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D6.2 Medical Radiation Protection Roadmap

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European Research Roadmap

For Medical Applications of Ionising Radiation for Better and Individualised Healthcare to Improve Patients' Lives

Vision statement

The vision of this roadmap is to provide guidance to European policymakers, funders, and the scientific and clinical communities regarding priority research, infrastructure development, and education and training actions related to medical applications of ionising radiation (IR). Proposed actions are prioritised regarding their impact on patients' life expectancy and/or quality of life, radiation protection as an integral part of quality and safety measures, and healthcare systems as well as their feasibility, providing time frames and cost estimations. The roadmap builds on the challenges and research needs identified in the EURAMED rocc-n-roll Strategic Research Agenda and also takes into account the European funding landscape for health and digital innovation, as well as actions carried out within the scope of the Strategic Agenda for Medical IR Applications (SAMIRA), to drive progress in personalised medicine using medical applications of IR in Europe.

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Abbreviations

ALLIANCE	European Radioecology Alliance
AI	Artificial Intelligence
AR	Augmented Reality technology
ART	Adaptive Radiotherapy
BT(s)	Breakthrough(s)
CDSS	Clinical Decision Support Systems
CEF	Connecting Europe Facility Programme
CoE(s)	Centre(s) of Excellence
CNS	Central Nervous System
CPD	Continuing Professional Development
CT	Computer Tomography
DG	Directorate-General
EANM	European Association of Nuclear Medicine
eHDSI	e-Health Digital Service Infrastructure
ECMP	European Congress of Medical Physics
ECR	European Congress of Radiology
EFOMP	European Federation of Organisations for Medical Physics
EFRS	European Federation of Radiographer Societies
ERPW	European Radiation Protection Week
ESTRO	European Society for Radiotherapy and Oncology
E&T	Education and Training
EU	European Union
EUCAIM	European Federation for Cancer Images
EURADOS	European Radiation Dosimetry Group
EURAMED	European Alliance for Medical Radiation Protection Research
ICD	Immunogenic Cell Death
IR	Ionising Radiation
LLL	Lifelong Learning
LNT	Linear-non-Threshold model
M2-like TAMs	M2-like Tumour-Associated Macrophages
MDSCs	Myeloid-Derived Suppressor Cells
MEDIRAD	Implications of Medical Low Dose Radiation Exposure
MEDICIS	Medical Isotopes Collected from ISOLDE
MELODI	Multidisciplinary European Low-Dose Initiative
ML	Machine Learning
MRI	Magnetic Resonance Imaging
MWA	Microwave Ablation Technology
NERIS	The European Platform on Preparedness for Nuclear and Radiological Emergency Response and Recovery
PACS	Picture Archiving and Communication System
PET	Positron Emission Tomography
PIANOFORTE	European Partnership for Radiation Protection Research
Q&S	Quality and Safety
R&D	Research and Development
RP	Radiation Protection
RFA	Radiofrequency Ablation technology
RT	Radiation Therapy

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SAMIRA	Strategic Agenda for Medical Ionising Radiation Applications
SHARE	Social Sciences and Humanities in Ionising Radiation
SPECT	Single-Photon Emission Computerised Tomography
SRA	Strategic Research Agenda
TAAs	Tumour-Associated Antigens
TME	Tumour Microenvironment
TOC	Therapy Operating Curves
Tregs	T regulatory cells
TRT	Targeted Radionuclide Therapy

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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Abstract

The roadmap for medical applications of ionising radiation (IR) is established within the Horizon 2020 EURAMED rocc-n-roll project. It takes into account the EURAMED rocc-n-roll Strategic Research Agenda (SRA) developed by the project but results not only from project-internal inputs but also from recommendations from the Implications of Medical Low Dose Radiation Exposure (MEDIRAD) project, the Strategic Agenda for Medical IR Applications (SAMIRA), and the latest achievements resulting from progress made during the implementation of SAMIRA through various current projects.

The EURAMED rocc-n-roll roadmap addresses a broad field of research and technological developments in medical applications of IR and matches the goals of various European funding programmes such as Horizon Europe, EURATOM, EU4Health, and the Digital Europe Programme. In addition to such European public funding, national publicly-funded and private sector efforts are essential for translating the advances in medical applications of IR from bench-to-bedside in the member states.

The SRA and roadmap are the EURAMED rocc-n-roll project's main goals and part of the 3rd pillar of the SAMIRA strategic agenda, notably "Innovation & Technological Development". However, this roadmap also includes the research needs for radionuclide supply and the quality and safety (Q&S) of applications of medical IR, which correspond to the 1st and 2nd pillars of SAMIRA, respectively.

This roadmap is developed in line with the SRA, based on a patient-centric approach. For example, personalised medicine shows great promise in patient care and can be effectively applied in radiation-based medicine, considering different stages of diseases at various phases of life. The roadmap presents potential breakthroughs that may significantly impact medical applications of IR with regard to patients' life expectancy and/or quality of life, radiation protection (RP), and healthcare systems.

Although the roadmap includes some indicators for priority setting and estimated resources and planning, its implementation will inevitably depend on the availability of human, infrastructural, and financial resources. Successful and efficient implementation of the roadmap will require a coordinated funding approach, including public (European and national funding bodies) and private resources.

The concept and proposed structure of the roadmap, based on the framework of the SRA, was presented and discussed among consortium members, the advisory board members, and relevant stakeholders during several EURAMED rocc-n-roll sessions at various conferences (ERPW 2021, ECR 2022, ECMP 2022, ERPW 2022, ECR 2023, ESTRO 2023). The consensus was achieved based on the criteria for prioritisation, mainly the impact on patient care and the healthcare system in Europe, and the inclusion of topics in the roadmap based on such impact and their feasibility. It was also considered how the roadmap would be implemented after the project ends, including defining the required human, infrastructural, and financial resources and relevant stakeholders (e.g., research institutes, healthcare systems and providers, industry). Depending on the implementation, the outcome will be improved individualised patient care for various diseases like cancer, cardiovascular, neurovascular, and inflammatory diseases, and a more efficient healthcare system. Quantifying the improvement is challenging as it will depend on the level of implementation, and thus on funding resources. The implementation also needs to be different for different diseases and throughout Europe.

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A consensus was also reached regarding the term and the definition of **breakthroughs (BTs)**: *research and technological developments that may substantially impact medical applications of IR from the perspective of patients' life expectancy and/or quality of life, RP, and healthcare systems.*

Eight BTs have been identified based on the identified research needs in the SRA. These BTs are divided into two groups, four directly linked to the patients' perspective and medical care, whereas the other four are more supporting and generic.

The eight BTs are:

- Improve/develop a diagnosis,
- Improve/develop therapy,
- Patient RP and benefit-risk balance,
- Patient relations (incl. dialogue and communications, data handling, ethics).
- Strategic positioning of applications of IR in medicine,
- Implementation, sustainability and organisation of IR-based medicine,
- Quality, safety and legislation in Europe,
- Career attractiveness and RP for workers.

These BTs are analysed regarding the actions they require, the necessary budgets, their feasibility, and potential timelines. The goal of research along the lines of the BTs is to benefit European patients in the best possible way. The corresponding research efforts would require a substantial amount of funding. The main message is that there is a chance to achieve remarkable changes in the life expectancy and quality of life of European patients and for the European healthcare systems by using the potential of implementing and fostering personalised medicine using IR. The main criteria for prioritisation are:

- the impact on patient care,
- the impact on the healthcare system in Europe,
- and inclusion of topics as outlined in this roadmap and the corresponding SRA, considering the impact mentioned above and their feasibility.

Due to the considerable amount of required funding, the efforts must be shared between public funding organisations, private organisations, universities and research organisations, and (university) hospitals throughout Europe. Given that research will be supported and performed according to the criteria like impact and feasibility developed in this roadmap and based on the proposed actions, there will be significant improvements for European patients using medical applications of IR and corresponding RP, thus achieving the best possible patient care.

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1. Foreword

The EURATOM call NFRP-2019-2020-13 for a coordination and support action in Horizon 2020 asked to develop a Strategic Research Agenda (SRA) and a Roadmap for developments in medical applications of ionising radiation (IR), including but not limited to radiation protection (RP). In response to this call, the EURAMED rocc-n-roll project set out to yield these documents. The EURAMED rocc-n-roll SRA identifies the research gaps in the field of medical applications of IR to show potential improvements for patient care for various diseases like cancer, cardiovascular diseases, neurovascular diseases, infectious diseases, and many other diseases. The EURAMED rocc-n-roll Roadmap describes the research and technological developments, based on the gaps identified in the SRA, that can substantially improve patient care regarding life expectancy and quality of life, how these goals can be achieved, and how and by which measures the corresponding necessary research can be implemented.

Therefore, this roadmap shall support stakeholders like patients and patients' representatives, healthcare providers, research platforms and medical associations, the industry, funding organisations and policymakers, as well as research organisations to prioritise research and to establish meaningful research programs and funding schemes to achieve the overarching goal of providing better healthcare for patients as defined above using radiation-based medicine throughout Europe.

The medical associations interested in medical RP established EURAMED, the European Alliance for Medical Radiation Protection Research, as a non-profit organisation in 2017. The founding members of EURAMED are 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). These were at that time also members of MELODI (the Multidisciplinary European Low Dose Initiative), which initiated the integration process of the RP research community, which is based on the strategic research agendas developed by the European RP research platforms, i.e., European Radioecology Alliance (ALLIANCE), The European Platform on Preparedness for Nuclear and Radiological Emergency Response and Recovery (NERIS), European Radiation Dosimetry Group (EURADOS) and Social Sciences and Humanities in Ionising Radiation (SHARE) besides EURAMED and MELODI. The previous roadmap for RP research established in European Joint Programme for the Integration of Radiation Protection Research (EJP CONCERT) [1] has been used as an example for establishing this roadmap.

The EURAMED rocc-n-roll project addresses the medical application of IR in this roadmap and is not limited to medical RP. Therefore, the methodology of developing the EURAMED rocc-n-roll roadmap shares similarities with the EJP CONCERT roadmap for RP research [1] but defines the research and technological development needs based on the patients' perspective and the identified disease areas by the SRA. In addition, certain generic medical developmental needs have been determined, covering common interests and synergies for different medical applications of IR and related RP.

The EURAMED rocc-n-roll SRA and this roadmap correspond one-to-one with the pillar Innovation & Technological Development of the SAMIRA Strategic Agenda [2], but also address the research needs in the pillars "Radionuclide supply" and "Q&S of medical IR applications". The roadmap takes into account the most recent developments following the SAMIRA strategic agenda, achieved through various projects such as but not limited to MEDIRAD, Medical Isotopes Collected from ISOLDE (MEDICIS), SAMIRA study on the implementation of the EURATOM and the EU legal bases with respect to the therapeutic uses

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of radiopharmaceuticals (SIMPLERAD), the “AI for Health Imaging” projects, a cluster of Horizon 2020 projects including e.g., Accelerating the lab to market transition of AI tools for cancer management (CHAIMELEON), Radiation risk appraisal for detrimental effects from medical exposure during management of patients with lymphoma or brain tumour (SINFONIA), Implementing verifiable oncological imaging by quality assurance and optimisation (i-Violin), Quality Assurance Through Clinical Audit in Diagnostic (including Interventional) Radiology, Radiotherapy and Nuclear Medicine (including Therapies) (QuADRANT), and European co-ordinated action on improving justification of computed tomography (EU-JUST-CT). In addition, the EURAMED rocc-n-roll roadmap is based on inputs from the project’s work packages, the EJP CONCERT joint roadmap for RP research [1] and broad stakeholder consultation.

The EURAMED rocc-n-roll roadmap is intended to be an instrument that will guide stakeholders to selectively fund the most effective medical developments using IR and related RP. It aims to be a source of information for funding bodies of the EURATOM programme, including the European Partnership for Radiation Protection Research (PIANOFORTE) project, Horizon Europe’s “Health” and “Digital, Industry and Space” clusters, the Digital Europe programme and the EU4Health programme, respectively, but also national funding organisations, national research institutes and universities as well as national authorities responsible for health and RP, private industries, and hospitals.

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2. Methodology

The roadmap has been developed from the perspective of the patient's benefit-risk balance and identifying the needs in the subsequent stages of life. The challenges in developing medical applications of IR and related RP are described in the EURAMED rocc-n-roll SRA as well as the corresponding research needs. These have been summarised in Figure 1 of the SRA, also shown below:

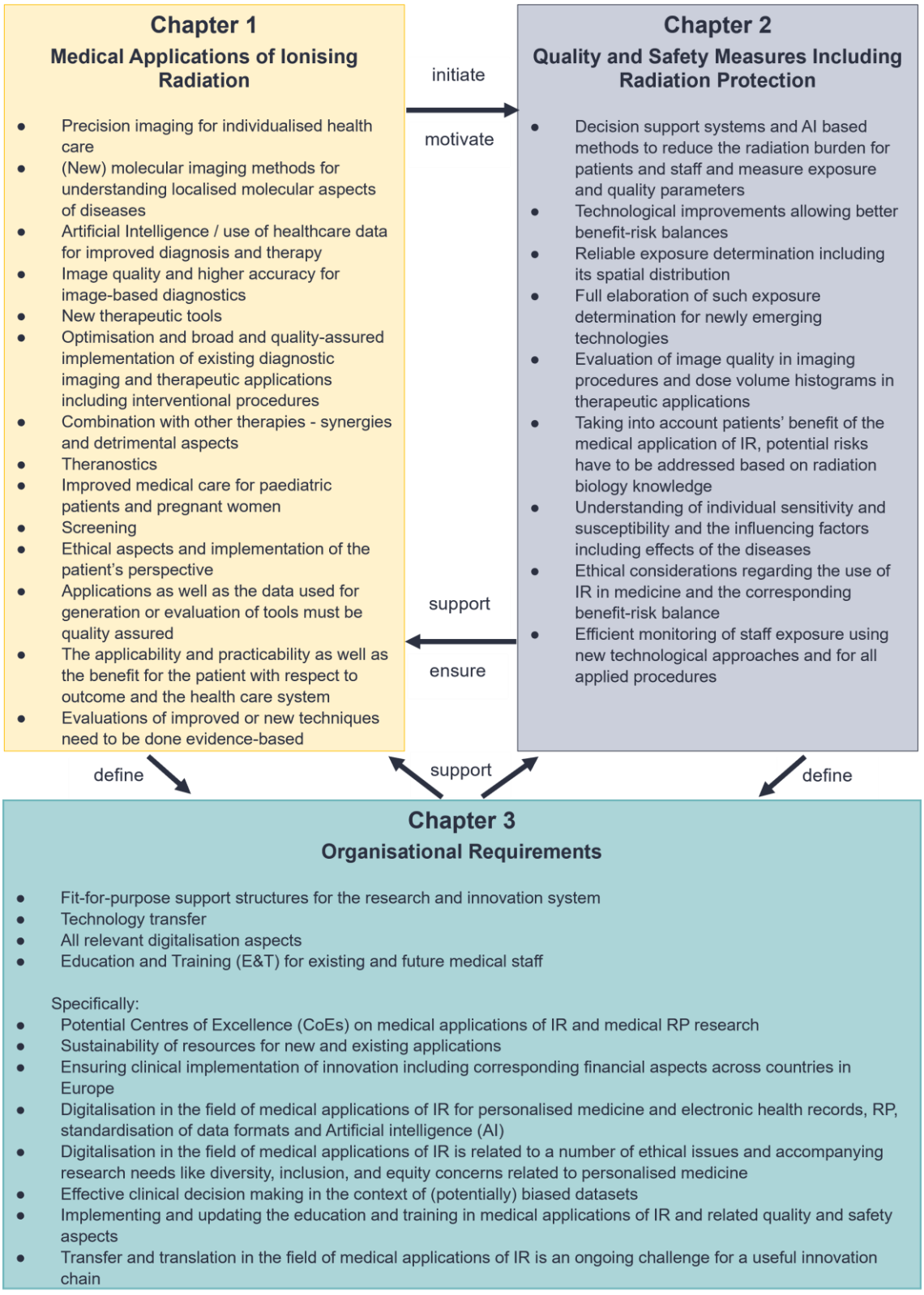

Figure 1. *(from EURAMED rocc-n-roll SRA) listing the topics identified in the SRA, ordered according to the chapters of the SRA.*

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In the development of this roadmap, other information sources considered include the SAMIRA strategic agenda, including its current implementation status and recommendations from various projects such as MEDIRAD. The research needs defined in MEDIRAD are strongly overlapping with the list mentioned above, but with an emphasis on radiation safety aspects. The EURAMED rocc-n-roll roadmap, along with the EURAMED rocc-n-roll SRA, can be viewed as an integrative part of SAMIRA (Figure 2).

