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Artificial intelligence for healthcare and well-being during exceptional times

A recent landscape from a European perspective

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Contents

Abstract

This report provides a detailed state of the art of the current and near-future applications of Artificial Intelligence (AI) in medicine, healthcare and wellbeing, particularly focused on their impact on people's physical and mental health, and in societal and environmental welfare, including future generations. It builds on previous analyses, is framed in recent historical circumstances of the COVID-19 pandemic and the war in Ukraine, and accounts for recent strategic policy priorities in related areas.

Aimed for a science for policy audience, and adopting a European perspective, the described outcomes are of interest for researchers studying the ethical and social impact of AI in medicine, healthcare, and wellbeing, for scientific and technological stakeholders, and for the general public.

The present analysis of the state of the art includes software, personal monitoring devices, genetic tests and editing tools, personalized digital models, online platforms, augmented reality devices, and surgical and companion robotics. It identifies the particularities of AI systems and applications, the opportunities and risks associated to them, as well as their availability level. This study proposes a methodology for the assessment of the social impact of these technologies, considering their maturity, availability, controversy, and sustainability, together with an integrated overview.

From this review, the report identifies 100 relevant topics in the field, supported with references, and analyses lessons learnt in the area from the mentioned historical circumstances and significant institutional appraisals. In addition, the present study recognizes five key expanding areas with particular significance in terms of social impact: AI tools for mental health, AI-mediated gene edition, AI tools for epidemiology and health data monitoring, AI-mediated neuro-technologies and AI-mediated inclusion of neurodiversity, and describes them in detail considering the proposed social assessment scales. This report also identifies novel AI-mediated challenges and risks related to the protection against biological threats, and links them to the concept of One Health (human, animal and environmental) and to the updated policy initiatives by the European Union, the United Nations, and the World Health Organization. Finally, the report outlines a series of controversial issues, namely gene edition for human augmentation and neuro-technologies for decoding of and interacting with cognitive signals.

From our analysis, we provide some science for policy challenges, aimed to translate the scientific and technical narrative into practical approaches for the benefit of the persons and society and towards an effective European-centric perspective in the field.

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This report is

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1 Introduction

1.1 Motivation and goals

Artificial Intelligence (AI) has become a major driving force in science and technology, with a profound overall impact in all aspects of society, and it has become an area of strategic importance and a key driver of economic development in the European Union (EU).

This reports is framed in the context of the HUMAINT (Human Behaviour and Machine Intelligence) project at the European Commission's Joint Research Centre. HUMAINT researchers on the societal impact of AI technologies (opportunities and risks) and develops methodologies for Trustworthy AI. The project also provides technical and scientific support to EU AI policies, mainly the AI Act and the Digital Services Act.

This report focuses on the impact of AI on the area of medicine and healthcare, building upon previous studies published in [5] [6] [7] [8] [9] This report presents the following contents:

i) An overview and classification of the current and near-future applications of AI in Medicine, Healthcare and Wellbeing according to their ethical and societal impact and the availability level of the various technological implementations. This analysis builds upon [5] and includes 480 new references -structured in 100 topics- mostly dated in 2021 and 2022.

ii) Based on the previous overview, we select a small set of use cases which are relevant in terms of societal opportunities vs risks. They belong to the domains of "Neuro-technologies" and "Epidemiology" (in a broad sense, also including Gene Editing), and they are identified as four use-cases, corresponding to main fields (key expanding areas):

- AI tools for mental health,
- AI-mediated gene editing,
- AI tools for epidemiology and health data monitoring,
- AI-mediated neurotechnologies (for cognitive signals), and
- AI-mediated inclusion of neurodiversity.

Additional fields of technical advances with significant social impact comprise AI-mediated drug discovery and personalized medicine. These use cases are analyzed from the perspectives of their features and impact on physical and mental health and wellbeing of persons, society, and the environment, including future generations.

iii) A set of insights in terms of conclusions, challenges and recommendations to be addressed in the next future.

It is important to note that this report covers a period (from June 2020 to September 2022) with two unexpected historical circumstances, the COVID-19 pandemic and the war in Ukraine. In addition, the first case of an autonomous machine killing humans was documented in 2021, and news on the creation of the first 'living machine' or 'xenobot´ were published in 2020. Notably, in 2022 the European Union and the United Nations have updated their strategic priorities in several related areas, particularly related to health. All these events have had a significant impact on the topics of this report. They have been thoroughly addressed accordingly and have contributed to the selection of the relevant use cases in terms of societal impact.

1.2 Limitations and disclaimer

This report covers the period from June 2020 to September 2022. It is based on a careful research and analysis of references available from public sources, following the common practice and standards of scientific methodology as detailed in Section 2.1. However, the expressions and views contained in this document –particularly its conclusions– are those of the authors and do not necessarily represent those of his institutions of affiliation. The examples and references to real systems and commercial devices and programs, online platforms and other available products have been selected because of their interest or relevance in relationship to the corresponding topic under analysis. Their selection in this report does not reflect any endorsement or evaluation (positive or negative) on their commercial interest.

1.3 Historical circumstances and significant events

In the period covered by the current report, June 2020 to September 2022, two extraordinary, historical circumstances are developing with significant impact in all aspects of life and society, in the EU and worldwide. This report analyses how AI technologies have been exploited in these two very different historical scenarios.

On the one hand, the peak and decay of the COVID-19 pandemic since its spread from China at the beginning of 2020. In Europe, by middle July 2022 [17] , there had been over 207.6 million cases and over 2.3 million deaths.

On the other hand, the Russian invasion of Ukraine, began in February of 2022 and still under development. This is the largest war in European territory since the Second World War. By the finalisation of this research, it is in a volatile and unpredictable status, causing severe destruction in the country, numerous deaths of civilians and strong migrations and displacements of population. By September 2022, there were over 7 million refugees in EU countries, and over 7 million persons who fled their homes inside Ukraine [18] .

In addition, the European Union and the United Nations have updated their strategic priorities in different areas related to the subject topics of this research. Other relevant events include:

— Possible first documented case of autonomous weapon killing humans (2021) In 2021, a report by the United Nations [19] about the Libyan civil war reported what it may be the first documented use of autonomous weapons to kill humans. Several nations are investing heavily in such weapons [20] , and this issue was already described in [5] .

— First publication on 'living machines' (2020) The first case of 'xenobots' built using frog stem cells was published in 2020 [21] , also described in [5] . Further research in 'self-reconfigurable' (potential) 'life-forms' is advancing [22] [23] [24] .

— Medical errors. An obvious filed of interest of AI systems refers to helping humans in performing complex tasks in demanding environments, particularly as related to reducing medical errors. Data from the USA /updated to 2016) indicate that about 251.000 deaths/year results from medical errors, being the third leading cause of death [25] . By comparison, in that country there were about 39.000 deaths/year due to car accidents (in 2020) [26] .

1.4 Policy context

This report has been developed in the context of a series of EU and international strategic policy priorities related to the protection of persons and of the societies under recent geopolitical challenges. These priorities have been highlighted in the following three declarations of the maximum authorities of the European Union and of the United Nations. We mention here the main aspects related to the present report.

1) The declarations (September 8, 2021) of the **President and Vice-President of the European Commission** about the future of the **EU's Open Strategic Autonomy** with regards to the presentation of the second annual Strategic Foresight Report by JRC. They both reflected on current challenges on climate change and digital transformation, potential impact on European values, and the need for an early, comprehensive understanding of emerging trends for tackling such important issues.

2) The declaration (October 10, 2021) of the President of the European Commission, at the **World Health Summit** [27] , which mentions potential risks such as Bioterrorism or the unintentional release of pathogens and the need for preparedness. In this speech, President Von der Leyen announced the creation of a new **Health Emergency preparedness and Response Authority (HERA)** [28] , and outlined several relevant aspects related to its tasks ad challenges, such as the preparation for health emergencies and their promptly detection and collective response, the assessment of health threads including with innovative methods, the sharing of data, or the assessment of new and emerging biological threats. The speech also mentioned the need to join forces with international counterparts to setup a global standard for health preparedness.

3) Finally, we identify as relevant to this report the declaration (August 5, 2021) of the **Secretary General of the United Nations** at his **Report on the General Agenda** [29] . This declaration mentioned the COVID-19 pandemic, and long-term challenges related to managing new technologies such as AI and gene editing (point 41) and artificial intelligence regulation (point 93).

2 Selected approach

2.1 Methodology

This reports build upon the methodology proposed in [5] . We build the landscape of applications of AI in medicine and healthcare, with a focus on its ethical and social impact, through systematic searches in standard scientific, academic, institutional, medical, corporate, and technical online platforms. In addition, our review incorporates examples (of social impact and growing concerns and debates) published in general press, social media, and other web-based sources. The majority of references are dated from the publication of a previous report [5] (June of 2020) to September 2022, in order to represent recent developments. Some other works considered of relevance are also included. Scientific references have been compiled using Mendeley Reference Manager® and Vancouver Citation Style Language (CSL). Press references mainly come from media included in the Top European Newspapers in English – TheBigProject [16] . Full (standard) citations correspond to the numbers in square brackets.

Once identified, references are first grouped by the two authors into topics, as presented in Section 3.1. The different topics are then assessed in terms of technological and ethical considerations with respect to those identified in previous report and summarized in Section 2.3, outlining most significant events and recent development in Sections 3.2 to 3.6. It is worthy to note that given the timeline of this report (June 2020 to September 2020) with respect to the two historical circumstances mainly considered (COVID-19 pandemic beginning of 2020 and Ukrainian war February 202), our analysis provides a more developed analysis on the link between AI and the first circumstance than on the second one.

From the identified topics and outlined recent developments, the authors then select five use cases which are described following a set of social assessment scales grounded in previous studies and presented in Section 2.2. The identification of topics, use cases and qualitative analysis is finally reviewed by a group of give experts including medical doctors and engineering researchers, listed in the acknowledgement section of the present report.

2.2 Social assessment

With the goal of assisting the development of quantitative and qualitative indicators for the social assessment of AI technologies, we propose a set of scales to provide, on the one hand, independent descriptive measures of the maturity, availability, controversy, sustainability and the extent of adoption of the technology under analysis, and, on the other hand, an integrated evaluation with a pictorial overview. Some of these metrics, such as concepts of 'controversy' and the 'overall social impact', are difficult to 'standardize' and 'categorize' -and may be subject to further updates-, as they relate to both the social, personal, and ethical realms.

2.2.1 Maturity (Technology Readiness Level, TRL)

The maturity of a technology can be evaluated using the 'Technology Readiness Level' (TRL) scale, originally defined by the NASA [30] and adopted in the European R&D&I environment [31] . It provides a qualitative description in a numerical scale in 9 steps (levels), which range from 1 (basic principles observed) to 9 (actual system proven in operational environment).

The values defined for the TRL scale are the following:

- TRL 1 – Basic principles observed.
- TRL 2 – Technology concept formulated.
- TRL 3 – Experimental proof of concept.
- TRL 4 – Technology validated in lab.
- TRL 5 – Technology validated in relevant environment (industrially relevant environment in the case of key enabling technologies).
- TRL 6 – Technology demonstrated in relevant environment (industrially relevant environment in the case of key enabling technologies).
- TRL 7 – System prototype demonstration in operational environment.

— TRL 8 – System complete and qualified.

— TRL 9 – Actual system proven in operational environment (competitive manufacturing in the case of key enabling technologies; or in space).

2.2.2 Availability (Technology Availability Level, TAL)

The availability of a technology can be evaluated using the 'Technology Availability Level' (TAL) scale which provides a qualitative description of the degree of availability of a technology in a numerical scale in 10 steps (levels), which range from 0 (unknown status, not considered feasible) to 9 (available for the general public).

The values defined for the TAL scale are the following:

— TAL 0. Unknown status. Not considered feasible according to references.

— TAL 1. Unknown status. Considered feasible according to related, indirect references.

— TAL 2. General/basic idea publicly proposed.

— TAL 3. Calls for public funding of research and development (R&D) open.

— TAL 4. Results of academic/partial projects disclosed.

— TAL 5. Early design of product disclosed.

— TAL 6. Operational prototype/'first case' disclosed.

— TAL 7. Products disclosed but not available.

— TAL 8. Available products for restricted (e.g. professional) users.

— TAL 9. Available for the public.

2.2.3 Controversy (Technology Controversy Level, TCL)

In order to analyze the different AI applications and their current status, in this Report it is proposed a novel scale named 'Technology Controversy Level' (TCL) to give a qualitative description of its 'degree of controversy'. It is recognized that this concept is very difficult to 'standardize', as it relates to societal and personal ethical thresholds, beliefs, and constructs, and that this scale may be subject to further updates.

As a reference benchmark, the proposed TCL scale is referred to the Human Rights as declared by the United Nations in 1948 [32] . The technology under analysis is therefore classified as 'controversial' if it contributes 'against' to (at least one of) the fundamental Human Rights (HR), and 'non-controversial' if it aims 'for the benefit of groups of vulnerable persons' or 'of mankind'. This qualitative and quantitative comparison is inspired on the Human Rights Indicators defined by the United Nations in 2012 [33] , and the concept of 'vulnerable groups' is based on the definition by the same organization [34] .

The corresponding value (level of controversy) of a given technology is defined in a numerical scale in 9 steps, with four 'positive' (i.e., controversial) and four 'negative' (i.e., non-controversial) levels from a 'zero value' or neutral reference (corresponding to 'not applicable'). They are also mapped to qualitative descriptions and to a color map following the visible spectrum, from dark blue ('definitely not controversial') to dark red ('highly controversial'). Color shades and their corresponding numerical coding in the common red-green-blue (RGB) system are detailed in Table 1. Note that a technology with a high positive TCL value (e.g., a system used for terrorism, with TCL = +4) is then considered a 'highly controversial' and 'negative technology'.

The values defined for the TCL scale and their corresponding qualitative and color levels are defined in the following Table.

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Table 1. Definition, steps, numerical values, and description of the proposed Technology Controversy Level (TCL) scale. Color shades may be modified (within their overall tone) according to printing or visualization devices to assure correct identification. RGB color codes are given in 8-bit description (from 0 to 255).

