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Nanotechnologies — Framework for identifying vocabulary development for nanotechnology applications in human healthcare

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TECHNICAL REPORT

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Nanotechnologies — Framework for identifying vocabulary development for nanotechnology applications in human healthcare

Nanotechnologies — Cadre pour le développement d'un vocabulaire d'identification des applications de nanotechnologies en santé humaine

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Foreword

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The committee responsible for this document is ISO/TC 229, *Nanotechnologies*.

Introduction

Terminology related to the use of nanotechnologies in human healthcare is on the rise as research in the field continues to intensify. The heightened focus in medical research on nanotechnologies is reflected by the number of medical and related scientific journals that are reporting on this research. The number of publications mentioning both nanotechnology and biology or medicine has increased logarithmically since approximately the year 2000.[1]

This Technical Report explains current concepts related to human healthcare in the clinical setting and identifies pertinent and timely categories most likely to be advanced by nanotechnologies. Certain aspects of human healthcare are expected to be advanced by nanotechnologies more than others, and standardization needs unique vocabulary to support the development of applications of nanotechnologies within it. It is recognized, for example, that physical chemists use the term "substrate" to describe a material surface supporting adsorption processes; this differs from a biologist's use of the term "substrate" to describe a substance that an enzyme acts upon.

Due to the keen public interest in the advancement of human healthcare, a common vocabulary is particularly relevant to the development of research proposals to gain funding and to communicate findings and results. This Technical Report provides a taxonomic framework to serve as the basis for the development of terminology related to the application of nanotechnologies in human healthcare. The framework identifies categories associated with the clinical value chain most likely to be advanced by nanotechnologies and describes some of the promising technologies being developed and utilized within the clinical workflow. It is intended that terms will be identified and harmonized definitions will be developed for them within the framework offered by this Technical Report.

Nanotechnologies — Framework for identifying vocabulary development for nanotechnology applications in human healthcare

1 Scope

This Technical Report will not attempt a formal, comprehensive definition of "nanomedicine". Instead, it will provide a taxonomic framework for the development of vocabulary for clinical applications of nanotechnologies in human healthcare. While it is understood that the origins of nanotechnologies for healthcare applications emerge from pre-clinical and translational research, the interest of this Technical Report is to determine where these technologies will impact the clinical value chain and the practice of medicine.

This Technical Report is intended to facilitate communications between developers and users of nanotechnologies, deliverers and users of medicine including the pharmaceutical, research and medical communities, regulatory professionals, and additional organizations and individuals who might interact with these groups, including biotechnology, diagnostic, and medical device companies, the life sciences, patent attorneys and patent offices, institutional review boards, ethics review boards, and accreditation organizations.

2 Symbols and abbreviated terms

nm nanometer

3 Framework

3.1 General

The term "nanomedicine" is used by the scientific community and government agencies to describe a field that is relatively undefined in terms of the affected health care segments and the specific advances in nanotechnologies for biomedical applications.

In addition, the relevant mechanisms currently associated with diagnosis and treatment in biological processes can be larger than approximately 100 nm (e.g. endocytosis). Several participants from the biological sciences work with 400 nm diameter particles as drug carriers, while others consider <1 000 nm or <500 nm as pertinent in exploring emerging applications. Overall, the products currently enabled by nanotechnologies that are available for commercial clinical use are characterized by *in vitro* bulk properties or systemic effects. Examples of nanosize objects of interest in healthcare applications are depicted in Figure 1.

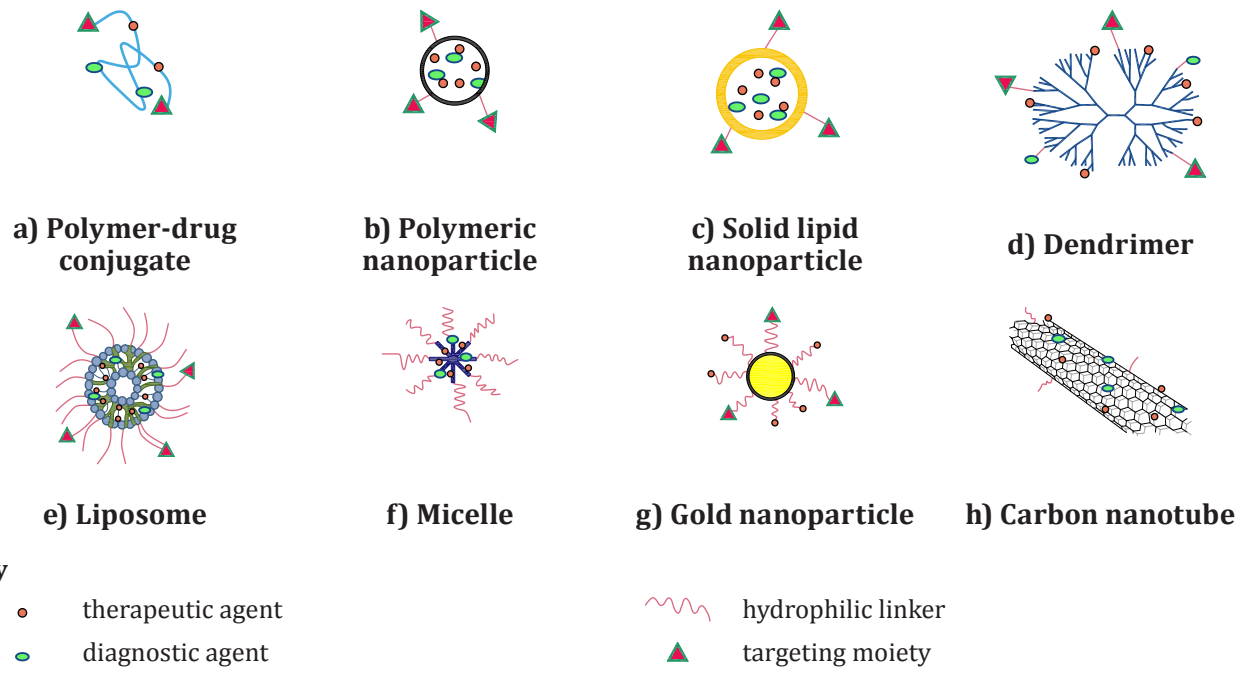

Figure 1 — Examples of nanosize objects of interest in healthcare applications[2]

In contrast, the current ISO definition of the term "nanoscale" stems from materials science and expresses in part the size range associated with quantum effects. The broad, enabling nature of nanotechnologies means that convergence with the biological sciences will continue to intensify. However, this Technical Report does not seek to suggest that current definitions in nanotechnologies, such as the approximately 100 nm upper boundary found in the ISO definition of the term "nanoscale",[3] be normalized to account for all size relationships in biological systems.

