. However, such policy prescriptions face key challenges related to the aspiration of innovating in a manner that explicitly takes societal norms and contexts into account.

These challenges go beyond systematically describing the ethical impacts and social risks that can be neatly grouped into manageable lists, as important as such exercises initially are. Anticipatory governance of emerging technologies requires systematically taking into account the social and institutional contexts within which they emerge and converge and recognizing that disruptive and potentially volatile innovations take place under conditions of uncertainty, complexity and ambivalence (TABLE 1) [75,114]. Unlike the predictive certainty towards which toxicological research and risk management approaches aspire, the scenarios outlined above are explicitly speculative and highly uncertain – and so, by extension, are the societal implications that they entail. Policy discourse about emerging technologies thus unavoidably contains elements of both science fiction and social science fiction [76]. Expectations about the future – as well as the analogies [77] and metaphors [78] that subtly shape and convey them – are related to values and can condition behavior, enabling and constraining long-term and collective healthcare policy outcomes. Acknowledging the role of expectations in policy discourse and taking them reflexively into account will be a central challenge for the responsible governance of emerging forms of nanodiagnostics, particularly those aimed at theranostics.

While models and categories can help decision-makers reduce uncertainty in order to make it more manageable, such reduction can come at the cost of oversimplifying real-world complexity. As a case-in-point, influential science policy models are often based on outmoded assumptions about science–society interactions (for a short animation, see [214]). Consider the persistent belief that knowledge flows in a linear and automatic manner from basic to applied research (FIGURE 1) [79]. This model tends to reinforce

Table 1. Responsible Development Challenges.

Governance condition	Description
Uncertainty	Lack of predictive certainty regarding possible technological directions, applications and impacts
Complexity	Beneficial social outcomes do not flow from science and innovation in a linear or automatic fashion
Ambivalence	Ambiguous reception of new developments among users, patients and other affected stakeholders

Data adapted from [75,114].

the assumption 'that more science inevitably leads to more social good' [6]. In actuality, progress in healthcare "results from a complex integration of scientific advances with technological, behavioral, social and cultural shifts" (FIGURE 2) [6]. Strengthening the links between and among diverse modes and sites of knowledge generation and use thus constitutes another key challenge to responsible science and innovation.

Finally, as is evident from the numerous and interrelated societal and ethical issues listed above, nanotechnology-enabled theranostic systems could easily come to be associated with a range of controversial consequences, whether intended or unintended. Since 'the public' actually consists of numerous 'publics' and stakeholder groups who are likely to perceive the same socio-technical systems and transformations in vastly different ways, the complex processes that give rise to shifts in healthcare delivery need to be flexible enough not to lock in prematurely to sub-optimal and socially undesirable pathways. For instance, the envisioned advantages of early detection need to be weighed carefully against the possible drawbacks listed above. Contrary to public deficit models, public ambivalence and concerns over new and emerging technologies are not simply based on a lack of understanding of the science, they can be tied to issues of trust, values and experience [80]. Lack of public trust in and deference to experts suggests that there are both formal and informal types of risk assessment at play in governance processes: ethical issues and risks that are identified as credible by experts and those that various stakeholder and public groups perceive independently from expert determinations as legitimate. This point was made