TCL		**Qualitative description**		**Color**	
Value	Definition (The technology is ...)	Level of Controversy	Value	Level of Controversy	RGB coding
-4	Definitely, for the benefit of mankind	Absolutely not controversial	'Highly positive'	Dark blue	[0, 32, 96]
-3	Beneficial for extended vulnerable groups	Strongly not controversial	'Very positive'	Blue	[0, 112, 192]
-2	Clearly beneficial for some vulnerable groups	Clearly not controversial	'Positive'	Light blue	[0, 176, 240]
-1	Possibly beneficial for one or more vulnerable groups	Plausibly not controversial	'Likely positive'	Green	[0, 176, 80]
0	Not affecting/related to Human Rights	Not applicable	Neutral	Yellow	[255, 255, 0]
+1	Possibly, against one or more Human Rights	Conceivably controversial	'Likely negative'	Amber	[255, 192, 0]
+2	Likely, against one or more Human Rights	Clearly controversial	'Negative'	Scarlet	[255, 51, 0]
+3	Very likely, against one or more Human Rights	Strongly controversial	'Very negative'	Red	[255, 0, 0]
+4	Clearly, against one or more Human Rights	Absolutely controversial	'Highly negative'	Dark red	[192, 0, 0]

Source: Own elaboration.

Figure 1. Classification of AI and AI-mediated technologies in Medicine and Healthcare according to their ethical and social impact. SW: software, AR: augmented reality, VR: virtual reality, IoT: internet of things. TAL: Technology Availability Level.

AI and AI-mediated technologies	Specific implementations.	TAL	Social Impact
Algorithms for computer-aided diagnosis.	SW for decision support in (most) clinical areas.	8, 9	Positive
Structured reports, eHealth.	SW for improved workflow, efficiency.	8, 9	
AR/VR, advanced imaging tools.	Tools for information visualization and navigation.	6, 7, 9	
	Image-guided surgery. Teleoperation.	4, 6, 9	
Digital pathology, 'virtopsy'.	SW for automated, extensive analysis.	4-9	
Personalized, precision medicine.	Tailored treatments. Prediction of response.	4-9	
	'In-silico' modeling and testing. The 'digital twin'.	4-8	
	Drug design.	4, 8	
Apps, chatbots, dashboards, online platforms.	The 'digital doctor' (assistance for professionals and for patients).	8, 9	
Companion and social robots.	For hospitalized persons, children & the elderly.	4-9	
Big Data collection and analysis.	Epidemiology, prevention and monitoring of disease outbreaks.	2-9	
	Fraud detection. Quality control, monitoring of physicians and treatments.	4-9	
IoT, wearables, mHealth.	Automated clinical/health surveillance in any environment/institution.	7, 8	
	Monitoring, automated drug delivery.	7-9	
Gene editing.	Disease treatment, prevention.	7, 8	
Merging of medical and social data. 'Social' engineering.	Prevention of episodes with clinical relevance (e.g. suicide attempts).	6, 8	Controversial
	Tailored marketing (e.g. related to female cycles).	6, 8	
Reading and decoding brain signals. Interaction with neural processes.	Treatment of diseases. Restoring damaged functions.	3-8	
	Brain-machine inferfaces.	5-8	
	Control of prostheses, exoskeletons. 'Cyborgs'.	2-7	
	Neurostimulation. Neuromodulation.	4-8	
	Neuroprostheses (for the central nervous system).	2-5	
	Mind 'reading' and 'manipulation'.	1-3	
Genetic tests. Population screening.	Disease tests. Direct-to-consumer tests.	4-9	
Personalized, precision medicine.	Individual profiling. Personalized molecules (for treatment) at 'impossible' prices.	3-8	
Gene editing.	'Engineered' humans.	2, 6	
	Gene-enhanced 'superhumans'.	2	
	Self-experimentation medicine. Biohacking.	2, 6	
Fully autonomous AI systems.	The 'digital doctor'.	2-5	
	'Robotic surgeon'.	2, 4	
Human-animal embryos.	Organs for transplants.	2, 4, 5	
	Hybrid beings ('chimera').	2, 4	
The quest for immortality.	Whole-brain emulation / 'transplant'.	1, 2	
The search for artificial life forms.	'Living machines' ('biological robots', 'biobots')	4, 6	
	Military.	2, 3	
Evil biohacking.	Targeting specific individuals or groups.	1, 2	
Weaponization.	From 'small labs' to military labs.	1, 2	
Bioterrorism.	From 'small labs'.	1, 2	Negative

Source: reproduced from [5].

2.2.4 Sustainability (Technology Sustainability Level, TSL)

In order to analyze the different AI applications and their current status, in this Report a novel scale is proposed named 'Technology Sustainability Level' (TSL) to give a qualitative description its 'degree of controversy'.

As a reference benchmark, the proposed TSL scale is referred to the 17 Sustainable Development Goals (SDGs) adopted by the United Nations in 2015 [35] "as a universal call to action to end poverty, protect the planet, and ensure that by 2030 all people enjoy peace and prosperity".

The SDGs are the following:

- GOAL 1: No Poverty
- GOAL 2: Zero Hunger
- GOAL 3: Good Health and Well-being
- GOAL 4: Quality Education
- GOAL 5: Gender Equality
- GOAL 6: Clean Water and Sanitation
- GOAL 7: Affordable and Clean Energy
- GOAL 8: Decent Work and Economic Growth
- GOAL 9: Industry, Innovation and Infrastructure
- GOAL 10: Reduced Inequality
- GOAL 11: Sustainable Cities and Communities
- GOAL 12: Responsible Consumption and Production
- GOAL 13: Climate Action
- GOAL 14: Life Below Water
- GOAL 15: Life on Land
- GOAL 16: Peace and Justice Strong Institutions
- GOAL 17: Partnerships to achieve the Goal

We define the overall TSL value of a given technology as follows:

- For each one of the SGDs, a value (Goal Level, GL) is defined in a numerical scale in 3 steps:
- 'positive' (GL = + 1), i.e., the technology 'favors' that Goal,
- 'negative' (GL = - 1), i.e., the technology 'is against' that Goal,
- 'zero value' reference (GL = -0), corresponding to 'not applicable'.
- The absolute TSL value is constructed as the sum of the 17 GL values corresponding to each one of the 17 SDGs.
- The total TSL value is obtained by normalizing the absolute TSL value. It therefore ranges from TSL = -1 (minimum) to TSL = +1 (maximum).

Each Goal can also be used to score any given technology in that field. For example, AI technologies in this Report are evaluated according to their prospective contribution to the 'GOAL 3: Good Health and Well-being'.

2.2.5 Extent of adoption (Technology Extent Level, TEL)

In order to evaluate the extent of adoption of a technology, in this Report it is proposed a novel scale[3] named 'Technology Extent Level' (TEL) to give a qualitative description its 'degree of adoption'. This is a qualitative metric of the 'market penetration' deemed necessary for a complete assessment of the social impact.

The corresponding value (level of adoption) is defined in a numerical scale in 10 steps (levels), which range from 0 (no users) to 9 (massive adoption).

The values defined for the TEL scale are the following:

- TEL 9 Massive adoption
- TEL 8 Common use (no publicity required)
- TEL 7 Customers/users through word-of-mouth
- TEL 6 Customers/users through general publicity, marketing
- TEL 5 Customers/users though targeted advertising
- TEL 4 Customers/users with explicit, definite support (e.g funding, discounts)
- TEL 3 Early adopters (innovators)
- TEL 2 Beta testers
- TEL 1 In-house use (inventors)
- TEL 0 No users

2.2.6 Integrated assessment

The social impact of a technology could be assessed by considering the four aspects described in the previous sections, namely its maturity, availability, controversy, sustainability and extent of adoption, and the corresponding scales, summarized in the following Table. Some graphical schemes as presented in Figure 2 can be developed by combining several of those metrics to generate a 'pictorial overview' to facilitate an overall evaluation.

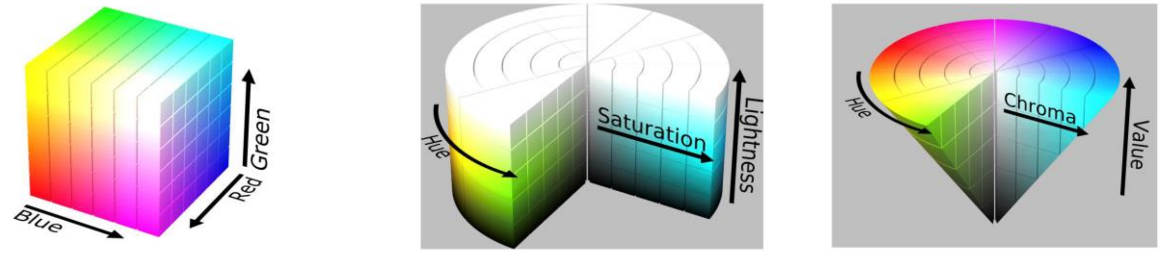
Table 2. Summary of features for the proposed evaluation of the social impact of a technology. SDG = Sustainable Development Goal (of the UN).

Feature	**Scale**		
	Name	**Type/Steps**	**Min/Max**
Maturity	Technology Readiness Level (TRL)	Discrete / 10	0/9
Availability	Technology Availability Level (TAL)	Discrete / 10	0/9
Controversy	Technology Controversy Level (TCL)	Discrete / 9	-4/+4
Sustainability	Technology Sustainability Level (TSL) for SDG 3	Discrete / 3	1
	Technology Sustainability Level (TSL) for all SDGs	Discrete / 3	0.18
	Technology Sustainability Level (TSL) for the technology	Continuous	-1/+1
Extent of Adoption	Technology Extent Level (TEL)	10	0/9

Source: Own elaboration.

Nevertheless, as indicated, the concepts of 'social impact' and of 'controversy' are difficult to 'standardize' and 'categorize' these analyses may be subject to further updates. The four defined scales may be combined into 3D visualization schemes with different color-coding maps to provide an easy-to-interpret pictorial overview. These figures may be developed from existing colormaps employed in optics, as shown in Figure 2.

Figure 2. 3D color-coding maps suitable for representation of technology evaluation scales. A shows the common RGB color space in cube geometry. B depicts the hue-saturation-lightness (HIS) color space in cylindrical symmetry. C shows the hue-chroma-value (HCV) color space in conical geometry.



A B C

Source: Wikipedia Commons.

2.3 Ethical considerations

The ethical aspects to be considered for the analysis of AI and AI-mediated applications in Medicine, Healthcare and Wellbeing are fully described in [5] , and summarized here. Ethical aspects to consider can be grouped in three partially overlapping sets.

The First Group (G1) includes topics currently under analysis, as raised by other areas of prior development of AI applications (e.g., social networks, online commerce, automation in factories, autonomous vehicles), such as:

— Data privacy, integrity and anonymity, legal responsibility and accountability, and other general aspects of the relationship of humans with (at least partially autonomous) machines [see also Second Group G2].

— The effects on medical professionals and on their relationships to both patients and employers, quality control and monitoring of workers. These effects include the need for professional updates, training and qualification, and on employment (lost and new jobs, deep changes in some specialties, the risk that some of them may even disappear).

— Security and reliability [see also Second Group G2].

— Metrics of performance, improved health outcomes and clinical pathways, reduction of medical errors, personalized medicine, and psychosocial outcomes. It is important to note that current AI systems may be good –even outperforming humans– at ‘narrow’, specific tasks while (still) failing in global, overview analysis.

— The existence of a ‘human-in-the-loop’ with or without the ability to override the system, and the questions that arise if there is no time/possibility for human intervention in a critical –even life or death– situation.

The Second Group (G2) includes topics –some of which may also be under analysis in other areas– of particular relevance for Medicine and Healthcare, such as:

— Explainability and interpretability of the systems. These concepts refer to being able to explain the ‘reasoning process’ of AI systems to a human operator. Although it may be required, the evolution of AI technology leads to systems too complex to be understood by a human. Since they may also provide support to humans (at least, in certain tasks), there is a need to consider if we could accept the results given by AI systems without being able to understand how they (‘the machines’) came to them.

— Trust and reliability. We need to evaluate when ‘a machine’ performs better than a human, what to do when they give conflicting opinions.

— Data quality. The generation of suitable databases and repositories of medical data and information for learning and development of AI systems is a major consideration in this area, which should be considered inline with privacy concerns.

- Data security. The social impact of malicious data alterations can be particularly severe since certain health issues (e.g. toxic consumption history, genetic disposition to diseases) may be manipulated to blackmail or discredit individuals and groups, for instance in processes related to employment and profiling.
- Additionally, increased security risks appear when 'physical devices' are involved, such as companion robots assisting persons with disabilities or the elderly, or surgical robots.
- Bias and fairness: in the medical field, it is important to ensure the lack of biases for different (e.g. ethnic, gender, age) groups in diagnosis, prognosis and treatments, the use of proper, representative data for training and the analysis of validity for different populations not involved in the training.
- The social impact of 'erroneous data for learning' can be very high in this context. System may not give any warning, but processing results may be incorrect.
- Empathy, including shared decisions and ('the machines') helping humans to make difficult decisions.
- Citizen (taxpayer) opinion and involvement in a 'patient-centric' model. Questions include the common-good in public-funded research, informed consent, citizen science, the 'reduced asymmetry' in information between the patient and the doctor, and citizen-generated (genetic, …) tests without a doctor prescribing them and analyzing their results.
- Test, benchmarking. There is a clear need for updated testing and evaluation procedures in this field, as key issue in which relevant changes are required in a given AI system.
- Regulation, and the legal aspects related to liability and malfunction. Regulatory frameworks are still developed incorporating liability aspects, to ensure accountability.
- Affordability and socio-economic impact. Global figures and market of AI in Medicine and Healthcare forecast very relevant, positive impact for the coming years. However, the economic analysis must include the social points related to health systems, the industries and the patients, as such technologies also risk evolving into a significant factor of inequality.
- Information for the public and professionals about the real efficacy of AI-mediated treatments and clinical tools, especially against severe diseases of deep social interest – such as cancer– as compared to the many 'announcements' of 'spectacular (initial) results' which, are not later proven to be particularly useful in routine clinical use.
- The availability of trustworthy, open-access information –warranted by public services– is essential to reduce the risks of 'fake-based' medicine and to protect citizens from 'digital health scammers',
- The question of whether (or not) harnessing AI systems under human control on life and death decisions. Should we allow 'a machine' to take such decisions (on us, on a relative)?

