# D5.1 Report on review of the current state of ethical and legal discussion with respect to non-curable AD and PD

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Revision and history chart

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## List of abbreviations

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| AD | Alzheimer's disease |
| AI | Artificial intelligence |
| CJEU | Court of Justice of the European Union |
| CFREU | Charter of Fundamental Rights of the European Union |
| ECHR | European Convention on Human Rights |
| ECtHR | European Court of Human Rights |
| ECJ | European Court of Justice |
| ESC | Embryonic Stem Cells |
| hES cells | Human Embryonic Stem Cells |
| iPS cells/iPSC | Induced Pluripotent Stem Cells |
| ML | Machine Learning |
| PD | Parkinson's disease |
| NCDs | Non communicable diseases |
| NDDs | Neurodegenerative diseases |
| WP | Work Package |
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# Executive summary

COMMUTE explores the linkage between COVID-19 and neurodegenerative diseases, setting two goals: to understand the comorbidity between COVID-19 and NDDs at the causal level and to translate of the actionable insights into personalized health applications. [1]

One of the objectives of WP5 is to monitor and conduct research on arising legal and ethical questions throughout the project. This report (D5.1) is result of the COMMUTE Legal and Ethical Framework Analysis (T5.3). The main findings of the research include:

- Ethical concerns on biomarker research on AD and PD, with a focus on the ongoing debates in the scientific field on the socio-psychological impact on individuals of AD and PD biomarker disclosure which might cause adverse psychological effects. This concern will be addressed by hosting symposia on recommender systems and patient engagement workshops, examining plausible scenarios to mitigate negative impact on individuals and develop an ethical understanding on how to deploy such AI recommender systems in the future.
- An analysis of the legal and ethical implications of stem cell research in COMMUTE (WP4), particularly in relation to human dignity, the right to life, and the right to mental and physical integrity, found no barriers to COMMUTE activities.
- The most effective approach to implementing the right of patients with neurodegenerative diseases (NDDs) to informed consent within the AI-driven recommender system will be discussed in regular patient engagement in (T5.2) and stakeholder workshops (T3.5). Recommendations from these workshops will be shared with partners and relevant COMMUTE stakeholders to raise awareness of the legal and ethical implications, including patients' right to informed consent for medical treatment.
- Rights of data subjects and impact assessment on data protection in COMMUTE are addressed in the Data Protection Impact Assessment (DPIA), which will be attached to this report.
- Implications for fundamental rights under the EU Charter, particularly concerning the classification of patients by AI systems using biomarkers (such as labeling patients as "high risk"), should be addressed through a human-centric approach to AI modeling. This approach includes raising AI developers' (WP3) awareness of individual vulnerabilities in light of COVID-19 and neurodegenerative diseases (NDDs).
- The framework for using AI as a decision support system and the requirements for training and/or validation datasets for these systems under Chapter 2 of the proposed AI Act (which under the adopted AI Act, reflects the requirements for high-risk AI systems) have been analyzed. The activities under COMMUTE project may fall under the research exemption reflected under Article 2(6) and Article 2(8) of the AI Act.

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[1] COMMUTE GA, p.3

An analysis of the interplay between existing regulatory frameworks in the medical sector (particularly the Medical Devices Regulation) and the proposed EU legal framework for AI regarding AI systems as decision support systems using biomarkers reveals that in the case of marketability, the AI recommender system developed within the project may fall under Class IIa and Class IIb, laid down under the Medical Device Regulation.

# Introduction

This deliverable presents an assessment of applicable legislations and ethical guidelines relevant to the COMMUTE project. This legal and ethical framework serves as a guide for the Consortium on ensuring lawful and ethical compliance throughout the course of the project. The final iteration of the legal and ethical framework of COMMUTE, which addresses post-project legal and ethical recommendations will be provided at the end of the project. (M48)

## *Project summary*

COMMUTE explores the linkage between SARS-CoV-2 (COVID-19) and neurodegenerative diseases (NDDs), namely Alzheimer (AD) and Parkinsonism (PD). NDD is an umbrella term for illnesses caused by the progressive loss of neurons and their associated functions, Alzheimer's disease and Parkinson's disease being two of the well-known NDDs[2]. The COVID-19 has arguably the best coverage over the widest variation possible and is therefore ideally suited to study the effects of infections with SARS-CoV-2 on large quantities of heterogeneous individuals.

COMMUTE aims to answer the question, whether infection by SARS-CoV-2 causes effects that result in a higher risk for the development of NDDs in the population, using two different approaches: a hypotheses-free, data-driven approach is building on available big data and the application of cutting-edge AI/ML technologies. Both approaches inform and support each other through an intensive crosstalk between computational and experimental biology methods.

Understanding the comorbidity between COVID-19 and NDDs at the causal level is the first goal of the COMMUTE project.[3] The second goal is the translation of the actionable insights into personalized health applications.[4] On the AI/ML side, the targeted outcome for translation into practice is a set of qualified biomarkers and predictive features that will be used for an AI-powered, model-generated recommender system that will allow for individualized risk assessment and personalized recommendations (WP3). On the side of the biomedical assay systems under WP4, COMMUTE will use cell-based assays based on clear pathophysiology mechanism understanding for drug-repurposing screenings in collaboration with REMEDI4ALL, the largest of the EU drug repurposing platforms.[5]

## *Status and content of the present report*

The D5.1 report is a review of the current state of ethical and legal discussion concerning non-curable AD and PD. The report is due in M12 and will be reviewed and updated in M18. D5.1 is part of T5.3 COMMUTE Legal and Ethical Framework Analysis (M01-M19) that aims to analyze the ethical and legal framework applicable to COMMUTE and identify legal and ethical requirements early on in the project, as well as

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[2] Robillard, J. M., C. A. Federico, K. Tairyan, A. J. Ivinson, and J. Illes. "Untapped Ethical Resources for Neurodegeneration Research." *BMC Medical Ethics* 12 (June 2, 2011): 9. https://doi.org/10.1186/1472-6939-12-9.

[3] COMMUTE GA, Description of Action Annex 1 Part B, p. 14, sec. 1.1.3.

[4] Ibid.

[5] COMMUTE GA, Description of Action Annex 1 Part B, p. 14, sec. 2.1.1.1.

addressing emerging questions (brought about by emerging legislation or project developments) throughout the project.

In accordance with T5.3 GA the report includes analysis of:

- the fundamental rights framework in relation to COMMUTE, including implications of fundamental rights when classifying patients with the help of AI systems using biomarkers, in particular the legal and ethical implications of classifying patients as "high-risk";
- ethical requirements to medical research, in particular research involving humans, including the requirement of consent GDPR from patients with neurodegenerative diseases such as Alzheimer's (incorporating both legal requirements and ethical principles for the involvement of participants potentially in a vulnerable position) and stem cells research;
- questions related to data protection, such as the distinction between anonymous and pseudonymous data and consent under the GDPR from patients with neurodegenerative diseases such as Alzheimer's;
- the AI Act and framework for AI to be used as a decision support system and the following requirements for training/and or validation datasets ethical requirements regarding AI under Chapter 2 of the AI Act Proposal;
- the applicable regulations such as the Medical Devices Regulation.

An analysis of the legal and ethical implications of stem cell research was included in the report following a request from WP4's partner to the Legal and Ethical Helpdesk (T5.4).[6]

The Legal and Ethical framework will be updated in M18. UNIVIE will monitor current developments, relevant discourse of legal, ethics and health experts. Additionally, the analysis of existing and forthcoming practices and regulatory approaches and advise partners in the course of the project through workshops, calls and guidelines circulated via e-mail whenever necessary.

In preparing the report, desk research was conducted on various sources of international law, including the Oviedo Convention, international human rights law (such as the ECHR), and EU legislation (such as the EUCFR, GDPR, AI Act, and Medical Devices Regulation). National legislation, including constitutional provisions and laws on medical research and data protection, was also considered. Additionally, the report references case law from both international and national courts, as well as guidelines like the Ethics Guidelines for Trustworthy AI and relevant literature.

## Chapter I. Ethical Framework

COMMUTE aims to contribute advanced knowledge on the brain health research field while observing ethical research conduct. Article 14 of the COMMUTE Grant Agreement stipulates adherence of the project

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[6] Please refer to the section: Human dignity, the right to life and the right to integrity of this report

to the highest ethical standards and the applicable EU, international and national law on ethical principles[7]. This ethical framework outlines the relevant principles under the Ethics Guidelines for Trustworthy AI published by the High-Level Expert Group on AI (HLEG), the Declaration of Helsinki by the World Medical Association (WMA) and other internationally recognized ethical principles that are deemed relevant to the COMMUTE project.

Horizon Europe highlights ethics as a critical component of EU-funded projects especially with the rapid scaling of application of AI-driven technologies[8]. In the field of health, the convergence of AI and genetic technologies warrants unprecedented advancements, but experts also caution the scientific community on the ethical risks it poses. COMMUTE regards ethical compliance as detrimental to the success of the project. As such, legal and ethical compliance in the project is closely monitored by WP5 in coordination with the project coordinator (FRAUNHOFER). Led by WP5 Leader (UNIVIE), COMMUTE partners are tasked to ensure ethical questions arising throughout the project are mitigated. The Legal and Ethical Helpdesk will continuously monitor regulatory compliance of the project, specifically in regard to the use of health data, the development of AI-driven recommender system and arising ethical concerns in the field of biomarker research. The Legal and Ethical Advisory Board established in M6 of the project acts as an external advisory board to ensure COMMUTE partners effectively implements the human-centered approach by ensuring NDDs patient rights and end-user needs are actively considered in all stages of the project.

As stated in the COMMUTE Grant Agreement, WP5 will also organize annual workshops to foster meaningful discussions between the Consortium, patients, healthcare professionals and other key stakeholders to mitigate foreseen ethical issues in the field and ensure patients' interests are considered throughout the project. The first patient engagement workshop was held on 13 November 2024 at the University of Vienna in Austria. The workshop included two parts: a public panel talk on Preventive Medicine and Patient Rights[9] and an interactive workshop on ethical aspect of AI in healthcare. The partners were introduced to patients' perspective on AI driven healthcare and discussed human centric perspective in AI modelling in COMMUTE. The insights of the workshop will be distributed between the partners and published as a set of recommendations at the end of the project.[10]

Ethical issues in the COMMUTE project revolves around the convergence the AI technology development, predictive medicine and biomarker research. This ethical framework outlines the various ethical considerations relevant for the COMMUTE project:

1. Ethics approaches for the development of AI-driven recommender system (T3.5).

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[7] COMMUTE GA, Article 14.

[8] European Commission. Horizon Europe Work Programme 2023-2025: 4. Health. 2023. Accessed October 1, 2024. https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/wp-call/2023-2024/wp-4-health_horizon-2023-2024_en.pdf.

[9] Recording of discussion Preventive Medicine and Patient Rights. https://youtu.be/cAS4AgMb3jg.

[10] Please refer to D5.2 :1st Workshop with LEAB and Patient Representatives) for the full report

2. Biomarker-based diagnostics and prediction of dementia risk (in the light of a principally non-modifiable set of e.g. genetic predispositions and pre-existing comorbidities).
3. Discussion of healthcare ethics community on diagnostics that indicate high-risk, the psychological impact on patients.

## European Commission's Ethics Guidelines for Trustworthy AI and Ethics-by-Design approach to AI principle

COMMUTE aims to pave the way for the ethical use of an AI-powered recommender system that can aid health professionals assess the risk of developing NDDs. To achieve such purpose, the framework of a Trustworthy AI is considered for the AI/ML model development in COMMUTE. In 2019, the High-Level Expert Group of AI (AI HLEG), commissioned by the European Commission, published the Ethics Guidelines for Trustworthy AI[11] to ensure all AI stakeholders designing, developing, deploying, implementing, using or being affected by AI are equipped with the knowledge and tools to ensure that the fundamental rights as a basis for the Trustworthy AI are respected and embedded in the AI systems. The guidelines are based on the fundamental rights enshrined in the EU treaties, EU Charter and international human rights law. The AI HLEG guideline has outlined five fundamental rights as a basis for Trustworthy AI, the following are cited for their relevance to the COMMUTE project:

- **Respect for human dignity.** This involves treating individuals as moral subjects and not as mere objects (data points) that are sorted, shifted and manipulated. AI systems should serve to protect human integrity.
- **Freedom of the individual.** In the context of AI system, this principle aims to mitigate risk of indirect or unintended mental or behavioral manipulation.
- **Equality, non-discrimination and solidarity - including the rights of persons at risk of exclusion**. This highlights the need to ensure AI systems are trained using representative datasets and safeguard the system from developing biased outputs (due to exclusion of different population groups.[12]

Based on the abovementioned fundamental values, the AI HLEG have postulated four ethical principles in the context of AI systems: These are the principles of:

(i) **Respect for human autonomy**. This principle dictates that the allocation of functions between individuals and the AI system should follow human-centric design principles and leave meaningful opportunity for freedom of choice.

(ii) **Prevention of harm**. This principle emphasizes that no AI systems should be allowed to cause harm or adversely affect individuals' physically, mentally or psychologically.

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[11] European Commission. EU Ethics Guidelines for Trustworthy AI. High-Level Expert Group on Artificial Intelligence, 2019. https://digital-strategy.ec.europa.eu/en/library/ethics-guidelines-trustworthy-ai.