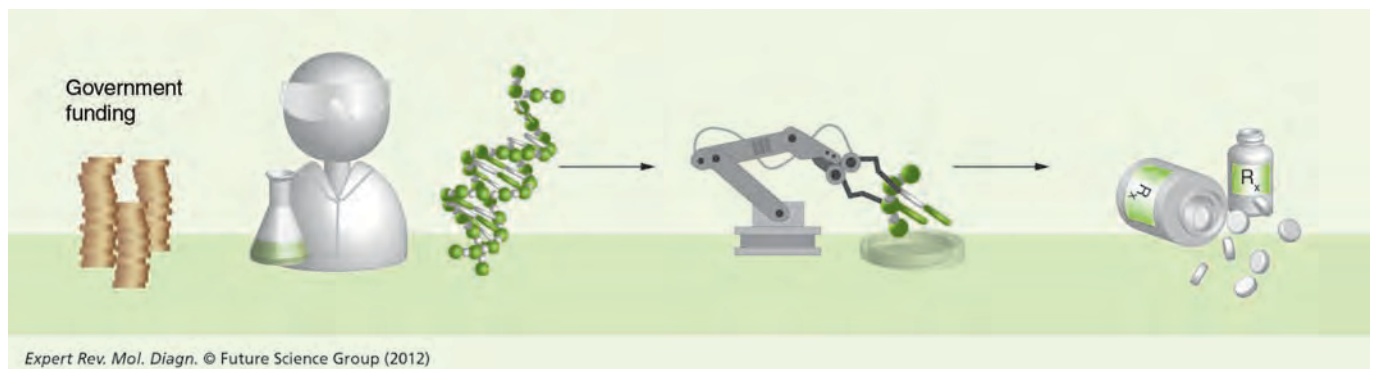


Figure 1. Innovation as a linear process. The traditional 'linear model of innovation' assumes that knowledge flows in a linear manner and that this automatically results in societal benefits.

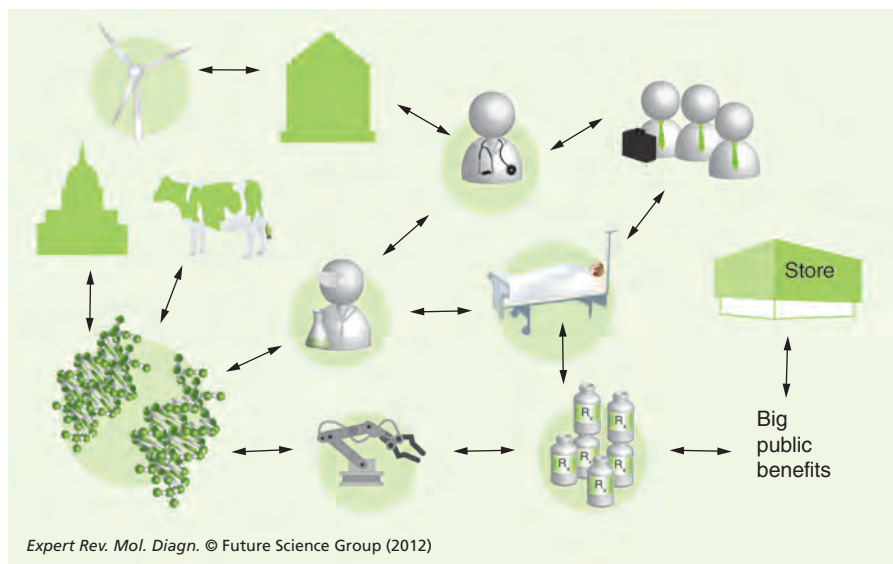


Figure 2. Innovation as a complex system. Progress in healthcare depends on interactions among scientific, technological, institutional and socio-ethical components.

during a US Congress hearing on nanotechnology by one witness, who stated that responsible development of nanotechnology must take into account both ‘real’ and ‘perceived’ risks [81].

Anticipatory governance

In response to these potentially disruptive, if not volatile, governance conditions, science policy makers have increasingly solicited the involvement of social scientists and humanities scholars in the design, conduct and assessment of activities aimed at the responsible development of nano- and bio-technologies [82]. Such ‘post-genomic’ roles for the social sciences are far more interactive than those previously afforded to them by research programs such as the Ethical, Legal and Societal Implications (ELSI) program of the Human Genome Project [83,84]. Anticipatory governance sees these interactive roles as building capacities for emerging socio-technical systems to be shaped by a diversity of stakeholder inputs and perspectives that are brought to bear on decision processes through a variety of channels [85,86].

Anticipatory governance, which has been cited in relationship to various aspects of personalized medicine [87,88], emphasizes three broad types of activity, which are meant to operate together as an ensemble: foresight, engagement and integration (TABLE 2) [89]. Foresight activities are designed to help stakeholders grapple productively at an early stage with a variety of socially embedded sources of uncertainty, both in the short and longer terms. In contrast to research that attempts to predict technological risks and impacts, foresight methods such as scenario development help analysts and practitioners anticipate social, technological, ethical and institutional elements [90–92]. Engagement activities go beyond traditional approaches that seek to remedy a ‘knowledge deficit’ in the public understanding of science [93,94]. Rather, engagements facilitate deliberation and the development of informed opinions among a variety of public groups [95], each of which potentially draws from unique knowledge and value systems and may have vastly different stakes

in policy outcomes. As part of the broader policy of public participation, public engagement has a long history [82] and can include scientific, state and civil society participants in large-scale, coordinated events [96,97].