The Third Group (G3) includes certain aspects barely -or not included at all- in many studies on AI applications in Medicine and Healthcare, such as:

- Humanization of care, allowing for more time with the patient that improves clinical outcomes and relieves high stress levels (burnout, suicide rates) of physicians. However, AI systems still lack the (much needed) ability of a physical (contact) examination.
- Social engineering, profiling based on merged medical, health and social data. This issue questions the use of such merged information for the preventive detection of events of clinical significance (e.g. suicide) and for commercial uses (e.g. tailored marketing, insurance, health care coverage or employment). A significant topic is the potential genetic screening of (the whole, groups of) population (detailed below).
- The availability of (unsupervised, unreliable) multiple data, genetic tests for anyone, with the risk of 'patient-generated' medicine.
- Limits to data use, and post-mortem data inheritance. A key question is related to the limit of use of very personal information (from Extended Personalized Medicine such as genetic, medical, biological data) when a person dies, e.g. if this personal data remains available for use by AI systems, if there is a post-mortem limit, if this data can be inherited, by a relative or a public institution, if what would be the purpose of additional processing, e.g. commercial use, scientific use (e.g. belonging to a person with a rare disease) or direct use to treat a disease.

- The expanding availability of crowd-sourcing of algorithms and processing power. The free sharing of expertise, know-how, and experience define a debate of 'solidarity' vs risks of malicious use.
- Reading and decoding brain signals. The hope for the severely impaired may be turned into 'mind reading' technologies challenging privacy at its basics.
- Interactions with neural processes, which can be applied to help in neurological, mental diseases and, potentially, to interfere with free will.
- Gene editing as an enabler for self-experimentation in humans, with the risk of unexpected results and the potential for change of the genetic heritage.
- Gene editing 'to design' humans and human-animal embryos. With the (already documented) risk of unexpected results in newborns and the unknowns derived from the creation of new types of human-animal beings ('chimera').
- The two sides of technology. With the (relatively) easy weaponization of many of the AI-mediated technologies and the corresponding high risk of bioterrorism.
- Whole-brain computerized emulation and 'head transplant', challenging the quest for immortality and the very definition of life.
- The search for artificial life forms (explicitly declared for military purposes), questioning the definitions of life (natural, artificial) and death.
- The balance of benefits versus risks and pitfalls and the very fundamental question of whether there should be (or not) limits to research and development?

Figure 3. Ethical and social aspects of AI and AI-mediated technologies in Medicine, Healthcare and Wellbeing sorted in three groups (G1, G2, and G3). Some key relevant issues, controversies, significant, and conflicting issues are outlined for each aspect.

(G1) Currently under analysis, as raised by other areas of AI applications.

Aspects.	Analyzed in relation to.
Data privacy, integrity.	Ownership. Authorization for data collection, sharing, mining, exchange.
Anonymity.	Surveillance anxiety.
Responsibility. Accountability.	Who is responsible in case of malfunction?
Effects on professionals and employment.	Lost & new jobs. Deep changes in some medical specialties (some may even disappear). Need of professional updating. Quality control, monitoring.
Security. Reliability.	Vulnerabilities. Data theft. Manipulation of the data used to train the systems.
Performance.	Improved health outcomes and clinical pathways. Reduction of medical errors. 'Personalized Medicine'. Psycho-social outcomes.
Human-in-the-loop?	Should a human operator override AI systems? Even if human is more 'error-prone'? What happens if there is no time to act?

(G2) Of particular relevance for AI applications in Medicine and Health Care.

Aspects.	Controversies.
Explainability.	Currently required by legislation. Some systems are (will be) too complex to be understood by a human. But they may give better results than a human.
Trust.	Does 'the machine' perform better than a human doctor? What to do if they (AI system, human doctor) give conflicting opinions? 'Digital health scammers'.
Data quality. Bias / fairness.	Do AI systems have biases/are fair with different (e.g. ethnic, gender, age) groups? Do they receive proper, balanced data for training? Are results valid?
Empathy.	Shared decisions? Help (the human) take difficult decisions?
Citizen (taxpayer) opinion and involvement.	Common-good in public-funded research, informed consent, citizen science. Reduced 'asymmetry' doctor-patient. 'Patient-centric' model.
Test, benchmarking.	How to evaluate results? Existing procedures for average groups are valid for individualized treatments? Comparison of AI systems 'against humans or machines'?
Regulation.	Lags behind technology. No international consensus.
Affordability. Economic impact.	Optimal treatments at 'impossible' prices? A factor of inequality? New models for health insurance and coverage?
Information for the public and professionals.	Pressure for new products. Real advances vs hypes and non-confirmed stories of success in areas of great interest (e.g. cancer cures). Risk of 'fake-based' medicine.
Life and death decisions.	Should we allow 'a machine' to take them (on us, on a relative)? The debate about lethal autonomous weapon systems.

(G3) Barely/not included in analysis of AI applications in Medicine and Heath Care.

Aspects.	Significant/conflicting issues.
Humanization of care.	Professionals with AI: More time with the patient, stress relief. AI systems: Currently, lack of physical exam/contact with patient.
Social engineering, profiling based on merged medical, health, social data.	Preventive detection of events (e.g. suicide) vs tailored marketing, insurance, health care, employment. Genetic screening of the population.
Availability of (unsupervised, unreliable) multiple data, genetic tests for anyone.	Risk of 'patient-generated' medicine.
Limits to data use? Post-mortem, inheritance.	Post-mortem use of individual (e.g. genetic) information?
Crowd-sourcing of algorithms, processing power.	Free sharing of expertise, know-how, experience. Solidarity vs risks of malicious use.
Reading, decoding brain signals.	Hope for severely impaired vs privacy at its basics.
Interaction with neural processes.	Help for neurological, mental diseases vs free will.
Gene editing as self-experimentation.	Risk of unexpected results. Change of genetic heritage.
Gene editing of (human, human-animal) embryos.	Risk of unexpected results in newborns. Creation of new beings ('chimera').
The two sides of technology.	'Easy' weaponization. High risk for bioterrorism.
Whole-brain emulation / 'transplant'.	The quest for immortality. Definition of life.
'Living machines' ('biological robots', 'biobots') The search for artificial life forms.	Definitions of life (natural, artificial) and death.
Benefits versus risks and pitfalls.	**Limits (or no) to research and development?**

Source: reproduced from [5].

3 AI landscape

3.1 Relevant topics

Table 3 presents 100 identified relevant topics which represent the literature update on AI systems in medicine, healthcare and wellbeing and their ethical and societal impact. Topics are sorted by alphabetic order and each topic is supported by a references dealing with it. We refer to page. 64 for a list of definitions related to the concept list.

Table 3. Literature update on AI systems in medicine, healthcare and wellbeing and their ethical and societal impact by alphabetic order of topics.

Topic	Name	References
1	Algorithmic impact assessment	[36]
2	Accountability	[37]
3	Autonomous weapons	[38] [39] [40] [41] [42] [43]
4	Big Data of the human body	[44] [45] [46]
5	Bioeconomy, geostrategy	[47] [48] [49] [50] [51] [52] [53]
6	Biometric databases after the Afghanistan war	[54] [55] [56] [57] [58] [59] [60]
7	Biometrics for (self and remote) monitoring	See 'Wearables'
8	Bioterrorism. Post-COVID-19 institutional awareness.	[61] [62] [63] [64] [65] [66] [67] [68] [69] [70]
9	Bioterrorism. Dual use of drug discovery to develop bioweapons, non-conventional threats.	[71] [72] [73] [74] [75] [76] [77] [78] [79] [80] [81]
10	Brain implants	See 'Neurotechnology for human cognitive, physical augmentation'
11	Brain learning, simulation	[82] [83]
12	Brain preservation and the quest for 'immortality'	[84] [85] [86] [87]
13	Cancer	[88] [89] [90] [91] [92]
14	Cardiac health	[93] [94] [95]
15	Clinical examples (others)	[96]
16	Challenges (overview)	[5] [6] [7] [8] [97] [99] [100] [101] [102] [103] [104] [105]
17	Citizen participation	[106]
18	Cloning pets and parasites.	[107]
19	COVID-19 detection, diagnosis	[108] [109] [110] [111] [112] [113] [114] [115] [116] [117] [118] [119] [120] [121]
20	COVID-19 epidemiology, tracking	[122] [123]
21	Cognitive augmentation	See 'Neurotechnology for human cognitive, physical augmentation'
22	Cosmetics and self-perception	[124] [125] [126]
23	Data Access. Open Access	[127]
24	Data quality	[128] [129][130]
25	Digital twin	[131][132]
26	Drug design, drug discovery	[133][134][73] [135][136][137] [138][139][140] [141] [142]
27	Education	[143][144]
28	Equity, fairness	[131][145] [146]
29	Ethics, ethical risks, concerns	[147][148][149] [150][151][152] [153][154][155] [156]
30	Explainability	[157][158]
31	Evaluation of human performance	[159]
32	Face recognition	[160][161] [162][163] [164]
33	Female, reproductive data monitoring	[165][166] [167][168] [169][170] [171][172] [173]
34	Gene decoding	[174][175][176]
35	Gene editing in humans	[177][178][179] [180][181] [182][183] [184][185] [186][187][188] [189][190] [191][192] [193][194] [195][196] [197] [198][199]

		[200][201] [202][203] [204][205] [206][207] [208] [209]
36	Gene editing for human augmentation	See 'Gene editing in humans'
37	Gene editing. Risks of unknown effects	[210][211]
38	Genetic data collection and gene editing for potentially malicious use and agroterrorism	[212][213]
39	Genetic data collection and gene editing for potentially malicious use and bioterrorism	[214][215] [216][217]
40	Health coaching	See 'Training', 'Wearables', 'Home, ambient intelligence'
41	Health in the metaverse	[218]
42	Health monitoring at borders	[219][220][221] [222]
43	Health monitoring	[223] See also 'Wearables', 'Home, ambient intelligence'
44	Home, ambient intelligence	[224] See also 'Wearables'
45	Human augmentation	[225][226] [227][22
46	Information, disinformation, misinformation	[229]
47	Interaction with humans	[230]
48	Institutional perspective - academia	[231][232][233]
49	Institutional perspective - politics	See 'Institutional perspective – law-enforcement, defense'
50	Institutional perspective – health	[234][235] [236]
51	Institutional perspective – law-enforcement, defense	[237][238][239][240][241][242] [243][244][245] [246][247][248] [249][250][251] [252]
52	Lack of tests	[253][254] [255]
53	Learning	See 'Training'
54	Lethal autonomous weapons systems	[256]
55	Living machines	[21][22] [23] See also 'xenobots'
56	Massive data collection for social manipulation	[257]
57	Massive data collection for social surveillance, scoring of citizens, COVID-19	[258][259] [260][261] [262][263] [264][265] [266][267] [268]
58	Massive data collection for law enforcement	[269][270][271] [272][273][274]
59	Mental health	[275][276][277] [278][279][280] [281][282][283] [284]
60	Mental health in the COVID-19 pandemic	[285][286]
61	Mental health. Self-perception, society, gender	[287][288][289] [290][291][292] [293]
62	Neurodiversity	[294][295][296] [297][298][299] [300][301][302] [303][304][305]
63	Neuroethics, social impact	[306][307][308] [309][310][311]
64	Neurotechnology, brain implants. Concepts	[312][313][314] [315][316][317] [318][319]
65	Neurotechnology for brain control	[320]
66	Neurotechnology for brain signal reading	[321][322]
67	Neurotechnology for human cognitive, physical augmentation	[323][324][325] [326][327][328] [329]
68	Neurotechnology for control of robots	[330][331]
69	Neurotechnology for control of weapons, military applications	[332][333][334]
70	Neurotechnology for control of prostheses	[335]
71	Neurotechnology for edition of brain content	[336][337]
72	Neurotechnology for treatment of mental, psychological disorders	[338][339][340]
73	New life forms	[341][342][343] [344]
74	Oncology	See 'Cancer'
75	Organ growing	See 'xenobots'
76	Pathology	[345][346]
77	Perception (of systems)	[347][348][349] [350][351]
78	Personalized Medicine / tailored treatments	[352][353]
79	Psychological health. Religion an cults	[354]

80	Radiology, radiomics, medical image analysis	[355][95][356] [357][358][359] [360][361][362] [363][364][365] [366][367]
81	Robotics	[368]
82	Robotic assistants	[369][370][371]
83	Robotic surgery, treatments	[372][373][374] [375]
84	Robotic 'health professionals'	[376][377][378] [379][380]
85	Robotic 'sex partners'	[381]
86	Robots and human cruelty	[382]
87	'Sentient' systems?	[383][384]
88	Surgery assistance	[385]
89	Synthetic biology	[386] [80]
90	Training	[329]. See also 'Neurotechnology for human cognitive, physical augmentation'.
91	Transparency	[387]
92	Trust and over-reliance	[388][389][390] [391][392][393] [394][395][396]
93	Ukraine war. Face recognition and body identification	[398][399]
94	Ukraine war. Electronic warfare. Weapons lab	[400][401]
95	Ukraine war. Control and manipulation of information	[402][403] [404][405]
96	Wearables - glasses	[406][407][408] [409]
97	Wearables - vision	[410]
98	Wearables – other sensors	[411]
99	Well-being, wellness	[412][413][414] [415][416]
100	Xenobots	See 'Living machines'.

Source: Own elaboration.

We observe that the list of selected topics can be grouped in different clusters or themes. These include: use of AI in areas of medicine such as cancer, cardiology, mental health, pathology, surgery or radiology; general ethical considerations of AI such as algorithmic impact assessment, accountability, equity, fairness, or explainability; areas with high social impact such as autonomous weapons, bioterrorism, or human gene editing; topics relating AI to related technological development such as the metaverse, neurotechnology or robotics; geo-political aspects such as geostrategy, institutional perspectives; and topics linked to our two target historical events, COVID-19 pandemics and Ukraine war. We present in the following sections the main conclusions driven from the table of topics and related references.

3.2 Technological and ethical considerations

As predicted in [5] [6] [7] [8] and [9] , AI systems and tools continue to expand into virtually all areas of medicine, healthcare, and wellbeing, with an expanding impact of the 'bioeconomy' related to health data and their analyses. However, since the COVID-19 pandemic outbreak, most scientific and clinical efforts by the international community have been concentrated -particularly in 2020 and 2021- to address its devasting health, societal, economic, and political consequences. Therefore, research, development, innovation, and technology deployment of AI-mediated tools in the topics of this analysis are predominantly centered in COVID-19-related areas. In addition, since the war in Ukraine began in February 2022, certain new applications have emerged.

