EURAMED
ROCC-N-ROLL
European Medical Application and Radiation Protection Concept

IMPROVING PATIENT CARE THROUGH NOVEL AND OPTIMISED MEDICAL APPLICATIONS OF IONISING RADIATION

A STRATEGIC RESEARCH AGENDA

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STRATEGIC RESEARCH AGENDA

VISION STATEMENT

The vision of the Strategic Research Agenda (SRA) is to provide an orientation document for European policymakers, funders, as well as the scientific and clinical communities interested in research, innovation and training related to medical applications of ionising radiation. The SRA aims to highlight current challenges and areas where research efforts are needed to ensure accessible, highest-quality, and safe personalised care for Europe's patients, leveraging the potential of digitisation, and to advance Europe's competitiveness in the field, based on consensus among identified stakeholders.

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EXECUTIVE SUMMARY

Shortly after the detection of X-rays in 1895 by Wilhelm Conrad Röntgen and radioactivity in 1896 by Henry Becquerel, the potential of medical applications of ionising radiation (IR) became clear. Diagnostic applications were basically established immediately, but also therapeutic applications were used only a few years later. Many important developments have been achieved since then making IR an important tool in modern medicine. IR is an ideal candidate for personalised and precision medicine due to its fundamental properties. Therefore, it is of utmost importance for various disease entities such as neurovascular, cardiovascular, and especially cancer-related diseases. Over the past decades technological advancements in generating and detecting IR, but also improved usage of digital data and large data sets including artificial intelligence (AI), have opened up new opportunities for more effective personalised care regarding the above-mentioned diseases but also for other disease entities like infections. This implies a broad range of potential new research fields. As the main goals of such research should be an improved healthcare for patients on an individual patient basis and correspondingly a more efficient healthcare system, the research should always be guided by clinically relevant questions with the aim to enable novel or improved care for Europe's patients.

This Strategic Research Agenda (SRA) entitled "Improving Patient Care through Novel and Optimised Medical Applications of Ionising Radiation" has been developed as part of the Horizon 2020 EURAMED rocc-n-roll project, a consortium of a multidisciplinary team of 29 partners from leading research institutions in 17 European countries in close collaboration with panels of external experts and in consultation with the wider stakeholder community. It provides an orientation document for European policy-makers, funders, as well as the scientific and clinical communities interested in research, innovation and training related to medical applications of ionising radiation, highlighting current challenges and areas where research efforts are needed to ensure accessible, highest-quality, and safe personalised care for Europe's patients.

Chapter 1 of this SRA addresses the most relevant research topics from the clinical perspective, which can be mainly summarised as:

- Precision imaging in personalised medicine can be a big step forward towards individualised care but its full potential has not been investigated and established yet.
- (New) molecular imaging methods need to be developed to enable understanding of molecular aspects of diseases on an individual patient basis.
- AI and the use of health data are promising tools for improving patient care, however, their potential is not completely understood and needs to be validated. Corresponding research is needed.
- Image quality and higher accuracy in imaging are prerequisites for optimised diagnosis and other imaging tasks. Methods for evaluation and optimisation have to be developed.
- New therapeutic tools including hadron therapy, FLASH therapy, interventional therapies and new radionuclide therapies need to be better understood to optimise their implementation and to allow more efficient therapies.
- Optimisation and broad, harmonised, and quality assured implementation of existing diagnostic imaging (e.g., radiography, computed tomography (CT), single photon emission computed tomography (SPECT) and positron emission tomography imaging (PET) as well as therapeutic applications (like radiation therapy (RT) and especially adaptive radiation therapy and interventional therapies) needs to be achieved for the best use of existing technologies.
- Combination with other therapies as well as synergies and detrimental aspects have to be understood to individualise and optimise treatment in Europe.
- Theranostics provides an important opportunity for optimising therapies by combining therapy with diagnostic information to individualise therapies. This field needs further development and evaluation.
- Medical applications of IR need to be performed with sufficient quality and safety measures in place. Such measures have to be developed and implemented for all of the above-mentioned topics.
- This is especially necessary for paediatric patients. It is most important to optimise procedures for paediatric patients as well as to develop new techniques to ensure the best use of IR for this vulnerable groups of patients. Similar aspects apply for pregnant women.
- Screening can be an important tool for early detection of certain diseases and thus support a better patient care and cost-effective health-care systems across Europe. The potential benefits as well as prerequisites for meaningful implementation have to be better understood, depending on the disease.
- Ethical aspects and implementation of the patient's perspective are mandatory tasks to be dealt with when applying IR in the medical context and should be addressed for the above-mentioned topics.

A few aspects are relevant for all above-mentioned topics:

- Applications as well as the data used for the generation or evaluation of tools must be quality assured. In many cases as e.g., for AI and corresponding data new methods need to be developed for such quality assurance. Key performance indicators (KPIs) might be an effective way to implement quality and safety aspects for performance of medical applications of IR.
- The applicability and practicability of any method for the use on an individual patient must be taken into account as well as the benefit for the patient with respect to the outcome and the healthcare system.
- Evaluation of improved or new techniques needs to be evidence-based.

These aspects are evaluated in detail and corresponding gaps as well as research needs are derived in chapter 1 on a general basis, from the patients' perspective and for various diseases.

Efficient implementation of medical applications requires that the benefit-risk balance is known and is as positive as possible. To achieve these prerequisites, corresponding radiation protection (RP) research is needed. Related questions and needs are described in chapter 2 as part of a quality and safety concept. RP research should always be an integral part of research on medical applications of IR, but the focus has to be on the possible benefits of medical applications of IR. However, the benefits are difficult to describe especially on an individual patient basis, at least as far as comparison with the potential individual risks is concerned. A number of topics have been identified as central for effective RP and for an improved benefit-risk balance for patients and with the potential to limit the risks for medical staff:

- Decision support systems and AI-based methods might help to reduce the radiation burden for patients and staff, measure exposure or quality parameters and lead to optimal procedures in terms of benefit-risk balance. This potential needs to be evaluated.
- All technological improvements allowing better benefit-risk balance should be used where suitable, according to the ALARA principle. This approach needs to be further established and RP-related technologies implemented accordingly.
- It is important to reliably determine the patient exposure associated with medical applications of IR, including its spatial distribution. Especially for some of the newly emerging technologies, such exposure determination is not yet elaborated completely like e.g., for some molecular imaging approaches, FLASH therapy, alpha-emitter radionuclide therapy and theranostics.
- Besides the exposure characterisation, also the evaluation of image quality in imaging procedures and dose volume histograms in therapeutic applications are necessary to allow a meaningful optimisation. This image quality assessment as well as dose volume histograms have to be available for everyday usage in all European hospitals and medical centres, which is not the standard today.
- As the benefits of applications should be clearly identifiable by evidence-based studies, the potential risks have to be addressed separately based on the exposure determination. To address the potential risks, a general understanding of the radiobiological processes is required, which is still not completely given for medical applications, especially due to localised exposure and different radiation types used.
- Individual sensitivity and susceptibility of individuals and the corresponding influencing factors need to be understood.
- The potential effects of the diseases on the radiation sensitivity of single organs and on the patients are of special importance in the context of medical applications of IR and need to be evaluated. Ethical considerations regarding the use of IR in medicine and the corresponding benefit-risk balance must be analysed.
- Staff must be monitored efficiently. This could be enhanced through new technologies, including AI, and should be explored, especially in the context of interventional procedures or application of specific radionuclides, neutron radiation, hadron, and FLASH therapy approaches.

The detailed analysis of the related proposed research needs and topics is described in chapter 2 and includes the perspectives of the different European RP research platforms (MELODI, EURADOS, EURAMED, NERIS, ALLIANCE and SHARE) as well as of the regulators.

Chapter 3 highlights the prerequisites for effective and meaningful research on the topics mentioned above as well as the aspects that are most relevant for effective implementation of such research into clinical practice across Europe. The following aspects are elaborated and identified as relevant actions and aspects:

- To address the needs of patients, researchers, and medical staff, categories for the classification of future potential Centres of Excellence (CoEs) for medical applications of IR and medical RP research are proposed.
- To facilitate the sustainability of resources for new and existing applications, investigations how laboratories and infrastructures with high-end radiation technology can be operated sustainably are needed.

- Clinical implementation of innovations is the major step for better healthcare and thus a key component of innovation in the field of medical applications of IR. It needs to be clarified how innovations can be made available and accessible across countries in Europe and how they can be made financially sustainable in the various healthcare systems.
- Digitalisation in the field of medical applications of IR can lead to ground-breaking outcomes, which could be addressed in a series of research recommendations on personalised medicine and electronic health records (EHR), RP and EHR, standardisation of data formats and AI.
- Digitalisation in the field of medical applications of IR will raise a number of ethical issues and accompanying research needs like diversity, inclusion, and equity concerns related to personalised medicine, public/patient trust issues related to electronic health systems and records and their digitisation. Advances in the use of AI and machine learning (ML) bring a plethora of ethical challenges and questions ranging from how to modify informed consent processes to ensuring effective clinical
decision making in the context of (potentially) biased datasets or non-transparent data origins.
- Important challenges in implementing and updating the education and training (E&T) in medical applications of IR and related quality and safety aspects, including RP for health professionals, consist of difficulties in including radiation-related and RP topics in undergraduate curricula, lack of continuing professional development (CPD) programs in RP, limited
availability of health professionals, whose attention may be diverted to other CPD efforts or introduction of new techniques or medical devices.
- Technology transfer and translation in the field of medical applications of IR is an ongoing challenge as a crucial component of the innovation chain.

Taking these aspects of chapter 3 into account, the ambition of this part of the SRA is to contribute to facilitating and accelerating research and positive outcomes through four interconnected axes of action to support addressing the research topics as elaborated in chapters 1 and 2:

- Fit-for-purpose support structures for the research and innovation system need to be developed.
- Technology transfer dimensions have to be addressed.
- Focused attention to all relevant digitalisation aspects is mandatory for efficient implementation.
- Implementation of a common framework including guidance and evaluation for E&T of existing and future medical staff to accompany these needed evolutions.

The general overview of the topics and connections are shown in fig. 1. More detailed descriptions of the above-mentioned topics as well as some further identified specific topics are covered in the detailed text of the relevant chapters. The above-mentioned bullet points show the most relevant topics for future research in the field of medical applications of IR identified by the EURAMED rocc-n-roll project experts and stakeholders interested in this field to improve patient care.

KEYWORDS

Healthcare,
European patients,
strategic research agenda,
ionising radiation,
radiation protection,
personalised medicine,
transfer,
medical challenges,
research needs,
new technologies

INTRODUCTION

In line with UN Sustainable Development Goal 3[1], timely access to affordable, preventive, and curative healthcare for all is high on Europe's political agenda and should be among the main goals of Europe's society.

The European Commission is building a European Health Union to foster and protect the health of Europeans and to strengthen the coordination and cooperation among member states in the area of healthcare. Key pillars of the European Health Union include the Europe's Beating Cancer Plan[2], aiming to reduce the cancer burden for patients, their families and health systems and its related SAMIRA Action Plan[3], the European Health Data Space[4], created to facilitate sharing of health data between member states, as well as a commitment to increased funding for health-related research and innovation. Europe's healthcare system must be easily accessible, effective, enable tailored and individualised diagnosis and treatment and must be centred on the patient's needs[5].

Medical applications of IR are a central part of such a healthcare system and plays a key role in all European Commission initiatives aiming to strengthen the European Health Union.

Since their advent, medical applications of ionising radiation (IR) have contributed significantly to the advancement of healthcare including revolutionising diagnosis by X-ray based and nuclear medical imaging as well as for therapies, particularly for cancer[6]. However, there is still a large potential for further improvements and even revolutionary changes. These improvements and changes need to be analysed and proposals for implementation are required.

The underlying idea of the approach presented in this unique strategic research agenda (SRA) on European level reaching beyond national agendas and/or those related to just dedicated topics, is to emphasise that patients suffering from known or unknown diseases benefit from IR-based diagnosis and treatment as an integral element of efficient medical care in Europe. **The potential benefits of applying IR in medicine must be clearly identified.** Certainly, the potential risks also need to be considered and put into a meaningful perspective and related RP will be taken into account as well, although the focus is on the potential benefits for the patients.

Recent developments in medical technology based on IR such as FLASH therapy, particle therapy, photon-counting CT and new molecular imaging approaches or AI-based methods offer better diagnosis and treatment or combined approaches for European patients as well as increased safety of the procedures, with more innovations already in the pipeline (or might do so in the future).

A reliable benefit-risk balance analysis must be performed to justify each application of IR for diagnostic or therapeutic purposes. To improve benefit-risk balance determination, more basic research on risk definition is required. This needs to include the development of a method to evaluate benefit and risk in a way that it can be compared and thus be balanced. Further evaluation will be necessary on this topic for which a first approach could rely on defining benefits as a reduction of risk, i.e. comparing the risk of performing an intervention with the risk of not performing it. However, this approach will also have potential problems as this definition is already difficult to compare for diagnostic and therapeutic approaches. In addition, these approaches would require evidence-based medical studies to determine such parameters.

Both existing and new methods need to be optimised to obtain the best benefit-risk balance for each individual patient. Europe needs a standardised approach which requires sufficient quality-assured infrastructure and well-trained staff who can apply the developed methodologies and apply harmonised procedures. One cornerstone on the way to harmonisation is to establish methods for quality-assured and safe application of IR in medicine. Every optimised or newly developed technology needs to be implemented in clinical practice, accompanied by strategies for quality management and safety procedures.

This document focuses on the research needed to make the best use of IR in medicine for the benefit in care for each individual patient across Europe. The identified research fields were derived from a consensus approach involving experts and researchers in radiation-based medicine and RP as well as other relevant stakeholders and are based on the patients' clinical needs in various disease entities. The needs for new therapies or diagnostic methods are directly related to the clinical needs in the different disease entities.

Chapter 1 is the central chapter and describes the clinical needs and opportunities in several disease entities. Medical application of IR follows by definition an individualised approach in many areas, hence personalised medicine can be implemented much easier in this field than in many other medical specialties. Using AI and ML in medical applications of ionising radiation is one promising area for improved individualised healthcare in the future. For example, a rapidly evolving field using IR is radiomics[7], currently being in its infancy. There are also many other technologies, which might be useful to provide new insights allowing better personalisation like molecular imaging, theranostics and others. Furthermore, there is a great potential for personalisation in medical applications of ionising radiation in relation with other omics areas, which could significantly improve patient-centred healthcare. The wording "patient-centred" might be debatable and "patient-related" or "patient-oriented" may seem more appropriate terms. The

latter might best suit the purpose of this document, in particular as it is not possible to integrate the patient opinion into all aspects of research, while the individual patient is in the centre of the medical procedures and related optimisation. However, since "patient-centred" is a standardised term in European healthcare, it has been used throughout this document with the meaning of "patient-oriented".

Once the clinical applications with the most promising research potential for better patient care have been identified, accompanying research to understand and limit potential harmful side effects have to be defined to ensure that all aspects of RP are considered. Research needed to optimise medical applications of IR with regard to RP is described in **Chapter 2**. The chapter presents an analysis of the current research interests of the European RP platforms*, the regulators as well as other stakeholders in terms of their relevance for medical applications of IR. Quality management and safe use of IR and as part of its RP are integral aspects of the clinical use of IR.

Chapter 3 highlights the necessary prerequisites, including infrastructure, education and training, and methods for fast and sustainable transfer into industry and clinical practice throughout Europe. Particular attention must be paid to data infrastructures, which serve as the basis for AI-based applications as one of the potentially promising tools for the future. This chapter also considers ethical and social science aspects related to the use of IR in medicine, particularly in connection with AI-based applications, but also regarding the use of personalised medicine approaches and decision-support.

The structure of the document can be easily understood from Fig. 1, which highlights the concept based on the application of IR for the benefit of the individual patient across Europe and includes the main topics in an abbreviated form.

The research needs identified in all three chapters differ in terms of focus but also in terms of the way they can be addressed. Each chapter closes with a dedicated summary for readers with specific interest in one of the chapters. The chapter summaries are complementary to the executive summary.

This document has been developed as part of the Horizon 2020 EURAMED rocc-n-roll project, a consortium of a multidisciplinary team of 29 partners from leading research institutions in 17 European countries in close collaboration with panels of external experts and in consultation with the wider stakeholder community. All identified research needs outlined in the document are based on evaluations by the expert panels and have been discussed in consensus building workshops. Stakeholder meetings and workshops were organised during the European Radiation Protection Week 2021 (online), the European Radiation Protection Week 2022 in Estoril/PT, the European Congress of Medical Physics 2022 in Dublin/IE, the ESTRO Congress 2022, and the European Congress of Radiology 2023 in Vienna/AT. The final draft of this document was discussed at an open stakeholder workshop in Brussels/BE in May 2023.

To ensure a comprehensive evaluation of research needs, efforts have been made to expand the stakeholder and expert community and interlink experts from the medical field, including clinicians and RP experts.

In summary, the medical use of IR has the potential to provide significant benefits to patients in diagnosis and treatment. To harness this potential requires broad communication and dialogue, involving patients, researchers, and clinicians.

This SRA will help

- clinicians to understand which potential applications of IR could help to increase their patients' benefit, which questions they could raise;
- researchers to identify key research questions based on the clinical gaps and corresponding clinical needs;
- policymakers and regulators to understand which legal aspects need to be addressed;
- policymakers and funding organisations to understand the identified gaps and derived research needs and to identify where research funding will bring the greatest benefit to Europe's patients.

* *European Alliance for Medical Radiation Protection Research (EURAMED)*
Multidisciplinary European Low Dose Initiative (MELODI)
European Radiation Dosimetry Group (EURADOS)
European Platform for Nuclear and Radiological Emergency Response and Recovery (NERIS)
European Radioecology Alliance (ALLIANCE)
Social Sciences and Humanities in Ionising Radiation Research (SHARE)

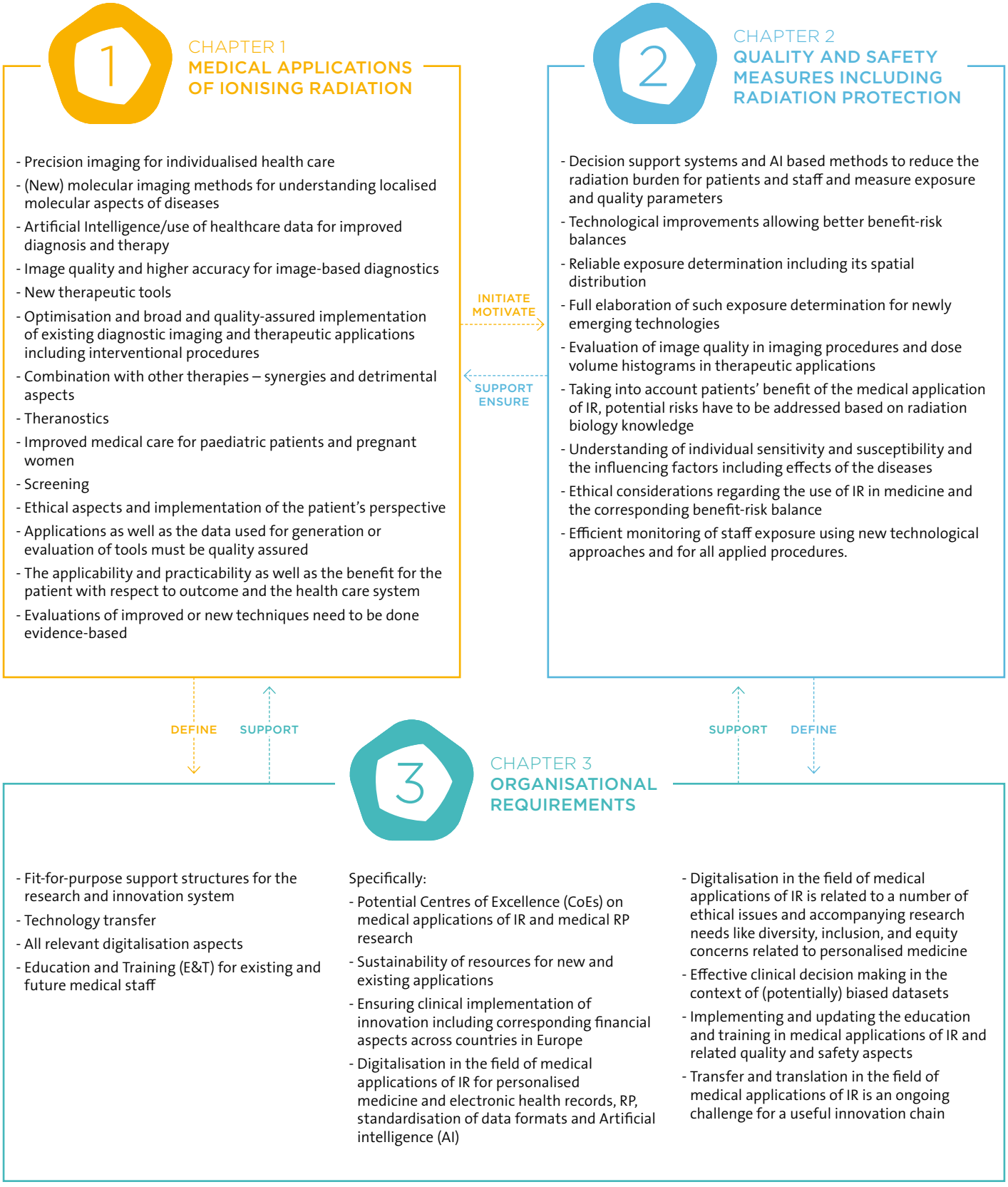

FIG. 1: SRA structure including the interlinks between the three main chapters. The arrows indicate the main focus on the medical applications (chapter 1) which initiate quality and safety related research (chapter 2), both of which define the organisational requirements (chapter 3). The bullet points list the identified topics which correspond to the explanatory sentences in the executive summary and are based on the identified topics and descriptions in the three main chapters.

CHAPTER 1
MEDICAL CHALLENGES AND CORRESPONDING RESEARCH NEEDS

INTRODUCTION

A primary objective of the EURAMED rocc-n-roll SRA for medical applications of IR is to evaluate the potential of IR applications to improve individualised patient care from a broad health perspective. Besides considering the development and investigation of better care through new diagnostic and therapeutic applications, it is important to also pay attention to related RP aspects.

It is necessary to show that applying IR for medical use is beneficial to the patients and that the benefit-risk balance can be optimised in different diseases. This benefit-risk balance is the major underlying concept for all diagnostic and therapeutic applications in medicine. It is well established in RP as well as in evidence-based medicine and should be applied for all types of medical use of IR. However, both benefit and risk are difficult to quantify in many cases, especially for individual patients, thus assumptions have to be made how the individual patient can be taken into account in the evaluation. In general, evidence-based studies for personalised medicine are not easy to generate as procedures are chosen and optimised for the individual patient and therefore the outcome always depends on many factors, and it is difficult to find enough similar conditions for achieving evidence. However, AI based methods for evaluating large data sets, even from different institutions, can help to identify correlations.

The different diseases for which IR-based diagnosis, prognosis, therapy, or treatment evaluation is indicated must be identified and potential developments have to be described. The application must be appropriate, justified, optimised, and personalised. This SRA therefore focuses on the diseases that are most relevant in terms of diagnostic and therapeutic approaches based on IR.

