COCIR
STRATEGIC RESEARCH AGENDA
UNDER HORIZON 2020 SEPTEMBER 2016

COCIR
SUSTAINABLE COMPETENCE IN ADVANCING **HEALTHCARE**

European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry

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INTRODUCTION TO STRATEGIC RESEARCH AGENDA

From its inception, the EU's Horizon 2020 innovation program included the key European Commission's objective of improving the lifelong health and wellbeing of all citizens. Chronic conditions such as cardiovascular disease, cancer, diabetes, neurological and mental health disorders and various functional limitations were highlighted as major causes of disability, ill-health and premature death. Non-communicable diseases present considerable social and economic costs. Persistent health inequalities must be addressed, and access to effective health care should be ensured for all Europeans.

It is the ambition of this Strategic Research Agenda (SRA) to target jointly the broad areas defined by Horizon 2020, the Horizon 2020 healthcare objectives and the World Health Organization (WHO) priority disease list for the European region. The objective is to address both unmet medical need and total economic burden of disease for society from a holistic health and social care approach including prevention, primary and specialist care and social care.

An appropriate European-level research and innovation response will make a crucial contribution to addressing these challenges, delivering better health and wellbeing for all, and positioning Europe as a leader in the rapidly expanding global markets for health and wellbeing innovations, including the increasing emphasis on rehabilitation and care in the home environment. However, realizing this vision and adapting Europe's research, development and innovation (R&D&I) ecosystem to the needs of today's health systems, that aim at placing individual patient needs at the core, requires the development of a new regulatory framework. Such an enabling regulatory framework must be aligned and respond to the practical needs of current R&D pipelines in order to effectively support the development of novel technologies. The existing regulatory framework should be revised to take into account the benefits of new technologies and their contribution to provide integrated solutions to respond to current challenges. For example, one area of significant advancement is the innovative use of companion diagnostics and biomarkers.

A successful response also depends upon excellence in research and a concerted effort to improve our fundamental understanding of health, disease, disability, development and ageing (including life expectancy). The seamless and widespread translation of the resulting and existing knowledge into innovative, scalable and effective products, strategies, interventions and services will be vital and will require long term and coordinated support for co-operation between multidisciplinary and multi-sector teams[1].
Only through combining the expertise of large and mid-size companies, academia, patient organizations, regulators and health authorities, all having a shared desire to change and improve, will we secure the necessary expertise for successful execution along the entire value chain.

THE STRUCTURE OF THIS STRATEGIC RESEARCH AGENDA HAS FOLLOWED THE FOLLOWING OBJECTIVES:

- Address the objectives of the EC to focus on major disease conditions;
- Take major technology trends and paradigm shifts into account, such as "quantitative imaging as a biomarker" (Zerhouni) or patient-centered health systems;
- Adhere to the insight that innovations need to be packaged as clinical solutions, addressing procedures along the patient pathways and relevant to specific diseases;
- Focus on both generic cross-cutting IT innovation such as clinical decision support, imaging solutions and distributed workflow as well as on disease specific clinical solutions;

Along a set of selected major acute and chronic diseases as prioritized by the EU, in particular cancer, cardiovascular, neurodegenerative, respiratory and age-related diseases, this document calls for collaborative research opportunities, e.g. in Horizon 2020, to stimulate and foster technological innovation in support of this. While some of the prioritized technologies will be very specific for one of the selected diseases, other technologies will be more generic and useful for a wider range of diseases. Both are important, as society needs to both deepen and broaden its impact on care and health.

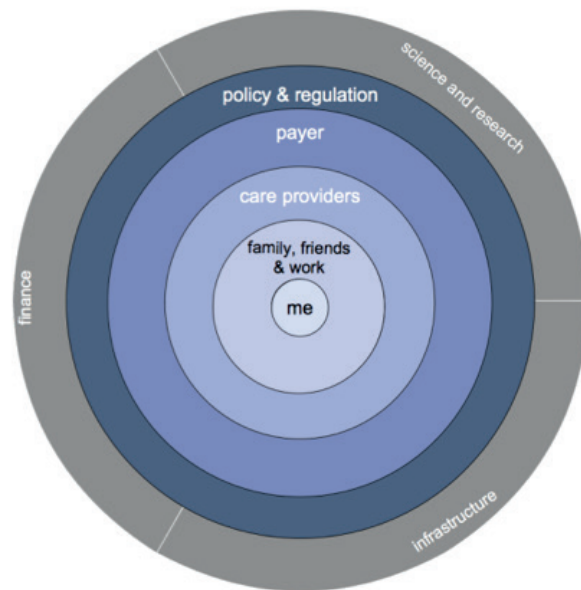1. EC proposal for Horizon 2020 regulation

Fig.1 Care stakeholders

Some of the proposed technologies will be used by professionals, others by patients/citizens and their environment, and yet others by policy makers and payers. All stakeholders will profit from specific technologies, tailored to their needs and integrated in an overall Integrated Care approach.

Along the cycles in health care (prevention, diagnosis, therapy and follow-up) and along the spectrum of all stakeholders the **COCIR Strategic Research Agenda** presents a list of specific challenges, the associated scope of research activities, and the deliveries and impact to be expected. They are centered around the chapters of e-Health, diagnostic and therapeutic imaging, radiotherapy and Health Economy Aspects including the Health Technology Assessment (HTA).

The first chapter of this SRA outlines some of the major trends in health systems and the contribution of the imaging, radiotherapy and health ICT industries to respond to some of the most pressing challenges. Certain diseases are then identified to frame the proposals included in this SRA. Chapter three develops the core proposals of the SRA in the areas of imaging, radiotherapy and eHealth. Finally, certain horizontal aspects concerning regulation and health economics are addressed.

1. OVERARCHING INTEGRATED CARE

Healthcare systems are ill equipped to meet the challenges posed by chronic illnesses. In a landmark report from 2001[2], the Institute of Medicine at the US National Academy of Sciences stressed the need for extensive reforms of health systems to respond to the needs of the chronically ill. According to the report, patients often must navigate through a fragmented health care system and adapt to the culture and procedures of health care organizations and professionals, rather than receiving care designed to focus on the individual patient's needs, preferences and values.

Traditional care practices in early medicine were first developed in an era when life expectancy was shorter, with acute events and infectious diseases being predominant causes of mortality and morbidity. In contrast to acute care, the primary goal when treating chronic conditions is not cure but rather to effectively manage the disease to maintain the patients' function and well-being. Moreover, many chronic diseases originate from a successful treatment of an acute situation in which the patient survives either returning to normal health or with some lingering morbidity to manage. This blurs the boundaries between acute and chronic manifestations of disease. Despite this clear difference in treatment goals, most healthcare systems throughout the world are still trying to manage chronic illness using an acute care approach, in terms of care processes, methods and structures. On the other hand, acute care, if delivered without accounting for the chronic conditions of the patient, is also inefficient and potentially dangerous.

As a result of the increasing prevalence of chronic conditions, the bulk of the economic burden is gradually shifting to chronic disease management. However, the resources allocated to acute care remain substantial and society still perceives acute care as a priority, because of its capacity to cope with abrupt changes in people's conditions, short-term life expectancies and high impact. The transition between acute and chronic care is too abrupt and the mutual influence on each other remains largely ignored. Adjusting care appropriately to address both acute and chronic elements will be beneficial.

To close the quality gap, this report calls for a reorganization of health care systems to ensure that they truly embrace **person-centered care** and are equipped to deliver **integrated care**.

1.1 DEFINITIONS:
INTEGRATED CARE, PERSON-CENTERED CARE AND PERSONALIZED MEDICINE

Despite the absence of a universally-accepted definition of integrated and person-centered care, there is growing insight into the essential components of both inter-related concepts.

Fig. 2 Phases in care

Integrated care can be defined as "the management and delivery of health services such that people receive a continuum of health promotion, disease prevention, diagnosis, treatment, disease management, rehabilitation and palliative care services, through the different levels of care, and according to their needs throughout the life course".

2. J.M. Corrigan, M.S. Donaldson and L.T. Kohn et al., A new health system for the 21st century. Crossing the Quality Chasm, Institute of Medicine (IOM), National Academy of Sciences, National Academies Press, Washington, DC (2001)

Person-centered care refers to "care that is focused and organized around the health needs and expectations of people and communities rather than on diseases". The goal of these concepts is to enhance quality of care and quality of life, patient experience and system efficiency for the whole spectrum from healthy citizens to patients with complex, long-term problems cutting across multiple services, providers and settings.

Integrated and person-centered care are approaches to healthcare management and delivery that should be viewed along the whole continuum of care from prevention, through diagnosis, treatment and follow-up.

Integrated care will be successful if it can prove that it contributes to cost-effectively deliver better care experience and improved health outcomes.

Person-centered care (PCC) encompasses health and wellness maintenance, and has evolved from the earlier concept of patient-centered care which spanned the phases of care when disease has already manifested itself. Today, person-centered care is widely considered to be the essential characteristic of effective care. Central to the concept is the view that care is a collaborative process between patients and health care providers. As such, it involves defining clinical problems in terms that both patients and providers understand, jointly developing care plans and setting goals, agreeing on implementation strategies and providing self-management training and support services, in addition to active, sustained follow-up: *"Nothing about me, without me"*. In short, it implies care that is coordinated across settings and over time[3]. Moreover, person-centered care should also integrate the growing trend of community-support through social media and specific disease-oriented or regional patient networks.
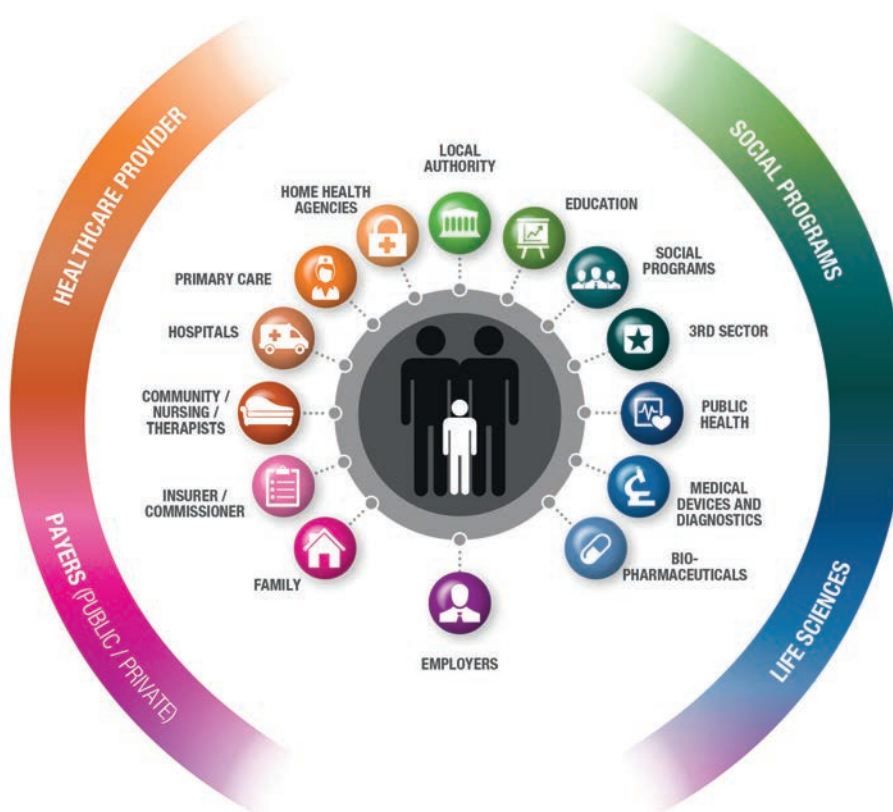
Fig. 3 The Integrated Care ecosystem (from COCIR's 2015 eHealth Toolkit)

3. http://www.health.org.uk/areas-of-work/topics/person-centred-care/person-centred-care/ Ekman, I. et al. (2011). Person-centered care — Ready for prime time. Eur J Cardiovasc Nurs, 10(4), 248-251. PCC has proven to be effective in shortening hospital stay, relieve uncertainty and increase self-efficacy in patients and reduce costs (Dudas, K., et al. (2013). Uncertainty in illness among patients with chronic heart failure is less in person-centred care than in usual care. Eur J Cardiovasc Nurs, 12(6), 521-528.; Ekman, I., et al. (2012). Effects of person-centred care in patients with chronic heart failure: the PCC-HF study. Eur Heart J, 33(9), 1112-1119.; Fors A et al. Person-centered care after acute coronary syndrome, from hospital to primary care - a randomized controlled trial. Int J Cardiology 2015 (in press)

Finally, Integrated Care and Person-Centered Care should be distinguished from Personalized Medicine. Although no official definition of personalized medicine exists, it can best be explained as a medical approach, tailored to the patient or a group of patients, for prevention, prediction and treatment. In other words, it moves away from the common "one size fits all" medical model towards more optimal tailoring of care to particular sub-groups of the population with common phenotypic and genotypic characteristics. As the European Commission has stated: "*personalized medicine has the potential to offer new treatment opportunities for the benefit of patients, including better targeted treatment, avoiding medical errors and reducing adverse reactions to medicines. It also recognizes the challenges (e.g. in research) to its successful incorporation into healthcare systems [4]*".

1.2 CHALLENGES FOR INTEGRATED CARE AND THE VALUE COCIR MEMBERS CAN ADD

1.2.1 CHANGING MEDICAL AND SOCIETAL CONTEXT

The increasing prevalence of chronic non-communicable diseases (NCD) (e.g. cardiovascular, cancer, diabetes) is mainly driven by an ageing population and, to a large extent, also by changes in lifestyle patterns. This effect is accompanied by an increasing complexity of medical treatment due to co- and multi-morbidities. Another global trend is the rise of infectious diseases and a loss of treatment options due to antimicrobial resistance.

New knowledge about the genesis of diseases, because of increased insights in the "-omics", but also about the role of non-health determinants of health, is opening up new opportunities for personalized medicine and population health management.

COCIR members can help discover even more by applying new imaging and health ICT technologies such as image analytics and sophisticated data mining techniques.

In addition to the medical perspective, there are health economic aspects to address: public health expenditure needs to be kept at a sustainable level and health related productivity losses should be minimized. In recent years, healthcare expenditure has risen consistently and sharply in all OECD countries (5% of GDP in 1970, 7% in 1990 and 10% in 2010), surpassing the rate of inflation. At present, healthcare systems in developed countries have been 'declared' unsustainable. Decision-makers need to find alternatives to deliver effective, better quality care to an increasing number of patients with complex medical conditions (e.g. multiple chronic illnesses).

Various policy approaches to tackle these challenges exist and need to be deployed jointly in order to maximize their effect. In the following sections we outline the nine elements that jointly delivered could conform an effective policy response to some of the most pressing challenges faced today by health system. COCIR's member companies may contribute to successfully deliver these approaches with their portfolio of medical imaging, radiation therapy, and health ICT solutions as well as with their R&I activities in these fields.

1.2.2 INTEGRATION OF CARE DELIVERY SYSTEMS

Integrated models of care are widely being discussed and tested in many EU health systems. The common goal is to develop integrated care models across the continuum of care that offers holistic health and social care to patients with complex chronic conditions. COCIR members contribute by offering and developing health ICT solutions that:

- Support the shift from episodic to longitudinal care

- Allow an efficient collaboration across all providers in hospital and ambulatory settings, including remote patient monitoring within non-clinical settings, e.g. home-based care and mobile health

- Enable and promote the adoption of evidence-based and standardized care protocols

- Provide reliable clinical decision support in cases where data volume grows beyond the capacity of human interpretation, e.g. genetic information, within the time available for care.

4 http://ec.europa.eu/health/files/latest_news/2013-10_personalised_medicine_en.pdf

1.2.3 PERSONALIZATION OF CARE

Personalization of health care is commonly seen as a key driver to improve health outcomes. In order to foster personalization of care, we need to have a better understanding of the causes and mechanisms underlying health, healthy ageing, and disease. This knowledge must be translated into the ability to monitor health and to prevent, detect, treat and manage the disease.

COCIR members are actively contributing to personalization of health and care by providing:
- Advanced imaging methods that are an essential element of a reliable diagnosis in many diseases, e.g. the precise location of obstructions in the cardiovascular system
- Functional imaging solutions that provide quantitative and reproducible information about tissue properties, e.g. to assess tumor activity and therapy response
- Imaging based therapy planning methods for minimal invasive surgery and radiation therapy that provide individualized treatment parameters for every individual patient
- Advanced predictive and prescriptive analytics, based on integrated processing of heterogeneous information sources including images, labs, genetic test, and other structured or unstructured clinical data.

1.2.4 OUTCOME-BASED PAYMENT MODELS

Some health systems across Europe are exploring new healthcare providers' payment models based on the link between specific healthcare services and the subsequent health outcomes. Outcome-based reimbursement models force healthcare providers to move to coordinated care pathways, shift from episodic to managed care and develop new frameworks for outcome evaluation and measurement.

Likewise, a higher degree of collaboration along the value chain between health and social care providers, payers, and pharma/ MedTech is expected in order to move towards outcome-based patient management.

COCIR members with innovative health ICT solutions (including imaging, radiotherapy and healthcare IT at large) have a solid technology and knowledge base to support healthcare providers and provide comprehensive answers to evaluate and assess health outcomes. Notably, ICT solutions can be used to
- Enable communication and collaboration between health and social care providers to provide patient-centered coordinated care
- Measure effectiveness, costs and broader impact of therapeutic interventions in terms of health outcomes.

1.2.5 PATIENT ENGAGEMENT

Empowering patients along the continuum of care can lead to more cost-effective healthcare systems and improved health outcomes. The concept of "shared decision making" and self-management requires transparency of processes, seamless exchange of health data between care providers and patients. e-Health and mobile services are increasingly being used and accepted to support prevention, early diagnosis and follow-up.

