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Chapter 12

Ethics of Nanomedicine

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Abstract

Nanomedicine is the application of nanomaterials and nanotechnologies in healthcare. Nanomedicine is a key enabler of e.g., mRNA COVID-19 vaccines, and enables digital twins, organ on chip and wearables. Introducing nanomaterials in the body in pharmaceuticals or implants raises nanosafety issues. Ethical impacts of nanomedicine are e.g., related to freedom, equality, data protection, and biosecurity. Researchers should contribute to Responsible Research and Innovation together with governments and other stakeholders. The principles of inclusiveness, anticipation, openness and responsiveness are leading.

Keywords

Nanomedicine, Ethics, Responsible Research and Innovation, Nanosafety

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1. Introduction

According to the European Technology Platform on Nanomedicine: "Nanomedicine is the application of nanotechnology to achieve innovation in healthcare. It uses the properties developed by a material at its nanometric scale (10^{-9}) which often differ in terms of physics, chemistry or biology from the same material at a bigger scale." [1]

The European Commission recently updated its definition of nanomaterial for regulatory purposes: "'Nanomaterial' means a natural, incidental or manufactured material consisting of solid particles that are present, either on their own or as identifiable constituent particles in aggregates or agglomerates, and where 50 % or more of these particles in the number-based size distribution fulfil at least one of the following conditions: (a) one or more external dimensions of the particle are in the size range 1 nm to 100 nm; (b) the particle has an elongated shape, such as a rod, fibre or tube, where two external dimensions are smaller than 1 nm and the other dimension is larger than 100 nm; (c) the particle has a plate-like shape, where one external dimension is smaller than 1 nm and the other dimensions are larger than 100 nm. In the determination of the particle number-based size distribution, particles with at least two orthogonal external dimensions larger than 100 µm need not be considered. However, a material with a specific surface area by volume of < 6 m^2/cm^3 shall not be considered a nanomaterial."

In this chapter, the concept of Responsible Research and Innovation will be briefly introduced and an overview will be given of ethical issues in nanomedicine for cancer therapy. How scientists could contribute to responsible governance of each ethical issue will be indicated.

2. Screening ethical impacts of nanomedicine

Which ethical issues does nanomedicine raise? A screening of expected ethical impacts of nanomedicine was performed, guided by the online Ethical Impact Assessment tools developed and tested in RiskGONE[1] [2,3]. These are based on the CEN Workshop Agreement 17145-2:2017 (E) [4]). The Ethical Impact Assessment starts with a self-assessment guided by a checklist of nine general ethical categories: health, privacy,

[1] Accessible via: http://www.enaloscloud.novamechanics.com/riskgone/EIA/

liberties, equality, common good, environment, sustainability, dual military use, and misuse. In addition to potential ethical risks, nanomedicine also offers expected ethical benefits. The strength of expected positive and negative ethical impacts should be estimated on a five point scale: 0=no, 1=minor, 2=moderate, 3=medium, 4=high, 5=severe. A rough estimate of the likely ethical risks and benefits of nanomedicine is depicted in figure 1.