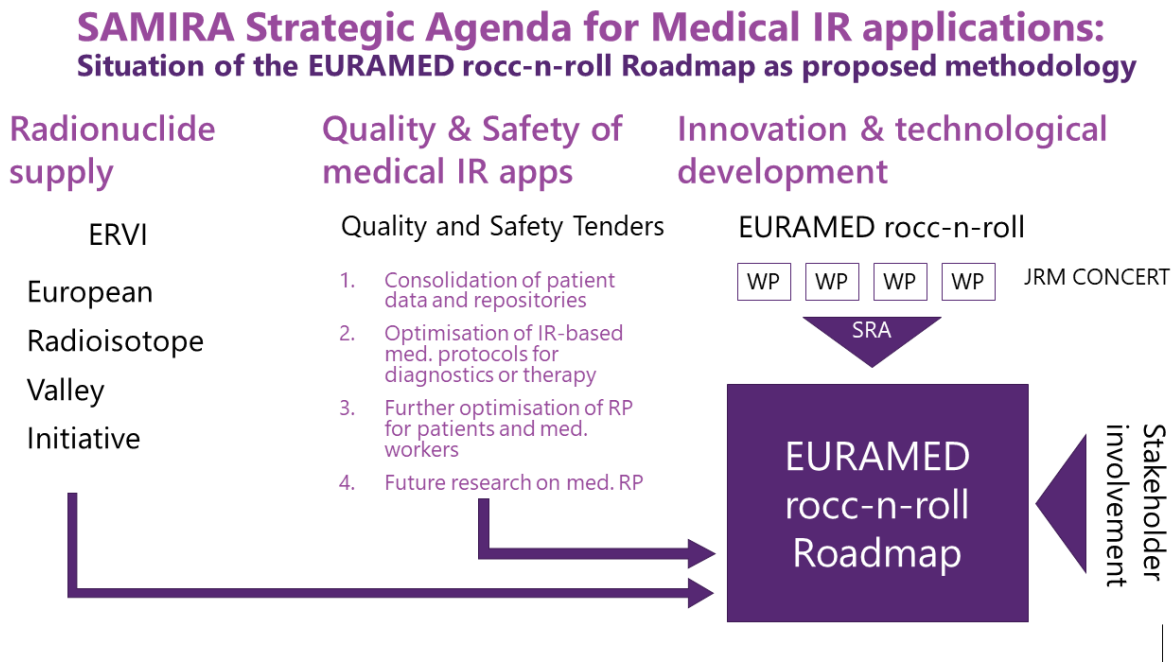

Figure 2. *The situation of the EURAMED rocc-n-roll roadmap within the scope of the three pillars of SAMIRA and their implementation. The schematic overview shows the information sources and stakeholders consulted in developing the Research Roadmap.*

This roadmap intends to develop an approach for prioritising the gaps, and research needs to be identified in the corresponding EURAMED rocc-n-roll SRA. A methodology similar to the CONCERT roadmap has been applied to approach this task. The topics from the SRA had to be categorised. To do that, BTs were defined as an integrative and interlinking approach between the different topics.

> The roadmap defines **breakthroughs** as
> *"Research and technological developments that may substantially impact medical applications of ionising radiation from the perspective of patients' life expectancy and/or life quality, radiation protection and health care systems".*

In general, two types of BTS were defined. The first type is linked to specific diseases or patients' needs that evolve along the patients' life stages. The second type consists of BTs of a more generic nature that have a broader application across different medical uses of IR or linked RP issues. The second group of BTs provides support and facilitates the developments that substantially impact the medical applications of IR, although they may not directly create that impact on the patient care. Nevertheless, they are listed as BTs because they are essential for the effective implementation of the research topics summarised in the BTs of the first group. This relationship is further elaborated when the BTs are explicitly named.

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3. Medical challenges related to different stages of life

Patients' most prevalent diseases and medical needs evolve over the lifetime. Various diseases like cancer, neurovascular and cardiovascular diseases, trauma conditions, and in the future maybe inflammatory processes or infections can be better diagnosed or treated based on developments in the medical use of IR, including molecular imaging approaches, theranostics, new therapeutic options, and better interventional procedures. The benefit-risk balance of one particular therapy or diagnosis is not constant over the lifecycle and is strongly related to the underlying disease.

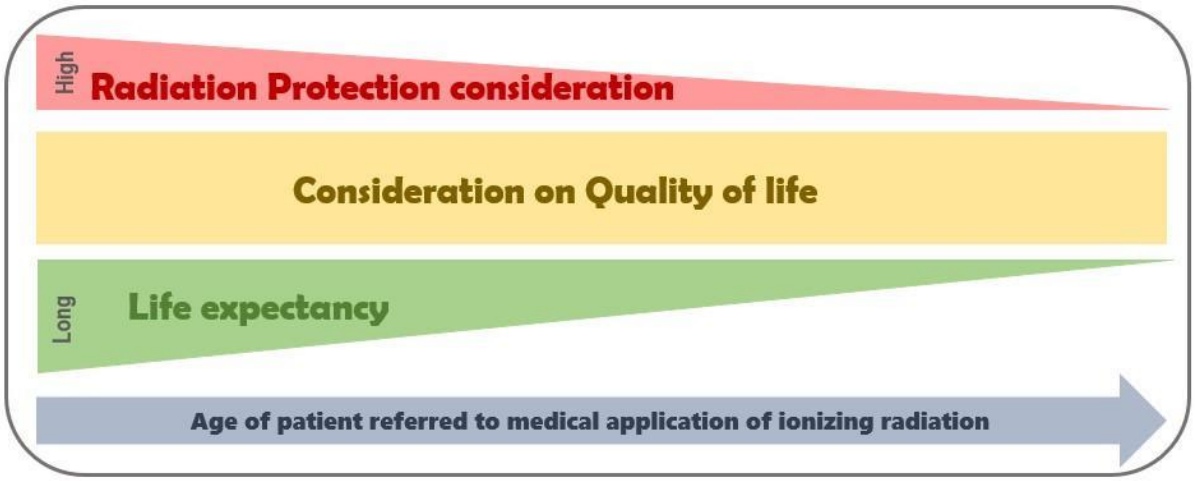

Figure 3. *Changing objectives: Prioritising RP concerns, consideration of the quality of life across ages*

In some cases, children and premature babies receive multiple diagnostic procedures or treatments. In general, the younger the patient, the more important the consideration of RP is concerning the development of late adverse effects such as secondary cancers. Protecting the unborn child during diagnosis and treatment is very important in pregnant women. In contrast, RP consideration might deserve the greatest attention for the unborn life and young children, while its consideration becomes less dominant along the course of life as life expectancy and, thus, potential detriments of IR decrease (Figure 3). In later stages of life, with the decrease of age-dependent radiation sensitivity, diagnosing and curing injuries and diseases will gradually become more important when weighting risks. Here, high-quality diagnosis and treatment of cardiovascular diseases and cancer as the main life-threatening diseases in the western world will often be more important for the individual life expectancy than risks of radiation exposure in medicine. Consideration of quality of life is a major aim of medical treatment in all phases of life, from children to elderly patients. In treating paediatric patients with cancer, for instance, offering high cure rates with minimised risks of treatment-induced cancer is a dominant consideration, and this is achieved, e.g., in paediatric Hodgkin's lymphoma by selective use of radiotherapy (RT) based on positron emission tomography (PET) assessment of response to chemotherapy [3]. On the opposite end, the quality of life of elderly patients with a metastatic tumour will significantly benefit from efficient treatment of metastases, such as external-beam RT [4] or radioligand therapy like lutetium-177 [177Lu]Lu-PSMA-617 in metastatic prostate cancer [5]. In this setting, RP is only a minor concern.

Along the course of life, diseases such as cancer, cardiovascular, and neurovascular disesases are more prevalent in middle-aged adults. People are exposed to radiation through screening, diagnosis and therapy, including interventional procedures, and thus are undertaking repeated exposures which still need to be evaluated in terms of dose and potential risks. In the case of acute life-threatening diseases, e.g., life-threatening traumas or myocardial

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infarction, the potential adverse effects of medical procedures involving IR may far be outweighed by the benefit of imaging and treatment. However, justification and optimisation remain major principles for the safe use of IR for medical applications for all life stages.

In rather chronic situations (cancers, neurology, cardiovascular, and other diseases), the benefit- risk balance strongly depends on the underlying disease. For example, medical procedures involving IR are crucial in oncology for diagnosis, treatment, and follow-up, and examinations may be performed often repeatedly within a short time. Here, again, the potential risks of IR are often outweighed because the priority is to properly diagnose, treat and monitor the tumour response. But whatever the clinical context, the need to develop dose reduction systems remains crucial for avoiding IR-related harm.

In clinical decision making, e.g., the palliative effects of treatments involving IR, like external beam RT or radionuclide treatment in metastatic patients, can in most cases be assumed to be clearly more important than radiation risks.

The above paragraphs also show exemplarily the complexity of patient information, especially in the context of various potential approaches for diagnosis or treatment and the corresponding patients' benefits and risks. More research is required for a personalised approach which needs to consider the underlying disease, the technological advances, and the fact that detriment models and the corresponding uncertainties do not consider various clinical conditions.

However, some general aspects are important and valid for all stages of life and all kinds of diseases:

- The benefit of the applications of IR must always outweigh the risks.
- The benefit-risk balance is strongly dependent on the underlying disease.
- There is a strong need to enhance optimisation and justification and to fill the gap between justification and optimisation processes.
- It is important to consider personalised patient information.
- The development of dose reduction tools is mandatory for safe use of IR in medicine in general, and in particular, Artificial Intelligence (AI)-assisted tools need to be developed where feasible and quality assured.
- The development of safety-driven technologies must be pursued.
- Repositories allowing lifelong tracking of dose exposures, biobanks and imaging databanks correlated with the clinical setting must be established to develop large-scale epidemiological studies.

BTs mainly addressing the patients' medical care in relation to their phase of life and those originating from a more generic medical perspective are presented in Figure 4 and Figure 5, respectively.

From the patients' perspective, the main BTs are shown in Figure 4 and include:

(1) Improve/develop diagnosis,
(2) Improve/develop therapy,
(3) Patient radiation protection and benefit-risk balance,
and
(4) Patient relations (including dialogue and communications, data handling, ethics).

To achieve these patient - oriented BTs, **more generic and supporting strategic BTs** are needed, as shown in Fig. 5. They are

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(5) Strategic positioning of applications of IR in medicine,
(6) Implementation, sustainability and organisation of IR-based medicine,
(7) Quality, safety (Q&S) and legislation in Europe,
and
(8) Career attractiveness and radiation protection for workers.

The research and development (R&D) BTs **(1–4)** should be the ultimate goal of all other supporting strategic BTs **(5–8)**.