From a conceptual perspective, there also remains a set of unsolved challenges about the social perception of AI technologies related to medicine, healthcare, and wellbeing. They were already highlighted in [5] and mention in Section 3.3:

- Trust and over-reliance on technology, including the willingness to accept, the betrayal aversion, and the question of whether there should always be a human-in-the-loop,
- Bias and unfairness: the need of unbiased balanced data for training algorithms, and the lack of metrics for the evaluation of performance

— Explicability, transparency, and responsibility. What happens when algorithms work precisely (i.e., they provide accurate results) but cannot be explained to (or understood by) a human being?

— Data safety, privacy, ownership, inheritance, and related issues.

3.3 Lessons of the COVID-19 pandemic

Early lessons of the COVID-19 pandemic in AI in medicine, healthcare and wellbeing were initially pointed out in the 2020 JRC Report [5] and later expanded in a specific analysis on the topic [6] . Some studies have been recently published on the overall analysis of AI systems in the COVID-19 pandemic by leading institutions [417] [418] [419] , including the Council of Europe [420] . From the updated state-of-the-art in this document, main lessons on these topics can be outlined as follows:

Telemedicine has settled

This point was clearly established shortly after the pandemic began. In the 2020 JRC Report accounting of early effects of the COVID-19 pandemic, it was headlined as "The boost of telemedicine" [6] . This initial trend has effectively settled as determined by the evolution of the disease [421] [422] , with forced confinement of the population and strongly limited in-person access to healthcare resources and professionals, particularly, for non-COVID-19 related issues. As in other aspects of human social interactions during the pandemic, the extensive acceptance and availability of advanced communication tools (e.g., video call platforms and applications) -even in resource constrained settings- have fostered adoption of telemedicine at all societal levels [423] , including population groups which may have been considered initially reluctant. However, after the COVID-19 experience, challenges remain [424] [425] .

Online platforms for psychological support arrived to stay

This issue was pointed out in the 2020 JRC Report [5] on the early assessment of consequences of the COVID-19 pandemic, as initial references pointed to the increasing use of AI-based tools for emotional support in the context of the severe social isolation measures being implemented. Chatbots [426] have played a significant role, being even credited with contributing to save lives in some studies. In a 2021 JRC Report [7] , the risk of malicious misuse leading to 'psychological hacking' was identified, particularly linked to people with psychological vulnerabilities and mental health issues. Currently, the adoption of online platforms for mental health support is gradually growing, although many challenges and unknown questions remain. A detailed use case on this topic is provided in Section 4.

Assistant robots, from reticence to adoption

This point was also established in 2020 as "Robotics: from fear to new roles and acceptance" [6] . They have proven successful as 'operational support' for human (e.g., for disinfection and work in contaminated areas), and for 'companion and social assistance' (for isolated persons and certain home tasks). New uses even point to robotic 'sex partners'.

The success of AI-mediated drug discovery and genetic data analysis

The surprisingly rapid development of COVID-19 vaccines has highlighted the power of AI tools for the modeling, design, and simulation of the complex interactions of drugs with the human organisms, ultimately leading to the successful development of the much-needed vaccines [427] . In certain types of data analyses, AI tools have allowed for time reduction rates from a month to less than a day [428] . As a direct consequence, barely six months after the outbreak of the (completely unknown) virus (SARS-CoV-2), early prototypes of 'candidate vaccines' were being tested. In addition, AI tools have also provided an invaluable help in speeding up diagnostic processes through genetic analysis, mostly by supporting polymerase chain reaction (PCR) and other molecular tests [420] . However, recent publications show how algorithms devised to look for innovative drug molecules using gene editing can be easily turned to design biological weapons. A detailed use case on this topic is provided in section 4. Drug development and data analysis define two areas of AI application of particularly significant consequences, emphasize the importance of the novel concepts of 'bioeconomy' and 'health geostrategies' and reflect their increasing role in the world economy and politics.

AI-mediated data analysis supports epidemiology but brings social risks

This point was pointed out in the 2020 JRC Report [6] as "A difficult balance: individual rights vs public health". Notably, it also relates to an early lesson of the current war in Ukraine (section 3.4) and it is further analyzed in section 4 and highlighted in [420] . Unfortunately, the concerns about the potential misuse of the health data -and related information -e.g., contact tracing'- go beyond from the much-required public health management to 'social scoring' and surveillance of citizens, and they have become a worrying reality in some countries. As mass data collection (e.g., for molecular tests of COVID-19) is conducted, there may not be a clear oversight and control of the final destination of the information, including genetic sequences of individuals- which may be compiled for developing AI platforms (as mentioned in [429] for China). Potential malicious misuse may even lead to the design of feature-specific, targeted pathogens and biological weapons (see section 4), with added fears of being tailored against certain population (e.g., ethnical) groups. This latter, strongly alarming possibility was also anticipated in the aforementioned 2020 JRC Report [5] and mentioned at the House Intelligence Committee of the USA [217] . The debate about privacy and the 'common good' has not reached a consensus answer, and these subjects remain as 'hot topics' of social concern and contest.

THE BOOST OF AI-MEDIATED PERSONAL DEVICES FOR HEALTH MONITORING

This point is partially related to -and evolves from- the previously discussed adoption of telemedicine. In the pandemic, under confinement, with strict restrictions for inter-personal interaction -significantly limiting the access to non-COVID-19 related healthcare, many people realized that personalized, automated monitoring systems could help them to keep trace of their own health, even reducing the 'difficult' -and, in many cases, costly- issue of visiting the doctor's office. The main difference from telemedicine adoption lays in the availability of AI-mediated systems which analyze biological parameters and generate 'recommendations' about how actual measurements refer to average bands of values, even triggering medical alarms. In addition, personal monitoring devices have rapidly advanced reducing invasiveness and increasing comfort for the user from fitness-related gadgets to stick-on and wearable sensors, and in the type and sensitivity of measurements, routinely including metabolic and cardiac parameters. An important aspect for device manufacturers is the regulatory change entailed in the evolution from the measurement of parameters to monitor sports performance to the purpose of medical diagnosis. Challenges remain about the training cases for algorithms and on the evaluation of their performance in different social (e.g., ethnic, age, gender) groups of population.

THE FAILURE OF DIAGNOSTIC AI-MEDIATED TOOLS

This is phrased as a striking conclusion, as it refers to the 'core' of medicine, i.e., the diagnosis of disease, and the harsh summary is that those tools developed 'to help fight the COVID-19' were not fit for -the much needed- clinical use. A 2021 meta-analysis review [419] , headlined that "Hundreds of AI tools have been built to catch COVID-19. None of them helped", with a further worrying statement: "*Many hundreds of predictive [AI] tools were developed. None of them made a real difference, and some were potentially harmful*". The causes of these negative results can be linked to the extreme time pressure on scientists to help combat the pandemic, but key reasons for failure had already been pointed out in the previous JRC Reports in 2020 [5] [6] under the headline of "Benefits and risks of data-driven algorithms", in which poor-quality (biased, insufficient, wrongly labeled) datasets for training algorithms, and the lack of standardized procedures for testing performance, were identified as major pending challenges for reliable AI systems in medical applications. Another 2022 review [417] [418] points out that, beyond *"some scattered successes … In general, … in diagnosing COVID-19, predicting its course through a population, and managing the care of those with symptoms, AI-based decision tools failed to deliver*". In addition to previously mentioned questions, human failures -in the selection of applications and in the interpretation of their results-, and a complex global context -on data sharing and governance- add to the faulty results. And those major challenges still remain.

SOCIETY DEMANDS TRUSTWORTHY INFORMATION

This point was pointed out in 2021 [6] as "Psychographics and the control of information", and it is further analyzed in section 4. In the context of the COVID-19 pandemic, two simultaneous -yet opposite- applications of AI tools for 'information flows' can be identified: on one side, the 'positive use' of such tools for 'knowledge sharing', as reported by the Council of Europe [420] . These systems allowed for fast, in-deep screening of thousands of research paper and communications on the effects, treatments, dynamics, and many other aspects of the pandemic, effectively enhancing efforts to fight the disease by the scientific community. But, on the other side, the 'negative use' of AI-mediated tools for the spread of 'excessive, false, and misleading information' about the disease, vaccines, and treatments. The malicious use of information in the COVID-19 pandemic has been so relevant that a specific term has been coined to designate the 'information epidemic' as 'infodemic'. Its impact relates directly to the degree of connectivity and on the availability of data sharing in a given environment, and, in the European region, this has been an area of interest. As documented, the COVID-19 infodemic has effectively damaged the health of citizens by inciting to breach the recommendations from authorities, and, particularly, to refuse vaccination and public health measures, with even deadly effects. It is also linked to negative emotional well-being and to the generation of social unrest and disturbances.

SOME ASPECTS COMMON TO OTHER AREAS

There are additional fields in which the evolution of AI-mediated technologies in medicine and healthcare in the context of the COVID-19 pandemics has evolved similarly as in in other domains of science and industry. They comprise the enhanced adoption for logistics and operation, particularly useful for health-related facilities under the very difficult circumstances of resource shortages, disruptions in supply chains and the pressure to operate at an overcharged rate with reduced personnel -e.g., who become sick or cannot travel to work).

3.4 Early lessons from the war in Ukraine

In February 2022, Russian troops invaded Ukraine, effectively beginning the current 'war in Ukraine'. As detailed in section 1.3, this is the largest armed conflict in European territory since the Second World War, and by the time of carrying out this analysis, it still presents an uncertain evolution. The nefarious consequences of war obviously impact the core topics of this report, i.e., the Health and Wellbeing of the population and the practice of Medicine. In addition, new challenges arise related to AI-mediated technologies in this conflict, mainly related to 'Digital Health' and 'eHealth[1]. From the current state-of-the-art and 'state-of-the-conflict' certain early lessons may be extracted for the future:

THE POTENTIAL OF EHEALTH FOR HELP

Medical and health services in conflict areas are severely stressed [430] and, in many cases, destroyed, with the additional burden of increasing shortages of qualified personnel, and the consequential damage to the civil population. Fostered by advances in communications technology -which allows for internet access in war zones [431] - eHealth services offer a potential for relatively easy deployment providing help in many clinical areas [432] , but there remain "*questions on safety and quality, data privacy and clinical efficacy*" and "*there is a need for further clarification of global norms relating to practice in this context*" [433] . Some areas of particular interest related to AI-mediated resources include mentoring and training services for low-skilled personnel at improvised facilities, remote (e.g., image based) tools for diagnosis, triage and surgical guidance, logistics support, and online platforms for mental health care. The latter is a newly defined area in a war context, as psychological and psychiatric effects are not usually attended in conflict zones since priorities refer to emergency relief with very limited resources. However, NGO teams on the ground alert on the much-needed help on these aspects, particularly for the civil population [434] . As detailed in section 4, AI-mediated tools could provide at least part of the required assistance. Advances in natural language processing can help overcome language barriers, and online platforms may be continuously available through remote access to the internet. Another area of active development refers to robotized medical equipment and, particularly, 'robotic surgeons'. Combined with augmented reality tools, they may contribute to providing high-level medical attention in field hospitals and zones with very limited availability of highly skilled personnel [435] .

THE ENHANCED NEED TO SAFEGUARD HEALTH DATA

The advent of digital resources has promoted a clear shift to 'all digital' medicine and healthcare, and as pointed out in a previous JRC report [5] , the domain of medical information (i.e., clinical records, analytics, and diagnostic images) has expanded to include genetic data. Notably, in 2020 (before the war began) Ukraine was recognized in the EU environment as an example of a definite transition to 'zero paper' and electronic health records started in 2018 [436] .

Recently, in the framework of the fight against the COVID-19 pandemic, molecular testing of the population has standardized, and many new data bases -both in public and in private facilities- have been generated. They contain increasingly detailed records of individuals, including full genome sequences, and the social implications of 'non-strictly medical' use to these types of data constitute a lesson from the COVID-19 pandemic (section 3.3).

1 AI-mediated weapons and drones are out of the scope of this report.

Beyond the requisites of privacy and security of medical data imposed by the current European and international regulations, new issues arise about AI-mediated uses of health data in the context of an armed conflict.

Prepare for a 'rebuild from nothing' scenario.

When the war in Ukraine began, the Government announced an operation to backup institutional data for a hypothetical 'rebuild from nothing' scenario [437] . The information published specifies that the process has been developed "… *to secure vital data so the Ukrainian government, education, and banking institutions can continue …*" and, from a technical perspective, it is being implemented through massive migrations to web clouds and other resources. Although there no explicit references to health data or medical records, they are likely included.

For populations displaced and for those living in damaged environments, the availability of identity, education and health data will clearly be extremely helpful in the difficult road to restoring or adapting their lives. However, this type of 'massive copy' of very sensitive information may require -as in the case of Ukraine- legislative updates, for example to allow such data storage in another country.

Secure access to health-related data in a war scenario.

There are two categories of data which require special protection under a war scenario:

— Identification and biometric data of the population and, particularly, of healthcare workers, as they can be employed to specifically target those individuals. Despite being violations of the international humanitarian laws for war, these attacks on healthcare professionals continue in war zones [438] , deeply increasing the damage to and the suffering of the civilian population.

— Genetic data (sequences) of individuals. As indicated, this risk and its potential misuses is described in the context of the COVID-19 pandemic (section 3.3).

A recent example of the consequences of an uncontrolled access to (at least) the former category of databases has taken place in the aftermath of the abrupt departure of the USA and other coalition allies from Afghanistan, in August 2021. According to [55] , in the confusion of the withdrawal, they left behind equipment employed for biometric identification (including iris scans) of local workers supporting the regime which are now under the control of the new Taliban Government. These devices comprised mobile scanning units connected to (or with built-in) databases with detailed personal, demographic and even social information, with the obvious risks of being used to track and target certain individuals, e.g., supposed opponents [439] .

New uses of facial recognition in conflict zones

The war in Ukraine has also demonstrated a new field of application of these powerful, AI-mediated tools: the identification of dead persons, even when faces are damaged.

This technique is documented to be used by the Ukraine Government [440] with a twofold purpose, i.e., to document civilian casualties in their own population for future prosecution of authors -under the suspicion of war crimes- and to identify enemy soldiers and directly transmit that information (e.g., through social networks) to their relatives [441] . The latter use presents a (questionable) 'new approach' to psychological and information warfare, as data about loss in the battlefields may not being disclosed, even to the families of the deceased.