Furthermore, a central, overarching aim is to improve the outcome of the research, especially for the patients on an individual basis.

The following subchapters describe some common aspects, the view of the patients as well as some specific disease-related topics for oncology, neurovascular, cardiovascular and some other important diseases or patient groups. Each subchapter first describes relevant aspects of current limits and potential future developments. This is followed by a list of research topics in the various fields.

1.1 COMMON INTERESTS AND IDENTIFIED SYNERGIES

There are several diseases where patients benefit from applications of IR. For all these diseases several aspects of the applications of IR are relevant. Nevertheless, there is still a need for optimisation in some of those aspects. There are new or emerging technologies and possibilities which are of overarching interest for medical applications of IR, and can be summarised into the following categories:

- Precision imaging in personalised medicine
- AI and use of healthcare data
- Image quality and higher accuracy
- Improved quality and safety
- Harmonisation
- Specific improvements of radiation based medical care for children
- Ethical aspects

For these, the gaps in knowledge or application are identified and the corresponding research needs are derived and noted at the end of this subchapter.

Precision imaging in personalised medicine

Healthcare is moving towards data-driven processes for patient care and medical research towards data-driven life science. In line with the need for large amounts of data, real-world data from clinical healthcare are required and are still not available in a sufficient way. It is still unclear how medical imaging could be personalised based on individual conditions.

Such conditions could be certain genotypes or phenotypes such as receptor expression or individualised radiation sensitivity. The influence of genotype and phenotype on cancer risk of IR are other areas with significant knowledge gaps. The knowledge about individual sensitivity is limited and the need for patient-specific dosimetry e.g., in radiopharmaceutical therapy is just one example where today's methods of deciding the treatment dose might lead to undertreatment of patients. A better understanding of individual radiobiological effects is indispensable to make use of the advantages of for example alpha-emitting tracers to develop more effective radiopharmaceutical treatment[8,9].

Considering the patient perspective is key in personalised imaging and the benefit-risk balance is crucial when using IR. The risk acceptance regarding IR may change during the healthcare process and is strongly related to the underlying disease. The patient might have a different relation to risk before diagnosis and after cure, independent of diagnosis. These aspects need to be better understood to foster a better patient-centred medical approach.

Molecular imaging with special probes such as radiotracers used e.g., in PET visualising more or less unique biochemical molecular pathways, make it possible to determine the existence of certain biomarkers related to specified diseases in patients and related to therapeutic options. In PET, more research is needed for tracer development. Research is currently ongoing in nuclear medicine to find even more specialised tracers for PET- and SPECT-studies. For example, the European initiative PRISMAP[10] – The European medical isotope programme: Production of high purity isotopes by mass separation is an attempt to facilitate the use of new radionuclides for the development of projects to find new tracers for specific diagnoses. The tracers can be aimed at both diagnostic and treatment purposes. This type of initiative is important since radionuclide production can be a bottleneck for research into future diagnostic and therapeutic methods. The development of MRI and X-ray based imaging methods such as photon counting CT (PCCT), or X-ray fluorescence are other modalities with opportunities for developments in molecular imaging. However, the relation between imaging biomarkers and disease, prognosis, prediction, and therapy response is still not completely understood in PET, MRI and PCCT, in particular considering the value of circulating biomarkers.

Imaging biomarkers, biological features visualised with radiological or nuclear medicine methods or provided by such methods for computer-based evaluation, are part of an evolving field[11]. Radiomics, deep learning and other AI-algorithms are some of the methods applied. The full potential of these approaches is still unknown. Integration of imaging biomarkers from structural and molecular imaging with different omics such as genomics or proteomics is another field of research revealing significant knowledge gaps. Integrated diagnostics has the potential to ramp up the value of included data, but there needs to be a better understanding of its full potential to solve technical integration issues and to build e.g., fully automated clinical decision support systems (CDSS) for their interpretation and management. As stated by NERIS, it is evident that AI and deep learning methods should be further explored for improving simulation models and to develop a new generation of CDSS applicable in medicine, e.g., for image recognition or evaluation also in the context of emergency preparedness.

Integrated approaches in therapy are evolving and offer large potential benefits using the imaging information. However, not all possibilities have been identified and there is no evidence-based evaluation available even for those that are used. These integrated approaches are described in the subsequent chapters on applications in specific diseases where relevant.

Main gaps regarding personalised medicine:

- Clinical data are missing to evaluate how personalised medicine can be adjusted to individual conditions.
- Genotype and phenotype and their relation to individual sensitivity are not known or only insufficiently known.
- Patient assessments of benefits and risks depend on various parameters, but this dependence is often unknown.
- Molecular imaging is relying on biomarkers. Their relation to the disease, the prognosis, predictions, and treatment response is not sufficiently described in all cases to make the best possible use from the molecular imaging approaches. New radiotracers and radionuclides for imaging are not sufficiently determined and evaluated.
- It is unclear how AI, radiomics and deep learning approaches can be optimally used for personalised medicine.
- Evidence-based evaluation is missing for integrated personalised medicine approaches combining imaging and therapy.

Artificial intelligence, machine learning and radiomics and secondary use of clinical and health data

AI and ML can potentially be transformative, based on the generation and evaluation of large digital datasets acquired by means of next generation sequencing (NGS), the use of algorithms for image processing, patient-related health records, data arising from large clinical trials and disease predictions. Oncology has been in the forefront to reap the benefits of AI for universal cancer management. This includes early detection, tailored or targeted therapy by obtaining genetic information from the patient, and predictions of future outcomes.

AI systems may also enable informed patient decisions. Clinical and scientific information sources will be merged into individualised counselling tools providing predictions for tumour control and risks that need to be taken to achieve certain therapeutic goals. Developing such tools, also with respect to psychosocial needs of patients and an easy integration into the interactions between doctors and patients, bears a high potential for individual patient care and satisfaction. This certainly includes setting up and using large data sets and reliable AI models, which will allow the analysis of individual patient data during diagnosis and therapy decisions. It is unclear how such data sets and models can be quality assured to ensure that the predictions for individual patients will be meaningful. Data must comply with a legal framework and need to be stored in a data format that is usable for the whole community.

Today, there is no usable framework for the legal issues of secondary usage of clinical and health data in cross-border collaborations within and outside Europe, which would be required as addressed by many bodies and several initiatives, and there are ongoing policy initiatives (above all the European Health Data Space proposal[12]) and projects starting to tackle this issue. All initiatives have the common goal to increase the data availability for research, validation, and quality assurance. Data transfer, storage, and sharing in accordance with FAIR principles create possibilities not only for AI development, research, validation, and implementation, but also for quality assurance and clinical research. Availability of large sets of high-quality imaging data is a prerequisite for the development of AI algorithms and radiomics. Where supervised learning should be used, the annotation of data is another issue of quality assurance. Applying principles of open science could be useful to gather even larger data sets. However, data protection rules for all patient data have to be taken into account and need to be followed rigorously. In all cases, it is an unsolved problem of how to ensure sufficient quality of the input data for the intended use of a dedicated model. It is unclear how this can be guaranteed.

Virtual reality (VR) and robotics are additional areas where there is a large potential for medical applications of IR. However, there is still a gap in analysing the benefits and potential risks related to the use of such technologies. In addition, it is required to understand what optimal conditions for use and which technologies would be required for such usage.

Main gaps regarding optimal use of digital technologies in medical applications of IR including AI:

- The unclear quality of data for the use in AI-based procedures including missing tools for quality assessment, the legal frameworks for the data as well as their format.
- There is no established method for model evaluation to ensure a positive benefit-risk balance for patients, especially outside the developing centres due to differences in input data or patients' specifics.
- The relation between AI-based models, especially in imaging or imaging-related procedures to physics-based models is in many cases unclear making it impossible to predict applicability and quality of such technologies and their limitations.
- Dedicated evaluations of new technologies like AI and VR and their impact on patient care are often missing or limited to specific installations and tasks.

Image quality – Higher accuracy

Accuracy in medical imaging will never reach 100 % but is currently far away from optimal and the possibility for early detection of diseases is still limited in many applications. The technology development of scanning equipment is still moving forward and PCCT is one recent example to potentially reach higher image contrast and resolution with decreased radiation dose[13]. Higher accuracy is also aimed at through AI algorithm-based reconstructions. Nevertheless, there is still a lack of proof, validation and demonstrated gain for the patients by using these techniques to improve diagnosis, benefit-risk balance, and cost-effectiveness. The same holds for new technological approaches in nuclear medical imaging technologies like whole body PET scanning, technologies for fast SPECT imaging systems as well as for hybrid imaging technologies.

Main gaps regarding image quality:

Image quality is usually not addressed within patient images themselves. Methods for this are still lacking,

- It is unclear which image quality is appropriate for certain diagnostic tasks is unclear, in particular for new emerging technologies like molecular imaging approaches.
- The potential of technological developments is often unclear or is not taken up in clinical scenarios.

Improved quality and safety

The nature and the quality of the radiation as well as the design of how radiation should be administered in relation to treatment effects, are areas that are not fully understood and utilised. Improved knowledge of the measurement or calculation of deposited dose is required. New treatment regimens such as heavy particles, protons, α-particles, and FLASH-therapy with ultra-high dose rate are continuously being researched and deeper insights are needed to ensure an even better, dedicated and thus safer clinical implementation of new technology and treatment regimens can be realised. Such insights would depend on suitable dosimetric approaches as discussed in chapter 2 on quality and safety and RP.

An increase in the number of examinations over a short time has been observed for some groups of patients. For patients with a long disease period, many examinations over a longer time frame can be justified. Considering the benefits for the patient e.g., for oncological staging or therapy control, the potential detriments have also to be described, which requires a better understanding of stochastic risks, also with respect to cumulative exposures. In this context, the question should be raised to design surveillance protocols, which are most important in non-oncological diseases. More knowledge is needed of the estimation of the benefit-risk balance taking all parameters into account.

Main gaps regarding optimised quality and safety:

- The still not complete understanding of the effects of different types of radiation and the way the radiation is applied as well as on the corresponding patient dosimetry to guarantee an optimised, safe, and quality assured implementation of new or optimised radiation-based treatment options.
- Science-based estimates of the benefit-risk balance for certain procedures and even more on the individual level are missing and need to be developed. Especially, there is a lack of knowledge about the best models for risk estimation and the relevant parameters influencing individual risks. This also influences communication of such risks to patients and others involved.
- KPIs for medical applications of IR for imaging as well as for therapeutic approaches are missing.

Harmonisation

In both imaging and therapeutic applications of IR in medicine, there are many recommendations on the selection of modalities, procedures and acquisition or treatment protocols for different diseases from both international and national societies, as well as national legislative efforts. Such recommendations are often not completely based on facts and scientific results for the respective clinical question. Therefore, evidence-based studies are still missing, leading to a gap in suitable recommendations that can be applied across Europe. Such a harmonisation could increase the consistency in assessment of patients in Europe. An additional challenge is that individualised benefit and risk assessment as well as dose calculation would be required, depending on available modalities, procedures, and acquisition or treatment protocols, in addition to individualised radiation sensitivity.

Main gap regarding harmonisation:

- Recommendations based on clear clinical evidence, which can be implemented in European countries, are missing.

Improvements of healthcare for children

Medical applications using IR are also used in paediatric patients. However, the application has always been discussed even more critically than for the general population due to the potentially increased detrimental effects and longer latency times. However, the potential benefits of applying IR in medical diagnosis and treatment also apply for children and they often are very promising or even the only diagnostic or therapeutic approaches in specific cases. Given the new AI-based approaches or new technologies for (molecular) imaging and new radiation therapy approaches like e.g., targeted therapies or hadron therapies, the benefits can be

improved further, and the potential risks can be reduced. However, the potential improvements for paediatric patients with respect to technological developments but also in relation to the specific requirements based on radiation sensitivity and general age-dependent aspects of radiation biology, are not studied sufficiently in detail and evidence-based evaluations are often missing as they are quite difficult to generate corresponding studies for paediatric patients.

Main gaps regarding improved patient healthcare:

- Evidence-based studies on improved benefits on individual paediatric patient base using new medical approaches are missing.
- Knowledge about potential risk reduction by new technologies based on more specific dose distribution in therapeutic applications, more (dose) efficient imaging also for therapy planning and new information generation due to molecular imaging approaches is insufficient.

The ethical aspects

For all above-mentioned fields, ethical aspects must be considered, if a new ethical dimension arises. While e.g., the implementation of new, more efficient detectors without other changes of procedures is relevant for patient diagnosis but does not change procedures in a way that necessarily warrants further ethical considerations, new ethical issues will arise in personalised or precision medicine with respect to imaging and therapy when assuming e.g., decisions regarding individualised therapeutic approaches. Ethics in RP is indispensable for instance to develop protocols that strike the balance between patient perspective and clinical needs. Further consideration of the ethical perspective has been underlined by the WHO to complete the basic principles of RP (justification, optimisation, and dose limits). A special area requiring a focus on ethics in particular is the increasing application of AI and ML in the medical application of IR and RP. Ethical considerations might be necessary at many stages from research to practice.

Main gap regarding the ethical aspects:

- Ethical considerations are not sufficiently developed for personalised medicine approaches and especially not in the context of the use of AI-based methods.

Based on the identified gaps, the resulting research needs have been identified as follows:

Research needs

In **Imaging and AI**, research is needed on:

- integrated diagnostics, biomarkers, molecular imaging, theranostics, and pathology for optimising patient care;
- secondary use of data as well as defining which imaging and clinical data is needed in alignment with the EHDS, EOSC and other ongoing projects such as the projects in AI4HI and the Digital Europe infrastructure project EUCAIM (EUropean Federation for CAncer IMages). It is necessary to integrate imaging data into existing genomic programmes in Europe. The possibilities using VR and AI should also be addressed in this context;
- improving image quality and accuracy especially in early detection and early treatment evaluation. Research is also needed to develop methods for automatic image quality measurements;
- new technical developments fostering improved imaging applications, e.g., monoenergetic X-ray sources.

In **therapeutic applications**, research is needed on:

- enhanced imaging to improve therapeutic applications in oncology as well as neurovascular and cardiovascular diseases. Treatment can be better aligned with individual sensitivity to IR but can and should also benefit from better predictions of outcome on an individual patient basis. Research facilitating such evaluations as well as new technologies for improved, individualised treatments is required;
- improved application of existing radiation therapy techniques like adaptive radiation therapy;
- evaluating, improving, and establishing new therapeutic procedures like interventional therapies, hadron-based therapies, targeted alpha therapies, and theranostics.

For **improved quality and safety** as well as **harmonisation**, research is needed on:

- cumulative radiation dose and risk in relation to surveillance protocols, especially in non-oncological diseases and paediatric patients;
- better integration of justification with optimisation, dose recording and image quality;
- the development of automatic KPIs for monitoring safety of procedures;
- the development of related interactive tools for self-learning training including the use of VR and AI.

For **improved paediatric patient healthcare**, research is needed on:

- dose distributions and dose reduction potential for paediatric therapeutic and diagnostic approaches based on new technologies;
- potential individualised medical applications of IR for paediatric patients;
- specific radiation biology aspects for paediatric patients.

In terms of **ethical implications**, research is needed on:

- the ethical implications of increasing use of AI/ML. New norms for ethics are required in relation to the use of AI/ML. Research on ethical evaluation of imaging and radiation therapy protocols is needed.

1.2 THE PATIENT'S PERSPECTIVES AND NEEDS

Benefit to the individual patient is the central aspect of the proposed approach in this SRA. The patient-centric approach has to take into account all aspects of engagement with medical care i.e., diagnosis, prognosis, therapy, and therapy follow-up.

Diagnosing and treating a disease at its earliest stage remains pivotal for efficient care. Early diagnosis provides the basis for informed decisions by the patient as well as optimal clinical treatment.

The role of imaging and treatment using IR should be clarified, particularly in competition or in combination with biological biomarkers. Besides optimal anatomical, functional and/or molecular imaging for standard diagnostics and treatment, the development and standardisation of radiomics and their integration to other omics are very promising but their possibilities and potential limitations are not yet fully understood, which makes it difficult for the patient to understand the predictions and proposed therapies. Understanding the possibilities and limitations of imaging and treatment integrated with omics e.g., in CDSS would be most helpful for defining new screening strategies based on imaging (morphological and functional), alone or in association with other biomarkers, which would offer better patient care by earlier detection of diseases.

Choosing the individual best treatment and predicting treatment efficacy is perhaps one of the most important aspects in the patients' interest. To choose, plan and perform individualised effective and unharmful treatments, to predict the treatment response and to detect intercurrent complications as well as to follow the patient over the course of the disease is vital in personalised medicine. This overall approach should be the basis of informed decisions by individual patients, as it empowers patients to actively participate in the decision-making process enabling and fostering patient agency. The current as well as the potential role and the value of IR-treatment and imaging in this context must be clarified. Currently, there is no empirical evidence on patient views on current practices let alone their views on future directions of developments. Trade-offs between public health approaches versus personalised approaches are also largely absent from the research field.

Precision medicine is assumed to be a key factor for improved patient outcomes, and socio-economic improvements in the healthcare sector, benefitting all patients and allowing patients to make decisions based on better information. These approaches are still at an early development stage and mostly advocated and/or used in academic settings. However, a broad implementation of these approaches facilitated through provision of clear evidence would make them accessible to a larger number of patients.

Safety of imaging and treatment procedures is of concern for patients and the benefit-risk balance of low-dose diagnostic procedures must be reconsidered in the view of the increasing and evolving knowledge in radiation biology. However, to ensure dose efficient safe imaging there is still a lack of definition of appropriate image quality and optimised exposure. In the field of high-precision and/or adaptive radiotherapy procedures or new treatment methods like protons or FLASH, high chances for cure and reduction of side effects, but also new questions arise. Patient awareness of these technical discussions is very limited and there is an open research question on the extent to which patient involvement in co-creating benefit-risk balance calculations should be factored into the research and development taking place at earlier stages than clinical implementation.

Patients need personalised treatment proposals taking into consideration their personal preferences, their medical history and their social situation. If it is the patient's wish and if feasible, close relatives should be included in the discussion on the treatment. Treatment proposals should aim to empower the patient, giving him or her control over the decisions about their life and treatment approaches. The patients' quality of life is central. This is not necessarily achieved in today's medical practice. Ideally, a treatment proposal should be the result of a multi-professional team including diagnostic, treatment clinicians and a paramedical support team, where relevant. Multidisciplinary and multi-agency approaches should be more the norm, and yet this presents significant challenges to current ways of working. There is a research gap in understanding how such approaches may benefit patients at various scales of operation. During all doctor-patient consultations, benefits and risks should be well explained and compared to other potential treatment options, and, if possible, the measures to mitigate the risks should be explained.

All patient-related documents and communication should be 'patient-friendly' taking into consideration the patient's situation and capabilities to understand the disease and the treatment options. To this end, all healthcare professionals need communication training. If digital tools are developed and used, it must be established that tools are also available for those patients that are not digitally competent or do not have access to digital services or devices.

Because of the existence of several early detection and screening programmes, non- or not-yet-patients also need to be informed on the benefits and risks of using IR in the diagnostic procedures they undergo. An over-reliance on existing patients to understand the patient perspective risks the development of systems which are non-objective i.e., if patients only become engaged at the point where there are immediate stakes, decisions and views will be different to more distanced views that could be gathered from groups where treatment is not an immediate need.

Main gaps regarding the patient needs:

- There is a lack of empirical evidence on patients' views on current practices and on future directions in the development of imaging tools that predict treatment efficacy and subsequent choice of individual treatment.
- The trade-offs between public health approaches versus personalised approaches with imaging and treatment from a patient perspective are unknown.
- Help for patients to better understand the possibilities and limitations of imaging and treatment integrated with omics is missing.
- Precision medicine approaches are not accessible to many patients and therefore do not allow patients to make decisions based on better information through provision of clear evidence.
- There is a lack of understanding how patients may benefit from multi-professional team approaches that include diagnostic, treatment clinicians and a paramedical support team at various scales of operation.

Based on the identified gaps, the resulting research needs have been identified as follows:

Research needs

Considering the **patients' perspective**, research is needed on:

- the implications of the personalisation of imaging and of effects of consecutive treatment;
- trade-offs between personalised and public health-based approaches to medicine in the context of IR applications;
- early stage understanding of patient views on existing and new imaging and treatment approaches in combination with other omics and AI-based CDSS systems for better healthcare on an individual patient basis;
- new procedures for patient informed consent where AI is being deployed for the development of dose reduction strategies to minimise detrimental effect related to IR, particularly with the support of AI and of the use of new detectors;
- dose reduction strategies for interventional radiology procedures, recurrent examinations, and radiation therapy. Specific research for paediatric patients should be prioritised and research should be conducted on how to develop procedures in situations where the patient does not give informed consent, but consent is provided by others;
- the development of a range of tools for evidence-based patient information for diagnostic and therapeutic procedures accompanied by appropriate training for the provision of patient-friendly communications;
- the development of guidelines for patient information.

1.3 APPLICATIONS IN ONCOLOGICAL DISEASES – BACKGROUND, GAPS AND NEEDS

The application of IR in oncologic diseases is a core tool for diagnosis, treatment, and follow-up. Various diagnostic methods like X-ray, CT, and nuclear medicine methods like PET, contribute to a precise classification and pre-therapeutic evaluation of individual cancer cases. For treatment, IR in different forms of radiotherapy, is a mainstay contributing to a magnitude of cancer cures[14]. After treatment, follow-up involving IR contributes to early detection and to the treatment of any relapses as well as to detection and treatment of side effects. Hence, relevant steps for optimal oncological healthcare are:

- Screening using IR-based imaging
- Diagnostic imaging
- Imaging in radiation therapy

For any treatment-related procedures, it can be stated that, when treating patients, it is important to balance the benefit and the risk between radiation therapy and other approaches (e.g., chemotherapy).

The discussion of each patient's treatment in a multidisciplinary tumour committee is the best guarantee that decisions are based on the evaluation of the benefits and risks of each possible approach. However, assessment of benefits and risks, especially in advance of the treatment is often based on a lot of assumptions and thus prone to large uncertainties. Implementation of best practices in oncology to reduce the risk of error and prevent harm to the patient must be seen as a priority among professionals and health organisations. The growing complexities of modern oncology require continuous updates and adjustments to meet new necessities. There should be open communication among the different professionals involved in the management of cancer patients.

In this context, the following treatment-related steps may involve IR:

- Interventional imaging in cancer patients
- Imaging for therapy: diagnosis, planning, facilitation, or follow-up
- Therapeutic applications

All steps have to be evaluated in terms of

- Patients' benefits and potential risks
- Cost-effectiveness

In future research, obviously all types of cancer need to be addressed. However, the most frequent tumours, such as breast, prostate, colon, or lung cancer, are the most studied with the most available data. Still, it is important not to forget about rare tumours. Special attention should also be paid to paediatric cancers and cancers in pregnancy.

The above-mentioned topics are addressed in the following parts of this subchapter including existing gaps. Based on this, research needs are summarised at the end of this subchapter.