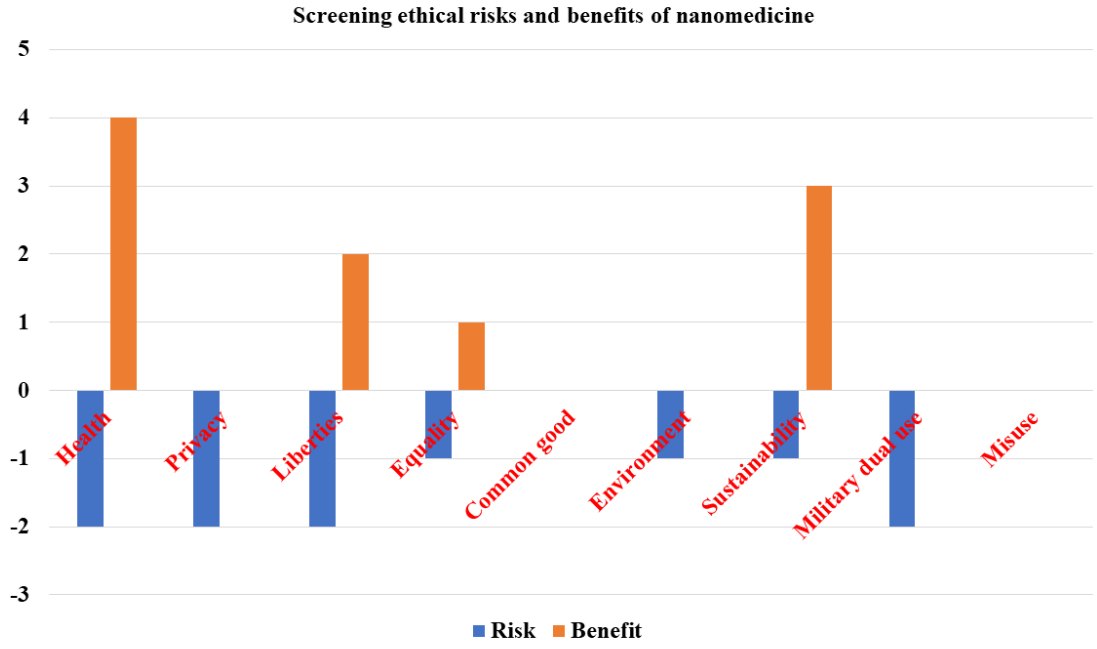

Figure 1. screening ethical risks and benefits of nanomedicine.

Related to health, all applications of nanomedicine, including mRNA COVID-19 vaccines, digital twins, organ on chip and wearables, raise general biomedical ethics issues such as the need for informed consent of patients [5], beneficence and non-maleficence [5]. The use of some nanomaterials inside the body in pharmaceuticals or implants, or in disposables, such as antimicrobial bandages, introduces uncertain nanosafety risks for the patient as well as for health professionals and relatives of the patient. These risks are additional to the health and safety risks of the used chemical substances in general. Nanosafety data is increasingly collected and curated, and some nanomaterials are shown to be more risky than others. In medical applications, expected benefits for health must outweigh the expected risks. Widespread use of applications of nanomaterials and nanoelectronics in diagnostics and lifestyle apps may contribute to influencing the healthcare system raising potential risks.

On the other hand, the use of nanomaterials in healthcare is intended to contribute to benefits for the health of patients treated with the nanomedicine. Widespread use of

applications of nanomaterials and nanoelectronics in diagnostics and lifestyle apps may contribute to influencing the healthcare system, which could also offer benefits.

Furthermore, the use of nanomaterials in diagnostics and health monitoring devices raises privacy and data protection issues. In combination with other emerging technologies, these risks could be more severe than of conventional technologies. No significant positive impacts on privacy and data protection of nanomedicine are expected.

Related to liberties, freedom may be at stake in some applications, for example, when groups of professionals or citizens are obliged to be vaccinated with nanovaccines, or when healthy people are coerced into taking preventive medicine or using diagnostics. In contrast, nanomaterials enabling wearable health monitoring devices may positively contribute to the freedom of patients who can stay home rather than being hospitalised.

Related to equality, nanomedicine may worsen global inequalities in access to healthcare, e.g. when encapsulation of pharmaceuticals leads to extension of the patent period. On the other hand, nanomedicine may also positively influence global inequalities in access to healthcare, for instance if miniaturisation of diagnostics makes it more affordable.

Using nanomaterials in nanomedicine raises uncertain environmental risks if they are released into the environment. These risks are additional to the health and safety risks of the used chemical substances in general. Nanosafety data is increasingly collected and curated, and some nanomaterials are shown to be more risky than others.

Related to sustainability, some negative impacts are expected on SDG3 (good health and wellbeing, 6 (clean water and sanitation), 14 (life on land) and 15 (life under water). The impacts of nanomaterials are not significantly higher than of current pharmaceuticals and medical devices. Vice versa, more significant positive impacts are expected, mainly on SDG3.