3.5 Other areas of development

Personalized medicine

This topic was thoroughly studied in the 2020 JRC Report [5] , and, beyond some technical advances, that analysis remains valid. Pending questions refer to conceptual difficulties in the change from population-level to patient-level models, the enhanced understanding of genomics, metabolomics, proteomics, epigenomics, microbiomics and other (data-driven) -omics, the need of standardized datasets for validation of models, and the potential sources of significant societal inequalities due to the cost barriers to access treatments.

Trust, explainability

This topic was also thoroughly discussed in the 2020 JRC Report [5] , and the challenges identified still persist. In addition, most relevant issues refer to:

- Open access, fair, balanced, standardized datasets for training and test. Data from one institution (i.e., linked to equipment, population, gender, geographic, demographic features) needs to be assess in terms of potential suitability for use elsewhere.
- Integration of many types of multimodal data (health records, imaging, signals from wearables and ambient sensor, genomics). Structured information gathering should be promoted with clear, effective tools for debugging and updating, aligned with the European Data Infrastructure.
- Reliable ground truth data sets. Problems arise related to the definition and labeling of 'gold-standards' by human or AI systems. Synthetic data helps but it is not a 'sustainable' solution. This is related to the additional lack of reproducible analytics and test tools.
- The need to define workflow protocol and clinical test scenarios.
- Patient privacy and data ownership concerns about data use agreements, de-identification, inheritance, and the conflict between individual rights and the common good.
- Integration of data sets and AI tools towards the One Health, considering aspects related to human, animal and environmental aspects and impact of technologies.

3.6 Significant institutional apprises

WHO Guidance on AI for Health (June 2021)

In June 2021, the World Health Organization (WHO) announced the publication of a Guidance specifically devoted to the ethical (and, indirectly), social aspects of AI technologies related to health [99] . As stated in its presentation, it is the result of almost two years of work by a specialized team, with 336 references, and it is obviously related to the contents of this report. In their overview, it is written that "*The report identifies the ethical challenges and risks with the use of artificial intelligence of health, six consensus principles to ensure AI works to the public benefit of all countries. It also contains a set of recommendations that can ensure the governance of artificial intelligence for health maximizes the promise of the technology and holds all stakeholders – in the public and private sector – accountable and responsive to the healthcare workers who will rely on these technologies and the communities and individuals whose health will be affected by its use*".

The document, of 186 pages, is structured in the following main 9 chapters: *1. Introduction. 2. Artificial Intelligence. 3. Applications of Artificial Intelligence for Health. 4. Laws, policies and principles that apply to use of artificial intelligence for health. 5. Key ethical principles for use of artificial intelligence for health. 6. Ethical challenges to use of artificial intelligence for health care. 7. Building an ethical approach to use of artificial intelligence for health. 8. Liability regimes for artificial intelligence for health. 9. Elements of a framework for governance of artificial intelligence for health.*

Council of Europe on Neurotechnologies and Human Rights (June 2022)

The Council of Europe has carried out detailed analyses and discussions about neuro-technologies and their potential impact on human rights [442] : *'Technological innovation often creates its own dynamic. Major technological breakthroughs in fields such as artificial intelligence, genome editing, and neuro-technology have the potential to advance biomedicine and healthcare. However, uncertainty exists about the impact and direction of these developments.'*

With the objective of 'embedding human rights in the development of technologies which have an application in the field of biomedicine', this institutions has proposed an Strategic Action Plan on Human Rights and Technologies in Biomedicine (2020-2025) [443]

European Parliament on Genome Editing on Humans (June 2022)

In June 2022, the European Parliament launched a detailed study including 'a survey of law, regulation and governance principles') on 'gene editing on humans' [444] .

WHO Policy Brief on Digital solutions to health risks raised by the COVID-19 (June 2022)

In June 2022, the World Health Organization (WHO) announced the publication of a Policy Brief specifically devoted to the health risks raised by the spread of 'excessive, false and misleading information' (i.e., by the so-termed 'information epidemic', or 'infodemic') about the COVID-19, centered in the European region [445] . As stated in its presentation, the European Regional WHO Office "*highlights the six policy considerations described here below: 1. Reinforcing multi-stakeholder networks for infodemic management. 2. Strengthening overall risk communication and community engagement. 3. Implementing continuous monitoring of online* *harmful and false content. 4. Improving digital literacy approaches and organizing infodemic management trainings. 5. Advocating for infodemic management through communication campaigns. 6. Ensuring safe online platforms, which protect people from harmful content. … with a shared objective of improving the Region's public health response to the COVID-19 infodemic and enhancing preparedness for future health emergencies*".

This document indicates that "*The exposure to false information – both online and offline – has been linked to increased health risks, having harmful or even deadly effects. Examples of negative behaviours include use of wrong or harmful treatments, lower uptake of protective measures including vaccinations, impaired mental health and emotional well-being, and lower trust in health-care providers*".

In addition, it also identifies a set of *"digital interventions designed to tackle infodemics: • "implementing fact-checking and false information reporting mechanisms • adopting social listening tools augmented by artificial intelligence, which can help analyse the large-scale fast-flowing data, assess risks and identify infodemic signals • creating monitoring programs, multi-stakeholders' coordination initiatives and national regulatory frameworks which respect the principles of freedom of expression • promoting digital health literacy and inoculation interventions that improve people's ability to spot misinformation*".

Creation of the new European Health Emergency Response Authority (HERA, July 2022)

As announced in 2021 (see section 1). Notably, the United States announced as well the creation of a new agency (Advanced Research Projects Agency for Health, ARPA-H) with a similar orientation in some aspects [446] .

Relationship to JRC research on these topics.

The previous documents by the World Health Organization, the Council of Europe, and the European Parliament present -as expected- some elements that are common to those included in the five previous documents published by the JRC as Science for Policy Reports and Science for Policy Brief [5] [6] [7] [8] [9] . In addition contents of the 2020 JRC Report [5] have been recently cited in discussions in the European Parliament [447] and, notably, this work is considered as a key reference in the sector by leading entities [448] .

4 Socially-relevant Use-Cases

AI technologies and AI-mediated tools present an extraordinary -and rapidly expanding- potential of impact in all areas of Medicine, Healthcare and Wellbeing. However, their features can be oriented, on one ('good') side, towards the benefit of persons, their physical and mental health and societal wellbeing, or, on another ('bad') side, towards malicious purposes, with the aim of damaging persons and society, also including future generations.

As highlighted in section 1, this report covers a period which includes two historical circumstances with significant impact in all aspects of life and society, i.e., the COVID-19 pandemic and the war in Ukraine. These two events, still under development, have a clear influence in the subjects of this analyses and have determined the identification of five core Use-Cases that we consider relevant from a societal perspective.

They are identified as the following five main fields (key expanding areas):

1. AI tools for mental health,
2. AI-mediated gene editing,
3. AI tools for epidemiology and health data monitoring,
4. AI-mediated neuro-technologies, and
5. AI-mediated inclusion of neurodiversity.

Other areas of significant technical advances comprise AI-mediated drug discovery and personalized medicine. In this section, we further develop these use cases using the methodology, social assessment scales and ethical considerations describes in section 2.

4.1 AI tools for mental health

The technology to be explored in this Use-Case refers to **AI-based online platforms for mental health care**.

SOCIAL IMPACT. CHALLENGES AND BENEFITS

Mental health identifies a subject of very serious concern -but relatively reduced public awareness- for the European society and worldwide. As discussed in the context of the consequences of the COVID-19 (section 3.3), the pandemic has fostered the adoption of AI-mediated tools. With clearly positive and negative aspects and a strong potential for help in the fight against a major health and social problem, this use of AI technology calls for further analysis.

Statistical data show the dramatic toll of mental health **in Europe**:

- According to [449] , before the pandemic and the war in Ukraine, "*3.7% of all deaths resulted from mental and behavioral disorders … and about 13.5 % of all hospital beds were psychiatric care beds*".
- Approximately 120.000 persons take their own lives per year, corresponding to 12.8 deaths per 100000 population, i.e., 1.3% of all deaths [450] (with some higher values, e.g., in 2016 there were over 165.000 suicides in the EU-27 [451]).
- After the pandemic, a 2021 flagship report by UNICEF about mental health in children [452] -not including the effects of the war in Ukraine- states that:

> *"As the coronavirus pandemic descended … powerful emotions enveloped the lives of many millions of children, young people and families … it will be years before we can really assess the impact of COVID-19 on our mental health … Indeed, the risk is that the aftershocks of this pandemic … will pose a risk to the foundations of mental health. Mental health is also a reflection of the ways their lives are influenced by the poverty, conflict, disease, and access to opportunities that exist in their worlds".*

That 2021 UNICEF report reveals that in Europe: 9 million adolescents aged 10–19 live with a mental disorder; suicide is the second most common cause of death among adolescents aged 15–19; and almost

1,200 children and adolescents aged 10–19 end their own lives every year (i.e., an estimated three lives per day lost to suicide).

While the effects of the COVID-19 pandemic on mental health are still under active research -and those derived from the war in Ukraine have not been considered at all- data from the USA indicate that about 40% of all adults have struggled with mental health and substance abuse [453] in the 2020-2021 period, and that one third of high-school students have experienced mental health issues, with one fifth having seriously considered suicide [454] It is expected that certain effects of the pandemic (including suicide rate trends) may increase in the long term when the contribution of emergency support and resources ends [455] and when the consequences of the war in Ukraine are considered.

As already indicated in previous JRC Reports [5] [6] - one of the main social effects of the disease was the enhanced adoption of online chatbots [426] and robotic platforms as conversational and social tools to overcome the difficulties of loneliness and isolation due to the 'new circumstances' (i.e., population confinement, quarantine, restricted interactions among people).

Rapidly, the number and features of such technologies has expanded. Commercially available options now range from online 'telemedicine' and 'telehealth' resources for access to and interaction with 'human professionals' [456] [457] to increasingly automated conversational chatbots to systems offering 'professional mental health support' and 'mental self-care' over the internet.

A clearly positive aspect of AI-mediated tools for telemedicine is the increased facility of contact between patients and professionals, particularly under restrictive circumstances that prevent direct, in-person interaction. In addition, as shown by early lessons from the war in Ukraine (section 3.4) AI-mediated tools have a clear potential to help persons in conflict zones. However, other challenging aspects remain, as the loss of empathy in the relation patient-professional, and the difficulties for access for non-technological savvy people, particularly in the elderly population [458] . This is obviously not a problem for children and adolescents in Europe, 'digital natives' for which the interaction with AI-mediated devices is fully integrated in virtually all aspects of daily life.

Nevertheless, a key difference arises when it refers to AI-mediated 'diagnosis', 'therapy', 'follow up' or 'support' -in the mental health realm with respect to other areas of medicine and healthcare- as AI systems interact directly with the person (patient), very possibly without any human monitoring or overview (i.e., openly substituting the interaction with the professional).

As an artificial platform 'talks' with the user, a variety of simultaneous processes may take place: an automated assessment of the status of the person could be performed -yet combined with other sources of digital information (e.g., from social networks)- to detect behavioral features and identify risks such as suicidal or violent ideations and trigger alarms -even to first responders-. But emotional links have also been recently described to arise and new risks of malicious activities happen, from 'digital health scammers' to the intended transmission of directions -even 'orders'- to persons, as identified in previous JRC Reports [5] [6] [7] , in which the term 'psychological hacking' ('psycho-hacking') was coined to designate the latter.

TECHNOLOGY ASSESSMENT

The application of AI-mediated technology defined as Use-Case 1: AI-based online platforms for mental health care can be evaluated as detailed in **Table 4.** Technology assessment of 'Use-Case 1: AI tools for mental health'. Values in arbitrary units..

From a social and ethical perspective, the assessment is twofold: on one side, it can be considered as clearly positive, as it allows for new, powerful tools for diagnostic and therapy, easing access to 'care' and even 'companion' platforms. On the other side, it can also be considered as clearly negative, since it opens new, uncontrolled risks for vulnerable groups of population.

In summary, it is considered an example of a Use Case to be carefully assessed to protect persons and enhance health while promoting social wellbeing.

Table 4. Technology assessment of 'Use-Case 1: AI tools for mental health'. Values in arbitrary units.

Feature	**Scale**	**Value**
Maturity	Technology Readiness Level (TRL)	8
Availability	Technology Availability Level (TAL)	9
Controversy	Technology Controversy Level (TCL)	+1

Sustainability	Technology Sustainability Level (TSL) for SDG 3	1
	Technology Sustainability Level (TSL) for all SDGs	0.29
Extent of Adoption	Technology Extent Level (TEL)	6

4.2 AI-mediated gene editing

The technology to be explored in this Use-Case refers to AI-mediated tools for gene (or genome) editing. This is a rapidly evolving field with strong, unsolved ethical questions. Two major expanding -and challenging- sub-areas are identified in which the role of AI technologies make substantial contributions: *human augmentation*, and the development of *novel biological threats*.

Let us briefly recall that human cells can be classified in two groups: somatic cells (constituents of the body) and germ cells (or sex cells, that give raise to eggs and sperm). Changes in a gene of a somatic cell stay in the cells and its descendants, but are not transmitted to other cells, and die with the person. Changes in a germ cell are passed to all cells of a new person (baby), and if s/he reproduces, to future generations.

A major challenge in genetics refers to the exploration of the human genome and the identification of all constituent genes, their roles and the effects of mutations and alterations. The extraordinary difficulty of exploring the data corresponding to the human genome and the urgent need for artificial intelligence tools to help in the task can be seen in the vast volume of information to investigate, as detailed in Annex 1.

AI-mediated tools are commonly used to explore genetic information, even to design synthetic 'life forms' (e.g., viruses) for medical and biological applications. Computational tools can also be integrated with gene manipulation technologies -such as CRISPR- to effectively 'modify' existing organisms (e.g., to produce genetically modified crops) but also for building new types of (living) organisms. Advances in technology make some parts of this research possible with relatively common laboratory equipment and low computational power.

GENOMICS AND NOVEL BIOLOGICAL THREATS. ONE HEALTH, ANIMAL AGROCRIME AND AGROTERRORISM

Engineered pathogens (e.g., viruses) are used in different areas of medicine and biology, with legitimate and beneficial purposes (e.g., as vectors to deliver drugs to cells in certain types of therapies) taking advantage of the capability to select and exploit specific features of infectious agents (e.g., their ability to propagate and target specific gene features).