[12] ibid

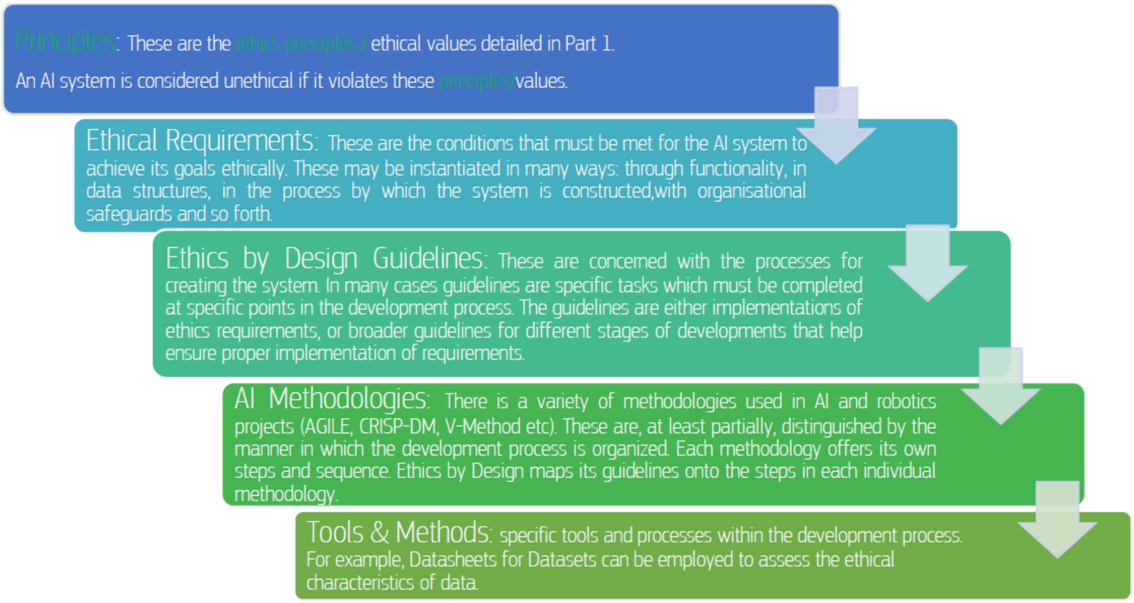
(iii) **Fairness**. The principle of fairness pertains to safeguarding individuals from unfair bias, discrimination and stigmatization that may result from the development of the AI system.

(iv) **Explicability**. AI explainability and transparency is crucial for building trust in AI systems. This involves the ability of users to understand the rationale behind the algorithms and the level of accuracy (e.g. margin of error) of the output of an AI system.

The principles act as an overarching guide to ensure the AI-driven recommender system to be developed in WP3 in COMMUTE. Careful considerations on the unintended negative effect of the AI system must be countered prior to deployment and use in clinical settings.

In 2021, the Directorate-General for Research and Innovation of the European Commission published 'Ethics By Design and Ethics of Use Approaches for Artificial Intelligence' as a follow-up to the AI HLEG ethics guidelines framework. The Ethics by Design approach calls for ethical considerations to be dealt with during the development phase of the AI:

> "Ethics by Design is intended to prevent ethical issues from arising in the first place by addressing them during the development stage, rather than trying to fix them later in the process. This is achieved by proactively using the principles as system requirements"[13]



Principles: These are the ethics principles / ethical values detailed in Part 1.

An AI system is considered unethical if it violates these principles/values.

Ethical Requirements: These are the conditions that must be met for the AI system to achieve its goals ethically. These may be instantiated in many ways: through functionality, in data structures, in the process by which the system is constructed,with organisational safeguards and so forth.

Ethics by Design Guidelines: These are concerned with the processes for creating the system. In many cases guidelines are specific tasks which must be completed at specific points in the development process. The guidelines are either implementations of ethics requirements, or broader guidelines for different stages of developments that help ensure proper implementation of requirements.

AI Methodologies: There is a variety of methodologies used in AI and robotics projects (AGILE, CRISP-DM, V-Method etc). These are, at least partially, distinguished by the manner in which the development process is organized. Each methodology offers its own steps and sequence. Ethics by Design maps its guidelines onto the steps in each individual methodology.

Tools & Methods: specific tools and processes within the development process. For example, Datasheets for Datasets can be employed to assess the ethical characteristics of data.

Figure 1. *The 5-layer Model of Ethics by Design (Source:* Directorate-General for Research and Innovation, European Commission)

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[13] European Commission, DG Research & Innovation. *Ethics By Design and Ethics of Use Approaches for Artificial Intelligence*. 2021. https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/guidance/ethics-by-design-and-ethics-of-use-approaches-for-artificial-intelligence_he_en.pdf

The model intends to provide a framework for developers to embed the fundamental values and ethical principles in AI systems requirements. By mapping the AI development methodology (e.g. tasks, objectives, goals) alongside the ethical guidelines, the AI system can be continuously assessed for ethical risks by stakeholders. AI systems are designed for different purposes and user needs; by employing the Ethics by Design methodological approach, AI developers and designers are urged to consider the risks and mitigate unintended negative effect of the AI during the development phase.

COMMUTE technical partners, led by WP3 leader (BSC), should work together to identify and address vulnerabilities and biases. The development of AI/ML recommender system that is intended to assist health professionals identify patients with an elevated risk of NDDs after a COVID-19 infection based on individual characteristics (e.g. biomarkers) pose ethical concerns that must be assessed at the course project. While the AI recommender system to be developed in COMMUTE is not expected to be tested on human subjects at the course of the project, ethical and societal impact of the future use of such AI system must be considered at the onset of the project.

## Ethical guidelines on AD and PD biomarker research

Biomarker research raises several ethical concerns that require careful consideration. As the research activities in COMMUTE deals with sensitive health data, including genetic and biomarker information, it is essential to ensure the data protection from unwarranted access. This includes handling all personal data—such as medical records, health data, and other identifying information—with strict confidentiality. These risks to data subjects' rights will be continuously monitored, assessed and documented throughout the project. In relation to this, a Data Protection Impact Assessment[14] was conducted by UNIVIE to ensure that the privacy of all data subjects is protected, and all data processing are in compliance with the GDPR.[15]

Contribution to early detection and diagnosis of NDDs is a core project outcome the COMMUTE project intends to achieve. The implications of biomarker research in the field of NDDs, especially the impact of potential future findings, and the ethical considerations of disclosing biomarker results, particularly when their predictive or diagnostic significance is uncertain remains a point of contention among experts.[16] Striking a balance between the potential advancements biomarker research can offer in the field of AD and PD and the ethical responsibility of researchers to uphold patient autonomy will be essential in defining the future of deployment of AI/ML tools to enable NDD diagnosis and early intervention.

### *World Medical Organization Declaration of Helsinki*

The WMA Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects is regarded by the medical research community as the guiding set of principles for human research ethics.

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[14] See attachment 1: Full report of the Data Protection Impact Assessment

[15] See Legal Framework for more details: GDPR - Processing of special categories of personal data.

[16] David Prvulovic, Harald Hampel. "Ethical considerations of biomarker use in neurodegenerative diseases—A case study of Alzheimer's disease." *Progress in Neurobiology*. Volume 95, Issue 4, (2011): 517-519, https://doi.org/10.1016/j.pneurobio.2011.11.009.

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and last amended on the 75th WMA General Assembly in Helsinki, Finland, October 2024. The WMA covers 37 principles that are categorized as follows: In the context of COMMUTE, we highlight one of the General Principles that promote the inclusion of patients' in shaping the research outcomes of the project, paragraph 6:

> "[…] Since medical research takes place in the context of various structural inequities, researchers should carefully consider how the benefits, risks, and burdens are distributed[…]. Researchers should enable potential and enrolled participants and their communities to share their priorities and values; to participate in research design, implementation, and other relevant activities; and to engage in understanding and disseminating results.

While COMMUTE does not intend to conduct trials that involve human participants during the project, the careful consideration of impact of the results of the project (AI-driven recommender system that has the capacity to predict likelihood of AD and PD diagnosis) on the scientific and medical community must already be considered at the onset of the project. Under T5.2, WP5 is tasked to ensure that patient engagement workshops are annually held and documented to inform the COMMUTE partners and project stakeholders of the best practices that can uphold the patients' interests and 'human-centered' approach of the AI/ML approach being undertaken in COMMUTE.[17]

## Current ethical debates on biomarker-based diagnostics and predictive medicine

The debilitating and irreversible nature of neurodegenerative diseases renders neuroscience research to focus on investigating the biological (genetic) factors that affect NDDs progression and possible therapeutic solutions. The prospect of finding preventive and therapeutic remedy to NDDs are encouraging with the emergence of biomarker-based diagnostic research. Scientific experts are also optimistic that the advent of AI-based tools will accelerate this process. This implies the use of experimental approaches that may entail ethical concerns. This section covers the foreseen ethical considerations relevant to the COMMUTE project.

COMMUTE makes use of advanced AI/ML methodology to develop robust computational strategies to understand the linkage of disease progression in AD and PD[18] of individuals who have been infected by COVID-19. Recent studies have shown changes in the human brain after COVID-19 infection, further studies also indicate an increased risk of individuals that tested positive for COVID-19 for neurodegenerative diseases characterized by pathological protein aggregation[19]. According to the statistical records of the World Health Organization[20] (2024), over 776 million people have reportedly been infected by COVID-19 worldwide. If recent studies linking COVID-19 and NDDs are moderately accurate, a certain percentage of the current world population are predisposed to developing NDDs.

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[17] COMMUTE, GA, p. 18.

[18] COMMUTE, GA, Annex I Part B

[19] COMMUTE, GA, Annex I Part B

[20] World Health Organization Data Chart. Accessed October, 2024 https://data.who.int/dashboards/covid19/cases

### Impact of disclosure of biomarkers

The International Programme on Chemical Safety, led by the World Health Organization (WHO) and in coordination with the United Nations and the International Labor Organization, defines a biomarker as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease"[21] Biomarkers are recognized as an effective means in assessing disease predisposition and predicting disease progression. Moreover, recent studies have established the potential of biomarker research to widen our understanding of drug treatments e.g. how certain drug treatment interacts with its target or whether a drug is likely to be safe in humans[22].

Biomarker-assisted diagnostic testing poses a critical issue. The question of disclosure remains a contentious topic among the scientific community. The right to information is classified as part of the 14 fundamental rights of patients identified in the European Charter of Patient Rights:

> "**Right to information**: Every individual has the right to access to all kind of information regarding their state of health, the health services and how to use them, and all that scientific research and technological innovation makes available."[23]

A key argument in using early diagnostic biomarkers is anchored on the assumption that making an accurate diagnosis during asymptomatic or very early symptomatic stages of the disease gives patients to reflect on the impact of the diagnosis as it progresses and adjust life plans. Disclosure of biomarker test results, however, can have unintended psychological impact to individuals such as anxiety and depression. This also can have negative implications especially in false-positive results scenarios. Questions are raised under which circumstances can it be justified to perform diagnostic procedures.[24]

#### Alzheimer's

In a 2016 systematic literature review conducted by Bemelmans, et al.[25] on the effects of disclosing Alzheimer's disease biomarkers to cognitively healthy individuals, the following effects were compared across 14 peer-reviewed studies on hypothetical or actual disclosures of AD biomarkers were analyzed. Three broad categories were presented:

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[21] Strimbu, K., and J. A. Tavel. "What Are Biomarkers?" *Current Opinion in HIV/AIDS* 5, no. 6 (November 2010): 463–466. https://doi.org/10.1097/COH.0b013e32833ed177.

[22] Wholley, David N. "Public–Private Partnerships in Biomarker Research." In *Genomic and Personalized Medicine*, edited by Geoffrey S. Ginsburg and Huntington F. Willard, 474–483. 2nd ed. Academic Press, 2013. https://doi.org/10.1016/B978-0-12-382227-7.00043-4.

[23] European Commission 2020. European Charter of Patient Rights (2002), accessed October 4, 2024. https://ec.europa.eu/health/ph_overview/co_operation/mobility/docs/health_services_co108_en.pdf.

[24] David Prvulovic, Harald Hampel. "Ethical considerations of biomarker use in neurodegenerative diseases—A case study of Alzheimer's disease." *Progress in Neurobiology*. Volume 95, Issue 4, (2011): 517-519, https://doi.org/10.1016/j.pneurobio.2011.11.009.

[25] Bemelmans, S. A., Tromp, K., Bunnik, E. M., Milne, R. J., Badger, S., Brayne, C., Schermer, M. H., and Richard, E. "Psychological, Behavioral and Social Effects of Disclosing Alzheimer's Disease Biomarkers to Research Participants: A Systematic Review." *Alzheimer's Research & Therapy* 8, no. 1 (2016): 46. https://doi.org/10.1186/s13195-016-0212-z.

1. Psychological: Anxiety, depression, test-related distress, coping, memory functioning

   Learning about the elevated risk for Alzheimer's through biomarker disclosure can cause anxiety and apprehensiveness, particularly if AD symptoms are currently present. This may center around the fear of cognitive decline, loss of independence, or the future burden on loved ones.

2. Behavioral: insurance uptake, health/lifestyle changes

   Planning for quality care is part of the patient-centered approach recommended to AD patients. However, disclosure of AD biomarkers may have a different impact on individuals who will encounter the dilemma of altering future plans. As the prediction rate of AI recommender systems are subject to certain margin of errors, decisions made by patients based on the biomarker pre-diagnostic tests may have negative impact on patients especially in cases when false positive results are produced.