Increasingly, advances in ICT technologies will enable higher engagement of patients in their health and involvement in care decision-making. COCIR members are providing related solutions for:
- Health data exchange platforms and intersectional connectivity between health providers, stationary and ambulatory spaces and patients
- Transparency through structured reporting of medical records
- Patient empowerment through selection of individualized treatment plans
- eHealth platforms and systems for new types of digital health services such as services for well-being, prevention, health consulting and after care.

1.2.6 PREVENTION AND EARLY DETECTION OF DISEASES

Early disease detection and prevention are key priority areas for European health policy makers. In this context, policy options are largely influenced by our understanding of the role of non-health determinants of health, such as environmental, behavioral (including lifestyle), socio-economic and genetic factors, in their broadest sense.

The challenge in this area will be to provide the evidence to inform policy strategies for prevention and early diagnosis which are at the same time cost-effective and contribute to reduce health inequalities.
COCIR members, with a long history of providing answers and technologies to increase clinical efficiency, have the relevant expertise to tackle the current challenge, bringing preventive medicine and early detection to the next frontier, by offering solutions for:

- Databases with related medical imaging and other patient information for population based health management
- Effective screening programs and improving the assessment of disease susceptibility, improving surveillance and preparedness
- Better understanding of diseases, providing related imaging, diagnostic technologies and advanced analytics on big data
- Early detection programs with an integrated approach, including medical imaging, molecular health and genomic data
- Health data management and interrogation across the entire continuum of care expanding further into the phases of prevention and after care

1.2.7 TECHNOLOGICAL INNOVATION AND ADOPTION

Current state of the art of deployed decision support systems, diagnostic tools, clinical guidelines and care pathways fail to respond to the complexity of today's healthcare delivery and are ill equipped to support holistic care. Moreover, in an interdisciplinary approach, almost by definition, the patient should be a partner. However, in traditional care approaches and processes, including ICT solutions, this is far from realized, constituting a real risk to patient safety, efficient use of resources, and quality of care.

Acknowledging and confirming the need for Integrated Care in order to achieve a high quality and future proof healthcare delivery, COCIR is fully aware of the many challenges still lying ahead. Integrated Care will only be fully implemented and adoption will be realized when cultural, financial and organizational challenges will be overcome, such as reluctance to share data, uncertainty about the legal framework and unclear business models.

COCIR as the industry association of health technology companies, wishes to specifically highlight the following technological challenges, that are further on detailed in this SRA Research Agenda:

- The development and integration of knowledge driven clinical intelligence and analytics
- The usability of clinical IT systems
- The connected data, semantic interoperability and collaboration
- The development and seamless integration of specific imaging related and personalized diagnostic and therapeutic approaches
- The development of quantitative imaging platforms with associated contrast / tracer mechanisms which provide high accuracy, precise, and reproducible diagnostic exams;
- The development of minimally-invasive and non-invasive therapies with real-time planning, guidance, decision-support, and treatment monitoring with improved clinical effectiveness and outcomes management
- The delivery methods of radiation therapies in the management of cancer patients and further improvements in the radiotherapy outcomes
- The improvement of radiotherapy planning, and delivery accuracy using cutting edge technologies.

1.3 IMPACT

<u>Integrated Care</u> is an essential step in the endeavor to build sustainable health systems, supporting the real short and long-term needs of all citizens. In essence this model responds to the health and social care needs of an ageing population with a stronger emphasis on wellness maintenance, disease prevention, screening, early diagnosis and early, minimally invasive intervention., (shifting from "curing the sick" towards "staying healthy"). Additionally, this approach provides important benefits for patients, health and social care workforce, providers and payers, including:

- Enabling population health management, including healthy living and prevention

- Creating person-centric solutions, with built in collaboration models across the health continuum

- Integrating data from disparate point solutions across hospitals, physician practices, insurance, and consumer settings

- Providing timely, actionable, and context-appropriate information to clinicians, patients and care givers

- Creating a continuously learning health ecosystem in which science, informatics, incentives, and culture are aligned for continuous improvement and innovation, all with best practices seamlessly embedded in the care process and new knowledge captured as an integral by-product of the care experience [5].

It becomes more and more clear that, even if healthcare technology alone may not be the single solution to move towards Integrated Care, it is an important foundational element

and an essential prerequisite. Technological innovations are urgently needed and COCIR expects these innovations to be beneficial for:
- Deploying the integrated care approach towards acute and chronic care and towards primary and secondary and tertiary prevention
- Providing new diagnostic and therapeutic insights
- Enabling the coordination of activities of all stakeholders around one specific patient/citizen;
- Sharing of health information
- Designing and adopting necessary policies and organizational structures.

Beyond technological innovation, COCIR is convinced that also the transition from technology and research, from proof of concepts and demonstrators, towards real Integrated Care implementation must be incentivized by supporting a holistic approach to deliver health and social care and multi-stakeholder communication and cooperation. This, in turn, enables new ways of collaboration in the R&D&I space.

5. IOM (Institute of Medicine). 2013. Digital data improvement priorities for continuous learning in health and health care: Workshop summary. Washington, DC: The National Academies Press.

2. SELECTION OF DISEASE CONDITIONS

The societal impact of innovations in healthcare is best appreciated when they focus on the most burdensome diseases, taking epidemiological and demographic trends into account. Therefore, a selection/prioritization of diseases is proposed for this SRA, which reflects the priorities of both, the healthcare community and the imaging, radiotherapy and health IT industries.

This disease focused approach is targeted at designing a R&D&I and innovation strategy that can support care across the different stages of the care continuum through standardized interfaces and a common IT backbone in order to avoid redundant, error-prone, multiple data entry and allow for efficient workflow and the use of knowledge from previous stages of care for subsequent treatment and care decisions.

2.1 CANCER

Cancer is one of the first three major deaths causes in Europe accounting for 23% of all deaths in 2012[2]. Cancer incidence is on the rise due to the ageing population, while at the same time, it becomes a manageable disease in many instances, with increasing survival rates[3] with leading countries with this regard namely Belgium, Sweden and Finland[4]. Extended survival rates are leading to increasing cancer prevalence and the need to improve follow-up mechanisms and care for patients at home.

Clearly, early detection of the disease is key. For instance, the use of single nucleotide polymorphisms (SNP) test reduces by 60% the incidence of metastatic cancer and by 37% the total cost of Breast Cancer[5]. While for screening, in-vitro biomarker tests are being improved, imaging plays a key role in localizing the disease, as a prerequisite for targeted biopsies and image-guided, minimally or non-invasive treatment. Furthermore, imaging as a biomarker is a key paradigm in therapy response assessment, providing information about changes in tumor size, perfusion and metabolism.

Additionally, radiotherapy is the key element in the cancer treatment capable of treating cancer based on an understanding of the cancerous tumor at the cellular level.

With increasing knowledge about the pathogenesis, based on an understanding of genomic, proteomic and metabolomics processes, quantitative imaging, not only of morphology, but also of physiological and metabolic processes, is key to providing successful care within the paradigm of personalized medicine. Under this new paradigm, the patient's likely response to a drug can be predicted based on genetic profiling information, and the response can be validated via imaging.

2.2 CARDIOVASCULAR DISEASES (CVD)

More people die annually from CVD than from any other cause, with an estimated 17,5 million deaths in 2012 (46% of all NCD deaths)[6]. Improved detection, speed-to-therapy, and highly accurate imaging-based diagnosis (e.g. for stroke) have improved chances of survival and post-event quality of life. Remarkable successes in image-guided therapy, typically associated with catheter-based implantation of innovative devices like stents and valves, and in targeted therapies like catheter based ablation (arrhythmia) thrombolysis (stroke) or embolization (aneurisms), have reduced mortality rates, leading to an increasing number of patients with chronic disease.

The recent advent of catheter-based renal denervation (for the treatment of hypertension) is an example of how the continuous flow of innovative applications, each with specific requirements for respective devices, keeps changing treatment decisions and the practice of healthcare. For instance, telemedicine showed 15% to 56% reduction of mortality in Cognitive Heart Failure patients[7]. This flow of innovations should be kept up as new technological advances allow for improved devices and real-time treatment planning, execution and monitoring, making use of miniaturization opportunities which allow for an increasing number of sensors to be inserted into the body, including imaging sensors.

2 European Cardiovascular Disease Statistics (2012), European Heart Network and European Society of Cardiology, September 2012
3 "Cancer Facts & Figures 2012", American Cancer Society, pp 18, 2012, PDF available for download
4 Survival of Cancer Patients in Europe, 1999 - 2007: The EUROCARE-5 Study. Eds: P. Minicozzi, R. Otter, M. Primic-Žakelj, S. Francisci, European Journal of Cancer, vol.51, issue 15, October 2015, pp 2099-2266.
5 http://www.healthpolicyandtechnology.org/article/S2211-8837%2812%2900044-5/abstract.
6 Global status report on non-communicable diseases 2014. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstre am/10665/148114/1/9789241564854_eng.pdf?ua=1, accessed 10 February 2015).
7 The Empirical Foundations of Telemedicine Interventions for Chronic Disease Management, Telemed J E Health. 2014 Sep 1; 20(9): 769–800., http://www.ncbi.nlm. nih.gov/pmc/articles/PMC4148063/ .

2.3 NEURODEGENERATIVE DISEASES

The most important among this group of diseases is Alzheimer's disease, which is on the rise due to the aging of the population, with a prevalence three times higher and a healthcare cost similar to that of all cancers combined[8]. Other diseases in this area include Parkinson's Disease, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, and Huntington's disease.
Innovative tools for the early diagnostic of Alzheimer's disease are being developed. Recently, new PET tracers have been approved for diagnostic imaging for Alzheimer's disease. Likewise, intelligent computer algorithms are being devised to support diagnosis and assist clinicians in differentiating this disease from other neurodegenerative diseases.
More progress is expected from future investments in research, together with the development of drugs, which can slow down the progression or even reverse the degenerative processes underlying the diseases.

2.4 RESPIRATORY DISEASES

Respiratory diseases have a substantial societal burden and tend to have a strong negative impact on patients' quality of life (asthma, sleep apnea, chronic obstructive pulmonary disease).

Imaging can help in the diagnosis of some of these diseases, such as lung function assessment, and holds promise for the validation of respiratory drug delivery, based on molecular imaging labels attached to drug molecules. Furthermore, (X-Ray and endobronchial) imaging plays an important role in novel therapy schemes for patients with benign or malignant airway obstructions (e.g. interventional placement of tracheal and bronchial stents & valves).

2.5 AGING-RELATED DISEASES

Type II Diabetes, Alzheimer's Disease, Degenerative Arthritis, Heart Disease, and Destructive Eye Diseases are the most common age-related diseases[9]. Two of them have already been addressed in this section. With regards to Degenerative Arthritis (Osteoarthritis) imaging (X-Ray, arthroscopy) plays an essential role in diagnosis[10]. Even though today the treatment is quite conservative, a number of visionary therapy concepts, including tissue engineering and stem cell based approaches, are on the horizon, and these are likely to require enabling technology and initial validation.

8   "Neurosciences Executive Edge", J.L.M. Zage, SG-2 IoC Analysis, based on CDC, US Census., April 2003
9   "5 most common age-related diseases ", Healthy Living, Nov 2008
10   Osteoarthritis (OA or Degenerative Arthritis)", W.C.Shiel and M.C. Stöppler, MedicineNet.com, Nov 2011

3. RESEARCH, DEVELOPMENT AND INNOVATION ACTIVITIES TO SUPPORT INTEGRATED AND PERSON-CENTERED CARE

For all the above-mentioned disease conditions, innovations in imaging, radiotherapy and eHealth are required in order to improve prevention, diagnostic, treatment and follow-up and, ultimately, improve patients' experience and health outcomes.

Under Horizon 2020 third strategic objective "Societal Challenges" in the area of "*Health, demographic change and wellbeing*"[11] [12], the EC has committed to fund activities that will contribute to improve the understanding of disease mechanisms, effective (imaging-based) screening programs, disease management (through Radiotherapy and eHealth), and the (image-guided) treatment of major and chronic diseases.

The focus for the activities proposed in this section is on clinical solutions defined as a solution to a clinical problem. As an example, if the clinical problem is diagnosis, then the clinical solution comprises not only an imaging system, but also software tools for image interpretation, potentially using other (non-imaging) sources of knowledge, as well as interfaces or components for integration with the respective clinical IT infrastructure (Electronic Patient Record/Electronic Health record etc.). Likewise, an image-guided therapy solution would comprise software tools for image-based planning of the therapeutic procedure, and imaging system for creating the respective images and for monitoring the procedure (preferably in real-time), as well as imaging and software tools for outcome assessment and reporting and potentially for decision making regarding follow-up examinations and further patient management.

For each of the innovative clinical solutions proposed in this section, collaboration with clinical users and other stakeholders in the health and social care system is encouraged and clinical validation efforts are expected to be part of the work.

This section is organized in three subchapters, Imaging, Radiotherapy and eHealth, each representing an innovative area supporting integrated, person-centered care pathway for the selected diseases previously identified. For all R&D&I activities proposed hereafter we have outlined specific challenges, defined a scope and described expected deliverables and impact.

3.1 IMAGING SECTOR

Medical Imaging has changed in recent years. Today, in medical imaging, the technological challenges have evolved significantly in the sense that, until the nineties, people sought - as the gold standard - the quality (that is, spatiotemporal resolution, contrast resolution, field-of-view coverage, dynamic range, etc) of the image from single system. The last decade has instead witnessed a further evolution: the challenge has shifted to include not only performance (both technological and clinical), of the individual machines, but also to expanding broader to include the ability of equipment to be integrated among heterogeneous platforms and to be fully interoperable with different networks that a provider may have.

Today, we increasingly encounter technological complexity and information overload in the use and integration of diagnostic systems spanning multiple modalities. In this light, software applications for clinical decision support play an increasingly important role since physicians need help in diagnosing areas of a medical image where there is a greater need for clinical attention.

Medical imaging has changed from a tool for qualitative description of diagnostic findings related to abnormalities in morphology towards a quantitative measurement tool for monitoring pathological changes in the body, with measurements extending from morphology to physiological functions and pharmacokinetic and metabolic process parameters across resolution scales spanning the organ-level to the molecular-level. Furthermore, imaging has undergone a redefinition, "not by the tools, but by the purpose", as "a core interdisciplinary science for generating, understanding and using spatially resolved biological information" (Zerhouni), to be understood in the context of the "Four Ps" describing the future paradigms in medicine:

- Predictive (outcome prognosis based on "bio-informatics" and data bases);

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11 "Horizon 2020 - The Framework Programme for Research and Innovation", Nov. 30, 2011, pdf available
12 http://ec.europa.eu/research/horizon2020/pdf/proposals/proposal_for_a_council_decision_establishing_the_specific_programme_implementing_horizon_2020_-_the_framework_programme_for_research_and_innovation_(2014-2020).pdf#view=fit&pagemode=none

- Personalized (treatment based on patient's genetic / metabolomic profile);
- Preemptive (an example being the vaccination against cervical cancer); and
- Participatory (patients and care providers form a team in decision making);

In this context, the term "Imaging as a Biomarker" has been coined, which is now being considered a key not only in diagnostic imaging, but increasingly also in image-guided interventions, image-guided therapy delivery, and in particular in imaging-based therapy response assessment.

Another line of technological development is emerging, focusing on the enhancement and on the use, of "lighter", "more accessible", "less costly" and "less invasive" methods for patient care, provided at substantially the same level of diagnostic benefit.
In the next ten years, medical imaging can radically change further. Future evolution will lead to not only high-performance medical imaging tools for highly-specialized examinations, but also value-based healthcare driven adoption of new "high-efficiency methods", with tight-integration within health networks for routine diagnostics and screening. In balance, these trends translate into the use of technologies which allow for identification and treatment of pathologies with greater efficiency, ensuring health / social cost containment and minimally–invasive treatments for the patient.

The greatest benefit from the introduction of these tools in clinical practice, using simplified applications, is undoubtedly to structure them in usage configurations that can also be used by less specialized health personnel, after appropriate training, enabling them to make a preliminary assessment of patients and to target only those who are in real need of further follow-up with appropriate specialized tests.

As a consequence, specific tasks for imaging are defined more directly in the context of providing care for a specific disease condition, and imaging systems are considered parts of clinical solutions supporting the respective procedures along the respective patient care pathways.

3.1.1 THEME 1:
IMPROVED AND QUANTITATIVE DIAGNOSTIC IMAGING

Specific Challenges
Challenges to be addressed in this innovation area relate to improvements of imaging systems in terms of sensitivity, spatial, temporal, and contrast resolution as well as acquisition speed. There is an overarching need in this area for anatomically and functionally intelligent algorithms to process the large volumes of data generated to extract quantitatively meaningful and the relevant (and quantitative) information from the image data, to help distill insight from the disparate exams performed on each patient. Improved and novel quantitative morphological, molecular and functional imaging solutions will be required for disease conditions, for which a quantitative assessment of patient-individual physiologic and metabolic processes via in-vivo imaging plays an important role in diagnosis and therapy assessment (for the latter, themes 3 and 5).

As in the past, innovation approaches will include pre-clinical, translational and clinical imaging, coupled with development of strong evidence from population studies to justify the clinical and cost effectiveness of these technologies.