Screening

The impact of imaging using IR on screened persons is still questioned, partly for RP reasons, partly because inter and intra observer's variability are limiting imaging reliability for an early detection. In addition, imaging reliability is strongly dependent on quality assurance processes, well-defined, for example, in breast cancer screening. Moreover, the lesion detection by the radiologist could be challenged by a poor image quality and/or limited experience, or a shortage of appropriately trained professionals. This is one of the reasons why hopes for the development of AI systems are so high and demonstrates their importance to improve readers' variability, performances, and availability. Nevertheless, it is still unclear what AI systems can really achieve. It is also questionable how evaluation of screening images should be done in the future (using AI as evaluation tool before and after reading by radiologists or instead or still relying on two readers etc.) and what quality is appropriate for screening procedures. Besides potentially implementing AI based procedures, there are many other questions remaining on imaging procedures as well as required image quality for various screening applications.

The following gaps regarding screening approaches have been recognised:

- AI systems in screening have demonstrated their importance to improve readers' variability, performances, and availability. Nevertheless, it is still unclear what AI systems can really achieve.
- Image quality requirements, especially for screening are not well described for many screening applications.

Diagnostic imaging

Optimal diagnostic imaging, in terms of personalised imaging, implementation of new methods like AI-based methods for diagnostic imaging and improving image quality, dose efficiency and safety for diagnostic imaging, is a very relevant task also for oncological imaging. However, these are topics related to diagnostic imaging at large and for all diseases without specific oncologic facets, apart from screening-related and molecular imaging aspects.

Therefore, they are not dealt with in this subchapter, but are described in subchapter 1.1. and are covered in the corresponding research needs.

Interventional imaging

Interventional procedures for oncological treatments are getting more prominent for cancer therapies. The number of tumour sites that can be dealt with is limited and only few localised metastases of limited size can be treated. However, for patients where these limiting factors are fulfilled, success rates seem to be promising.

Various methods are currently used to destroy these localised tumours under imaging control:

- Radiofrequency ablation
- Microwave ablation
- Afterloading techniques
- Seed implantation
- Localised drug delivery and others.

For many of these methods it remains unclear, whether and when the tumour has been completely destroyed, but also what happens in terms of inflammatory processes or regarding potential distribution of left-over tumour cells or DNA. As of now, the clarification whether and when the tumour has been completely destroyed seems to be an important unsolved issue as this might be correlated to recurrence rates or unneeded destruction of healthy tissue.

Main gap in interventional imaging in oncology:

- The clarification whether and when the tumour has been completely destroyed is an important unsolved issue in interventional ablative procedures.

Imaging for therapy preparation, facilitation, or follow-up

Optimal imaging for therapy preparation, facilitation or follow-up is determined by the same requirements in principle as diagnostic imaging. It is specifically important to address the potential of optimisation in terms of reducing exposure based on task dependent image quality requirements. As this can be addressed with the methods described before, there is no dedicated evaluation here, but referral is made to subchapter 1.1.

Molecular imaging approaches can be relevant for diagnostic applications but also for therapy preparation, facilitation, or follow-up. However, as currently molecular imaging is still most prominently being investigated regarding potentials in the contexts of theranostics and personalised therapy it is also dealt with in that context (see below).

Main gap in imaging for therapy preparation, facilitation, or follow-up:

- In repeated oncologic imaging, it is specifically important to address the potential of optimisation in terms of reducing exposure based on task-dependent image quality requirements.

Therapeutic applications

In the context of the treatment for oncological patients, besides the main pillars of surgery and radiation treatment, systemic therapeutic approaches are an important field of clinical practice and research. New substances are continuously being developed and increasingly being used. Unfortunately, their combination effects with IR do not have to be assessed in drug development and therefore bear unforeseeable risks often unknown in practice. On the other hand, for some substances, very beneficial effects have been observed in combination with radiation-based treatment, e.g., for the combination of immunotherapy and external beam radiotherapy. Due to the legislative background, those benefits and risks are also not always well described. Knowledge and infrastructure in radiation research are well positioned to address such topics of risks and benefits for different therapies or the combination thereof in an interdisciplinary manner.

Biology-driven personalised RT-enabling treatment based on the biological characteristics of the tumour and normal tissue is a promising approach for improved radiation oncology. Personalisation will be of benefit: leading to an improved tumour control on the one hand and to improved normal tissue protection on the other hand. However, in many cases biological characteristics of the tumour are still not known, at least not for the reaction to different RT procedures. Also, the link between imaging results, AI-based evaluation and omics data to the tumour biology is often not completely understood.

Adaptive radiation therapy (ART) incorporates changes in anatomy and/or deviations in planned delivered dose due to deviations in patient setup and changing appearance of tumour tissue to estimate the actual dose administered to a patient as treatment progresses. Anatomical changes and deviations in configuration can be identified by daily image-guided radiation therapy (IGRT). Imaging allows inter- and intrafraction motion monitoring and has become a standard procedure. New hybrid radiotherapy devices, incorporating improved CT scanning and/or MRI, allow more accurate imaging of the tumour during irradiation. The clinical applications of these new systems in ART need to be evaluated. This is of special interest as, simultaneously, the possibilities of treatment application in terms of sub-volume dose distributions with photons and other beam qualities are exploding. Merging improved

real-time onsite imaging with adaptive replanning and precise application will again improve tumour control and enable better normal tissue protection. The immediate evaluation and replanning of the dose distribution to be delivered is however, not applied in clinical routine yet. In addition, the characterisation of tumour tissue regarding its vitality and therefore need for treatment is not always feasible with sufficient spatial and or temporal resolution.

For external RT, it can be summarised that personalised medical approaches in treatment using IR need to be broadly implemented, as well as for the combination of RT with systemic substances as for even more personalised RT technology. Both have the potential to increase effect of treatment and to reduce side effects. Furthermore, new techniques like theranostics and RT methods using protons, ions, and neutrons etc., new imaging approaches as well as methods of AI have to be identified and evaluated that can be useful to the patients.

The use of heavy particles and protons allows better dose delivery and has radiobiological benefits. The potential clinical benefits they offer are at present being studied extensively. However, the availability of this technology is still limited. Studies will be needed on the benefit-risk balances for different patient groups and different diseases to decide how and where to further increase the availability of particle treatment throughout Europe.

FLASH RT (ultra-high dose rate) has been shown to induce the FLASH effect, whereby, according to quite a few animal and cell studies, normal tissue toxicities can be reduced while still maintaining local tumour control. There is a need to better understand the mechanisms to be able to develop a new technology.

Targeting specific cell membrane markers for both diagnostic imaging and radionuclide therapy is a rapidly evolving field in cancer research. Some of these applications have found a role in routine clinical practice and have been shown to have a significant impact on patient management. Several molecular targets are being investigated in ongoing clinical trials and show promise for future implementation. However, a comprehensive analysis about potential applications and candidates for new radiopharmaceuticals is missing.

It will be of high interest to explore the potential of combining the therapeutic aspect of theranostic tracers with external beam radiation. This combination will exploit the systemic effects of radionuclide treatment together with the local enhancement of the eradication of larger tumour bulks, which may be limited by the radionuclide treatment alone and the strength of local RT. On the other hand, side effects of both treatments can be minimised by the combination approach. While there are ideas on how such combination therapies may benefit individual patients, this has not been studied sufficiently, and also potential risks are not completely understood.

Molecular imaging and theranostics combining molecular imaging with targeted radionuclide therapy, mostly for metastatic cancer originated in the field of nuclear medicine and different strategies that produce imaging signals have been developed. Other molecular imaging techniques use ultrasound, MRI, or light (optical bioluminescence and fluorescence techniques). Emerging techniques such as photoacoustic, X-ray fluorescence or amide proton transfer imaging are under study. Molecular imaging aims to noninvasively investigate tumour phenotypes and assess functional and molecular responses to therapy. With the simultaneous increase in AI and the development of new imaging agents to interrogate new biological pathways, molecular imaging may soon become one of the most important elements of clinical patient management. However, many approaches are still in the phase of technological establishment, potential new markers are not yet evaluated, and an assessment of potential applications is lacking[15].

Main gaps regarding therapeutic applications:

- The combination of new systemic treatments with IR may bear chances and risks, which, due to the legislative background, are also not always well described. However, due to the frequency of combinations in real life, they urgently need to be addressed.
- AI-based evaluation of omics data to the tumour biology is not completely understood.
- ART has the potential to improve tumour control and enable better normal tissue protection. However, the implications of very frequent imaging and the characterisation of tumour tissue regarding its vitality and therefore need for treatment are not fully explored yet.
- Studies on the benefit-risk balances for different patient groups and different diseases to decide how and where to further increase the availability of particle treatment throughout Europe are missing.
- FLASH: there is a need to better understand the mechanisms to be able to develop this new technology so it can potentially be used in patients.
- A comprehensive analysis about potential applications and candidates for new radiopharmaceuticals is missing.
- The potential of the combination of the therapeutic aspect of theranostic tracers together with external beam radiation has not yet been explored.
- Emerging technologies and tracer development for theranostics combining molecular imaging with targeted radionuclide therapy, together with AI applications may become more important for clinical patient management but are still in the phase of technological establishment. Therefore, potential new markers are not yet evaluated, and an assessment of potential applications is lacking.

Cost-effectiveness

Applying the implications of health economics research in oncology to the diagnosis and treatment of patients offers new opportunities to improve access to the best therapies, improve clinical outcomes and reduce overall healthcare costs for patients, payers, and the healthcare system as a whole. Once established and broadly available in selected clinical scenarios, advanced imaging may help to avoid unnecessary treatments. Furthermore, modern radiation treatment of tumours may offer economic advantages over drug treatment or surgery with similar outcomes. A thorough analysis of potential savings but also increased costs in relation to the individual benefit as well societal benefits, which should be based on fixed criteria, is missing.

Main gap regarding cost-effectiveness:

- Applying the implications of health economics research in oncology to the diagnosis and treatment of patients offers new opportunities to improve access to the best therapies, improve clinical outcomes, and reduce overall healthcare costs for patients, payers, and the healthcare system as a whole. However, a thorough analysis of potential savings but also increased costs in relation to the individual benefit as well societal benefits, which should be based on fixed criteria, is missing.

Research needs

For **imaging and screening**, research is needed on:

- imaging for early detection and screening using low dose radiation and image analysis tools like AI;
- dose minimisation in screening related to image quality, new detectors, new emitters, and AI, as well as on dose repetition related to epidemiological follow up and a policy for setting up registries;
- the appropriateness of imaging-based individual health assessments (IHA) in persons with known risk factors for early detection of specific diagnoses;
- liquid biopsy/circulating biomarkers in comparison with imaging considering the highest sensitivity and highest specificity. There is also a need for large scale comparative studies for different cancers.

For **treatment**, research is needed on:

- the combination effects of IR and (new) systemic treatments. Learning about these effects and the corresponding risks and potential benefits will lead to the chance to use beneficial combination effects (like with radiotherapy and immunotherapy), but also to avoid potential harm (like with radiotherapy with antiangiogenic drugs);
- preclinical and clinical radiation oncology on personalisation of radiation therapy based on biology driven indicators;
- the transfer of information from imaging and biology into treatment concepts, including individualised doses and volumes concerning tumours and their inhomogeneous aspects as well as individually assessed normal tissues in terms of anatomy, physiology, and individual sensitivity to treatment;
- improved image quality in oncological imaging to enhance radiation therapy accuracy and staging to ensure improved benefit-risk balance for patients;
- integrated diagnostics, biomarkers, molecular imaging, theranostics, and pathology.
- the use of non-photon external ;
- further in-vivo and in-vitro studies for FLASH therapy approaches, which are well controlled, including high precision 4D dosimetry to better establish the potential advantages of FLASH therapy. Similar approaches are needed for highly spatially structured therapeutic applications;
- further studies on (targeted) radionuclide therapies and their potential improved benefit-risk ratios;
- evaluation of theranostic approaches;
- promising new molecular imaging methods for many radiation therapy-based approaches named above.

On **cost-effectiveness**, research is needed on:

- the combination of cost-effectiveness with Patient Reported Outcome Measures (PROMS) and Patient-Reported Experience Measures (PREMS) from patients to elaborate on this issue;
- a unified list of criteria for determination of cost-effectiveness.

1.4 APPLICATIONS IN NEUROVASCULAR DISEASES – BACKGROUND, GAPS AND NEEDS

There are a number of clinical neurovascular scenarios in which patients currently benefit most from the application of IR or might benefit from in the future. These clinical scenarios include, but are not limited to:

- hyperacute ischemic stroke, which has been a devastating health issue, which is the first cause of disability and second cause of deaths worldwide;
- intracranial aneurysms, which may result in rupture and intracranial haemorrhage; the latter results in death in 25 % of cases and in disability in another 50 % of cases; prevention and treatment before rupture is important; treatment in the acute phase by endovascular means is mandatory within the first 48 hours; if left untreated, the result in rebleeding with a devastating risk of death of 65 %;
- arteriovenous malformations of the central nervous system (CNS);
- intracranial and cervical artery atheromatosis;
- arteriovenous dural fistulas/ shunts;
- dissections traumatic and spontaneous of cervical and intracranial arteries;
- paediatric pial malformations and vein of Galen malformations.

Over the past decades, the treatment of vascular diseases of the CNS has undergone substantial evolution, especially in the therapeutic arsenal of neurosurgery, interventional neuroradiology, and radiosurgery, taking into account the advances in research and development of equipment and material, as well as the better pathophysiological understanding of neurovascular diseases, obtaining remarkable clinical outcomes.

Nevertheless, it can be stated as a gap that:

- There is still potential for further development of materials and procedures as well as for more comprehensive understanding of the pathophysiological conditions.

X-ray guided endovascular interventions performed in state-of-the-art bi-plane angiosuites, are today used as a gold standard for the treatment of many neurovascular diseases as minimally invasive techniques, with an important impact on the often-devastating natural history of ischemic and malformative vascular pathologies of the CNS.

Recent guidelines regarding the management of intracranial aneurysms (IAs) and subarachnoid haemorrhage, as well as the endovascular therapy of acute ischemic stroke designate endovascular interventions as key therapeutic modalities in the management of these diseases[16–18]. Arteriovenous malformations of the brain, even those that until recently were considered untreatable because they are deep seated and/or have deep venous drainage, can now benefit from novel techniques and new endovascular materials that allow the elimination of malforming nidi[19,20]

Nevertheless, several gaps exist in the standardisation and availability of these treatments:

- This lack of standardisation and availability is partly due to the relatively recent and very quickly evolving endovascular discipline of interventional neuroradiology, as well as due to the variability of resources in Europe, regarding these technologically advanced techniques.
- In addition, the exponential evolution of several technological advances and translational research aspects lacks guidance and consensus regarding the needs and opportunities for a better exploitation of these ground-breaking resources, for the best benefit of the patient.
- Exploration of additional potential benefits from new technological developments as well as new materials like AI-based methods, molecular imaging approaches e.g., for characterising vessel walls and maybe inflammations is missing.
- The currently used procedures often result in long interventional times, which need to be reduced. The procedures include essential 3D information, but ways need to be found to reduce acquisition time and reconstruction time. The potential need for repeated procedures has to be reduced as they often result in quite some X-ray exposure especially to the patients.
- Better understanding of the potential of new technologies and the corresponding benefits for patients suffering from neurovascular diseases is needed. It still needs to be understood how interventionalists can make better use of existing data like previous scans and exams. The dissemination of data has to be improved and fostered.
- There is a lack of standardisation of the procedures throughout Europe including X-ray exposure times, dose reduction and optimisation, required technologies and resources as well as the required training.

There are also gaps regarding evaluation and investigation of potential approaches:

- Newer techniques of flow dynamics evaluation including computational fluid dynamics studies, new (especially molecular) imaging approaches, radiomics studies, genetic analyses and endothelial function and response to shear stress and inflammation can potentially be used for personalised rupture risk assessment in unruptured IAs. The surrogates for the evaluation of the risk for a rupture are still unknown. The methods are not yet evaluated and standardised.
- New molecular imaging techniques for risk evaluation e.g., like high spatial and temporal resolution, nuclear medical imaging techniques and X-ray fluorescence imaging techniques for e.g., inflammation characterisation and wall structure evaluation are not yet sufficiently developed to be used in clinical practice.
- Radiomics in the management of IAs may provide additional input for the personalised estimation of IA rupture risk, provided that the input is valid and adequate.
- Increased inflammation in cellular level and endothelial instability are related to potential biomarkers for AVM assessment of rupture risk: Various potential molecular biomarkers like e.g., cytokines, NOTCH pathways and microRNAs were associated with an increased haemorrhage risk. The exact pathways are unknown and potential aspects for diagnosis and treatment are unclear.
- Genotype-targeted molecular inhibition could be a potential emerging treatment. However, the exact possibilities of such biomarkers are not known so far and should be better understood. Corresponding imaging methodologies would be helpful.
- Endovascular or liquid biopsy constitutes a promising concept under development for obtaining molecular signatures through blood components, without necessity of a biopsy, allowing for a minimally invasive potential diagnostic tool. However, the potential in interventional procedures and for neurovascular diseases in general is still entirely unclear.

In terms of personalised medicine, it is necessary to tailor the management (active follow-up versus intervention) as well as interventions according to the patient's individual risk of rupture in the regional anatomy and the physiology of the patient.

Optimised approaches for follow-ups are required to avoid long and tedious follow-ups based on personalised indications and alternative techniques and treatments allowing more stable therapeutic outcomes.

To do so, the following gaps have been identified:

- Thorough evaluation and implementation into the clinic of image and protocol optimisation for alternative techniques such as computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are missing.
- The synergies and role of the genetic, hemodynamic, and biological factors for the pathogenesis and evolution of IAs and AVMs are not yet sufficiently investigated.
- Patient-specific treatment planning with realistic computational fluid dynamics (CFD) simulations and optimisation of flow diversion techniques based on new (molecular) imaging approaches and materials for IA treatment could be a major step for better patient treatment but are not yet completely developed.

AI techniques with rapid analyses of big volume data have proved promising in the automated detection of IAs from digital subtraction angiography (DSA) and MRA studies, with very encouraging results. Such techniques are able to combine personalised patient data and/or quantification of flow techniques, to implement computational fluid dynamics analyses in the equations. Potential imaging-based AI applications mainly contain six aspects: quantification, notification tools, diagnostics, registration of images, image classification, prediction of rupture risk and risk prediction for therapy.

Nevertheless, there are still gaps for these approaches:

- Especially, when such tools are used for therapy preparation or during therapy, their outcome must be quality assured. It is unclear how this can be achieved.
- The use of radiomics for the prediction of complications and/or outcomes of endovascular treatments is currently not sufficiently addressed. The potential of angiographic parametric imaging-derived radiomics features to predict complications and embolisation outcomes of IAs treated by pipeline embolisation devices has not yet been fully evaluated and understood.
- The potential of quantitative proteomics to further elucidate the different expression of proteins between ruptured and unruptured IAs, and its future role in identifying proteomic profiles at risk of rupture is still unknown.
- New, self-expandable, bioabsorbable flow diverters, new metallic aliases, and fabrication techniques to provide better visualisation of stents, as well as new surface modification coatings need to be evaluated to help improve the radiation based interventional procedures.
- A lack of guidelines in neurovascular interventions taking into account all such new developments and consequently a lack of large, multicentre studies on the effectiveness of novel endovascular techniques is observed.
- New therapeutic interventional procedures coupling imaging, e.g., with microwave ablation therapy that could be useful for therapies of malformations are missing.
- An optimisation of software tools (e.g., based on AI methods) to differentiate the arterial from the venous site in the nidus is missing.

- Lack of understanding of pathophysiological mechanisms of formation and evolution of brain AVMs through molecular and omics techniques which might allow better individualised treatment of the patients.
- The definition of imaging profiles for optimal clinical outcomes or prevision of procedural complications of thrombectomy including the definition of clot types and anatomical types favourable for specific techniques of thrombectomy is missing and could improve outcomes.
- Tools to define patients at risk of stroke are missing.

To allow a more standardised approach for patients suffering from stroke, the development of portable diagnostic devices seems a suitable solution. Also, for stroke similar approaches as above, including new (molecular) imaging, approaches and AI could be useful for optimised patient care.

Potentially, remote/robotic interventions could improve patient outcomes compared to transferring the patient, which would need developments on augmented reality and teleproctoring.

However, there are gaps related to such scenarios:

- The potential drawbacks as well as potential benefits are not thoroughly evaluated so far.

All the above-mentioned aspects lead to the following research needs:

Research needs

For **neurovascular diseases**, research is needed on:

- elucidation and association of the synergies and texture of the genetic, hemodynamic, and biological factors for the pathogenesis and evolution of intracranial malformation diseases (IAs), brain AVMs);
- development and investigation of AI – radiomics and molecular imaging techniques in the evaluation of risk of rupture of IAs;
- development and implementation of patient-specific treatment planning with realistic CFD simulations and optimisation of flow diversion techniques and materials for IA treatment;
- evaluation of patient-specific treatment planning for brain AVMs based on new software in the angiosuite, artificial intelligence techniques (artificial Intelligence-Based 3D Angiography) and omics – radiomics;
- enhancing the understanding of pathophysiological mechanisms of formation and evolution of brain AVMs through molecular and omics techniques;
- improving and providing novel neuro-endovascular material and techniques are desirable;
- molecular biomarkers – liquid biopsy for brain AVMs need to be investigated;
- emerging treatments based on molecular information: Genotype-targeted molecular inhibition for intracranial aneurysms and AVMs need to be developed and implemented;
- radiomics, omics, metabolomics, and blood biomarkers in the diagnosis of salvageable brain tissue for hyperacute ischemic stroke for better patient treatment;
- the further investigation of miRNA-based treatments for brain ischemia;
- remote/robotic interventions, augmented reality and mixed reality interventions and the associated software and hardware developments as relevant improvement possibilities for patient care.

1.5 APPLICATIONS IN CARDIOVASCULAR DISEASES – BACKGROUND, GAPS AND NEEDS

Applying IR for diagnosis and treatment for patients suffering from cardiovascular diseases is of great value and increasing interest due to the emerging possibilities, especially in interventional and minimally invasive procedures.

All aspects are related to imaging improvements and the corresponding role of imaging procedures for different statuses of the disease: Imaging can play a role in cardiovascular disease (CVD) prevention and screening, imaging for diagnosis and during treatment, especially with respect to molecular imaging approaches and VR applications.

Role of imaging in CVD prevention

In some situations, the use of CVD risk enhancers, particularly coronary artery calcium assessed by CT, may help to inform the clinician-patient discussion.

- Despite the huge number of published papers, there is still a gap regarding clear randomisation of enrolled patients, which limits the outcome of this research in terms of real changes of clinical practice. In particular, the difficult choice between anatomical or functional tests is due to a lack of adequately designed prospective, randomised, outcome studies.

Cost-effectiveness and radiation risk in cardiovascular screening

The recent DANCAVAS Study assesses the cost-effectiveness of CVD screening vs. no screening from the perspective of European healthcare systems[21].

However, a number of gaps remain, including:

- Further assessment of the population heterogeneity and evaluation of the obtained results is required for a better understanding of the indication that cost effectiveness may be more attractive for younger men without CVD at baseline. In addition, the role of radiation dose in the evaluation of patients with known or suspected CVD, according to the adherence in the clinical management as indicated by the current guidelines of the European Society of Cardiology (ESC) see[22] and its effect on cost-effectiveness needs to be understood.