However, synthetic pathogens may also be tailored for malicious purposes, such as selectively damaging or destroying living beings (humans, animals, plants). This type of malicious applications have evolved from early concepts of state-developed, military biological weapons [459] [460] [461] [462] to the general realm of non-conventional threats (NCTs), under the title of 'biological threats' (biothreats) with an extraordinary potential for bioterrorism.

As highlighted in a 2020 JRC Report [5] , for the surprise -and shock- of the scientific and law-enforcement communities, in 2018 it was openly published (later banned from access) how to 'fabricate' a functional strain of horsepox, a pathogen very close to the eradicated human smallpox, using only a university-type of laboratory valued in about $100.000.

Recently, in 2022, it has been exposed how the same AI tools employed for drug discovery in the race for vaccines and treatments for COVID-19 could be oriented to design pathogens simply by switching the 'direction' of certain algorithms to maximize (instead of minimizing) lethality and other factors. The alarming possibilities which derive from the science and technology underlying these results comprise a wide variety of biological threats, from unintended cross-contamination and health risks related to borders [463] to agents for bioterrorism to bioweapons.

A serious issue of concern refers to potential attacks to genetically modified organisms (GMOs), such as certain types of plants. GMOs are characterized by very specific alterations (i.e., editing) of particular genes, which could, in turn, be targeted by pathogens precisely engineered to destroy those types of crops, with the corresponding damages in in food production chains and economical and societal consequences for the affected zones. These areas constitute the newly identified sectors of animal agrocrime and agroterrorism [464] [465] , with the worrying possibility of using animals (e.g., insects) to spread agents [466] . Another scenario derives from the potential targeting of specific human (e.g., ethnic) groups. Such application would lead to particularly harmful scenarios and societal damage. Obviously, these 'ideas' represent the opposite view from the intended goal of One Health [467] based on the interaction of human, animal and environmental care.

As discussed in the context of the consequences of uncontrolled access to health-related data in a war zone (section 3.4) this possibility has been recently pointed out in the House Intelligence Committee of the USA.

In addition, the commercial availability of 'genetic manipulation kits', for education, R&D and even for do-it-yourself approaches presents the risk of accidental leaks (of pathogens) by 'garage scientists' performing 'risky' tasks without the supervision and the security measures proper of professional use.

The COVID-19 pandemic has shown the devastating effect of the spread of a new, unknown virus. Notably, even during major peaks of the pandemic, European and international police, law-enforcement –EUROPOL [66] , INTERPOL [65] , UNICRI [67] , CTPN [68]– and military institutions –NATO [61] - have published reports and organized specific conferences and research initiatives to alert on the enhanced risk of biological threats related to the (accidental or deliberate) spread of (natural or engineered) pathogens. This challenge also relates to population displacements (e.g., caused by wars and by climate change), and to the need of enhanced health monitoring in borders.

On an opposite approach, AI-mediated tools also present a strong potential for combination with many physical, optical, chemical, and biological technologies for the detection of biological threats [468] , even for at-a-distance exploration of human and animal bodies to develop effective procedures for screening [469] . As detailed in section 3.6, the European Union and the United Nations have strongly alerted against these novel threats, and the EU has recently launched a new Health Emergency Response Authority (HERA) to lead this field.

IMPROVE HEALTH SCREENING AT BORDERS.

The uncontrolled spread of the COVID-19 pandemic has clearly shown the need to enhance health screening at borders for the protection of society. This challenge may be substantially aggravated when migrations involve millions of people under very limited health and sanitary conditions, possibly exacerbated by severe weather and the climate change. As indicated in section 3.6, this unmet challenge belongs to the recently updated priorities of the EU and international institutions.

HUMAN AUGMENTATION

Human gene editing is a subject of increasing social and ethical debate, particularly as referred to germline editing [470] , and about whether it should be allowed, funded, and researched. These issues are strongly linked to the development of AI tools as they constitute key enabling factors -particularly, as combined with the CRISPR technology- for efficient and precise gene editing and, therefore, for the progress in the field. Major, unsolved questions [5] , include difficult scientific matters:

- Which are the genes and the alterations in DNA sequences required to achieve
    - resistance to diseases
    - physical traits (e.g., hair or skin color)
    - enhanced (physical, mental) abilities
- Which are the risks for individuals undergoing edition? And for the (e.g., biological) environment? and
- Should 'self-experimentation medicine' be allowed?
- If edition is performed on germline cells, which are the effects on and the risks for future generations?
- Should research be allowed on 'non-viable embryos[2]' (e.g., those leftover from in-vitro fertilization treatments, or other created for research).

and deep ethical concerns linked to individual beliefs and social features [5]:

- Should gene editing be allowed only for adults, in somatic cells (i.e., without potential transmission to future generations?

2 Those who would not result in a live birth.

— What about the (supposedly) on-going research to obtain 'super-soldiers'?

— Should germline edition be researched to eliminate genetic disorders, particularly those that do not have any treatment option? This is the view of some groups of patients suffering from such conditions -and their families and advocates-, to prevent others from experiencing the disease, but there is no agreement as other people question that eliminating genetic disorders -some not considered as a disability- will improve life [471] .

— Should germline editing be allowed to obtain children with 'desired features'?

— Can gene editing constitute another factor substantial factor of inequity? Would it be available only for the wealthiest groups?

— If gene editing for human enhancement becomes extended, would it generate 'predominant' groups of 'enhanced humans' versus 'non-enhanced people'?

Until recently, these questions were part of science fiction plots. However, they are now coming closer to reality, thanks to advances in the required technologies and to the increasing role of artificial intelligence tools. Many countries -including European nations- have discouraged or banned germline editing [470] .

TECHNOLOGY ASSESSMENT

According to the topic content in references, this Use-Case (AI-mediated gene editing) can be evaluated as detailed in **Table 5**.

From a social and ethical perspective, the assessment is twofold: on one side, it can be considered as potentially positive, as it may allow for 'beneficial' human augmentation or the prevention of the inheritance of diseases. On the other side, it can also be considered as clearly negative, since it may open the door to strong social 'divides' (e.g., 'enhanced' vs 'non-enhanced' persons), and unexpected biological threats, even affecting future generations.

Overall, it is considered an example of a topic with risks to be urgently assessed to protect persons and social wellbeing.

Table 5. Technology assessment of 'Use-Case 2: AI-mediated gene editing'. Values in arbitrary units.

Feature	Scale	Value
Maturity	Technology Readiness Level (TRL)	5
Availability	Technology Availability Level (TAL)	6
Controversy	Technology Controversy Level (TCL)	2
Sustainability	Technology Sustainability Level (TSL) for SDG 3	1
	Technology Sustainability Level (TSL) for all SDGs	0.18
Extent of Adoption	Technology Extent Level (TEL)	4

4.3 AI tools for epidemiology and health data monitoring

The technology to be explored in this Use-Case refers to *AI-based mass gathering of data of the population under a pandemic*, and their analytics and use.

SOCIAL IMPACT. CHALLENGES AND BENEFITS.

These issues are discussed as one of the lessons of the COVID-19 pandemic (section 3.3), also linked to an early lesson from the war in Ukraine (section 3.4).

TECHNOLOGY ASSESSMENT

According to the topic content in references, Use-Case 3 (AI tools for epidemiology and health data monitoring) can be evaluated as detailed in **Table 6**.

From a social and ethical perspective, the assessment is twofold: on one side, it can be considered as potentially positive, as it allows for enhanced public health management, particularly under such circumstances as pandemics or infectious disease outbreaks.

On the other side, it can also be considered as clearly negative, since it may open the door to population 'scoring' and 'classification', potentially leading to surveillance and damage to civil and individual rights and liberty.

Overall, it is considered an example of a topic with risks to be urgently assessed to protect persons and social wellbeing.

Table 6. Technology assessment of 'Use-Case AI-mediated epidemiological monitoring of the population. Values in arbitrary units.

Feature	**Scale**	**Value**
Maturity	Technology Readiness Level (TRL)	1
Availability	Technology Availability Level (TAL)	2
Controversy	Technology Controversy Level (TCL)	3
Sustainability	Technology Sustainability Level (TSL) for SDG 3	1
	Technology Sustainability Level (TSL) for all SDGs	0.17
Extent of Adoption	Technology Extent Level (TEL)	2

4.4 AI-mediated neuro-technologies (for cognitive signals)

The technology to be explored in this Use-Case refers to *AI-based mediated reading, decoding, and manipulation of cognitive signals of the human brain*.

SOCIAL IMPACT. CHALLENGES AND BENEFITS.

The social and ethical perspective of this area of technology is clearly twofold: on one side, it can be considered as potentially positive, as it may allow for improved control of prosthesis and brain-computer and –machine (BCI, BMI) interfaces (e.g., for the severely disabled). On the other side, it can also be considered as clearly negative, as it may open the door for non-invasive intrusion in persons' minds (e.g., monitoring attention, cognitive surveillance) with unknown effects and applications. There is a strong debate in European and international institutions and stakeholders about the need and the limits of 'Neuroethics' guidelines and 'Neurorights'.

TECHNOLOGY ASSESSMENT

According to the topic content in references, this Use-Case 4 (AI-mediated neurotechnologies (for cognitive brain signals)) can be evaluated as detailed in **Table 7**.

Overall, it is considered an example of a topic with social risks to be urgently assessed to protect persons and social wellbeing.

Table 7. Technology assessment of 'Use-Case AI-mediated neurotechnologies (for cognitive brain signals)'. Values in arbitrary units.

Feature	**Scale**	**Value**
Maturity	Technology Readiness Level (TRL)	3
Availability	Technology Availability Level (TAL)	4
Controversy	Technology Controversy Level (TCL)	1
Sustainability	Technology Sustainability Level (TSL) for SDG 3	1
	Technology Sustainability Level (TSL) for all SDGs	0.24
Extent of Adoption	Technology Extent Level (TEL)	1

4.5 AI-mediated inclusion of neurodiversity

SOCIAL IMPACT. CHALLENGES AND BENEFITS.

AI-mediated inclusion of neurodiversity is a 'novel' topic of interest identified within the broad area of neurotechnologies. It refers to the use of AI-based technologies to allow for the inclusion of persons with neurodiversity in the job market, particularly in the sector of information and communication technologies.

This normalization also shifts their social perception and roles, from underestimation and miscommunication to valuing competitive advantages and business opportunities. This topic is different from the research and development of technology-mediated approaches for treatment of psychiatric and developmental disorders (e.g., using neurostimulation techniques).

An early analysis is presented for autism spectrum disorders (ASDs), as there has been a specific 3-year program [472] funded by the European Parliament, entitled 'Autism Spectrum Disorders' in Europe (ASDEU), devoted to "*to research autism prevalence, costs, diagnosis, and interventions throughout Europe. Its overall aim was to find ways to improve care and support for people with the condition and their families*". Their goals included "*Review autism policies in all European countries and come up with recommendations for an EU public health plan to support member states to respond to the needs of autistic people and their families*".

Autism spectrum disorders

People with ASDs usually present difficulties to interpersonal communication using 'common channels and codes' (speech, non-verbal language, social skills), -in varying degrees, together with significant, mostly unexplored, features for diverse thinking, such as being detail-oriented and pattern-thinkers.

Their many challenges for communication and 'cultural-fit' -currently even considered as 'incapacitants' by some social sectors- can be overcome with the help of available AI-mediated systems, from 'keyboard-type' to VR environments -and, perhaps, with other types of brain-computer interfaces-. AI-based tools can help uncover the potential of persons with ASDs for a variety of much-needed (and valued) tasks (e.g., software design, cybersecurity).

Results of the ASDEU research showed that "overall ASD prevalence estimates varied among European countries, from 4.4 - 19.7 per 1,000 aged 7-9 years", with an average of 12.2 per 1,000 (one in 89) children aged 7-9 years. In comparison, the incidence of autism in the United States is 1 in 34 among boys and 1 in 144 among girls [294] , with an average of 1 in 54 children aged 8 years.

The ASDEU study also showed a large health and economic burden, and included the following recommendations for policymakers:

- Encourage member states to adopt cross-sectoral national strategies or action plans to respond to the needs of autistic people, in line with the United Nations Convention on the Rights of Persons with Disabilities and international recommendations.
- Promote coordination between member states of all policies related to autism.
- Produce guidelines to harmonize practices and promote quality of support and care across Europe.
- Adopt principles of best practice and foster exchange between member states.
- Promote training of professionals across sectors.
- Support research, networks of experts and partnering for progress.

Notably, the executive summary of this project does not include any mention to the possibilities for inclusion provided by AI-mediated tools identified in this report. This can be explained as those possibilities have started to be explored very recently (after the end of the ADEUS program), as linked to the latest advances in neurotechnology.

AI-mediated technologies for persons with ASD is a novel concept and a clear example of multidisciplinary overlapping of AI, medicine, engineering, and social development, with definite ethical dimensions and very positive consequences.

The proposed approach of AI-mediated inclusion also presents a clear interest (not studied) for including persons with other types of cognitive or psychological disorders, and even mental health issues. The on-going development of new types of brain-computer interfaces would provide increasingly better technological tools to improve and expand the described inclusion.

Technology assessment

According to the topic content in references, the Use-Case 5 (AI-mediated inclusion of neurodiversity) can be evaluated as detailed in **Table 8**.

Table 8. Technology assessment of 'Use-Case 5: AI-mediated inclusion of neurodiversity'. Values in arbitrary units.

Feature	Scale	Value
Maturity	Technology Readiness Level (TRL)	1
Availability	Technology Availability Level (TAL)	2
Controversy	Technology Controversy Level (TCL)	-3
Sustainability	Technology Sustainability Level (TSL) for SDG 3	1
	Technology Sustainability Level (TSL) for all SDGs	0.3
Extent of Adoption	Technology Extent Level (TEL)	0

Overall, from a social and ethical perspective, the assessment of this Use-Case 5 is clearly positive, and an example of a topic to be fostered and supported for the benefit of persons and social wellbeing, including future generations.

5 Conclusions

5.1 Discussion

Artificial Intelligence, scientific medical research, human rights and policy are closely interrelated, particularly in the realms of Medicine, Healthcare and Wellbeing. In the rapidly evolving world of today, under the recent historical circumstances, there is a need for an effective approach in the EU and worldwide to new challenges, leading the advancement of science and technology while protecting society and democracy, and paving the way for sustainable progress for the future generations.