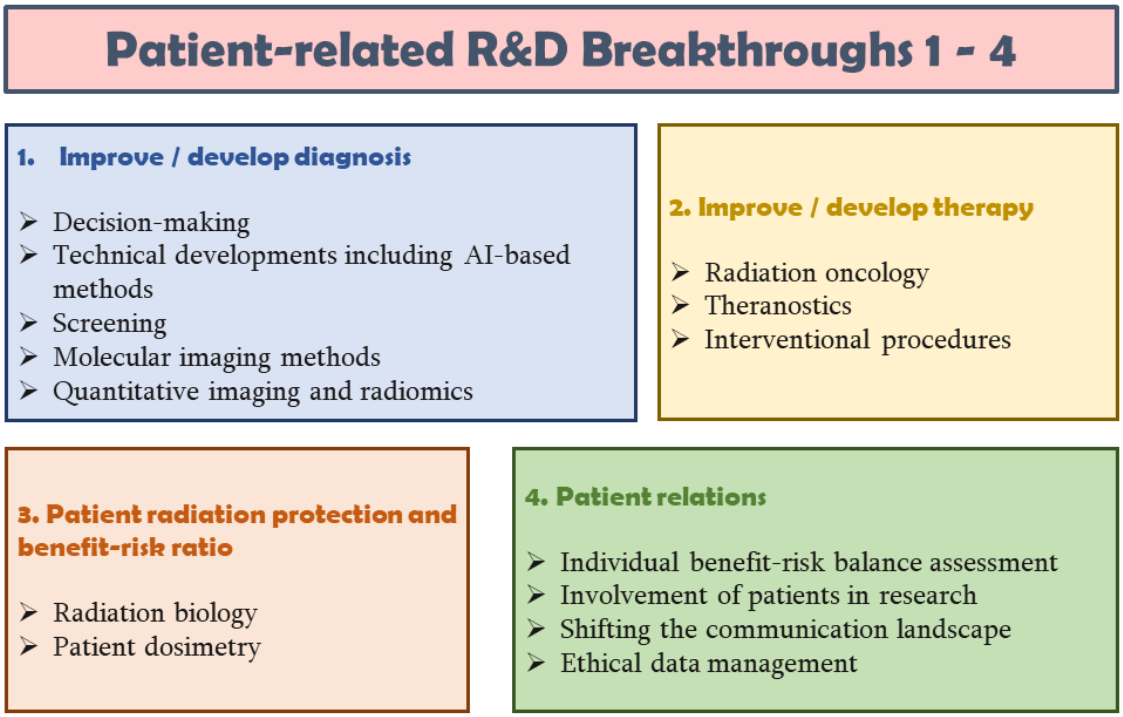

Figure 4. *Patient-related R&D BTs 1–4.*

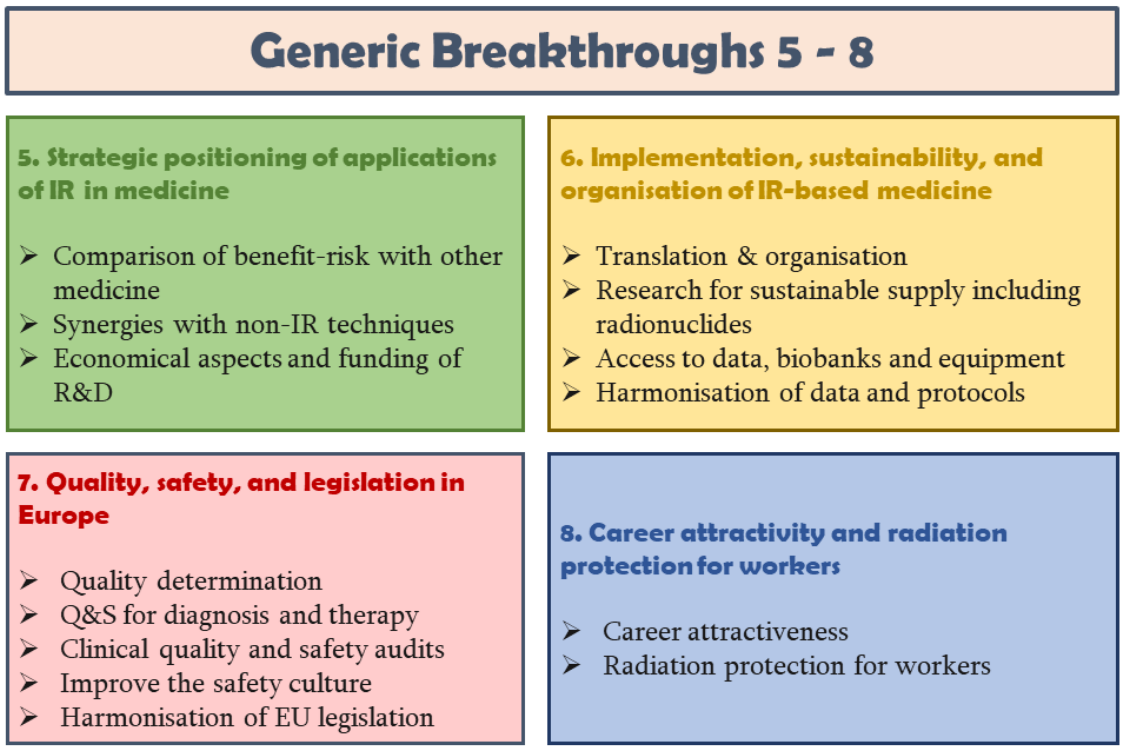

Figure 5. *Generic BTs 5–8.*

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Again, it must be highlighted that not all BTs will in all aspects represent research and technological developments that have the potential to change patients' care and quality of life directly, but especially BTs 5 to 8 are most relevant to implement the required research for better, more efficient and more safe healthcare to individual patients based on IR and for the implementation of the results and are thus supporting BTs, which are important to enable the substantial impacts of the potential achievements of BTs 1 to 4. An overarching concept of all BTs is the development of suitable metrology for evaluating innovations and developments.

The gaps and research needs identified in the EURAMED rocc-n-roll SRA, as also depicted in Figure 1, are listed in the following again in a little more detail and are correlated to the BTs in which they should be dealt with:

Concerning the clinical perspective for potential improvements regarding medical applications, the following topics have been identified as most relevant:

- Precision imaging for individualised healthcare (BTs 1 and 2)
- (New) molecular imaging methods for understanding localised molecular aspects of diseases (BTs 1 and 2)
- AI/use of healthcare data for improved diagnosis and treatment (BTs 1, 2, and 6)
- Image quality and higher accuracy for image-based diagnostics (BTs 1, 2 and 7)
- New therapeutic tools including hadron therapy, FLASH therapy, interventional therapies, and new radionuclide therapies (BT2)
- Optimisation and broad and quality-assured implementation of existing diagnostic imaging as well as therapeutic applications, including interventional procedures (BTs 1 and 2)
- Combination with other therapies – synergies and detrimental aspects (BTs 2 and 5)
- Theranostics (BTs 1, 2, and 6)
- Improved medical care for paediatric patients and pregnant women (BTs 1, 2, and 3)
- Screening (BTs 1 and 2)
- Ethical aspects and implementation of the patient's perspective (BTs 3 and 4)

A few aspects are relevant to be considered for all of such topics mentioned:

- Applications, as well as the data used for the generation or evaluation of tools, must be quality assured. In many cases, e.g. for AI and corresponding data new methods need to be developed for such quality assurance (BTs 6 and 7)
- The applicability and practicability of any method for use on an individual patient have to be taken into account, as well as the benefit for the patient concerning the outcome and the healthcare system (BTs 1, 2, 3, 4, 5, 7, and 8)
- Evaluations of improved or new techniques need to be conducted evidence-based (BTs 1, 2, 3, 4, 5, and 7)

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Several topics have been identified to be central for the safe use of IR, including effective RP as well as for increasing the benefit-risk balance for patients and limiting risks for medical staff:

- Decision support systems and AI-based methods might help reduce the radiation burden for patients and staff and lead to optimal procedures regarding benefit-risk balance (BTs 1, 2, 4, and 6)
- Technological improvements allow better benefit-risk balances (BTs 1, 2, 3, 6, and 7)
- Reliable exposure determination, including its spatial distribution (BTs 3 and 7)
- For newly emerging technologies, such exposure determination is not yet elaborated completely (BTs 3, 7, and 8)
- Evaluation of image quality in imaging procedures and dose volume histograms in therapeutic applications (BTs 1, 2, and 7).
- Taking into account patients' benefits of the medical application of IR, potential risks have to be addressed as well based on radiation biology knowledge (BTs 1, 2, 3, and 5).
- Individual sensitivity and susceptibility and the influencing factors need to be understood, including the effects of the diseases (BTs 3 and 5).
- Ethical considerations regarding the use of IR in medicine and the corresponding benefit-risk balance (BT4)
- Staff must be monitored efficiently using new technological approaches and all applied procedures (BT8)

The conditions necessary for effective and meaningful research on the topics mentioned above, as well as those aspects that are most relevant for the effective implementation of such research into clinical practice across Europe, are listed below:

- To address the needs of patients, researchers, and medical staff, categories for classifying future potential Centres of Excellence (CoEs) on medical applications of IR and medical RP research are proposed (BTs 3, 4, 5, 6, and 8).
- To facilitate the sustainability of resources for new and existing applications, it needs to be investigated how laboratories and infrastructures with high-end radiation technology can be operated sustainably (BT6)
- It needs to be evaluated how standardisation of reimbursement can be assured across countries in Europe (BTs 1, 2, 4, and 6)
- 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 looking for personalised medicine and electronic health records, RP and electronic health records, standardisation of data formats for RP and AI for RP (BTs 3, 6, 7, and 8)
- Digitalisation in the field of medical applications of IR will raise several ethical issues, and accompanying research needs like diversity, inclusion, and equity concerns related to personalised medicine, public/patient trust issues related to (BTs 4 and 6)

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electronic health systems and records digitisation, Advances in the use of AI/Machine Learning (ML) brings a plethora of ethical challenges and questions ranging from how to modify informed consent processes to ensure 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 Q&S aspects, including RP for health professionals, include 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 (BT8)
- Technology transfer and translation in the field of medical applications of IR is an ongoing challenge (BTs 1, 2, and 6).

Taking into account these aspects, four interconnected axes of action are identified for Chapter 3 of the SRA, referring to the supportive aspects needed for the research and implementation of medical applications of IR:

- Development of fit-for-purpose support structures for the research and innovation system (BTs 6, 7).
- Technology transfer dimensions (BTs 1, 2, and 6).
- Focused attention to all relevant digitalisation aspects (BTs 4 and 6)
- Management of the E&T for existing and future medical staff to accompany these needed evolutions (BT8)

Dedicated examples of typical tasks for BTs will be described in detail in the following chapter, and their evaluation will be made clear for some potential examples in Chapter 5.

The overarching vision of the roadmap is to provide guidance to European policymakers, funders, and the scientific and clinical communities concerning priority research, infrastructure development, and E&T actions related to medical applications of IR. The proposed actions are prioritised based on their potential impact on patients' life expectancy and/or quality of life, RP as an integral part of Q&S measures, and healthcare systems while also considering their feasibility, time frames, and cost estimations. The roadmap builds upon the challenges and research needs identified in the EURAMED rocc-n-roll SRA and takes into account the European funding landscape for health and digital innovation. Additionally, actions carried out within the scope of the SAMIRA Strategic Plan are considered. All these potential funding opportunities should be used to drive progress in personalised medicine using medical applications of IR in Europe.

The definition, the vision and the actions that need to be implemented to achieve the vision of each BT are elaborated on below.

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4. Breakthroughs

4.1. Breakthrough 1 – Improve/develop diagnosis - innovation and development for better screening, early detection, and diagnosis

Vision

Today, in the context of patient care, imaging for screening, diagnostic imaging, and imaging for therapy preparation and evaluation already play a crucial role in many cases and for many diseases. This holds for diseases like cancer, neurological and neurovascular and cardiovascular diseases, but many other diseases as well. Many medical imaging applications are based on IR, an integral aspect of diagnostics.

The vision is to revolutionise patient care by improving diagnostic value, enhancing accessibility, optimising performance, and elevating safety standards. This can be achieved by leveraging cutting-edge and developing new hardware technologies and harnessing the power of data-driven approaches, such as AI, to drive innovation.

To achieve this vision, several actions have to be taken. These actions are related to:

- Clinical decision making
- Technical developments
- Screening
- Molecular imaging methods
- Quantitative imaging

All these actions require the following elements:

- basic research on clinical questions and biology
- basic research on novel technological approaches
- research on metrological approaches for quantifying the new or optimised information
- research on possibilities for patient-centred implementation
- research on ethical implications
- technological transfer
- clinical studies to prove evidence for the advantages of the proposed new or optimised methods

Actions

4.1.1. Clinical decision making

State-of-the-art clinical decision support systems (CDSS) for the justification process are very promising for improving the appropriateness of imaging procedures, but their implementation is still limited, and more research is needed to enhance acceptance of these systems in clinical practice. This will include evaluating and describing the medical practitioner's role in taking final decisions based on the trained use of the CDSS system. These systems must become more integrated into the framework of medical application of IR and RP and, in particular, the optimisation process. Research is needed to fill the gap between justification and optimisation processes on a personalised basis considering the clinical indication and the patient characteristics.

AI-based CDSS must be developed in several ways, including the generation and use of structured and quality-assured data, model developments, and useful test and validation strategies. New fields for CDSS need to be envisaged and would need more research, including the following examples:

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- CDSS to develop an integrated diagnosis based on omics and imaging biomarkers needs to be developed and evaluated as a reliable tool.
- CDSS for optimised use of liquid biopsy and imaging can benefit faster and more personalised diagnosis.
- CDSS for an optimal use of imaging biomarkers (multispectral, functional, anatomical, clinical indication) can offer faster and more accurate decisions on individualised patient care and allow the best possible use of imaging information.
- CDSS has to be analysed and made robust for bad input data like images with pure image quality and the corresponding uncertainties.

Based on imaging and omics data, CDSS can also foster individualised approaches in RT and nuclear medicine. All omics, including radiomics, need to be developed in a way that allows a better prediction of which kind of therapy can be most successful and which body parts need to be spared from IR on an individual patient basis. The prescribed doses, types of radiation or activities can be based on CDSS predictions to maximise the benefit-risk balance.

4.1.2. Technical developments, including AI-based methods

Current technical developments focusing on high-end imaging systems are extremely important to revolutionise or at least optimise safety, performance, and market uptake. Interest for low- and middle- income countries (LMICs) must be considered. Multispectral imaging is very promising and needs to be more widely implemented, and information complexity would likely benefit from CDSS for their routine use (see above).

The development of new detectors and X-ray emitters with better performances will be crucial.

Examples:

- Photon counting Computed Tomography (CT) will provide additional information and help to improve the benefit-risk balance of CT imaging.
- Whole body PET/CT or PET/ Magnetic Resonance Imaging (MRI) and single-photon emission computerised tomography (SPECT)/CT can improve the molecular information with faster acquisition and partly even with less radiation burden.
- Mobile devices generate more flexibility and can foster the broader implementation of imaging methods throughout Europe and beyond, particularly in the point-of-care setting.
- Due to their energy-resolving possibilities, CdZnTe detectors allow more efficient imaging and additional information.
- AI-based image reconstruction methods can help reduce the required exposures while maintaining diagnostic performance or making better use of information gathered as long as these methods are evaluated with sufficient quality assessment and control.
- Monoenergetic, new X-ray sources shall help provide more accurate and additional information with even less exposure to the patients if they are transferable into clinics.

Imaging especially used for RT is described in BT2.

New innovations in imaging technology are leading to the development of smaller, lighter, and more affordable devices, thereby enhancing the availability of imaging in a point-of-care setting. The ultrasound field has made significant progress in this direction, and similar advancements should be encouraged in other areas, such as portable digital radiography and portable CT scanners. Additionally, research is still needed to explore the potential of ultra-low field MRI. Although future developments like ultra-low field MRI show promise, they fall outside

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the scope of this roadmap. Nonetheless, promoting the affordable use of MRI instead of X-rays would be a noteworthy breakthrough.

AI is already employed in imaging during technical steps, such as emission, image enhancement, and processing. However, there remains a gap for broad clinical use due to the absence of appropriate databases, validation, and regulatory approval in certain areas. Research is required to develop publicly accessible curated databases, which will facilitate the advancement of AI technologies in the field of imaging for clinical applications.

4.1.3. Screening

Imaging-based health screening programmes today are limited to breast cancer, and the implementation of screening programmes is ongoing in lung cancer.

Tools for automatic assisted detection must be widely developed, tested, and adopted, requiring large-scale studies considering local clinical aspects. CDSS for standardisation of the screening decision process have to be developed.