3.2 The clinical value chain

3.2.1 General

In recognition of the advancements that are anticipated in the clinical practice of medicine associated with nanotechnologies, relevant applications of nanotechnologies in human healthcare can be identified by their location in the clinical value chain (see Figure 2).

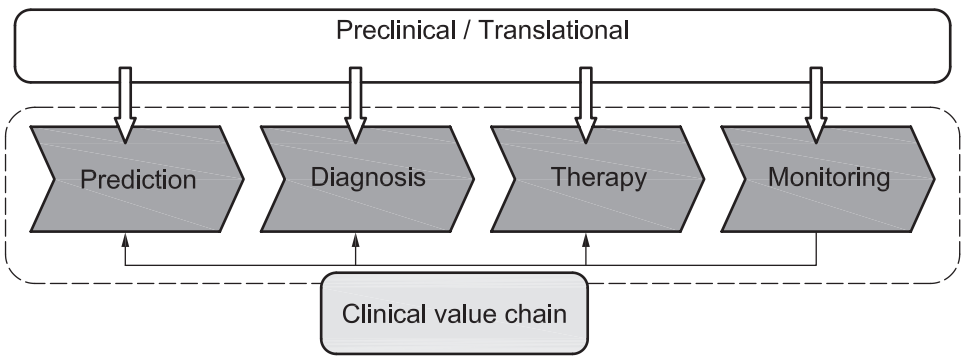

Figure 2 — The clinical value chain

The clinical value chain suggested for use in this Technical Report consists of 4 segments. The prediction and prevention segment includes nanotechnologies that are used to predict, or prevent

disease, conduct disease screening, and which are used in disease surveillance. The diagnosis segment includes nanotechnologies that are used for *in vitro* and *in vivo* detection, classification, grading, etc. of disease. The therapy segment includes nanotechnologies that are associated with therapy for disease. This includes drugs and other medicines (e.g. biopharmaceuticals), surgical implants, materials, devices, and surgical aids, and alternative therapies (e.g. stem cells). The monitoring segment includes nanotechnologies that are used to monitor disease after therapy to evaluate the efficacy of treatment and the progression or remission of disease, recurrence, side effects, etc.

Underlying these segments are pre-clinical and translational activities. That is, fundamental nanotechnology developments in academia, life science, and the biopharmaceutical industry are undertaken with the objective of having an eventual impact or application in one or more of the clinical value chain segments. These might be nanotechnologies used to understand basic life processes or nanotechnologies that support products used in a clinical setting (see Figure 3).

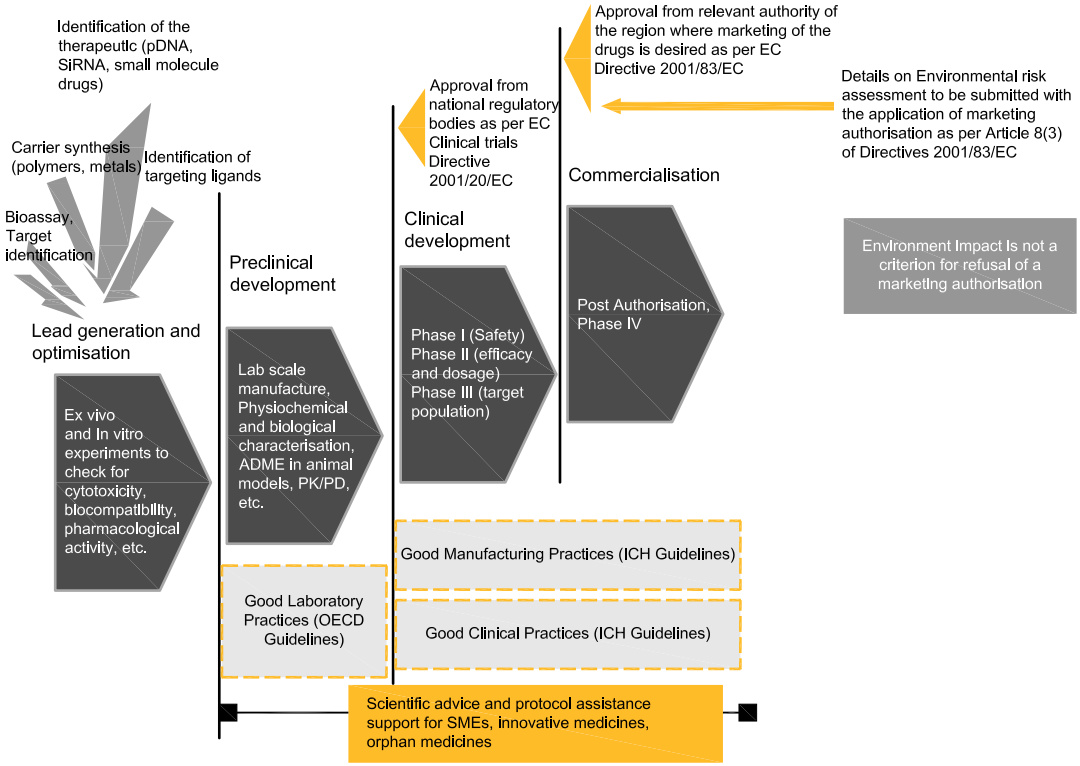

Figure 3 — Illustrative example of the general stages of development for nanotechnologies used in medicine, which highlights the European Union's approach[4]

3.2.2 Prediction and prevention

Prediction and prevention inlcudes technologies that permit accurate screening to identify the risk or susceptibility to disease or disease recurrence, prognosis based on one or more indicators, public health surveillance of disease and immunization to prevent disease. Products enabled by nanotechnologies in this value chain segment include sprays, coatings, antiseptics and vaccines.