Finally, some dual use nanomedicine research, such as targeted drug delivery crossing the blood-brain barrier raises biosecurity issues.

3. Responsible Research and Innovation

The term ‘responsibility’ is not clearly defined but is commonly used when someone voluntarily responds to a perceived need by taking care of someone or something. It is also used as another word for accountability, when someone is held responsible by others for taking care of something. In line with social contract theory [6], governments take responsibility for protecting the rights and security of their citizens and their territory, and citizens hold their governments responsible for these tasks. In daily life, citizens have individual responsibilities for taking care of themselves and others, and for complying with regulations. Science and technology escape this traditional division of responsibilities because they may introduce uncertain and unforeseen new risks which are not governed by existing legislation. Therefore, science and technology call for new forms of collective responsibilities, with role responsibilities allocated to governments, scientists, industry, civil society organisations and citizens [7].

Different approaches could be envisaged to organising responsibility for science and technology. In the traditional division of labour, "*Science takes the credit for penicillin, while society takes the blame for the bomb*" [8]. Responsible Research and Innovation implies that scientists and all stakeholders should imagine and discuss ethical and societal aspects of new technologies and, together, change course early. This is less easy than it looks, because of the Collingridge Dilemma [9], summarised as follows: In the early stages of innovation, the technology is flexible, but potential future impacts are unclear. In late stages of innovation, the impacts are known, but by then, the technology is entrenched and inflexible. Responsible Research and Innovation (RRI) implies collective responsibility for the impacts of technology on society. Governments keep the main authority for protecting their citizens against potential risks and societal impacts of emerging technologies. They are also stimulating innovation by different means including funding R&D. To complement governmental responsibilities, governments demand co-responsibility for societal impacts from:

- The scientific community, research organisations and individual scientists
- Large industrial companies and small and medium enterprises engaged in R&D and innovation
- Civil society organisations, including trade unions, environmental and consumer movements.

The concept RRI comprises guidelines for taking this collective responsibility. Several definitions are used, but all stress the need for the four core values: i) inclusiveness, ii) anticipation, iii) openness and iv) responsiveness [10]. Inclusiveness means that all people have the right to participate in science and reap the benefits. Anticipation calls for reflecting on potential future impacts on society and the environment already during the research phase. Openness requires the publication of results of scientific research and communication about it to all people in understandable terms. Responsiveness implies that scientists should engage in public dialogue with citizens and stakeholders and take their views into account in research strategies.

RRI is a horizontal requirement in EU funded research, introduced under the Horizon 2020 programme, stimulating researchers to take more responsibility for ethical and societal impacts of research [11]. The European Commission distinguishes six keys: I) Public engagement means that projects funded by the EU must include (two-way) communication with stakeholders and citizens about the results. II) Gender equality calls for equal participation of men and women in management and research, and for addressing gender-specific issues in the research. III) Science education implies that training and education of young scientists and engaging with schools or science museums are needed. IV) Open access and open science calls for publishing results in open access publications, and offering open access of research data, etc. V) Ethics means researchers should explore and address ethical issues of the research. VI) Governance requires contributing to responsible governance and policy making of science and technology (this is mainly addressed to policy makers).

Preceding the insertion of RRI principles as horizontal requirements in Horizon 2020, the European Commission adopted in 2008 the Recommendation on a voluntary Code of Conduct for Responsible Nanosciences and Nanotechnologies (N&N) Research. "*The Code of Conduct invites all stakeholders to act responsibly and cooperate with each other, … to ensure that N&N research is undertaken in the Community in a safe, ethical and effective framework, supporting sustainable economic, social and environmental development.*" Scientists and other stakeholders in nanoresearch are asked to respect these seven principles: meaning, sustainability, precaution, inclusiveness, excellence, innovation, and accountability [12]. The recommendation is still referred to in the ethics guidelines to applicants of EU Horizon Europe funding.