Scope
Activities are required in the following areas to address challenges targeting improved imaging systems and interpretation software for quantitative and precise person-centered studies:

CANCER

- for **breast cancer**: digital X-Ray mammography and tomosynthesis, breast ultrasound, energy-resolved breast CT, molecular breast imaging, new or hybrid breast imaging modalities, software for computer-assisted screening and lesion detection and characterization as well as treatment planning

- for **prostate cancer**: multi-parametric MR imaging and spectroscopy, 31P choline PET, PET-MR, and contrast-enhanced ultrasound for lesion localization & characterization, as well as decision support software combining imaging information with in-vitro biomarker information

- for **lung cancer**: high resolution, ultra-low-dose CT and high sensitivity PET/CT and SPECT-CT for screening and diagnosis, computer-assisted detection and assessment of lung nodules - involving CT but also combined, real-time, motion corrected MR and PET, and optical imaging approaches

- for **liver cancer**: MR and/or US imaging and elastography, dual-energy CT, PET, and PET/MR for lesion detection and assessment as well as for differentiation of metastases from primary cancer

- for **head and neck cancer**, and whole-body examinations: efficient tools for tumor and lymph node detection, localization, contouring, and quantification, and whole-body or region specific metastasis screening using e.g. diffusion-weighted MR with simultaneous PET imaging

- for **cancers in superficial tissue layers** (e.g. melanoma): high-resolution optical or ultrasonic interrogation of superficial structures e.g. Optical Coherence Tomography (OCT) or ultrahigh frequency ultrasound (e.g. high-resolution EBUS) for 3D cellular-level images of epithelial structures in dermatology or endoscopy.

- for all cancer types: integration of decision support tools with in-vitro biomarker data and digital pathology systems, image segmentation and registration tools (see also section 2.3)

CARDIOVASCULAR DISEASE

- for **Arrhythmia**: extra- or intra-body imaging for image-guided ablation therapy incl. monitoring of thermal lesion characteristics and modeling for real-time treatment planning and prediction of therapy response.

- for **Atherosclerosis**: imaging of macrophages in coronary plaques for prevention of sudden cardiac death, through energy resolved CT, nanoparticle-enhanced MRI and 18FDG PET imaging or through intravascular imaging sensors (e.g. IVUS or OCT), molecular imaging of Annexin V, of Protease Activity, and of Angiogenesis

- for **Heart Failure:** Radiographic (X-Ray, CT), ultrasound, nuclear and magnetic resonance imaging

- for **Advanced Heart Disease**: future developments in imaging and "smart" devices in support of stem cell therapy, device therapy for remodeling control, percutaneous valve interventions

- for **Stroke**: CT image analysis, MRI, Vascular X-ray, CT- and MR-Angiography, analysis software

NEURODEGENERATIVE DISEASE

- for **Alzheimer's Disease**: PET/CT, MRI, Simultaneous PET-MR, or other new interrogation modalities, as well as image interpretation and lesion characterization with corresponding decision support tools

- for **Amyotrophic lateral sclerosis:** MT and Diffusion Tensor Imaging with MR or other novel neuroimaging methods

- for **Parkinson's Disease and related disorders**: SPECT, PET, MRI, PET-MR, etc for structural and functional imaging of associated structural, pathophysiological and pharmacological changes

- for **Huntington's Disease** and related disorders: CT and MRI for atrophy, functional MRI for cognitive change assessment, SPECT for perfusion imaging

AGING-RELATED DISEASE

- for Degenerative Arthritis: quantitative X-ray, CT and MR imaging, spectral CT

Expected deliverables

Expected deliverables are new and/or improved imaging and image analysis / interpretation systems, software tools and solutions for increased clinical efficiency and better patient outcomes, which will be validated through suitable clinical trials.

Expected Impact

Expected impact will be earlier detection and characterization of lesions and more accurate and reliable, quantitative diagnosis, allowing for optimized, personalized treatment as the next step. The impact on society will be reduced mortality for the major diseases and reduced cost through improved efficiency and the prevention of cost resulting from late detection, inadequate treatment of disease and improving the Quality of Life. The impact of the focus on clinical solutions on the research base will be an increased understanding of clinical and patient needs for all contributors to the innovation across the involved disciplines.

3.1.2 THEME 1BIS:
LIGHT HIGH-EFFICIENCY DIAGNOSTIC IMAGING TOOLS: INSTRUMENTATION FOR LOCAL / OUTPATIENT MEDICINE

Specific Challenges

The "challenge" is to have "high efficiency" tools in Healthcare, because they enable cost reduction, while dramatically reducing the invasiveness of procedures and maintaining diagnostic and therapeutic effectiveness in a context increasingly oriented towards bringing healthcare to the patient instead of having the patient go to the medical facility.

Industrialized societies (North America, Europe, Japan and Australia) have an aging population with a strong increase in life expectancy and quality of life. Spending on healthcare increases exponentially with age and the costs for diagnostics are still growing too. In these countries, the major diseases can be diagnosed early and it will be happening more and more over the next few years. If we take as a reference the statistics, it shows that two-thirds of deaths are concentrated in cardiac diseases and cancer.

The growing burden of chronic diseases and disabling conditions, such as rheumatic disorders, have become increasingly expensive for both individuals and for the society at large. Statistics from the World Health Organization indicate that morbidity, an index that determines the effects of the disease on quality of life, tends to grow strongly in developed countries. Ever earlier diagnosis and timely information will improve patient care by reducing the cost of healthcare.

This issue tries to answer these requirements / objectives, taking into account that the latest developments in electronics allow the realization of diagnostic systems for "light" or "value-based" diagnostic imaging, while largely preserving advanced performance and high image resolution capabilities. IT developments will also make it possible to equip these devices for sophisticated applications for analysis that enable their use even by someone with basic levels of knowledge and skill. Furthermore, the use of systems of connectivity and network integration open the way to the possibility of monitoring remote execution, allowing a local physician to consult a specialist in near-real-time in the case of critical emergency situations.

The results for genuine commercial viability must also take into account a very low production cost of the product to facilitate potential acceptance by cost-sensitive markets. Proposals should consider the study for original design and production solutions that allow for greatly reduced manufacturing product costs. Proposals should also consider a strategic component for clinical research to structure the application pathways, to ensure availability to local care providers, and to develop the training path that must be adopted to realize the full clinical benefit of new solutions.

Scope

Activities required to address these challenges are aimed at the development of diagnostic techniques which are compact, easy-to-use and of reduced cost, capable of being completed in "real-time" to ensure optimal clinical examinations that fit seamlessly in an eHealth network, with a level of performance comparable to more premium equipment.

Similar systems can be effectively used for applications in the emergency room and hospital wards. Beyond that we also think in simpler situations, such as the screening of subjects that face diagnostic assessment during the routine check-ups for various reasons (e.g. to practice competitive sports, or as part of occupational medicine, or routine checks for pregnant women conducted directly by obstetrics specialists directly on the field).

But the greatest benefit from the introduction of these tools in clinical practice, using simplified applications, is undoubtedly to structure them in usage configurations that can also be implemented by local health personnel, after appropriate training, enabling preliminary assessment of patients and to triage care accordingly.

Expected deliverables

Expected deliverables are new medical imaging systems more patient-centered, prevention oriented, efficient, resilient to crises, safe and sustainable. These systems should provide connectivity and network integration to operate in an integrated care environment supported by ICT systems and services suitable mainly for usage on outpatient, emergency and home care.

Expected impact

Expected impact will be availability of tools suitable for direct introduction of diagnostic into the framework local and emergency medical practice:

- Increased patient satisfaction enjoying the benefit of an immediate response on the part of its local physician, without the stress of specialist control;
- A qualitative leap in the outpatient, emergency and home care provision;
- Cost savings in diagnostic studies;
- Reduction of wait times for specialist centers and radiological specialist clinics that can engage effectively on a high level of investigation only, leaving out routine cases;
- Point of care of an integrated network that will support early hospital discharge, delivery of healthcare in remote, sparsely populated and difficult to access regions, eHealth services for mobile EU patients, and pre/post operation care outside the hospital environment;

3.1.3 THEME 2:
IMAGING GUIDED THERAPY PLANNING, DELIVERY AND MONITORING

Specific Challenges

Challenges to be addressed in this innovation area relate to improvements of clinical solutions for image-guided therapy, comprising imaging systems, interventional devices and implants, device tracking and navigation solutions, and software for therapy planning, prediction, and monitoring of delivery as well as outcome validation. In this area, the innovation focus for imaging systems is on optimal characterization for the lesion to be treated as well as for organs-at-risk, and on real-time therapy delivery and performance, allowing for online adaptation of therapy plans (e.g. in response to detected patient motion). In many cases, diagnostic or preparatory images from one modality have to be registered, potentially in real-time, with images acquired in during therapy delivery / monitoring, and the registration algorithms should be able to cope with organ motion and deformation. Interventional devices need to be visible in the respective imaging modalities, or localizable/trackable via suitable real-time navigation technology and/or steerable via suitable mechanisms, e.g. via robotic means. If intra-body sensors are used (imaging and other sensors), their signals need to be properly integrated with images from extra-body modalities, an example being the registration of an image from an endoscope with a virtual image of the same scene generated from a suitable CT data set. Imaging-based therapy monitoring must offer real-time performance or low latency, and provide not only anatomical information, but also information related to changes in tissue properties, like temperature, perfusion, metabolic state, or elastic properties in response to thermo-coagulation.

To ensure person-centered care, real-time decision support is needed to dynamically tailor interventions to optimize therapy delivery in the procedure room. All clinical solutions need to be streamlined for workflow in the procedure and in the broader context of department scheduling, and hospital operations. All solutions should be validated in a clinical context, which requires suitable software for viewing (including overlay of information from other modalities and of device models or other supportive graphics), planning, real-time user interaction with 3D data, and compliance with latency requirements in the case of real-time procedures.

Scope

Activities required to address these challenges, aiming at novel and improved systems for image-guided therapy delivery and monitoring (such as in MR-guided LINAC procedures for radiation therapy and MR-guided HIFU procedures for high intensity focused ultrasound ablation procedures), are:

CANCER TREATMENT

- for **minimally invasive interventional cancer therapy**: real-time imaging of changes in tissue properties in response to therapy - e.g. swelling, temperature increase, coagulation in response to thermal therapy, RF ablation, or other focal therapy– using MR- and / or Ultrasound-thermometry and / or elastography, or other tissue contract mechanism (see Theme 4)

- for **non-invasive cancer therapy**: real-time imaging of changes in tissue properties in response to externally heat generated, RF, radiation dose, or other focal energy deposited by external means - e.g. imaging of temperature distribution, tissue pH, tissue oxygen concentration, or therapeutic agent concentration - e.g. radiation sensitizers, drugs for photodynamic therapy, molecules for thermal therapy via externally applied RF fields, radioactive molecules which are locally released (as in SIRT[13]), or chemotherapeutic drugs contained in nanoparticle or microbubble carriers with suitable imaging contrast, to be subjected to image-guided targeted / localized release mechanisms

- for **interventional devices and sensors**: improved and intelligent catheters, biopsy and injection needles, ablation electrodes, stents, and valves which are optimally visible in relevant imaging modalities, sensors for intra-body imaging (e.g. Ultrasound, optical imaging and / or spectroscopy), for tissue and perfusion characterization (e.g. pressure, pH, oxygenation, flow perfusion, etc.), and intra-body therapy delivery devices (e.g. intravascular ultrasound, miniature X-ray sources and radioactive seeds for brachytherapy)

- for **device localization and navigation**: novel localization and navigation systems (electromagnetic, optical, ultrasonic) as well as shape sensing approaches (e.g. via fibre Bragg gratings).

- for **robotic positioning devices**: catheters which can be remotely steered via electromagnetic or mechanical means, robotic manipulators, both for positioning of devices relative to the patient (from outside the body) or for (micro) manipulation of endovascular device end effectors.

TREATMENT OF CARDIOVASCULAR DISEASE

- for **atherosclerosis or other causes of vessel stenosis**: novel methods for real-time (fluoroscopic, ultrasonic, or optical) imaging; quantitative imaging of changes in blood flow, including novel software for the determination of flow dynamics (such as flow speed, turbulence, fractional flow reserve, instantaneous wave-free ratio); quantitative determination of therapy-relevant information (lesion morphology, composition, stenotic degree, stent position relative to vessel anatomy), and novel methods for applications in the context of hybrid operating rooms[14]

- for **Arrhythmia**: real-time fusion/integration of information and predictive modeling for interventional decision support from different 3D information sources, e.g. registration of pre-interventional CT and/ or MRI, endocardial mapping, trans-esophageal echo (TEE) with 2D X-Ray or 3D MR fluoroscopy, suitable viewing of the integrated information, hemodynamic monitoring, catheter-based ablation devices with imaging capability for validation of the "transmurality" of lesion formation, guidance for optimal electrode lead placement e.g. in cardiac resynchronization therapy.

- for **interventional devices and sensors**: improved catheters, stents, and valves which are optimally visible in relevant imaging modalities, sensors for intra-body imaging (e.g. ultrasound, optical imaging and / or spectroscopy), for tissue characterization (e.g. pressure, pH, oxygenation, composition), and intra-body therapy delivery devices (e.g. RF, ultrasound ablation)

- for **catheter steering and localization**: catheters which can be remotely steered via electromagnetic or mechanical/robotic means and which can be located via electromagnetic localizers or optical shape sensing approaches.

TREATMENT OF NEURODEGENERATIVE DISEASE

- for **Parkinson's Disease**: Improved 2D X-Ray and 3D MR fluoroscopic imaging for electrode placement in conjunction with pacemaker implantation

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13 Wikipedia: "**Selective internal radiation therapy** (SIRT) is a form of radiation therapy used to treat cancer. The treatment involves injecting tiny microspheres of radioactive material into the arteries that supply the tumor."
14 Wikipedia: "A **hybrid operating room** is a surgical theatre that is equipped with advanced medical imaging devices such as fixed C-Arms, CT scanners or MRI scanners"

Expected deliverables

Expected deliverables are new and/or improved clinical solutions for image-guided therapy, comprising novel imaging and therapy delivery devices and systems in conjunction with intelligent sensors and device localization means, for increased clinical accuracy and efficiency, leading to better patient outcomes, which will be validated through suitable clinical trials.

Expected Impact

Expected impact will be an increase of the number of patients which are treatable, less invasiveness of the treatments, translating to lower risk and shorter hospitalization and rehabilitation times. Clinical throughput will increase since higher volumes of patients in need can be addressed with the same resources given the improved workflow and outcomes. The impact on society will be reduced mortality

for the major diseases and reduced cost. The research base will benefit from an increased understanding of clinical and patient needs for all contributors to the innovation across the involved industries (devices, imaging, navigation systems) and clinical disciplines.

3.1.4 THEME 3:
IMAGING BASED THERAPY PLANNING AND RESPONSE ASSESSMENT / OUTCOME PREDICTION

Specific Challenges

Challenges to be addressed in this innovation area relate to improvements in efficiency and patient outcomes of treatments which use images as the basis for a minimally-invasive or non-invasive approach. In the first case, a specific task is to define the path for each respective interventional device (catheter, needle, or electrode) to the target anatomy, based on diagnostic images in which the lesion is visible. In the second case (non-invasive therapy), the primary task is to plan for the optimum dose distribution (of radiation, heat, or other cytotoxic agent) to be delivered to the target, while maximally sparing nearby normal issue in organs-at-risk.

In most cases, real-time imaging is available during the procedure, and the plan, as well as the treatment delivery (e.g. dose), may have to be adjusted to changes in anatomy and function, preferably in real time. Furthermore, if the imaging method used for real-time monitoring does not provide sufficient lesion contrast, the diagnostic images may have to be overlaid onto the intra-procedural images, again using deformable registration, preferably in real time.

To ensure person-centered care, decision support is needed to deal up-front with co-morbidities and other person-specific factors known to modulate response to treatment e.g. genetic and epigenetic factors.

Ideally, the treatment can be monitored by the applying clinician using the intra-procedural real-time imaging modality, in order to make sure damage to organs-at-risk is avoided. This can employ imaging of energy deposition, tissue temperature, elasticity, and other therapy-related parameters. The measurement of these parameters can also be used to validate that a stent has been correctly placed or that the delivered thermal energy or dose distribution actually agrees with the plan. This will allow for improved outcome prediction and provide information about the probability of complications.

Both planning and response assessment require suitable tools for sophisticated information viewing, processing, and user interaction (e.g. haptics, augmented reality, etc.), device control and knowledge-based decision support (including scheduling and reporting), as well as an integration with patient records, image archives and data bases via a suitable Healthcare IT infrastructure.

Scope

Activities in order to address these challenges, aiming at novel and improved systems for therapy planning, monitoring, response assessment and outcome prediction are required in the following areas:

CANCER TREATMENT
- for **minimally invasive interventional cancer therapy**: interventional path planning, simultaneous real-time visualization of device models and therapy plans on top of fused diagnostic and fluoroscopic or ultrasound imaging data, imaging-based tissue characterization, ablation therapy simulation and modeling, imaging for quantitative assessment of agent/drug concentrations and therapy effects, outcome prediction and validation software tools, detection of organ motion and deformation, software supporting real-time adaptation of therapy plans to account for such effects.

- for **non-invasive cancer therapy**: software for identification and characterization of target and at-risk organs and tissue

properties (e.g. tissue oxygenation, elasticity, temperature) from images, computation of energy deposition for different therapy approaches (MR-HIFU, MR-LINAC, External Beam Radiation Therapy), simulation / modeling of therapy, investigation of biological effects of therapy and prediction of outcome, software for handling motion and deformation as mentioned above.