3. Social: communication of results, perception of risk in relation to family history

   Disclosure affects not just the individual but also their family members and loved ones who may also become anxious about future planning for an uncertain future. It can also have an effect on how the individual is perceived, certain stigma may be attached to the implications of having a "risk marker" for a serious disease.

*Recommendations to clinicians dealing with AD patients:*

Alzheimer Europe developed general and specific recommendations for clinicians, this section highlights some aspects that may also be used as a guide for COMMUTE.

- Clinicians should be transparent about the capacity of current therapies and interventions possibility to create beneficial change and about their limitations.
- Clinicians should also be transparent about the uncertainty of the clinical progression toward cognitive impairment or AD dementia. Risk prediction for cognitive impairment or AD dementia does not bring certainty or information about the likely course or progression of the disease.
- Clinicians, researchers or counsellors should guide and inform the person on positive actions they can take upon receipt of results, such as positive lifestyle changes, support groups they can join and clinical trials from which they might benefit.
- Clinicians should consider the personal utility that risk prediction for cognitive impairment may have for the individual. Some people may want to use this information to participate in a dementia prevention clinical trial, and/or to prepare themselves and their families for a possible future with AD.[26]

## Parkison's

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[26] Full position statement can be accessed on the Alzheimer Europe website: https://bit.ly/AE_RiskDisclosurePositio.

Parkinson’s disease (PD) is a progressive neurological disorder and remains without a cure.[27]. The International Parkison’s and Movement Disorder Society defines the clinical features of Parkison’s disease (PD) to include both the motor symptoms e.g. tremor, limb rigidity, gait and balance problems as well as non-motor issues such as neuropsychiatric symptoms including mood disturbances and cognitive changes; autonomic dysfunction, pain and sleep issues[28]. The PD biomarker research is more focused on validating the accuracy of PD diagnosis as currently, clinical diagnosis of PD can only be made definitively with post-mortem brain examination[29]. Nevertheless, such research can enable medical professionals effectively manage early PD symptoms.

In the study of Bavli et al.[30] on the ethical implications arising from the implementation of a novel AI predictive tool designed to support PD patients, concerns of participants were more focused on the potential harm of exploiting hope of patients and family that such AI tools can eventually cure or alleviate their conditions. While this concern is not exclusively attributed to AI technologies, the risk of forming new vulnerabilities and instigating physical and emotional suffering for individuals and their families who rested hope to the promises of new medical interventions that do not deliver the expected or desired results must be considered when introducing AI tools to PD patients.[31]

### Ongoing ethical discourse*:*

Addressing the ethical challenges of biomarker research on AD and PD remain a shared concern among the neuroscience research field. The right not to know biomarker results is part of the ongoing ethical debate on the impact of disclosure: the individual’s “right to know the truth” and the need to allow the individual to plan for the future; vs concerns about harming the individual and the intention to protect the individual from potentially adverse psychological effects, including anxiety, depression, and suicidal thoughts. Both the principle of respect for autonomy and the principle of nonmaleficence and/or beneficence play a major role in deciding in favor or against full disclosure.[32]

Part of the ethical discussion of AD and PD biomarker research is the broader question of how to manage the byproducts of scientific advancements at the societal level. The impact of scientific discoveries has the

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[27] Bavli, I., Ho, A., Mahal, R., et al. “Ethical Concerns Around Privacy and Data Security in AI Health Monitoring for Parkinson’s Disease: Insights from Patients, Family Members, and Healthcare Professionals.” *AI & Society* (2024). https://doi.org/10.1007/s00146-023-01843-6.

[28] International Parkison’s and Movement Disorder Society. “Parkinson's Disease & Parkinsonism”, accessed 08 October 2024. https://www.movementdisorders.org/MDS/About/Movement-Disorder-Overviews/Parkinsons-Disease--Parkinsonism.htm.

[29] Kyla Y. Yamashita, Sweta Bhoopatiraju, Bret D. Silverglate, George T. Grossberg. Biomarkers in Parkinson’s disease: A state of the art review. *Biomarkers in Neuropsychiatry*, Volume 9 (2023). https://doi.org/10.1016/j.bionps.2023.100074.

[30] Bavli, I., Ho, A., Mahal, R. *et al.* Ethical concerns around privacy and data security in AI health monitoring for Parkinson’s disease: insights from patients, family members, and healthcare professionals. *AI & Soc* (2024). https://doi.org/10.1007/s00146-023-01843-6.

[31] Eijkholt, M. “Medicine’s Collision with False Hope: The False Hope Harms (FHH) Argument.” *Bioethics* 34, no. 7 (2020): 703–711. https://doi.org/10.1111/bioe.12798.

[32] Porteri, C., Albanese, E., Scerri, C., Carrillo, M. C., Snyder, H. M., Martensson, B., Baker, M., Giacobini, E., Boccardi, M., Winblad, B., Frisoni, G. B., and Hurst, S. “The Biomarker-Based Diagnosis of Alzheimer's Disease. 1 - Ethical and Societal Issues.” *Neurobiology of Aging* 52 (April 2017): 132-140. https://doi.org/10.1016/j.neurobiolaging.2016.07.011..

potential to change societal arrangements. The European Textbook on Ethics in Research[33] highlights that potential effects of research in nanobiotechnologies and predictive medicine warrant social control or regulation. The COMMUTE project aims to concurrently explore solutions to these ethical dilemmas by hosting symposia on recommender systems in WP3 (T3.5 Stakeholder Workshops in ES, DK and GER) and patient engagement workshops in WP5 T5.2 (Patient involvement via a series of workshops) to engage interdisciplinary experts and patient rights' advocates in examining plausible scenarios, mitigate negative impact to individuals and develop an ethical understanding on how to deploy such AI recommender systems in the future.

## Chapter II. Legal framework: Fundamental rights and freedoms

In this part of the report, the concept of human dignity and several fundamental rights will be considered with a focus on their aspects relating to COMMUTE. In particular, the report dwells on human dignity, right to life, integrity, equality and non-discrimination, privacy (including the right to protection of personal data), and freedom of scientific research. The scope and application of these rights will be defined based on the most relevant international law, including the Charter of Fundamental Rights of the European Union (CFREU), European Convention on Human Rights (ECHR), the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Oviedo Convention) and its protocols, and national sources such as the constitutions and relevant national legislation of the countries of the COMMUTE partners. Then, the relevance of these rights will be outlined in relation to COMMUTE.

Rights and freedoms in focus in this report are subject to limitations, which must in general be provided for by law, pursue the aim recognized in the CFREU and the ECHR and be proportionate to a particular legitimate aim pursued. There is a difference in how this test on legality of limitations is formulated in the CFREU and the ECHR, for instance CFREU provides a specific article devoted to the scope and interpretations of the rights and the test on legality of any limitation of a right (Article 52(1)). In comparison, the ECHR does not have a specific article explicitly outlining the test, but the latter is formulated by the ECtHR in its practice. Another difference is the aims of limitations. The EUCFR names two aims, which legitimize limitations of human rights: general interest recognized by the EU or the need to protect the rights and freedoms of others (Article 52(1)). The ECtHR refers to such aims of possible limitation as the protection of public health, public morals, public order, national security, and the rights of others, or the prevention of disorder or crime.[34] These differences are not substantial for the purposes of this report. Therefore, the report references both the CFREU and the ECHR, along with their respective courts and practices, on the assumption of their coherence.

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[33] European Commission. European textbook on ethics in research. 2010. https://op.europa.eu/en/publication-detail/-/publication/12567a07-6beb-4998-95cd-8bca103fcf43

[34] Council of Europe. "Convention for the Protection of Human Rights and Fundamental Freedoms." Council of Europe Treaty Series 005, Council of Europe, 1950, Article 2(2), Article 5(2), Article 6(1), Article 8(2), Article 9(2), Article 10(2), Article 11(2).

Unlike rights and freedoms, human dignity has a special status in international and national law. It is recognized as inviolable, as articulated in *Article 1 of the CFREU* and *Article 1 of the German Grundgesetz (Basic Law*). Its relevance to the present report is that human dignity can be considered as a ground for limitation of a right, in particular, of the freedom of research. Another pertinent ground for possible limitation of the freedom of research, often going together with human dignity, is the protection of morals.[35] Application of this ground might be complicated, as an understanding of what is moral might differ from person to person and from state to state. According to the position of the ECtHR, there is no uniform concept of morals within the states of the Council of Europe.[36]

The search of boundaries of morality on health research often relies on ethics. Adopted in 1964 the Declaration of Helsinki formulated ethical principles for medical research, highlighting that "the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects." [37] Ethics in health research provides a structured framework to address the complexities and diversity of individual and cultural morals. While morals are subjective and vary between individuals and cultures, ethics offer a standardized approach to ensure that research is conducted responsibly and with respect for participants.

## 1. *Human dignity, the right to life and the right to integrity*

Human dignity,[38] right to life[39] and to integrity[40] are highly relevant to the COMMUTE project, particularly in relation to the research methods employed, such as cell research and AI-driven machine learning. Additionally, one of the project's outputs is an AI-based tool designed to make predictions and categorize individuals based on the analysis of their health data. These research methods and the resulting tool may have implications for human dignity, life and integrity of a person, as the methods have legal and ethical limitations. The COMMUTE partners should ensure that their activities in the project does not diminish human dignity.

### A. Human dignity: Scope and application

Every person has human dignity. This principle is mentioned in the preamble and Article 1 UDHR (1948), preambles of the ICCPR and IPESCR, Article 2 TEU (1992), Articles 1 and 25 of the CFREU, preamble of the Oviedo Convention (1997) and national law.

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[35] For instance, the *Biotech Directive* refers to morality in Article 6, Recitals 36-40.

[36] European Court of Human Rights, *Müller and Others v. Switzerland*. Judgement (Chamber) 10737/84, May 24, 1988.

[37] Ethical principles for medical research involving human subjects, Declaration of Helsinki, *WMA General Assembly, June 1964,* Article 7. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

[38] UDHR, Article 1; ICCCPR, preamble; IPESCR, preamble; TEU, Article 1; CFREU, Article 1, 25; Oviedo Convention, preamble; German Grundgesetz (Basic Law), Article 1.

[39] ICCPR, Article 6; CFREU, Article 2; ECHR, Article 2.

[40] CFREU, Article 3; ECHR, Article 3; ICCPR, Article 7.

The references to human dignity might be found in relation to various issues from minimum standards of reception of asylum seekers[41] to fair and just working conditions.[42] This concept is used to protect vulnerable people like the elderly[43] or minors.[44] Other human rights principles can be understood as flowing from human dignity, as for instance the right to informational self-determination in interpretation of German Constitutional Court.[45] It requires putting a person at the center of discussions affecting people. This ubiquitous character of human dignity is reflected in the practice of the ECtHR, although ECHR does not explicitly mention human dignity, the ECtHR regularly refers to it in its interpretations of the ECHR.[46] The first reference to this concept by the ECJ was to find discrimination against transsexuals in the workplace.[47] ECJ proclaimed human dignity to be a general principle of the EU law.[48]

One of the aspects where human dignity is referenced is in reference to health in a broad sense. It is referred to interpret complex moral questions of abortion,[49] end-of life situations like assisted suicide,[50] uses of human embryos.[51] For instance, Directive 98/44/EC on the legal protection of biotechnological inventions requires patent law to "respect the fundamental principles safeguarding the dignity and integrity of the person" (Recital 16) and characterizes inventions excluded from patentability as being offensive against human dignity (Recital 38). [52]

Human dignity is especially relevant to COMMUTE, as WP4 involves research on stem cells, raising considerations of compliance with both international and national legal and ethical regulations. Additionally, the work on machine learning and AI models for predicting health risks introduces further ethical and patient engagement issues (WP3). These considerations will be addressed in more detail in section 1 and section 4(C).

## B. The right to life: Scope and application

The right to life (Article 6 ICCPR, Article 2 CFREU, Article 2 ECHR) has broad content and a corresponding variety of negative and positive obligations of states, including the institution of an accessible health care

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[41] *Council Directive 2003/9/EC of 27 January 2003 laying down minimum standards for the reception of asylum seekers*, O.J. (L 031), 6.2.2003, 18–25.

[42] Charter of Fundamental Rights of the European Union, 2000 O.J. (C 364) 1., Article 31.

[43] Charter of Fundamental Rights of the European Union, Article 25.

[44] Council Directive 2007/65/EC of the European Parliament and of the Council of 11 December 2007 amending Council Directive 89/552/EEC on the coordination of certain provisions laid down by law, regulation, or administrative action in Member States concerning the pursuit of television broadcasting activities.

[45] *Census Act Decision* (Volkszählungsurteil), BVerfGE 65, 1, Federal Constitutional Court of Germany, 15 December 1983.

[46] East African Asians v UK (1973) 3 EHRR 76, SW v UK, para. 44; European Court of Human Rights, *Pretty v. the United Kingdom*. Judgment (Fourth Section) 2346/02, April 29, 2002.

[47] European Court of Justice, *Case C-13/94 P v. S and Cornwall County Council* [1996] ECR I-2143.

[48] See European Court of Justice, *Case C-36/02 Omega Spielhallen-und Automatenaufstellungs-GmbH v. Oberbürgermeisterin der Bundesstadt Bonn* (2004) ECR I-9609.

[49] European Court of Human Rights, *M.L. v. Poland*, Judgement (First Section) 40119/21, December 12, 2023.

[50] *Pretty v UK.*

[51] European Court of Human Rights, *Parrillo v Italy*, Judgement (Grand Chamber) 46470/11, August 27, 2015.