Registries of cumulative dose exposures must be established to properly assess the safety of image-based screening on a long-term perspective. Examples of screening applications using imaging procedures based on IR include

- breast cancer screening, which is currently established European-wide,
- lung cancer screening as potentially established using low-dose CT for certain population groups, and
- colon cancer screening depends on biochemical pre-screening results.

The progress mentioned above is needed for all these examples to improve the screening possibilities.

4.1.4. Molecular imaging methods

Nanoparticles and X-ray fluorescence can increase spatial and temporal resolution in imaging of inflammatory, malignant, and neurodegenerative diseases. As such molecular imaging can be “switched” on and off, time-dependent dynamical studies would be feasible. Corresponding imaging procedures, disease markers, and tracers must be developed and evaluated.

The potential to link molecular chemistry in oncological disease, tracer development and PET scanning to diagnose, prognose and perform treatment planning need to be further validated through trials.

4.1.5. Quantitative imaging and radiomics

Quantitative imaging has already started to be developed, but more is needed.

Radiomics is a fast-evolving field which needs continuous support for its development, including integrated diagnosis development and implementation which should be supported.

The contribution of quantitative imaging and radiomics for early treatment evaluation, treatment response, and prognosis must be validated through large trials.

In addition, a comprehensive standardisation approach must be completed in close cooperation with other international initiatives.

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4.2. Breakthrough 2 - Improve/develop therapy - innovation and development for better therapies, theranostics and interventional procedures

Vision

Today, in the landscape of treatment of patients, the application of IR plays a continuously important role in oncology, cardiovascular and neurovascular diseases. Due to the great successes in patient care, including high curing rates and limited side effects, this will probably remain the case for the next decades.

In oncology, there is the potential to develop basic biological or clinical understanding and/or technologies to improve treatment efficiency even more. In neurovascular and cardiovascular therapy, new imaging procedures improve real-time imaging, and new techniques will improve patient outcomes. New imaging procedures and techniques will improve radiologic intervention in cardiovascular and neurovascular pathologies and potentially in cancer treatments using minimally invasive procedures.

The vision is to significantly improve the treatment outcome for each patient individually, considering cure or disease control, side effects, quality of life, and patient's social situation without neglecting costs. To achieve that, fostering the development of patient-tailored therapies and the corresponding research in technological, biological and clinical aspects is mandatory. Research on how to quantify the therapeutic approaches is a prerequisite for meaningful outcomes studies.

The general concept of patient-tailored therapies is possible, and its implementation has already started in radiation oncology and neurovascular and cardiovascular diseases. However, in all fields, imaging biomarkers can even further improve patient or therapy approach selection and outcome in the future. In addition, theranostics can detect and target the disease area as soon as challenges like the patient's individual treatment planning are solved. Improved treatment will include the application of combined therapies to increase synergy and, therefore, the efficiency of the treatment and will simultaneously reduce adverse effects [6,7].

AI combined with advanced robotics may allow for remote interventions, even those which require highly advanced technical and anatomical skills [8].

Based on this vision, several actions are derived which are attributed to

- therapeutic applications in radiation oncology,
- theranostics, and
- interventional procedures.

As in BT1, all actions require work according to the following structure:

- basic research on clinical questions and biology,
- basic research on new technological approaches,
- research on metrological approaches for quantifying new or optimised therapeutic applications,
- research on possibilities for patient-centred implementation,
- research on ethical implications,
- technological transfer, and
- clinical studies to prove evidence for the advantages of the proposed new or optimised methods.

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Actions

4.2.1. Radiation oncology

In Europe, about 60% of cancer patients are cured. RT plays a key role in this remarkable achievement, but there is still significant potential for improvement. More and more sophisticated individualisation of treatment strategies is a key element in improving outcomes in patients with poor prognoses and reducing toxicity. Biomarkers or imaging markers can identify patients most likely to benefit from a given selection of a more appropriate single or combination therapy. Strategies to improve outcomes rely on optimised use and broad implementation of existing technologies and new technological advances in combination with or in addition to advances in understanding cancer biology.

There are different areas in which progress needs to be made:

- New hybrid RT devices, incorporating improved CT and/or MRI, allow more accurate tumour irradiation. The potential of various clinical applications of the new systems in adaptive radiotherapy (ART) needs to be evaluated. Merging improved real-time on-site imaging with adaptive replanning and precise application will improve tumour control and enable better normal tissue protection.
- The use of protons and heavy particles potentially allows even better dose delivery and has radiobiological benefits, as the availability of this technology is still limited. Identifying which patients will benefit most from this technology is necessary.
- Combination effects of IR and new systemic agents (immunotherapy and new targets) is an important issue for personalised patient care. Understanding such combination effects will lead to the chance to produce a synergistic effect or avoid side effects when the therapies are used in a combined manner.
- Biology-driven personalised RT enabling treatment based on the biological characteristics of the tumour and normal tissue is a promising research area in preclinical and clinical radiation oncology. Information from imaging and biology must be transferred into treatment concepts, including individualised doses and volumes concerning tumours and individually assessed normal tissues regarding sensitivity. Personalisation will lead to improved tumour control and improved normal tissue protection. Personalised targeted radionuclide therapies can be another option for personalised RT but need to be evaluated in terms of dosimetric suitable approaches and randomised clinical trials for evaluation of potential benefits.
- In preclinical research, FLASH RT has been shown, in a majority of studies, to reduce normal tissue toxicities while maintaining local tumour control. Research is needed to better understand the mechanisms of action in order to be able to develop this new technology for safe and effective use in humans.

4.2.2. Theranostics

Several pharmaceuticals have been and are being developed that specifically target disease states, mostly in oncology. This has led to rapid development within nuclear medicine of the so-called “theranostic revolution”, as it is now possible to perform diagnostic imaging and therapy with the same molecular agent. As this agent is administered systemically, it enables the diagnosis and treatment of disseminated metastatic disease, in contrast to traditional RT using external beams or brachytherapy for local targeting.

- New targets are being investigated either on the tumour cell membrane itself or in the tumour stroma. Currently approved theranostic procedures are successful and lead to changing practice. Potentially, complete cures can be obtained by making these therapies more patient-specific by taking into account not only the targeting but also

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the distribution kinetics of the molecular radionuclide therapy agent, as determined by dosimetry measurements on the patients. An attractive option would also be the combination of theranostic agents with local treatments like resection or external beam RT for larger lesions.

- Especially in targeted radionuclide therapy, biokinetic and dosimetric models are needed for the radiopharmaceuticals and the respective building blocks (vector molecules and radionuclides) to be able to determine the benefit-risk balance and shape, therefore, the future of nuclear medicine-based personalised medicine for individual patients. Patient-specific therapy is enabled by the development of theranostic agents that can be used both for imaging and therapy. Personalised therapy is achieved through dosimetric assessments of organs at risk and target volumes, considering the radiobiological dose constraints. Further research is needed to identify biomarkers and radiomics features that allow further personalisation using the patient's individual radiation sensitivity. Also, biomarkers for early detection of response to radionuclide therapy are needed.
- When the mechanism of action is better known, combinations of radionuclide therapies with other systemic treatments like chemotherapy, immunotherapy, or radiation sensitisers can be designed to enhance the overall effectiveness of the treatment. Inhibition of DNA repair mechanisms can enhance the therapeutic effect, although different agents than customary used in external beam RT would be needed for this combination as the absorbed dose is delivered over a prolonged period. Combination therapies may enable the treatment of tumours that are resistant to existing therapies by attacking the tumour through different action mechanisms.
- In order to synergise local effects on larger lesions with potentially unfavourable micro-dose distribution or systemic application, combining radionuclide therapy with external beam RT will increase tumour control. Here, efforts are needed to bring nuclear medicine dosimetry in line with those in radiation oncology.
- Alpha-particle emitter therapy is particularly of interest in overcoming treatment-resistance due to, e.g., hypoxia by its high LET radiation, which can create cellular damage irrespective of the oxygen concentration. As the path-length of the alpha-particles in tissue is in the sub-mm range, interactions on the sub-organ and cellular scale must be considered. The consequential heterogeneity of the dose distribution by alpha-particle emitters needs to be studied to allow for therapies with the best possible benefit-risk balance for individual patients. The Relative Biological Effects of alpha-emitter radiopharmaceuticals must be studied at relevant clinical endpoints. Quantitative imaging procedures for alpha-emitters with low gamma-ray emissions need to be developed.
- New theranostic options can be developed based on nanoparticles currently developed for molecular imaging procedures and could also be used for therapeutic applications by using potential dose enhancements in the surrounding of such nanoparticles.

4.2.3. Interventional procedures

Interventional procedures can be used for various clinical diagnostic or treatment applications. The therapeutic applications include those for minimally invasive cancer treatment procedures using, for example, radiofrequency ablation (RFA) technology or microwave ablation (MWA) technology, but also applications for other diseases like neurovascular diseases and cardiovascular diseases.

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Interventional neuroradiology, image-based neurosurgery, and cardiovascular procedures

Over the past 20 to 30 years, the treatment of vascular diseases of the central nervous system (CNS) has undergone significant evolution, leading to exponential development in the therapeutic arsenal of neurosurgery, Interventional Neuroradiology, and Radiosurgery. These advances are attributed to the progress in R&D of equipment and materials, along with a better understanding of the pathophysiology of neurovascular diseases, resulting in remarkable clinical outcomes.

In the last 20 years, X-ray-guided endovascular interventions have brought about a paradigm shift in the treatment of intracranial vascular diseases, particularly ischemic stroke in the hyperacute phase, intracranial aneurysms, and arteriovenous malformations of the CNS, then performed in state-of-the-art bi-plane angiosuites. These techniques have progressively established themselves as the gold standard for the treatment of numerous neurovascular diseases as they are minimally invasive techniques. They have a significant impact on the often devastating natural course of ischemic and malformative vascular pathologies of the CNS [6,7]. This is also the case for cardiovascular interventions.

- Due to the delicate nature of small-diameter and fragile vessels, which require meticulous care during navigation and manipulation, especially in neurovascular therapeutic applications, and the necessity for additional information regarding factors like inflammatory aspects or tissue and blood flow characteristics, further technological and biological advancements are essential. These developments will enable even better and more individualised healthcare for patients. Technological progress may involve better detectors, faster systems, new X-ray sources, novel (molecular) imaging approaches, and new or improved catheters and materials.
- Moreover, advancements in all interventional procedures will also focus on AI, enabling lower dose applications, improved online analysis, and computer-aided decision-making for the different treatment options. Potential imaging-based AI applications primarily encompass four aspects: quantification, notification tools, diagnostics, and risk prediction for therapy [8].
- Augmented reality (AR) technology integrates digital information into the direct view of an existing physical environment. Using specially-designed headsets, medical practitioners can see virtual objects superimposed on the real environment. Data from various sources can be projected and utilised during the intervention, enhancing procedure planning by leveraging data and AI, procedure guidance using mixed reality and procedure optimisation [9].
- Robotic platforms for robotic-assisted endovascular interventions offer the potential for procedure optimisation in terms of radiation, time, and material reduction. Remote, robotic-assisted interventions are seen as a significant breakthrough for interventional neuroradiology, neuroendovascular, and cardiovascular procedures. These advancements enable patients in remote and rural areas to benefit from the same level of expertise available in large tertiary centres [10,11].
- Regulation, ethics, and consensus will be of crucial importance in the next few years to effectively harness the tremendous potential of the aforementioned research advances for the best interests of patients.
- However, one significant concern is the safety of patients with all these new possibilities, as it may often require double exposures without and with contrast media.

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Technological approaches such as multi-energy imaging or AI-based solutions may offer potential solutions in this context.

Interventional Procedures for oncological treatments

Interventional procedures for oncological treatments (image guided interventions) are becoming more prominent for tumour therapies while not being as established as cardiovascular and neurovascular interventions. The main possibilities are given for a limited number of tumour sites or only a few localised metastases limited in size.

Given these conditions, various approaches are today performed to destroy these localised tumours, all under imaging control. The methods for tumour destruction include

- radiofrequency ablation,
- microwave ablation,
- afterloading techniques,
- seed implementation, and
- localised drug delivery, among others.

For many of these methods, it remains unclear whether and when the tumour is destroyed, but also what happens in terms of inflammatory processes or regarding the potential distribution of left-over tumour cells or DNA. The clarification of whether and when the tumour is destroyed seems to be an important unsolved issue, as this might be correlated to recurrence rates or unneeded destruction of healthy tissue. Therefore, developing new X-ray or nuclear medicine-based imaging tools in combination will be an important feature for improving patient outcomes on an individual patient basis. Such developments must include new X-ray sources providing more monoenergetic or focused beams and AI-based characterisation methods.

These new approaches allowing breakthroughs in patient care will benefit strongly as all therapeutic applications from CDSS. In addition, many aspects of neurovascular and cardiovascular interventions, like better resolution and less exposure, will also improve the patients' long-term outcomes for interventionally-treated oncological patients.

4.3 Breakthrough 3 – Patient Radiation Protection - improved understanding of adverse effects and patient dosimetry

Vision

RP of patients is an essential but not the only element determining the benefit-risk balance of medical applications based on IR. The vision of this BT is to improve the understanding of dose-effect relationships in the field of realistic medical exposures to the patient population and on individual levels and to develop the tools and technologies necessary to balance the RP of patients with diagnosis quality and treatment outcome. It should be noted that knowledge on dose-effect relations acquired in other than medical contexts or various medical contexts may be very different and, as such, not necessarily relevant: other doses, other dose rates, other radiation qualities, and the fact that patients may have altered health status can impact the adverse effects.

The vision of BT3 is that a better understanding of both the adverse effects, including acute and late effects (next to the desired effects) of medical applications using IR will lead to an improved benefit-risk balance for patients: Too little dose to the patient may result in a suboptimal treatment (or suboptimal diagnosis), whereas too high doses result in more harm than necessary. Reducing the uncertainty related to the adverse effects of treatment and diagnosis is the key to improvement.

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Optimised RP relies on the following aspects:

- An improved understanding of the adverse effects separated into acute and late effects can be obtained through specific radiobiological studies in clinical settings.
- Patient-specific dosimetry tailored to selected medical applications of IR is required, and dosimetry concepts, techniques, and methodologies must be developed.

This generic BT supports the benefit-risk determination on an individual and patient population level, described in BT3 and BT5, respectively.

RP research activities should improve the understanding of the adverse effects and patient dosimetry of medical applications of ionising defined in BT1 and BT2, as well as the harmonised implementation into clinical practice in Europe. Thus, the following actions are derived.