- for **interventional devices and sensors**: computer models of devices (geometry and therapeutic action depending on control parameters, e.g. for thermo-ablation), image segmentation / machine vision and decision support software for detection of devices and implants relative to target and risk organs and for adaptive planning
- for **device localization and navigation**: models of localization and navigation means / processes and of systematic errors, and respective prediction of overall location-dependent accuracy
- for **robotic positioning devices**: models of the devices, their kinetic behavior (degrees of freedom and operational volume), and location-dependent accuracy

TREATMENT OF CARDIOVASCULAR DISEASE

- for **atherosclerosis or other causes of vessel stenosis**: computer models of fluid dynamics and biological fluid-structure interactions in vessels, planning software using these
- for **Arrhythmia**: real-time fusion/integration of information and quantitative modeling from different 3D information, e.g. registration of pre-interventional CT and/ or MRI, endocardial mapping, trans-esophageal echo (TEE) with 2D X-Ray or 3D MR fluoroscopy, suitable viewing of the integrated information, catheter-based ablation devices with imaging capability for validation of lesion transmurality.
- for **interventional devices and sensors**: computer models (and libraries) of available implants (stents, grafts, valves, …) and their properties (e.g. size and shape before and after unfolding), computer models of sensors and their properties, to be used in planning & monitoring software
- for **catheter steering and localization**: models of steering mechanisms to be taken into account in planning

NEURODEGENERATIVE DISEASE

- for **Parkinson's Disease**: dedicated brain model (atlas of morphology and function) to be taken into account in therapy planning

Expected deliverables
Expected deliverables are new and/or improved tools for planning of more accurate image-guided therapy, comprising models of delivery devices and systems in conjunction with computer models of the biophysical therapeutic processes in vivo, as well as for validation and outcome prediction.

Expected Impact
Expected Impact will be improved efficiency and accuracy of treatments, translating to lower risk, shorter duration, higher patient volumes, more efficient throughput, and lower cost of procedures. The impact on society will be reduced mortality for the major diseases and reduced cost for therapeutic procedures. The research base will benefit from an increased understanding of the parameters in therapy planning which are critical to therapy success.

3.1.5 THEME 4:
ENABLING TECHNOLOGIES FOR NOVEL IMAGING AND IMAGE-GUIDED THERAPY APPROACHES

Innovative enabling technologies for imaging and image-guided therapy comprise novel, disruptive components for existing imaging systems, completely new imaging methods, or novel approaches towards biomarker quantification or imaging of tissue properties or functions not previously assessable.

3.1.5.1 NOVEL RADIATION DETECTOR TECHNOLOGY

Specific challenges
Challenges to be addressed in this innovation area relate to improvements in dose exposure, imaging field-of-view, sensitivity, spatial, temporal, and contrast resolution, as well robustness to artifacts for existing and novel imaging systems which are based on radiation (X-Ray, CT, SPECT, PET).

Scope
Activities in order to address these challenges are required in the following areas:
- for **digital detector technology**: novel scintillator materials, novel photodetectors, advanced materials for direct conversion detectors, novel solid state detectors (using e.g. CMOS technology) with "active/intelligent" pixels, novel calibration and correction approaches
- for **photon counting detectors**: use of novel direct conversion materials for the assembly of photon counting detectors suitable for very high count rates and high spatial resolution

Expected deliverables
Expected deliverables will be new, cost-effective, digital detectors, ready for integration into systems.

Expected Impact
Expected impact will be creation of novel imaging systems with unprecedented capabilities (see below).

3.1.5.2 ENERGY-RESOLVED X-RAY AND COMPUTER TOMOGRAPHY IMAGING SYSTEMS

Specific challenges
Challenges to be addressed in this innovation area relate to the introduction of a new dimension for X-ray based imaging systems: energy resolution, allowing to capture diagnostic information not previously assessable. Energy resolution enable improved diagnosis in X-Ray (e.g. by eliminating bones) and turn CT into a truly quantitative imaging modality, allowing for improved tissue characterization and precise determination of local concentration of novel molecular contrast agents for k-edge imaging.

Scope
Activities in order to address these challenges are required in the following areas:
- for **energy-resolved X-Ray systems**: integration of energy-resolving detectors with high dynamic range into flat panel based X-ray systems, calibration and correction software, automatic bone reduction and other intelligent post-processing algorithms;
- for **energy-resolved ("Spectral") CT systems**: integration detectors with high energy-resolution and high dynamic range into CT systems, novel image reconstruction, analysis and interpretation approaches for spectral CT, including algorithms for quantitative information extraction;

Expected deliverables
Expected deliverables are imaging systems with advanced and disruptive capabilities for the quantitative extraction of diagnostic information, therapy planning, monitoring, and outcome prediction.

Expected Impact
Expected impact will be improved diagnostic and treatment capabilities with huge patient benefits.

3.1.5.3 MAGNETIC PARTICLE IMAGING

Specific challenges
Challenges to be addressed in this innovation relate to Magnetic Particle Imaging (MPI) systems and imaging protocols. MPI is a completely new imaging modality, currently only available for small animal imaging, which holds promise regarding highly sensitive and ultrafast volumetric angiographic, functional and molecular imaging based on iron oxide nanoparticle tracers. Clinical viability for this new pre-clinical modality is challenging and the compelling need with associated evidence / proof points in clinical populations to be proven.

Scope
Activities in order to address these challenges are required in the following areas:
- for **innovative clinical systems**: components and concepts for new imaging geometries, efficient field generating coil geometries and power amplifiers, novel ultra-low noise signal amplifiers;
- for **MPI data acquisition protocols and advanced applications**: acquisition protocols for imaging of the cardiovascular system (in particular the coronary arteries), real-time determination of functional parameters (flow, organ perfusion and motion, pharmacokinetics, tumor rim enhancement, real-time imaging of MPI-visible interventional devices and implants, manipulation of magnetic devices using the magnetic field generation capabilities of MPI, therapeutic applications of MPI for RF heating of therapeutic nanoparticles, molecular imaging of functionalized particles, tracking of iron oxide labeled therapeutic cells;

Expected deliverables
New MPI systems and applications, enabling new diagnostic imaging examinations and procedures for real-time 3D fluoroscopic interventional imaging without radiation. Demonstration of validated clinical need and effectiveness of this modality in terms of impact on healthcare outcomes and costs to society will be expected in these activities.

Expected Impact
Patient benefit from novel diagnosis and image-guided therapy approaches.

3.1.5.4 HYPERPOLARIZED MRI

Specific challenges
Challenges to be addressed in this innovation area relate to improvements of Magnetic Resonance Imaging in new applications requiring high sensitivity, e.g. for the study of in-vivo metabolic processes.

Scope
Activities in order to address these challenges are required in the following areas:
- for **equipment for hyperpolarizing suitable substances**: improved systems based on dynamic nuclear polarization principles, and systems based on novel optical hyperpolarization approaches based on orbital angular momentum transfer, allowing on-the-fly hyperpolarization
- for **novel applications of hyperpolarized MRI**: translational research towards novel clinical protocols, e.g. for in-vivo metabolism studies in Oncology, and their clinical validation

Expected deliverables
Expected deliverables are novel or improved systems for hyperpolarization of substances and validated applications based on suitable imaging and spectroscopic imaging protocols.

Expected Impact

Expected impact will be patient benefit from novel MRI capabilities in diagnosis, therapy planning and execution based on personalized information about in-vivo metabolism.

3.1.5.5 X-RAY PHASE CONTRAST IMAGING

Specific challenges

Challenges to be addressed in this innovation area relate to novel imaging systems using coherent X-ray beams, allowing to create a new type of contrast, providing additional diagnostic information.

Scope

Activities in order to address these challenges are required in the following areas:

- for **X-Ray phase contrast imaging (XPCI) systems**: systems for XPCI mammography and "tomosynthesis", with optimized geometries for the coherence-generating gratings, concepts for phase contrast CT, methods for calibration, artifact reduction, and image reconstruction.
- for **novel applications of XPCI**: tools to visualize/present the XPCI information to the radiologist in conjunction with the information based on X-ray absorption, development of new diagnostic procedures for suitable applications, and their clinical validation

Expected deliverables

Expected deliverables are novel XPCI-based imaging systems enabling improved diagnosis.

Expected Impact

Expected impact will be patient benefit from more accurate diagnosis for specific diseases.

3.1.5.6 MR- AND ULTRASOUND-BASED IMAGING OF NOVEL TISSUE PROPERTIES

Specific challenges

Challenges to be addressed in this innovation area relate to enabling imaging of novel tissue properties with MRI and Ultrasound, aiming to extract novel information, preferably in real time, for improved diagnosis and monitoring of image-guided therapy, in particular of thermal ablation therapy.

Scope

Activities in order to address these challenges are required in the following areas:

- for **Magnetic Resonance Imaging**: systems and methods for precise, reproducible, and quantitative (vendor-independent) imaging of tissue properties such as temperature, elasticity, oxygen concentration, pH value and tissue conductivity, and for quantitative determination of concentrations of molecular labels (in drugs, therapeutic cells, etc.)
- for **Ultrasound Imaging**: system and methods for precise, reproducible, and quantitative (vendor-independent) imaging tissue properties such as temperature, elasticity, and for quantitative determination of concentrations of microbubble drug containers.

Expected deliverables

Expected deliverables are novel or improved MR and ultrasound systems with extended capabilities.

Expected Impact

Expected impact will be patient benefit from novel MR and US capabilities in diagnosis and therapy.

3.1.5.7 NOVEL INTERROGATION MODALITIES E.G. OPTICAL COHERENCE TOMOGRAPHY, PHOTOACOUSTIC, DIFFUSE OPTICAL TOMOGRAPHY, ELECTRICAL IMPEDANCE TOMOGRAPHY, ETC.

Specific challenges

Challenges to be addressed are related to the morphological and functional characterization capabilities of new modalities, including performance specifications spanning spatiotemporal resolution, contrast resolution, acquisition speed, penetration depth and miniaturization. Also, extensive Health Technology Assessment is due for new technologies.

Scope

Activities will be required for reaching faster real time systems, with deeper penetration and with the optimal physical size of the probes according to the clinical application.

Expected deliverables

Expected deliverables are improved second generation systems with established and validated clinical applications. The clinical effectiveness and impact of these new systems in population health assessments will be expected as an essential element to determining clinical viability and adoption.

Expected Impact

Expected impact will be patient benefit from novel modality derived information in diagnosis and therapy.

3.1.5.8 HYBRID IMAGING SYSTEMS

Specific challenges

Challenges to be addressed in this innovation area relate to novel and improved combinations of different modalities into hybrid imaging systems offering advantages in workflow and functionality.

Scope

Activities in order to address these challenges are required in the following areas:

- for **PET-MR and SPECT-MR Systems**: integration for simultaneous acquisition capabilities (removing or minimizing sources of mutual interference), calibration and MR-based attenuation correction, applications and post-processing algorithms for utilizing simultaneity (e.g. pharmacokinetic analysis, MR-based motion correction for PET and SPECT reconstruction);
- for **CT-MPI and MRI-MPI Systems**: integration for acquiring anatomical reference images for MPI, utilization of simultaneity for functional MRI-MPI imaging, pharmacokinetic analysis and real-time therapy monitoring and outcome validation based on both modalities;
- for **Hybrid Systems Employing Ultrasound for Image-Guided Therapy**: combinations of X-Ray fluoroscopy, CT or MRI with 3D ultrasound for real-time monitoring and outcome validation;

Expected deliverables

Expected deliverables are novel or improved hybrid systems with extended capabilities. The clinical effectiveness and impact of these new systems in population health assessments will be expected as an essential element to determining clinical viability and adoption.

Expected Impact

Expected impact will be patient benefit from novel hybrid system capabilities in diagnosis and therapy.

3.1.5.9 ADVANCED USER INTERFACE TECHNOLOGY

Specific challenges

Challenges to be addressed in this innovation area relate to novel and improved technologies for the interaction between technologists

and radiologists with systems for diagnostic imaging and image-guided therapy, addressing presentation of information to users (e.g. augmented reality or virtual reality for novel immersive systems for visualization and interpretation of information immediately within the context of the clinical setting itself), efficiency and intuitiveness of interaction (touch, voice, gestures, haptic feedback) and latency requirements (hand-eye coordination). Better user interfaces will allow the systems to be handled by less skilled users, e.g. in growth markets.

Scope

Activities in order to address these challenges are required in the following areas:

- for **Information Presentation**: novel methods for presentation of 3D and 4D (3D over time) multi-modality image data (e.g. holographic display), overlay of geometric (e.g. device models) and functional (e.g. flow, pharmacokinetic) information over diagnostic or fluoroscopic images, using e.g. augmented reality or virtual reality concepts and approaches

- for **User Interaction**: novel methods for intuitive interactive manipulation of 3D and 4D (3D over time) multi-modality image data (e.g. holographic display), overlay of geometric (e.g. device models) and functional (e.g. flow, pharmacokinetic) information over diagnostic or fluoroscopic/ultrasonic images

Expected deliverables

Expected deliverables are imaging systems with more efficient user interfaces, requiring less specialization and time-consuming expert training. More streamlined means of educating clinical staff with platforms that offer more natural interaction and learning than conventional systems.

Expected Impact

Expected impact will be increased efficiency and shorter procedure times, leading to lower cost.

3.1.5.10 IMAGE RECONSTRUCTION, PROCESSING AND INTERPRETATION

Specific challenges

Challenges to be addressed in this innovation area relate to improvements of image reconstruction speed and quality - e.g. for iterative reconstruction of low-dose CT images, and improved speed and outcome of post-processing algorithms in the areas of image segmentation and elastic image registration, as well as faster and better software tools for computer-assisted image analysis and interpretation, in particular in the context of knowledge-based decision support systems for person-centered care.

Scope

Activities in order to address these challenges are required in the following areas:

- for **Image Reconstruction**: novel algorithms for iterative reconstruction (and calibration, artifact correction, etc.) for all tomographic imaging systems, novel approaches to compounding / volume stitching (integration of sub-volume images into a single compounded, larger data set);

- for **Hardware Accelerated Computation**: employing multi-core computer architectures and networks of advanced graphic processing units (GPUs) for the acceleration of the above-mentioned types of algorithms and for addressing the above-mentioned challenges;

Expected deliverables

Expected deliverables are improved speed and real-time capabilities for volumetric imaging systems.

Expected Impact

Expected impact will be patient benefit from more efficient diagnosis and real-time therapy guidance.

3.1.6 THEME 5:
DEVICES AND TECHNOLOGIES FOR IMAGE-GUIDED INTERVENTIONS

Image-guided intervention procedures benefit from innovations in intelligent devices and implants, and medical robotic technologies allowing to efficiently place these inside the body.

3.1.6.1 INTELLIGENT INTERVENTIONAL DEVICES AND IMPLANTS

Specific challenges

Challenges to be addressed in this innovation area relate to novel and improved and "intelligent" interventional devices and implants such as needles and catheters with integrated sensors (e.g. ultrasound and optical / spectroscopic imaging) and actuators (drug release, biopsy tissue harvesting, focal ablation or generation of therapeutic radiation), and with features supporting localization and tracking (e.g. optical shape sensing) as well as (mechanic or electromagnetic) steering capabilities, and stents, valves and other implants with sensors and potentially even wireless communication capabilities.

Scope

Activities in order to address these challenges are required in the following areas:

- for **Intelligent Devices**: novel catheters, needles and therapeutic devices (e.g. electrodes, ultrasound or radiation-generating probes) with good visibility / contrast in the relevant interventional imaging modalities (X-ray, MR, Ultrasound, MPI), miniaturized imaging or therapy devices suitable for integration with such devices (e.g. OCT, Optical spectroscopy, cMUT ultrasound transducers, miniaturized X-Ray sources, lasers), integrated mechanisms for focusing therapeutic heat or radiation, drug release, pressure and elasticity sensors, and sensors for characterizing the chemical / molecular environment at the needle/catheter tip;

- for **Intelligent Implants**: implants with high visibility / contrast in relevant imaging modalities (as above for devices), sensing and wireless communication capabilities, mechanically intelligent design for optimal endoluminary insertion, placement, and mechanical unfolding;

Expected deliverables

Expected deliverables are novel or improved devices and implants with extended capabilities.

Expected Impact

Expected impact will be patient benefit from more efficient, intelligent therapies with better outcome.

3.1.6.2 MEDICAL ROBOTICS FOR IMAGING AND IMAGE-GUIDED THERAPY

Specific challenges

Challenges to be addressed in this innovation area relate to means of supporting image-guided interventions with novel or improved robotics-based technology for computer-assisted or interactive placement of interventional devices according to predefined therapy plans or fluoroscopic feedback.

Scope

Activities in order to address these challenges are required in the following areas:

- for **Automated Robotic Placement of Rigid Devices**: innovative manipulator concepts with suitable safety features for computer-controlled placement of rigid devices into the body (typically: needles, electrodes, rigid endoscopes), with application-dependent degrees of freedom;

- for **Robotic Devices with End-Effectors**: innovative interventional devices capable of manipulating tissue locally inside the

body via suitable miniaturized end-effectors (biopsy harvesting, suturing, positioning distal sensors or therapeutic actuators of any nature relative to a local, in-body target;

- for **Interactive Robotic Navigation of Flexible Devices**: robotically controlled catheters or flexible endoscopes, wireless control of self-propelled devices inside the body;

Expected deliverables

Expected deliverables are extended placement and positioning capabilities of interventional devices.

Expected Impact

Expected impact will be patient benefit and shortened procedure times (with associated cost reduction potential) enabled by the use of advanced interventional devices with robotic capabilities.

3.1.7 THEME 6:
CONTRAST AGENTS, TRACERS AND DRUG CONTAINERS

Nanoparticle and molecular engineering technologies have enabled the development of novel imaging contrast agents and tracers, for oncologic, neurologic and cardiovascular disease conditions.