Two application areas that are useful to highlight the contribution of nanotechnologies to this segment of the clinical value are the prevention of surgical site infections and the use of informatics to predict and reduce drug side effects by identifying patients at risk. Surgical site infections encompass inadvertent infections occurring inside the hospital or physician's office, the prevention of which can include the use of disinfectants, sterile surfaces, protective gowns, air handling, and appropriate waste disposal. The use of nanotechnologies for preventing adventitious infections might be the source of new terms, e.g. "nanotextured surface" to describe a product designed by the coating industry to ensure a sterile environment. Bioinformatics and nano-informatics might be used to evaluate disease prevalence, drug design, acceptable test protocols, dose metrics, and toxicity.

3.2.3 Diagnosis

Nanotechnologies for diagnostics encompass *in vivo* as well as *ex vivo/in vitro* evaluations. Nanotechnologies can be used to advance sensing systems to improve the accurate and early detection and diagnosis of disease. There are multiple components in the diagnostic process ranging from the manufacturing setting (e.g. reagent and detection systems) to the selection of target analytes (e.g. cells, proteins, tissue structures) and the organism setting (*in vitro/ex vivo* or *in vivo*) (see Figure 4).

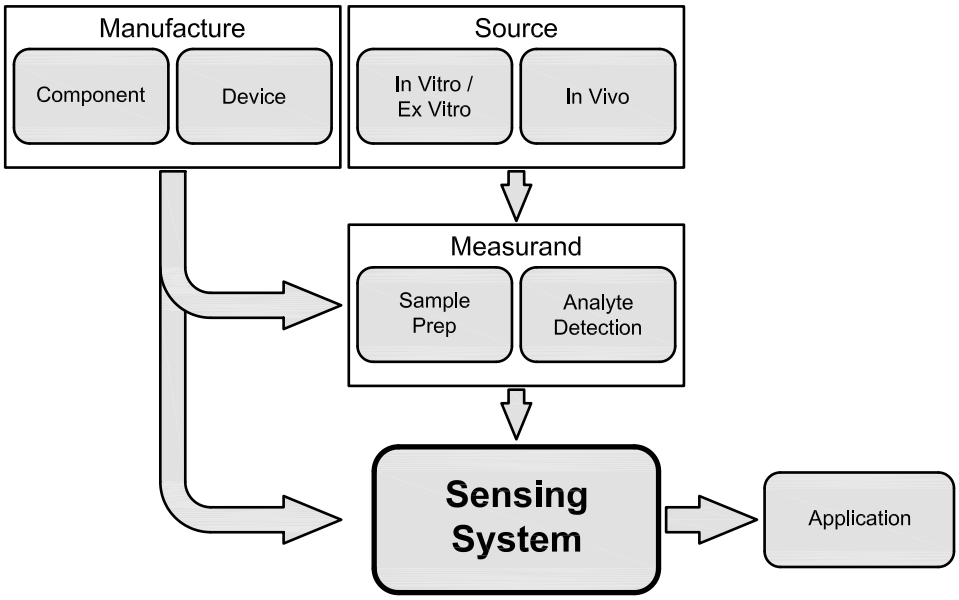

Figure 4 — Overview of nanotechnologies in diagnostics

For example, when a new nanoparticle is developed for *in vivo* imaging, this diagram approach could be applied to understand the application area and technology as follows (Figure 5):

— **Manufacture** — Method of synthesis of the nanoparticle. Further details could be added, such as additional nanotechnology that is required for the manufacturing process.

— **Source** — Context of use of the nanoparticle. In this case, the nanoparticle is designed to image a living patient.

— **Measurand** — This nanoparticle is designed to be delivered into and enhance the visualization of the patient's lymphatics.

— **Sensing System** — The actual diagnostic action occurs with placement of the patient in the MRI device and detecting the nanoparticles with the lymphatics.

— **Application** — The goal of the use of the nanoparticle is for the detection of metastatic cancer in the patient's lymphatics.

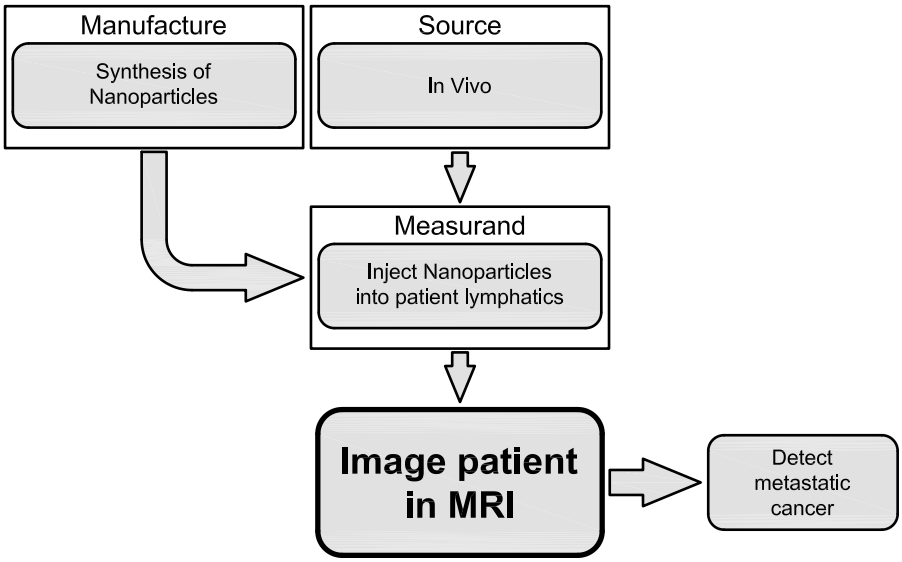

Figure 5 — Example of understanding a diagnostic application for terminology development

3.2.4 Therapy

Applications of nanotechnologies in the therapy segment of the clinical value chain include the delivery selective and targeted drug therapies, material modifications, and medical devices. Specific areas of therapy that could be advanced by the use of nanotechnologies in this clinical value chain segment include clinical indication tools, understanding of route of administration, reduced inter and intra-subject variability, improved dose-response relationship(s), faster achievement of maximum amount of drug in blood stream, and limiting the effect on pharmacokinetics of a drug once absorbed.