4. Nanosafety

Introducing some nanomaterials in the body may cause diseases, even if they are administered in the form of therapeutic drugs. In line with the biomedical ethics principles of beneficence and non-maleficence, unintended health risks should be less than the intended curative benefits of nanomedicine. Toxicity varies greatly between different kinds and particle sizes of nanomaterials. To help reduce the uncertainty of possible impacts of nanomaterials on health, safety and the environment, nanomaterials safety data has increasingly been collected in projects, mainly funded by the European Union and national governments in the last twenty-odd years and curated in online databases. The European Observatory on Nanomaterials (EUON) is hosted by the European Chemicals Agency and brings together all information on nanomaterials safety and regulation, covering nanomedicine [13]. It offers a one-stop-shop to nanomaterials data collected in several public databases [14]. The collaboration of researchers participating in risk assessment and life cycle analysis research on nanomaterials to contribute sound nanosafety data is a prerequisite to responsible risk governance of nanomaterials. The EU includes contractual obligations to comply with RRI principles openness and open science, in EU funded research in Horizon 2020. Scientists should be aware of and respect these and other regulations governing nanosafety data.

Nanomaterials R&D increasingly incorporates safe-by-design: Integrate risk assessment in the research process from basic research onwards. More recently, the concept is broadened to safe and sustainable by design. This is defined as: "*A pre-market approach to chemicals that focuses on providing a function (or service), while avoiding volumes and chemical properties that may be harmful to human health or the environment, in particular groups of chemicals likely to be (eco) toxic, persistent, bio-accumulative or mobile. Overall sustainability should be ensured by minimizing the environmental footprint of chemicals in particular on climate change, resource use, ecosystems and biodiversity from a life cycle perspective*" [15,16].

From an ethical perspective, the RRI principle 'anticipation' governs nanosafety issues of nanomedicine. This calls upon researchers to reflect on potential future impacts on human health, society and the environment already during the research phase. More specifically,

the EU nanocode calls for applying the precautionary principle: "anticipating potential environmental, health and safety impacts of N&N outcomes and taking due precautions, proportional to the level of protection, while encouraging progress for the benefit of society and the environment" [12].

5. Drug delivery

A wide variety of nanomaterials are used in targeted drug delivery, including liposomes, lipid nanoparticles, polymeric nanoparticles, polymeric micelles, dendrimers and nanogels [17]. Following successful application of nanomedicine in COVID-19 mRNA vaccines, nanomaterials are increasingly applied in regulating immunity [18].

5.1 The right to benefit from science

This application of nanomedicine raises issues related to global inequalities in access to healthcare, as illustrated by the COVID-19 vaccination status published by the World Health Organisation. On 7 July 2022, over 12 billion vaccination doses were administered and over 4 billion people were fully vaccinated, but in several, mainly African countries, still less than 20% of the population were vaccinated [18]. This is an apparent violation of the UN covenant on socio-economic rights: "*Article 12 - 1. The States Parties to the present Covenant recognize the right of everyone to the enjoyment of the highest attainable standard of physical and mental health. 2. The steps to be taken by the States Parties to the present Covenant to achieve the full realization of this right shall include those necessary for: ... (c) The prevention, treatment and control of epidemic, endemic, occupational and other diseases; ...*" [19]

From the perspective of RRI, governments and other involved stakeholders are urged to foster 'inclusiveness', respecting the basic human right of all people to participate in science and reap the benefits. However, the corresponding article in the UN covenant on socio-economic rights calls for balancing distinct rights of citizens in general on the one hand and researchers and other stakeholders involved in scientific research on the other: "*Article 15 - 1. The States Parties to the present Covenant recognize the right of everyone: ... (b) To enjoy the benefits of scientific progress and its applications; (c) To benefit from the protection of the moral and material interests resulting from any scientific, ... production of which he is the author.*" [19] The RRI-key 'Open science' of the European Commission gives more practical guidance for researchers, urging them to publish in open access publications, and offer open access of research data [13]. Related to this, patenting nanomedicine raises ethical dilemmas: "*[Nanomedicine could blur] the balance of interests whereby diagnosis, therapy and research should be available to patients without patents being a hindrance… There are risks of overly broad patents being granted that may hinder their therapeutic availability… [there is a] need for research into the manner in which the patent system can properly balance the need to reward innovation and ensure availability."* [20]. Nanodrug delivery is sometimes used to extend the patent protection of blockbuster drugs delaying cheaper generic drug manufacturing.