3.1.7.1 NANOPARTICLE IMAGING CONTRAST AGENTS / TRACERS FOR ONCOLOGY AND NEUROLOGY

Specific challenges

Challenges to be addressed in this innovation area relate to novel or improved contrast agents and tracers supporting diagnostic imaging and image-guided interventions. Contrast agents and tracers are fundamental to a large number of respective procedures and need to be optimized for safety and image contrast at minimal doses. New radiopharmaceutical tracers should exhibit minimal logistic requirements and maximal specificity for the investigation at hand. For a number of innovative imaging systems (e.g. MPI, and Spectral CT using k-edge imaging involving Gold and Bismuth) no tracers are available yet which have received regulatory approval for use on humans. Challenges include (fluorescent) tracers for pre-clinical and translational optical imaging. The scope of nanoparticles includes functionalized particles which attach to target molecules specific to the disease (process) under consideration, and to therapeutic particles - such as particles for thermal therapy via external RF excitation or particles used as containers of drugs or other therapeutic molecules suitable for localized release by external means under imaging control.

Scope

Activities in order to address these challenges are required in the following areas:

- for **Contrast Agents**: novel, oncology-specific clinical X-ray, CT and MRI contrast agents with low side effects and high contrast at low dose, novel pre-clinical contrast agents suitable for translational molecular imaging, including optical contrast agents, novel microbubble contrast agents for ultrasound (preferably suitable as containers of therapeutic molecules), novel concepts and agents for multi-modality contrast (e.g. MRI contrast agent in microbubble containers), contrast agents with functionalized molecules for targeting specific pathologies or metabolites.

- for **Tracers and Functionalized Particles**: novel radioactive tracers for PET and SPECT with high specificity and minimal radiopharmaceutical logistics requirements (depending on half-life of isotopes), iron oxide MPI tracers for intravenous and oral administration (yielding maximum MPI signal and allowing for high spatial resolution in MPI), tracers based on functionalized particles for targeting specific pathologies or metabolites via (molecular) imaging, and tracer particles /molecules for labeling and tracking / localizing drugs, therapeutic cells or (e.g. coated) implants.

- for **Therapeutic Agents and Molecules**: Novel molecules and viral vectors suitable for imaging in the context of targeted therapy (thermal, drug or gene therapy), novel particles suitable for thermal therapy via external RF excitation (e.g. gold, iron oxide

particles), particles with other therapeutic effects which can be locally triggered by external means under image-based monitoring (photosensitizers, radiosensitizers, drugs activated locally by focused ultrasound), particles which can be used as drug containers (e.g. liposomes) allowing for targeted delivery, mechanisms which allow for imaging-based determination of (therapeutic) cell viability.

Expected deliverables
Expected deliverables are novel or improved contrast agents and tracers with extended capabilities.

Expected Impact
Expected impact will be patient benefit from novel imaging and therapy approaches employing these.

3.1.7.2 NANOPARTICLE IMAGING CONTRAST AGENTS / TRACERS FOR CARDIOVASCULAR DISEASES

Scope
Activities in order to address these challenges are required in the following areas:

- for **Contrast Agents**: novel, oncology-specific clinical X-ray, CT and MRI contrast agents with low side effects and high contrast at low dose, novel pre-clinical contrast agents suitable for translational molecular imaging, including optical contrast agents, novel microbubble contrast agents for ultrasound (preferably suitable as containers of therapeutic molecules), novel concepts and agents for multi-modality contrast (e.g. MRI contrast agent in microbubble containers), contrast agents with functionalized molecules for targeting specific pathologies or metabolites:

- for **Tracers and Functionalized Particles**: novel radioactive tracers for PET and SPECT with high specificity and minimal radiopharmaceutical logistics requirements (depending on half-life of isotopes), iron oxide MPI tracers for intravenous and oral administration (yielding maximum MPI signal and allowing for high spatial resolution in MPI), tracers based on functionalized particles for targeting specific pathologies or metabolites via (molecular) imaging, and tracer particles /molecules for labeling and tracking / localizing drugs, therapeutic cells or (e.g. coated) implants;

- for **Therapeutic Agents and Molecules**: Novel molecules and viral vectors suitable for imaging in the context of targeted therapy (thermal, drug or gene therapy), novel particles suitable for thermal therapy via external RF excitation (e.g. gold, iron oxide particles), particles with other therapeutic effects which can be locally triggered by external means under image-based monitoring (photosensitizers, radiosensitizers, drugs activated locally by focused ultrasound), particles which can be used as drug containers (e.g. liposomes) allowing for targeted delivery, mechanisms which allow for imaging-based determination of (therapeutic) cell viability;

Expected deliverables
Expected deliverables are novel or improved contrast agents and tracers with extended capabilities.

Expected Impact
Expected impact will be patient benefit from novel imaging and therapy approaches employing these.

3.1.8 THEME 7:
IMAGING RELATED ICT

Specific challenges
Challenges to be addressed in this innovation area relate to improvements of person-centered care. It addresses the overall quality of care via information technology, supporting efficient workflow along the patient pathways and for a specific disease, and enabling care givers to adhere to clinical guidelines and other best practice standards such as the most appropriate image acquisition protocols associated with lowest risk to the patient (e.g. minimizing radiation dose and risks arising from use of contrast agents). Full access to patient data and knowledge sources (e.g. on clinical guidelines, side effects) and data bases for every procedure along the patient pathway (without repeated, error-prone entry of similar information) requires seamless integration of imaging and image-guided therapy

procedures into information systems. IT connectivity and decision support for patients and clinical staff are required on departmental, hospital, and regional health network level, and data and (digital, standardized) reports containing the information extracted from images need to be transferable among clinical specialist (e.g. in multi-disciplinary tumor boards) and to the referring physician.

Scope

Activities in order to address these challenges, aiming at novel and improved healthcare information technology software tools and systems in support of imaging-related procedures, are required in the following areas:

CANCER

- for **Screening and Early Detection**: oncology information systems and connectivity software for archiving, distribution and processing of images, tools for computer-assisted image analysis, interpretation and annotation, tools for integrating imaging information with non-imaging information and for structured reporting of imaging findings to referring physicians, software for information import from and export to cancer registry software, IT support for tele-radiology and remote consulting,

- for **Staging and Choice of Therapy**: integration of digital pathology information and processing of automatically extracted information from respective images, tools for collaborative decision making by multi-disciplinary cancer care teams, tools for knowledge-based decision support for choosing between alternative therapy regimes and for selection of patients regarding clinical trial eligibility, tools supporting the scheduling of imaging and image-guided therapy procedures, tools to extract quantitative imaging biomarker information for tumor metabolism analysis and identification of potential responders (personalized medicine) to specific therapy regimes

- for **Therapy Delivery, Monitoring and Outcome Prediction**: tools to establish inter-operability and communication between imaging and image-guided therapy systems and between therapy planning and delivery systems from different vendors, archiving, retrieval and real-time streaming data transmission support for high bandwidth 2D and 3D imaging during therapy delivery, IT support for structured dose reporting related to X-Ray-based imaging

CARDIOVASCULAR DISEASE AND NEURODEGENERATIVE DISEASE

- for **Diagnostic Workup / Triage and Choice of Therapy**: Cardiovascular and neurology information systems and connectivity software for archiving, distribution and processing of images, tools for computer-assisted, knowledge-based image interpretation and annotation, tools for integrating imaging information with non-imaging information and for structured reporting of image-derived diagnostic information to referring physicians, IT support for tele-radiology / consulting, IT tools enabling the integration of implant / device library information into therapy planning;

- for **Therapy Delivery, Monitoring and Outcome Validation**: tools to establish inter-operability and communication between diagnostic imaging systems and fluoroscopic interventional imaging systems and sensors from different vendors, archiving of real-time streaming data from high bandwidth 2D and 3D fluoroscopic imaging (X-ray/CT, Endoscopic, MRI, Ultrasound, Magnetic Particle Imaging) during therapy delivery, IT support for structured dose reporting related to interventional X-Ray-based imaging;

Cutting across all phases of care and clinical application, activities will be required in developing and curating Big Data population health repositories which integrate imaging and non-imaging biomarker metrics. Voluminous Big Data archives will require corresponding data mining and analytics development to generate actionable insights about disease screening, diagnosis, management, and outcomes trends.

Expected Deliverables

Expected deliverables are new and/or improved health information technology practices / process workflows, infrastructure, algorithms, and technical/clinical standards, e.g. for system interoperability, that enable precision medicine which utilizes the entire spectrum of available population health information spanning imaging and non-imaging studies. Validation of clinical effectiveness as well as impact on patient outcomes and health care system costs will be key deliverables expected of these activities.

Expected impact

Successful activities in this domain will enable person-centered care delivery and generate a wealth of insights about population health and the translation of those insights into actionable tasks in the delivery of precision medicine. Overall healthcare operations should

be streamlined with the delivery of the right care to the right patient and the right time to minimize length of hospital stays, maximize quality of life, and minimize costs to society.

3.1.9 THEME 8:
CLINICAL VALIDATION STUDIES

Clinical validation studies provide evidence of clinical value from the application in a clinical context, evidence which will become increasingly important for the adoption of new medical technologies. Clinical trials can be formulated to prove benefits relating to a number of performance criteria, e.g. to efficiency / throughput, ease-of-use / user skill requirements, patient waiting times, survival times and quality-of-life improvements resulting from improved outcomes, improved collaboration between care providers, and, last but not least, patient satisfaction. Results from clinical trials are primarily intended for and used as evidence in regulatory approval processes, but can also create results which are suitable for marketing to both care providers and the patients, who increasingly accept out-of-pocket payments for innovative procedures.

Furthermore, clinical trials for disease-focused solutions provide evidence of clinical value for all the contributors of components to that solution at the same time, e.g. the providers of the involved imaging system(s), the providers of the interventional device(s) and the navigation technology employed, and the provider of the software tools and IT infrastructure solution. Thus, the investments into clinical validation per participating industrial vendor could be reduced (given that the overhead costs could be shared to some extent), and cross-industry collaboration is supported. This strengthens the role of the public-private partnership underlying the envisaged funding scheme as an innovation acceleration concept.

3.1.9.1 CLINICAL TRIALS FOR VALIDATING NOVEL IMAGING APPROACHES AND IMAGING AS A BIOMARKER

Challenges
Challenges to be addressed in this area relate to defining clinical trials such that the envisaged disease-focused clinical solutions can be validated in a manner that medical evidence for key performance indicators can be established, clearly proving the value/ benefit of innovations with breakthrough character and high disruption potential such as most of those mentioned in section 2.2.1 and 2.3.1. Quantitative imaging as a biomarker – in some cases as surrogate endpoint – has become the most important paradigm in medical imaging science, as the key to assessing disease in-vivo[15]. As new imaging methods claim to be quantitative, clinical validation becomes even more important than in the past.

Activities
Activities in order to address these challenges are required in the following areas:
- for **Novel Imaging Approaches**: validation of clinical solutions involving novel energy-resolved X-Ray and computer tomography imaging systems, Magnetic Particle Imaging, Hyperpolarized MRI, X-Ray Phase Contrast Imaging, and hybrid Imaging Systems,

  for **(Quantitative) Imaging as a Biomarker**: validation of clinical solutions involving novel software tools for image segmentation and registration, approaches to computer-assisted image analysis and interpretation, quantitative MR- and Ultrasound-based imaging of novel tissue properties, quantitative imaging of concentrations of tracers and tracer-labeled drugs and therapeutic molecules and cells using spectral CT, MRI, Ultrasound and MPI, verification of accuracy of absolute quantification methods

Expected Deliverables
Expected deliverables are evidence that innovations lead to increased efficiency, cost reduction, improved outcome, and other key performance indicators, and novel metrics for their measurement

Expected Impact
Expected impact will be accelerated acceptance of validated innovations by payers and care providers.

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15 "Major Trends in the Imaging Sciences: 2007 Eugene P. Pendergrass New Horizons Lecture", Elias A. Zerhouni, Radiology. 249(2): 403–409, Nov. 2008 – available for download

3.1.9.2 CLINICAL TRIALS FOR NOVEL IMAGE-GUIDED THERAPY SOLUTIONS

Challenges

Challenges to be addressed in this area relate to defining clinical trials such that the envisaged disease-focused clinical solutions can be validated in a manner that medical evidence for key performance indicators can be established, clearly proving the value/ benefit of innovations with breakthrough character and high disruption potential such as those mentioned in section 3.1.6 and 3.1.8.
Clinical validation trials involving respective innovations need to establish evidence that image-guided therapy solutions allow a less invasive procedure approach, higher precision of interventions, more focal therapies with improved sparing of organs-at-risk, improved outcomes and survival rates, and higher quality of life for patients through reduced complication rates and long-term side effects.

Activities

Activities to address these challenges are required in the following areas:

- for **Minimally Invasive Interventional Therapy Delivery and Monitoring**: validation of clinical solutions involving novel interventional devices employing in-body sensors and delivery devices, novel imaging methods for planning and guiding of the interventional approach towards the target, the focal delivery of the therapy, and for the quantitative real-time monitoring or immediately post-delivery in-vivo assessment of tissue response to therapy.
- for **Non-Invasive Image-Guided Therapy Delivery and Monitoring**: validation of clinical solutions involving novel therapy approaches employing ultrasound-, RF-, radiation- or ion beam based energy delivery from outside the body, planned, guided and monitored by real-time imaging of morphology for organ motion and deformation detection and of tissue properties, e.g. for risk organ protection

The Therapy Planning and Response Assessment components of the above two activities include validation of clinical solutions for the (knowledge-based) planning of the interventional path(s) to the target(s) and the local delivery of therapeutic doses of e.g. heat, radiation dose, or drugs, real-time adaptation of plans in order to correct for organ motion and deformation, unforeseen changes in the evolving distribution of heat, dose or local drug concentration delivered, and imaging of tissue property changes in response to the delivered therapy, for confirmation of delivery of therapy according to plan, i.e. outcome validation.

Expected deliverables

Evidence that innovations lead to increased efficiency, cost reduction, improved outcome, and other key performance indicators, as well as novel metrics for measuring them.

Expected impact

Expected impact will be accelerated acceptance and wide scale deployment of validated innovations by payers and care providers.

3.1.9.3 CLINICAL TRIALS FOR VALIDATING NOVEL HEALTHCARE IT SOLUTIONS

Challenges

Challenges to be addressed in this innovation area relate to defining clinical trials such that the contribution of novel healthcare IT solutions to be validated, such as those mentioned in section 2.2.4, can be validated independently from the imaging systems and treatment delivery approaches applied in the respective clinical solution(s) under consideration.

Activities

Activities in order to address these challenges are required in the following areas:

- for **Oncology**: validation of clinical solutions involving novel oncology information systems, tools for computer-assisted image analysis, interpretation and annotation, IT solutions for information management (involving imaging information from diagnosis and digital pathology and non-imaging information), decision support tools and tools supporting inter-disciplinary team collaboration (radiology, radiation oncology, medical oncology, surgery), IT solutions for workflow management including structured reporting of

imaging findings to referring physicians, information import from and export to cancer registry software, and IT support real-time high bandwidth transmission of 2D and 3D fluoroscopic streaming data, and for tele-radiology and remote consulting;

- for **Cardiovascular Disease and Neurodegenerative Disease**: validation of clinical solutions involving novel cardiovascular and neurology information systems, inter-operability between diagnostic imaging systems and fluoroscopic interventional imaging systems and sensors from different vendors, connectivity software, tools for computer-assisted, knowledge-based image interpretation and annotation, tools for structured reporting of information on diagnostic findings and outcome of catheter-based interventions to referring physicians, IT support for tele-radiology / consulting, IT tools enabling the integration of implant / device library information into therapy planning;

- for **Minimally-Invasive Therapy Delivery in the cardiovascular, neurovascular and oncologic spaces in particular**: validation of healthcare IT in clinical solutions related to inter-operability and communication between diagnostic imaging systems and fluoroscopic interventional imaging systems and sensors from different vendors, IT support for structured dose reporting related to interventional X-Ray-fluoroscopy, for real-time high bandwidth transmission of 2D and 3D fluoroscopic streaming data, and for tele-radiology and remote consultations;

Expected Deliverables

Expected deliverables are evidence that Healthcare IT innovations under consideration lead to increased workflow efficiency and consistent quality of care, cost reduction, improved collaboration between clinical disciplines and healthcare providers at different levels, and other key performance indicators, as well as novel metrics for their measurement.

Expected Impact

Expected impact will be accelerated acceptance of validated innovations by payers and care providers.

3.2 RADIOTHERAPY SECTOR

3.2.1 INTRODUCTION

The fight against cancer has been identified by the World Health Organization as one of the priorities of the Strategic Development Goals developed for the period 2016-2020. In 2012 alone, there were 14,1 million new cases of cancer across the globe and 8,2 million cancer deaths[16]. This health crisis is expected to worsen over the next 15 years, primarily because of the ageing of the global population; in the year 2030 it is estimated that there will be 24,6 million new cancer cases and 13 million deaths due to cancer[17].

Cancer also poses a substantial economic burden with an estimate global cost of US$8,3 trillion from 2011-2030[18].

It is widely recognized that radiotherapy (or radiation therapy) is an essential part of any cancer control strategy. The radiotherapy field is constantly changing to meet the diverse needs of cancer patients; consequently, technology and clinical solutions are in a continuous development. In this rapidly changing environment, it is necessary for the radio-oncology community to continuously generate evidence regarding the clinical benefits new technological developments.

Evidence may take the form of dosimetry comparisons of different treatment techniques, data-guided Radiotherapy treatments, evidence-based guidelines for the appropriate use of radiotherapy within patient pathways, and use of cancer registries for retrospective outcomes analysis.