Molecular imaging of cardiovascular disease

Advances in hybrid imaging technologies like PET/CT and PET/MRI as well as improved image analysis techniques meanwhile allow the non-invasive assessment of disease activity in the heart as a clinical reality. Whilst the lack of specific radiotracers was previously an important barrier, there is an array of new tracers allowing to measure inflammation, infection, fibrosis activity, calcification activity, myocardial sympathetic activity (cardiac innervation imaging) and thrombus formation as it occurs in the body, potentially heralding a new era of cardiovascular imaging[23].

There are, nevertheless, two gaps associated with the use of molecular imaging of cardiovascular disease:

- Despite its numerous benefits, molecular imaging remains expensive and not readily available at all centres.
- Also, there are still limitations in terms of spatial and temporal resolution parameters.

Virtual reality

The interest in the use of VR is increasing, especially in cardiac practice and before cardiac interventions.

There is still a gap for the use of VR:

- Integration of VR with an algorithm model to provide integration of imaging data before cardiac intervention could be a relevant next step for cardiologists performing such therapeutic applications[24]. However, this is not established in the hospitals and not sufficiently evaluated.

Research needs

For **CVD prevention**, research is needed on:

- the usefulness of incidental findings of CVD in CT of other clinical indications, including useful evaluation;
- CVD prevention and how it can be fostered through imaging procedures like imaging marker development.

For **CVD screening and cost-effectiveness**, research is needed on:

- the low dose effect on CVD detection, including repeated examinations;
- the use of the EURECA data[25,26] after their exploitation, to open the door to a new research strategy for reducing the cost-effectiveness caused by radiation exposure;
- the evaluation of the real impact of the adoption of the current guideline to understand if the adherence to the best diagnostic and prognostic algorithm can help to reduce not-indicated invasive and non-invasive exams.

For **molecular imaging approaches**, research is needed on:

- inflammation detection in molecular imaging studies of the myocardium and coronary arteries.

For the **use of VR**, research is needed on:

- improving VR technologies and to evaluate the pros and cons of using VR in cardiovascular imaging and interventional procedures, including education and training. It needs to be investigated, whether the procedures get faster and show fewer side effects for patients, but also whether the stress level for medical staff might be increased.

1.6 IONISING RADIATION APPLICATION IN OTHER CLINICAL SITUATIONS – BACKGROUND, GAPS AND NEEDS

This subchapter focuses on disease areas where medical applications of IR play a specific role or are likely to play an increasing role in the future and on patient populations where safety aspects including RP are of specific importance. The elaborations will be limited to those diseases and patient groups that have not been dealt with in previous subchapters[27].

Pregnancies

Pregnant women are obviously one of those patient groups where the benefit-risk balance must be addressed most carefully and differs from all other patient groups. Therefore, measures can and should be taken to improve the RP of the foetus. This can include dedicated imaging procedures with reduced or without using IR, RT approaches allowing better located dose distributions as well as corresponding communication approaches.

There are still gaps for such aspects, namely:

- There is still a lack of exposure characterisation of the foetus.
- Potential benefits of new therapeutic approaches are unknown for this vulnerable group.
- A clear unified strategy for communication with pregnant patients regarding information content is missing.

Paediatric patients

Children are considered as having an increased risk related to exposure with IR. Improper imaging and therapeutic protocols are risk factors as the resulting dose delivery is, in general, higher than necessary. Alternative diagnostic imaging based on non-IR (US, MRI) should be sought as well as the use of the most performant equipment in terms of quality.

This directly relates to the following gaps:

- European guidelines when to use which technology would be beneficial[28], but do not yet exist. Such guidelines will need to incorporate patient views and recognise that, for example, reduction in exposures to IR will be in a trade-off with use of other technologies (e.g., MRI can be a frightening experience for children), which is partially missing in current national documents.
- Finally, the relation between childhood exposure and stochastic effects is still controversial despite recent large-scale studies.

Cystic fibrosis

Given the long timeframe of cystic fibrosis and the need to repeat imaging examinations over the course of the disease, clear indications concerning timing and selection of the most appropriate imaging modality should be provided, taking into account the clinical scenario and patients' conditions.

This implies the following gaps:

- Clear guidelines how this can be done, including the potential use of imaging based on IR or non-IR methods, are missing[29].
- Other chronic diseases are also concerned by this lack of guidance.

Infectious diseases

Infectious diseases still represent a large part of the disease burden to European patients and the healthcare system. Often, they are interlinked or are the cause for further diseases such as certain cancer types or neurovascular or cardiovascular diseases.

The following gaps are identified in this context:

- The long-term effects of infectious diseases like those caused by Covid-19 are still unclear and imaging could play a role in their assessment. Thus, better diagnostic procedures providing more insights into such disease processes seem to be an important step for better patient care in the future but are currently not evaluated and further developed.
- New molecular imaging approaches based on nuclear medicine or e.g., on X-ray fluorescence and nanoparticles could improve diagnostic possibilities significantly, but do not exist or are currently not used in clinical practice in the area of infectious diseases.
- The potential of specific combinations with therapeutic applications like theranostics or nanoparticle-based therapies could be explored.

Orthopaedic applications

Patients with orthopaedic diseases could also benefit strongly from new technologies including AI, especially for imaging procedures.

This is related to the following gaps:

- Automatic measuring of the cobb angle would e.g., improve the diagnosis of scoliosis, but is not implemented in clinics across Europe.
- Applying surface imaging to understand the bone-implant contact and potential changes of implant surfaces still needs to be developed.

Research needs

Regarding **pregnant women**, research is needed on:

- improving estimation of the radiation exposure of the foetus during radiologic imaging, nuclear imaging and maternal RT;
- alternative RT approaches like hadron therapy could be investigated regarding the special effect on pregnant women and the foetus;
- defining an appropriate information setting for pregnant women who undergo an exposure to IR for whatever clinical purpose.

For **paediatric patients**, research is needed on:

- more comparative studies (IR vs non-IR methods);
- molecular epidemiological studies to study the causative relation between exposure and cancer;
- radiobiology in therapy with protons and heavy particles and in radionuclide therapy;
- risk assessment for paediatric patients undergoing radiation therapy;
- theranostics in paediatric malignancies;
- the specific ethical conditions of paediatric treatment.

With respect to **cystic fibrosis** (and more broadly for **chronic diseases**), research is needed on:

- evaluation of whether MRI could be an alternative to diagnosis of cystic fibrosis to imaging using low dose CT or very low dose CT.

With respect to **infectious diseases**, research is needed on:

- new radiation-based imaging approaches and methodologies for improving diagnostics of infectious diseases and to evaluate potentials to use those for better prevention of follow-up diseases as well as to assess long-term effects.

SUMMARY OF CHAPTER 1

Chapter 1 has identified potential developments and improvements focussing on patient benefits in various clinical scenarios on individual patient basis and addressing the needs for optimisation of quality and safety aspects and subsequently the benefit-risk balance. **The Key Messages of SRA Chapter 1 are:**

KEY MESSAGE #1

Applications of IR and medical quality and safety related research are proposed based on:

- Common interests and identified synergies
- AI, ML and radiomics, secondary use of clinical and health data
- Infrastructures for data sharing to develop data driven research and healthcare
- Imaging biomarkers, precision imaging in personalised medicine
- Image quality – Higher accuracy
- Improved quality and safety
- Harmonisation of evidence-based recommendations, ethical and legal issues
- Improvements of healthcare for children
- Ethical aspects

(For more details related to this Key Message, see section 1.1 of this document.)

KEY MESSAGE #2

To address the patient's perspectives and needs in a patient centric approach, all aspects during diagnosis, prognosis, therapy, and therapy follow-up must be addressed. Diagnosing and treating a disease at its earliest stage remains pivotal for efficient care. Research should be based on:

- Communication and information
- Precision or personalised medicine including diagnosis and treatment
- Benefit-risk

(For more details related to this Key Message, see section 1.2 of this document.)

KEY MESSAGE #3

The use of IR in oncologic diseases is central and can be summarised in screening, diagnostic, and therapeutic use. In addition to the aspects in Key Message #1, evidence is needed on:

- Screening in oncologic diseases
- Implications on new treatment modalities, theranostics, interventional treatment, and integrated treatment strategies
- The real effect of AI in screening and diagnosis

(For more details related to this Key Message, see section 1.3 of this document.)

KEY MESSAGE #4

Interventional radiology together with neurosurgery have advanced the treatment of neurovascular diseases. To continue this, developments and research should in addition to the aspects in Key Message #1 be based on:

- Biological and genetical factors
- Material development
- AI, ML, radiomics for neurovascular diseases

(For more details related to this Key Message, see section 1.4 of this document.)

KEY MESSAGE #5

The use of IR and RP in cardiovascular disease have large potential to benefit many human beings. Especially the developments in interventional procedures in molecular imaging are promising. In addition to the aspects in Key Message #1 research should include understanding of:

- The role of imaging in CVD
- Screening and prevention in CVD
- Molecular imaging in CVD
- VR in CVD

(For more details related to this Key Message, see section 1.5 of this document.)

KEY MESSAGE #6

Use of IR and corresponding RP includes almost all diagnoses and most of the patients in healthcare. Some additional aspects for some more seldomly seen diagnoses and situations like for instance non-malignant diseases with a long disease period, infectious diseases, musculoskeletal diseases, and diseases in pregnant women or children are:

- Repeated examinations with IR over a long time
- IR exposure of the foetus and unborn child
- Ethical considerations for unborn and children

(For more details related to this Key Message, see section 1.6 of this document.)

As it has been outlined in the previous subchapters, the need for research on multi spectral usage of IR and RP to translate scientific results to clinical achievements is high. In all evaluated disease areas, including cancer, neurovascular, cardiovascular, infectious, and other diseases or organ systems, a broad spectrum of knowledge gaps is identified.

The data driven research is on focus in imaging and radiation treatment and all kinds of research in this field need large amounts of quality assured data. To make Europe world leading in data driven research, the structure of data lakes for data sharing of real-word clinical data must be developed in a structured way, allowing both centred and federated solutions. Initiatives such as the EHDS and the project EUCAIM are important to prepare infrastructures that enable such research. Furthermore, the semantic interoperability and legal framework must be more equally interpreted in the member states. Then, the development of AI/ML-radiomics to solve clinical questions or AI-driven increase of image quality as well as treatment research can speed up and move to a translational stage to take results into clinical routine.

The combination of methods as in integrated diagnostics or integrated treatment or theranostics is another evolving field of research. By combining structural and functional imaging, more information about the disease and normal tissue is gained, but research is needed to evaluate which combinations give added value to the patient. Furthermore, imaging biomarkers and biomarkers in liquid biopsies could potentially add value to each other, but further research is needed in this respect as well. Unfortunately, research is often done in silos without taking the possible strength of combinations into account.

It has been more than 120 years since W.C. Roentgen discovered the X-rays in 1895, and decades since nuclear medicine, PET, CT, and MRI were invented and still, technological groundbreaking research is done. Today it is not known how far the new technique in PCCT, FLASH treatment and other novel techniques can move the limit of detection and treatment. Only scientifically sound research will tell. The technical validation followed by randomised and then real-world studies is time consuming and costly but must be done.

A large focus on personalised health and personalised medicine is based on evolving knowledge of individual conditions dependent on environmental or genetic settings. These conditions might influence both imaging and treatment for the individual. The biological background, including radiation sensitivity, influencing imaging and treatment outcome is gaining increasing interest and more knowledge can add value in precision medicine. Imaging, and especially molecular imaging, gives a possibility to whole body precision medicine since for instance receptor distribution can be visualised and quantified. The impact on individual treatment design and outcome is still not fully known but is another important area to explore.

All different aspects of research in imaging and treatment using IR aim at safer, earlier, and more accurate diagnosis, prognosis, treatment planning and evaluation as well as treatment outcome. The patient needs to be in the centre of all research regarding medical applications of IR, which means explicit involvement of relevant patient groups during technical research and development as well as engagement with non-patients prior to clinical application.

CHAPTER 2
THE CORRESPONDING QUALITY AND SAFETY MEASURES WITH A FOCUS ON RADIATION PROTECTION APPROACHES

INTRODUCTION

This chapter is intended to describe what needs to be evaluated and improved to ensure the best quality and safety of medical applications of IR as described in chapter 1. This means each diagnostic or therapeutic measure has to be evaluated carefully and has to be as safe as possible and quality assured. This will include measurements of exposure, but also of patient-based image quality, dose volume histograms for treatments and outcome documentation / follow-up. This chapter focuses on the effects that the application of IR for diagnostic or treatment-related purposes have on patients, and the research needed to describe, characterise, and understand these effects as well as to avoid or minimise detrimental effects as much as possible. The context of repeated exposures over the course of diseases or over life has been considered in each section below. The related research needs are based on the clinical perspective. Thus, the first subchapter (chapter 2.1) describes the overarching perspective on all research topics relevant for medical RP from the perspective of researchers and practitioners directly working in healthcare. This evaluation is augmented with input from medical experts representing the European Association of Nuclear Medicine (EANM), the European Federation of Organisations for Medical Physics (EFOMP), the European Federation of Radiographer Societies (EFRS), the European Society of Radiology (ESR) and the European Society for Radiotherapy and Oncology (ESTRO). Subchapter 2.1 thus mirrors the current version of the strategic research agenda on medical radiation protection, which is an updated version of the EURAMED Common Strategic Research Agenda for Radiation Protection in Medicine (Common strategic research agenda for radiation protection in medicine 2017). It indicates the needs identified by the medical community related to radiation protection in medical applications and is thus linked to chapter 1, in which the research needs regarding the medical applications are described.

Relevant aspects for medical radiation protection research have also been determined by the other European radiation protection research platforms regarding:

- Radiation biology
- Dosimetric perspectives
- Social sciences and humanities
- Emergency preparedness
- Radioecology

These identified aspects are based on the strategic research agendas of the corresponding European radiation protection platforms MELODI[30], EURADOS[31], SHARE[32], as well as ALLIANCE and NERIS[33].

Aspects that overlap with the agenda derived by the medical communities are highlighted in subchapter 2.1. Subchapter 2.2 thus addresses topics additionally identified by the platforms MELODI, EURADOS, SHARE, ALLIANCE and NERIS.

Chapter 2 also includes a subchapter on the regulators' view on research needs and related requirements, reflecting the implementation stages needed, as well as the regulatory approach to radiation issues related to medical applications of IR. Aspects raised in the EURAMED strategic research agenda as well as by the regulators are highlighted in subchapter 2.1. Subchapter 2.3 describes complementary aspects from the regulators point of view.

The chapter concludes again with a summary.

2.1 COMMON STRATEGIC RESEARCH AGENDA FOR RADIATION PROTECTION IN MEDICINE

This part of the document is based on an updated version of the Common Strategic Research Agenda for Radiation Protection in Medicine, the EURAMED SRA[34] as developed by EANM, EFOMP, EFRS, ESR and ESTRO, and adopted by the newly founded EURAMED platform. The update is based on inputs from the EURAMED scientific committee, the executive board as well as on input obtained during various stakeholder events. It reflects the medical perspective on RP-related research in the context of medical applications of IR. Common interests shared with the other RP research platforms in Europe MELODI, EURADOS, SHARE, ALLIANCE and NERIS are also highlighted in this subchapter.

Background

Over the last 10 to 15 years the structure of research funding by the European Commission (EC) has gradually changed. The intention is to bring together all interested parties to facilitate European research projects in the field of RP research and "to set up a European umbrella structure for the administration of radiation protection research calls". To this end, SRAs have been developed and are updated by the various RP platforms MELODI, EURADOS, EURAMED, NERIS, ALLIANCE and SHARE.

The advantages of such SRAs include:

- providing guidance on/help to identify the most relevant and urgent research topics in the fields they cover;
- demonstrating the importance of research areas to the stakeholders;
- justifying research expenditure in defined areas;
- facilitating discussions with other members of the scientific community in the field of RP;
- determining important topics and informing research calls of the EC and within partnerships.

The development of a medical RP SRA has been considered particularly important given the numerous applications of IR in the medical field and the fact that the medical use of IR is the largest man-made source of exposure to the human population. It is crucial for the effectiveness of medical RP research that the results of the research projects are directly transferred into clinical practice, i.e., translational research.

The original medical RP SRA has been the cornerstone for a common platform of the European medical societies dealing with topics related to the use of IR. In October 2017 EURAMED was launched by EANM, EFOMP, EFRS, ESR, and ESTRO (see www.euramed.eu for detailed information). EURAMED as a platform intends to foster medical RP research and is thus related to the overarching SRA presented here within chapter 2. Subchapter 2.1 presents the RP perspective of the medical associations dealing with IR.

Subchapter 2.1 is divided into subtopics describing the specific research aspects considered crucial for establishing optimal RP in the field of medical applications.

It is important to highlight that improving the use of IR in medicine by pure fundamental research would lack impact and influence unless it is translatable to everyday clinical practice and has immediate impact on clinical routine. It is also important that the results of the research are not only translatable but actually transferred into the clinic. Therefore, it is essential that the research is undertaken in a concise manner by persons educated and trained for good medical practice. The results have to be evaluated in clinical practice and have to be made public in a way that they are easy to access (results and implementation guidelines available on the internet) and allow implementation of the developed methodologies. It is also essential that the same level of importance is placed on educating the staff working in the field to guarantee a direct clinical impact and to ensure high-level, standardised medical care and related RP fully exploiting and profiting from all research conducted with regard to RP in the medical field throughout Europe. This aspect is now embedded in the overall context of the EURAMED rocc-n-roll SRA and can be found in chapter 3.4. Implementation aspects and requirements regarding infrastructure are dealt with in chapter 3 and not part of this subchapter on RP aspects.

Research Topics

2.1.1
New technologies for the medical use of ionising radiation with a potential for radiation protection

New technologies have been and shall be developed in the future which might generate a big advantage for the patient outcome. Some of these innovations might also have a strong impact on RP in the medical context and some of them are thus especially suited for paediatric patients. This might include diagnostic as well as therapeutic applications. In the following some technologies are listed that already match these criteria, but further new developments might come up in the future and the possibilities of such developments with respect to RP should be taken into account.

Current examples are:

- Monoenergetic X-ray sources which could be used for optimised radiation therapy, but mainly also for dose and image quality optimised imaging procedures reducing potentially the dose per examination or new imaging procedures. In this context, further research for movable monoenergetic sources seems to be important.
- FLASH therapy could reduce the radiation-induced effects in healthy tissue while maintaining the tumour control probability with the radiation oncology approach. Research is needed in this area as described in chapter 1 to understand effects as well as to investigate the clinical transferability.
- A different approach to FLASH therapy with similar effects is the proton- or ion-based therapy which aims to spare dose to the healthy tissue and thus reduce side effects. In terms of research, evaluation of the different application schemes is necessary as well as clinical research on the outcome benefits.
- AI-based methods, e.g., for image reconstruction in various scenarios as well as noise reduction or artefact reduction could be used for imaging using less IR and should be evaluated regarding their potential, especially for CT, PET, SPECT, and interventional procedures. Quality assurance, data quality and safety have to be taken into account, especially with RP issues in mind.
- AI-based pseudo imaging for therapy planning might also be an option for RP. However, again the equivalence has to be tested and methods for quality assurance have to be developed.
- AI can also be used for various aspects of dosimetry and dosimetry planning.
- Theranostics might allow more individualised therapeutic approaches potentially increasing the benefit/risk balance of therapeutic applications and thus reducing the radiation exposure of individual patients.
- Molecular imaging can help characterising radiation effects as well as disease aspects on an individual patient basis and can thus be seen as a tool for medical RP for individual patients. Research is needed to develop and establish corresponding approaches finally available for clinical application. In this context, as well as for targeted therapies, nanoparticles could play a larger role in the future.
- Photon counting detectors might play a significant role for dose reduction in imaging, e.g., in CT applications. The potential benefits need to be evaluated in terms of RP and future applications with RP possibilities as for example in interventional procedures.

2.1.2
Measurement and quantification in the field of medical applications of ionising radiation

A key priority for RP research in radiation oncology, nuclear medicine and also interventional and diagnostic applications of IR is to improve techniques and methods for measurement and quantification. The research approaches will need to be multidisciplinary and innovative. The key research questions in measurement and quantification research are:

Characterisation of exposure

An improved assessment of the benefit-risk balance as a major tool of RP requires the development of better methods to measure radiation exposure, especially of patients[35] as also indicated by EURADOS.

The characterisation of exposure in this subchapter is focussing on clinically relevant exposure determination, especially of patients. A dedicated focus is set on exposure characterisation in the context of the currently existing exposure scenarios but also on possible improvements or new scenarios based on the suggestions in chapter 1.

The basic quantity for the characterisation of exposure is absorbed dose, so wherever possible dose measurements or calculations/calibrations should be stated in terms of absorbed dose, or it should be possible to refer the stated values back to absorbed dose[36]. One of the main challenges for future research is the pronounced anatomical heterogeneity of (absorbed) doses within and between critical organs in all areas of medical uses of radiation as also highlighted by EURADOS. This needs to be supplemented by optimisation of models and model parameters to translate absorbed doses into equivalent, organ, biologically effective doses, or any other, indirect dose entities. Accurate and precise measurements with known uncertainty[37,38] are a prerequisite for the adequate implementation of dosimetric techniques into medical practice and medical routines, specifically for different types (qualities) of radiation and levels of spatial resolution. Therefore, the following issues need to be addressed in research:

- Calibration of dosemeters for medical applications is currently performed using secondary standards non-specific to the radiation fields used in medical application of IR leading to undefined measurement uncertainties. Therefore, exact measurements require calibration against radiation fields specific to medical applications. This is partly possible but not in all calibration settings as sometimes industrial settings are used. Research about transfer approaches is necessary. In addition, the new dosimetric quantities will need to be considered for calibration tasks.
- There is a limited availability of dosemeters for use inside the human body, which implies, that currently simulations of radiation transport and deposition are necessary, e.g., using Monte-Carlo (MC) methods[39,40] normalised to the measured quantities.
- More than one million workers are exposed to IR in Europe, many of them are working in medical applications[41]. Real-time measurement of doses is relevant to reduce doses to staff. Therefore, the development of specific dosemeters is required, allowing real-time monitoring, e.g., of eye structures and extremity/finger doses from interventional radiology/ cardiology and nuclear medicine. The existing dosemeters are either not for online measurements or they suffer from technological limitations e.g., for high dose rates as in pulsed radiation fields or size or practicability. The challenge in this area is to provide reliable, accurate and real-time measurements related to personal dosimetry.
- In the case of heterogeneous fields, like those in interventional radiology, the sensitivity of workers' dose assessment with respect to the dosimeter positioning and the influence of the partial shielding is needed to improve dose accuracy.

Dosimeters in the clinical environment will often need to work also in pulsed fields. They have to be accurate in such fields when needed for the purpose and this needs to be tested.