Cancer therapy is a dominant field that leverages advancements in nanotechnology. In this area, nano-objects of interest include nanowires, gold (functional metallic), magnetic nanoparticles, viral nanoparticles, polysaccharide nanocarriers, nanobiosensors, nanomicelles, nanoscale liposomes, nano-arrays, nanobioconjugates, nanochannels, stealth nano-objects, nanomembranes, DNA complexes, molecular motors, and protein coronas.

For material modification and manufacture applications, key classes of nano-objects include synthetic nanoparticles, dendrimers (e.g. hyperbranched polymers, dendigrafts, and dendronised polymers), nanogels, nanosuspensions, solid lipid nanoparticles, nano shells, nanopores, nanocapsule, nanoneedle, nanoporous membrane, and nanofilms.

In the area of medical devices, applications of nanotechnologies include the development of artificial muscles, nanoscale knee and lymph sleeves, nanowire and needle scaffolds, tissue and vessel re-enforcement, dental applications, drug delivery devices, and nano-coatings on medical devices, such as ball and socket joints in hip joint replacements.

3.2.5 Monitoring

Post-therapy applications being advanced with nanotechnologies show promise regarding the ability to accurately monitor the progress of disease treatment, recovery, and recurrence. Nanotechnologies of interest can fall into the categories of microchip sensors or nanoparticles, ligands, and reagents that, depending on the intended use, can interact with human systems *in vivo* or *ex vivo* (see Figure 6).

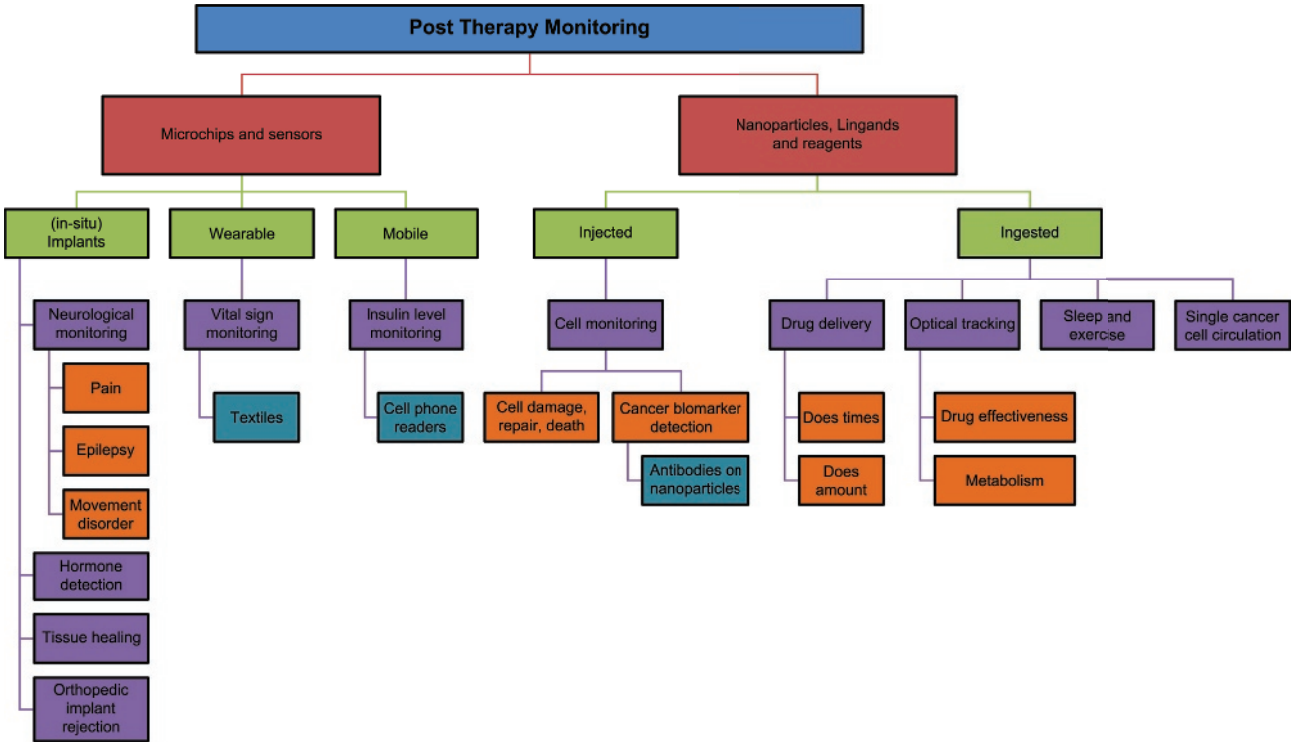

Figure 6 — Nanomedicine monitoring applications

Examples of technologies and applications in this value chain segment include electrochemical sensors, biomarker and neurological monitoring, disease monitoring, and optical tracking of drug delivery. Analytical lab-on-a-chip miniaturized sensor technology designed to be ingested or implanted can be used to monitor and record details of medication, metabolism, and vital signs.[6] Sensors for monitoring purposes can be incorporated in wearable and mobile applications such as textiles and cellular phones, or implanted (e.g. an integrated glucose monitor and insulin dispenser).[7] [8]

4 Terminology development within the clinical value chain

4.1 General

There is inherent inter-dependence between the clinical value chain segments and the nanotechnologies that could be employed. This can be viewed in the emerging field of theranostics,[9] [10] [15] which tightly integrates diagnostic and therapeutic components. All value chain segments could make use of sensor technologies; however, the measurands are focused on the particular objective of each value chain segment. For example, in the case of diagnosis, a nano-based imaging agent could be used to detect and localize cancer within the body in order to classify and grade the extent of disease. In the context of monitoring, this same or a similar agent and imaging methodology could be used to determine the effect that a drug or other therapy is having in combating disease.

A method for determining the appropriate segment or segments in which nanotechnologies targeted toward human healthcare fit into the clinical value chain, in order to identify associated terminology, is illustrated in Figure 6.