In recent years, advances in radiotherapy have dramatically changed the delivery of cancer care. In an era of personalized medicine, radiotherapy beams may be selected among a diversity of beam modalities, then shaped and modulated to conform to the predicted shape of tumors. Radiotherapy offers the means to optimize the delivery of a prescribed dose to substructures of the tumor, potentially

16 Ferlay, 2015
17 Atun, 2015
18 Bloom, 2011

sparing more normal tissues. Furthermore, radiotherapy provides local tumor control and the potential for curative treatment, which is not always achievable with surgery or chemotherapy. Notably, radiotherapy aims at maximal preservation of the normal form and function of the targeted and surrounding organs[19]. This advanced treatment tool thereby enables clinicians to treat in a curative manner when treating early stage primary tumors, cure localized disease, and to palliate and minimize symptoms of incurable cancers.

Treatment modalities like surgery, chemotherapy and radiotherapy may be combined to create a comprehensive, customized treatment plan for a cancer patient. If the patient requires radiotherapy as part of his or her course of treatment, a physician may utilize one or more of the numerous radiotherapy modalities: external beam radiotherapy such as 3D CRT, IMRT, SRS, and SBRT, brachytherapy, and proton therapy. The choice of delivery method depends on the patient's predisposition, geometry of the disease, treatment history, and other factors which the physician must assess pre-treatment. Once the delivery method is determined, the dose per treatment and the number of treatments may exploit the distinct temporal biological effect of the dose.

The technical approach to radiotherapy sometimes limits the treatment prescription to maximum and minimum doses. In many cases, the physician's intent for patient care varies across time, and cannot be described by these parameters alone. While other techniques for cancer care may not be able to adapt treatment in light of changing patient circumstances, radiation oncologists have the opportunity and often the necessity to adapt treatment based upon current patient information. Determining and documenting this patient information is thus vital to the field of radiotherapy.

In addition to its clinical effectiveness, radiotherapy can be highly cost-effective. One radiotherapy machine can treat tens of thousands of patients over an average ten-year life span, which can extend beyond 20 years for some advanced modalities[20]. This results in better cost-effectiveness compared to most alternative treatment options. Different studies have demonstrated that radiotherapy is cost-effective for both curative and palliative cancer therapy[21]. Finally, a recent Lancet Oncology Commission study demonstrates that building radiotherapy capacity in low- and middle-income countries could lead to the saving of 26,9 million life years and produce the benefit of US$278,1 billion over the next 20 years[22]

Radiotherapy relies heavily on technological innovations to advance the new frontiers of patient care. Academia and industry have a joint responsibility to develop efficient and effective technological solutions that do not operate in a vacuum but are rather determined to serve patients in an ever transforming environment. Academic and industrial research and development in the field of radiotherapy has a long history of developing cost-effective, advanced solutions with proven benefits for patient outcomes. With the global burden of cancer continuing to increase at a dramatic rate, new therapy approaches are needed to address the changing frontiers in cancer care. Given the crucial role played by radiotherapy, a continued commitment to R&D and innovation is more important than ever.

3.2.2 CHALLENGES

In recent years two major trends have become apparent: the dramatic increase in our understanding of cancer and concomitant surge in the global cancer burden. These trends pose two challenges to the traditional delivery of radiotherapy:

- **A.** **The Complexity Challenge** – as we become aware of more factors that may influence a patient's response to treatment, how can we ensure that treatment is sophisticated enough to address the complexity of each cancer case?
- **B.** **The Volume Challenge** – in light of the rising incidence of cancer worldwide, how can we make treatment easier to deliver so that all patients have access to quality cancer care?

In particular, challenges in the radiotherapy sector relate to our understanding the natural history of the disease, personalizing treatment delivery, improving motion management, untapping the potential of big data and standardization of clinical practice.

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19 Atun, 2015
20 Lopes, 2015
21 Barton, 2006
22 Atun, 2015

a) Biology

A large set of data is available to the physician during diagnosis, over the course of radiotherapy treatment and during follow up. The available data can be used to demonstrate both the advantages and limitations of the treatment.

For example, the practitioner ideally has access to different image modalities providing diagnostic anatomic information to outline healthy tissue and the disease (and their structural properties). Unfortunately, the evaluation of these images is frequently ambiguous and not standardized. Education and assistance to develop reproducible delineation is necessary as well as standardized guidelines that demonstrate how image information translates into organ structure definitions.

A physician can gauge the state of the tumor and organs at risk using functional imaging like CT, PET and MRI but it is not often clear how these data are to be interpreted. Functional images may be used as biomarkers to determine which radiotherapy treatment is predisposed to be successful and which might yield sub-optimal results. Biomarkers can also assist physicians in adapting treatment across the course of care, such as through the de-escalation of tumor dose based on changing patient data. The question remains, which biomarkers will have the most prognostic power, and how can the physicians accurately and consistently interpret the data that they provide?

Any cancer treatment poses a burden on healthy tissues, but the toxicity of the delivery dose to healthy tissue is often difficult to predict for an individual patient and depends on many factors including age, medical preconditions, sex, nutrition habits, and others. But distinctly it also depends on the individual state of the patient during treatment. Radiobiology explores the effects of the ionizing dose to tissue in general, and to particular organs at the cellular level.

Radiobiology thereby provides a vital resource to physicians considering dose volume effects for organs during treatment planning, which are often non-linear in dose. Based on the number of structures to be considered, this can become a complex iterative process in therapy planning, for which physicians require optimal resources.

Individualizing treatment also entails acknowledging that tumors are not homogenous in dose response, and creating mechanisms to respond appropriately to consequent challenges. The treatment plan and delivery should distinguish different regions of a tumor consistently, which is also valid for organs at risk since organs display a substructure which is neither constant in time (in position and biology) nor easy to assess from one image modality alone. Imaging before the daily treatment (interfractional) is as important as post treatment (functional and anatomic) and within the time of delivery (intrafractional).

Outside the main field of treatment, a minimal dose effect to healthy tissue should also be included in the overall assessment of the treatment. This assumption includes minimizing the additional burden due to x-ray based imaging dose (as x-ray imaging is being used in most of patient position verification systems).

b) Physics

Imaging and the precise delivery of energy dose require robust understanding of the underlying physics. Designing safe and precise accelerators is as important as the surrounding environment, including supportive tools like treatment planning systems, immobilization devices, imaging and complex workflow enabling software solutions. The limitations of delivery machines and treatment modalities need to be understood and integrated into the planning process. This is also valid for the development of dose measurement tools.

Treatment delivery is not instantaneous, but is usually implemented in a series of daily treatment sessions called *fractions*. There is an interplay effect of the complex plan delivery and inter- and intra-fractional patient motion (tumor growth, respiratory, bowel movement, heartbeat and blood flow). The patient needs to be modelled in position and across time for the therapy planning process and the correct correlation in time used during treatment. Adapting the patient model during the entire course of treatment is an important segment of currently ongoing research, since many of the necessary data are not sufficiently available.

c) Modern Radiotherapy Individualization

Radiotherapy is moving towards genuine personalized medicine. Anatomic imaging and the growing availability and usage of functional imaging are important to enhance understanding the patient's state in time. Physicians need to assess the situation both at the time of

diagnosis and as close to real-time as possible during the individual fractional treatment. Patient data are important for the complete course of the therapy, including post treatment assessment.

New adaptive treatment protocols are therefore necessary to advance the ongoing individualization of care. In this paradigm, time-resolved imaging is an important cornerstone of the implementation of adaptive radiotherapy.

The current combination of imaging and treatment delivery machines uses imaging in slightly different ways in relation to treatment. A 3D or 4D image dataset is acquired before the treatment[23]. During treatment, existing solutions rely on surrogates like markers on the patient to estimate the patient anatomy use bony anatomy or implantable fiducial markers (e.g. tiny gold seeds) to allow for precise tracking of the tumor during treatment, or assume the patient-geometry to remain still. With continuous 2D or 3D imaging during treatment the clinician can adapt the treatment in real time by triggering the beam fluency with the tumor position (gating) or use sophisticated computer algorithms to predict where the tumor will be throughout treatment to track the delivered dose in the patient while adapting the treatment in real time, which requires knowledge of the patient's individual dose accumulation and the development of a completely seamless workflow during the course of treatment.

Research institutes and private sector partners are dedicated to developing the proof of principles for information-guided workflows in a complex, real-time planning and delivery environment as described above. The Radiotherapy industry has the challenge and the opportunity to collaborate in developing and realizing these clinical concepts creating safe and accurate tools and devices on a large scale.

d) Statistics
Since biological models alone cannot describe or predict radiotherapy treatments entirely, dose response models have to be derived from data of large cohorts of patients. The data provided to physicians and practitioners are increasing exponentially. Large databases and registries are needed to store relevant data on treatments for the majority of all cancer treatments (radiotherapy and other modalities).

The clinical outcome is not only based on the control and inactivation of tumors, but also considers other parameters like quality of life, short and long term complications, sequel diseases, and other parameters. Statisticians may help continuously optimize cancer treatment and the evidence base for radiotherapy from the outcome analyses of the defined registries.

e) Cost effectiveness
European member states have different healthcare management systems, and also face unique socio-economic situations in their respective countries. The access to radiotherapy consequently varies across Europe substantially, both in terms of the use of radiotherapy equipment and in the implementation of the latest technology tools and devices. In middle income countries in particular, the lack of trained personnel can limit the access and quality of radiotherapy delivery. The general absence of standardization in practice may also restrict further improvement of efficiency and effectiveness in radiotherapy.

Simplification of the inherent complexity of the treatment flow (through automation and advanced education initiatives) may help avoiding situations in which the deficit of trained personnel creates bottlenecks in the development of radiotherapy capacity. Healthcare providers could also deliver radiotherapy using more technically advanced systems without requiring more expertise to run them. Automation will further support radiotherapy in the lower-middle-income states, where funds and knowledge of running advanced systems might be limited. Automation of the planning and delivery processes will eventually increase the cost-effectiveness of Radiotherapy in comparison to alternative cancer treatments.

Data are becoming increasingly available and healthcare providers are willing to share them. The availability of these data can leverage the potential of Radiotherapy to provide solutions characterized by an optimum balance between treatment cost and increased cure.

3.2.3 ACTIVITIES
Two new trends in radiotherapy research have emerged to address the challenges described above, which represent the new frontiers for revolutionizing cancer care:

23   For patient *positioning verification and repositioning of the patient*

    A.   **Personalization** – seeks to optimize quality for each individual according to his/her circumstances

    B.   **Standardization** – streamlines treatment delivery to make it easier for clinicians to treat large volumes of patients, seeking to optimize quality for the patient community as a whole

The ultimate goal of the radiotherapy industry is patient-oriented innovation. Together, these two research frontiers have the potential to make this goal a reality by contributing to two equally important dimensions of patient-centered solutions: specific solutions at the individual patient level and broad solutions at the society level.

Personalization: Addressing the Complexity Challenge

Radiotherapy is essentially personalized medicine, created to address vast diversity in the manifestation of cancer. The delivery of radiotherapy is intrinsically dependent on the individual characteristics of each patient. Two tumors are never the same, with significant variation in shape, density, cellular makeup, location in the body, response to treatment, and many other factors.

Such dramatic disease variation requires an adaptable, customizable treatment modality. From conception, radiotherapy was developed as such a treatment modality. Every step along the patient pathway from simulation to follow-up can be adapted and optimized to fit the unique characteristics of each individual patient.

In recent years, the advent of new technologies has deepened our understanding of cancer. We know more than ever about the factors that influence cancer progression and response to treatment, and our analysis of each new cancer case has become more complex as a consequence. But with this new knowledge come new challenges: how can treatment be customized to improve outcomes on a patient-by-patient basis?

A plethora of research initiatives seek to address these challenges by increasing the complexity and adaptability of treatment via personalized medicine. The section below summarizes some of the most promising directions for personalized radiotherapy research: targeted treatment, radiobiology, adaptive radiotherapy, and motion management. Taken together, these initiatives seek to enhance treatment sophistication to provide each patient with the best solution for his or her individual case.

a) Biology

Our increasing understanding of cancer up to the cellular level shows significant promise to transform the entire field of cancer care, including detection, treatment decision-making and assessment of therapeutic response. New imaging technology enables us to look beyond snapshots of patient anatomy to biological information and processes at the cellular and molecular data. A concrete example is oxygenation levels, which have been found to influence sensitivity to radiation and other treatment methods; cells that are hypoxic (oxygen-deficient) are resistant to radiotherapy. Human solid tumors are invariably less well-oxygenated than normal tissues, and there may be varying levels of hypoxia within a single tumor[24].

Biologically conformal radiation therapy (BCRT) aims to bring the known complexity of tumors and sensitive structures at the cellular and molecular level into treatment delivery. To this end, BCRT takes biological information (e.g., tumor structure, clonogen density, radio sensitivity, functional importance) and provides customized, non-uniform dose distributions on a patient-specific basis. For example, a dose of higher intensity can be delivered to certain parts of tumors when necessary, as in the case of hypoxia, via a simultaneous integrated boost (SIB) to enhance the efficacy of treatment[25].

Thus, radiobiology has opened up a new frontier of cancer research that examines and addresses the biological variations that could impact treatment efficacy. As we glean more and more relevant organ information via biological imaging, this data must be integrated into treatment planning and delivery to achieve truly individualized care.

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24   Brown, 2007
25   Xing, 2005

b) Motion Management

Significant changes in patient anatomy can occur not only between treatment sessions (e.g., weight loss), but also during treatment itself, as when a patient breathes. Respiratory motion is not segregated to the lungs, but also moves internal organs and the tumor itself. One approach to mitigate the risk of under-dosing the tumor is the application of large safety margins around the tumor: expanded areas of treatment to include positions into which the tumor may move, which exposes healthier structures to the treatment dose.

Accounting for motion during treatment has the potential to reduce these additional margins to the tumor, which minimizes side effects associated with irradiation of healthy tissue and organs. Clinicians may also provide a higher treatment dose to the tumor itself or minimize the number of fractions of a treatment. Current motion management techniques include:

➢ **Free breathing**: In some circumstances, the breathing motion is simply ignored as its amplitude is considered to be reasonably small. In such scenario the minimal motion is accounted for by defining extra margins covering the whole target trajectory.

➢ **Breath hold:** Prior to treatment, clinicians can capture and observe the full motion of the tumor over the respiratory cycle using 4D imaging technology. By asking patients to hold their breath at a certain point (or control their breathing externally) within the respiration cycle (full exhale or inhale), clinicians can more accurately predict the location of the tumor during imaging and treatment and deliver the radiation accordingly.

➢ **(Respiratory) Gating:** In-room imaging allows real-time monitoring of patient breathing or other organ motion. The motion may be captured by surrogates like infrared reflective markers on the patient, fluoroscopic tracking of implanted markers, video tracking of chest outlines or by intrafractional imaging like MR-imaging, ultrasonic imaging, and electronic portal imaging during treatment. These methods enable clinicians to determine a "gating window" encompassing a range of tumor positions that are optimal for treatment and turn the beam on only when the tumor is determined to be located within this window.

➢ **Tracking:** based upon the integration of a computerized model of the tumor motion or direct intrafractional imaging of the tumor motion, the therapy system can adjust the parameters of the radiation to reflect the current tumor position in real time.

Motion management solutions therefore have significant implications for patients by reducing safety margins and thus permitting higher doses to tumors and lower doses to surrounding healthy tissues. In general, motion management solutions have the potential to make treatment more efficient by reducing the time required for a given treatment session, as well as by reducing the number of treatment fractions needed for a complete course of care.

c) Modern Radiotherapy Individualization and Adaptive Radiotherapy

Adaptive radiotherapy seeks to provide solutions to patient variability problems by creating closed loop treatment processes in which plans can be modified using systematic feedback of measurements (e.g. via imaging).

In changing the traditional, linear patient pathway for radiotherapy in which the initial simulation is used to create a unitary plan for the entire course of treatment, the physician's intent for the treatment may be altered. This may involve utilizing different techniques and treatment modalities, or adapting existing treatment plans and the overall joint approach of surgery, chemotherapy and radiotherapy for the patient.

However, clinicians face several challenges in systematically and accurately modifying plans. Images taken of a patient over a six to eight-week period will almost certainly reveal a high level of variation, not just in the tumor, but in the fundamental anatomy of the patient. Comparing these images may make re-planning or other changes necessary, but images with high levels of difference cannot be compared by a simple overlay technique known as rigid registration. Rather, images must be altered and fused to facilitate an "apples-to-apples" comparison through a process called deformable registration.

Deformable registration also has the potential to resolve differences in images taken from distinct imaging devices or protocols, for which there is an ever-growing need due to the increasing use of multi-modality imaging. Clinicians use deformable registration methods for auto-contouring of patient volumes (atlas based auto-segmentation) and for more precise dose accumulation through dose warping of recalculated fractional doses. This facilitates understanding the complete effective dose delivered to the patient, which is necessary to apply meaningful biological models.

Deformable registration is still in its infancy; there is a clear need for a robust image registration algorithm to fuse images, as distorting images without rhyme or reason will ultimately result in poor prescriptions and treatment planning. The creation of sound methodologies and validation techniques for deformable registration is an area for future development[26]

Finally, in developing solutions to these technical challenges, integration into practical and safe workflows must be addressed: adequate quality assurance strategies will have to be designed in order to review the updated treatment plans and prescriptions, and to ensure that they can be safely delivered to the patient.

There is a need for continuous research in various fields of adaptive radiotherapy in order to ensure that we have the methodologies and technologies necessary to respond to change of the patient over the course of care and, in doing so, to optimize the delivery of radiotherapy treatment to the patient.