[52] European Parliament and Council. *Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions*. Official Journal of the European Communities, July 6, 1998.

system.[53] In this aspect, the right to life overlaps with the right to right to the highest attainable standard of physical and mental health, enshrined in Article 12 CESCR.[54]

The right to life is interrelated with the concept of dignity. These two notions might conflict when dignity is used as a basis for an autonomous choice[55] in the end-of-life situations,[56] which is closely related to the discussion on research on embryos and stem cells in general.[57] These methods are planned to be employed in COMMUTE. National legislation in certain countries may impose restrictions or outright bans on specific research practices, such as embryonic research. It is crucial that partners ensure full compliance with both international and national laws while advancing the objectives of the project. Question of research on biological materials will be dealt in more detail in subsection C(i).

## C. Right to physical and mental integrity: Scope and application

The right to mental and physical integrity (Article 3 CFREU, Article 3 ECHR, Article 7 ICCPR) is intrinsically linked to human dignity. Under the ECHR, the right to physical and mental integrity is protected by Articles 8(1) as part of a right to a private life. Article 3 CFREU focuses on the protection of physical and mental integrity in the sphere of medicine and biology, which also distinguishes it from Article 35 CFREU on the right to health care, which focuses on the positive obligations of states to provide access to health care. In the fields of medicine and biology, the right includes the prohibition of eugenic practices, in particular those aiming at the selection of persons, the prohibition on making the human body and its parts as such a source of financial gain, the prohibition of the reproductive cloning of human beings (Article 3 (b,c,d) EUCFR).

### *i. Prohibition on making the human body and its parts as such a source of financial gain*

One of the aspects of the right to physical and mental integrity, which have relevance to COMMUTE in the light of stem cells research is prohibition on making the human body and its parts a source of financial gain (Article 3 (2(c) CFREU). This principle is also known as altruism. Art. 21 of the Oviedo Convention states that “The human body and its parts shall not, as such, give rise to financial gain.” Organs and tissues proper, including blood, should not be made an object of trade, like smartphones, for instance, however, "technical acts (sampling, testing, pasteurization, fractionation, purification, storage, culture, transport,

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[53] Human Rights Committee, *General Comment No. 36 Article 6: Right to Life*, CCPR/C/GC/36, 2019, 26.

[54] CESCR, *General Comment No. 14: The right to the highest attainable standard of health (article 12 of the International Covenant on Economic, Social and Cultural Rights)*, E/C.12/2000/4.

[55] European Court of Human Rights, *Vo v France*, Judgment (Grand Chamber) 53924/00, July 8, 2004; European Court of Human Rights, *A.B.C v Ireland.* Judgement (Grand Chamber) 25579/05, December 16, 2010.

[56] *Pretty v UK*.

[57] Blackford, R. “Stem Cell Research on Other Worlds, or Why Embryos Do Not Have a Right to Life.” *Journal of Medical Ethics* 32, no. 3 (2006): 177–80. https://doi.org/10.1136/jme.2004.011346.

etc.) which are performed on the basis of these items may legitimately give rise to reasonable remuneration".[58]

This principle is reflected in the EU legislation, requiring donors of organs to be unpaid and voluntary. [59] EU Member states shall take measures to encourage voluntary and unpaid donations of blood,[60] of tissue and cells,[61] including in spheres of gene therapy, somatic cell therapy and tissue engineering[62].

The EU has established a framework for data altruism, including the Data Governance Act, which aims to ensure the proper collection and processing of data made available for altruistic purposes[63]. Similarly, altruism aims to ensure the quality of the donated biomaterial, however the efficacy of this principle is being contested.[64] Moreover, the above-mentioned EU legislation is being criticized as failing to prevent the commercialization of the human body.[65] One of the reasons behind the complexity of application of principle of altruism, is that definition of the human body and its parts remains open. It has special importance for the research on human embryos. In 1998 the European Group on Ethics in Science and New Technologies expressed the view that "because of a lack of consensus, it would be inappropriate to impose one exclusive moral code" regarding research on human embryos.[66] Since then, the understanding of what an embryo is has still not been fully established. The CJEU had to answer this question in *Brüstle v Greenpeace* what a human embryo under Article 6(2)(c) of the Biotech Directive is and whether exclusion of patentability applies to inventions, whose production involves the destruction of a human embryo.[67] Although the Biotech Directive is applicable to scientific research only to a limited extent as its purpose is the protection of inventions used for industrial and commercial purposes: " Article 6(2)(c) of the Directive

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[58] *Explanatory Report to the Convention on Human Rights and Biomedicine*, Council of Europe, 1997, para. 132.

[59] *Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation*, Official Journal of the European Union, L 207, 14 August 2010, 14-29, Art. 13.

[60] *Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 laying down standards of quality and safety for the collection, testing, processing, storage, and distribution of human blood and blood components*, Official Journal of the European Union, L 33, 8 February 2003, 30-40, Recital 23.

[61] *Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells,* Official Journal of the European Union, L 102, 7 April 2004, 48-58, Article 12(1), Recital 18.

[62] Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products, Official Journal of the European Union, L 324, 10 December 2007, Recital 15.

[63] Regulation (EU) 2022/868 of the European Parliament and of the Council of 30 May 2022 on European data governance and amending Regulation (EU) 2018/1724 (Data Governance Act) (Text with EEA relevance).

[64] For instance, Thornton, V. "The Role of Altruism in an Organ Donation Policy." *Ethics, Medicine, and Public Health*, vol. 6 (2018): 44–51. https://doi.org/10.1016/j.jemep.2018.07.004.

[65] See Lenk, Christian, and Katharina Beier. "Is the Commercialisation of Human Tissue and Body Material Forbidden in the Countries of the European Union?" *Journal of Medical Ethics*, vol. 38, no. 6 (2012): 342–46. https://doi.org/10.1136/jme.2010.038760.

[66] Opinion on ethical aspects of research involving the use of human embryos in the context of the 5th Framework Programme, 1998, para. 2.4.

[67] Court of Justice of the European Union, *Brüstle v. Greenpeace*, C-34/10, judgment of October 18, 2011.

also covers use for purposes of scientific research, only use for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it being patentable."[68]

In this case, the invention in question made it possible to resolve the technical problem of producing an almost unlimited quantity of isolated and purified precursor cells having neural or glial properties, obtained from human embryonic stem cells, and intended to be used to treat neurological disease like Parkinson's disease.[69] The CJEU looked into whether human embryonic stem cells constituted human embryos in the sense of Article 6(2)(c) of the Biotech Directive. The CJEU observed that the Biotech Directive seeks to harmonies protection of biotechnological invention and thus the understanding of what a human embryo is should be uniform in the EU[70] and understood in a wide sense[71] as "any human ovum…as soon as fertilized"[72] and as well as non-fertilized human ovum "capable of commencing the process of development of a human being."[73] The CJEU found that the destruction of a human embryo violates human dignity and, therefore, inventions based on such destruction cannot be patented.[74]

The CJEU in *Brüstle v Greenpeace* noted that the decision on what a human embryo is should consider the state of the art in science.[75] Since then discussions on the ethics of human embryo research do not cease.[76] New biotechnologies like somatic cell nuclear transfer and the use of pluripotent stem cells open possibilities to create embryos in vitro.[77] National legislation, even in EU states, regarding definition of embryo varies. "Legally, an embryo is not the same in Germany—where only the fertilized ovum is considered as such after the fertilization process has been completed—as it is in Spain—where a distinction is being made between embryo and pre-embryo—or in the Netherlands where it is a cell or group of cells with the potential to develop into an embryo."[78] These variations pose obstacles to research with human embryos and embryonic stem cells, a researcher moving from one country to another might not be able to continue her work. [79]

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[68] *Brüstle v Greenpeace*, para. 46.

[69] *Brüstle v Greenpeace*, paras. 16-18.

[70] *Brüstle v Greenpeace*, paras. 27, 28.

[71] *Brüstle v Greenpeace*, para. 34.

[72] *Brüstle v Greenpeace*, para. 35.

[73] *Brüstle v Greenpeace*, para. 36.

[74] *Brüstle v Greenpeace*, para. 52.

[75] *Brüstle v Greenpeace*, para. 37.

[76] Baldwin, Thomas. "Morality and Human Embryo Research: Introduction to the Talking Point on Morality and Human Embryo Research." *EMBO Reports* 10, no. 4 (2009): 299–300. https://doi.org/10.1038/embor.2009.37.

[77] De Miguel Beriain, Iñigo, et al. "Re-Defining the Human Embryo: A Legal Perspective on the Creation of Embryos in Research." *EMBO Reports*, vol. 25, no. 2 (2024): 467–70, https://doi.org/10.1038/s44319-023-00034-0.

[78] Ibid.

[79] For instance, in Germany, the Embryo Protection Act (ESchG) and the Stem Cell Act (StZG) prohibit research on and with human embryos and a number of procedures, used in international medical research using human embryonic stem cells (Ministry of Education and Research, "Human embryos in medical research: Taboo? - Justifiable? - Opportunity?" accessed October 13,2024. https://www.gesundheitsforschung-bmbf.de/ELSA-Konferenz/15650.php#:~:text=Due%20to%20the%20regulations%20of,participation%20in%20corresponding%20projects%20abroad).

Induced pluripotent stem cells (iPS cells/iPSCs) might be an alternative: iPS cells can be produced by reprogramming adult skin or blood cells from donors or patients.[80] However, there is some evidence to suggest that iPS cells exhibit certain genetic and epigenetic differences from Human Embryonic Stem Cells (hES cells/hESCs): iPS cells can retain epigenetic patterns from the adult cells from which they are generated and require further research.[81]

Another issue that raises discussions is the context of prohibition on using the body and its parts as such a source of financial gain is organoids for research, in particular brain organoids. The main reasons behind that are, firstly, the tension between the altruistic motivations of donors and the interests of commercial parties, secondly, some donors might be dependent on a commercial party because of their health condition, and thirdly, the close relational value of donors toward "their" organoids.[82]

### *ii. Prohibition on making the human body and its parts as such a source of financial gain and legal and ethical consideration of stem cells research in COMMUTE (WP4)*

Human dignity, the right to life, and the right to physical and mental integrity impose significant legal and ethical limitations on stem cell research. National legislation must be adhered to in order to ensure compliance with these fundamental rights.

Stem cell research is permitted to be conducted by law in the country where the research is performed as long as it meets the standards of applicable national ethical requirements. In COMMUTE WP4 partners are discussing possibilities to use different cell types, namely iPSCs, Embryonic Stem Cells (ESC), iPSC lines and also brain organoids. According to our research and answers of partners to our questionnaire WP4 partners (Germany, Luxembourg, the Netherlands, Spain) have different national legislation on stem cell research. The question arises of what legal consequences might be if the partners will need to transfer cells between the labs.

In Germany stem cell research is regulated with the German Stem Cell Act and the Embryo Protection Act.[83] The import of stem cells derived from embryos (ESC) before 1 May 2007 is allowed,[84] Although the process to derive ESC is still banned in Germany. German partner, Fraunhofer, will work with iPSC, produced in-house and supplied by WiCell (USA), in compliance with German legislation. Regarding the question of what legal and ethical implications might arise if there is a need to transfer ECS, supplied by

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[80] German Primate Center. "Stem Cell Research." DPZ, accessed October 13, 2024. https://www.dpz.eu/en/info-center/knowledge/stem-cell-research.html.

[81] Scesa, G., R. Adami, and D. Bottai. "iPSC Preparation and Epigenetic Memory: Does the Tissue Origin Matter?" *Cells* 10, no. 6 (2021): 1470. https://doi.org/10.3390/cells10061470.

[82] For a literature review on the matter see, Jongh, Dide de, Emma K. Massey, Ekaterine Berishvili, Laura Mar Fonseca, Fanny Lebreton, Kevin Bellofatto, Juliette Bignard, et al. "Organoids: a Systematic Review of Ethical Issues." *Stem Cell Research & Therapy* 13, no. 1 (2022): 1–337. https://doi.org/10.1186/s13287-022-02950-9.

[83] *Embryonenschutzgesetz* vom 13. Dezember 1990 (BGBl. I S. 2746), zuletzt geändert durch Artikel 1 des Gesetzes vom 21. November 2011 (BGBl. I S. 2228). Accessed [date]. https://www.gesetze-im-internet.de/eschg/.

[84] Stafford, Ned. "Germany Liberalises Law on Stem Cell Research." BMJ 336, no. 7649 (April 19, 2008): 851. https://doi.org/10.1136/bmj.39552.538356.DB.

Wicell (USA) from partners from Spain and the Netherlands to labs in Germany. In this scenario, such transfer might be legal and ethical, if the stem cells derived from embryos before 1 May 2007.

In Spain Law on Biomedical Research (Law 14/2007)[85] gives definition to embryo[86] and fetus,[87] allows and sets conditions for the research with human embryos and fetuses[88] and permits the use of any technique for obtaining human stem cells for therapeutic or research purposes.[89] BBRC, a COMMUTE partner from Spain, plans to use iPSC, produced in-house and supplied by CIRM_MTA commercial (USA) and WiCell (USA), which is in compliance with Spanish law.