Integration activities seek to expand the scope of expert practices and decision processes, simultaneously elucidating broader values potentially at stake and increasing the creative options for responding to them [98]. As a complement to public engagement activities, and an application of ELSI research [83], integration takes place in the course of normal work routines whether in laboratories, clinics, institutes or government bureaucracies [99–103]. Integrative activities draw on a variety of descriptive and prescriptive approaches both to identify societal and ethical issues and to inform research and innovation decisions.

Some aim to articulate and assess the moral significance of technologies being researched in the laboratory [61,104,105], studying the performance of technological ‘ancestors’ to reveal shortcomings, which can in turn improve the design of patient studies and the identification of the eventual end measures for the technology under research [104]. Others seek to open ‘reflective spaces’ for critical dialogue [106]. Integrative activities can also be multisited, catalyzing reflection with a variety of public groups, institutional processes and specialist workplaces [107].

One integration approach, Socio-Technical Integration Research (STIR), has explored the possibility and utility of implementing responsible innovation policies in over two-dozen public and private laboratories in North America, Europe and East Asia [108,109,215]. The program entails an ‘embedded’ social scientist who uses a generic protocol to map science and innovation decisions and facilitate critical reflection in real time [98]. The interdisciplinary collaboration is then assessed in terms of whether it stimulates or enhances the ‘midstream modulation’ of technological development [110]. Findings suggest the potential for collaborative arrangements to bring the often competing goals of responsibility and innovation into a mutually productive relationship: study participants have been observed to become more reflexively aware of the societal contexts of their work, in turn enhancing their decision processes and often altering the direction of their research and professional activities [98,111,112].

Whether in substituting one chemical catalyst for another, altering research and training methods, or initiating public outreach to communicate findings to clinical patients, knowledge practitioners in diverse settings have plenty of opportunities to reflect on the broader implications of their choices. Those who participate in integrative programs like STIR may be better able to identify and strengthen links between the routine technical activities and their broader social, ethical and policy contexts. Building more critically reflective and socially responsive capacities into expert and specialist decision processes does not, by itself, guarantee progress in healthcare;

but it may be an increasingly necessary component within a suite of approaches aimed at responsible healthcare innovation, in light of the complex, uncertain and highly ambivalent conditions under which nanodiagnostics and theranostics are likely to emerge.

Reflexive nanodiagnostics research and theranostics system design therefore pursues innovative visions in light of public values and operates with the understanding that technological design and institutional design coproduce one another [113]. Anticipatory governance requires building reflexive capacities into and throughout the multiple phases, activities and settings within which science and innovation takes place. These settings and the people who populate them are diverse, and they will therefore apprehend governance uncertainties, complexities and ambivalences differently. Different stakeholder groups will imagine a given theranostic system differently, depending on their values and expectations. Involving these stakeholders in foresight, engagement and integration activities can help clarify the values that are at stake, as well as the technological and institutional design choices that are most promising.

Expert commentary

Despite emerging capacities in biomedical and nanotechnological research to advance and integrate diagnostics, therapeutics and monitoring, these have not increased efficacy, led to new proven treatments, or ushered in the age of personalized medicine and theranostics. If nanodiagnostic and theranostic instruments are to be developed, stronger connections will need to be built among various and diverse knowledge-generating activities, social groups and institutional processes. However, if nanodiagnostics and theranostics are to be developed responsibly, these connections will also need to foster the capacity for individuals and institutions to make robust and productive decisions under conditions of uncertainty, complexity and ambivalence.

For instance, theranostic devices and systems used by patients themselves may empower patients to diagnose and treat disease and increase treatment efficacy. They may also decrease patient autonomy and create new healthcare problems, particularly if too much of the wrong type of information is available. To increase the likelihood of overcoming persistent healthcare policy problems rather than reinforcing them or introducing new ones, alternative governance methods should be put into practice for early and regular stakeholder dialogue and interaction. However, dialogue is not enough. Deliberations on shared goals, disagreements and trade-offs need to be linked to and integrated with the expert and institutional decision processes that are responsible for producing knowledge, designing technologies and prescribing and implementing policy.