5.2 Communicating nanoscience

Public trust in COVID-19 mRNA vaccines is influenced by communication on research. To illustrate the importance of good science communication, by end of May 2021, Eurobarometer polled opinions of 26,106 Europeans of 15 years and over on their attitudes to COVID-19 vaccination. "*Key reasons for not getting vaccinated are the belief that COVID-19 vaccines have not yet been sufficiently tested and worries about the side effects of the COVID-19 vaccines, with 85% and 82%, respectively, answering these reasons are 'important'. Respondents would be keener to get vaccinated if 'more people have already been vaccinated, they see that it works and there are no major side effects' and if there is 'full clarity on how vaccines are being developed, tested and authorised' (mentioned by 30% and 26%, respectively). Overall, the benefits of vaccination against COVID-19 are recognised: 76% agree that all in all the benefits of COVID-19 vaccines outweigh possible risks. However, there are concerns about the safety of COVID-19 vaccines: half of respondents agree that COVID-19 vaccines are being developed, tested and authorised too quickly to be safe*" [21]. The responsibility of researchers is in line with the value of 'openness', meaning that scientists should publish results of scientific research and communicate about it to all people in understandable terms. In EU-funded research, scientists are encouraged to include (two-way) communication with stakeholders and citizens in research projects.

5.3 Ethical dilemmas of nanodrug delivery

Some nanomaterials can be used to cross the blood-brain barrier introducing ethical dilemmas, where an action simultaneously causes good and bad effects. Expected benefits include more effective and safer treatment of brain tumours. However, the brain also becomes more vulnerable to accidental biosafety and human-made biosecurity issues. Some nanomaterials can raise dual use biosecurity issues, most notably in interdisciplinary research on converging technologies (Nano, Bio, Info, Cogno). Nanoscience research of concern targets molecular manipulation of virulence factors or directed traversal of the blood-brain barrier by nanoparticles. Preventing misuse is a collective responsibility of governments, scientists, industry and civil society. Researchers should in any case be aware of biosecurity regulations and measures in their laboratory [22].

In addition, nanomaterials can be used in theranostics [23], such as drug delivery systems incorporating sensors and medicine circulating in the bloodstream release the drug when detecting disease biomarkers. This raises an ethical dilemma. While theranostics will allow the cure to be administered without delay upon detection of the specific disease biomarkers, the physician or patient cannot intervene. If the drug is released erroneously, who is accountable for accidental release? How can "*researchers and research organisations ... remain accountable for the ... human health impacts that their N&N research may impose on present ... generations*" [12]? What should researchers do? While pharmaceutical companies and regulators carry most responsibility for any negative consequences of theranostics products after they are finally available on the market, the RRI-principle 'anticipation' suggests that scientists already during the research phase should reflect on

potential future impacts on society and the environment and raise discussion timely to avoid foreseeable negative impacts.

6. Personalizing therapies and diagnostics

Nanomaterials and nanotechnologies are enabling technologies for development of personalized and precision medicine, as well as organ-on-chips. These applications give rise to some ethical issues and dilemmas.

6.1 Personalized and precision nanomedicine

Nanomedicine enables personalized medicine, because it allows adapting a drug to a specific cohort of patients [24]. However, the introduction of personalised medicine raises dilemmas. For example, early (nano)diagnostics could be used to reveal personal genetic sensitivities for e.g., cancer or diabetes, allowing early treatment of the disease before the onset of symptoms, or prescribing preventive measures such as diets or changes in lifestyle. Related to this, nanomedicine is expected to enable precision medicine, promising benefits to patients and citizens. For example, "*intelligent nanoparticle design can improve efficacy in general delivery applications while enabling tailored designs for precision applications*" [25].