In Luxemburg, there is no specific regulation on stem cell research. In general, medical research is regulated by Law relating to hospital establishments and hospital planning,[90] Grand-Ducal Regulation relating to the application of good clinical practices in the conduct of clinical trials of medicinal products for human use,[91] Grand-Ducal amending for the purposes of transposition of Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for the application of good clinical practice with regard to investigational medicinal products for human use, as well as the requirements for granting authorization to manufacture or import such medicinal product[92] and Law establishing the National Commission for Data Protection and Implementing Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.[93] This regulation provides that “Clinical trials are conducted in accordance with the amended Declaration of Helsinki on the ethical principles applicable to medical research involving human subjects, adopted by the General Assembly of the World Medical Association, published in Annex A of this Grand-Ducal Regulation.”[94]

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[85] Law of July 3, *On Biomedical Research*, 14/2007, Article III. http://www.boe.es/buscar/act.php?id=BOE-A-2007-12945.

[86] Ibid, Article “Embryo": a phase of embryonic development that extends from the moment in which the fertilized oocyte is in the uterus of a woman until the beginning of organogenesis, and which ends 56 days after the moment of fertilization, excluding from the calculation those days in which development could have stopped”.

[87] Ibid, "Fetus": an embryo with a human appearance and its organs formed, which matures from 57 days after the moment of fertilization, excluding from the calculation those days in which development could have stopped, until the moment of birth”.

[88] Ibid, Preamble III and Chapter II.

[89] Ibid, Article 33(2).

[90] Law of March 8, 2018, *Relating to hospital establishments and hospital planning*, A222. http://data.legilux.public.lu/eli/etat/leg/loi/2018/03/08/a222/jo.

[91] Grand-Ducal Regulation of 30 May 2005 relating to the application of good clinical practices in the conduct of clinical trials of medicinal products for human use. http://data.legilux.public.lu/eli/etat/leg/rgd/2005/05/30/n5/jo.

[92] Grand-Ducal Regulation of 10 January 2007 amending for the purposes of transposition of Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for the application of good clinical practice with regard to investigational medicinal products for human use, as well as the requirements for granting authorisation to manufacture or import such medicinal product. http://data.legilux.public.lu/eli/etat/leg/rgd/2007/01/10/n1/jo.

[93] Law of 1 August 2018 establishing the National Commission for Data Protection and implementing Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), amending the Labour Code and the amended law of 25 March 2015 establishing the treatment regime and the conditions and procedures for the advancement of civil servants. http://data.legilux.public.lu/eli/etat/leg/loi/2018/08/01/a686/jo.

[94] Grand-Ducal Regulation of 10 January 2007, Article4 (2).

Partners from Luxembourg will work with an in-house iPSC line, which is in line with their national legislation. Moreover, if there is a need to transfer ESC to Luxembourg, that will be also compliant with the national legislation, as the latter does not outlaw ESC.

In the Netherlands the Dutch Embryo law[95] gives such definition to embryo “a cell or coherent set of cells with the ability to grow into a human being”[96] And to the fetus "embryo in the human body”.[97] The Law allows research on embryos under certain conditions,[98] including the obligation not to allow embryos to develop outside the human body for longer than 14 days.[99]The partner from the Netherlands, AMC, plans to work with ESC from WiCell (USA) and with the iPSC line, which originated from GIBCO (EU). Both activities are compliant with national legislation, as well as the possible transfer of cells from other EU states during the COMMUTE project.

WP4 partners are currently in the process of obtaining necessary national law authorizations to conduct biomaterial research to ensure that activities in the project are regulatory compliant. WP5 Leader (UNIVIE) will provide legal analysis and support on drafting necessary contracts (e.g. Material Transfer Agreement) to WP4 partners to ensure regulatory compliance are adhered to throughout the project. A summary of the legal analysis will be included in the Legal and Ethical Framework update on M18.

## *2. Right to equality and Non-Discrimination*

### *A. Scope and Application*

The right to equality and the principle of non-discrimination (Article 26 ICCPR, Article 14 ECHR, Article 21 CFRE) are essential for human rights but challenging to implement because of their complex interpretation. Equality is understood multidimensionally as a requirement to address disadvantage and prejudice attached to a specific protected characteristic such as race, gender, or religion by way of accommodation of difference.[100] To achieve substantive equality states are obliged to adopt anti-discriminatory legislation, prohibiting direct and indirect discrimination to ensure that all people in similar

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[95] *Embryo law*, BWBR0013797. Government of the Netherlands, valid from July 1, 2021. https://wetten.overheid.nl/BWBR0013797/2021-07-01.

[96] Ibid, Article 1(c ).

[97] Ibid, Article 1(d).

[98] Ibid, Article 3(1).

[99] Ibid, Article 24(4). The Health Council of the Netherlands recommended prolonging this period up to 28 days due to technological developments, which make it possible to cultivate embryos outside the human body for up to 14 days and the scientific importance of the research with embryos beyond 28 days. https://www.healthcouncil.nl/documents/advisory-reports/2023/10/31/the-14-day-rule-in-the-dutch-embryo-act.

[100] Fredman, Sandra FBA KC. *Equality: Concepts and Controversies*. In *Discrimination Law*, 3rd ed., Clarendon Law Series. Oxford, 2022; online edn, Oxford Academic, 19 January, 2023. https://doi-org.uaccess.univie.ac.at/10.1093/oso/9780198854081.003.0001. Accessed 30 Sept. 2024.

situations are treated equally.[101] When prohibition is not enough for substantive equality, states are required to adopt special protective measures.[102]

The right to equality and the principle of non-discrimination are highly relevant to the COMMUTE project, as its AI-based predictive algorithm will analyze the health data of vulnerable patients, making predictions and categorizing them based on their health status.

### *B. Equality and Non-Discrimination in AI-Driven Healthcare*

Convergences of some of the challenges that AI poses might lead to the discrimination of some vulnerable groups of people. AI models make decisions by learning from the training data and are guided by parameters set by the developers. The training data might be biased, for instance, if it includes biased diagnoses[103] or biased historical data.[104] If AI is required to make diagnoses and recommendations, it should be guided by standards in the field. Thus, the standard for decision making has a particular significance, and if the standard is discriminatory, the AI will reproduce this bias.[105] A study showed that a commercial algorithm, used in the U.S. healthcare system made biased decisions assigning the same level of health risk to black patients as to the white patients, although in reality, the state of health of black patients was worse. [106] The algorithm took into consideration the amount of money Black patients spend on healthcare, disregarding that in general black patients spend less than the white because of their lower income.[107]

The question of liability arises. This is not an abstract question, as various AI tools have been already used to support decision-making in health care.[108] Who is responsible for the wrong decision: the AI developer, the AI provider, a medical professional, the hospital, or do they all share responsibility (and how)? The legal framework needs to be adapted to include AI in the liability considerations.[109] Nowadays most

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[101] ECRI General Policy Recommendation N°7 (revised) on national legislation to combat racism and racial discrimination, adopted on 13 December 2002 and revised on 7 December 2017.

[102] Convention on the Elimination of All Forms of Discrimination against Women New York, 18 December 1979, Article 11.

[103] For instance, Ana I. Balsa, Thomas G. McGuire, and Lisa S. Meredith, "Testing for Statistical Discrimination in Health Care," *Health Services Research* 40, no. 1 (2005): 227-52, https://doi.org/10.1111/j.1475-6773.2005.00351.x.

[104] Shahbazi, Nima, Yin Lin, Abolfazl Asudeh, and H. V Jagadish. "Representation Bias in Data: A Survey on Identification and Resolution Techniques." ACM Computing Surveys 55, no. 13s (2023): 1–39. https://doi.org/10.1145/3588433.

[105] Alami, H., Lehoux, P., Auclair, Y., de Guise, M., Gagnon, M., Shaw, J., Roy, D., Fleet, R., Ag Ahmed, M., and Fortin, J. "Artificial Intelligence and Health Technology Assessment: Anticipating a New Level of Complexity." *Journal of Medical Internet Research* 22, no. 7 (2020): e17707. https://doi.org/10.2196/17707.

[106] Obermeyer, Ziad, et al. "Dissecting Racial Bias in an Algorithm Used to Manage the Health of Populations." Science 366, no. 6464 (2019): 447-453. https://doi.org/10.1126/science.aax2342.

[107] Ibid.

[108] Khosravi, M., Zare, Z., Mojtabaeian, S. M., and Izadi, R. "Artificial Intelligence and Decision-Making in Healthcare: A Thematic Analysis of a Systematic Review of Reviews." *Health Services Research and Managerial Epidemiology* 11 (March 5, 2024): 23333928241234863. https://doi.org/10.1177/23333928241234863. PMID: 38449840; PMCID: PMC10916499.

[109] Bottomley, D., and Thaldar, D., "Liability for harm caused by AI in healthcare: an overview of the core legal concepts." *Frontiers in Pharmacology* 14 (December 14, 2023): 2023.1297353. doi: 10.3389/fphar.2023.1297353.

jurisdictions refer to the standard of care in defining liability for medical decisions.[110] AI might make this standard of care more complicated to apply if for instance, the algorithm does not explain its decisions.[111]

The proposed 2022 AI Liability Directive (AILD) does not address situations where healthcare professionals make decisions assisted by AI tools, as the directive applies only to fully automated AI systems.[112] While the AI Liability Directive is still under consideration,[113] New Product Liability Directive (PLD) was adopted and published 18 November 2024.[114] Its scope includes software and AI tools (except free and open-source),[115] extends the number of potential liable parties[116] for a defective[117] product, defines rule of burden of proof[118] and imposes procedural obligations like disclosure.[119] PLD as well as AILD does not address directly situations where healthcare professionals make decisions assisted by AI tools.

Another issue of concern is the security of sensitive data which AI uses to learn and/or make its decisions.[120] The general risks of reidentification of data subjects, legal and ethical limitations and data sharing or providing access to the data between researchers should be considered and might impact the research progress.[121] In relation to discrimination, the training data poses specific challenges, as it might be “imbalanced” (lack information about certain groups) or reflect past discrimination.[122]

These AI challenges might result in continuous discriminatory practices against vulnerable groups, as AI as such will not change existing bias, but reproduce it. A full legal analysis of the AI Liability Directive and New Product Liability Directive and its impact on the future deployment of AI/ML recommender system currently being developed in COMMUTE will be included in the next iteration of this report in M18.

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[110] Vanderpool D. The Standard of Care. Innov Clin Neurosci. 2021 Jul-Sep;18(7-9):50-51. PMID: 34980995; PMCID: PMC8667701.

[111] Price WN, Gerke S, Cohen IG. Potential Liability for Physicians Using Artificial Intelligence. JAMA. 2019;322(18):1765–1766. doi:10.1001/jama.2019.15064.

[112] European Commission. 2022. Proposal for a Directive of the European Parliament and of the Council on Adapting Non-Contractual Civil Liability Rules to Artificial Intelligence (AI Liability Directive). COM/2022/496 final, Recital 15. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52022PC0496.

[113] Legislative Train Schedule, AI liability directive. https://www.europarl.europa.eu/legislative-train/theme-legal-affairs-juri/file-ai-liability-directive

[114] Directive (EU) 2024/2853 of the European Parliament and of the Council of 23 October 2024 on liability for defective products and repealing Council Directive 85/374/EEC (Text with EEA relevance), PE/7/2024/REV/1. https://eur-lex.europa.eu/eli/dir/2024/2853/oj.

[115] Ibid, Article 4(1), Recital 13.

[116] Article 8.

[117] Ibid, Article 7.

[118] Ibid, Article 10.

[119] Ibid, Article 9.

[120] M.I. Jordan, T.M. Mitchell, Machine learning: Trends, perspectives, and prospects. Science349,255-260(2015).DOI:10.1126/science.aaa8415.

[121] Topol, E.J. High-performance medicine: the convergence of human and artificial intelligence. Nat Med 25, 44–56 (2019). https://doi.org/10.1038/s41591-018-0300-7.

[122] Information Commissioners Officer. “What about fairness, bias and discrimination?” Accessed October 11, 2024. https://ico.org.uk/for-organisations/uk-gdpr-guidance-and-resources/artificial-intelligence/guidance-on-ai-and-data-protection/how-do-we-ensure-fairness-in-ai/what-about-fairness-bias-and-discrimination/#:~:text=The%20fact%20that%20AI%20systems,less%20favourably%20without%20objective%20justification.

### C. Legal implications of classifying patients with the help of AI systems using biomarkers, in particular, the legal and ethical implications of classifying patients as "high-risk" in COMMUTE

The task of classification of patients based on their health status with the help of AI means that AI will be assisting in decision-making, which impacts patients. The impact relates to their health, interfering with their right to privacy and integrity. Moreover, such a decision might interfere with the right to equality as the aim is to differentiate between patients with high-risk and lower risk to health. The clinicians might be guided by this decision when diagnosing and deciding on the treatment. These factors point to a significant impact of AI use on fundamental rights.

Developers of AI healthcare decision-making assisting tools must ensure that the AI training data and parameters it would be guided are not biased to avoid the risk of AP reproducing the bias. Moreover, the algorithm of how AI makes its decisions should be understandable to clinicians to such an extent that they should be able to make informed decisions with the help of AI.

COMMUTE does not include the task of launching the AI healthcare decision-making assistance tool to the market, meaning it will not be used in day-to-day practice by the end of the project. However, to ensure that the AI-driven recommender system does not violate the principle of non-discrimination, partners must ensure that the system's decisions are accurate, fair, and free from bias, thereby upholding fundamental rights and avoiding the perpetuation of existing inequalities. To address these concerns, COMMUTE adopts a human-centric approach to AI modeling, which includes understanding and accounting for individual vulnerabilities in light of COVID-19 and neurodegenerative diseases (NDDs). Partners, including WP3, will gain insight into these vulnerabilities through regular patient engagement and stakeholder workshops.