- Non-uniform spatial (3D) and temporarily varying (4D) dose distributions can lead to differences of up to several orders of magnitude regarding the doses in exposed tissues as described by measured or simulated dose distributions[42]. Therefore, micro-dosimetric measurement devices and techniques for use within and between cells, the anatomical structures of organs and the human body are necessary, e.g., for dosimetric use with regard to individual structures in the eye, the brain and the heart, and also other organs depending on the basis of future research results.
- Different types of radiation (photons, electrons, protons, heavy ions, secondary neutrons) are used for and/or associated with medical purposes. The correct determination of doses to and dose-distributions within patients at different levels of spatial resolution is necessary depending on the required purpose in terms of radiobiological questions or optimisation of procedures. Also mixed fields and energy spectra need to be taken into account for reliable measurements and calculations of dose-distributions. This is also highlighted by EURADOS.
- Knowledge on track structure and/or microdosimetry of internal emitters (alpha, beta, Auger) is a prerequisite to predict the associated biological effects[43]. Therefore, computational methods need to be further developed and connected to the results of corresponding research on measurements and calibration procedures (see above).
- Development of updated or alternative quantities and concepts for describing the anatomical dose distributions within organs, tissues, and the body as the basis for predicting health effects, rather than mean absorbed doses (e.g., dose averaged over an organ) or dose volume histograms. This might also be important in the context of FLASH therapies.
- Dose management systems need to deliver comparable results (same values or transferrable values). Investigations about differences as well as standardisation are required.
- Methodologies have to be developed for determination, description measurement and calculation of doses outside the planning target volume (PTV) for radiation therapy, i.e., the peripheral dose. This is urgently required to build and optimise prediction models for secondary tumours, but also tissue effects, and to enable comparison of different techniques and/ or technologies.

This research would be a prerequisite for the accurate and precise evaluation of the dose as the basis for better RP of the patient and medical personnel as explained below. It is therefore important that the measurement approaches are standardised and calibrated or at least compared with each other.

Individual dosimetry

Individualised patient dose assessment methods, e.g., by adjusted phantoms for measurements[44], size-specific conversion factors, dose measurements taking into account imaging parameters shielding etc. are needed to allow an accurate patient dose estimation[45] and risk assessment[46]. Many dose distributions would depend on individual patient constitution (e.g., size, weight, shape, age and biological factors such as the distribution and kinetics of radioactive markers[47] or susceptibility to different therapeutic procedures). Therefore, the following dosimetric procedures need to be addressed in research:

Further development of computational methods for dose distribution calculations based on patient-specific and equipment-specific characteristics for all medical procedures using IR, including for example CT, interventional and nuclear medicine procedures as well as radiotherapeutic procedures avoiding different dose indicators for different types of procedures in order to get comparable meaningful information about the organ doses of individuals for which the methods need to be standardised. In this context, it is also elaborated by EURADOS that for patient dosimetry in CT and interventional radiology examinations, more reliable and standardised dose estimations are needed for the optimisation of patient doses. This could also improve the use of DRLs, as well as enable adequate setting of achievable dose levels and skin dose alerts. Moreover, personalised dosimetry could benefit from (near) real-time standardised computational solutions and software, allowing to determine dose distributions at the patient's skin and within organs, based on actual patient anatomy for adult and paediatric patients. Big data, deep learning, increased computational power and the availability of comprehensive preclinical and patient (imaging) data steer towards personalised dosimetry and allow considering individual sensitivity within the medical field as also indicated by EURADOS. The independent scientific validation of software and computational approaches is largely missing.

- Development of optimal measurement protocols in nuclear medicine for accurate estimation of absorbed doses using patient-specific and equipment-specific characteristics. Refinement, validation and implementation of new biokinetic models for dosimetry in molecular radiotherapy using for example physiologically based pharmacokinetic (PBPK) models for the individual assessment of biokinetics[48], including uncertainty budgets[49] as also highlighted by EURADOS. New precise biokinetic data of many radiopharmaceuticals (including daughter nuclides) at optimal time points need to be acquired (through improved and standardised quantitative imaging and compartmental modelling) and used for dose optimisation of paediatric nuclear medicine and for radionuclide therapy including treatment planning. This requires traceability of activity quantification for patient administrations, imaging, and pre-clinical research. Accurate dosimetry also requires appropriate and new computational models for organs of interest, including organ sub-structures.
- Development of methods to estimate or measure the actual delivered radiation dose in radiotherapy. As also indicated by EURADOS, in modern radiotherapy dosimetry should be based on the capabilities to individually map the type, deposited energy and linear energy transfer of each particle for realistic beam intensities, which is not done in clinical routine today. Moreover, online dosimetric validation during treatment, to support quality control and in-vivo dosimetry, is needed, which requires dosimetry techniques for checks at all stages of the radiotherapy chain. Harmonisation of radiotherapy dosimetry throughout Europe is not given, as there are no inter-centre audits or intercomparison programs for emerging treatments to complement existing programs for photon radiotherapy.
- Development of a unique dose indicator that describes the absorbed dose to organs in order to perform risk assessment.

This research would be essential for accurate and precise determination and evaluation of indication-, therapy-, and subgroup-specific doses, respectively, and therefore risks of radiation-induced morbidities of individual patients. This attributes to a better RP of individual patients and medical personnel.

Quality metrics for diagnostic imaging and therapy

For the use of quantitative imaging, standardised protocols for each clinical indication and/or common clinical indications for specific diseases need to be developed[50]. Therefore, the following issues need to be addressed in research:

- Dosimetric and image quality metrics need to be developed to fully assess the impact of novel detector or source technologies (e.g., low- or lowest-noise as well as energy resolving detectors) and image reconstruction methods available for reducing radiation exposure to the patients. To this end, research is needed on which requirements (system stability, noise reduction, influence of individual patient characteristics, iterative reconstruction parameters) have to be met for quantitative imaging to yield reliable and reproducible results.
- Measuring methods (e.g., phantoms, reading protocols, etc.) need to be improved or developed and standardised to address the improvements in medical technology as well as new methods, e.g., particle therapy or new molecular imaging technologies.

- Image quality metrics directly derived in patient images could be a meaningful tool for adjusting images quality to the needed and appropriate image quality. Corresponding definitions, method developments as well as evaluations have to be performed to foster individualised patient RP in imaging procedures together with dose evaluation.
- There is an increasing need also for quality metrics of treatment plans to allow easier quality assurance to facilitate comparability of methods used in radiation therapy and to allow more standardised research regarding clinical treatment outcomes.

This research enables the translation of quantitative techniques to widespread clinical use for the benefit of the patient. In addition, this research is also a prerequisite for the harmonisation of practices and quality assurance. It should be mentioned that harmonisation refers to the procedures of deciding on the patient treatment rather than to the diagnostic or therapeutic procedures, as these will depend on the individual patient and the given possibilities and equipment in clinical centres. The goal is to ensure an almost equal high-level diagnosis or treatment across Europe, even with different equipment and possibilities. Therefore again, the measurement procedures need to be standardised and validated against each other.

Sources and influences of uncertainty

Uncertainties need to be determined for all techniques described above, be they measurements or computations. Many components independently contribute to the uncertainty in the determination, reporting and performance of medical applications and in its characterisation[38,51]. It is of utmost importance to develop methods to assess the contributions of different stages in the chain of medical interventions to be able to define the relevant points of optimisation, which means putting effort into those parts of a medical application scheme, where there is the highest benefit. Therefore, the following issues need to be addressed in research:

- quantification of the influence and sensitivity of different parameters (technique dependent, system dependent, patient dependent, medical staff dependent);
- development of methodologies for classifying different influencing parameters and to build a system that allows the optimisation of medical applications of IR for individual patients or methods.

Knowledge of the integral uncertainty and its components is key to identifying the most relevant steps, to allow for prioritisation and targeted optimisation and thus, making more effective use of clinical and research resources.

2.1.3 Normal tissue reactions, radiation-induced morbidity, and long-term health problems

A key priority for RP research in radiation oncology, nuclear medicine and also interventional and diagnostic applications of IR is to improve health risk estimates. The corresponding research approaches need to be multidisciplinary and innovative. Radiation biology research should include a structured approach via Adverse Outcome Pathways towards well-defined end points to get a holistic view on the side effects of IR as also indicated by MELODI.

The key research questions related to tissue reactions and biological risk research are:

Exposure-associated cancer risk: dose, dose-distribution, and dose-rate dependence

Knowledge of the dose dependence of the radiation induction of primary or secondary cancers, in particular in relation to dose inhomogeneities and dose rate, is of major importance in order to optimise therapeutic efficiency and reduce unwanted side-effects. In radiation oncology, this refers to high doses within the PTV as well as to out-of-PTV doses, as low as 1-5 Gy, in particular in intensity-modulated and image-guided radiotherapy but also in brachytherapy and molecular (radionuclide) radiotherapy[52]. It also needs to include other, additional treatment modalities, particularly chemo- and biologically targeted therapy. Diagnostic procedures must also be considered, especially in view of interventional or fluoroscopic procedures or nuclear medical imaging techniques and those applied in preparation for treatment. The need to understand these aspects and the relevance for detrimental effects is also highlighted by MELODI.

Non-cancer effects in various tissues and radiobiology-based effect models for individual morbidity endpoints

Radiation-induced morbidity (cancer and non-cancer diseases and disorders) may be observed early or late (occurring after 3 months to at least 5 years after radiation exposure), not only in the tissues and organs exposed to high doses. Also, very late health effects (occurring after more than 5 years to many decades after exposure) may not only be observed in high dose radiotherapy (> 5 up to 50 Gy) but also in the intermediate (0.5 to 5 Gy) or in the low dose (< 0.5 Gy) ranges. Examples of these very late occurring normal tissue morbidities, which may be induced by localised radiation exposure outside the planning target, volume of radiotherapy or by repeated interventional procedures are: cardiovascular or cerebrovascular diseases, functional or structural damage to eye structures, various delayed, persistent immunological changes, progressive microvascular injuries but also late and very late developmental and functional detriments after radiation exposures in

diagnostic procedures and paediatric radiotherapy and many more radiation-associated health disorders. The contribution of other treatment modalities, particularly chemo- and biologically targeted therapy, to the development of very late side effects is currently poorly understood and needs also to be considered along with any diagnostic procedures, especially for interventional or fluoroscopic and nuclear medicine procedures and those applied in preparation for treatment.

Skin reactions in interventional procedures have been studied for years. But there are still areas that require additional research actions. The threshold of 2-3 Gy for peak skin dose at least for photon radiation has little chance to produce skin reaction in most patients and to use it as trigger level for follow-up programs might produce an unnecessary workload for clinicians. This might be partially caused by a poor accuracy in the estimation of the skin dose due to the complexity of dose calculations in these kinds of procedures. Therefore:

- a more precise knowledge on the probability to produce skin reactions and their severity is needed;
- more research efforts are needed to perform the clinical follow-up of more patients (with real risk of injuries) to better understand the rationale of radiation-related skin injuries in interventional practices;
- better structured radiation dose reports are needed to achieve better estimations of patient peak skin doses in interventional procedures. And better tools have to be designed to permit medical physics experts to estimate peak skin doses to patients accurately.

Current morbidity risk models and normal tissue complication probability (NTCP) models are largely empirical or based on hypothetical data-fitting models of assumed processes of damage development and lack the evidence of a mechanistic basis. Moreover, they do not consider the influence of the position of the doses within one organ, or the interaction of dose distributions in "corresponding" organs, such as lung and heart, or the effect of additional treatments, such as chemotherapy[9,53]. These factors, however, must be included to get appropriate estimates for the patterns of risk of any individual patient with regard to modern techniques in radiotherapy, nuclear medicine, and radiological diagnosis.

Individual patient-related radiation sensitivity and early biomarkers of response and morbidity

The adverse effects may be different for individual patients as also highlighted by MELODI, defined as individual radiation sensitivity for immediate effects of healthy tissues such as skin erythema after external radiotherapy on one hand, and individual radiation susceptibility for long-term adverse effects on the other hand. Dose-effect relationships may depend on the initial health state, history, and lifestyle. So far, predictors and influencing factors remain unclear to a large extent[54]. The individual sensitivity of patients may be considered in the choice of specific diagnostic procedures and/or therapeutic strategies. This can be based on intrinsic factors (age, gender, genomics, proteomics) of their tumours or different normal tissues but also on concomitant diseases impacting on general or specific normal tissue tolerance, lifestyle (e.g. reduced lung/liver tolerance due to smoking and alcohol consumption) or previous/parallel treatments.

In a number of tumours, biological factors affecting radiosensitivity, i.e., predictive factors, such as local hypoxia, tumour heterogeneity or viral infections, were identified. Such investigations need to be extended and may also consider the early response of the tumour to a specific treatment. Imaging biomarkers of tumour radiosensitivity are needed in this context, as well as biomarkers of morbidity, which can be identified before or early in the treatment phase, may help in the selection of the adequate treatment of the individual patient. These have been rarely studied so far. However, patients with a high risk for a certain, severe, morbidity symptom may require a change in dose distribution and in treatment strategy, or follow-up protocols may need to be adjusted to the individual morbidity risk pattern based on early biomarker expression[55].

Radiobiological mechanism of radiation-induced side-effects and protective strategies

The radiobiological molecular mechanisms of radiation-induced morbidities in normal tissues and organs are very complex and vary between different signs and symptoms of morbidity in the same organ and between different organs. Also, the tumour responses to therapeutic exposure to IR, including radiotherapy using hadrons, are currently largely unknown. The radiobiological molecular mechanisms are even more complex for combined radiotherapy and chemo- or biologically targeted treatment strategies. These mechanisms need to be clarified for specific clinical morbidity endpoints in order to develop specific strategies for protection, mitigation, or management of the clinical consequences of exposure. As indicated also by MELODI, relevant preclinical 2D and 3D models and identification of biomarkers are needed to fill gaps in clinical findings and in dose-effect relationships in broader dose (rate) ranges than clinically relevant.

They are even more important for medical radiation procedures in paediatric patients given the evidence showing that the complexity and severity of morbidities and developmental injury and the risks of therapy-induced malignant diseases are particularly high after radiotherapy (in almost all instances in combination with chemotherapy). This has also been highlighted in the MELODI SRA.

Similarly, novel strategies for improving the diagnostic and/or therapeutic efficacy for the application of IR may be based on the synergistic combination with upcoming technologies such as combinations with high intensity focused ultrasound and biology-based approaches relying on tumour genomics, proteomics or metabolomics including local enhancement of drug delivery.

It is for example also highlighted by MELODI that when the mechanism of action of IR exposure is better known, combinations of radionuclide therapies with other treatments like chemotherapy, immunotherapy or radiation sensitisers can be designed to enhance the overall effectiveness of the treatment as described in chapter 1.3. The upregulation of immune-response by radiotherapy in combination with immune check-point inhibitors to enhance therapeutic effects is a field to be addressed. The inhibition of DNA repair mechanisms might enhance the therapeutic effect, although different agents than customary used in external beam radiotherapy might be needed for this combination as the absorbed dose is delivered over a prolonged period. Combination therapies will possibly enable to treat tumours resistant to current treatments by attacking them through different action mechanisms. Combination therapies will potentially result in further adverse effects too and are therefore relevant in terms of updated RP insights.

Both the protective and sensitising strategies need to be established and validated in preclinical as well as in subsequent clinical studies. These investigations need to focus on the efficacy of the novel approaches and also on their selectivity for the respective target tissue to guarantee a therapeutic gain.

2.1.4 Optimisation of radiation exposure and harmonisation of practices

According to the European Basic Safety Standard Directive (BSSD)[56], the RP of individuals subject to public or occupational exposure must be optimised with the aim of keeping the magnitude of individual doses, the likelihood of exposure and the number of individuals exposed as low as reasonably achievable (ALARA) taking into account the current state of technical knowledge, economic and societal factors. The optimisation of the protection of individuals subject to medical exposure should be consistent with the medical purpose of the exposure. This is also especially important when using IR on children.

The EU Directive on patients' rights in cross-border healthcare[57] calls for a concerted strategy in terms of harmonisation of clinical practices, meeting patients' expectations of the highest quality healthcare, including when they seek treatment away from home. As before, it must be highlighted that harmonisation means to harmonise the procedures on how to decide the patient treatments rather than the diagnostic or therapeutic procedures themselves, as these will depend on the individual patient and the given possibilities and equipment in clinical centres.

According to the literature, high variability of mean effective doses or organ doses of patients across Europe persists across all medical IR procedures and is seen across single countries, hospitals or even at the departmental level[58]. This variability exists despite technological developments facilitating reductions in patient dose, thus highlighting the importance of harmonisation of IR procedures and the development of new and more efficient optimisation methods including evaluation criteria. For this optimisation, there needs to be a general definition as to what is an acceptable level of quality, what kind of optimisation should be performed and what is the optimal level. With the main goal of maximising the clinical outputs of the procedures while minimising the exposure of patients and staff, the key research questions are:

Patient-tailored diagnosis and treatment

The comprehensive tailoring of imaging and therapeutic procedures in terms of the clinical question, anthropometric and physiological parameters of each patient, especially children, and lesion-specific characteristics is a key challenge that is largely yet to be fully addressed.

Furthermore, imaging is essential to patient-tailored therapy planning, therapy monitoring and follow-up of disease, as well as targeting non-invasive or minimally invasive treatments, especially with the rise of theranostics.

For the reasons given above, and in view of reducing radiation exposure to the patients by individually tailoring their diagnosis and treatment, research needs to be conducted with regard to the following currently unresolved issues:

- Development of quantitative imaging biomarkers for each common clinical indication and/or specific disease/organ, and their standardisation with regard to required image quality in conjunction with related radiation exposure.
- Recent advances in imaging using specific radiotracers will provide additional tools for better characterisation of a lesion at the molecular level. This will provide an insight into lesion heterogeneity and targeting, with perspectives in guiding biopsy of lesions, prediction of treatment response and image guided therapy.
- For optimal treatment prescription in targeted radiotherapy, the knowledge of the dose-response relationship is essential. In targeted radiotherapy, patient-specific dosimetry is essential for both the prediction of the adverse events of a treatment and of the tumour response[59].
- Research on the requirements that have to be met for quantitative imaging to yield reliable and reproducible results, e.g., in view of system stability, image reconstruction techniques, influence of individual patient characteristics and applied radiation exposure.

- Development of approaches for low-dose time-resolved volumetric imaging (4D), e.g., of blood flow or volume distribution (perfusion) as well as organ-motion dependent imaging, especially in view of therapy planning and treatment response imaging.
- Development of body-mass index (BMI) specific image acquisition protocols and specific dose-reduction algorithms for obese patients and paediatric patients, since obese patients require higher than average radiation doses and children can maybe be imaged with reduced exposure, and exploitation of techniques normally used for radiation exposure reduction to achieve diagnostic image quality.
- Development of approaches for low-dose treatment-response and follow-up imaging solely focussing on the detection of "change" (relative to a standardised baseline acquired at higher radiation exposure) providing reliable diagnostic assessment, e.g., through development of standardised disease- or treatment-specific imaging protocols especially for those patients frequently imaged.
- Research to identify underlying relationships between demographic, disease-related, and 'omics' biodata and image and treatment data for fully developing personalised medicine in order to offer the best medical diagnostics and treatment associated with the lowest possible dose to each individual patient.

The benefit of this research could be to develop systems for diagnosis and treatment allowing more efficient treatment techniques, which may also offer economic benefits. This research could also provide further insights into disease processes of individual patients and therefore foster precision medicine.

Full exploitation and improvement of technology and techniques

Despite the potential for the exponential growth in the technological features of medical imaging equipment to decrease patient doses, such benefits are not always realised in daily clinical practice[60]. This subchapter focusses on the implementation whereas subchapter 2.1.1 highlights new developments.

Research on development, improvement, clinical applicability, and full clinical exploitation of (new) technology and techniques for offering diagnosis and treatment delivery associated with the lowest technically possible radiation exposure to the patients is required. In this context, the following topics need to be addressed by research:

- Low-dose CT imaging enabled by low tube potentials and current-time products in view of its clinical applicability, indication, standardisation as well as its potential diagnostic and technical limitations.
- Novel image reconstruction techniques enabling low- or lowest-dose image acquisitions, with regard to their routine clinical applicability and their limitations in view of ensuring diagnostic accuracy and reliability.
- Novel detector technology in medical imaging in view of its clinical applicability and potentially associated technical limitations.
- Diffraction-enhanced imaging and other newly developed approaches.
- Further development, implementation and application of patient- and disease-adapted techniques and protocols of combined modalities as for example SPECT/CT[61], PET/CT, whole body PET, PET/MRI and LINAC-MRI.
- Optimisation of image guidance procedures in radiotherapy.
- Strategies for a reduction in peripheral doses in radiotherapy, e.g., by defining indications for ion therapy.
- Using AI based methods for therapy and nuclear medical applications for therapy planning, control, and predictions of (optimised) dose distributions. This has to be harmonised across clinical centres within Europe.
- Research for, and production of, novel radionuclides and radiopharmaceuticals for either improving diagnostic and therapeutic outcome or reducing associated exposure.
- Data-crawling and mining approaches based on large-scale data contained in imaging and treatment biobanks e.g., for extracting indication-specific acquisition or treatment protocol parameters along with associated patient exposure data for the purposes of diagnosis and treatment optimisation, standardisation and harmonisation (through the definition of European DRLs) as well as for extraction of higher-order patterns of disease, its diagnostics and treatment along with associated doses, and the possible interrelation of this data e.g., to genomic data (radiogenomics).

Research with regard to technology development may remain basic research, which is institution- or manufacturer-driven and controlled. This is the current scenario, although it requires and relies heavily on input and feedback from medical research and routine clinical applications. Research on clinical applicability, improvement and full exploitation of technology and techniques enabling radiation exposure reduction is driven by, and requires, active medical research in the fields of radiological diagnosis and radiopharmaceutical and therapeutic treatment. There needs to be an emphasis on the close link between technology developments at research institutions, especially at manufacturers' sides, and the clinical research facilities with feedback options in particular, to define a process to consolidate the achievements in terms of harmonisation.

Any optimisation in medical imaging techniques, including dose reduction strategies, must be evaluated thoroughly in terms of the resulting image quality. In determining whether an image is diagnostic or fit for purpose it is important to take into account not only the physical measurements of image quality (e.g., signal to noise ratio (SNR), modulation transfer function (MTF), and detector quantum efficiency (DQE), but also to include psychophysical methods (e.g., contrast detail assessment and spatial resolution assessment), and clinical, diagnostic performance approaches such as visual grading analysis (VGA), receiver operating characteristic (ROC), and psychometric scales. The current variability, absence of validated approaches and guidelines represent a significant barrier to effective optimisation research. The promising approach of evaluating image quality directly on patient images shall be pursued further, since it may be the only method that can cope with image processing of CT-reconstructions algorithms based on deep learning. The 1996 European Guidelines on Quality Criteria for Diagnostic Radiographic Images[62] aimed to provide some assistance with image quality assessment, but these were very limited, have deficiencies, were never validated and are now dated. There is thus an urgent need for establishment of robust, validated approaches to facilitate this critical aspect of optimisation research.

Technologically meaningful developments are required and need to be evaluated with respect to the possible output for patients, staff, and the public, at varying levels of maturity in terms of the status of a technology status as a product line and their applications in the medical environment has to be fostered, but also evaluated.

In this context, multi-professional engagement together with educational institutions and equipment manufacturers will facilitate the required development of strategies for the harmonisation of IR procedures and standards of practice, since several studies have highlighted the heterogeneous use of technology and the unanticipated patient and staff dose increases due to focussing on faster possible procedures or on better images, for example. This is of particular importance in paediatric populations as well as for patient cohorts requiring multiple consecutive diagnostic, radiopharmaceutical, or therapeutic procedures.