Some ethical issues must be addressed before introducing personalised or precision nanomedicine in healthcare practices. To begin with, the diagnostic devices collect personal data from the patient. Where and how is this data stored? Is the data storage properly secured against unlawful access? Who should be given access to the test results and for which purposes? In addition, the widespread adoption of early diagnostics may infringe on the autonomy of the person. For example, healthy people may feel obliged to test because of social pressure. Furthermore, personal freedom may be limited by prescribed diets or lifestyle changes. While governments and industry carry most responsibility for ensuring that final personalised nanomedicine products do not infringe on privacy and autonomy of citizens, the value 'responsiveness' calls upon scientists to engage in early public dialogue with citizens and stakeholders and take their views into account in research strategies, while the personalised nanomedicine is still under development.

In addition to these effects on patients themselves, the introduction of personalised or precision nanomedicine increases existing questions of distributive justice in healthcare systems. For example, increased funding for precision medicine for some patients may be balanced by decreased funding addressing health inequalities for others. While researchers do not have the main responsibility for avoiding such consequences, they should at least ensure representativeness of data cohorts allowing fair benefits sharing [20]. This way, they can live up to the value of 'inclusiveness', and respect the universal human right of all people to participate in science and reap the benefits.

6.2 Organ-on-chip

"An organ-on-chip is a fit-for-purpose microfluidic device, containing living engineered organ substructures in a controlled microenvironment, that recapitulates one or more aspects of the organ's dynamics, functionality and (patho)physiological response in vivo under real-time monitoring" [26]. Currently, many different human organs and tissues are incorporated in such chips (for example, beating human heart cells), and some even experiment with integrating a complete set of individual organs into a human-on-chip system [27]. Applications include preclinical drug development, and toxicity testing of chemicals. Foreseen benefits include the possibility to replace animal testing with human organs-on-chips. In the longer term, cells from identifiable patients may be used to grow organs-on-chips for personalised diagnostics or in the development of orphan drugs. Like other diagnostics, diagnostic uses of organ-on-chip raises common bioethics issues, briefly mentioned earlier. However, common biomedical privacy and informed consent procedures may have to be revised if cells and tissues from identifiable patients are used to grow organs-on-chips, to manage issues related to personalised medicine. This is especially sensitive if the organ-on-chip is used to diagnose orphan diseases with only small numbers of patients whose privacy is difficult to protect.

In addition, communication about organ-on-chip technology must be sensitive to public perception issues. Scientists should be transparent about the challenges of the real scientific research work in the laboratory, and be careful how they discuss big ambitions (e.g., 'human-on-chip') which may take a long time to materialise. In line with the value 'responsiveness', researchers should engage in public dialogue with citizens and stakeholders and take their views into account in research strategies.

7. Wearables

Nanomaterials and nanotechnologies enable miniaturisation of biosensors and diagnostic devices, contributing to the increasingly widespread use of wearable nanodiagnostics. Some such wearables are explicitly marketed as medical devices subject to regulations, such as the EU medical devices regulation. However, other devices, such as mobile body vital sign tracking devices, are launched as lifestyle gadgets subject to less stringent regulations. In 2015, the European Group on Ethics (EGE) identified gaps in EU regulation on safety of digital health products [20]. Subsequently, the EU updated its medical devices Regulation (EU) 2017/745: "*Certain groups of products for which a manufacturer claims only an aesthetic or another non-medical purpose, but which are similar to medical devices in terms of functioning and risks profile should be covered by this Regulation.*" [28] In addition, the EGE recommended that scientists, industry and other stakeholders must comply better with existing legislation and standards. In line with the value 'responsiveness', researchers should engage in public dialogue with citizens and take their views into account in research strategies for developing innovative health monitoring wearables for both medical and non-medical purposes.