## 3. Right to protection of personal data

The right to protection of personal data (Article 8 CFREU) plays a crucial role in the COMMUTE project as partners handle sensitive health data. It is crucial that they ensure full compliance with GDPR[123] requirements for data controllers and processors throughout the project’s duration. In particular, the data security should be achieved by way of application of anonymization and/or pseudonymization.

### A. Scope and application

The right to the protection of personal data can be understood as a part of a broader right to the protection of private life and as a separate right. The ECHR has one article devoted to the protection of private life

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[123] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (GDPR).

(Article 8), which extends to personal data protection.[124] In comparison, CFREU has two separate articles on respect for private and family life (Article 7) and focusing specifically on protection of personal data (Article 8). This approach to the right to personal data protection as a separate right is supported on national level, for instance German Constitutional Court elaborated on "informational self-determination" In the Census decision.[125]

In Article 4(1) GDPR defines personal data focusing on how data may relate to a person “any information relating to an identified or identifiable natural person”) and whether this person can be identified based on this data (“…by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person”).

Health data has a heightened protection as this data is a sensitive one and its disclosure might cause harm to a data subject. The need to treat this data under certain conditions is recognized in the GDPR as well as in the practice of the ECtHR.[126] Article 9(1) of the GDPR classifies health data as a special category of personal data or sensitive data in terms of Recital 51 and EDPB/Art. 29 WP. Recital 51 clarifies that inter alia health data is “sensitive in relation to fundamental rights and freedoms and merit specific protection as the context of their processing could create significant risks to the fundamental rights and freedoms”.

## B. *Measures to protect data privacy: anonymization and pseudonymization*

To avoid risks to personal data, certain mitigating measures should be adopted, among the most popular ones are anonymization and pseudonymization.

### i. *Anonymization*

GDPR does not mention anonymization as such, recital 26 GDPR gives a definition to anonymous information as "information which does not relate to an identified or identifiable natural person or to personal data rendered anonymous in such a manner that the data subject is not or no longer identifiable”. Therefore, anonymous data does not fall under the scope of GDPR protection. The Data Protection Directive 95/46/EC, superseded by GDPR, included recital 26, which referred to “ways in which data may be rendered anonymous and retained in a form in which identification of the data subject is no longer possible.” The Article 29 Working Party (now replaced by the European Data Protection Board) warned about the residual risk of re-identification linked to anonymization techniques.[127] Studies show researchers

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[124] European Court of Human Rights, *Catt v. the United Kingdom.* Judgement (First Section) 43514/15, January 24, 2019.

[125] *Volkszählungsurteil*, 65 BVerfGE 1, 68-69 (1983).

[126] European Court of Human Rights. *Y v. Finland*, Judgment (Fourth Section) 20511/03, 17 July 2008.

[127] Article 29 Data Protection Working Party. *Opinion 05/2014 on Anonymisation Techniques*, 0829/14/EN WP216, adopted April 10, 2014.

in clinical trials consider that anonymisation techniques by themselves are insufficient to protect patient privacy and accompany their use with controlled access.[128]

### *ii. Pseudonymization*

Pseudonymization is defined in Article 4(5) of the GDPR as "the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person." Pseudonymization means that the individual could still be identified indirectly (without putting a name, they could be distinguished out of a group of persons) as one attribute is replaced by another.

Article 29 Working Paty clarified that "pseudonymization is not a method of anonymization. It merely reduces the likability of a dataset with the original identity of a data subject, and is accordingly a useful security measure".[129] There is a fine line between anonymized and pseudonymized data, as the use of anonymization techniques in the context of the current state of developing technologies cannot guarantee the full absence of risk of reidentification. For instance, there is a debate if some types of data like genetic data can be effectively anonymized at all.[130]

The risk of re-identification should be assessed on a case-by-case basis, as indicated by the judgment of the General Court in case T-557/20.[131] The Court concluded that determining whether data is personal requires evaluating whether the data can be re-identified by a specific entity or if such re-identification is reasonably possible. In the context of the COMMUTE project, this implies that the data processed should be assessed from the perspective of whether it can be de-identified. These concerns are addressed in the DPIA.

## *C. Consent under the GDPR from patients with neurodegenerative diseases such as Alzheimer's in COMMUTE*

The data processed in the framework of COMMUTE is health data, the processing of which requires justification under at least one of the conditions specified in Art. 9(2) in addition to conditions for lawfulness of the processing of personal data, outlined in Art. 6(1).

UNIVIE conducted the data protection impact Assessment (DPIA) of the data processing in the COMMUTE. DPIA identified five risks: illegitimate access to personal data, unwanted modification of personal data,

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[128] Rodriguez A, Tuck C, Dozier MF, Lewis SC, Eldridge S, Jackson T, Murray A, Weir CJ. Current recommendations/practices for anonymising data from clinical trials in order to make it available for sharing: A scoping review. Clin Trials. 2022 Aug;19(4):452-463. doi: 10.1177/17407745221087469. Epub 2022 Jun 22. PMID: 35730910; PMCID: PMC9373195.

[129] Opinion 05/2014 on Anonymisation Techniques, 0829/14/EN WP216, ARTICLE 29 DATA PROTECTION WORKING PARTY, Adopted on 10 April 2014.

[130] Johanna Rahnasto, Genetic data are not always personal—disaggregating the identifiability and sensitivity of genetic data, *Journal of Law and the Biosciences*, Volume 10, Issue 2, July-December 2023, lsad029, https://doi.org/10.1093/jlb/lsad029.

[131] Judgment of the General Court (Eighth Chamber, Extended Composition), Case T-557/20, 26 April 2023.

personal data disappearance or loss, re-identification of data subjects and AI-related risk. All the risks range from low to medium, which is explained by the fact that the majority of the data comes from existing datasets with retrospective data, and no collection of new clinical data is planned during COMMUTE. Mitigation measures such as physical access control, measures to preserve data quality, anonymization or pseudonymization, minimization of the amount of processing of personal data have already and continuous monitoring of possible AI-related concerns building on the expertise of the partners, have been addressed by the partners, thereby reducing the risks.

In COMMUTE, partners use datasets which hold mostly pseudonymised data. The data providers specified in the COMMUTE DPIA that the data is treated confidentially and stored so that it is not possible to identify the data subject. Anonymisation is used in one study, Predi-COVID, when feasible.[132]

The data processed in COMMUTE includes information on vulnerable groups, specifically individuals with Neurodevelopmental diseases (NDDs). Two partners—LIH and UCPH—indicated in the DPIA questionnaire that their datasets include data on vulnerable groups. These are the following datasets: CON-VINCE/ORCHESTRA/PrediCOVID cohorts, ND-collection cohort and Danish National Registries and Electronic Healthcare Records. Individuals with NDDs have the right to give informed consent to participate in research studies or to share their health data with researchers. When they lack the capacity to provide consent themselves, this can be done via a proxy.[133] COMMUTE partners process this data for scientific research purposes under Article 9(2)(j) of the GDPR, applying safeguards outlined in Article 89(1), such as pseudonymization and anonymization referred above. This approach aligns with Recital 33 of the GDPR, which allows flexibility in the degree of specificity and granularity of consent in the context of scientific research. The purposes of research conducted in COMMUTE are communicated through the COMMUTE website[134] and other dissemination events such as public discussions.[135] These measures intend to implement transparency safeguard when the circumstances of the research do not allow for a specific consent. Together with other safeguards[136] (detailed in the DPIA), these measures ensure compliance with GDPR requirements.

## 4. *Freedom of scientific research*

Freedom of scientific research (Article 13 EUCHR, Article 10 ECtHR) is a central pillar of the COMMUTE project, as partners seek to apply advanced research methods, such as AI and cell-based research, to

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[132] See, COMMUTE DPIA for details.

[133] Kim SY. The ethics of informed consent in Alzheimer disease research. Nat Rev Neurol. 2011 May 24;7(7):410-4. doi: 10.1038/nrneurol.2011.76. PMID: 21610690; PMCID: PMC3475518.

[134] COMMUTE website. https://www.commute-project.eu/en/about.html.

[135] See the recording of a public discussion on Predictive Medicine and Patients Rights: https://youtu.be/cAS4AgMb3jg.

[136] Article 29 Data Protection Working Party. Guidelines on Consent Under Regulation 2016/679, WP259 rev.01, 2018. https://ec.europa.eu/newsroom/article29/document.cfm?action=display&doc_id=51030.

develop and validate AI-driven tools for treating neurodegenerative diseases (NDD). In pursuing these goals, partners must carefully balance their freedom of research with respect for human dignity and patients' rights, including the right to life, bodily integrity, equality, non-discrimination, and privacy.

### A. Scope and application

Freedom of scientific research is a right outlined in legal texts along with other concepts. Article 13 EUCHR covers three concepts: artistic, scientific and academic.  ECHR does not confer a separate right on freedom of scientific research, but this right is covered in Article 10 on freedom of expression.

"Research" is defined on the EU level as "creative work undertaken on a systematic basis in order to increase the stock of knowledge, including knowledge of man, culture and society, and the use of this stock of knowledge to devise new applications".[137]

EU has the aim of protecting the freedom of research in its design. Article 179 of the TEU proclaims that "the Union shall have the objective of strengthening its scientific and technological bases by achieving a European research area in which researchers, scientific knowledge and technology circulate freely, and encouraging it to become more competitive, including in its industry, while promoting all the research activities deemed necessary by virtue of other Chapters of the Treaties."[138]

EU adopted Horizon Europe as a funding programme for research and innovation.[139] The programme promises to facilitate collaboration and strengthen the impact of research and innovation in developing, supporting and implementing EU policies while tackling global challenges with the budget for the period 2021-2027 of EUR 93.5 billion.[140]

Freedom of research is impossible to implement without access to data, which is at the core of modern research. To ensure access to data the EU adopts a policy intended to make the EU a role model for a society empowered by data. [141] An integral part of the measures to pursue this aim is the Data Governance

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[137] Council Directive 2005/71/EC of 12 October 2005 (OJ L 289/15) on a specific procedure for admitting third-country nationals for the purposes of scientific research, Art. 2(b).

[138] Consolidated version of the Treaty on the Functioning of the European Union. Official Journal of the European Union C 326, 26 October 2012. PART THREE - UNION POLICIES AND INTERNAL ACTIONS, TITLE XIX - RESEARCH AND TECHNOLOGICAL DEVELOPMENT AND SPACE, Article 179 (ex Article 163 TEC).

[139] European Commission. *Horizon Europe*. European Union. Accessed October 11, 2024. https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe_en.

[140] Ibid.

[141] European Commission. *European Data Strategy*. European Union, https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/europe-fit-digital-age/european-data-strategy_en.

Act,[142] Data Act,[143] And not yet in force European Health Data Space.[144] These acts are intended to ensure the creation of a European single market for data by way of setting clear and fair rules on access and re-use of data and at the same time ensuring the protection of privacy of the data subjects.

Freedom of research is not an unlimited right, and in particular, it should not violate human dignity. The Court of Justice ruled that patent protection on inventions based on human embryonic stem cells is forbidden in the EU because the destruction of an embryo violates human dignity.[145] The EU Horizon does not support research, which:

"– aim at human cloning for reproductive purposes;

– intend to modify the genetic heritage of human beings which could make such changes heritable (except for research relating to cancer treatment of the gonads, which may be financed);

– intend to create human embryos solely for the purpose of research, or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer".[146]

The understanding of the boundaries for scientific research based on human dignity is intertwined with ethics. In the EU the ethical perspective in decision-making related to scientific research can be traced to 1991 when the European Commission the Group of Advisers on the Ethical Implications of Biotechnology, which was replaced in 1997 by the European Group on Ethics in Science and New Technologies ('EGE'), which mandate was renewed indefinitely in 2021.[147] The EGE provide independent advice at a horizontal level to the Commission on all Union policies and legislation where ethical, societal and fundamental rights dimensions intersect with the development of science and new technologies.[148] and develop in-depth analyses and specific recommendations addressing major ethical challenges in opinions and statements.[149] The EGE identified shifts in the perception of health and healthcare, including a sense of agency of the patients in the production of medical knowledge and innovation.[150] The EGE addressed ethical questions

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[142] European Parliament and Council of the European Union. *Regulation (EU) 2022/868 of the European Parliament and of the Council of 30 May 2022 on European Data Governance and Amending Regulation (EU) 2018/1724 (Data Governance Act) (Text with EEA Relevance).* Official Journal of the European Union, L 152, June 3, 2022, pp. 1–44.

[143] European Parliament and Council of the European Union. *Regulation (EU) 2023/2854 of the European Parliament and of the Council of 13 December 2023 on Harmonised Rules on Fair Access to and Use of Data and Amending Regulation (EU) 2017/2394 and Directive (EU) 2020/1828 (Data Act) (Text with EEA Relevance).* Official Journal of the European Union, L 351, December 28, 2023, pp. 1–78.

[144] European Union. "European Health Data Space." Accessed October 9, 2024. https://health.ec.europa.eu/ehealth-digital-health-and-care/european-health-data-space_en.

[145] Court of Justice of the European Union. *Case C-34/10 Oliver Brüstle v Greenpeace*. ECLI:EU:C:2011:669, October 18, 2011.

[146] European Commission. *Horizon Europe Work Programme 2023–2025, 13. General Annexes*. C(2024) 2371 of 17 April 2024. European Commission, 2024.

[147] Commission Decision (EU) 2021/156 of 9 February 2021 renewing the mandate of the European Group on Ethics in Science and New Technologies. Official Journal of the European Union, L 46/34, 10 February 2021.

[148] Ibid, Preamble, sec 5.