Clinical and dose structured reporting

Clinical reporting

A medical imaging procedure workflow involves several steps, ending with a clinical report. Currently, medical imaging reports are often presented with little or no structure to the text. This can show difficulties in understanding the content of the report both for referring physicians and patients. The development of a structured reporting system will improve the clinical outcome of a medical imaging procedure, by focusing on the essential message, in a harmonised way, thus facilitating the communication process along the clinical pathway of the patient. This could be more easily achieved e.g., by using large language models for generating the structured reports. The medical procedures must be based on structured referrals as well.

There are many advantages of such reports, including improved follow-up for returning or chronic patients, easy retrieval of pertinent information enabling clinical and translational research, integration of the information in imaging biobanks, and automated translation.

Another related issue is the lack of a centralised medical databank on imaging procedures for each individual patient on a national and European level, often leading to unnecessary repeated diagnostic procedures and hence unnecessary radiation exposure. Harmonisation of clinical reports could facilitate the development of such a centralised medical registry at a European level. Also, a centralised dose data collection algorithm for therapeutic procedures would allow improved analyses of dose-effect relationships for adverse events, including stochastic radiation sequelae.

Dose reporting

Structured dose reporting in radiation diagnostics and therapy (or at least documentation of administered activities in nuclear medicine) is a growing area of focus and will benefit all professions directly involved in the IR procedures and patients undergoing such procedures in the years to come. However, the adequate specification of absorbed dose distributions has not yet been sufficiently addressed in research and clinical practice[63]. In radiation oncology, structured dose reporting needs to address absorbed doses in organs at risk and/or at their subvolumes, that are relevant for adverse event endpoints. The latter needs to be specified and their scaling to be defined. Moreover, anatomy-related dose distributions in the irradiated volume and in the periphery, at least down to the 1% isodose, need to be reported or re-constructible from the documented treatment information and then specifically related to potential radiation sequelae. Structured absorbed dose reporting in radiopharmaceutical therapy has been addressed by ICRU, but is not yet implemented in clinical dosimetry software, nor its uncertainty[64].

The main benefits would be:

- to establish a model for providing information, in radiation diagnostics and nuclear medicine, about patient dose exposure in an easily accessible way (e.g., by integrating visual scales for the referring physicians to understand the level of exposure);
- to facilitate the rapid determination of local, national, and European DRLs;
- to facilitate establishment, in radiation oncology, of dose response relationships for adverse events in organs at risk as well as for stochastic radiation effects both close to the PTV and in the periphery of the patient.

Structured dose reporting in radiation diagnostics (or documentation of administered activities in nuclear medicine) is an essential tool for the harmonisation of the dose management systems and the comparison of doses, creating a comprehensive, common language for health professionals. Such structured dose report in radiation therapy applications would help to establish firm dose-effect relationships for adverse deterministic and stochastic events. Current lack of standardisation of dose management systems (DMS) tools need to be addressed as previously mentioned.

Protection of staff, patients, carers, and general public

Aside from the optimisation of protocols and procedures, their standardisation and their personalisation, it is of the utmost importance to optimise RP using existing RP measures[65]. To optimise RP in terms of applicability and best benefit for staff and patients, the establishment of key indicators of safety and quality in RP is essential according to the general ALARA principle discussed before. The primary goal of the development of safety programmes is to reduce morbidity risks from excessive exposure to IR for specific procedures and population, e.g., interventional radiology and the paediatric population. Another focus is on the cost-benefit analysis of the implementation of RP devices and safety programmes. Neither proven criteria of cost nor proven criteria of benefit have been established so far. Research must explore both external and internal radiation exposure and their associated protection measures. The use of dosimetric approaches described in 2.1.2 is an important aspect for RP, especially for staff and for those working in interventional departments.

2.1.5
Justification of the use of ionising radiation in medical practice

The principle of justification is one of the key pillars of RP underlined in the revised European BSSD[56]. This principle focuses on weighing the benefits versus the risks. A dedicated focus needs to be drawn to applications of IR to pregnant women or when pregnant women are potentially exposed in the context of medical applications of IR as staff or carers or the public. Exposure of the unborn needs to be determined in this case. Further important elements are patient communication, as the basis for shared decision-making including the patient rights for influencing the decision, as well as the appropriateness of the radiological procedure with respect to the clinical setting. The key research questions concerning the justification of the use of IR in medical practice are:

Benefit-risk balance assessment and communication

While the clinical benefit of a diagnostic or interventional imaging procedure is assumed to be established, an estimation of the risk related to effective dose exposure for a given patient is a difficult step because the current estimations are for a general population. The linear no threshold model (LNT) is used in RP, but the model is questioned for low and very low doses and dose rates. The LNT model is based on an extrapolation of the exposures from the Hiroshima-Nagasaki bombardments. As medical exposures being completely different with regard to radiation quality and doses as well as dose distributions, they might have a different impact from the physical and radiobiological point of view. The LNT model is intended for RP purposes. Its usability for modelling cancer induction might not be supported by all radiobiological data (see for example Scott and Tharmalingam 2019). The effective dose (ED) concept is often applied for purposes not fully supported by scientific evidence. This approach was meant to derive average risk factors of exposures for an average population and not for individual risk assessment, it can be, however, used for system or methods comparison. These aspects must be clearly communicated to staff and especially to patients. The current uncertainties in this area make the establishment of a reliable benefit/risk assessment virtually impossible.

Therefore, there is the urgent need for research aimed at risk estimation for an individual patient. However, it is unclear how this can be implemented for the stochastic mechanisms based on epidemiologic data. Increased risk factors for organ-specific patient groups or patient-parameter based changes on optimal imaging procedure setups may be investigated as a promising

approach. For the development of such a research programme for diagnostic imaging and interventional procedures, a reference to a centralised repository of imaging data would be an important resource for data mining and the following risk assessment (see sections 2.1.3 and 2.1.4). This is expected to finally result in better individual risk-related dose quantities for patient dosimetry.

Although the benefits for the patients seem to be obvious in many cases, there is also still a need for quantifying such benefits and thus develop tools for measuring the benefits. This implies e.g. measurements of image quality in patient images, proper use of Dose-Volume histograms, evidence-based studies about patient outcome etc.

The proposed research will have a direct benefit for the patient in general and especially in the context of screening methods based on the use of IR. Specific attention should be given to new screening approaches like lung cancer screening programs.

Most new therapeutic radiation technologies are clinically introduced to reduce exposure to healthy tissue. In the near future, an increasing number of cancer patients will be treated with particles (e.g., protons and carbon ions). Although particle therapy will result in lower dose levels to many critical structures as compared to the currently used photon-based technologies, the consequences in terms of reduction of late and very late side effects remain to be determined and have to be weighed against the higher costs.

In the context of the current drive for patient empowerment and involvement in the decision-making process, the development and subsequent evaluation of novel tools for patient communication have become necessary. Some professional organisations such as the American College of Radiology (ACR), ESR, the Radiological Society of North America (RSNA) and national clinical societies have developed communication guidelines and platforms for diagnostic imaging, however, a unified approach regarding methodology and content is currently missing. As highlighted by SHARE and NERIS, effective communication is seen as a critical challenge by the medical field, although it is usually concerned with patient communication rather than dialogue between other key actors. Evaluation of the effectiveness of communication between researchers towards more effective RP in medical applications is needed, i.e., ensuring effective interdisciplinarity. Specifically, information on the research process itself is required for all groups involved: clinicians, patients, and researchers, particularly in relation to the increased use of large data sets, ML and AI, where there is the risk of even more black-boxing. Open science needs to become part of the RP discussion and the impact of Open Science approaches on the patient needs to be understood. How can the patient be enabled to feed into research needs while avoiding this causing disproportionate burden on health systems?

The proposed research work will aim to develop a European evidence-based electronic communication platform focused on all types of diagnostic imaging using current information technology that is endorsed by the relevant professional organisations, patient organisations, and other relevant stakeholders. The European platform will be designed in a way to allow for localisation and adaptation to the national/regional settings. The establishment of such a system has to be based on the successful completion of the cost-benefit research activities outlined above.

Improvement of use of evidence-based guidelines

Clinical imaging guidelines are intended to help physicians decide when an imaging study would be useful and identify the most appropriate examination for a particular patient. In recent years, imaging guidelines, in view of the referral process, have received much attention from the RP community and international organisations given the increasing number of medical imaging procedures and studies that have shown that about 30 % of the imaging procedures performed in Europe were found to be inappropriate[66]. The European BSSD[56] requires that clinical imaging guidelines are available in all EU Member States.

There is the recommendation that the awareness and use of clinical imaging guidelines in Europe need to be improved and novel approaches are needed for that purpose[67]. Many clinical guidelines for referrals are existing, but they are hardly deployed in clinical practice. The actual benefit of the deployment of such guidelines should be evaluated. More pilot programs should be launched to advance in this task.

The proposed research work should identify and develop methods to improve the use of clinical imaging guidelines in Europe, especially in view of the referral process at large. i.e., through incentives, regulatory requirements, IT tools, etc. The research work is related to a key priority in medical RP as outlined among others in the Bonn Call for Action[68] and must be relevant for all diagnostic applications of IR. To define the proposed methods, an evaluation and impact assessment of the use of currently existing European and national guidelines must be performed with an emphasis on evaluating the usability of the guidelines and their impact on daily clinical practice[66,69] as also indicated by the regulatory bodies and experts.

It is important to describe how to improve the dissemination, integration into the clinical workflow and use at large of clinical imaging guidelines in view of the referral process. In addition, methodologies, and guidelines for adoption/localisation/adaptation of the guidelines need to be proposed.

2.2 ADDITIONAL ASPECTS IDENTIFIED BY THE NON-MEDICAL RADIATION PROTECTION PLATFORMS

2.2.1 Radiation biology perspective

Radiation biology is indispensable for the understanding of the beneficial modes of action in medical applications of IR as described in subchapter 2.1. In addition, this field of science also identifies adverse effects of IR, which is the scope of this subchapter. Radiation biology is thus an essential contributor to the development of knowledge to optimise doses for diagnosis or treatment to obtain an optimal *benefit-risk* balance. Radiation biology – in the context of RP – focuses on the biological processes related to short- and long-term risks, either on the general or the individual-patient level. Besides the adverse effects of IR described earlier, such as various cancers and non-cancer diseases such as (cardio) vascular and neuro-cognitive conditions, lens opacities, also alterations in the immune system including immune dysregulation and inflammatory reactions need to be taken into account.

To understand the mechanisms described in subchapter 2.1, the role of various molecular pathways needs to be understood, such as DNA repair mechanisms and cell signalling pathways, and whether these mechanisms mediate the effects of radiation. Specifically, radiobiological research on healthy tissues, the identification of biomarkers and radiomics are needed to link changes at tissue, cellular and subcellular levels and to study the role of epigenetics and the bystander effect. In particular, improved understanding of the role of specific target cells, such as stem cell/progenitor cell, DNA damage as a function of radiation quality will advance RP insights for medical applications of IR.

2.2.2 Dosimetry perspectives

Track structure has been proven to show a strong correlation with the induction of early biological effects, particularly the occurrence of DNA single and double strand breaks. As later biological endpoints also show dependence on radiation quality, there could also be a correlation of track structure characteristics and the probability of inducing these later effects, such as chromosomal aberrations or cell death. This fundamental knowledge might have a direct impact in addressing current optimisation criteria in diagnostics, radiation therapy and RP, such as "biologically weighted" doses delivered in hadron therapy and dose calculation in inhomogeneous irradiations such as those of short-range α-and β-emitters used in nuclear medicine. The geometrical correlation of energy deposition and cellular damage, however, is unclear, risk estimation models would depend on such knowledge, as well as the use of high-Z nanoparticles in radiotherapy, the chemical aspects of the IR interactions with biological matter and the temporal correlations of radiation interaction events. These aspects require improved micro- and nano-dosimetric measurement and simulation techniques, which are necessary as indicated in subchapter 2.1. In addition, neutron dosimetry measurement techniques should be improved because the increasing use of accelerators for medical and research purposes generates high-energy neutrons; however, current neutron dosemeters are not properly characterised for such high energies.

Uncertainties for dose estimates are not only relevant for patient RP measurements but also in epidemiology. These uncertainties are still not always easy to access and dose results are difficult to validate for such purpose. Within such epidemiological studies the assessment of the dose uncertainty distribution has a large influence on the risk estimates, especially when stochastic model sets are concerned. A well-established methodology is required to decrease the sources of uncertainty and subsequently the biases in risk estimates. Validation of calculated doses is needed by using methods for retrospective dosimetry and the uncertainty analysis in the calculated doses and estimation of their influence on the radiation-risk coefficients must be better known.

When medical accelerators of high energies are used, properly characterised neutron dosemeters should provide an accurate assessment of the workers' dose. Challenges in this field include improvement of in-vivo measurements at hospitals as well as the standardisation of protocols for life-long dose assessment, the related software and dose uncertainties. Harmonisation of software in nuclear medicine is also required by regulators as mentioned in subchapter 2.3.

For the new operational quantities recently introduced by ICRU, their impact on dosimeter and instrument design, the associated standards, as well as the dosimeter and instrument calibration are unknown. Also, any potential additional health outcomes of relevance to be used in detriment calculation, or any changes in the values of radiation weighting factors, should be complemented by considerations on consequences for the definition of RP quantities.

2.2.3
Social science and humanities perspectives

There are many critical topics related to medical RP which go beyond the immediate application context, which include ethical and societal dimensions of policy and practice.

The majority of the SHARE SRA[32] was found to have relevance to the field of RP relating to medical applications. A specific relevance is notable in the context of the growing digitalisation of health and medicine, which has widespread societal implications that are not all completely understood. A version of the SHARE SRA was produced that centred on research relating to medical applications and associated RP needs.

It was recognised that, while patient involvement is a critical aspect of stakeholder engagement in research in medical radiation applications, there were two major challenges to be addressed:

- stakeholder engagement is uneven geographically across Europe and across medical applications, and
- all members of society will be a patient at some point. Therefore, the notion of patient may need to be broadened and a focus on the medical use of IR approached from a wider societal perspective.

Awareness is important, but it is not yet broadly given that focused attention to equality, diversity and inclusion is necessary at all stages of research and development. This is particularly the case given the systematic exclusion that has been present in some areas of past medical research and practice (e.g.[70]). The advent of AI risks is further exacerbating existing inequalities, if groups previously excluded from R&D advances do not engage with new digital advances. There needs to be an acknowledgement that some communities have pre-existing trust issues with the medical establishment. Building trust and engagement with already disaffected groups will be essential to ensure that the development and roll-out of new technologies progresses in an equitable manner.

Research and innovation relating to medical applications of IR is currently not always conceived as transdisciplinary and inclusive, i.e., integrating science, citizens', and other stakeholders' inputs from the start. Current approaches to medical research and innovation in many cases do not centre patient perspectives in terms of direct involvement from patient groups in setting research agendas or co-developing advances. How to successfully integrate alternative perspectives and priorities to medical research requires investigation. A major challenge is how to collect appropriate and sufficient social science data in order to maintain the patient perspective as a central component of research related to medical applications of IR and RP.

2.2.4
Emergency preparedness perspectives

In case of nuclear accidents or other types of emergencies there are potentially a number of people that will be patients and will cause RP issues in the hospitals as well. In addition, there are accidents related to medical application of IR mainly in therapeutic applications e.g., regarding errors in teletherapeutic radiation beam application or very seldomly with lost sources in the body. Both areas can learn from each other.

There is still the need to develop countermeasures and strategies for accidental exposures[71]. The governance of preparedness needs to be improved, societal and ethical aspects have to be investigated for radiological emergencies and models should be improved using artificial intelligence and better knowledge databases. Health surveillance in such situations needs to be addressed, decision making should be improved including uncertainties, and stakeholder engagement and communication must be taken into account.

Looking at countermeasures and countermeasure strategies, it is important to use realistic scenarios for nuclear accidents and accidental medical exposures, including relevant individual countermeasures and complementary actions (i.e., victim triage, biodosimetry, use of radioprotector/radiomitigator drugs, management guidelines, resource optimisation, etc.).

With respect to governance of preparedness, societal and ethical aspects, it is clearly visible that it is necessary to improve the guidance framework and tools to support sustainable strategies of preparedness to the management of post-accident situations including risk for evacuees and patients.

Health surveillance is a key component of emergency preparedness. This includes risk assessment and general aspects of treatment of affected people, including reflections on the well-being of vulnerable people, justifying medical procedures and ethical aspects, and is thus directly related to medical applications. An interlink between the medical communities and the radiation researchers is mandatory and should be addressed.

2.2.5
Radioecology perspectives

Meanwhile, medical radioisotopes make a large contribution to radioactive waste in many countries and their radioecological effects should be taken into account in a harmonised way throughout Europe.

It is important to understand the behaviour of relevant radionuclides and exposure pathways. In this category, the priority is to identify all radionuclides and release pathways. It is necessary to identify any speciation issues that might have significant implications. The focus of the pathway identification should be on unusual exposure routes specific for medical radionuclides. A lifecycle analysis of radionuclides is relying on many aspects to be addressed first. This includes the following specific topics:

- European survey on the extent of use of radiopharmaceuticals from production to patient use to waste disposal
- Physical and chemical speciation of the most environmentally relevant, longer-lived medical radionuclides, highlighting the environmental interactions
- Identification and systematic description of environmental exposure pathways for people (workers and the public) and wildlife
- Lifecycle analysis "radionuclide factsheets" from a human and environmental safety perspective

In addition, datasets, and assessment methods, identifying the relevant data gaps, are needed. The following specific topics should be addressed:

- Compilation of terrestrial and freshwater transfer parameter values (CR, Kd, TB1/2, etc.) and identification of data gaps for medical radionuclides
- General approach to define scenarios (atmospheric, coastal, river, terrestrial, urban) for transfer to humans and biota in clinical treatments and the radiopharmaceutical industry
- Improved radio-ecological dispersion models for use in discharges impact assessment
- Methodological guide on what radionuclides are relevant and the requirements for assessment to people and wildlife
- Generic assessment modelling system for release/processing of releases from hospitals and radionuclide production facilities
- Estimation of dose to the general public from routine and accidental releases for demonstration of dose assessment procedures involving medical facilities[72]
- Demonstration scenarios for wildlife dose rates arising from routine and accidental releases for medical facilities

2.3 SPECIFIC INTERESTS OF REGULATORY BODIES

The evaluation of regulators´ needs and expectations relevant to medical radiation research has been based on the European basic safety standards of the Council Directive 2013/59/Euratom. This already indicates that the focus was on radiation-related regulation. In particular, the content of the following articles requires active participation of the research community: articles 5, 55 and 56 related to the concepts of justification and optimisation; articles 57(1) and 58.b (together with article 16.1.b of Annex I in the medical device regulation) related to the provision of information regarding medical exposure; article 60 "equipment" (in particular 60.1 related to quality assurance programmes); article 61 "Special practices"; article 63 "Accidental and unintended exposures"; Article 64 related to estimation of collective doses and article 104 "Inspections". A general challenge for regulators is the different adoption of the BSSD by the member states. In addition, it must be mentioned that there are also some aspects that are evaluated and taken care of by regulatory bodies like the European Medicines Agency (EMA) that regulates e.g., radiopharmaceuticals and contrast media.

The needs of regulators have been structured in three fields: 1. quality assurance regarding AI, 2. quality assurance regarding other technologies (non-AI) and 3. screening and individual health assessment.

2.3.1 Research needs regarding artificial intelligence

Applications of AI include potential benefits for the work of regulators. Current and future repositories can collect large amounts of patient and worker exposure data that can be considered as "big data". Research is needed to harmonise this automatic collection and transmission Ulanovsky for example using dose management systems and aligning with the EHDS presented by the Commission on the 3rd of May of 2022), as well to make adequate information available (to regulators, researchers, and the public), and to manage data protection issues. AI algorithms are needed to find patterns within these data. These patterns can serve to identify facilities with especially efficient protocols (e.g., regarding dose and image quality), alert authorities and users in case of inefficient results or potential incidents. AI algorithms could also help to define a fair system of inspections/audits, as well as to improve or standardise dosimetry reporting.

Research needs to regulate the use of AI systems

Many of the urgent needs of regulators arise from the recent applications of AI, in particular ML algorithms. The difficulty for regulators is to ensure that planned and systematic actions are in place to ensure that AI-enabled software will perform satisfactorily in compliance with agreed standards over its lifetime. Methodologies, metrics, and criteria for the potential classification as "high risk" (in the sense of the European AI Act) need to be developed and agreed to define a common set of references. This work needs a concerted effort of all stakeholders, including vendors and national professional societies. Specific research questions relevant to regulators involve the following topics (non-exhaustive list):

- Diagnostic radiology procedures: evaluation of algorithms for justification, optimisation, image processing and deep-learning-based dose modulation identification of dose reduction systems in a holistic way
- Nuclear medicine reconstruction algorithms in PET-CT
- Radiation therapy: synthetic computed tomography, automatic segmentation, treatment planning systems; adaptive external beam radiation therapy or automated quality assurance models

Associated technical topics are also explored in subchapter 3.3; social and ethical issues are explored in more detail in subchapters 2.1, 2.2.3 and 3.3. Consequences of the medical device regulation are dealt with in subchapter 3.5.

2.3.2
Research needs on quality assurance regarding other technologies

Regarding non-AI technologies, the medical RP community has identified a need for research towards personalised dose assessment for patients and towards harmonisation of methodologies, which in turn require the proper set-up of shared data repositories. Further, the current science behind communication of individual patient dose and risk assessment is a critical role for all RP workers to understand, including the regulator. The following research needs were identified specifically for diagnostic and therapeutic applications:

In diagnostic radiology, the online availability of harmonised exposure data (including among others, information about patient size, age at exposure, sex, image quality and procedure complexity after interventions) could help to upgrade the concept of DRLS and to adapt the dosimetry methods to real patient anatomy (rather than standard phantoms), both contributing to optimisation and personalised risk assessment. Uncertainties and traceability to primary standards in the dose estimates and risks need to be more carefully addressed, in particular for cumulative doses from subsequent examinations. Research to harmonise quality assurance methods should include emerging technologies such as photon counting CT, monochromatic X-rays, dark-field imaging, and phase-contrast imaging.

In molecular radiation therapy there is a need to benchmark different dosimetry software packages, develop common, more accurate methodologies for dosimetry and foster focused radiobiology research in molecular radiation therapy (in particular for new isotopes like Ac-225, trans-uranes, Ho-166, Lu-177, Pb-212, Tb-161). Research is also needed to harmonise quality assurance in the fields of FLASH therapy (proton, electron), heavy ions and stereotactic radiosurgery (e.g., ZAP-X).

2.3.3
Research needs regarding screening and individual health assessment

Radiological procedures forming a part of a screening program have to be justified in advance before being implemented by national health ministries following a cost-effectiveness analysis or technical assessment, where appropriate. When healthy individuals are offered a radiological procedure that is not part of a formally approved screening programme, then this scenario is denoted as “Individual health assessment” (IHA). In this scenario, imaging is not justified and there is potential for a large number of individuals receiving more harm than good, particularly if the used individual examination carries a higher risk and the false positive rate from the examination is high. However, the development of personalised medicine could be a breakthrough and should be considered in the justification of IHA.