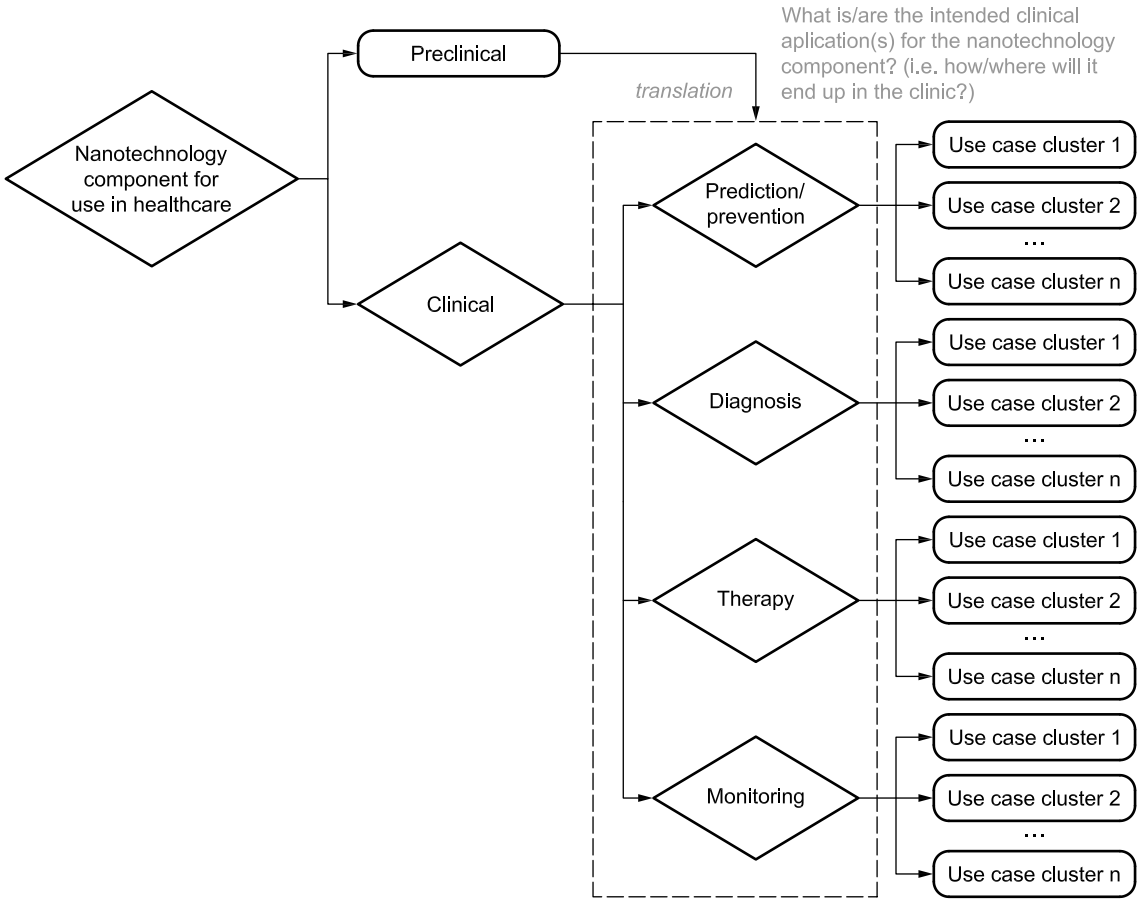

Figure 7 — Placement of nanotechnologies into a corresponding clinical value chain segment(s)

As shown in Figure 7, a nanotechnology component can be placed within the appropriate clinical value chain segment based on its intended use(s). This determination can be made during preclinical development or anytime thereafter. Responses to the following questions can be used to guide the placement of nanotechnologies in the value chain and identify associated terminology.

— What is the intended use of the nanotechnology component?

— What is the investigation or treatment objective?

— What is the intended result of the investigation or treatment?

4.2 Identifying terms in need of definition in the clinical value chain

4.2.1 General

A review of the current literature on nanomedicine and related terms has found many areas where there are suggested definitions of terms as defined in the literature. A summary of these is provided in Annex A. The entries are divided into the following areas:

— clinical indication;

— generic clinical terms;

— route of administration;

— class of nano-object;

— modification and manufacture;

— other.

The first three areas are covered by well-established terms in the medical literature. It is therefore appropriate to focus on the class of nano-object and modification and manufacture.

As noted at the outset of this Technical Report, the term “nanomedicine” is increasingly used by the scientific community and government agencies to describe the applications of nanotechnologies in human health care. However, no single definition for this term is actively promoted. Additional terms are identified for each clinical value chain segment from the published literature or using the method offered by this Technical Report. Consistent with the purpose of the clinical value chain, identified terms look outward toward integrating nanotechnologies with existing medical applications, rather than emphasizing that they are sourced from nanotechnologies.

There is also a lack of clarity around the use of nanotechnology related to medical devices. For example, in Australia there is no available definition of nano-specific devices, and the requirement to do so is only a recommendation to have “lists of available nanotechnology infrastructure and equipment” within the following 2009 report: “Nanotechnology in Australia, Trends, Applications and Collaborative Opportunities”[5]. This is an area that requires the application of standardization principles, especially as labelling can be confusing. For example, the “Accu-chek” blood glucose monitoring machine[35] which uses a nano descriptor on the product packaging does not contain nanomaterial. The term “nano” is used to emphasize the very small amount of blood that the equipment requires in order to perform its analysis.

Perhaps due to this confusion, some countries are proposing the use of product databases. For example, Denmark intends to create a database of products containing nanomaterials. Specifically, under a draft amendment to the Danish Chemicals Act, the Minister of the Environment would have the authority to write a detailed order establishing the rules for a national database of mixtures and articles containing or releasing nanomaterials. The order would also require producers and importers to report products containing or releasing nanomaterials. The information in the database is intended to form the basis of an evaluation of whether the content of nanomaterials in products on the Danish market poses a risk for consumers and the environment. The Ministry plans for the first reports to be due in early 2014.[11]

The current conclusion is that discovering what nano-enabled or nano-enhanced medical devices are currently available in the market place is almost an impossibility given that to date, no country appears to have a system in place to record them. Based on literature review, while research is being done, this appears to be mainly in the field of drug delivery systems.

4.2.2 Prediction and prevention

There are relative merits associated with the use of bio-, bionano-, nanobio-, and nano- when modifying root nouns such as “material”. A specific example is in defining a reinforced polymer that consists of a 30 nm nanoparticle mesh for organ repair procedures. In addition, common definitions for terms such as nano-informatics, bionano-informatics, nanomedicine informatics, nanodelivery, nano-ontologies, and nanobiosystem could be useful.