Actions

4.3.1. Improved understanding of the adverse effects through tailored radiobiological studies

Risks related to exposure to IR depend on the doses, dose rates, types of IR, fraction of the body exposed and the type of exposed organs and tissues, each exhibiting different radiosensitivities. The adverse effects may differ for individual patients, defined as individual radiosensitivity for immediate effects on healthy tissues, such as skin erythema after external RT and individual radiosusceptibility for long-term adverse effects. Dose-effect relationships may depend on the initial health state, history and lifestyle. Research to improve the understanding of the adverse effects and patient dosimetry must be tailored to selected medical applications of IR:

- Internal partial body exposure via targeted radionuclide therapy (TRT) with different radiation qualities. The most important risks are related to exposure of the bone marrow, kidneys, and liver.
- External therapies with different dose rates, fractionation schemes or dose-volume histograms, including FLASH RT and hypofractionated radiation. Some of these therapies are applied sequentially or in combination with chemotherapy or immunotherapy.
- (Multiple) CT and PET, especially diagnostic exposures related to cardiac catheterisation in young children, are relevant, and external RT resulting in individual differences in risks.
- Thoracic RT, including paediatric and adult Hodgkin Lymphoma and breast cancer therapy, are known to cause various cardiovascular damages.
- Orbito-ocular/central nervous system/head and neck RT, including targeted RT and repeated diagnostic imaging examinations, such as (repeated) brain CT scans, may induce cognitive impairment, especially in paediatric cohorts.

Large patient datasets and biobanks should be available for radiobiology projects to forward basic knowledge on mechanisms resulting in adverse effects of IR. 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. Radiobiological research on normal tissues, the identification of biomarkers and radiomics are needed to link changes at tissue, cellular, and sub-cellular levels and to study the role of epigenetics and the bystander effect. In particular, an improved understanding of the role of specific target cells, such as stem cell/progenitor cells, and DNA damage as a function of radiation quality will advance RP insights for medical applications of IR. Radiation biology

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research should include a structured approach *via* Adverse Outcome Pathways towards well-defined endpoints to get a holistic view of the side effects of IR.

4.3.2. Patient dosimetry tailored to selected medical applications of ionising radiation and research needs for dosimetry concepts, techniques, and methodologies

Understanding or quantifying of adverse effects in the frame of medical applications of IR are based on accurate dose estimations. Along with the development of new medical applications of IR, there is a need to develop dosimetry techniques and the measurement of doses, particularly in radiosensitive organs.

For patient dosimetry in CT and interventional radiology examinations, research towards more reliable dose estimations is needed to optimise patient doses. Online dosimetric validation during treatment and harmonisation of RT dosimetry may improve the benefit-risk balance of such therapies. Personalised dosimetry will benefit from (near) real-time standardised computational solutions and software.

Within radionuclide therapy, the relationship between administered activity, absorbed dose and biological effects is not yet as well understood as within external beam RT. With the growing interest in beta- and alpha-emitting radiopharmaceuticals, there is a need for accurate preclinical and clinical (dosimetry) research at the sub-organ level that will provide fundamental data to help patient treatment planning in nuclear medicine. New precise biokinetic data of several radiopharmaceuticals (including daughter nuclides) at optimal time points must be acquired (through improved and standardised quantitative imaging and compartmental modelling) and used for dose optimisation of paediatric nuclear medicine and radionuclide therapy. This requires traceability of activity quantification for patient administrations, imaging and preclinical research. Accurate dosimetry also requires the development of appropriate and new computational models for organs of interest, including organ sub-structures.

If nanoparticles will be used for imaging technologies or dose enhancement applications in radiation therapies, it is mandatory to develop suitable microdosimetry concepts that can provide reliable results in the proximity of such nanoparticles depending on the distribution of such particles.

Research needs for dosimetry concepts, techniques, and methodologies include investigating the relationships between track structure, radiation qualities, and individual disease-dependent biological early and late effects based on improved micro- and nanodosimetric measurement and simulation techniques, requiring the development and/or evaluation of appropriate metrological approaches.

Estimation of uncertainties and validation of dose results are an important prerequisite for retrospective epidemiological studies on existing epidemiological data but also to support the development of future (molecular) epidemiological studies.

4.4. Breakthrough 4 – Patient relations (incl. dialogue and communications; data handling; ethics)

Vision

Patient/citizen perspectives should play a key role on multiple levels of the healthcare system (whole system, individual conditions, R&D). A truly patient-centred healthcare system is needed in which diagnostic and treatment procedures are evidence-based and which take patient perspectives seriously. Full account must be taken of existing inequalities in healthcare systems, including access to healthcare and available treatments. The baseline of existing

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inequity must be acknowledged to direct resources and ensure maximal impact from future R&D.

Such a patient-centred approach will start with an individual patient-specific evaluation of the benefit-risk balance of each measure for diagnosis and treatment. This needs to include a prediction of the potential benefit of a procedure but also a potential risk associated with the procedure. For many applications of IR-based medicine, the potential benefits are well described (e.g., required diagnosis, better preparation of treatment options, treatment of disease etc.). Risks associated with a procedure using IR can be addressed with much more uncertainty, and in many cases, these risks cannot be determined on an individual patient basis due to the dose range, the disease, unknown patient-specific influencing factors etc.

The patient must be the principal driving force underpinning decision-making in relation to their condition. Care must be exercised for all patients who cannot take their own decisions and where patients have limited capacity to act, or decision-making is devolved to others (e.g., very young or very aged patients). Communication difficulties are inherent for all patients, and greater efforts are required to improve this situation. This is particularly true in complex medical cases and where decisions are devolved. As a principle, patients should be involved in decisions in the healthcare pathway, from diagnosis to treatment to follow-up.

Patients and potential patients should be involved in all stages of R&D directly related to the medical application of IR and in the evaluation of outcomes. Patient perspectives are currently seen downstream from basic research and technological developments. The concept of ‘upstreaming’ public involvement is well developed in many areas of scientific R&D. Ways must be found to upstream patient/citizen involvement in medical applications R&D, at least regarding the technological developments, meaning to involve patients in relevant stages of applied science.

The conception of patients as mere receptacles of medical interventions to active agents and deciders must be shifted; citizens are not just the subjects of clinical practice but need to be active agents in deciding the future of healthcare systems. Patients and/or patient organisations should be involved in setting research agendas, research design, evaluation of funding proposals, advisory bodies, etc.

As AI/ML and digital approaches become more prevalent, attention must be directed towards the ethical challenges that arise from this shift. Issues regarding data ownership, future uses of data, changes to informed consent, and other related issues all require re-evaluation in the context of a more digitised health and medical landscape.

The priorities are to:

- allow the development of patient-specific, disease- and procedure-dependent benefit-risk assessment,
- transform the research approach to be underpinned by patient perspectives and participation,
- shift the communications landscape, including in the decision-making points, and
- create equitable, fair, and ethical approaches to data management and use.

To set these priorities in place, the corresponding actions were identified.

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Actions

4.4.1. Individual benefit-risk balance assessment

To assess the individual benefit-risk balance for a radiation-based procedure used as a medical diagnosis or treatment application, several steps need to be taken. These steps involve determining various relevant parameters, both general and patient-specific parameters.

Some of these parameters are related to general assumptions on the effects of low-dose exposure, taking into account factors like age, gender differences, dose rate dependencies, irradiation conditions, diseases, etc. However, there are still unclear aspects of the effects of low-dose exposures, even on a population basis, which are addressed within radiation biology and epidemiology research, as described in BT3. Aspects such as individual radiation susceptibility and sensitivity will play a central role as well as influences of the disease on radiation effects. Circulating biomarkers and imaging biomarkers, combined with AI, should be investigated as indicators for predicting individual radiation risk. It is essential to address the uncertainties in this assessment. Research is needed to understand influencing factors, identify and implement biomarkers or imaging markers, and finally, evaluate tools and provide training to clinicians to enable suitable risk appraisal when required, considering the uncertainties for individual patient cases.

Regarding the potential benefit for the individual patient, the assessment can and should begin with clinical evidence for groups of patients. This means that evidence-based studies are necessary for all new developments, improvements, and revolutionary changes to prove the benefits for patients. Based on this evidence, patient-specific parameters, starting from disease parameters, genetic and other conditions, all types of -omics results, imaging results, and input from CDSS, as well as quantitative imaging and radiomics, must be considered.

Defining standards and harmonising approaches to achieve an individual patient benefit-risk balance assessment within Europe is crucial. To do so, achieving a consensus on the procedures and scenarios for which individual benefit-risk balance assessment have to be performed and determining which parameters need to be included in each scenario are of utmost importance.

4.4.2. Transform the research approach to be underpinned by patient perspectives and participation

Currently, research agendas relating to medical applications are predominantly set by academia, industry, and medical professionals rather than patients. These research agendas are often not needs-driven but more opportunistic and based on prior developments. Introducing patients into the early stages of agenda setting and research priority setting would be a new approach to the future of healthcare developments. Involvement in reviewing research and clinical trial proposals can improve design and future patient involvement. This, in turn, can improve funding outcomes by focusing on the best-designed research from a patient perspective.

Patients should not merely be seen as subjects of medical intervention but should be regarded as active participants. As such, they should be included on steering committees of research projects, clinical trials, and other relevant initiatives, providing them with a voice in the direction and progress of the work. By involving patients (and other stakeholders), the focus on ultimate patient benefits can be maintained throughout the R&D process, ensuring that the endpoints remain patient-centred.

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For the ultimate benefit of patients, all outcomes of medical research, including trials and negative results, should be considered valuable and need to be reported. This practice is essential to prevent future disappointments in costly research endeavours or dead ends.

There is a need to explore ways to maximise patient involvement in new transdisciplinary formations and to comprehend the benefits and limitations of resulting research programs.

One of the primary objectives is to prioritise the sharing of best practices in patient involvement across Europe. Identifying these best practices and understanding the mechanisms for sharing and dissemination is crucial. For instance, in Belgium, patient involvement in reviewing first-in-human clinical trial protocols is already established.

When conducting research into population-based screening using IR, it is essential to consider the specific preferences of civilians who are not yet patients. These preferences may not be uniform across Europe.

If possible, widespread equipment that meets the technical requirements should be selected wherever possible to ensure accessibility and availability across Europe.

4.4.3. Shifting the communications landscape

Dialogue between healthcare professionals and patients and the corresponding communication, presents an ongoing challenge, and a significant shift is necessary to achieve the proposed improvements outlined elsewhere in this roadmap, as seen in Chapter 2 and BTs 1, 2, and 3. Patients express a vital concern regarding the quality of communication, including written communication, often finding it lacking in true dialogue (with one-way communication from clinician to patient being the norm). Additionally, patients frequently experience a lack of checking for understanding and a sense of not being genuinely heard. The introduction of diagnostic health pathways, while aimed at streamlining processes, has, for many, resulted in a conveyor belt approach and fewer opportunities for meaningful communication between clinicians and patients. It is crucial not to underestimate the value of taking time to inform, discuss, and make decisions, even in the face of technological advancements pushing for efficiency, speed, and automation.

As communication is central to all interactions and positive patient outcomes, direct patient involvement in the communication training of professionals (e.g., radiographers, radiologists, and nuclear medicine specialists) must be implemented.

Benefit-risk balance-based decision-making for individual patients will be improved if good communication and discussion with patients are integrated into the final treatment choice. It must be acknowledged that in numerous instances, the patient may be parents (e.g., paediatric patients) or other representatives (e.g., next of kin for patients without mental capacity). The following presents a potential process for effective communication and decision-making in an individual encounter and can act as a model.

- Identify the potential benefits and risks of RT or imaging for the patient; this includes understanding the patient's medical history, current condition, and the goals of treatment or imaging procedure.
- Determine the importance of each benefit and risk to the patient. Some benefits and risks may be more important to the patient than others. For example, a patient with a terminal illness may prioritise symptom relief over potential long-term side effects. In diagnostic procedures, the patient may prioritise the accuracy of diagnosing a suspected serious condition over radiation exposure.
- Explain to patients that statistics of risk and benefit are based on a group of patients and that this translates into "odds" for an individual patient.

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- The patient should be provided with clear information about the benefits and risks of RT or diagnostic procedure. The patient should be given the opportunity to ask questions and express their preferences before making a joint decision.

It follows from the above that research is urgently needed into effective ways of communicating risk, including presenting risk and benefit values in ways understandable to patients and translating statistical risk into individual odds. Training needs for the professionals include comprehension of the extent to which patients respond to dialogue and make informed decisions.

4.4.4. Create equitable, fair and ethical approaches in R&D and data management and uses

Public debates around innovative technological developments need to be conducted carefully. Before bringing innovative applications to market, research on societal perspectives is required. The absence of such considerations risks a lack of public acceptance. Ideally, responsible research and innovation processes will be deployed, whereby societal research is conducted concurrently alongside future technological advances.

It needs to be accepted that there are limits to the involvement of patients under certain circumstances (e.g., best practice suggests potential advances are not solely consulted with patients who will directly benefit). The example of gene editing for inborn errors and discussing the possibility (in the future) with parents (to be) of children with these conditions is a current case.

Research into potential treatments that cannot be delivered equitably or to the intended population should not be prioritised, or, as a minimum, not before the availability of future treatments has been ensured, e.g., in the case of actinium for treatment. If insufficient attention is paid to this matter, this will further entrench existing inequalities.

Currently, patients are viewed as the 'endpoint' of technical developments in AI and digital-based approaches to healthcare. In AI-enhanced and enabled medical approaches, a new set of ethical challenges arise, requiring patient/citizen input at the earliest stages of development. New methods of including stakeholder perspectives in AI/ML development and implementation must be forged. In clinical settings, all participants must be cognisant of the origins and limitations of the data and algorithms underpinning clinical information and therefore informing decision-making.

Informed consent issues are numerous and need investigation and reform. Consent is rarely comprehensive. AI and ML use huge amounts of patient data; even if anonymised, these data can be traced back to an individual patient. It should be standard practice to ask patients permission to use their data for research. Appropriate levels of consent to enable supervision of future uses is key, and the importance of regulation that protects patients need to be recognised.

4.5. Breakthrough 5 – Strategic positioning of applications of ionising radiation in medicine

Vision

Within all medical capabilities, the applications of IR should provide and develop its therapeutic and diagnostic capabilities in an optimal way so that (1) its unique possibilities and qualities are maximised, and risks are minimised, taking into account (2) patients' benefits and (3) optimal use of healthcare resources. Many diagnostic techniques based on IR do not have alternatives nowadays, as shown by the growing use of computed tomography and nuclear medical imaging. A growing understanding of the mechanisms underlying diseases enables the medical profession to develop new methods of prevention, diagnosis, prognosis, and

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treatment. Therefore, new applications are rapidly evolving, and it is necessary to keep track of developments, test medical applications and exploit new opportunities.

It should be noted that the benefit-risk balance is not the only criterion that will determine the market position of radiation-based medical techniques. In addition, cost-benefit acceptance criteria across European countries, as well as the sustainability and accessibility including societal acceptance (e.g., increased exposure of patients, running of nuclear reactors, societal acceptance of AI-based technologies), protection of the environment and the feasibility in terms of technologies and human resources such as skilled personnel and lifelong learning will also play a major role. These aspects are described in priorities of other BTs 3, 4, 6, 7, and 8. A holistic view should be developed to keep the optimal position of IR applications in medicine.