8. Artificial Intelligence and big data

Converging with digital twins, Artificial Intelligence (AI) and big data, nanomedicine fosters increasing citizen participation in healthcare. On the one hand, personal health data collected through medical and non-medical wearables is considered a valuable resource for discovering disease pathways and for informing the development of new therapies. Privacy and data protection principles call for restricting access to these sensitive personal data to persons with a need to know them, including patients and medical professionals treating these patients. Secondary use of these data for research purposes is subject to informed consent and rules for anonymization or pseudonymization. The use of AI in analysing big health data could lead to disclosure of the identity of individual patients or other infringements on biomedical ethical principles. When personal data is used to develop new pharmaceuticals or therapies which are sold by commercial companies, questions of ownership of the data and what would constitute a fair share in the benefits emerge. On the other hand, converging (nano)technologies enable miniaturisation of diagnostics devices, bringing self-tests within reach of consumers and patients, who may not be properly trained to interpret the test results. This influences trust between the patient and the doctor, and puts pressure on the organisation of the healthcare system. The EGE (2015) is concerned that this convergence may shift the balance towards 'All for Health' rather than 'Health for All' (SDG 3) [20]. This means that citizens may be coerced increasingly to share their health data or submit to early testing before symptoms of diseases become noticeable. It is not clear whether these trends in healthcare technologies and markets will genuinely contribute to improved public health and universal access to healthcare.

Koen Bruynseels and colleagues discussed ethical implications of digital twins in healthcare [29]. As in engineering, digital twins are increasingly used in healthcare and virtual self models are continuously updated with increasingly refined personal health data of individuals. This enables three fundamental changes of what is considered normal health: The normal state can be defined in increasingly high resolution, can be increasingly personalised, and the personal health status becomes increasingly transparent. This again raises unprecedented privacy and data protection issues, and may drive the demand for preventive therapies before the unset of symptoms. It may also contribute to blurring the boundary between humans and machines, shift the boundary between disease and health, and could contribute to a shift from therapy to human enhancement [29].

Two conflicting RRI-values are at stake in these current trends in converging technologies for healthcare: inclusiveness and anticipation. Inclusiveness means that all people have the right to participate in science and reap the benefits. This appears to welcome the general trends in digitalisation of health, because affordable and easy to use diagnostics are expected to become within reach of larger segments of the population, and preventive measures can be taken earlier, before people fall ill. On the other hand, anticipation calls for reflecting on potential future impacts on society and the environment already during the research phase. From this perspective, researchers are advised to consider philosophical analyses of longer term and wide ranging impacts of digitalisation of healthcare [20,29] and engage in public dialogue about these potential consequences.

9. Human enhancement

As briefly touched upon in section 7, nanomedicine may not only be used in healthcare, but also to enhance the physical or mental capabilities of healthy people. More traditional examples of sensitive trends in nanomedicine are nanotechnologies enabling neuro-prosthetics, or connecting human brains online via the internet. This raises many ethical issues, such as the following. Healthy individuals using nanomedicine to improve specific physical or mental traits, may accidentally expose themselves to unexpected health risks. As Paracelsus already warned: only the dose determines the toxicity of a substance [35]. When for instance nanopharmaceuticals are taken curatively, the benefit of fighting the disease generally outweighs the health risks of the drugs. When the same substances are taken by a healthy person, the risk-benefit balance shifts towards the risks. In addition to the impacts on the individual, use of human enhancement technologies by elite groups has implications for the organization of society, and may topple the balance between freedom and solidarity. On a more abstract level, human enhancement also raises discussion of religious and cultural aspects (e.g., 'playing God') [30].

Guided by the RRI-value 'anticipation' researchers should reflect on potential future impacts on society already during the research phase. The RRI-value 'responsiveness' calls for engaging in public dialogue with citizens and stakeholders and take their views into account in research strategies.

Conclusions

Nanomedicine can be applied in drug delivery, diagnostics and pharmaceutical research. Converging with other emerging technologies, nanomedicine enables digital twins, organ on chip and wearables monitoring vital signs. Introducing nanomaterials in the body raises nanosafety issues. Nanomedicine raises ethical issues related to freedom, equality, data protection and biosecurity, and may impact on the healthcare system. Nanomedicine may enable human enhancement, raising ethical and religious concerns. Researchers should contribute to Responsible Research and Innovation through different case-dependent strategies. The principles inclusiveness, anticipation, openness and responsiveness are leading.

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