4.2.3 Diagnosis

For any given diagnostic nanotechnology, basic characteristics can be evaluated for the identification of terminology development using the diagram provided in Figure 7. An example of how this approach can be used to identify associated terminology is illustrated in Figure 8 using the diagnostics segment of the clinical value chain.

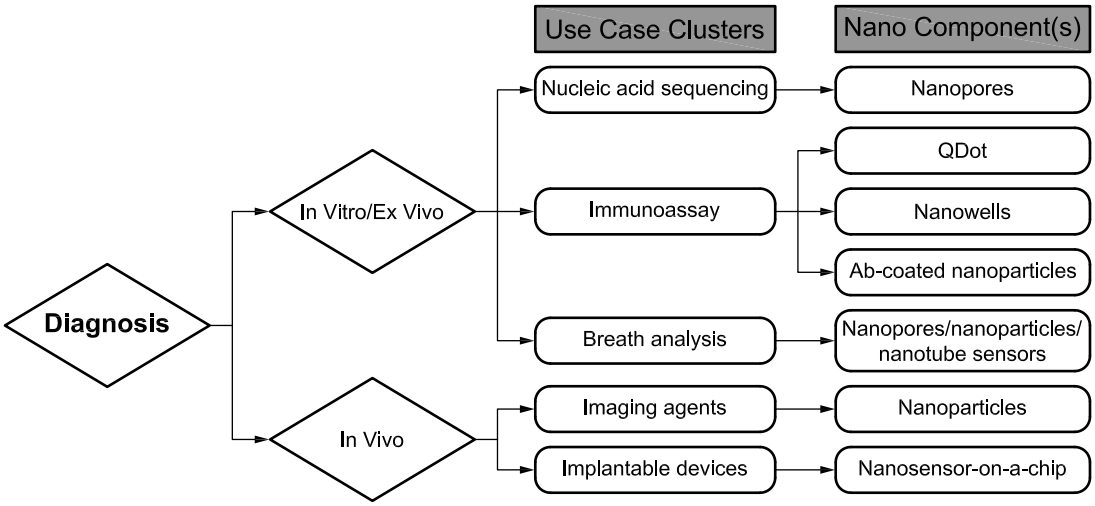

Figure 8 — Terminology development process related to diagnostics value chain segment

4.2.4 Therapy

Certain terms in therapy have existing ISO definitions including nanotoxicology, nanobiotechnology, nanoscience, and stealth nano-object.[3] [12] [13] Others can lend themselves to common terminology development, including gene therapy, nanotherapeutics, imaging agents, nanoneurotechnology, nanoneuroprotection, transfection, wrapping, and functional agent.

4.2.5 Monitoring

Terminology associated with sensing technologies bears study for evaluating definition needs for the monitoring segment of the clinical value chain. Possible candidates for consideration include nanosensor and nanobiosensor. In the area of nanoparticles, ligands and reagents, the term nanoparticle has an existing ISO definition.[14]

4.2.6 Further identification of potential terms

A list of references for several sourcing terms that are being actively used in healthcare applications of nanotechnologies is provided in Annex B. In this regard, it should be recognized that there is a relationship between standard terminologies that is captured in informatics. Lexical semantics, the meaning of words when combined into sentences and phrases, will differ among groups and it is prudent and valuable to understand that these nuances exist when conducting broad spectrum keyword searches.

Annex A
(informative)

Nanomedicine terms as defined in current literature

Note that the definitions listed in this Table have not been agreed through an ISO body. Therefore, at present, they are simply a source of information and opportunities for term standardization in the future. Furthermore, the definitions are just examples and are not meant to be all-inclusive of terms used in the field.

Table A.1 — Nanomedicine terms as defined in current literature

Area	Nanotechnology term or branch of medicine	Definition from the external literature	Example literature reference
Clinical indication N.B. Only those reported for "nanomedicine" applications are included.	Cardiovascular	Of or relating to the heart and blood vessels.	Oxforddictionaries.com
	Cancer	The disease caused by an uncontrolled division of abnormal cells in a part of the body.	Oxforddictionaries.com
	Anti-inflammatory	(Chiefly of a drug) used to reduce inflammation.	Oxforddictionaries.com
	Anti-neoplastic	Acting to prevent, inhibit or halt the development of a neoplasm (a tumor).	Medicinenet.com
	Asthma	A respiratory condition marked by spasms in the bronchi of the lungs, causing difficulty in breathing.	Oxforddictionaries.com
	Dermatology	The branch of medicine concerned with the diagnosis and treatment of skin disorders.	Oxforddictionaries.com
Diseases	Autoimmune diseases	Of or relating to disease caused by antibodies orlymphocytes produced against substances naturally present in the body.	Oxforddictionaries.com
	Vaccines	A substance used to stimulate the production of antibodies and provide immunity against one or several diseases, prepared from the causative agent of a disease, its products, or a synthetic substitute, treated to act as an antigen without inducing the disease.	Oxforddictionaries.com
	Photodynamic therapy (imaging)	Photodynamic therapy (PDT) is a treatment that uses a drug, called a photosensitizer or photosensitizing agent, and a particular type of light. When photosensitizers are exposed to a specific wavelength of light, they produce a form of oxygen that kills nearby cells.	Cancer.gov
Generic clinical terms	Dosimetry	Measurement of an absorbed dose of ionizing radiation.	Oxforddictionaries.com