Policy makers should strive to recognize that problems are coproduced, meaning that technological and social dimensions are closely intertwined. Thus, informed consent procedures, which currently play such a large role in regulating clinician–patient interactions, as well as in legal and institutional health policies, cannot be separated from the technological conditions and the democratic values that also regulate patient–clinician interactions and that are easy to take for granted. Anticipatory governance provides a framework for rethinking public health

Table 2. Anticipatory Governance Conditions.

Governance capacity	Description
Foresight	Unlike prediction, foresight uses various means to anticipate implications of diverse plausible futures
Engagement	Public debate and deliberation aimed at both understanding and informing policy decisions
Integration	Critical reflection by experts that expands the scope of their decision frames and alternatives
Data adapted from [88].	

policy goals, strategies and evaluation. For instance, foresight activities can assist experts, policy makers and public groups in imaging the complex sociotechnical dimensions along which the future of healthcare delivery may change.

Counterintuitively, the cascade model of disease and the drive for a more data-rich environment may converge to produce an overly simplistic understanding of personalized health coupled to an overly rich flow of data that leaves key health variables underdetermined. Nanodiagnostics and theranostics systems and devices should be designed to allow for multiple sources of understanding the interactions between the body, lifestyle and the environment. Studies that examine the integration of Western and Chinese medicine could be a source of inspiration, at least as far as exploratory research is concerned. Public engagements among patients, physicians and policy makers can clarify which core value conditions ought to be maintained, where possible, and which are more appropriate to accommodate technological disruptions. Integrative activities that introduce greater contextual sensitivity into expert, specialist and bureaucratic decision processes can not only identify potential sources of social strain and conflict, but they can incrementally adapt and ‘modulate’ existing practices and trajectories with larger governance goals in mind.

Healthcare administrators hope that active patients will manage self-care better, thereby easing the economic constraints on the healthcare sector. Theranostic instruments that integrate diagnostic as well as therapeutic functions and that may be used by patients themselves, support and enforce this general interest in patient’s self-management. While initiatives to transfer healthcare tasks to patients may liberate patients from frequent hospital visits, it may also lead to cases of abandonment and neglect. This may be detrimental to patient’s well-being and may ironically conflict with the ideals of patient centeredness that justify some visions of personalized medicine. Determining how to preserve patient well-being in healthcare under such conditions will require significant preparedness and social and organizational learning. It will also require significant flexibility, which system designers and knowledge architects must start building capacity for sooner rather than later. Finally, it may require experimentation with integrated high-tech/low-tech systems.

Five-year view

We do not expect much by way of clinically proven beneficial theranostic devices, techniques or systems to emerge within the next

5 years. Nanodiagnostics research will progress largely as it has, we expect, despite persisting economic strains. However, we do not anticipate increased public expenditures in this field and we caution that public investments in science and innovation are increasingly vulnerable to politicization. With this in mind, it is important to note that expectation backlash may follow upon overpromising. For instance, the possibility of developing disease-modifying, tailored treatments is often put forward as an important argument for offering nanodiagnostics, even when no treatment options exist. The history of medicine shows that the realization of such promises is in no way guaranteed. It seems likely that in 5 years from now (and probably for much longer) nanodiagnostics research will be vibrant and exciting, while therapeutic options lag behind. And when treatments do eventually begin to emerge, we hope they will do so against a broad-based approach that has learned from the ongoing efforts aimed at anticipatory and reflexive governance.

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Key issues

- Emerging capacities for personalized medicine present a number of compelling scenarios, but with potentially challenging societal issues that may stress traditional policy models.
- Theranostic systems that maintain continuous health may transform existing concepts and goals of healthcare, empowering patients not only to care for themselves but also diminishing or removing the guidance and support of medical experts.
- Informed consent may no longer be a suitable way to protect patient autonomy in theranostic healthcare settings that alter the basis of patient autonomy and choice.
- To diminish negative impacts and premature lock-in to suboptimal technological trajectories, anticipatory efforts are needed to deal with uncertainty, complexity and ambivalence.
- Anticipatory governance employs a suite of foresight, engagement and integration activities that are aimed at building institutional capacities for responsible innovation.
- Socio-Technical Integration Research provides evidence that the potentially conflicting goals of responsibility and innovation can, under certain conditions, be brought into productive and synergistic relationship.

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