Therefore, the following priorities within this BT are proposed:

- Comparison of benefit-risk balances of radiation-based and other medical diagnosis or treatment options
- Evaluating potential synergies between radiation-based and other techniques
- Investigating economic aspects and securing funding of R&D

These priorities need to be followed by implementing the following actions.

Actions

4.5.1. Comparison of benefit-risk of radiation-based and other medicine

High-level screening of developments inside and outside the field of medical applications of IR

Benefit-risk balances of radiation-based therapies should be compared with other medical therapies and diagnostics. This requires keeping pace with the continuous improvement of mechanistic and epidemiological understanding of disease development and cure and being aware of technological developments that may impact the development of new or improved diagnostic techniques. These ongoing research activities are useful for determining the current and future position of medical applications of IR. Moreover, this accumulated knowledge will reveal new opportunities for new developments at an early stage, not only in stand-alone developments but also towards synergies between radiation-based and other techniques.

Benefit-risk balances of selected existing and emerging diagnosis and treatment applications

To compare benefit-risk balances of radiation-based medicine and other medical therapies and diagnostic procedures is a complex issue. It requires knowledge of existing and emerging therapies and diagnostic procedures and the corresponding benefits and risks.

Even in radiation-based medical applications, the risks are often not well known and are an essential subject of ongoing studies. The dose-effect relationships on healthy tissues other than medical exposures to IR have been studied for decades and demonstrate that differences in types of radiation, dose rates, tissues and the primary health status of humans may alter the effect of exposures. Irradiating for diagnostic or therapeutic purposes, a diseased area might show additional influences and effects which are difficult to study. In addition, the trade-off between benefit and risk differs for diseased persons.

Radiobiology and dosimetry are essential disciplines to assess and improve accuracies of benefit-risk balances. Even within radiation-based medicine, the adverse effects of external, mainly photon beam irradiation, cannot be extrapolated to other types of radiation like electrons or heavy ions, different application schemes like directional irradiation of body parts or therapy applications like, e.g., FLASH or even internal exposure. For example, EANM has provided guidelines to advance radiobiology in nuclear medicine [12], requiring a selection and

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standardisation of radiobiological techniques and minimal dosimetric requirements as prerequisites to tumour and normal tissue radiobiology. To improve (pre)clinical studies in the field of nuclear medicine, there is a need to validate a list of selected radiobiological and dosimetric techniques and develop standard procedures. This also holds for many new diagnostic and therapeutic schemes.

A literature survey on benefit-risk balances for other than radiation-based medical diagnoses and therapies is needed. For non-ionising radiation-based medicine, there is often easier access to the benefits of such procedures on average for patients suffering from certain diseases in certain disease statuses as there are a lot of clinical and follow-up studies for interventions like surgical procedures or minimally invasive studies or pre-market phase II and III validation studies for new medical drugs. Assuming the new personalised drug therapies, this is, on the other hand, getting more and more complex again as the use of targeted, individualised drugs can hardly be tested easily on their benefits in sufficiently large cohorts as many patient-specific aspects will influence the outcome of a therapy. To describe risks of such individualised therapies is more standardised as basic toxicity considerations followed by animal toxicity studies, and then phase I and II medical studies are done according to standard protocols for drug validation and certification. For interventional and surgical procedures, for example, liquid biopsy investigations, blood testing etc., complication rates are documented in the literature.

However, in some cases, these studies are confined to specific complications, and obtaining overall estimates of risks and benefits remains challenging for radiation-based approaches as well as other interventions. To make these studies comparable, it is essential to incorporate the same criteria for both types of procedures. Additionally, the psychological factors for the patients must be taken into account, although finding effective ways to do so remains an unresolved issue to this day. Lastly, it is crucial to acknowledge that economic risk factors also need to be included as risks since they may have diverse impacts on health systems and societies once materialised.

4.5.2. Synergies between radiation-based and other techniques

RT only does not always result in the expected effect, at least not only. Irradiation may trigger immunogenic cell death (ICD) that promotes the release of tumour-associated antigens (TAAs), changes the tumour microenvironment (TME) and activates the immune system to exert an anti-tumour immune response. On the other hand, radiation may also induce the release of myeloid-derived suppressor cells (MDSCs), M2-like tumour-associated macrophages (M2-like TAMs), T regulatory cells (T_{reg}s), N2 neutrophils, and immunosuppressive cytokines (TGF-beta, IL-10) to promote immunosuppressive microenvironment. Immunotherapy has been gradually affirmed as the most likely direction to cure cancer in tumour therapy by the medical community. Thus, some approaches are already ongoing to couple radiation-based therapies with other types of therapies. For a long time now, RT has been an accompanying therapy with surgery, but in recent times, combinations with immunotherapy are also used. In this sense, it is mandatory to differentiate between combined therapies intending to optimise the therapeutic effect of improving tumour control and such intending to use the combination to reduce side effects. This reduction of side effects can also be relevant for diagnostic use of IR.

In both types of combined procedures, comprehending the cross-correlation of the therapeutic (or partly diagnostic) approaches becomes exceedingly important. To achieve this, a thorough understanding of the immunological basis and its time-dependent influencing factors is necessary. This requires dedicated immunological biomedical research and corresponding modelling approaches. Moreover, the inclusion of individual radiation sensitivity or

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susceptibility, as well as individual sensitivity to other types of therapies, will be imperative in such investigations.

Combined therapies for improved tumour control:
After evaluating potential mechanisms for positive supporting effects for tumour control, like potential influence on the tumour microenvironment, studies that describe the exact mechanisms and their dose/exposure dependence are needed. This will include basic *in vitro* and *in vivo* biological studies, modelling approaches and finally, hopefully, human-based studies allowing a better therapy in terms of tumour control with limited side effects. This certainly needs to be investigated and optimised depending on diseases like different types of cancer.

Combining therapies with IR therapeutic or diagnostic applications for protection against side effects of IR:
As potential side effects depend on individual radiation sensitivity and susceptibility, and the specific biological aspects influencing these factors remain largely unclear, it is most relevant for the optimal diagnostic and therapeutic use of IR with minimal detrimental side effects to understand the underlying biological effects and their influencing factors on an individual patient level. Such understanding should pave the way for developing approaches to optimise procedures and discover protective medicines that can target effects that are generally applicable or specific to individuals, thus enhancing the overall safety and efficacy of IR utilisation.

For both approaches, it should be emphasised that the final approaches must be fostered by studies that follow the rules of evidence-based medicine.

4.5.3. Investigating economic aspects and securing funding of R&D

When combining two different types of therapies, the initial assumption might be that this would increase the economic burden. However, this aspect requires a more detailed investigation. It is possible that the costs of therapy could be reduced, as the combined effects may lead to better tumour control, allowing for the achievement of tumour control with a lower-than-standard number of drugs and/or a lower radiation dose than typically prescribed. Moreover, if it becomes feasible to limit side effects or secondary cancers, the follow-up costs will be reduced. Such developments would not only impact the costs for healthcare systems within Europe but also have economic implications, such as better reintegration of patients into society and the workforce by improving patients' quality of life, and reduction of associated costs. Further research and analysis are needed to fully assess the potential economic impacts of these combined therapeutic approaches.

Similar approaches have to be dealt with and elaborated in general for all types of applications of IR in medicine, independent of whether it is new or existing approaches. For all these evaluations, it needs to be assured that all the methods must be validated using evidence-based medicine methods.

These potential different effects, which should be considered when elaborating on the potential new and existing methods of medical applications of IR, should be a relevant aspect to determine the required funding of R&D for the development and evaluation of such methods. Both evaluations and the securing of the funding are most relevant for the strategic positioning of medical applications of IR.

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4.6. Breakthrough 6 - Implementation, sustainability, accessibility, and organisation of ionising radiation-based medicine

Vision

The vision is to implement sustainable, innovative patient-centred healthcare in hospitals throughout Europe and the underlying research within the European Union (EU). This needs to be fostered by implementing an ecosystem of European infrastructures working with a common strategy based on the current landscape of infrastructures [13,14], to encourage and ensure sustainable implementation of IR-based medicine focusing on patient benefit, at the European level. This ecosystem needs to be set up to enable and foster clinically-driven research for personalised radiation-based medicine and allow universities and university hospitals to elaborate on methods for improved disease knowledge and patient care.

The goal is to achieve an efficient and sustainable ecosystem among the existing research infrastructures: Centre(s) of Excellence (CoE(s)) dedicated to research, CoE(s) dedicated to education, and CoE(s) dedicated to care. All CoEs should link with each other and the university hospitals to support each other and identify the gaps.

For certain topics, centres need to provide both excellent diagnosis and therapy. Missing expertise has to be built up. Good research must be implemented in a way that the research is linked to the clinical needs.

The final objective is to coordinate and push actions to facilitate transfers of various innovations from basic research to bench-to-bedside care as efficiently as possible.

To achieve the objectives, actions regarding the following aspects should be performed:

- Translation and organisation
- Research for sustainable supply, including radionuclides
- Access to data, biobanks and equipment for research and patient care
- Harmonisation of data and protocols

Actions

The ordering of the actions can be considered a top-down approach:

4.6.1. Translation and organisation

This subtopic is focused on how to translate the clinically-driven research as well as the basic research on disease biology and technology developments into clinical practice, including the steps of transfer of the results into industrial products, translation into clinical practice, harmonisation of practices, and E&T of medical staff. These aspects must be well organised and coordinated to facilitate the clinical implementation to achieve the final goal of efficient translation into care and, thus, patient benefit. Networks and CoE structures can help to organise such translation more effectively.

The patient care aspect of the implementation must also address five main challenges as described:

- The first challenge is providing high technology and costly treatments so that patients throughout Europe can reach such centres in terms of geographic distance. Thus, enough centres for clinical care need to be established.
- The challenge of equal opportunity for all patients must be addressed. This requires support for low-income regions to provide the same level of healthcare everywhere throughout Europe.
- Facing timing factors of highly specialised diagnosis and treatments, especially considering the first two challenges, is the third challenge. Telemedicine and support

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systems need to be implemented. Incentives for healthcare providers and staff might be necessary.

- The costs for research need to be covered, including costs for effective translation to reduce costs for patient care on the long-term perspective, including a suitable reimbursement or financing strategy for costs of patient care. Doubling facilities or investments for research needs to be balanced and avoided where feasible.
- The fifth challenge is to foster cooperative research and implementation strategies based on a common European strategy instead of competition.

4.6.2. Research for sustainable supply and accessibility, including radionuclides

This action refers to guaranteeing a sustainable medical technology supply, especially of newly developed technology and/or radionuclides. This requires research on how such sustainable supply can be achieved, which will include the search for new cheaper, and easier-to-handle ways to produce technology or radionuclides [15–17], ways to guarantee reimbursement or financing and broad distribution. Implementing such methods is mandatory for the efficient use of newly developed technologies, especially individualised therapy approaches with a dedicated focus on nuclear medicine applications. However, similar aspects will also need to be considered for new therapeutic or diagnostic technologies or, for example, new contrast media, e.g., based on nanoparticles.

4.6.3. Access to data, biobanks, and equipment for research and patient care

Access to data, biobanks, corresponding imaging information, equipment, and corresponding research infrastructures is a central aspect of clinically driven research resulting in basic and applied research which can be implemented in clinical practice. Therefore, sufficient infrastructures and/or a CoE structure are required, which will provide access to and support the management of research material like patient data, bio-samples, and research equipment. Extracted data from research can also be used in medical applications, e.g., validation of diagnosis and treatment, providing recommendations/guidelines for optimising future data collection, storage, and management.

4.6.4. Harmonisation of data and protocols

The harmonisation of data requires the development of guidelines providing recommendations for data collection for each disease, e.g., which types of data have to be collected for which purpose, documenting the parameters of diagnostic procedures and treatment, immediate and long-term responses, and monitoring the outcome and further follow-up. These data collections will be the basis for validating the efficiency of treatments for a better understanding of the mechanisms of a disease and optimal ways of diagnosis.

The harmonisation of protocols is oriented to clinical application and is focused on facilitating the implementation and harmonisation of protocols in hospitals in Europe to ensure best practices are adopted as broadly as possible. This will help to maximise the chances for each individual patient to receive better healthcare. Nevertheless, fostering innovation beyond the standard protocols is also important.

Certainly, all the subtopics mentioned above need to be implemented, which will require certain resources in terms of workforce and funding, as it will be addressed in Chapter 5.1. In addition, for this BT, it is necessary to transfer local strategies to national strategies and then to a European strategy.

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4.7. Breakthrough 7 - Quality, safety, and legislation for medical application of ionising radiation in Europe

Vision

The SAMIRA action plan calls to ensure the best possible protection while fully benefiting from all advantages of the applications of IR in medicine [2]. This rightful demand poses a challenge to Q&S programmes and the supporting regulation based on corresponding research. The programmes must be flexible enough to allow innovative improvements to enter the market without delay. However, they also have to be strict enough to recognise apparent innovations that do not represent significant advantages or even could cause harm (for example, by complicating or hindering diagnosis or therapy or by introducing misleading information etc.). Research must allow and foster the fast and reliable recognition of such potential improvements, but also disadvantages.

Quality, safety, and legislation must work under the principle that preventing incidents is much more desirable than dealing with their consequences. Therefore, a conservative approach for the sake of safety is unavoidable. This approach has been established in Europe in the past decades with fairly good results, but there are still big inequalities within and between countries, as is also stressed in the SAMIRA action plan. This needs to be reduced in the future by implementing this roadmap. The actions described below include:

- Quality determination,
- Q&S for diagnosis and therapy,
- Clinical Q&S audits,
- Improve the safety culture,
- Harmonisation of EU legislation for medical care, RP, medical devices, manufacturing and marketing authorisation.

These actions are meant to foster innovation while improving the current degree of safety.

Actions

4.7.1 Quality determination

Current quality tests in medical applications of IR are generally based on a two-level scale: either the tested system is OK (“acceptable”), or it is not. These tests are easy to apply and interpret, but they do not favour optimisation because they cannot evaluate the advantages of alternatives that are “acceptable”. Quality determination has to be based on objective parameters that provide well-defined scores so that optimised approaches can clearly show their advantages.

This goal requires developing key performance indicators (such as patient exposure, patient time for diagnosis and treatment(s) or patient pathway, image quality parameters in imaging where feasible for the patient images or dose volume histograms in therapy or outcome measures), or applying existing research results like therapy operating curves (TOC) [18].