Research is needed to develop and evaluate tools and practical methodologies for the justification of radiological procedures to be performed as part of an existing health screening programme (for example justification of digital breast tomosynthesis for breast cancer screening). In addition, harmonised guidelines are required to define new screening programmes for the early detection of disease through the use of radiological procedures, such as for lung cancer screening, colorectal cancer screening, screening for osteoporosis and, possibly, for some neurodegenerative diseases as treatments become more available.

Finally, other tools and practical methodologies are required to evaluate existing screening programmes taking into consideration the situation in different European member states. Research is required to investigate, which existing guidelines are being followed locally and why, in order to ensure proper understanding and harmonisation.

SUMMARY OF CHAPTER 2

KEY MESSAGE #1

New technologies in the medical use of ionising radiation have the potential to improve patient outcomes and radiation protection. Current examples include:

- Monoenergetic X-ray sources for optimised radiation therapy and imaging, FLASH therapy to reduce radiation-induced effects in healthy tissue, and proton or ion-based therapy to spare healthy tissue.
- AI-based methods can be used in dosimetry as well as for image reconstruction, noise reduction, and artefact reduction in various imaging procedures.
- Theranostics and molecular imaging offer individualised therapeutic approaches and help to characterise radiation effects and disease aspects.
- Photon counting detectors show potential for dose reduction in imaging, such as CT applications.

(For more details related to this key message, please see section 2.1.1 of this document.)

KEY MESSAGE #2

The following topics related to measurement and quantification methods in medical applications of IR should be addressed:

- Exposure characterisation, particularly for patients, using absorbed dose as the basic quantity. Challenges include anatomical heterogeneity, calibration of dosemeters, real-time monitoring, dose accuracy in heterogeneous fields, and non-uniform dose distributions.
- Accurate patient-specific dose assessment methods and computational models.
- Optimal measurement protocols in nuclear medicine and radiotherapy.
- Standardised protocols and metrics for diagnostic imaging and therapy to reduce radiation exposure and improve quality.
- Improve measurement techniques, dose estimation, and validation for accurate risk assessment.

(For more details related to this key message, please see sections 2.1.2 and 2.2.2 of this document.)

KEY MESSAGE #3

Research in radiation oncology, nuclear medicine, and interventional applications aims to improve health risk estimates. Key research areas include understanding dose-dependent cancer risk and non-cancer effects.

- Research is needed to understand adverse effects and optimise doses in medical applications of interventional radiology
- Current models lack a mechanistic basis and fail to consider dose distribution and additional treatments
- Individual patient-related factors and early biomarkers are important
- Radiobiological mechanisms and protective strategies need clarification
- Combination therapies and novel approaches can enhance efficacy

(For more details related to this key message, please see sections 2.1.3 and 2.2.1 of this document.)

KEY MESSAGE #4

The European BSSD calls for harmonisation of clinical practices and high-quality healthcare across borders.

- Variability in patient doses across Europe highlights the need for harmonisation of interventional radiology procedures.
- Research areas include patient-tailored diagnosis and treatment, technology improvement, clinical and dose reporting, and staff and public protection.

(For more details related to this key message, please see section 2.1.4 of this document.)

KEY MESSAGE #5

The principle of justification, patient communication, and appropriateness of radiological procedures are crucial in medical applications of interventional radiology.

- The role of imaging in CVD
- Screening and prevention in CVD
- Molecular imaging in CVD
- VR in CVD

(For more details related to this key message, please see section 2.1.5 of this document.)

KEY MESSAGE #6

The following topics related to social science and humanities, emergency preparedness and radioecology should be addressed:

- Ethical and societal dimensions, patient involvement, and equality in medical radiation applications.
- Improve governance, develop countermeasures, enhance decision-making, and address stakeholder engagement and communication.
- Harmonise the understanding of radioecological effects of medical radioisotopes, identify radionuclides and exposure pathways, and assess environmental interactions and safety perspectives.
- Data and assessment gaps: Compile transfer parameter values, define scenarios, improve dispersion models, develop assessment methodologies, and estimate doses to the public and wildlife from medical facilities.

(For more details related to this key message, please see sections 2.2.3, 2.2.4, and 2.2.5 of this document.)

KEY MESSAGE #7

Regulatory needs are based on the BSSD. Active participation of the research community is required in various articles related to justification, optimisation, provision of information, equipment quality assurance, accidental exposures, collective doses, and inspections:

- Research needs regarding AI Harmonising data collection, managing data protection, developing AI algorithms for pattern identification, regulating the use of AI systems, and evaluating algorithms for different medical applications.
- Research needs on quality assurance: Personalised dose assessment, harmonisation of methodologies, communication of individual patient dose and risk assessment, and research in diagnostic radiology and molecular radiation therapy.
- Research needs regarding screening and IHA: Justification of radiological procedures in screening programs, development of guidelines for new screening programs, evaluation of existing screening programs, and consideration of personalised medicine in IHA.

(For more details related to this key message, please see sections 2.3.1, 2.3.2, and 2.3.3 of this document.)

CHAPTER 3
ORGANISATIONAL REQUIREMENTS AND CORRESPONDING RESEARCH

INTRODUCTION

Chapter 3 shows ways how to address the full spectrum of tasks and questions raised in the first two chapters in the most suitable and effective way. Future research should build on existing resources in terms of equipment, human resources, excellence in terms of organisations and the links between them, etc. Sustainability of resources is key for the quality of the research as well as the translation and use of its results. This is also true for the education of research staff. A concept is needed to create sufficiently educated staff and to improve the translation of future research results. This chapter describes how promising approaches can be defined and successfully implemented. In addition, new opportunities for research and implementation of medical applications of IR emerge, especially thanks to recent advances in the fields of data generation, storage, exchange, and use (data bases/repositories), AI and other aspects of digitalisation. Apart from their great potentials, the use of these technologies in diagnostics and therapy also raises major concerns. Those concerns refer, among others, to decision making by machines, to patient informed decisions, often linked to the use of digital procedures including AI and new technologies, or unequal access to the most advanced medical equipment and therapy. Moreover, the challenges and opportunities for implementing these options should be identified. For example, setting up an EU-wide dose-, image- and biological data repository requires joint efforts and harmonisation of regulations. Moreover, a strategy needs to be developed to guarantee the efficient collection, management, maintenance, and sharing of data across countries and medical fields.

From a patient perspective, of course, the efforts should focus on improving the efficiency and effectiveness of care, deploying the best available techniques, and transferring the latest progress and knowledge into practice across Europe. The organisation of this efficient and effective provision of care needs to be implemented and a patient-centred approach is essential for providing individualised, optimised, and personalised care through all phases of life combined with the benefits expected from a societal perspective.

This chapter, therefore, explores a set of topics following pragmatic goals, such as:

- the development of fit-for-purpose support structures for the research and innovation system;
- fast and widespread technology transfer;
- development, critical evaluation, and application of all relevant digitalisation aspects;
- the management of Education and Training (E&T) adapted to the needs of existing and future medical staff to implement these evolutions in daily practice.

These four proposed topics and related actions are interconnected in order to facilitate and accelerate research and positive outcomes.

3.1 NETWORKS AND CENTRES OF EXCELLENCE

To guarantee the most efficient and reliable approach for the different research tasks addressed in the scope of the SRA, it is of great importance to fully leverage the available resources, in particular the excellent centres, universities, hospitals, researchers and facilities and their respective contribution to the research work.

The main part of this section is to recommend possible organisational frameworks or structures of a future centre of excellence (CoE) dedicated to medical applications of IR and medical RP research linked to the needs of the researchers, of the medical staff and, most important, the needs and requirements of patients. It is based on asking "what exists in Europe today?" and "what is needed?", complementing the observation by the question "what is missing?" By this set of questions, the strengths and weaknesses of the actual situation have been determined for a reasonable implementation of the research proposed by the SRA in a relatively short time period.

Current definitions and priorities of a CoE vary largely between countries and disciplines[73,74]. Medical applications of IR are a very broad topic. Therefore, it is necessary to take advantage of these different approaches and to combine the different strengths of the existing excellent contributing centres and/or to build networks among them. These networks shall evolve and grow, so that more centres will be empowered to become excellent. This section describes what can be the meaning of the concept of a CoE for the topic of medical applications of IR and provides the criteria that could be helpful/meaningful for the further development of the CoEs, based on the scope of the SRA. This long-term programme can be developed at different levels – international, national but also regional – applying protocols that will facilitate translational activities "from bench to bedside", resulting partly in success stories in medical care to ensure the highest benefit for the patients.

Within the medical field, the CoEs evolve in three directions:

- Describing "excellence" in clinical care
- Linking it to clinical research
- Extending it to all other prior steps of research including the most fundamental parts linked to mechanisms and infrastructures

For evaluation purposes, "excellence" is, first of all, based on a team and all the links that it can build to foster the transfer and integration of innovation from the outside.

Based on the CoEs that have been described in the literature and the analysis regarding their suitability for medical applications of IR and related RP research of the existing research infrastructures in the area of RP and basic and clinical research for various diseases, six potential options for a CoE structure have been identified for a future general scheme of the organisation to support excellent research in the field of medical application of IR and corresponding RP in Europe:

1. No dedicated CoE but only networks e.g., between existing technology-based or disease-related national centres or infrastructures;
2. A unique CoE, as described above, localised in one country covering all the requirements to develop research activities reported in this SRA;
3. One or more unique CoEs in Europe (one per disease) as described above in 2);
4. A CoE as described in 2) but distributed across Europe; up to one per country, probably requiring high-level support from national governments;
5. Disease-oriented CoEs as described in 3) but distributed across Europe; up to one per country (with the same requirements as in 4);
6. CoEs as described above per country, but focused on one topic and disease (example: imaging and oncology) to develop research activities linked to recommendations reported in this SRA.

For the options 4, 5 and 6, links between local CoEs should be developed. On one side, the concept of a network of CoEs is an answer to the problem of low international mobility of patients, on the other side it can also support high mobility of data and extended exchanges between researchers or facilitate centralised or distributed analysis. A high level of sharing experiences and skills is important to create tangible benefits for patients across Europe. It is about creating a critical mass, bringing together excellent infrastructures and clinical research opportunities, coordinated with a global vision and strategy keeping a strong focus on the patients' interests. This should allow an orientation on personalised radiation-based medicine, which is still the missing key-element in building the excellence research and clinical care structure in Europe. Further details can be found in[75].

To foster the implementation of the research priorities proposed in this SRA in order to increase the benefits for European citizens and patients, a comprehensive method for evaluation is required. A SWOT analysis is the basis for the proposed structure taking into account 22 relevant criteria organised into 3 categories for CoEs. More details can be found in deliverable 4.2 of the EURAMED rocc-n-roll project[76].

Categories for Classification of Centres of Excellence (CoEs)

- Activity (i.e., constitution)
- Objective (i.e., practice)
- Impact

These criteria can also be used as a tool or guideline for each team in order to support the further development and improvement of centres to achieve their own goals and interests.

To fully deploy the expected impact, it is strongly recommended that the potential CoE(s) progress(es) in all three categories, instead of only specialising in one.

The "Activity" Category for CoE Classification consists of six elements:

- Open access data repository
- Biobank
- Interdisciplinarity
- Management strategy and leadership
- National self-declaration, external recognition/national or international certification, accreditation
- Open access technology/equipment

The "Objective" Category for CoE Classification consists of 10 elements:

- Translational research to care
- High standards of care and leadership
- Clinical research
- Integrating innovation
- Transferring innovation
- Integrated practice unit
- Integrated healthcare delivery model
- Network of researchers beyond the CoE
- Personalised medicine – individual patient care, patient-centric view
- Knowledge of diseases including the associated biology and fundamental mechanisms of disease

The "Impact" Category for CoE Classification consists of six elements:

- Impact on society
- European impact
- Education and training
- Dissemination connected to learning
- Economic impact, sustainability of technologies including imaging technologies and medical care products
- Structuring European healthcare support systems

At this point, the most suitable option does not need to fulfil all the criteria. Moreover, it also does not exclude other options, which might be chosen for other reasons. However, what is essential is building the network across Europe, bringing together care and research from the whole community – researchers, clinicians, and patients.

The biggest challenge for option 1 could be the missing strategy and potential problems linked to this gap. Options 2 and 3 have a high risk of a strong national focus. This problem would not occur in options 4 and 5, however, the use of different data formats as well as possible competition between centres including the risk of redundancies or overlaps in resources and infrastructures and thus, lack of efficiency might be counterproductive, especially taken into account the high costs of technology development in the medical field as well as the costs for clinical studies. Option 6 offers the most promising strengths and opportunities, but only if there will be an efficient umbrella structure and a clear common goal and strategy established to guide all these centres. This certainly offers – also in terms of personalised medicine – the largest potential benefits for the research on medical applications of IR in Europe and the best possible clinical care for patients. This option could appear as the ideal form of organisation but is not easy to realise due to numerous barriers, both technically and legally, and presumably high costs. Option 6 with its umbrella structure is the most appealing and promising and seems to be worthwhile the efforts. It seems advisable that an institution establishes such an umbrella structure that has proven experience in running large scale projects in the clinical context on a European level translating efficiently science from lab to clinical care with the necessary financial/economical sustainability. For this option, partnerships with different universities and university hospitals are mandatory for the majority of research projects to gain the highest potential advantage making use of the benefits of research competition among different groups. The centre units are seen as enabling, supporting, and initiating structures. The CoE structure should foster the whole chain of medical innovation for personalised radiation-based medicine: From basic research to translation, education and training, implementation into clinics to improve patients' benefits.

3.2 SUSTAINABLE RESOURCES AND NEW AND EXISTING APPLICATIONS

If the research in the described area of medical application of IR should be efficient and meaningful for better treatment including diagnosis and therapy of patients suffering from various diseases, it is necessary to guarantee sustainability in terms of resources and access to state-of-the-art technology. This refers for example to new and existing types of radionuclides as well as new types of sources for radiation therapy or diagnosis and also detection approaches of IR or conditions of applications. For each of these new technologies, it is important to prove by evidence-based studies that they really provide benefits to patients, as outlined in chapter 1, before they can be implemented in the medical use of IR.

Sustainability can be assessed in three aspects: environmental, societal, and economical. Justification of the procedure is an important factor in RP as well as for the environmental impact assessment[77].

New applications of IR in the medical field must first and foremost address the unmet needs of patients and healthcare. Potential overlap with available treatments and diagnosis outside the field of medical applications of IR should be evaluated in evidence-based studies wherever feasible. Developments in fields where IR offers a clear advantage over other technologies should be encouraged.

The long-term nature of clinical studies and other developments in the medical context require that potentially new developments are thoroughly evaluated from a sustainability and cost-benefit perspective. Cost-benefit assessment should include the effectiveness of the therapies including relapse and secondary effects on the short and the long term. Innovative diagnosis should bring an added value compared to existing technologies in terms of earlier diagnosis and improved staging of diseases[78].

New applications cannot be developed at any cost, and return-on-investment for society can be considered as a key criterion. A maximum threshold of acceptable cost-benefit ratio for patients and society could be considered to guarantee equality of treatment of patients at European level. Affordability in the different EU member states is a prerequisite both for new and existing technologies.

Innovative new applications can only be viable if raw materials, active ingredients such as radiopharmaceuticals, installations and infrastructures are and will be available for the next decades at reasonable costs. A dialogue with owners of essential infrastructure and pharmaceutical companies and their planning and financial requirements is essential[79]. Research is needed on how costs of production and or maintenance can be kept within a reasonable limit or can even be reduced.

The viability of new applications should take into account the availability of competent personnel fostered by life-long learning in the full translational chain from bench to production, and to bedside.

Environmental criteria include nuclear waste issues, natural resource needs, energy demand, and impact of installations and transport on the environment. An optimised use of resources also includes the establishment of harmonised regulations and collaboration at EU level, such as intended by initiatives such as SAMIRA and others. Justification of IR procedures should also include its sustainability in all aspects[80].

Harmonisation and structuring of clinical studies for radiotherapies should strive for a better understanding of mode of actions through standardised radiobiological testing and improved dose-response assessments. Maintaining high quality healthcare already leads to high budgets in the European countries' healthcare systems with differences in availability of existing high-end radiation technology. As new radiation devices and radiopharmaceutical therapies come at considerable costs, the budget for healthcare needs to be guaranteed to allow applications of IR in all European countries.

Evaluation of new applications should also include acceptance by patients and the society in terms of acceptance of AI-based decision-making, use of patient data, biobanks, and other privacy related issues. Both technology readiness as societal acceptance are important factors in acceptance of new and maintaining existing technologies.

Reimbursement or financing schemes sometimes allow only temporarily to finance medical radiation technology while still in the phase to prove its efficacy in terms of patient outcome. The reimbursement or sufficient budgeting needs to be guaranteed in all European countries to get the new technologies embedded in the clinical practice and allow smoother transition until formal approval is obtained. Studies need to address the topics of reimbursement and budgeting of technologies in clinical routine across Europe as well.

For the sustainable implementation of new emerging technologies in the field of medical applications of IR as well as the corresponding RP, three main questions need to be addressed:

- How can laboratories and infrastructures with high-end radiation technology be operated sustainably taking into account the relatively high costs of equipment and maintenance?

- How can standardisation of reimbursement or budgeting be assured across countries in Europe for implementation of innovation for medical application of IR?
- How can the efforts for the corresponding medical radiation procedures be accepted across countries?

To address these questions, the following recommendations could be followed:

- Standardised decision metrics for reimbursement or budgeting schemes for new and existing technologies across Europe need to be developed.
- Personalised medicine comes at a considerable cost, which requires sufficient funding schemes.
- Research centres of excellence and public-private partnerships are potential enabling approaches for high-level research and translation maintaining the knowledge and research in medical radiation applications.
- It is mandatory to develop and implement best practices for radiation safety, as the safe and efficient use of medical radiation technology is essential for sustainability. This implies proper training of the healthcare professionals and ideally standardisation of RP measures.
- Radiation dose optimisation has an important sustainability impact; minimising the amount of radiation while maintaining image quality is a central aspect of this. Advanced imaging techniques are needed for this goal.
- Continuous research is necessary to develop new technologies and methods that are more efficient, safer, and more environmentally friendly as these assure sustainability, especially if this research also leads to affordable products.
- Equal access to modern radiation technology is essential for sustainability. Ensuring that high quality medical radiation technology is available to future generations and everywhere throughout Europe is of utmost importance. Education and training programs for healthcare professionals are needed as well as policies like professional guidelines that promote the development and use of the highest standards in medical radiation technology. Such training programs are not funded in all European countries at the same level, which causes barriers and insufficient implementation of technologies.
- Mobility of workers among Europe would be very beneficial in the context of optimal use of technologies from an EU perspective, but there is no mutual recognition of training. There is a barrier for quick translation of new technology. Specifically, staffs are keen to be trained, but they need support like financial support and supportive work schedules.

3.3 DIGITALISATION AND CORRESPONDING ETHICAL ISSUES

As stated in the general introduction of this chapter, great opportunities can be envisioned for the medical application of IR as well as for the corresponding RP approaches. Subchapter 3.3. describes which research is needed to foster the use and implementation of such approaches in the future European medical use of IR. Also, some tasks, questions and concerns related to such an (in principle) beneficial application of digital approaches have been mentioned during the preparation of this SRA. It will be mandatory to accompany such research on digitalisation and related topics with research, answering such ethical questions and concerns in order to increase acceptance for the new approaches. For that, it is necessary to define which questions need to be addressed by new approaches in the field of ethics as well as in general terms by social sciences and humanities including transparent and inclusive communication with society.

3.3.1 Digitalisation issues

As the topic of digitalisation in the field of medical applications of IR is a very dynamic field, the tasks to be addressed, as well as the recommendations, are derived from literature and the most recent congresses. The recommendations regarding digitalisation aspects are divided into four categories:

- Recommendations for personalised medicine and electronic health records
- Recommendations for improved medicine, RP, and electronic health records
- Recommendations for standardisation of data formats for medical applications of IR and corresponding RP
- Recommendations for AI for RP

Recommendations for **personalised medicine** and **electronic health records**:

- Leverage FHIR (Fast Healthcare Interoperability Resources) standard to facilitate the integration of diverse data types, such as radiological imaging, histopathological imaging, and genotype data, into electronic health records (EHRs) in support of AI-based personalised medicine.
- Utilise standardised data models and ontologies to ensure the consistent interpretation and integration of medical data across different EHR systems.

- Address technical and ethical challenges in integrating AI-based decision support tools with EHRs that incorporate patient-specific data from multiple sources, including imaging data and genomic data.
- Train and validate ML algorithms using the rich data contained within EHRs, ensuring patient privacy and data security with the help of FHIR.
- Identify and overcome barriers to the widespread adoption of AI-based personalised medicine approaches that rely on the integration of data from EHRs.
- Assess the impact of AI-based personalised medicine approaches on clinical workflows and train healthcare providers to effectively incorporate these tools into their practice.

Recommendations for improved medicine, RP, and electronic health records:

Enhanced and new methods need reliable data bases for improving radiation based personalised medicine. Radiation biology for RP purposes in medical applications of IR is based on different types of studies, including large datasets of patients for epidemiology and molecular epidemiology. Therefore, recording information on the individual patients' health history and lifestyle in cohorts is essential to develop personalised radiation medicine. The following is therefore needed:

- Implement strategies to ensure that EHRs accurately capture patient radiation exposure data and use this information to improve RP in medical imaging.
- Engage and educate patients on better medical applications of IR and RP practices in medical imaging and utilise EHRs to support these efforts.
- Employ EHRs to ensure compliance with RP guidelines and regulations in medical imaging.
- Weigh the benefits and drawbacks of using EHRs to track radiation exposure as well as outcomes in patients.
- Integrate EHRs with other technologies, such as dose monitoring systems and quality assurance programs, to enhance RP in medical imaging.

Recommendations for **standardisation of data formats** for medical applications of IR and corresponding radiation protection:

- Develop a standardised data format that accommodates the diverse needs of different imaging modalities and vendors in the context of improved imaging or therapeutic applications and corresponding RP.
- Address challenges in implementing a standardised data format, such as accommodating different imaging modality requirements and overcoming vendor resistance.
- Encourage the medical imaging community to collaborate and develop a framework that can accommodate the diverse needs of different imaging modalities and vendors, ultimately improving patient safety and optimising imaging protocols.

Recommendations for **artificial intelligence** (AI) for radiation protection:

- Address potential biases and enhance generalisability in AI-based RP systems by including diverse patient populations, imaging modalities, and clinical scenarios during the development and validation process.
- Focus on developing robust, generalisable AI algorithms with strong user acceptance by involving healthcare professionals in the design and evaluation process, ensuring that these solutions are tailored to address the specific needs and challenges faced in RP.
- Advocate for the integration of RP in several European initiatives in large-scale data repositories and health data infrastructures that support the collection, storage, and sharing of radiation exposure data. This could facilitate the development and validation of AI-based RP solutions while ensuring data privacy and security.
- Establish proper validation strategies for AI-based RP solutions, addressing potential discrepancies between reported performance in literature and real-world clinical effectiveness.
- Define clear tasks for AI solutions and design systems that can be seamlessly integrated into existing workflows, fostering collaboration between artificial and human intelligence to optimise RP efforts.

3.3.2 Ethical Issues

As indicated before, digitalisation in the field of medical applications of IR will raise a number of ethical questions, addressed below.