We discuss here some challenges aiming to highlight the key expanding areas related to the analyzed topics and translate their scientific and technical narrative into practical approaches for the benefit of the persons. As indicated, this reports expands on previous work. Although there has been significant progress in the challenges proposed in that document, they remain valid as well, and are hereby also referred to for consultation.

Promote One Health and prevent AI-mediated biological threats to society

Biological threats define a major source of concern for European and international institutions. The COVID-19 pandemic has shown the devastating consequences for health, society, and economy of the uncontrolled propagation of an unknown virus (the SARS-CoV-2), for which there was no vaccine or treatment. As demonstrated by its rapid worldwide spread, pathogens may easily propagate among humans across geographical regions, as there are no effective detection procedures suitable for non-invasive, traveler-respectful implementation of health screening of persons at border controls. Population migrations and settings under limited health and sanitary conditions, exacerbated by extreme weather phenomena and climate change, present additional risks for the emergence of human and zoonotic viruses, bacteria, and other infectious organisms. In striking contrast, in the EU and in most other countries, there are remarkably effective procedures and regulations to protect flora and fauna from possible infectious agents entering through borders and prevent the spread of diseases in animals and plants.

In addition, it has been recently shown how certain AI tools can be (relatively) easily combined with gene editing technologies to generate new pathogens, even tailored to specific features or organisms (e.g., genetically modified crops and, potentially, of human groups), with a strong prospective for weaponization and use for bioterrorism.

A different -yet clearly related- area of concern refers to the applications of gene editing for human augmentation. There even exist certain groups who advocate for 'self-experimentation medicine' and 'do-it-yourself' gene 'therapies', purposedly aimed to enhance human performance. This 'science fiction' idea was demonstrated as real by the 'successful' -yet extremely questionable- experiment which led to the birth -in China, 2018- of the first two humans with engineered germline modifications (edited genes) which may be transmitted to future generations, with unknown effects.

The protection of society -including future generations- against existing and new, natural or engineered, accidentally leaked or deliberately delivered, biological threats is a definite institutional priority. Notably, the EU launched the Health Emergency Response Authority in 2022. AI tools present a clearly dual perspective in this field: on one side, technologies for strongly controversial applications (e.g., human augmentation, germline editing) or for directly malicious use (i.e., development of potential agents for bioterrorism) could be restricted from generalized availability and subjected to controls for access and use similar to those implemented for radioactive materials, with a clearly defined precautionary approach. On the other side, those AI tools useful to detect and fight risks, undertaking existing challenges in epidemiology, health monitoring and border control could be institutionally fostered to take advantage of their potential.

Leverage the potential of AI to help in mental health care

Mental health issues constitute a dramatic health and social problem in Europe, particularly important in children and adolescents, as a major cause of death and long-term suffering for people and families. These negative effects will be very likely boosted by the consequences of the COVID-19 pandemic and the war in Ukraine. In the wake of the COVID-19, AI-mediated tools have rapidly expanded from conversational chatbots and 'emotional support' (e.g., reducing the psychological impact of isolation) to supposedly 'diagnostic' and 'therapy' online platforms. Their easy access and availability offer potential advantages for many users, including those in resource-limited settings or in conflict zones. However, as identified in this report, AI-mediated tools in the context of mental health issues also pose clear challenges about 'the contents' that may be transmitted to users, particularly to most vulnerable groups (e.g., children, sick people, the elderly), digital health scammers and even the risk of 'psychological hacking'. The use of AI tools in mental health care offers a clear opportunity of help, while calling for further analysis of the most questionable issues. A coordinated technical and regulatory approach by public institutions and professional stakeholders could make a successful contribution addressing a dramatic European (and worldwide) health and social problem.

Enhance health data protection for scenarios of conflict

In view of the complex geopolitical situation in different areas of the world, particularly in the western border of the EU, it may be of interest to prepare two common 'emergency preparedness mechanisms', available at the national level, for

— health data backup (even in another country), suitable for a 'rebuild from nothing' scenario, and

— emergency blockage of access to -and remote disabling of- databases with health (biometric, genetic) data of the population and with identification data of healthcare workers, to avoid uncontrolled use of genetic information of individuals, and to protect the identities of the clinical personnel.

These mechanisms would be activated by any EU nation that may suddenly find itself in a scenario of 'extensive damage' or 'total destruction', e.g., due to extreme weather or geological events, or war. This 'emergency preparedness strategy' would take advantage of the inter-related structures and procedures -including regulatory processes- within the EU, and of its geographical extension.

Implement a dynamic assessment of the social impact of technology and its perception

AI-mediated technologies for medicine, healthcare and wellbeing could be subjected to an 'ethical and social assessment' beyond currently required technical requisites (e.g., for CE mark). This additional analysis would be partially inspired by the Ethical Appraisal of European Research Council projects and integrated with existing regulatory processes, including -as described- the evaluation of 'controversy' -and 'potential of harm', including for future generations- and sustainability. This evaluation should particularly try to avoid such unwanted effects as bias (based on demographic, ethnical or clinical, health-related features) and unfairness.

Citizens should be engaged with science and technology to contribute to and take decisions related to their own well-being. There is a need of outreach programs for 'informed debate' to enhance policy and governance to develop a secure, sustainable advancement of AI technology for the benefit of the current European society and of future generations The proposed implementation of the social assessment of technologies should be carried out fostering public-private mutual responsibility and partnership. It is important to highlight that new regulatory updates should not suppose -nor be perceived as- additional, complex, dis-encouraging bureaucracy to difficult the advancement of science and technology, but, on the opposite, a set of reliable and trustful procedures that fosters innovation while protecting citizens from risks -including some unknown but potentially expected- and transmit to society that products and devices that enter the EU market have being responsibly and sustainably developed.

Defining a precautionary approach for R&D in sensitive areas such as the decoding of cognitive brain signals

As proposed in the JRC Report published in 2020 [5] , a 'precautionary approach' should be employed in those areas of AI and AI-mediated applications with higher risks of unknown, potentially damaging consequences (e.g., modifying germlines or creating new forms of life) or conflict with human rights. Within the latter realm, research and development of neurotechnologies related to reading, decoding and manipulation of cognitive brain signals defines a particularly defying area.

Foster institutional and international collaboration

The availability and dissemination of reliable, trustworthy information constitute essential factors to implement successful policies for the welfare of people and society, in daily life and, particularly, in times of crises and extraordinary circumstances, when citizens turn to their leaders for orientation and guidance.

As highlighted by the COVID-19 pandemic, AI-mediated tools can effectively help in the design, management, and monitoring of public health strategies, and in the dissemination of appropriate recommendations and data. New applications, devices and platforms have opened the way to challenging advances that share concepts from Artificial Intelligence, Medicine, Healthcare and Wellbeing. However, simultaneously, it has also been experienced how those technologies can be employed to promote and disseminate false and misleading information leading to serious health damage -even deaths- and deep social unrest.

Several European and international institutions conduct studies on different -yet definitely complementary- aspects of Artificial Intelligence in Medicine, Healthcare and Wellbeing. While JRC Reports focus on science advances and technological updates with a social perspective, other entities aim at the protection of society, legal issues, and governance, in a rapidly evolving, truly multidisciplinary scenario. New areas arise as those topics relate to -and are modified by- health monitoring at borders, migrations, the effects of climate change and conflicts -as unfortunately shown by the war in Ukraine-, uncontrolled research in neurotechnologies, human gene editing -with unknown potential effects on future generations- and malicious uses of AI-mediated health technologies for bioterrorism.

The President of the European Commission in (September 8, 2021) declared that *"early and better information about trends [in global challenges, … digital transformations, …, external and internal interferences] will help us tackle such important issues in time and steer our Union in a positive direction"*.

Enhanced collaboration among stakeholders would substantially the visibility and impact of their respective contribution, with the common goal of providing policy makers -and society- with most advanced trustworthy information and resources to lead the way and promote and educated citizen debate on the most challenging topics.

Promote trustworthy information and an educated citizen debate

Lessons from the COVID-19 show the importance of trustworthy information about major health issues, and the damaging consequences of the spread of 'excessive, false, and misleading information', i.e., of an associated 'information epidemic' or 'infodemic', particularly in a highly digitally connected society as in Europe.

New challenges for public health may be expected to come in the relatively near future from well-known but 'difficult' areas in term of their social impact (e.g., cancer, mental health) but, particularly, from controversial new fields in which 'flashy' developments may suddenly happen. The latter ones include gene editing for human augmentation -including self-experimentation medicine-, neurotechnologies -with the potential of 'mind reading and manipulation'- and the (accidental or deliberate) propagation of novel (natural or engineered) pathogens.

AI-mediated tools play a significant role both in the spread of infodemics and in the identification and neutralization of malicious content. They should be fostered to promote the protection of society -particularly, most vulnerable groups- against the effects of pernicious information (e.g., to avoid rejecting public health measurements) while allowing for educated citizen debate, i.e., what is to be funded by taxpayers, and how to protect future generations without hindering advances.

Recent documents on the subject by international stakeholders (e.g., WHO Policy Briefs) should be integrated with European studies (e.g., JRC Reports and surveys by the European Parliament and the Council of Europe), for effective implementation in the EU.

Towards the technological sovereignty of the European Union

In the evolving international scenario, it has become clear that 'technological sovereignty' is major goal for the EU, as the energy crisis in the context of the war in Ukraine has shown how the dependence of other actors in strategic sectors may severely limit -even damage- the ability for decisions and the progress of society. Definite actions should be implemented to retain European talent -particularly, young- and to foster the competitiveness of EU institutions and companies, scientists, and other (e.g., regulatory) stakeholders.

5.2 Summary of contributions

This reports provides a detailed state of the art of the current and near-future applications of Artificial Intelligence in Medicine, Healthcare and Wellbeing, particularly focused on their impact on people's physical and mental health and in societal and environmental welfare, including future generations. It builds on and updates a previous analysis published in 2020.

Unexpectedly, this study is carried out under the extraordinary, historical circumstances of the COVID-19 pandemic and the war in Ukraine, with their staggering toll of victims, deaths, and migrations in Europe and worldwide, and their subsequent effects in the health and life of persons, and in all areas of society, industry, and economy.

In addition, there have been initial reports of the first documented use of an autonomous system to kill humans, and of the first steps in the creation of hybrid life forms ('xenobots').

From this review, the report identifies four key expanding areas of Artificial Intelligence applications in Medicine, Healthcare and Wellbeing in the near-future with particular significance in terms of their potential benefits and risks, and on how they may change human behavior and affect basic rights, even for future generations. They comprise AI tools for mental health, AI-mediated gene editing, AI tools for epidemiology and health data monitoring, and AI-mediated neurotechnologies.

Other expanding fields refer to the social interests of AI-mediated inclusion of neurodiversity, and to the technological developments in AI-mediated drug discovery and personalized medicine.

The analysis proposes a methodology and metrics for the assessment of the social impact of technologies, considering their maturity, availability, controversy, and sustainability, together with an integrated overview. It identifies novel AI-mediated challenges of very serious concern related to the protection of societies against biological threats –potentially even affecting future generations-, and links them to the recently updated priorities and proposed responses highlighted by the European Union, the United Nations, and the World Health Organization.

From this discussion, it is formulated a set of policy insights in terms of challenges and recommendations towards an effective European leadership and technological sovereignty in this sector.

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List of acronyms and abbreviations

Acronyms and abbreviations employed in this Report and related references are listed here. It is important to note that some of them are also used -with the same or different meaning and expression- in other contexts of science and technology, even in areas related to Medicine, Healthcare and Wellbeing.

AI	Artificial Intelligence
AR	Augmented Reality
ASD	Autism Spectrum Disorder
BARDA	Biomedical Advanced Research and Development Authority (of the USA)
BCI	Brain Computer Interfaces
CAD/CADx	Computer Aided Diagnosis
CADe	Computer Aided Detection
CBRNE/CBRNe	Chemical, biological, radioactive, nuclear and explosive (agents, devices, events). When the letter 'e' is written in lower case, it refers to improvised explosives (as opposed to military and industrial ones).
CDC	Center for Disease Control (USA)
CDSS	Clinical Decision Support System
CoE	Council of Europe
CNN	Convolutional Neural Networks
COVID-19	Coronavirus disease 2019
CT	Computed Tomography
CTPN	Counter Terrorism Preparedness Network (international collaboration)
DIY	Do-It-Yourself
DL	Deep Learning
DNA	Deoxyribonucleic acid
DS	Decision Support
DTC	Direct-to-Consumer (genetic) test
EC	European Commission
ECDC	European Center for Disease Control (of the EU)
ED	Emergency Department
HER	Electronic Health Record
EU	European Union
EU-27	The 27 member countries of the EU (as economic group, for statistical purposes).
EUROPOl	European Union Agency for Law Enforcement Cooperation
FDA	Food and Drug Administration (USA)
GDPR	General Data Protection Regulation
HCI	Human-Computer Interaction/Interface
HERA	Health Emergency Response Authority (EU)
HR	Human Rights
ICT	Information and Communication Technologies

ICU	Intensive Care Unit
IGS	Image Guided Surgery
INTERPOL	International Criminal Police Organization
IOI	Intra-Operative Imaging (during a surgical procedure)
IO	Intra-Operative (inside the OR, during the procedure)
IoT	Internet Of Things
IT	Information and Telecommunications
Infodemic	Information pandemic
IMDRF	International Medical Device Regulators Forum
JRC	Joint Research Centre (of the European Commission)
(L)AWS	(Lethal) Autonomous Weapons System
ML	Machine Learning
MR(I)	Magnetic Resonance (Imaging)
NATO	North Atlantic Treaty Organization
NCT	Non-conventional threat
OR	Operating Room
PCR	Polymerase chain reaction (test)
PET	Positron Emission Tomography
R&D	Research and Development
R&D&I	Research and Development and Innovation
RBG	Red, Blue, Green (color coding)
SaMD	Software as a Medical Device
SAR/SR	Socially Assistive Robot, Social Robot
SARS-CoV-2	Synthetic acute respiratory syndrome coronavirus 2
SME	Small and Medium Enterprise
SW	Software
TAL	Technology Availability Level
TRL	Technology Readiness Level
UN	United Nations
UNESCO	United Nations Educational, Scientific and Cultural Organization
UNICRI	United Nations Interregional Crime and Justice Research Institute
USA	United States of America
VR	Virtual Reality
WHO	World Health Organization
WIPO	World International Patent Organization
WMA	World Medical Association

List of definitions

In the context of this Report, the terms listed as follows are to be understood as declared in this section. Their definitions are quoted from the indicated references and links.