It is imperative to enhance the cooperation between regulation and basic research to develop appropriate measures. For instance, in the case of the first generation of iterative reconstruction algorithms in CT, it was discovered a few years after introduction to the market, that many of such algorithms were merely a fad and provided no significant benefits compared to the originally used reconstruction algorithm-filtered back-projection. This result was made possible by the application of modern methods utilising mathematical algorithms called “model observers”. However, due to powerful marketing from certain vendors and limited technical tools available to the authorities, healthcare systems invested substantial resources in software that ultimately offered minimal improvement. To prevent such situations in the future, it is essential to employ modern quality assurance methodologies, especially as new

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technologies like ML algorithms are already emerging in the market. Despite some of these products have received approval from regulatory bodies like the US Food and Drug Administration and/or obtaining a CE mark, the validity of their databases has not been confirmed, and there is no established methodology to pursue such confirmation yet. Strengthening the cooperation between regulatory bodies and basic research will be crucial in ensuring that new technologies are thoroughly evaluated, and their benefits are accurately assessed before significant investments are made in their implementation.

With the help of the European Health Data Space and the e-Health Digital Service Infrastructure (eHDSI), which is implemented by the European Commission and EU member states through the Connecting Europe Facility (CEF) Programme, it must be possible to create a vast database of patient and phantom images for research purposes. Such a database is necessary for training and/or validating of AI-algorithms. Instead of creating a new infrastructure with hundreds of servers, efforts could be directed to achieve efficient communication among all picture archiving and communication systems (PACS) in the EU. The images can be labelled locally following the guidelines of a European ad-hoc group, and only labelled images would be part of the EU database so that hospitals (or their patients) can still decide which images they share.

Another crucial aspect is the implementation of AI-powered automation to optimise image acquisition protocols, aiming to achieve the necessary information for diagnosis, interventional procedures, therapy planning, staging, and control with the least possible exposure. This optimisation can potentially be coupled with an optimised application of therapeutic procedures. Consequently, the quality of IR applications could potentially be improved significantly. However, it is essential to verify these advancements on an individual patient basis, necessitating the automated use of quality metrics once again. AI can potentially be used to allow an automated system to determine how and where to assess the quality parameters. For example, in imaging, AI can help segmenting specific areas in patient images to be evaluated, or in therapy, it can e.g. track tumour responses. It could be feasible to adapt the therapeutic approach to the disease progression on an individual patient basis enhancing the overall quality of such therapeutic procedures.

4.7.2 Q&S for diagnosis and therapy

Up to now, dosimetry has been based on indirect measurements and simulations, not the actual energy deposition in patient tissues. Basic research with dosimetry methods could allow, in the long run, real-time dosimetry during treatment, using, for example, appropriate biomarkers that indicate the actual energy deposition in the tissues or describe the precision of the simulation tools correctly. The exposure information and insight into the individual sensitivity and susceptibility of the patient must play a role in CDSS. This information is especially valuable for the personal file of patients and future data management and needs to be implemented in the Q&S system.

Uncertainty in dosimetry of both diagnostic and therapeutic applications reveals significant room for improvement. The so-called "characteristic functionals," used to describe objects such as imaged organs or tumours in diagnostic and therapeutic applications [19,20], can aid in the analysis and reduction of these uncertainties in the long run. By combining better individualised patient models with AI applications, the uncertainty of dose distributions in organs, particularly in organs at risk, can be reduced. This might become particularly important for new therapeutic techniques such as hadron therapy, neutron therapy, or FLASH therapy, along with their corresponding quality assurance programs and regulations.

In the particular case of diagnosis, the main purpose is achieving a proper image, whereas the corresponding dose to the patient is only a “side-effect”, or a means to achieve the proper image Therefore, dosimetry constitutes only one part of the process aimed at ensuring Q&S.

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Essential concepts such as diagnostic reference levels should be expanded to encompass evaluations of image quality, including factors like detectability or noise, and not solely rely on exposure parameters' values (e.g., dose-length product or "CTDIvol" in the case of CT).

4.7.3 Clinical quality and safety audits

Technical methods involving phantoms for quality control must give way to more clinically relevant approaches, such as utilising actual patient images to assess the quality of the examinations. The availability of an algorithm for automatically scoring patient investigations or therapies would provide a valuable tool for retrospective evaluation and optimisation in both therapeutic and diagnostic applications. This kind of patient-centric approach is also in line with SAMIRA.

Audits conducted by internal or external colleagues and inspections carried out by regulatory agencies should be established, partially through algorithms, to regularly assess the quality parameters of a certain facility. Examples for such quality parameters can be e.g., dose and image quality in diagnostic examinations. However, another crucial aspect of inspections should involve direct involvement from colleagues who can demonstrate good practice, provide feedback based on their own experiences, and comprehend innovative solutions from their peers [21]. While the broad implementation of clinical audits is currently constrained by human resources, it is essential to encourage the development of remote audit methods in the future, even though further research is still necessary.

Quality control for nuclear medicine must encompass additional aspects, such as evaluating the production process of radionuclides and radiopharmaceuticals, ensuring continuous monitoring of activity levels in the radiopharmaceuticals used, implementing RP measures throughout production, application, and waste disposal, determining injected amounts of radiopharmaceuticals for the individual patients, and addressing potential contamination on floors and sanitary objects etc. These considerations become particularly critical with the introduction of new radiopharmaceuticals, especially in the context of personalised nuclear medicine diagnostics and treatments or even theranostics.

4.7.4 Improve the safety culture

In order to enhance the benefit-risk balance for patients, as well as ensure the safety of workers and the public, it is crucial to establish and improve an understanding for the safety issues associated with medical applications of IR. This involves comprehensive documentation of safety-related matters, including incidents and events. Moreover, providing the best healthcare for patients necessitates a strong emphasis on their safety, which in turn, benefits not only the patients but also the workers and the general public. It is essential to acknowledge that achieving a high level of safety in the medical use of IR requires significant effort and is non-negotiable. Safety-related considerations must be thoroughly addressed for all diagnostic or therapeutic procedures, both before and during their execution. A safety culture should be implemented or enhanced where it already exists.

The International Atomic Energy Agency's initiative on safety and security culture beautifully describes hints to improve safety culture, but these are not specifically tailored to medical applications of IR. For this context, the RP culture has also been described by SHARE [22]. Raising awareness for and understanding such a safety culture and fostering the implementation of it are urgent action points that will significantly enhance patient care and optimise the healthcare use of IR.

4.7.5 Harmonisation of EU legislation for medical care using ionising radiation, including radiation protection, medical devices, and radiopharmaceuticals

Strengthening the links between researchers, clinicians, and regulators, and fostering the exchange of experiences among EU countries, are essential prerequisites for harmonising EU

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legislation. This is particularly relevant for establishing improved connections between regional, national, and European regulators. Presently, manufacturers may argue against certain quality assurance measures, citing the challenge of implementing different methods in each country when a regulatory agency introduces additional tests, like type testing for marketing authorisation of CT devices.

Given that the interests of EU countries align, successful methods employed in one country should be readily communicated and applied in others. Cooperation between regulatory bodies is crucial at both the European and national or regional levels. Another approach related to legislation to enhancing the transfer and translation of innovations involves extending the system of adopting legislation methods from European countries, as well as from the United States and Canada.

Harmonising exposure data formats is another area where legislation can significantly contribute to patient safety. All dose management systems installed in Europe must be required to provide standardised output with basic (and potentially pseudonymised) data. This would facilitate the establishment of alert levels, search for patterns, incident prevention, and continuous updates of European dose reference levels [21]. To achieve this, the eHDSI should incorporate a dedicated section for anonymised data, thus addressing all data protection issues and enabling the collection of necessary data for setting European reference levels. Ideally, this data should include exposure parameters, but also other quality parameters, such as image quality, assessed with objective tools.

4.8. Breakthrough 8 - Career attractiveness and radiation protection for workers

Vision

The various applications of IR in medicine as well as medical RP are essential components of modern healthcare. This field encompasses a range of professions, including radiologists, radiographers, medical physicists, nuclear medicine professionals, and radiation oncologists. Despite the importance of these roles, attracting university students to pursue a career in medical application of IR or RP can be a challenge. In the same way, it can be challenging to keep the educated and trained young professionals in the field.

Lifelong learning (LLL) is essential to ensure continued improvements in medical applications of IR and the corresponding RP and to engage and motivate health professionals in this scientific field by developing a multidisciplinary and collaborative approach towards implementing better radiation-based healthcare and an RP culture. Considering that these activities aim to improve patient outcomes and the safety of patients and staff, they will act as a trigger to make these professions more attractive, which might even include incentives in case a lack of educated staff persists.

There is a crucial need to improve the knowledge of radiation-based medicine and RP through valuable, well-funded, and structured research [23]. To achieve this objective, it is of utmost importance to develop dedicated E&T programs for researchers, especially those outside the clinical departments, including those involved in preclinical research, who utilise medical imaging procedures in their studies but may not be fully aware of the significance and necessity of E&T in RP.

The following priorities within this BT are proposed:

- Increasing the attractiveness of a career in medical applications of IR
- Increase awareness of radiation-based medicine and medical RP
- Highlight the diverse range of career paths
- Emphasise the rewarding aspects of a career in the field

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- Provide opportunities for students to gain practical experience in the field
- Improve RP for workers

To achieve these priorities, the following actions must be performed:

Actions

4.8.1. Career attractiveness in medical applications of ionising radiation and corresponding radiation protection

As a first measure, it is important to increase awareness for the field of radiation-based medicine and medical RP:

- Among university students: This can be achieved through education and outreach efforts. Higher education institutions are autonomous and develop new courses in response to a perceived need, considering various parameters, including maintenance of the range of expertise essential in everyday clinical practice and research and staff expertise. Universities need to offer courses that provide an introduction to radiation and its uses in healthcare, as well as the importance of RP. Relevant information must also be incorporated into existing courses like e.g. health sciences, physics, or engineering. Outreach programs must be organised to educate students and researchers about the field and the available career opportunities.
- Amongst health professionals: This can be achieved through dedicated LLL programs to develop knowledge, skills, and competencies in the field of medical use of IR and RP to improve patients' outcomes and patients' and staff's occupational safety through a holistic, multidisciplinary, and collaborative approach. Specific time and budget must be allocated to guarantee the establishment of these actions.

The diverse range of career paths available in the various applications of IR in medicine and medical RP must be highlighted as a second measure. Many students may not be aware of the range of professions that exist within this field. By showcasing the various roles and career paths available, universities can help students understand the breadth of opportunities available. This needs to include showcasing the roles of professionals involved in medical RP and applications of IR in medicine. Universities can also connect students with professionals in the field through mentorship programs, internships, and job shadowing opportunities.

The third important measure is to emphasise the rewarding aspects of a career in radiology, nuclear medicine, RT, medical physics, and medical RP. Students interested in this field will likely be motivated to help people and make a difference in their communities. By highlighting these professionals' positive impact on patient care and outcomes, universities can appeal to students' desire to make a difference. They can also emphasise the important role that professionals working with IR play in ensuring patient safety, which can be an appealing aspect of the profession for students interested in health and safety. In addition, radiation-based medicine and the corresponding RP often benefits from new technological developments so that careers can include a continuous possibility to work with new fascinating technological approaches to better help patients.

Finally, providing opportunities for students to gain practical experience in the field is important. This should include internships, research opportunities, or job shadowing. By providing students with the opportunity to see the real-world application of IR and medical RP, they can better understand the field's importance and the impact they can have as professionals. This can also help students to develop important skills, such as problem-solving, critical thinking, and communication, which are essential for success in this field [24].

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4.8.2. Radiation protection for workers

Medical applications of IR rely on a dedicated team of professionals, including medical doctors, radiographers, nurses, caring staff, radiochemists, and medical physicists, among others. Many of these roles involve direct patient care during exposure, such as caring duties in the nuclear medicine departments, holding tasks during X-ray investigations, observing or performing tasks related to the interventional procedures. Consequently, staff members working in the medical context are inevitably exposed to IR as part of their duties. Given the importance of these roles, the attractiveness of corresponding jobs is paramount. This includes to guarantee the well-being of the staff, ensuring the best possible health conditions. Therefore, it is imperative to include RP for workers and the corresponding measures and foster research to enhance safety by improving RP of the medical staff. Nowadays, there is an increasing availability of online tools for assessing staff exposure. These systems should be developed to be highly accurate in all relevant scenarios. Moreover, such tools should be utilised for training purposes to educate staff on how to reduce radiation exposure, such as adopting better positions in interventional suites and minimising exposure times. Additionally, when introducing new or improved technologies into the clinical routine, feasibility studies must incorporate considerations for workers' RP.

Overall, a proactive approach to RP is essential for safeguarding the health of medical professionals and maintaining the quality of patient care in the field of IR to guarantee the attractiveness of careers in the field of medical applications of IR.

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5. Analysis of proposed breakthroughs

The feasibility and affordability of the BTs must be analysed, along with the potential timelines for their implementation. This analysis is performed in the following subchapters.

For each BT, a comprehensive assessment is conducted, outlining the budgetary requirements and potential timeline. It explicitly mentions the different stages involved, such as technical development, preclinical and clinical studies, and eventual implementation. Additionally, the funding options for these activities are explored, including identifying the stakeholders who need to be involved in various funding aspects.