[149] Ibid, sec. 6.

[150] European Group on Ethics in Science and New Technologies. *Opinion on the Ethical Implications of New Health Technologies and Citizen Participation*. European Commission, European Group on Ethics in Science and New Technologies, 2016.

regarding genome editing.[151] The EGE also adopted a statement on the role of ethics in European and global governance, linking ethics to fundamental rights, democracy and the rule of law.[152]

In summary, freedom of research is a fundamental human right, which has a specific value for the EU, materialized in financial support of research and innovation and regulatory efforts to facilitate access to data across the EU. At the same time, this freedom should not violate human dignity and the right to privacy. The balancing exercise between them and the freedom of research should be guided by public morals and ethics, the latter having a unified understanding due to the adoption of international conventions and declarations concerning ethics and health research.

### *B. Freedom of scientific research and data management in COMMUTE (WP2)*

COMMUTE contributes to the freedom of scientific research using Disease Maps and knowledge graphs (KGs) to encompass the data in the areas of NDDs and COVID. Since Disease Maps and cause-and-effect KGs are new tools in translational clinical research, COMMUTE will organize annual workshops on the algorithmic utilization of KGs for data- and knowledge integration, pattern interpretation and their integration in modern AI methodologies (T2.2). These workshops will be open to everybody interested and are part of the technical dissemination activities in COMMUTE. The aim is to promote and facilitate new tools among researchers.

### *C. Freedom of scientific research and patient engagement in COMMUTE (WP5)*

T5.2 includes involvement of patients and other stakeholders such as healthcare professionals, and health care institutions by providing a series of annual workshops. The workshop will aim to incorporate the interests of patients and other stakeholders by on the one hand presenting arising, identified challenges in the project and the proposed solutions to them and on the other hand entering into an exchange of ideas concerning these arising challenges. The goal is to achieve a better understanding of user expectations and needs as well as to foster an understanding of the users' perspective. Input and insights from the workshop will be gathered, shared with partners in written form after every workshop, and published as a set of recommendations at the end of the project. UNIVIE as a legal and ethics partner will coordinate the workshops and introduce arising legal and ethical challenges as well as proposed solutions. Partners involved in the task are connected with possible end-users of the project's outcome (FRAUNHOFER, BBRC, LIH), in order to involve a wide network of stakeholders in the workshops.

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[151] European Group on Ethics in Science and New Technologies. *Opinion on the Ethics of Genome Editing*. European Commission, European Group on Ethics in Science and New Technologies, 2021.

[152] Ibid.

# Chapter III. Legal Framework: Artificial Intelligence Act and Medical Device Regulation

## AI Act

COMMUTE project builds on available data and the application of AI/ML technologies, in order to provide an answer on whether infection by SARS-CoV-2 causes effects which lead to a higher risk for the development of NDDs at population-level.[153] This first iteration of the report on the review of current state of ethical and legal discussion provides of an overview of the relevant requirements and guidance for the development of trustworthy AI/ML technologies.

Introduced as a Proposal for a Regulation on artificial intelligence by the European Commission in April 2021[154], the Artificial Intelligence Act (AI Act) has been adopted on 1st of August 2024.[155] The novel piece of legislation aims to ensure the trustworthiness of AI which is being developed and used in the European Union. The AI Act seeks to ensure that high-risk AI does not interfere with fundamental rights, democracy, the rule of law, and environmental sustainability. Thus, based on its potential risk and level of impact, AI is met with certain obligations.[156]

### a. Subject Matter and Scope

Article 1 defines the subject matter of the AI Act, namely*:* Harmonized rules for the placing on the market, the putting into service, and the use of artificial intelligence systems (‘AI systems’) in the Union; Prohibitions of certain AI practices; Specific requirements for high-risk AI systems and obligations for operators of such systems; Harmonized transparency rules for certain AI systems; Harmonized rules for the placing on the market of general-purpose AI models (‘GPAI models’); Rules on market monitoring, market surveillance, governance, and enforcement; Measures to support innovation, with a particular focus on small and medium enterprises (‘SMEs’), including start-ups.

The AI Act will pertain to providers which are placing on the market or putting into service AI systems or placing on the market general-purpose AI (GPAI) models in the Union, irrespective of whether the establishment of these providers is located within the Union or in a third country. This regulation is further

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[153] COMMUTE Grant Agreement, Description of the action (DoA), p.3.

[154] European Commission. Pr*oposal for a Regulation of the European Parliament and of the Council on the European Health Data Space*. COM(2021) 206 final, April 2021. Accessed October 13, 2024. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52021PC0206.

[155] European Commission, “European Artificial Intelligence Act comes into force”. Accessed October 13, 2024. https://ec.europa.eu/commission/presscorner/detail/en/ip_24_4123.

[156] European Parliament. “Artificial Intelligence Act: Deal on Comprehensive Rules for Trustworthy AI.” Press Room. Last modified December 9, 2023. Accessed January 9, 2024. https://www.europarl.europa.eu/news/en/press-room/20231206IPR15699/artificial-intelligence-act-deal-on-comprehensive-rules-for-trustworthy-ai.

applicable to AI system deployers located within the EU. Additionally, the AI Act remains has further extra-territorial application, as it applies to providers and deployers of AI systems located in third countries, as long as the output produced by the system is utilised in the European Union.

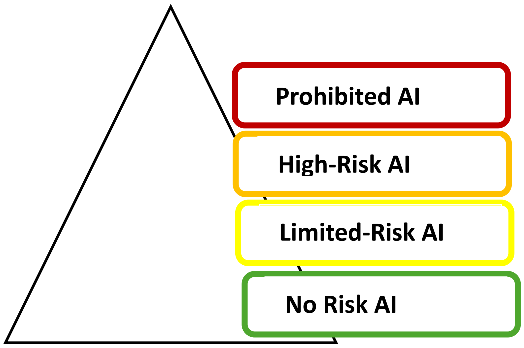
Article 3 AI Act covers the following definitions:

- "AI systems" are defined as "a machine-based system designed to operate with varying levels of autonomy and that may exhibit adaptiveness after deployment and that, for explicit or implicit objectives, infers, from the input it receives, how to generate outputs such as predictions, content, recommendations, or decisions that can influence physical or virtual environments".
- "Provider" refers to "a natural or legal person, public authority, agency or other body that develops an AI system or a general-purpose AI model or that has an AI system or a general-purpose AI model developed and places them on the market or puts the system into service under its own name or trademark, whether for payment or free of charge."
- "Deployer" refers to "any natural or legal person, public authority, agency or other body using an AI system under its authority except where the AI system is used in the course of a personal non-professional activity".
- "Placing on the market" means the first making available of an AI system or a general-purpose AI model on the Union market;
- "Making available on the market" refers to any supply of an AI system or a general-purpose AI module for distribution or use on the Union market in the course of a commercial activity, whether in return for payment or free of charge.

b. Regulating AI systems

The AI systems are categorised into four levels, according to a risk-based approach. The four risks levels are illustrated in the Diagram below.

Figure 1: Risk Categories



c. Prohibited AI practices

Any AI systems which are not in line and do not comply with EU values and infringe upon fundamental rights are banned under the AI Act. This includes purposefully manipulative or deceptive techniques, exploitation of vulnerabilities, evaluation or classification of natural persons, social scoring, 'real time' remote biometric identification, risk assessment for criminal offences, facial recognition, emotional inference, biometric categorization systems.[157]

The AI Act provides for an exception to the prohibition of manipulative and exploitative practices in the context of medical treatment (psychological treatment or physical rehabilitation), when this is conducted in line with applicable law, medical standards, such as receiving the consent from the individual or their representative.[158] Emotional recognition systems are allowed when they are intended for medical and safety reasons.[159] 'Real-time' remote biometric identification is also allowed when the usage is strictly necessary situations such as targeted crime prevention or the localisation or identification of a person suspected of having committed a criminal offence.[160]

d. High-risk AI systems

There are two situations in which an AI system is classified as high risk:

Firstly, an AI system is considered to be high-risk if the following two conditions are met: (1) the AI system is intended to be used as a safety component or a product or is itself a product and (2) is required to undergo a third-party conformity, with a view to the placing on the market or putting into service of that product, pursuant to the Union harmonisation law.[161]

Secondly, any AI systems which fall under one the eight specific areas mentioned under Annex III ought to be considered to be high risk.[162] These systems however may not be considered high-risk where they do not pose a significant risk of harm to the health, safety, or fundamental rights of natural persons, and fulfills the following conditions: it is intended to perform a narrow procedural task, it improves the result of a previously completed human activity, it is intended to detect decision-making patterns or deviations from prior decision-making patterns and is not meant to replace or influence the previously completed human assessment or is intended to perform a preparatory task for an assessment relevant to the purpose

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[157] AI Act, Article 5(1).
[158] AI Act, Recital 29.
[159] AI Act, Article 5(1)(f).
[160] AI Act, Article 5(1)(h).
[161] AI Act, Article 6(1).
[162] AI Act, Article 6(2).

of the use cases listed in Annex III.[163] Nevertheless, an AI system referred to in Annex III is considered to be high-risk where the AI system performs the profiling of natural persons.[164]

The COMMUTE project will integrate the AI/ML models obtained from experimental validation into a web-based, recommender system which will be developed by WP3. The AI recommender system may aid general practitioners in offering advice to a patient, help doctors decide whether the patient shall be further referred to a medical specialist and propose and provide personalized lifestyle recommendations.[165] Due to the health-related objective, the AI recommender system may fall under the definition of a ‘safety component’, Article 3(14) AI Act.[166]

Therefore, the AI recommender system developed within the project may be considered a safety product categorised as a high-risk AI system. Nevertheless, the second condition under Article 6(1)(b) is not applicable since the prototypic AI recommender system developed by COMMUTE project serves solely as a proof-of-concept and the placing of the market of this system will not take place within the project’s timeline.[167] The impact of the AI Act on the post-project phase of COMMUTE shall be covered in the final iteration of the Legal and Ethical Framework due at the end of the project (M48).

A more comprehensive list of practical examples of use cases of AI systems which are considered high-risk or not high-risk will be provided by the Commission, no later than 2 February 2026.[168] WP5 Leader (UNIVIE) shall then prepare a legal memorandum and a workshop on the AI Act to ensure that the technical partners remain informed of the implications of the AI Act especially in the post-project phase.

### Requirements for high-risk AI systems[169]

The AI Act aims to mitigate any associated risks by placing specific obligations on providers of high-risk AI systems.[170] Understanding potential implications and legal requirements is necessary since the nature of the AI recommender system may result in its classification as a high-risk AI system. The respective obligations are the following:

- Implement and maintain **a risk management system** across the high-risk AI system’s lifecycle. (Article 9)

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[163] AI Act, Article 6(3).

[164] Ibid.

[165] COMMTE Grant Agreement, Description of Action Annex 1 Part B, p 20.

[166] [166] AI Act, Article 3(14) defines ‘safety component’ as a “component of a product or of an AI system which fulfils a safety function for that product or AI system, or the failure or malfunctioning of which endangers the health and safety of persons or property”.

[167] COMMUTE Grant Agreement, Description of Action Annex 1 Part B, p.28.

[168] AI Act, Article 6(5).

[169] This section reflects the requirements for high-risk AI, previously reflected under Chapter 2 of the AI Act Proposal.

[170] AI Act, Article 8.

- Manage **data and data governance** to guarantee that training, validation and testing datasets are relevant, sufficiently representative and, to the greatest degree possible, free of errors and complete according to the designated purpose. (Article 10)
- Prepare and update the **technical documentation** which demonstrates compliance, as well as providing authorities with the relevant information for evaluating the compliance with the law (Article 11)
- High risk AI systems must be designed with the ability for **record-keeping**, in order to enable it to automatically record events relevant for identifying national level risks and significant changes during the AI system's lifecycle. (Article 12)
- Provide instructions to downstream deployers to facilitate their compliance. (**transparency and provision of information to deployers**) (Article 13)
- High risk AI systems must be designed to allow deployers to implement **human oversight**. (Article 14)
- High risk AI system must achieve suitable levels of **accuracy, robustness, and cybersecurity.** (Article 15)
- Set up a **quality management system** to guarantee compliance.(Article 17)

e. Limited Risk AI systems

The third category, limited-risk AI systems is concerned with the risk associated by lack of transparency of the use of AI.[171] AI systems which fall under this category includes for example chatbots and deep fakes. Article 50 of the AI Act introduces specific transparency requirements on providers of limited-risk AI systems. Individuals which are interacting with AI systems must be informed of this fact, unless this is obvious from the point of view of a natural person who is reasonably well-informed, observant, and circumspect. Nevertheless, the transparency obligation does not apply to AI systems authorized by law with the scope to detect, prevent, investigate or prosecute criminal offences, provided that the rights and freedoms of third parties are respected and safeguarded.[172]

f. Minimal or no Risk AI systems

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[171] European Commission. "Shaping Europe's Digital Future: AI Act." Accessed January 9, 2024. https://escienceediting.org/journal/view.php?doi=10.6087/kcse.341.

[172] AI Act, Article 50.