Table A.1 *(continued)*

Area	Nanotechnology term or branch of medicine	Definition from the external literature	Example literature reference
	Gene therapy	The transplantation of normal genes into cells in place of missing or defective ones in order to correct genetic disorders.	Oxforddictionaries.com
	Nanotherapeutics	The use of nanomedicine in therapy.	Lamprecht[36]
	Nanopharmaceuticals/ nanopharmaceutics	Drug delivery systems or biologically active drug products at the nanoscale/ the study/science of dosage from design at the nanoscale.	Duncan and Gaspar[16]
	Targeted drug delivery	Targeted drug delivery refers to predominant drug accumulation within a target zone that is independent of the method and route of drug administration.	Torchilin[37]
	Thermanostic	Nanotheranostics which aims at blending both therapeutic and diagnostic functions within a single nanoscaffold.	Sumer and Gao[38]
	Inorganic nanoparticles (imaging agents)	Nanoparticles that are used as a site-targeted agents which enhance a selected biomarker that otherwise might be impossible to distinguish from surrounding normal tissue.	McCarthy and Weissleder[39]
	Nanomedicine	The use of nano-sized tools for the diagnosis, prevention and treatment of disease and to gain increased understanding of the complex underlying pathophysiology of disease. The ultimate goal is improved quality-of-life.	Duncan and Gaspar[16]
	Nanoneurotechnology	Neurological diseases and particularly the applications of nanoparticles to treat and diagnose them.	Robert et al.[40]
	Nanotoxicology	Application of toxicology to nanomaterials.	ISO/TS 80004-5[12]
	Nanobiotechnology and nanoscience	Innovative techniques to deliver drugs targeted to the site of inflamed organs, such as the lungs. Nanoscale drug delivery systems have the ability to improve the pharmacokinetics and pharmacodynamics of agents allowing an increase in the biodistribution of therapeutic agents to target organs, resulting in improved efficacy with reduction in drug toxicity.	Jain[41] Nanoscience defined in ISO/TS 80004-1[3]. See below.
	Nanoneuroprotection and nanoneurotoxicity	Nanoneuroprotection: nano-drug delivery is an effective means to potentiate and prolong drug effects in the central nervous system. Nanoneurotoxicity: cellular toxicity induced by nanoparticles that enter into body fluids by various means.	Sharma[42]

Table A.1 *(continued)*

Area	Nanotechnology term or branch of medicine	Definition from the external literature	Example literature reference
	Nanobiotechnology (version 2)	Scientific research at the nanoscale investigating fundamental cellular mechanisms such as molecular forces, molecular motors, and cellular electrochemical phenomena.	Duncan and Gaspar[16]
	Nanobiotechnology (version 1)	Application of nanoscience or nanotechnology to biotechnology or biology.	ISO/TS 80004-5[12]
Route of administration N.B. Only those reported for "nanomedicine" applications are included. These can all be found in the medical literature	Oral, buccal, sublingual	Of or relating to the mouth (oral, buccal); relating to, near, or on the side toward the tongue (lingual).	Oxforddictionaries.com
	Intravenous	Existing or taking place within, or administered into, a vein or veins.	Oxforddictionaries.com
	Intramuscular	Situated or taking place within, or administered into, a muscle.	Oxforddictionaries.com
	Pulmonary	Of or relating to the lungs.	Oxforddictionaries.com
	Intranasal	Lying within or administered by way of the nasal structures.	Merriam-webster.com
	Intratracheal	Occurring within or introduced into the trachea.	Merriam-webster.com
	Subcutaneous	Situated or applied under the skin.	Oxforddictionaries.com
	Topical	Relating or applied directly to a part of the body.	Oxforddictionaries.com
	Transdermal	Relating to or denoting the application of a medicine or drug through the skin.	Oxforddictionaries.com
	Ocular	Of or connected with the eyes.	Oxforddictionaries.com
	Intrathecal	Occurring within or administered into the spinal theca.	Oxforddictionaries.com
	Intraperitoneal	Existing within or administered by entry into the peritoneum.	Merriam-webster.com
Class of nano object	Gold nanoparticle	Nanodisperse colloidal gold (5 nm to 150 nm in size).	Duncan and Gaspar[16]
	Polysaccharide nanocarriers	Chitosan/carboxymethyl-â-cyclodextrin loaded with unfractioned or low-molecular-weight heparin.	Oyarzun-Ampuero et al.[43]
	Nanowire	Conductive or semi-conductive particles with a crystalline structure. NOTE Already defined in ISO/TS 80004-2.	Shinde et al.[17]
	Magnetic nanoparticle	Diagnostic tool composed of nanosized materials with magnetic or paramagnetic properties.	Shinde et al.[17]

Table A.1 *(continued)*

Area	Nanotechnology term or branch of medicine	Definition from the external literature	Example literature reference
	Nanobiosensor	Nanobiosensor is defined as a compact analysis device that incorporates biological (nucleic acid, enzyme, antibody, receptor, tissue, cell) or biomimetic (macrophage-inflammatory proteins, aptamers, peptide nucleic acids) recognition elements.	Jain[18] Boulaiz et al.[19]
	Nanopharmaceuticals	Nanopharmaceuticals are a relatively new class of therapeutic-containing nanomaterials that often have unique "nanoproperties" (phyisiochemical properties) due to their small size (compared with their bulk-phase counterparts) a high surface-to-volume ration and the possibility of modulating their properties. Basically, they are nanoparticles intended for a broad spectrum of clinical therapeutic applications with the potential to target a particular organ or tissue site, either passively or actively.	Bawa[44]
	Nanohorns	SWCNTs tubes of diameter between 2 nm and 5 nm aggregated to give a spherical form that resembles a "sea urchin".	Lacotte et al.[20] Duncan and Gaspar[16] ISO/TS 80004-3[21]
	Nanosphere	Spherical particles of nanometer dimensions. They are biodegradable and self-assembling and have potential as drug carriers and imaging agents.	Zhang et al.[45]
	Nanocarrier	Nano-object or objects which are at a larger scale but which carry nanoscale payloads able to transport a diagnostic or therapeutic agent either on its surface, within its bulk structure or within an internal cavity. NOTE 1 Transport might target a specified, precise location. NOTE 2 Includes transport of medical payloads to specific cells and tissues, for example, anticancer agent, antibiotic, other drug release, or for imaging and sensing functions.	ISO/TS 80004-7[13]
	Nanomicelles	Nanosized vesicular carriers formed from amphiphilic monomer units.	Part of suspension work in nanostructured project
	Nanocrystal	Top down size reduction of crystalline active pharmaceutical ingredients.	Being defined in TC 229
	Nanosome/ liposome/ nanoliposomes	Vesicular nanostructures formed by a bilayer composed of phospholipid and cholesterol molecules. Characterized by extended, two-dimensional and clearly separated hydrophilic and hydrophobic regions.	Boulaiz et al.[19]