5.1 Analysis of proposed breakthroughs in terms of budget and resources needed

The first two BTs are directly related to enhancing patient-specific healthcare. Patient-centred approaches hold the largest promise for improving patients' lives and contributing positively to European societies, and are ideally suited to radiation medicine for diagnosis and treatment. These approaches also present significant potential for new advancements and optimisation, thus establishing a foundation for European leadership in combating especially cancer but also neurovascular, cardiovascular and rare diseases, and other medical conditions. While these BTs are the major drivers of improved patient-centred healthcare they are for sure also those which would require the largest budgets to achieve the goals in a meaningful manner. This is mainly given by the fact that research for implementation of improved diagnosis and or improved therapy will need to address various steps:

- Basic research on clinical questions and biology
- Basic research on new technological approaches
- Research on possibilities for patient-centred implementation
- Research on ethical implications
- Technological transfer
- Clinical studies to prove evidence for the advantages of the proposed new or optimised methods

The funding required for each of these individual aspects will vary depending on the extent of divergence from existing methods, the technological necessities involved, and the size of the necessary clinical studies. Estimating the required budgets for particular diseases or specific methods can be approached as follows:

- A: Basic research on clinical questions and biology (0.5 to 10 million euro)
- B: Basic research on new technological approaches (1 to 50 million euro might apply, e.g., to new hadron therapy sources)
- C: Research on possibilities for patient-centred implementation (1 to 5 million euro)
- D: Research on ethical implications (0.5 to 3 million euro)
- E: Technological transfer (0.5 to 20 million euro)
- F: Clinical studies to prove evidence for the advantages of the proposed new or optimised methods (2 to 10 million euro)

Given that these BTs hold the potential for significant advancements in patient-tailored healthcare, securing sufficient funding is paramount to foster and strengthen European healthcare leadership. Considering the obviously high requirements on funding resources, it is essential to devise a comprehensive plan for which Directorate-General (DG) (e.g. DG ENER, DG SANTE, DG CONNECT, DG RTD) the BTs are of interest and relevance, and which related funding streams would be appropriate means for funding related projects. Incorporating a European funding component is crucial to ensure widespread acceptance of the research and the integration of these methods into clinical practice across Europe. Such a European

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component of funding is also necessary to allow all potential innovations to be evaluated and followed upon across Europe independent of regional or national funding options. It can be suggested to explore co-funding schemes (e.g. European-national or public-private partnerships) and that European funding should be used at a first stage to concentrate on some major possible developments or potential role model funding. In the initial stages, European funding efforts could concentrate on some major possible developments, for instance:

BT1 example: AI-based image evaluation, e.g., staging and classification of therapy of lymphoma (A: 3 million euro /B: 2 million euro /C: 2 million euro /D: 2 million euro /E: 1 million euro /F: 4 million euro - total 14 million euro),

BT1 example: molecular imaging for a certain type of cancer, e.g., breast cancer with X-ray fluorescence imaging (A: 2 million euro /B: 5 million euro /C: 2 million euro /D: 2 million euro /E: 4 million euro /F: 5 million euro - total 20 million euro),

BT2 example: theranostics for a certain cancer type like prostate cancer (A: 1 million euro /B: 2 million euro /C: 3 million euro /D: 2 million euro /E: 5 million euro /F: 5 million euro - total 18 million euro) or,

BT2 example: proton therapy for children, e.g., on brain tumours (A: 1 million euro /B: 8 million euro /C: 4 million euro /D: 1 million euro /E: 2 million euro /F: 5 million euro - total 21 million euro) or similar.

The numbers provided are rough estimates for specific examples taken into consideration and may vary significantly, as mentioned earlier. These examples should be seen as really as just examples used to showcase the approach used for estimating costs; other examples may hold equal importance and value. Funding from member states or other third-party institutions should expand the applications to cover other disease entities and leverage the examples already set by projects supported by European funding. While single projects may focus on a single or several steps to reach the BT, overall, it needs to be ensured that the entire chain is funded to guarantee the optimal benefit for the patient and the European healthcare system.

BT3 focuses on RP for patients. Developments for dosimetry are one of the tasks in this context. For most of the currently available applications, considerable progress has been made in this area. Additional advancements, such as camera-based and software-based dose assessment, can be achieved through projects funded with 1 to 3 million euro. However, developing methods to assess dosimetric parameters relevant to new technological advancements, like hadron therapy, neutron therapy, or FLASH therapy, would be more expensive. Budgets ranging from 3 to 10 million euro appear to be more realistic in such cases. It might be possible to co-fund these projects between the EURATOM programme and EURAMET initiatives. Understanding radiation biology is another crucial aspect of patient-specific RP and individual benefit-risk assessment on an individual basis. While many studies have been conducted in the last decades, certain major aspects of radiation types other than X-ray or gamma rays, including internal exposure and individual sensitivity or susceptibility, remain insufficiently understood. Some research can be conducted under the umbrella of PIANOFORTE or future co-funded partnership projects, but additional projects, each requiring funding between 3 and 6 million euro, seem necessary.

The subsequent stage needs to be a benefit-risk appraisal at an individual patient level, which is part of BT4. Meaningful research in this area is partly already underway, as seen in the SINFONIA project, which is being funded with slightly less than 6 million euro. This suggests that funding in a similar range will be necessary for dedicated disease-specific schemes.

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When discussing the use of IR for medical tasks, it is crucial to place patients at the centre of this approach. The implementation of patient-centred approaches, as proposed in the EURAMED rocc-n-roll SRA, is expected to have a very significant impact, particularly if individual benefit-risk appraisals for existing and new procedures can be developed as mentioned before. Ethical considerations must also be taken into account for potential application of existing and new methods, especially if there are proposed differences in diagnostic or therapeutic applications based on individual patient specifics. Consequently, suitable communication methods must be employed to inform patients about their disease status and the available options for diagnosis and treatment. To facilitate these efforts, corresponding research would need to be funded, allowing for the development of ethical considerations for the application of existing and new radiation-based diagnostic and therapeutic procedures. This funding requirement may range from 0.5 million euro for single projects up to a few million euro for the development of general aspects and approaches. The same financial considerations apply to improvements in suitable patient communication.

The medical use of IR should be viewed as an integral part of the comprehensive scheme for diagnosing and treating diseases. Therefore, its utilisation requires evaluation in terms of its benefits and risks when compared to other medical approaches. Furthermore, it is essential to assess whether IR can be more effectively combined with other medical procedures. By standardising and making the benefit-risk appraisal comparable across various approaches, new dimensions of clinical care can be achieved, especially when coupling of therapies and procedures is taken into account. These combined procedures can lead to optimised applications based on an improved or understanding of the corresponding biology and clinical aspects. Developing a generalised benefit-risk appraisal will require funding of at least 5 million euro. The optimisation of combined approaches will necessitate between 2 and 10 million euro, depending on the need for basic biological or clinical research, as explained for BTs 1 and 2, especially regarding clinical studies.

Ensuring the implementation and sustainable utilisation of new developments is a prerequisite for the meaningful allocation of resources and optimising benefits for patients across Europe, as described in BT6. The funding required for this approach, particularly for the associated research, strongly depends on the application area. If new radionuclides are developed, research for sustainable production could be cost-effective if it can be accomplished using existing infrastructures. However, it might become rather expensive if new systems such as cyclotrons or synchrotrons are needed to generate the radionuclides. Similar considerations apply to the development of new detectors or new biological markers. The necessary funding for such applications can range from 0.5 million euro to 20 million euro or even more. In such cases, private-public partnerships appear to be the most suitable approach for sharing funding. This approach also applies to translating technologies into industrial products, as the costs will again depend on the specific technologies involved.

To foster the research that facilitates medical BTs, the establishment of accessible databases and infrastructures linked to the clinical research approaches is a critical aspect of effective research and the implementation of medical developments. Creating or installing and managing relevant, accessible databases will require at least funding similar to the scale of the currently running European Federation for Cancer Images (EUCAIM) project, especially when aiming for the integration of imaging and other data. This indicates a budget in the range of 17 to 20 million euro, at least, for the implementation of such a database. On the other hand, installing infrastructures can likely leverage existing facilities, assembling them under a strategic and management umbrella that defines the needs and resources for individualised radiation medicine. In such a scenario, the funds required are possibly limited to 3 to 5 million euro.

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All developed and optimised procedures can only be truly beneficial if they are quality assured, following the actions defined in BT7. This quality assurance should ideally be performed on a daily clinical basis for each individual patient whenever possible. Ensuring the safe use of IR medicine is of paramount importance, and this includes fostering the establishment of a safety culture. The safe implementation of these procedures is a key pillar of the SAMIRA plan, and it will require corresponding funds for successful implementation. The amount of funding required will depend on the novelty of the approaches and may range from 2 million euro to 10 million euro, depending on the complexity of the procedures. Additionally, once basic standards for quality assessment are developed, an additional 5 to 10 million euro will be needed.

The safe use of IR strongly relies on the E&T of workers and researchers, as highlighted in BT8. As mentioned earlier, achieving this will necessitate more effective and targeted E&T approaches and structures. One potential solution could involve funding the concept of European universities, integrating research and healthcare education. To set up such a European university, a minimum of 15 million euro would be required. Additionally, the implementation of hands-on workshops and webinars on a European level is essential, which would need an additional 5 to 10 million euro in funding. Designing meaningful teaching approaches is crucial for funding webinars and electronic teaching methods, while the actual implementation can leverage existing E&T platforms. This aspect would require funding between 2 and 5 million euro, at least.

Safety is a critical concern for healthcare professionals, particularly regarding their RP. To address this, developments must be made using newly emerging technologies such as digital cameras, AI-based evaluation, and the replacement of dose calculations with AI-based methods, among others. Many of these developments can be built upon current advancements, making their implementation costs fall within the range of a few million euro for most relevant exposure situations. Some of these initiatives can be partially covered by projects funded through PIANOFORTE calls or future RP co-funded partnerships. However, dedicated funds, possibly in a private-public partnership scheme, will be necessary if new technological developments, including the use of other particle types, require advanced dosimetric and RP research.

Both aspects, RP of workers as well as the E&T aspects contribute to the career attractiveness as described in BT8 and need to be implemented to allow a world-leading safe medical use of IR and corresponding research.

5.2 Breakthroughs' impact and feasibility

The evaluation of impact and feasibility serves as indicators for priority setting. As with section 5.1, a concise list of feasibility indicators and potential impact for each BT has been developed.

BTs are defined as research and technological developments that have the potential to significantly impact medical applications of IR, particularly in terms of patients' life expectancy and/or life quality, RP, and healthcare systems. Both impact and feasibility are considered important indicators to assess specific project proposals (innovations) to implement such BTs into medical practice.

Regarding impact, the following categories of indicators shall be used to evaluate project proposals:

- number of European patients potentially benefiting from the innovation
- improvement of life quality of patients, including patient comfort and patient safety, including RP
- increased life expectancy

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- improved healthcare from a societal perspective, including financial and organisational improvements

Table 1 provides an indicative evaluation of the different BTs concerning their potential impact based on experts' opinions at the highest aggregation level of the BTs. It is evident that enhancements in diagnosis and therapies will have the most significant impact on life expectancy and patient comfort. On the other hand, generic BTs, such as those related to research supporting the translation of research efforts or the harmonisation of legislation, will score highest in the impact category of improved healthcare organisation and economy.

When considering the overall funding of research, it is crucial to maintain a reasonably balanced approach to the progression of all types of BTs to optimise the advancement of medical applications of IR. However, it is essential to acknowledge that without improvements concerning BTs 1 and 2, there will not be a relevant impact on patients' lives throughout Europe.

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	Number of patients benefiting from innovation	Improvement of life quality (comfort and radiation protection)	Increased life expectancy	Improved healthcare system (societal perspective and organisational improvements)
Patient related BTs				
BT1 - Improve/ develop diagnosis	**very high**	**high**	**high**	**high**
Decision-making	very high	high	high	very high
Technical developments including AI based methods	very high	high	unclear	high
Screening	very high	unclear	high	very high
Molecular imaging methods	high	very high	high	high
Quantitative imaging and radiomics	high	very high	high	high
BT2 - Improve/ develop therapy	**high**	**very high**	**very high**	**high**
Radiation oncology	high	very high	high	high
Theranostics	medium	high	high	high
Interventional procedures	high	very high	very high	very high
BT3 - Patient radiation protection and benefit-risk ratio	**very high**	**high**	**medium**	**medium**
Radiation biology	very high	high	medium	medium
Patient dosimetry	very high	medium-high	medium-low	medium
BT4 - Patient relations	**very high**	**high**	**medium - low**	**medium**
Individual benefit-risk balance assesment	very high	very high	medium-low	medium
Involvement of patients in research	medium-low	medium-high	medium	high
Shifting the communication landscape	very high	high	medium-low	medium
Ethical data management	very high	high	unclear	high
Generic BTs				
BT5 Strategic positioning	**medium-high**	**potentially high**	**potentially high**	**very high**
Comparison of benefit-risk with other medicine	high	high	high	very high
Synergies with non-IR techniques	medium	potentially high	potentially high	high
Economical aspects and funding of R&D	medium	high	high	very high
BT6 Implementation and sustainability	**high**	**high**	**high**	**high**
Translation & organisation	high	high	high	high
Research for sustainable supply including radionuclides	medium	medium-high	medium-high	medium
Access to data, biobanks and equipment	medium	medium-high	medium	high
Harmonisation of data and protocols	very high	medium-high	high	high
BT7 - Quality, safety and legislation in Europe	**high**	**high**	**medium-high**	**high**
Quality determination	high	high	medium-low	high
Q&S for diagnosis and therapy	high	high	medium-high	high
Clinical quality and safety audits	high	high	high	medium-high
Improve the safety culture	medium-high	high	medium-low	medium
Harmonisation of EU legislation	high	high	medium-high	medium
BT8 - Career attrativeness and radiation protection of workers	**high**	**medium-high**	**medium**	**high**
Career attractiveness	high	medium-high	medium	high
Radiation protection for workers	medium-low	medium	medium-low	medium-high

Table 1. Suggested evaluation of BTs' potential impact. The impact of research projects to be funded will have to be evaluated in more detail. The different impact-related indicators may serve as guides for funding research proposals, amongst other indicators. Eventually, a balanced scoring on the different impact indicators is suggested to evaluate a full research work programme, including all research projects. The category looking for the number of patients / citizens benefitting from improvements is defined really along the lines on how many persons will really see a change (not are affected at all).

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Feasibility indicators constitute the second group to consider when prioritising and financing research projects. However, it is essential to note that developing medical applications from bench-to-bedside is always a significant challenge, yet ultimately crucial. Clinical studies lasting more than 10 years are not exceptional; rather, they are the norm. Nonetheless, projects and BTs can be categorised according to the aspects mentioned for BTs 1 and 2 in Chapter 5.1. Therefore, the indicators should be used with great care to avoid funding only easily achievable goals. In general, all BTs appear feasible, at least in exemplary cases. However, the requirements and necessary resources will differ. While BTs 1 and 2 are likely to have the most substantial potential impact on patients' benefits, they will also demand more effort to make them feasible.

Regarding feasibility, it is crucial to carefully advance the various BTs proposed in the roadmap while keeping the primary objective of enhancing the diagnosis and treatment of patients through medical applications of IR. The potential feasibility of project proposals and their likelihood of eventually being implemented in the healthcare system can be assessed based on the extent to which the project:

- has the potential for a broad base of support in the research phase all over Europe.
- requires a change in policy on EU or national level.
- will appeal to the interest and investment of industrial partners.
- can count on sufficient production of radionuclides and logistic solutions.
- needs the construction of new reactors or other big infrastructures.
- the medical application will be achievable (logistically, financially, technologically) for a sufficiently large group of patients in Europe (the required size of the patient group to be decided in a societal consensus or based on political decisions).
- will need changes in organisation or recruitment of skilled personnel in hospitals.

5.3 Timeline of the breakthroughs

The BTs will consistently adhere to specific logic, contingent upon the individual projects. However, we propose here a general timeline for the BTs. It should be acknowledged that the timelines for BTs 1 and 2 are based on exemplary projects commencing in year one. It is desirable and feasible to pursue additional projects with similar timelines.

The estimated timeline for the implementation of the BTs is shown below in a Gantt chart representing the BTs:

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Figure 6. *Gantt chart for the implementation of the BTs*

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