The AI Act permits the unregulated use of minimal or no-risk AI systems, which are not imposed to fulfil any specific obligations. Examples of low-risk AI systems provided by the European Commission are video games or spam filters.[173]

### g. The AI Act and COMMUTE Project

#### Research exemption

The AI Act carves out an exemption for AI systems and models, including their output, which are developed and put into service solely for scientific research and development.[174] The Regulation is not applicable to the AI systems and models prior to their placement on the market or put into service.[175] Nevertheless, the obligations found under the AI Act become applicable the moment the AI model or system is made available on the market. Additionally, requirements concerning regulatory sandboxes and testing in real-world conditions are applicable regardless of whether the AI systems or AI models are already put into the market or into service.[176]

The final results obtained from the workstream in COMMUTE projects are: firstly*, a mechanism associated, easily measurable biomarkers that form the basis for actionable knowledge in digital devices (recommender systems usable for GPs to assess personalized risk); secondly, qualified candidate biomarkers that form the basis for mechanistic understanding and diagnostics of comorbidity and thirdly, mechanism-associated, putative targets and qualified assays for drug repurposing screenings.*[177]

After the experimental validation (WP4), the AI/ML models will be embedded into a web-based, personalized recommender system. This recommender system will be developed at a later stage in the project and it will serve only as a proof of concept. In order to introduce the software into medical routine, a prospective validation obtained through dedicated clinical study and approval by a regulatory agency are necessary.

The necessary steps for obtaining a prospective validation (i.e, dedicated clinical study and approval by a regulatory agency) for the translation of the software into a medical routine, overpasses the scope of the COMMUTE project. The validation of the AI/ML algorithms will not reach the required level for market access by the conclusion of the project.[178]

In light of these findings, it can be concluded that the proof-of-concept AI recommender system developed within the COMMUTE project run time will fall under the research exemption prescribed under Recital 25 and Articles 2(6) and 2(8) of the AI Act. This arises from the fact that the prototype will not be completed

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[173] European Commission. “Shaping Europe’s Digital Future: AI Act.” Accessed January 9, 2024. https://escienceediting.org/journal/view.php?doi=10.6087/kcse.341.

[174] AI Act, Article 2(6).

[175] AI Act, Article 2(8).

[176] AI Act, Recital 25.

[177] Grant Agreement, Description of Action Annex 1 Part B, p.14.

[178] COMMUTE Grant Agreement, Description of Action Annex 1 Part B, p.28.

within the COMMUTE Project timeline and is intended solely as a proof of concept of the research conducted within the Project and for the use by clinicians involved in the Consortium.

The developed prototype is required to undergo a thorough evaluation process, as the initial assessment may classify the prototype to fall under the high-risk AI system. Consequently, the design of the prototype must ensure compliance with the AI Act in order to meet the necessary standards for being put into the market. Recommendations on how to ensure regulatory compliance of the developed AI/ML recommender system in the post-project phase will be included in D5.6 (Recommendations on ethical and legal considerations of COVID-19 – NDD comorbidity) due in M48.

Within the context of the COMMUTE project, the interplay between the AI Act and the AI recommender system will be continuously monitored, specifically given the AI system's potential classification as high-risk AI. Therefore, the legislative framework will be closely monitored, and any relevant recommendations may be disseminated by UNIVIE, in its capacity as the legal partner, as an academic contribution. Additionally, these insights will be incorporated into Deliverable D5.7 Joint symposium with ethics / legal experts from other projects funded in this call on ethical and legal aspects of COVID-19 - NDD comorbidity.

# Medical Device Regulation

## a. General Overview and Scope

The Medical Devices Regulation (MDR) entered into force on 31st May 2021 and it is replacing the Medical Devices Directive and the Active Implantable Medical Devices Directive.[179] The revision of laws concerning medical devices draws upon the need to align with the last 20 years development. The aim is to ensure a robust, transparent and sustainable regulatory framework while maintaining a high safety standards and support innovation. [180]

The MDR concerns medical devices which are placed on the market or which are used in medical treatment and/or diagnosis of humans. The Regulation covers rules on medical devices along with affiliated accessories[181], and the product classes lusted in Annex XVI which do not have a medical function.[182]

## b. Medical Device Definition

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[179] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, OJ L 117, 5 May 2017, 1–175 (MDR).

[180] European Commission. "New Regulations for Medical Devices." Accessed October 13, 2024. https://health.ec.europa.eu/medical-devices-sector/new-regulations_en#mdr.

[181] MDR, Article 1(1).

[182] MDR, Article 1(2).

Medical device is defined as "*any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:*

- *diagnosis, prevention, monitoring, prediction, prognosis, treatment, or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
- *investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,*
- *providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,*

*and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means*."

The prototypical AI recommendation system developed within COMMUTE would most probably qualify as a medical device as it aims to help general practioners in, doctors and provide personalized health recommendations.

c. Classification of Medical Devices

In light of the intended purpose of the device and the associated risk, medical devices are divided into distinct classes. Additional obligations are places on specific classes which need to be respect, in addition to the relevant obligations found under MDR. The legislation prescribes the following classes: Class I, Class IIa, Class IIb, Class III.

Article 2(4) MDR states that software is deemed to be considered an active device, which refers to "*any device, the operation of which depends on a source of energy other than that generated by the human body for that purpose, or by gravity, and which acts by changing the density of or converting that energy*."[183] Annex VIII of MDR lays down 22 classification rules specific to invasive and non-invasive devices. Rule 11 focuses on software as medical device, according to which software may fall under the following classes:

A) Class IIa: software intended to "provide information used to take decisions with diagnosis or therapeutic purposes" or "monitor physiological processes"

B) Class IIb: software intended "for monitoring of vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger to the patient" or "a serious deterioration of a person's state of health or a surgical intervention"

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[183] Additionally, Article 2(4) states that "*devices intended to transmit energy, substances or other elements between an active device and the patient, without any significant change, shall not be deemed to be active devices*."

C) Class III: software intended to provide information which is used in taking decisions which may cause “death or an irreversible deterioration of a person's state of health”

D) Class I: all other software

The European Court of Justice has previously addressed the question of whether software *that compares patient data with medicines that a doctor is considering prescribing* ought to be classified as a medical device.[184] The Court found that while the software was not used directly in or on the human body, this software is considered a medical device within the meaning of the MDR because it is used for the "prevention, monitoring, treatment or alleviation of disease"[185] and therefore has a specific medical purpose.

The AI recommender system developed in the COMMUTE project may be qualified under Class IIa, as it will provide information required for taking decisions regarding the treatment and the diagnosis of patients with neurodegenerative conditions. The Ai recommender system may also fall under Class IIb if any risks to the patient’s health may be inflicted. This holds true for the majority of AI tools that will be developed and used within the health and medical field.[186]

d. MDR and COMMUTE

One of the end goals of the COMMUTE project is to develop *a mechanism-associated, easily measurable biomarkers that form the basis for actionable knowledge in digital devices (recommender system usable for GPs to assess personalized risk*[187]). The applicability of the MDR to the COMMUTE recommender system is dependent upon whether it will be placed on the market. Since the recommender system serves solely a proof-of concept role, it will be used solely for validating research conducted within the Project. Any marketability of the AI system does not fall under the scope of COMMUTE’s run time. Nevertheless, the development of the recommender system needs to have in sight the general obligations under MDR, for the future possibility of providing the AI system on the market.

The recommendations generated by trained AI-models will be evaluated and tested together with COMMUTE clinical partners. In the case where positive outcomes are obtained from the recommender AI system, this would be advanced into a fully developed tool for end-users. Therefore, collaboration with an eHealth software company, which will take on the necessary regulatory approvals, will be pursued. This step is beyond the scope of academic R&D and it will take place at the end of the COMMUTE project.

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[184] European Court of Justice, *C-329/16 Syndicat national de l’industrie des technologies médicales (Snitem), Philips France v Premier ministre, Ministre des Affaires sociales et de la Santé*. Accessed October 13, 2024. eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:62016CC0329&from=NL.

[185] Ibid, para 53.

[186] [186] Emilia Niemiec, ‘Will the EU Medical Device Regulation Help to Improve the Safety and Performance of Medical AI Devices?’ (2022) 8 Digital Health 1, 3

[187] Grant Agreement, Description of Action Annex 1 Part B, p.14.

In the possibility that the recommender system will be developed and placed on the market, it may fall under Class IIa or Class IIb, since its scope would be to aid GPs in taking decisions in regard with diagnosis purposes. Following this, COMMUTE may need to consider the obligations prescribed for medical devices in case that the recommender system developed within the project will fall under Class IIa or Class IIb. t. Additionally, Article 52(6) MDR, lays down the conformity assessment procedure which ought to be considered by manufacturers of class IIa devices.

e. Interplay AI Act and MDR

As seen above, the AI Act lays down the mandatory requirements with which the high-risk AI system must comply with in order to be placed on the market. Additionally, the AI Act refers in Recital 46 to the New legislative Framework, according to which a product may be subject to various Union harmonisation laws (which are laid down under Annex 1 of the AI Act). MDR is one of the legislative acts mentioned under Annex 1. In light of this, providers of products which contain high-risk AI systems ought to express flexibility and respect requirements found in both AI Act and MDR.[188]

Therefore, since the MDR does not explicitly regulate AI, the AI act aims to bridge the existing legal gap.[189] Article 43(3) of the AI Act lays down the obligation of a provider of an AI system which is part of a medical device, to follow the relevant' regulation conformity assessment rules.[190] A medical device which includes an AI system which impacts its safety will be classified as high-risk, adding a layer of conformity for AI systems provided in the health space.[191]

# Conclusion

The report addresses the legal and ethical considerations relevant for the COMMUTE project. Ethical analyses included, in particular, the Ethics Guidelines for Trustworthy AI published by the High-Level Expert Group on AI (HLEG), the Declaration of Helsinki by the World Medical Association (WMA). Moreover, the establishment of the COMMUTE Legal and Ethical Advisory Board (LEAB) serves as an external advisory body, ensuring that COMMUTE partners effectively implement a human-centered approach by actively prioritizing the rights of NDD patients and the needs of end-users at every stage of the project. The ethical concerns identified in the reports concerns biomarker research on AD and PD and the right not to know biomarker results and possible negative impact from disclosure and other ethical issues will be addressed in COMMUTE by hosting symposia on recommender systems WP3 and patient engagement workshops in

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[188] AI Act, Recital 46.

[189] Timo Minssen, Barry Solaiman, Lea Köttering, Jakob Wested, and Abeer Malik, "Governing AI in the European Union: Emerging Infrastructures and Regulatory Ecosystems in Health," in *Research Handbook on Health, AI and the Law, ed. Barry Solaiman and I. Glenn Cohen* (Cheltenham: Edward Elgar Publishing, 2024), 311–331.

[190] AI Act, Article 43(3).

[191] Minssen et al., "Governing AI in the European Union," op. cit.

WP5. The first workshop has been already taken place in November 13, 2024. The partners were introduced to patients perspective on AI driven healthcare and discussed human-centric perspective in AI modelling in COMMUTE.

As part of legal framework, the rights to human dignity, to life, mental and physical integrity, privacy, freedom of scientific research and principle of non-discrimination, enshrined in the CFREU and the ECHR and national legislation were outlined in this report. The analysis of the legal and ethical implications of stem cell research in COMMUTE (WP3), particularly in relation to human dignity, the right to life, and the right to mental and physical integrity found no barriers to the planned research activities in relation to COMMUTE. Nevertheless, WP5 leader (UNIVIE) shall continue to monitor arising legislations in coordination with all COMMUTE partners to ensure regulatory compliance throughout the project.

The most effective approach to implementing the right of patients with neurodegenerative diseases (NDDs) to informed consent within the AI-driven recommender system will be discussed in regular patient engagement (T5.2) and stakeholder workshops (T3.5). Recommendations from these workshops will be shared with COMMUTE stakeholders to raise awareness in the field of the legal and ethical implications, including patients' right to informed consent for medical treatment.

As COMMUTE processes data on vulnerable groups, including individuals with neurodegenerative deceases (NDDs), safeguard measures such as pseudonymization, anonymization, transparency are implemented to comply with GDPR requirements regarding consent from patients with NDDs. In more detail data protection issues in COMMUTE are addressed in the Data Protection Impact Assessment (DPIA), which will be attached to this report.

Implications for fundamental rights under the EU Charter, particularly concerning the classification of patients by AI systems using biomarkers (such as labeling patients as "high risk"), will be addressed through a human-centric approach to AI modeling. This approach includes raising AI developers' (WP3) awareness of individual vulnerabilities in light of COVID-19 and neurodegenerative diseases (NDDs).

The framework for using AI as a decision support system and the requirements for training and/or validation datasets, in particular Artificial Intelligence Act (AI Act) has been adopted on 1st of August 2024 have been analyzed. The COMMUTE AI-powered, model-generated recommender system is not deployed in a manner that falls under Article 3 of the AI Act, and therefore cannot be classified as prohibited, high-risk, limited-risk, or no-risk AI. However, the COMMUTE AI model has been designed to meet the requirements for trustworthy AI (as outlined in Chapter I on the ethical framework) and is thus built to align with the principles of the AI Act.

An analysis of the interaction between existing regulatory frameworks in the medical sector—particularly the Medical Devices Regulation—and the proposed EU legal framework for AI-based decision support systems using biomarkers reveals that Article 43(3) of the AI Act requires providers of AI systems incorporated into medical devices to adhere to applicable conformity assessment rules. Any medical device with an AI system that impacts its safety will be classified as high-risk, introducing an additional layer of conformity requirements for healthcare-related AI systems. In light of these findings, COMMUTE's commitment to adopting a human-centric perspective ensures that its AI-driven, model-based recommender system aligns with current EU legal and ethical standards. This D5.1 report will be reviewed and updated in M18.

# Attachment I. Data Protection Impact Assessment Report.

DPIA COMMUTE
v3_final.pdf