Table A.1 *(continued)*

Area	Nanotechnology term or branch of medicine	Definition from the external literature	Example literature reference
	Nanoemulsion	Mixture of two-phase insoluble liquids in which vesicles in the dispersed phase are surrounded by the continuous phase.	Boulaiz et al.[19] ISO/TS 80004-4[22]
	Nanosuspension	A suspension of drug nanoparticles in a liquid.	Shinde et al.[17] ISO/TS 80004-4[22]
	Solid nanoparticles	Material containing a solid core at room temperature and not necessarily in a spherical form.	Boulaiz et al.[19]
	Nanoshell	Concentric spherical nanoparticles consisting of a dielectric core and metal shell.	Shinde et al.[17]
Modification (manufacture)	Nanoengineering	Nanontechnology is an anticipated manufacturing technology giving thorough, inexpensive control of the structure of matter, where other terms such as molecular manufacturing, nano-engineering, etc. are also often applied.	Rieth[46]
	Synthetic nanoparticle platform	Nanoparticle platform technology that allows for the precise control of combination drug therapy.	Kolishettia et al.[47]
	Dendrimers	Regularly branched three dimensional structures with a treelike form and a molecule as a central core. NOTE Viewed as a polymer and not a nanoparticle.	Boulaiz et al.[19]
	Nanogels	Nanogels are swollen nanosized networks composed of hydrophilic or amphiphilic polymer chains. They are developed as carriers for the transport of drugs, and can be designed to spontaneously incorporate biologically active molecules through formation of salt bonds, hydrogen bonds, or hydrophobic interactions.	Kabonov and Vinogradov[48]
	Viral nanoparticles	Viral nanoparticles are well-characterized, monodisperse structures (many solved at atomic resolution) that can be produced in large quantities. The basic VNP structure can be "programmed" in a number of ways so that the internal cavity can be filled with drug molecules, imaging reagents, quantum dots and other nanoparticles, whereas the external surface can be decorated with targeting ligands to allow cell-specific delivery.	Yildiz et al.[49]
	Solid lipid nanoparticles	Sub micron colloidal carriers (50 nm to 1 000 nm in size) composed of a physiological lipid, dispersed in water or in an aqueous surfactant solution	Shinde et al.[17]

Table A.1 *(continued)*

Area	Nanotechnology term or branch of medicine	Definition from the external literature	Example literature reference
	Nanoshells	Spherical nanoparticles with a dielectric core and metal shell (e.g. silica core and gold shell).	Bardhan et al.[50]
	Nanopores	Aerogel, which is produced by cell gel chemistry. NOTE See ISO/TS 80004-7:2011, 2.13. [13]	Campbell[23]
	Nanofilms	Nanoscale polyelectrolyte multilayer films that carry drugs for biomedical applications.	Jiang et al.[51]
Other	Nanomedicinista	Nanomedicine researchers.	Duncan and Gaspar[16]

Annex B
(informative)

Nanomedicine ontology and terminology resources

Table B.1 — Nanomedicine ontology and terminology resources

Resource title	Reference (URL)	Description
NCI Thesaurus (NCIt) [24]	http://ncit.nci.nih.gov/	NCIt provides a reference terminology to NCI and standardized vocabularies for other organizations (including FDA and CDISC). This structured vocabulary has terms that broadly support clinical care, translational and basic research, and public information and administrative activities. For nanomedical applications, this terminology has an extensive set of drugs and other chemicals as well as descriptors, investigation types and instrumentation related to nanoparticles and nanomaterials.
NCI Meta-Thesaurus (NCIm) (includes NCI Thesaurus as well as several other vocabularies)[25]	http://ncimeta.nci.nih.gov/	NCIm provides a broad, concept-based mapping of terms from over 70 biomedical terminologies, whose 3 600 000 terms are mapped to 1 400 000 concepts representing their shared meanings. NCIm gives access to a great diversity of biomedical terminologies including NCIt, MeSH, DICOM, ICD, NPO, NDFRT, and SNOMED.
MeSH (Medical Subject Headings)[26]	http://www.ncbi.nlm.nih.gov/mesh	MeSH is the controlled vocabulary used by NLM to index PubMed and other NLM holdings. It has broad coverage of biology, chemistry and medicine. ChEBI (Chemical Entities of Biological Interest) — http://www.ebi.ac.uk/chebi/ ChEBI is a dictionary of molecular entities focused on small chemicals. It has a large number of chemicals and annotates them with synonyms, chemical relationships, chemical roles and biological roles.
National Drug File (NDFRT)[27] [28]	http://bioportal.bioontology.org/ontologies/1352 http://ncit.nci.nih.gov/ncit-browser/pages/vocabulary.jsf?dictionary=National%20Drug%20File%20-%20Reference%20Terminology-&version=June2013	NDFRT is produced by the Veterans Health Administration and organizes the drug list into a formal representation. NDFRT is used for modeling drug characteristics including ingredients, chemical structure, dose form, physiologic effect, mechanism of action, pharmacokinetics, and related diseases.
NanoParticle Ontology (NPO)[29]	http://nano-ontology.org/	NPO represents the knowledge underlying the description, preparation, and characterization of nanomaterials in cancer nanotechnology research.
Ontology for Biomedical Investigations (OBI) [30] [31]	http://purl.bioontology.org/ontology/OBI http://ncit.nci.nih.gov/ncit-browser/pages/vocabulary.jsf?dictionary=Ontology%20for%20Biomedical%20Investigations&version=Summer2012	OBI is an ontology of biomedical investigations; it includes terms that represent the protocols, instrumentation and material used, the data generated and the types of analysis performed on it.

Table B.1 *(continued)*

Resource title	Reference (URL)	Description
Unified Code for Units of Measures (UCUM) [32]	http://unitsofmeasure.org/trac/	UCUM is a coding system intended to include all units of measures used in international science, engineering, and business and designed to facilitate electronic communication.
Unit Ontology (UO)[33]	http://purl.bioontology.org/ontology/UO	UO is a formalized representation of metric units of measure designed to be used with PATO and other OBO foundry products.
Translational nanomedicine: status assessment and opportunities[34]	James S. Murray, Richard W. Siegel, Judith Stein, J. Fraser Wright, Nanomedicine: Nanotechnology, Biology, and Medicine 5 (2009) 251–273.	This article briefly explores scientific, economic, and societal drivers for nanomedicine initiatives; examines the science, engineering, and medical research needs; succinctly reviews the US federal investment directly germane to medicine and health, with brief mention of the European Union (EU) effort; and presents recommendations to accelerate the translation of nano-enabled technologies from laboratory discovery into clinical practice.

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