Personalised medicine

Unequal distribution of resources and variations in national health systems mean that the delivery of personalised medicine remains a distant prospect in most circumstances. Alongside, the limitations to the utility of personalised approaches need to be defined. There will be diseases and conditions for which personalised approaches deliver cost-effective benefits and others where a personalised approach remains questionable from a health system perspective. The drawing together of multiple data sets required for personalisation leads to a range of ethical questions around data management, data ownership, consent for secondary uses, systems of trust and data governance. Any development of standards must take into account diversity, inclusion, and equity requirements. It is also relevant, to investigate the potential ethical implications of implementing new technologies where the sustainable supply cannot be guaranteed.

e-health

The promise of electronic health systems has been around for some time. Some countries have made significant advances in this regard, others are struggling for a variety of reasons. Apart from the physical infrastructure and connectivity required, the economic resources to develop in areas, such as electronic patient records, are limited. Alongside the techno-economic constraints, issues of governance of such systems and public trust are key. Standardised approaches (e.g., Electronic Discovery Reference Model (EDRM)) require effective regulation and an appropriately trained workforce. How such standardised approaches work in practice, in particular across different national and cultural contexts, is not currently understood. Transferability across borders (of systems, of countries etc) is yet to be investigated. Public/patient trust in such systems is not uniform across Europe; how to advance public trust in electronic records is a major hurdle to their implementation.

AI and its consequences

The advent of AI implies a lot of promises and hype. There are a range of technical challenges remaining, yet attention to the ethical dimensions is imperative if even a fraction of the promise is to be delivered. Discussion of standardised data formats is premature when we do not yet know the levels of willingness of patients to participate with AI-enhanced or AI-delivered services. Patient engagement at the developmental stages of the technology development is needed. Attempts to engage patients at the end of the line run the risk of relegating technological advancements to the cupboard; non-implementation would be a costly mistake.

The challenge of equity in the production and use of large data sets is widely stated and yet insufficient attempts have been made to either a) understand the impacts of biased datasets in the medical applications arena and b) create data sets that are more representative of populations and inclusive of patient diversity. Future developments are reliant on a more integrated approach to research that draws together relevant fields of study from both the technical and social sciences. Concurrently, the route on how to translate the benefits of working with large data into more personalised approaches is unclear.

Advances in the use of AI/ML as promising tools bring a plethora of ethical challenges and questions ranging from how to modify informed consent processes to ensuring effective clinical decision making in the context of (potentially) non-transparent data origins. It must be ensured that the responsibility remains to the human beings at critical points, which should be considered in the context of this ethical and social science research.

Overall, a range of research questions are outstanding and must be answered to make progress toward radiation applications in medicine and the corresponding protection improvements. The unmet research needs include:

- Can the existing patterns of public trust in electronic health systems be understood and how can any discrepancies identified be addressed?
- What are the implications of the use of biased data sets on: training algorithms; on decision making; and on patient outcomes?
- How can ML-based developments be progressed in open and transparent ways, ensuring that trustworthy and reliable AI is the outcome?
- How can the drive towards standardisation be assured to take account of equity, diversity, and inclusion criteria?
- What are the most effective ways of engaging patients (and other relevant stakeholders) within the research and development process in order to ensure better (more meaningful) results and more efficient technology diffusion?
- How to perform effective transdisciplinary research in the development of AI advances? What are the implications for clinical practice and which new training needs will arise?

3.4 EDUCATION AND TRAINING

The research on medical application of IR as well as its implementation and consistent Europe-wide use, including all related aspects of medical RP (research, implementation, and standardised use) are probably one of the (if not the) most relevant prerequisites for a better healthcare delivery. Education and training will need to be directed towards researchers in the field, medical specialists, medical physics experts, radiographers, and healthcare authorities. The proposed suggestions about a future education and training concept are based on surveys about the current status as well as observed drawbacks and limitations. This future education and training concept needs to be applied in all future EC-funded projects linked to medical applications of IR to ensure a Europe-wide uptake of newest technologies and approaches and a harmonised healthcare supply across Europe. Furthermore, dedicated measures for the implementation of optimised and new applications of this kind are required. In addition, the impact of such education and training measures based on the proposed concept needs to be evaluated. There are several challenges for implementing new and updated existing education and training measures in RP for health professionals, such as:

- Difficulties in including related topics in the undergraduate curricula for healthcare researchers or healthcare practitioners.
- A lack of continuing CPD programs in the field of medical application of IR, related quality and safety aspects including RP is obvious. Such programs need to be combined with education and training programs to really enable continuous high-level use of modern technology. Such technology is sometimes not available for practical courses, which should be addressed as well.
- Healthcare professionals are involved in several other duties requiring CPD in other clinical areas, and therefore a dedicated training approach, namely for the introduction of new medical devices and/or diagnostic and therapy technologies, is needed.

In the last few years, there have been several EC-funded projects related to E&T in medical applications of IR and corresponding RP for health professionals, but several survey results still show evidence of several gaps in effective implementation in daily clinical practice. Most of the projects, mainly the RP 175[81], give an indication about what to teach and what knowledge, skills and competences health professionals should have, however, there is a lack of guidance in how to teach and when to teach. Still, there are also aspects on what to teach, which are not sufficiently adopted and used, such as the issue of uncertainties in measurements, but also in clinical care applications or in patients' outcomes.

The results from the EURAMED rocc-n-roll project survey[82] revealed different radiation medicine related and RP E&T experiences and problem perceptions across Europe, such as the absence of RP topics as a part of undergraduate curricula, a heterogeneity of compliance with RP 175 and the BSSD regarding E&T in RP or a lack of harmonisation of legislation across EU countries/regions. This is, however, mandatory for the best and safe use of IR in medical applications providing a huge benefit for European patients.

Following the results stated above, nine principal opportunities, especially for education and training for medical application of IR and corresponding RP, were identified:

- Many recommendations have been made in the course of previous programmes. However, much of this work is between 10 and 15 years old. The opportunity to systematically review all recommendations and to propose up-to-date recommendations based on the findings of the review should be addressed in the near future.
- It is relevant to focus E&T in medical applications using IR and RP on the needs of the current and future clinical workforce (including consideration of different areas of practice and different professions and the need to build knowledge, skills, and competences, directly related to benefit-risk balance communication with patients and the public). This has to be coupled to CPD programs.
- E&T in RP should be focused on the needs of the current and future medical radiation application and protection researchers (outside the clinical departments and including pre-clinical research).
- It is of utmost importance to propose a sustainable and harmonised model for E&T in medical use of IR and RP (many past programmes have not succeeded in producing sustainable outcomes).
- Accreditation or endorsement at European level of a recommended gold standard model of E&T in medical applications of IR and especially in related RP aspects by EURAMED and/or the professional societies EANM, EFOMP, EFRS, ESR, ESTRO would be a major benefit for the healthcare system and the related research aspects.
- It is necessary to identify differences in contents and regulations of E&T in medical applications of IR and RP in EU Member States and to propose a European standard for mandatory E&T course contents and certification based on consensus.
- Well-trained future generations of medical use of IR and RP experts with sufficient knowledge, skills, and competences are very important to cover future needs of E&T.
- Ensuring health professionals working within medical imaging and RP research are afforded education and training in evolving science e.g., AI in Radiology so they are equipped to work in multidisciplinary teams to research areas of priority.
- Post graduate education supports the diversification of competencies to include AI and other emerging technologies in medical imaging. Due to the rapid technology breakthroughs in the field of imaging and how this can be managed at European level across all professional stakeholder groups require continuing strategic planning and consideration of postgraduate competencies to specialise in emerging fields.
- To develop and deliver at European level online training programmes targeting all relevant professional groups to increase accessibility.
- To develop E&T in medical applications of IR and corresponding quality and safety including RP during the undergraduate course programmes.

A SWOT analysis from the EURAMED rocc-n-roll project[83] identified a lack of effective implementation of RP principles in daily practice. Therefore, strategic planning is needed at European, national, and local levels, based on efficient governance structures and expert leadership.

Professional societies and stakeholders need to have sufficient resources to achieve a pan-European RP training network, which is sustainable and accredited across multiple national domains.

Four aspects have been identified as strengths and opportunities:

- Existing structures and training recommendations
- RP training needs assessment and E&T model(s) development
- E&T dissemination, harmonisation, and accreditation
- Financial support

The weaknesses and threats analysis identified two themes:

- Awareness and prioritisation at a national/global level
- Awareness and prioritisation by healthcare professional groups and researchers

Further information can be found in Rainford et al. 2022.

3.5 TRANSFER AND TRANSLATION

Currently, only few research projects in the field of medical application of IR, and in particular in the field of medical RP, involve industrial partners and really aim to transfer research results into developments and new or improved products. In many cases, even those results that could be easily applied in hospitals or other medical units are only rarely translated into daily clinical or medical use. In this subchapter, concrete suggestions are developed, based on surveys that have been conducted among partners from the EURAMED rocc-n-roll project and stakeholders, especially including clinicians and industry representatives to find out how the participation of industry could be improved by generating tangible benefits for all partners. They also inquired how the implementation of research results can become easier and more realistic for future research projects and programmes of the EC and the Member States, and how exploitation strategies can optimise already the outcome of current funding programmes. In this process, a good understanding and analysis of the current translation environment is essential. Potential regulatory hurdles, such as the Medical Device Regulation (MDR)[84], are analysed and suggestions are made for avoiding them in future versions.

Translation of scientific breakthroughs into useful technology as well as the transfer of this technology into clinical applications take time. Both are complex processes requiring specific skills which are rarely found in research and/or an academic environment, which can be a serious bottleneck[85]. A slow development and acceptance process is observed in all medical developments, with the exception, perhaps, of the response to the recent pandemic when a speedy development of vaccines was essential, and a huge number of resources was mobilised for this in short term. Medical applications using IR are showing a rapid development in establishing more patient-specific medicine. The technology is showing great progress, but many barriers obstruct its introduction in the clinic. A large spectrum of applications in this field illustrates this progress:

- New imaging biomarkers
- Integrated diagnostics
- Expansion of interventional radiology applications
- Many novel theranostic radiopharmaceuticals being authorised
- Launch of new charged particle beam therapies and image-guided radiotherapy
- In many of these applications, AI technology is introduced to improve diagnosis and therapies.

Based on a Delphi process with a nominated group of 20 medical radiation experts, recommendations for the ten most important barriers to technology transfer and translation were prioritised from a list of important barriers derived in a Delphi process after three Delphi rounds of surveys among 130 responders[86].

1. Commercial software is often a black box. When using clinical data (e.g., images) in basic research, it is difficult to judge what happened to the data (e.g., post-processing effects), which can lead to biased study results. Open-software tools might be one potential way to reduce the black box character of methods. However, these are difficult to implement in clinical scenarios for accountability reasons.
2. Robust and efficient database structures that facilitate research across different repositories/platforms through secure data storage and information exchange are needed.
3. The translation of novel research not only requires skilled personnel, but also access to high-end imaging and/or radiotherapy equipment. Such conditions are heterogeneous in Europe, i.e., some research will only be conducted at very few institutes or with very few healthcare providers.
4. Experience and expert knowledge vary greatly and is concentrated in few academic centres. Translation is considered as a research process and needs a relevant environment in terms of skills, multidisciplinarity and funding which is scarce and non-uniformly distributed across Europe.
5. Adequate training is often a challenge as clinical demands minimise the number of staff and average time spent on end user training (often working around clinical work/examinations/procedures).
6. The clinical setting is usually very complex with multiple technologies and software systems working together; this can only be solved by multidisciplinary integration.
7. There is a need for multidisciplinary approaches to education and training involving a team of educators with RP expertise from a broad range of professions/disciplines.
8. There is a lack of funding and funding opportunities, particularly for basic RP research.
9. Lack of general awareness (in the public and among healthcare workers from outside the radiation-based medicine fields) of the benefits, risks, and applications of IR.
10. Access to modern technology / up-to-date equipment in radiology, nuclear medicine, or radiotherapy is limited by financial factors due to the high cost of resources, with end-users often lagging behind commercial development.

Apart from the transfer of research breakthroughs to technical developments, also the translation and use of this technology in the clinical setting shows a serious time lag. Several programs have been proposed to improve the translation of research into medical technology and its adoption into clinical practice with varying success rates. The following provisions should be considered:

- There is no magic solution to improve the translation process, but the development of appropriate centres should be addressed.
- Regulatory requirements may be regarded as obstacles that have to be evaluated. Finding appropriate ways, including international common standards and accreditations, may help to create the proper environment.
- Proper funding mechanisms and cooperation between actors to design research for successful translation is critical.
- Proper reimbursement or financing mechanisms are required to foster innovation and adoption of innovative technology, including RP practices, in clinical practice.
- Standardisation should allow multiple providers to follow these standards, as a monopoly might lead to high prices.

Funding

Funding programmes are needed for translation projects or for improving the access to modern technologies for research projects and healthcare across Europe. Public-private partnerships (PPP) offer more than a simple financing but also assistance towards tangible outcomes. Affordable products are a key factor to speed its widespread use and of mutual advantage. Managed equipment services are a good example of cooperation and risk sharing between healthcare providers and manufacturers to improve the availability of advanced equipment and technology required for research and translation.

Regulatory framework

The requirements for clinical evaluation introduced with the MDR or by implementation of EMA guidelines are posing a serious burden for companies and therefore might be limiting their resources to invest in R & D, namely for SMEs. However, safety aspects do need to play the major role for implementing new medical technologies, medicine products like contrast media and radiopharmaceuticals or approaches. Thus, new ways for collaborations need to be developed to allow efficient testing.

Reimbursement and financing schemes

- Reimbursement or financing plays a key role in enabling the adoption of medical technologies and is an effective tool to advance innovation. The availability of reimbursement for a new technology is a key decisional factor for both clinical centres and companies.
- Reimbursement or financing systems in the EU are lagging behind innovation and should be as uniform as possible throughout Europe. Funding should integrate the needs of multidisciplinary resources in dedicated organisations.

Reimbursement or financing policy for high-quality healthcare should be aimed at advancing innovation. A two-step approach is proposed:

- One step based on considering the common criteria for financing evidence-based intervention.
- Another step for innovative therapies with definitive value yet to be proven.

Consideration should be given to the introduction of a financing scheme for personalised medicine and RP practices in healthcare settings to promote higher level of adoption:

- Encouraging the use of best practices
- Encouraging the use of new technologies
- Radiobiology-driven patient-tailored therapies
- Support healthcare institutions with costs associated with training, deployment, and maintenance of software solutions

SUMMARY OF CHAPTER 3

Chapter 3 has highlighted the necessary prerequisites, including infrastructure, education and training, and methods for fast and sustainable transfer into industry and clinical practice across Europe, with a particular emphasis on data infrastructures, which serve as the basis for AI-based applications as one of the promising tools for the future. This chapter has also considered ethical and social science aspects related to the use of IR in medicine, particularly in connection with AI-based applications and the use of personalised medicine approaches and decision-support. **The Key Messages of SRA Chapter 3 are:**

KEY MESSAGE #1

To address the needs of patients, researchers, and medical staff, categories for the classification of future Centres of Excellence (CoEs) on medical applications of IR and medical RP research are proposed based on:

- Activity
- Objective
- Impact

(For more details related to this Key Message, see section 3.1 of this document.)

KEY MESSAGE #2

To facilitate the sustainability of resources for new and existing applications, three essential questions should be addressed:

- How can laboratories and infrastructures with high end radiation technology be operated sustainably, taking into account the relatively high costs for equipment and maintenance?
- How can standardisation of reimbursement or financing of innovative technology and procedures be assured across countries in Europe?
- How can the efforts for the corresponding medical radiation procedures be accepted across countries?

(For more details including specific recommendations related to this Key Message, please see Section 3.2 of this document.)

KEY MESSAGE #3

Digitalisation in the field of medical applications of IR can lead to ground-breaking outcomes, which could be addressed in a series of research recommendations based on:

- Personalised medicine and electronic health records
- Improved medicine by IR applications, RP, and electronic health records
- Standardisation of data formats for medical applications of IR and RP
- AI for RP

(For more details including specific recommendations related to this Key Message, please see Section 3.3.1 of this document.)

KEY MESSAGE #4

Digitalisation in the field of medical applications of IR will raise a number of ethical issues and accompanying research needs:

- Diversity, inclusion, and equity concerns related to personalised medicine
- Public/patient trust issues related to electronic health systems and records digitisation
- Advances in the use of AI/ML brings a plethora of ethical challenges and questions ranging from how to modify informed consent processes to ensuring effective clinical decision making in the context of (potentially) biased datasets or non-transparent data origins

(For more details including unmet research needs related to this Key Message, please see Section 3.3.2 of this document.)

KEY MESSAGE #5

Important challenges in implementing and updating the education and training in RP for health professionals include:

- Difficulties in including RP topics in undergraduate curricula
- Lack of CPD programs in RP
- Limited availability of health professionals, whose attention may be diverted to other CPD efforts or introduction of new techniques or medical devices

(For more details including principal opportunities related to this Key Message, please see Section 3.4 of this document.)

KEY MESSAGE #6

Technology transfer and translation in the field of medical applications of IR is an ongoing challenge; few research projects in the field include industrial partners and really aim to transfer research results into developments and new or improved products. Recommendations for the ten most important barriers to transfer and translation were rigorously prioritised based on a Delphi process.

(For more details including prioritised barriers related to this Key Message, please see Section 3.5 of this document.)

Taking into account these Key Messages, the ambition of this part of the SRA is to contribute to facilitating and accelerating research and positive outcomes through four interconnected axes of action:

- Development of fit-for-purpose support structures for the research and innovation system
- Technology transfer dimensions
- Focused attention to all relevant digitalisation aspects
- Management of the E&T for existing and future medical staff to accompany these needed evolutions

CONCLUSION

The evaluation of the current state of the art regarding the medical use of IR as well as the potential new developments and improvements have shown that patients all over the world, and especially in Europe, already benefit tremendously from such medical applications. The expert panels of the EURAMED rocc-n-roll project as well as the stakeholders and all other involved experts could show, however, that there is still a lot of room for improvement to provide better care for diseases that are already diagnosed or treated by IR but also for diseases, where this is not yet that relevant. IR supports the adaptation of procedures for diagnostic and therapeutic applications to individual patients and therefore for optimal personalised medicine. To achieve this improvement, close collaboration between the various research directions as well as funding institutions is indispensable. The potential for improved healthcare in Europe is huge, both on an individual patient basis as well as for the public healthcare system, in particular by strengthening the cooperation between the healthcare sector and the radiation research field.

The SRA demonstrates that clinical needs as well as clinically relevant questions should drive the definition of research questions to generate the highest possible benefit of medical applications of IR. This involves that the view of patients on their (potential) diseases and the expected and desired diagnostic procedure and treatment need to be a central aspect for assessing research possibilities and research needs in this field. The dignity of the patient needs to be taken into account. The clinically relevant questions then need to initiate basic biological research as well as technological developments including the full potential of the digital revolution. Such developments can be various and have the potential enable completely new diagnostic and therapeutic applications.

To ensure the most efficient use of IR, it is mandatory to carefully assess the benefit-risk balance of each application. In general, it can be assumed that the benefit of medical applications outweighs by far the risks associated with IR, provided the justification and optimisation is done appropriately. To evaluate the benefit-risk balance, it is necessary to quantify the exposure and to understand the detrimental effects and its biological reasons including individual aspects. In terms of minimising potential side effects, it is mandatory to optimise all medical procedures using IR by reducing exposure, especially of the healthy tissue, without deteriorating the diagnostic or therapeutic performance, which need to be evaluated in a transparent, accessible, and evidence-based way.

To foster this research and to allow an efficient transfer and translation and a broad implementation in clinical practice across Europe certain prerequisites have to be met. One of these prerequisites is the further establishment and usage of suitable infrastructures. It seems most reasonable to foster this by establishing a Europe-wide Centre of Excellence structure for personalised medicine based on the application of IR in a distributed but well-coordinated structure. This distributed structure, as well as all university hospitals involved, will have to collaborate with the industry and the regulatory bodies to drive the development of clinically relevant technologies and procedures but also its fast translation into the clinical routine. The hurdles for technology transfer and translation need to be reduced as outlined in the corresponding chapter. This also includes measures to foster the sustainable supply with radiopharmaceuticals and technologies for applying IR in medicine in the best possible way. Finally, continuous effort has to be made to enable life-long learning, education and training of researchers and clinical staff so that the developed methods will be broadly implemented in clinics across Europe.

While additional topics might come up in the future, this document lists all research topics that have been identified by the above-mentioned experts and stakeholders as promising to improve the life of European patients. The related research work must be performed in a structured way. To achieve that, the research tasks have to be aligned into categories, which should be meaningful in terms of outcome, especially for patients across Europe. Such a structure and a corresponding alignment, as well as a possible approach for its implementation, is developed in the EURAMED rocc-n-roll Roadmap linked to this document.

ABBREVIATIONS

AI	Artificial Intelligence
ALARA	As Low As Reasonably Achievable
ALLIANCE	European Radioecology Alliance
ART	Adaptive Radiation Therapy
AVM	Arteriovenous Malformation
BSSD	Basic Safety Standards Directive
CDSS	Clinical Decision Support Systems
CFD	Computational Fluid Dynamics
CNS	Central Nervous System
CoE	Centre of Excellence
CPD	Continuing Professional Development
CT	Computed Tomography
CTA	Computed Tomography Angiography
CVD	Cardiovascular Disease
DMS	Dose Management System
DQE	Detector Quantum Efficiency
DRL	Diagnostic Reference Level
EC	European Commission
ED	Effective Dose
EHDS	European Health Data Space
EHRs	Electronic Health Records
E&T	Education and Training
EMA	European Medicines Agency
EOSC	European Open Science Cloud
ESC	European Society of Cardiology
EUCAIM	European Federation for Cancer Images
EURADOS	European Radiation Dosimetry Group
EURAMED	European Alliance for Medical Radiation Protection Research
FAIR	Findability, Accessibility, Interoperability, and Reusability
FHIR	Fast Healthcare Interoperability Resources
IA	Intracranial Aneurysm
ICRU	International Commission on Radiation Units and Measurements
IGRT	Image-Guided Radiation Therapy
IHA	Individual Health Assessment
IR	Ionising Radiation
KPI	Key Performance Indicator
LNT	Linear No Threshold model
MC	Monte-Carlo methods
MDR	Medical Device Regulation
MELODI	Multidisciplinary European Low Dose Initiative
ML	Machine Learning
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MTF	Modulation Transfer Function
NERIS	European Platform for Nuclear and Radiological Emergency Response and Recovery
NGS	Next Generation Sequencing
NTCP	Normal Tissue Complication Probability models
PCCT	Photon Counting CT
PBPK	Physiologically-Based Pharmacokinetic models
PET	Positron Emission Imaging
PREM	Patient Reported Experience Measurement
PROM	Patient Reported Outcome Measurement
PTV	Planning Target Volume
ROC	Receiver Operating Characteristic
RP	Radiation Protection
RT	Radiation Therapy
SHARE	Social Sciences and Humanities in Ionising Radiation Research
SNR	Signal to Noise Ratio
SRA	Strategic Research Agenda
TRT	Targeted Radionuclide Therapy
US	Ultrasound
VGA	Visual Grading Analysis
VR	Virtual Reality

DISCLAIMER

The opinions stated in this report reflect the opinions of the authors and not the opinion of the European Commission.

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