Targeted Treatment

Recent innovations in radiotherapy have significantly increased our ability to deliver precise treatment. For example, Stereotactic Body Radiotherapy (SBRT) is a progressive treatment technique that uses numerous small, highly-focused and accurate radiation beams to deliver potent doses in 1 to 5 treatment sessions. Alternatively, particle therapy is an advanced modality which uses charged particle beams – most generally protons, in some exploratory cases ions of Carbon, Helium or other particles – to deliver treatment. Particle beams have the benefit of delivering low dose proximal to the tumor and virtually no dose distal to the tumor. With unprecedented levels of precision made possible through advanced techniques like these, treatment beams can conform to the exact shape of each unique tumor, minimizing exposure of surrounding healthy structures. The development of these highly precise, effective and minimal invasive techniques has drastically increased the ability to customize treatment delivery to the specific conditions of each patient, and has benefited patient groups previously declared inoperable[27].

In light of these benefits, the radiotherapy industry continuously seeks to push technology to its limits in order to further enhance the ability to deliver precision treatment. Researchers are currently exploring the potential to diversify trajectories: expanding the variety of radiation beam paths into the patient by increasing the angles from which the beam is delivered (moving toward a full sphere of movement), as well as the variety of field sizes that can be delivered while doing so.

Diversification of these beam delivery approaches (encompassing the choice of beams as well as their trajectories) may empower clinicians to surmount enduring challenges in treatment delivery: how to avoid healthy areas of the body while treating the cancerous tumor. Doing so not only has clear benefits for special patient groups as seen with the invention of SBRT, but also advances the ability of clinicians to personalize care for patients: greater precision allows treatment to be customized further to target the exact, unique shape of each tumor while making adjustments based on the specific anatomy of the patient to avoid vital organs and healthy tissues.

Standardization: Addressing the Volume Challenge

In contrast to the personalization approach which considers each patient as an individual, the volume problem requires considering the "Big Picture": the flood of new cancer patients, anticipated to increase rapidly over the next decade. In 2012 alone, there were 14.1 million new cases of cancer across the globe, expected to rise to at least 24.6 million new cases by 2030, about 50-60% of which will require radiotherapy treatment[28].

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26 *Sortiras, 2012*

27 *SBRT may be used to treat early stage lung cancer patients who cannot tolerate surgery due to comorbidities. These patients were previously observed without cancer therapy or received conventional radiotherapy, both of which yielded 3-year survival rates of 20-30%. SBRT can provide more than double the rate of primary tumor control than conventional radiotherapy, and can increase 3-year survival rates dramatically to 55.8% (Timmerman 2010). SBRT has also drastically improved the treatment of Hepatocellular carcinoma (HCC), the third leading cause of cancer mortality globally. Previously, less than 30% of HCC patients were eligible for surgical treatment (resection and transplantation) due to tumor size, location within the liver, vascular invasion, poor liver function, and other factors. The use of SBRT as a primary treatment or as a bridge to transplant thus expands access to care for a large group of patients previously considered ineligible for treatment (Schulz 2013).*

28 Atun, 2015

Such a dramatic influx in new patients demands affordable, clinically effective treatment modalities, exemplified by radiotherapy. One radiotherapy machine can treat tens of thousands of patients over an average life span, resulting in lower cost per patient compared to other alternative treatment options[29].

The volume problem requires the development of solutions that promote accessibility. To that end, clinicians and researchers look for ways to streamline delivery; to make treatment more efficient so that it can be delivered to more patients in shorter time frames; and to make treatment delivery easier and replicable so that it can be delivered by clinicians with lower levels of training.

These goals are captured under the broad concept of standardization. Standardization specifically refers to the creation of reliable, reproducible, evidence-based methodologies and guidelines for care. By aggregating data from a broad group of patients, clinicians can determine the optimal way to perform treatment based on average responses and outcomes.

The pillars of standardization are:
 ➢ **Evidence-based medicine:** determining the most likely paths for success based on thorough examination of big data and clinical trials
 ➢ **Safety:** promoting the use of best practices
 ➢ **Efficiency:** saving time and resources by use of guidelines; avoiding "reinventing" the wheel
 ➢ **Accessibility:** disseminating evidence-based guidelines to facilitate training of new users
 ➢ **Automation:** minimizing sources of errors and optimizing efficiency of the overall process.

Many areas of radiotherapy research seek to advance standardization. Clinical trials test existing standards of treatment delivery to see if they may be optimized or adapted. "Big data" – the systematic collection of patient outcomes data (from diagnosis to outcomes) – can be retrospectively analyzed to better inform outcome prediction. Decision support through the creation of guidelines promotes safety and efficiency of treatment delivery, and is further enhanced through new software developments that connect centers across the globe, thereby enabling the dissemination of best practices.

These new areas of research thus seek to address the volume/access challenge facing clinicians today: how can we cope with the vast influx of new cancer patients, particularly in emerging countries lacking infrastructure and experienced personnel to deliver treatment? How can we ensure that we are using treatment methods that are tried and true, thus increasing the likelihood of a positive outcome? How can we ensure quality of care for as many patients as possible?

a) Statistics – Clinical Trials
Radiotherapy trials, when they occur, usually do not compare the outcomes of treatment with lack of treatment (i.e., one patient pool receives a placebo), but rather compare one treatment scheme against another one considered as "standard of care": the primary outcome under investigation may refer to the clinical protocol, the delivery method or the fractionation regimen.

The United Kingdom Standardization of Breast Radiotherapy trials (START) tested the standard regime of 50Gy delivered in 25 fractions against a variety of other regimens. After several iterations, a new regimen was found to be just as safe and effective: 40Gy delivered in 15 fractions. This new regimen provided lower overall dose, minimizing exposure to surrounding normal tissues while maintaining the same level of safety and efficacy. In addition, by adopting this new standard, the UK was further able to reduce costs on a broad scale: with fewer treatment sessions, more patients can be treated in the same time period and fewer resources are used (e.g., personnel and infrastructure). The implications of adopting a new standardization regimen thus extend beyond benefits to the patients to the national health sector in general.
Clinical trials thus are, and will always be, a critical component of radiotherapy research. It is vital to continuously test current standards of care to ensure that they still represent the optimal guidelines for patient care, and to make amendments as needed that might maximize outcomes across a broad patient pool or to incorporate new techniques as relevant. The ultimate goal is thus to make sure that the basis for universal patient care is at the highest level possible, rather than to customize care on an individual basis.

29 Lopes, 2005

However, conducting clinical trials is not possible in all contexts, either because the frequency or specificities of the disease makes it very difficult to recruit the number of patients needed to detect statistically significance difference, or because the rapid evolution of the technologies significantly reduces the relevance and applicability of the trial conclusions. It is therefore of paramount importance to recognize that clinical trials are not the unique validation approach towards technological innovations in radiotherapy.

The collection of clinical data from a wide variety of diverse sources can help to address the above problem, as well as further outcome prediction and provide decision support for clinicians. Methodologies like Rapid Learning enable clinicians to retrospectively examine clinical data repositories and use that knowledge to ameliorate practice[30]. Linking data sources in registries across institutes enables us to learn from more patients, identify data quality issues and design more optimal guidelines.

Thus, developing the collection and analysis of big data is vital to the future of radiotherapy. Research into new innovations that facilitate the collection, dissemination, and indexing of big data, such as electronic hospital records and oncology information systems, seeks to help clinicians gather better data more easily, and to organize this data in ways that are most helpful to facilitate analysis. Similarly, researchers are also seeking to build more robust analysis methods, biological dose response models to use these data in the best possible manner and provide the means to deliver evidence based healthcare.

b) Cost-Effectiveness
Standardization, at its core, aims to support evidence-based decisions in patient care. The use of guidelines is vital to achieve this goal. Guidelines are formed from the compilation of clinical data and best practices, and as such are always formulated on the basis of robust evidence.

Guidelines for care are often utilized at the national level, indexed by disease site and stage of disease such that a clinician can understand best practices for her patient. For example, the National Institute for Health and Cancer Excellence in the United Kingdom provides guidelines for clinicians varying from patient pathways according to disease sites to the use of certain technologies, to recognition and referral.

Such guidelines have several benefits:

- Inexperienced users can benefit from the experience and knowledge of others, and thus make informed decisions for their patients;
- Homogenization of patient pathways promotes safety through utilization of tried and true methods, rather than untested methods that may therefore increase risks;
- The use of guidelines promotes efficiency in the delivery of health services by minimizing the need to "re-create the wheel" with every new case.
- New software and other technologies enable connectivity between centers across the globe to further enhance decision support and cancer care. For example, knowledge-based treatment planning, an innovation that creates new networks between institutions, can provide pre-configured plan models developed by international experts to use as baselines for developing treatment plans. In another approach, treatment planning automation seeks to optimize the prescription itself to develop the optimum possible plan individually for each patient.

Further progress in this field seeks to increase the linkages between centers, and facilitate both the collection of relevant data and the translation of this data into support tools such as guidelines or quality assurance checks. As such, decision support remains a vital component of the radiotherapy research agenda.

3.2.4 EXPECTED DELIVERABLES
Ongoing research activities in the field of radiotherapy seek new, innovative solutions to enhance the effectiveness and efficiency of cancer care. With the ultimate goals of improving patient outcomes and promoting access to cancer treatment, current and future research activities anticipate to deliver a series of specific deliverables:

30   Dekker, 2014

1. **Better understanding of the biology of tumors and healthy tissues (up to the cellular level)** via ongoing initiatives in radiobiology research. The incorporation of biological data into treatment planning and delivery has the potential to greatly influence the course of treatment for a patient through the development of biological markers to predict and guide clinical outcomes and the aggregation and analysis of patient data into databases and registries.

2. **Greater treatment efficiency and minimization of side effects** through motion management research in the field of physics, as well as through faster delivery of highly modulated treatments for highly conformal dose distributions.

3. **Integration and introduction of new imaging and treatment methods into patient pathways** through modern radiotherapy research, which broadly seeks to promote the individualization of cancer care. To this end, it is anticipated that modern RT research will further the goals of interventional therapy using minimally invasive techniques to personalize treatment, minimize side effects, and improve outcomes.

4. **Evidence-based medicine that seeks higher integration of diagnosis, imaging, treatment planning and delivery with outcome analysis** via statistics research, as well as the tools to handle large databases for meaningful data extraction and decision support tools.

5. **Radiotherapy systems with significantly less expensive core components using significantly less energy** through cost-effectiveness research. These cost saving measures have the potential to promote accessibility of radiotherapy for patients and communities with limited resources.

6. **Better quality assurance and automation of processes** in terms of both specific components as well as workflow between these.

3.2.5 EXPECTED IMPACT

Radiotherapy research always strives to improve quality of care, but it is equally important for researchers to think about the individual patient who will be treated as well as the healthcare landscape at large. To this end, two strands in Radiotherapy research have emerged: personalization and standardization.

These two research areas are not isolated from each other, and in fact interact in a complex manner. Some level of conflict is inherent; standards are developed to provide universal ways of providing treatment, while personalized plans are developed to individualize ways of providing treatment. And yet, both of them also feed into one another. A new way of treating one patient may, if robustly tested through clinical trials, inform and alter existing standards of treatment.

Research activities in the disciplines of radiotherapy are expected to have a significant impact on both individual patient treatment as well as universal standards of cancer care through:

1. **Individualized cancer care** enabled through improved (measurable) diagnosis, treatment and follow-up of the individual patient, and the aggregation of these individual measurements to enable the creation of standards and evidence-based guidelines for patient care.

2. **Lower overall cost burden for the health-care provider** through enhanced cost effectiveness and greater treatment efficiency.

3. **Process integration of cancer care across all treatment modalities**, to facilitate use of the optimal modality of treatment or combination of treatments (chemotherapy, radiotherapy, immunotherapy, and surgery) for each patient. The integration of distinct cancer treatment methods into one unified and comprehensive care pathway has the potential to enhance patient care in terms of both efficiency and efficacy.

4. **Better patient health outcomes and minimization of severe side effects.**

5. **More predictable treatment outcomes** enabled both by greater understanding of unique cases on the individual level, as well as through aggregation and analysis of patient data via robust databases and registries.

The concomitant tension and feedback loops between standardization and personalization thereby form the basis of quality patient care. While we want to ensure that each patient is receiving evidence-based care that adheres to safety standards and best practices, we also want to make sure that any of the patient's individual characteristics or circumstances that might impact the treatment outcome is considered in developing and delivering the course of care. Striking an adequate balance between the two forces, is the ultimate goal of radiotherapy and health care in general.

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3.3. GENERAL HEALTH ICT RELATED ACTIVITIES

3.3.1 ICT SUPPORT FOR INTEGRATED CARE

The concept of Integrated Care – care that crosses the boundaries between hospital, primary, community and social care – has emerged as one of the most promising concepts to ensure the sustainability of the healthcare systems in Europe and beyond.

Providing more access to better and safer care at contained costs can only be answered through transforming the current care delivery mechanisms around a more patient-centric approach encompassing health and social care, and enabled through eHealth.

The upcoming era of Integrated Care will need care providers using eHealth to collaborate and share patient data, knowledge and insights in the context of day-to-day operations. This should focus on disease prevention, continuous care, disease management and population management, hence "crossing the boundaries of isolated systems".

As mentioned above, Integrated Care is the overall umbrella combining all necessary clinical, social, operational, technical and administrative activities: evidence based screening of patients, planning and executing of preventive, diagnostic, therapeutic and follow up/monitoring actions both locally or from distance, financial management, integration in the home environment, coaching, education, motivation and inclusion in the community. As such, eHealth can simply be defined as well as the ICT support for Integrated Care.

eHealth describes the application of information and communications technologies (ICTs) across the whole range of functions that affect the health sector. "eHealth", "healthcare IT", "health ICTs" and "health informatics" are synonymous. eHealth includes tools for health authorities and professionals as well as personalized health systems for patients and citizens. eHealth can therefore be said to cover the interaction between patients and health-service providers, provider-to-provider or provider to payer transmission of data, or peer-to-peer communications between patients and/or health professionals. It can also include health information networks, Electronic Health Records, telemedicine services, and personal wearable and portable communicable systems for assisting prevention, diagnosis, treatment, health monitoring and lifestyle management.

eHEALTH COMPRISES SIX CATEGORIES OF SYSTEMS:
1. Hospital information system (HIS)
2. Clinical information system (CIS) Electronic Medical Record (EMR)
3. Other General Practitioner or specialty systems
4. Integrated health information exchange networks (HIE/EHR)
5. Telemedicine and Mobile Health
6. Secondary-usage non-clinical systems (data analytics, public health, research and pharma)

AMONGST OTHERS, eHEALTH COVERS THE FOLLOWING SIX SERVICES:
1. Healthcare delivery support systems
2. Patient Data management
3. Health information exchange
4. Remote health services and social care support
5. Data analytics, public health, biomedical research support and pharma
6. Health education

While the above definition is clear, many different interpretations of eHealth exist. This only reflects the fact that eHealth is an open and constantly evolving discipline, because it incorporates new advances in technology and responds and adapts to the changing health needs and contexts of societies.

At the same time, eHealth covers many different applications and solutions. Just to name a few:

- The EMR (Electronic Medical Record) or EPR (Electronic Patient Record) is the backbone of many eHealth services. An EMR or EPR is an institution/practice-wide record of data about the clinical condition of the patients, the diagnostic, therapeutic and care procedures performed and the prescribed and administered medication.

- The EHR (Electronic Health Record) is the longitudinal and complete medical record of an individual, accessible and amendable by authorized people. An EHR is supposed to be composed from multiple sources and can be physically stored in a central place or conceived as a virtual distributed system.

- The PHR (Personal Health Record) is the collection of clinical data, owned and managed by the patient/citizen but often not physically hosted on the patient's computer.

- Systems for "Active and Healthy Aging" and "Ambient Assisted Living" enabling elderly people to connect with formal and informal health care providers, family and friends.

- Data sharing platforms (like XDS for documents) Telehealth refers to the delivery of health care services, health care education and health information services at a distance using technological solutions/platforms. Telehealth enables the care providers to assess, diagnose and monitor patients remotely, recommend treatment and e-prescribe medications[31]. It also refers to technologies that allow patients to manage their conditions independently through the use of telecommunications technology. Telemedicine is applied to a wide array of services in diverse settings including tele-dermatology, tele-pathology, tele-endoscopy, tele-cardiology, tele-psychiatry, tele-pharmacy, telemetry, tele-obstetrics and tele-radiology.

After more than 30 years of widespread use of ICT in health we still face disconnected and incompatible systems, although a lot is already done to overcome the interoperability challenge. Currently, EMRs are not able to share rich clinical content and discrete data as a daily routine, telemedicine platforms are often heterogeneous and initiatives have a too narrow local focus.

However, some remarkable opportunities can be outlined:

- In the domain of home-care, different projects are underway that connect sensors in the home of the patient, often with proprietary data exchanges and local decision support for the patient. With Cloud technology maturing, it is now more and more possible to make content accessible for many more stakeholders. Data can then be aggregated and merged with other sources to form a comprehensive picture of the clinical condition of the patient. This means that systems, collecting data in the home of the patient can more and more contribute to enrich the information that is already stored in EHRs systems.

- Devices for measuring, collecting, aggregating, displaying or forwarding data are becoming increasingly mobile, and even more, these devices don't need to be specifically designed for the use case. The smartphone and other mobile platforms are gradually becoming the de facto computing standard. This allows users to use their own devices and integrate e-health in their daily life.