Agroterrorism	*Subset of agrocrime, understood as terrorist attacks directed against crops and livestock, in an effort to disrupt a population's economy and food supply.* Reference: https://www.interpol.int/Crimes/Terrorism/Bioterrorism/Animal-agrocrime-and-agroterrorism
Animal agrocrime	*Unlawful act or omission concerning animals or animal products that violates legislation, and has negative consequences on animal health, animal welfare, public health, food safety, food authenticity or national security.* Reference: https://www.interpol.int/Crimes/Terrorism/Bioterrorism/Animal-agrocrime-and-agroterrorism
Big Data	*Digital data that, through its volume or complexity, surpasses human analytical abilities and traditional data processing methods.* Reference: https://en.unesco.org/courier/2018-3/lexicon-artificial-intelligence and https://en.wikipedia.org/wiki/Big_data
Bioterrorism	*Deliberate release of viruses, bacteria, toxins or other harmful agents to cause illness or death in people, animals or plants.* Reference: https://www.interpol.int/Crimes/Terrorism/Bioterrorism
CRISPR	*Clustered Regularly Interspaced Short Palindromic Repeats. Set of techniques used to target specific stretches of genetic code and to edit DNA at precise locations. Using CRISPR techniques, it is possible to modify genes in living cells and organisms [by removing, adding, or replacing DNA sequences]. CRISPR is considered as simpler, faster, cheaper, and more accurate than older genome editing methods.* Reference: https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/questions-and-answers-about-crispr and https://www.genome.gov/about-genomics/policy-issues/what-is-Genome-Editing
Declaration of Geneva	*World Medical Association's (WMA) policy adopted by the Second General Assembly in Geneva in 1947. It builds on the principles of the Hippocratic Oath and remains as one of the most consistent documents of the WMA. With only very few and careful revisions over many decades, it safeguards the ethical principles of the medical profession, relatively uninfluenced by zeitgeist and modernism'. The WMA furthers states that 'the Oath should not be read alone, but in parallel with the more specific and detailed policies of the WMA especially the International Code of Medical Ethics, which followed the Declaration of Geneva as early as 1948'.* Reference: https://www.wma.net/what-we-do/medical-ethics/declaration-of-geneva/ https://www.wma.net/policies-post/wma-international-code-of-medical-ethics/
Deep Learning	Machine learning technique based on neural networks and large scale data sets.
Deoxyribonucleic acid	*Hereditary material in humans and almost all other organisms. Nearly every cell in a person's body has the same DNA. Most DNA is located in the cell nucleus (where it is called nuclear DNA), but a small amount of DNA can also be found in the mitochondria (where it is called mitochondrial DNA or mtDNA).* Reference: https://medlineplus.gov/genetics/understanding/basics/dna/
Digital Health	*Use of digital technologies in healthcare, including categories such as mobile health (mHealth), health information technology, wearable devices, telehealth and telemedicine, and personalized medicine. potential to improve the ability to Digital health technologies use*

	computing platforms, connectivity, software, and sensors for health care and related uses. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device. They include technologies intended for use as a medical product, in a medical product, as companion diagnostics, or as an adjunct to other medical products (devices, drugs, and biologics). They may also be used to develop or study medical products. Reference: https://www.who.int/behealthy/digital-health ; https://www.fda.gov/medical-devices/digital-health-center-excellence/what-digital-health
Disinformation	*Information that is false and deliberately created to harm a person, social group, organization or country.* Reference: https://en.unesco.org/fightfakenews
eHealth	*Use of information and communication technologies (ICT) for health.* Reference: https://www.who.int/ehealth/en/
Genome	*Entire set of DNA instructions found in a cell. In humans, the genome consists of 23 pairs of chromosomes located in the cell's nucleus, as well as a small chromosome in the cell's mitochondria. A genome contains all the information needed for an individual to develop and function … The human genome contains about 3 billion nucleotides*. Reference: https://www.genome.gov/genetics-glossary/Genome
Genome (or gene) editing	*Method for changing the DNA of organisms, including plants, bacteria, and animals. Editing DNA can lead to changes in physical traits, like eye color, and disease risk … Genome editing technologies … act like scissors, cutting the DNA at a specific spot. Then scientists can remove, add, or replace the DNA where it was cut.* Reference: https://www.genome.gov/about-genomics/policy-issues/what-is-Genome-Editing
Germ line	*Sex cells (eggs and sperm) that sexually reproducing organisms use to pass on their genomes from one generation to the next (parents to offspring). Egg and sperm cells are called germ cells, in contrast to the other cells of the body, which are called somatic cells.* Reference: https://www.genome.gov/genetics-glossary/germ-line
Global Health Ethics	*The Global Health Ethics Unit from the World Health Organization 'provides a focal point for the examination of ethical issues raised by activities throughout the Organization. The unit also supports Member States in addressing ethical issues that arise in their own countries. This includes a range of global bioethics topics; from public health surveillance to developments in genomics, and from research with human beings to fair access to health services'.* https://www.who.int/ethics/en/
Health	As defined by the World Health Organization, *Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*. The Universal Declaration of Human Rights states, in its 25th Article, that *Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care* […]'. Reference: https://www.un.org/en/universal-declaration-human-rights/index.html The World Health Organization Constitution was the first international instrument to enshrine the enjoyment of the highest attainable standard of health as a fundamental right of every human being ('the right to health'). Reference: https://www.who.int/en/news-room/fact-sheets/detail/human-rights-and-health
Hybrid threats	*Metaphor that brings complexities and dilemmas related to a changing global environment*

to the fore. It is often used interchangeably with references to hybrid war, to capture the interconnected nature of challenges (i.e. ethnic conflict, terrorism, migration, and weak institutions), multiplicity of actors involved (i.e. regular and irregular forces, criminal groups) and diversity of conventional and unconventional means used (i.e. military, diplomatic, technological).

Reference: https://www.europarl.europa.eu/RegData/etudes/ATAG/2015/564355/EPRS_ATA(2015)564355_EN.pdf

Infodemic

Or Information Epidemic. *The spread of excessive, false, and misleading information on COVID-19, causing reduced effectiveness of national response efforts, threatening lives and livelihoods of populations, and encouraging risk-taking behaviors that can seriously harm health and lead to mistrust in health authorities.*

References: https://cdn.who.int/media/docs/librariesprovider2/country-sites/who-digital-synthesis-doc_v5a_i.pdf?sfvrsn=1dc34e0_1&download=true

In-silico

Medical, biological research performed on computer or via computer simulation, that is, 'in chips', as opposed to being conducted in living organisms (in-vivo) or in a laboratory environment outside living organisms (in-vitro).

Reference: https://en.wikipedia.org/wiki/In_silico

In-vitro

Medical, biological research performed outside living organisms, that is, 'within the glass', in a laboratory environment as opposed to being conducted in living organisms (in-vivo).

Reference: https://en.wikipedia.org/wiki/In_vitro

In-vivo

Medical, biological research performed in living organisms.

Reference: https://en.wikipedia.org/wiki/In_vivo

International Medical Device Regulators Forum

Group of medical device regulators from around the world that have voluntarily come together to harmonize the regulatory requirements for medical products that vary from country to country. Their current members represent medical device regulatory authorities in many countries. The European member is the European Commission Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs. The USA member is the Food and Drug Administration. The World Health Organization is an Official Observer.

Reference: https://www.fda.gov/medical-devices/cdrh-international-programs/international-medical-device-regulators-forum-imdrf

Machine Learning

Machine Learning is a branch of artificial intelligence (AI) and computer science which focuses on development of systems that are able to learn and adapt without following explicit instructions imitating the way that humans learn, gradually improving its accuracy, by using algorithms and statistical models to analyse and draw inferences from patterns in data.

Reference: https://data.europa.eu/doi/10.2760/860665

Mal-information

Information that is based on reality, used to inflict harm on a person, social group, organization or country.

Reference: https://en.unesco.org/fightfakenews

Medicine

Science and practice of establishing the diagnosis, prognosis, treatment, and prevention of disease. Medicine encompasses a variety of healthcare practices evolved to maintain and restore health by the prevention and treatment of illness.

Reference: https://en.wikipedia.org/wiki/Medicine

Misinformation

Information that is false but not created with the intention of causing harm.

Reference: https://en.unesco.org/fightfakenews

Non-conventional threats

Broad term to include threats to security of (mainly) non-military origin, such as climate change, resource scarcity, infectious diseases, natural disasters, irregular migration, drug trafficking, information security and transnational crime. It usually refers to chemical, biological, radioactive, and nuclear (CBRN) agents and events, and it can also include improvised explosives (CBRNe).

Reference: [15]

One Health

Integrated, unifying approach to balance and optimize the health of people, animals and the environment. It is particularly important to prevent, predict, detect, and respond to global health threats such as the COVID-19 pandemic. The approach mobilizes multiple sectors, disciplines and communities at varying levels of society to work together. This way, new and better ideas are developed that address root causes and create long-term, sustainable solutions. One Health involves the public health, veterinary, public health and environmental sectors. The One Health approach is particularly relevant for food and water safety, nutrition, the control of zoonoses, pollution management, and combatting antimicrobial resistance.

Reference: https://www.who.int/news-room/questions-and-answers/item/one-health

Social Impact (of a technology)

Risks, uncertainties, ethical dilemmas and other issues (besides economical, scientific or technological impacts) that come together with technological innovations and may affect the society at any level, from individuals to structured groups and states. The social impact of a technology may influence –and even determine– its acceptance, rejection, or modification.

References: [12]

Software as a Medical Device

The International Medical Device Regulators Forum (IMDRF) defines it as 'software intended to be used for one or more medical purposes that performs these purposes without being part of a hardware medical device'. Use of Software as a Medical Device is continuing to increase. It can be used across a broad range of technology platforms, including medical device platforms, commercial 'off-the-shelf' platforms, and virtual networks, to name a few. Such software was previously referred to by industry, international regulators, and health care providers as 'standalone software', 'medical device software' and/or 'health software', and can sometimes be confused with other types of software.

Reference: https://www.fda.gov/medical-devices/digital-health/software-medical-device-samd

Sustainable Development Goals

United Nations define them as the blueprint to achieve a better and more sustainable future for all. They address the global challenges we face, including those related to poverty, inequality, climate, environmental degradation, prosperity, and peace and justice. Health is the Sustainable Goal number 3.

Reference: https://www.un.org/sustainabledevelopment/sustainable-development-goals/

The Global South

Emerging term (used by the World Bank) to refer to countries located in Asia, Africa, Latin America and the Caribbean and considered to have low and middle income. The Global South is one half of the global North-South divide and does not necessarily refer to geographical south. Most people in the Global South live within the Northern Hemisphere

Reference: https://en.wikipedia.org/wiki/Global_South

The Goal of Health

Sustainable Goal number 3 of the United Nations needed to ensure healthy lives and promote well-being for all at all ages.

Reference: https://www.un.org/sustainabledevelopment/health/

The West

Emerging term used in analogy to The Global South by the World Bank. It refers to countries located in Europe, North America and other regions considered to have high income. The West does not necessarily refer to geographical west.

Universal Health Coverage — One of the Sustainable Development Goals agreed by Member States of the United Nations to try to achieve by 2030. UHC means that all individuals and communities receive the health services they need without suffering financial hardship. It includes the full spectrum of essential, quality health services, from health promotion to prevention, treatment, rehabilitation, and palliative care.

Reference: https://www.who.int/news-room/fact-sheets/detail/universal-health-coverage-(uhc)

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Annexes

Annex 1. The Big Data of the Human Body and Life

The Human Genome

The Human Genome Project, initially released in 2000 [473] , estimated that humans have between 20000 and 25000 genes. The completed genome has been published in 2022 [474] . As summarized in [475] and [476] :

- Genes constitute the functional units of heredity. They are specific sequences of DNA, packed (i.e., arranged one after another) in structures called chromosomes in the nucleus of cells. Genes contain the information for producing proteins that generate physical attributes and particular functions of cells. Each chromosome contains many genes.
- DNA is composed of four building blocks (chemical bases called nucleotides): adenine (A), guanine (G), cytosine (C), and thymine (T), that attach to each other (A with T, and G with C) to form chemical bonds called base pairs.
- DNA has two strands that twist into the shape of a spiral ladder called a helix. The nucleotides attach to each other (A with T, and G with C) to form chemical bonds called base pairs (equivalent to the ladder's rungs), which connect the two DNA strands. Each base is also attached to a sugar molecule and a phosphate molecule (equivalent to the sides of the ladder).
- The order of the sequence of the bases determines the information that it carries. Alleles are forms of the same gene with small differences in their sequence of DNA bases.
- Each gene has from several hundreds of DNA bases to over 2 million bases. - Each human cell normally contains 23 pairs of chromosomes (46 in total). Twenty-two of these pairs (called autosomes, numbered by size) are the same in both males and females. The 23rd pair (called the sex chromosomes, identified as X and Y) differ between males and females. Females have two copies of the X chromosome, while males have one X and one Y chromosome.
- Every person has two copies of each gene, one inherited from each parent.
- Human DNA consists of about 3 billion bases. More than 99 percent of those bases are the same in all people. These small differences contribute to each person's unique physical features.
- Many unknowns remains related to the effects of the layers of biochemical regulation and about the effects of the environment on the role and expression of genes (epigenomics) [477] .

The Human Brain

The human brain is an organ with an average volume [478] [480] in (European descent) males of 1,274 cm3 and of 1,131 cm3 in females, corresponding to an approximate mass of about 1.3 kg (equivalent to around 3 pounds).

In June 2021, Google, the Lichtman laboratory at Harvard University and Connectomics, released the largest dataset available mapping the human brain. Called the "H01" dataset, it corresponds approximately to one cubic millimeter of tissue and encompass about 183 trillions of annotated synapses.

To have an idea of the magnitude of the challenge of mapping the human brain and the extraordinary potential of AI for it, it is interesting to note that in the same volume of mouse brain, there are about 4 km of nerve fibers, and they could only be delineated from a extensive set of images using advanced AI tools for pixel-by-pixel segmentation, just one year before the H01 dataset, in 2019 [479] .

Proteins

Virtually all existing protein structures have been solved in 2022 [142] . This is a substantial milestone in knowledge about living beings with an extraordinary potential for research and development in both 'natural' and 'artificial' (i.e., computational) biology and medicine.

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