- Healthcare providers are increasingly realizing the potential of extending the clinical view on the patient beyond the scope of the own EMR/EPR. More and more systems consider building connectivity into the EMR/EPR to either import or view data from external systems. In turn, the data captured in their own EMRs/EPRs systems is providing data to the external world. By "writing locally" and "reading globally" EMR/EPRs could grow to a de-facto EHR. On the other hand, we are seeing traditional EHR platform vendors adding interactive functionalities to their systems (scheduling, workflow support, decision support), and by doing this their systems are evolving gradually to an EMR. The convergence between EMR/EPR and EHR is one of the most significant trends that will change the face of health ICT significantly.

- The health care delivery mechanisms and financial models are scrutinized nowadays. New approaches try to holistically organize health (and well-being), coordinate the care between the stakeholders, and give a more prominent place to the citizen/patient. This is what Integrated Care stands for.

Integrated Care and its supporting technologies cannot be seen separately from the organizational context. For example, the human aspect of this transformation must be carefully addressed. Most healthcare providers are not ready and they will need to train their workforce to acquire new skills. It is also critical to take into account change management and new medical practices and tools in this transition.

31 On the application of telemedicine in monitoring and continuity of care, it was shown that, for example, telemedicine leads to 15% to 56% reduction of mortality in Cognitive Heart Failure patients. The Empirical Foundations of Telemedicine Interventions for Chronic Disease Management, Telemed J E Health. 2014 Sep 1; 20(9): 769–800., http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4148063/

Reconciliation between the one who pays and the one who gets the benefits, as well as adequate financial incentives and structures for health and social care providers, is another challenge to overcome to support the adoption of eHealth in daily clinical routine practice.

Ultimately, eHealth technologies will only enable the transformation of today's healthcare delivery model into tomorrow's outcome-based healthcare model, if the above-mentioned challenges are overcome.

The following section illustrates COCIR's vision on what are the priorities for further research and innovation. The topics have been organized around 4 key themes, under the umbrella of Integrated Care, and each of them attempts to provide a response to an identified unmet need in eHealth.

1. Smart and knowledge driven clinical intelligence and analytics
2. Usability
3. Connected data
4. Remote health services and social care support

3.3.2 THEME 1:
SMART AND KNOWLEDGE DRIVEN CLINICAL INTELLIGENCE AND ANALYTICS

IT needs to close the gap between producing clinical data, analyzing the data and feeding results back into the clinical system: healthcare activities observe and act → create new data →   medical research analyzes this data and → creates new medical knowledge, → to be used in healthcare activities
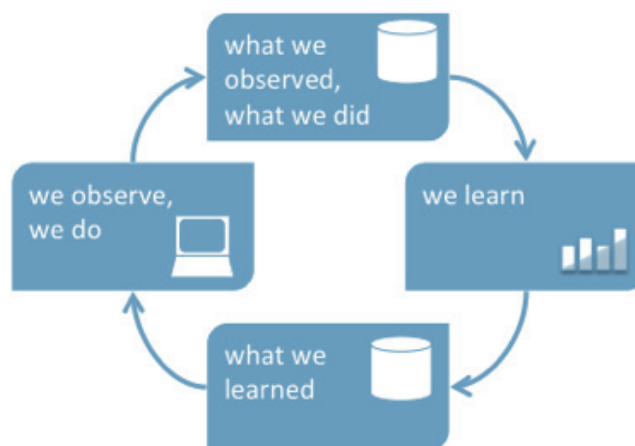
This cycle must be executed for all phases in healthcare (prevention, diagnosis, treatment and follow up), across all stakeholders, including the patient, across geographical and institutional boundaries and across all kinds of data: sensors, devices, images, EMR, social media, molecular-/omic data, etc. Closing the circle ultimately leads to personalized, translational and integrated care.

The first topic in this theme focuses on the operational systems (primary use): decision support and workflow, represented by the left box in the picture above. The second topic focuses on the right box in the picture: analytics.

The top and bottom boxes represent the formalization and sharing of data and knowledge and can be covered by both topics as well by the topics within the theme on "connected data".

3.3.2.1 TOPIC: CLINICAL DECISION SUPPORT, ADAPTIVE AND FEDERATED WORKFLOW

Specific Challenges
Health ICT has not yet delivered on its promises with regards to assisting professionals in making the right decisions at the right time

and for the right patient. Decision support systems and support for clinical pathways often fail because they are not enough context aware and patient specific. To a large extent, this is the result of technology trying to solve everything up front. Even if a very well designed care pathway for diabetes is used, the patient may have some additional unforeseen conditions making the pathway unusable. Comorbidity is a typical example of a situation where the system should adapt itself and create a new pathway based on existing medical knowledge. The world is just too complex to foresee everything up front. Just In Time (JIT) technology may overcome this by reasoning on the totality of medical knowledge, clinical information and global context of the patient, past experiences and evidences from existing data.

Scope

In this topic the focus is on the operational systems where users observe, decide and act (primary usage of clinical data). Further research and innovation is needed in the following areas:

- Inter-operability of rules and guidelines
- Dealing with comorbidities and a dynamically changing clinical context
- Storage of acquired knowledge in well accessible shared and distributed repositories and blend with pre-existing expert opinion (seamless mixing of evidence and eminence based medicine)
- The creation and use of predictive and prescriptive analytical tools and the integration of Clinical Decision Support in clinical workflow.
- Workflows, distributed across stakeholders, dynamic and adaptive to changing context. This requires further research focusing on:
- Just-in-time workflow generation, ensuring dynamic and goal oriented guidance (effectiveness) to a specific user (doctor, patient, health coach, payer, …) considering the existing information, medical knowledge and available resources (efficiency).
- Sharing and interoperability of workflows, integration in operational systems
- Solution for the current (static) clinical pathways' inability to cope with comorbidities and non-standard clinical contexts.

Expected deliverables

New and novel or improved health ICT tools and systems for information management, knowledge representation, workflow optimization and decision support, which will be validated through suitable clinical trials and ultimately support Integrated Care.

Expected Impact

- Improved interaction between patients and their care providers, and more active participation of patients in the healthcare processes from screening, through enrolment in specific care programs and follow-up of therapies
- Improved coordination and secure information exchange among the care-givers involved in health, social and informal care services and the patient
- Better, more specific and dynamic care workflows to manage comorbidities and other complex cases
- Reduced admissions, re-admissions and days spent in acute care, and improvements in daily activities and quality of life at home of non-self-sufficient older persons

3.3.2.2 TOPIC: MULTI-SOURCE / MULTI-APPROACH ANALYTICS, COMBINING CLINICAL DATA, IMAGES, GENOMICS, PHENOMICS, ENVIRONICS AND SOCIAL DATA

Specific Challenges

Evidence Based Medicine requires the analysis of massive amounts of multi-modal and multi-sourced (big) data. Business Intelligence software is more and more used, mainly to process financial and operational data. This is useful by itself, but it is only through linking these sources with clinical data that the relevance of diagnostic and therapeutic activities (and hence their value) can be measured. By bringing together massive amounts of data, hidden patterns can be retrospectively detected and knowledge created, complementing traditional ways of doing clinical research (prospective clinical trials). Analysis activities need to go beyond traditional BI dashboards (descriptive analytics) towards the so called predictive analytics (predict the future by looking back) and prescriptive analytics (decision support).

Scope

The aim of projects should be to demonstrate the feasibility and added clinical, operational or financial value of bringing different data sources together with a concrete use case, a working prototype and generic underlying technologies. While building this, existing standards should be used but also, where needed, actions should be undertaken to bring insufficient standards to the next level. The focus of this topic is not so much the interoperability of heterogeneous systems, but rather the value that analytics can bring in general, provided that data can be accessed. Other focuses of this topic are the combination of different analytical approaches and methodologies, leveraging each other and feeding the results of analytics into operational systems (prescriptive analytics) as an approach for decision support, and overlapping with the previous topic.

Further research and innovation is needed in the following areas:

- Smart analysis of data (data mining, analytics, temporal reasoning, safety patterns detection) to create interoperable knowledge, models, guidelines and rules to close the loop between analytics and decision support;
- Combine clinical data in the EMR with imaging data to enhance risk stratification or the predictive value of analytical systems;
- Combine specific image related analytical approaches such as Deep Machine Learning, with statistical analysis on structured clinical data;
- Combine free text analysis with analysis of structured data;
- Combine clinical data in the EMR with genome data for personalized diagnostic and/or therapeutic decision support;
- Combine clinical data in the EMR with environmental data (weather forecast, pollution forecast) to steer therapies and behavioral advice (e.g. COPD);
- Combine clinical data in the EMR (phenotype) with genomic data (genotype) to learn more about specific diseases, diagnostic accuracy of devices or methods, and therapeutic approaches;
- Combine clinical data in the EMR with financial, operational and human resource data to optimize workload and resourcing in different settings of Integrated Care;
- Investigate how to connect different initiatives without imposing one standard: investigate interoperability between standards rather than choosing just one standard;
  - Combine clinical data in the EMR with patient generated data via sensors to e.g. Enable disease monitoring/therapy adherence;

Expected deliverables

It is expected that projects, working on this topics, will deliver new technologies, more evidence of added value and better standards for combining different and heterogeneous sources of data across the whole spectrum of acute and chronic care, healthcare, wellness and beyond. Solutions and approaches are expected to be able to combine data without enforcing a single standard upon the sources and rather focus on interoperability between standards, networks, ecosystems, etc.
Collaboration and convergence between different projects is important, avoiding to end up with "yet another solution" to solve interoperability, internally in the project, but not solving interoperability with the rest of the world.

Expected Impact

In the long run the impact of this research topic would be that the promises of the added value of sharing of big data and improving the outcome for patients is validated, and that bringing data together is made realistic and feasible in real life, not only in lab or pilot environment.
Combining many sources of data should lead to a better understanding of diseases and a better assessment of the value of different diagnostic and therapeutic approaches.

3.3.2.3 TOPIC: PERFORMANCE ISSUES WHILE SCALING OUT (COMBINATORIAL EXPLOSION)

Specific Challenges

Bringing together big data sources and huge amounts of medical knowledge to steer analytical processes and reasoning for decision

support will cause the so-called "combinatorial explosion". Exponential explosion of possibilities, options in decision support systems, covering multiple domains at the same time in order to solve the co-morbidity problem and just-in-time contextual changes will be a huge challenge for reasoning engines.

Big data is a challenge for analytical engines. Approaches within memory data bases increase speed at the price of cost and/or size while more traditional approaches suffer from slow performance.

Ontology based reasoning and inference are often done in academic setting with limited amounts of data or small ontologies. Transition to a clinical setting is a challenge and hinders to usage of semantic technologies in real life.

Scope

There will be a need for technologies capable of dealing with huge amounts of data as well as huge amounts of medical knowledge. Engines to process this data and to use the complex medical knowledge will need to be scalable and performant. Further research and innovation is needed in the following areas:

- Research on approaches to increase performance and scalability of reasoning, analytical and semantic inference engines;
- Partitioning and parallelization of reasoning, iterative reasoning, streaming reasoning, the usage of reasoning networks;
- Benchmarking engines and different scalability approaches;
- Investigation of the specifics of clinical data and medical knowledge and the impact on scalability;

Expected deliverables

- New approaches to cope with the combinatorial explosion of data and medical knowledge;
- a new generation of reasoning and analytical engines, demonstrated in prototypes and with a simulation of a realistic clinical setting;
- Comparative study of different approaches, engines with the creation of a useable criterion framework;

Expected Impact

Successful project results should vastly increase the usage of decision support in real life clinical settings and help solving the problem of complex medical contexts with ploy medication and multimorbidities.

3.3.2.4 TOPIC: ICT SUPPORT FOR POST MARKET SURVEILLANCE (PMS), ADVERSE EVENT DETECTION AND HEALTH TECHNOLOGY ASSESSMENT (HTA)

Specific Challenges

Having access to huge amounts of data can potentially help to assess the safety and the effectiveness of drugs, medical devices, including software. These assessments are usually done in a pre-market context and often executed as an observational and/or interventional clinical trial. While this is still useful and necessary, there is a growing consensus that this is not good enough. Clinical trials are a "nice picture of a dirty world". With very strict inclusion and exclusion criteria, the patient cohort investigated is narrowed down to assess the relationship between exposure to the drug/device and specific outcomes and its statistical significance. Obviously this is what the researchers are looking for, but actually, the only statement one can make is that the drug/device is working for a specific patient group that has the same characteristics than the one investigated. This means that the use of the drug/device in the real world can lead to totally different results. Therefore, we need to assess the safety and effectiveness of the drug/device after its introduction on the market. Post Market Surveillance (PMS) enables assessment of long-term effects of a given drug/device, and the influence of changing contexts.

On the other hand, Health Technology Assessment (HTA) allows to measure the cost-effectiveness of a new technology in terms of health outcomes and costs, while most importantly, compare it with other interventions. HTA thus provides concrete data to policy makers to help them make informed decisions as to whether or not a specific technology should be reimbursed, stay on the market, etc. Better knowledge about and quantification of the real performance and safety of drugs/ devices, but also policies, behavioral and societal approaches will help to make informed decisions about care pathways, guidelines and policies needed in Integrated Care.On top of all this, the same technologies used to gather and analyse data for PMS and HTA can be used to detect adverse events in a timely manner to prevent patients' harm.

Scope

Solutions must be built to re-use data and learn from it for detecting potentially harmful patterns, for assessing and measuring the efficacy of health processes, devices and drug. Further research and innovation is needed in the following areas:

- Investigation, benchmarking, creation of predictive algorithms;
- Combine and analyze data to predict adverse events;
- Create Data Sharing Platforms to assess performance and safety of drugs, devices, software, guidelines, policies;
- Investigate inclusion of existing data sharing networks, security and privacy technologies;
- Investigate/make/reuse tools to measure and quantify risks, effectiveness, cost (e.g. Monitoring and Assessment Framework for the European Innovation Partnership on Active and Healthy Ageing - MAFEIP);
- Collaboration between Pharma, MedTech, Software Vendors and regional and EU agencies;
- Patient Safety dashboards, both local and regional;

Expected deliverables

- The creation or the use of algorithms for predictive analysis, performance and safety analysis;
- The creation or reuse of data sharing platforms to support;
- PMS/HTA processes;
- New methods and approaches to assess risk, benefits and cost-effectiveness of technologies;
- The creation of status and trending dashboards for follow up of patient safety/performance of new or existing drugs, devices, guidelines, etc.;

Expected Impact

- Enable evidenced-based policies and reimbursement;
- Earlier detection of potential adverse events and hence a safer health care environment;
- Support the growth of Pharma and MedTech industries and advance medical research in general;

3.3.3 THEME 2:
USABILITY

3.3.3.1 TOPIC: REPRESENTATION OF RICH PATIENT DATA AND CLINICAL THINKING

Specific Challenges

It is a well-known fact that many IT systems are under-used and users often describe the use of ICT systems in their daily practice as "more work", "not so useful" and "difficult". Usability is the key, and both user interfaces and workflows must be better adapted to the specific needs of the different stakeholders. A delicate balance must be found between "enough" and "too much". In times of "big data", information overload is a threat. On the other hand, each click is considered as a click too much. Because it is impossible to consider all possible situations up-front, we need smart adaptive just-in-time systems to present to the user, just what he needs and nothing more. This is even more the case for the patient at home, where contexts can differ very significantly and where the decreased flexibility of the user (sick people, old people) cannot compensate a rigid design of a user interface. Software should not only be smart but also kind. Research on how to make kind software must be an important part of upcoming research initiatives.

Scope

This topic is about making ICT tools "kind" to people, adapted to the needs of a specific stakeholder in specific situations. Further research and innovation is needed in the following areas:

- Representation of rich medical data and clinical thinking: techniques to summarize, filter, and present large amounts of information, revealing underlying patterns and relationships that can advance medical science. Techniques applicable to data sets ranging from of the individual patient records up to global populations;

- Adaptive user interfaces: user interfaces that dynamically adapt themselves to their user and the context in which they are used, offering the best possible user experience on changing device parameters, shifting user tasks, and varying environmental context;

- The internet of (healthcare) things. User experience paradigms for interacting with complex webs of healthcare devices, working with their data streams, governing, decision making in a mobile world;

- Serious gaming in healthcare: using game theory, user interfaces and practices for the promotion of desirable health and healthcare choices through positive psychology;

Expected deliverables

- New and novel or improved health ICT tools and systems for information management and knowledge representation for all stakeholders, including the patient;

- Validation through suitable clinical trials;

- New ways of measuring the effectiveness and "kindness" of new GUI approaches;

Expected Impact

Improved semantics, usability and adaptability of ICT systems for IC, taking into account of the complex relationship between technologies and their social and human context of application. Simply put: kind software, actually used by all stakeholders, strongly supporting the Digital (Health) Agenda of the EU.

3.3.4 THEME 3:
CONNECTED DATA

3.3.4.1 TOPIC: HOW TO GROW TO A WIDESPREAD IMPLEMENTATION OF AN EHR?

Specific Challenges

Traditionally isolated local EMR's (Electronic Medical Records) have been deployed for health care providers such as hospital staff GP's, community based paramedical workers, nurses, clinic staff, admins and clerks. Patients have more and more access to their own data and we are seeing a growing number of initiatives to give patients/citizens interactive (read/write) access to their data, creating a Personal Health Record (PHR). The PHR service to patients however is often bound to a specific hospital (or hospital group) and a specific software vendor. The same constraint holds for GP's trying to access their patients' data during or after hospitalizations: they often have to log in to a portal provided by the specific hospital.

Hence, the idea of a longitudinal health record for the patient, across all institutions, providers, regions, etc. This is the so-called Electronic Health Record (EHR).

However, there are still different approaches to arrive to an EHR, all featuring specific advantages and disadvantages. In addition, multiple questions remain unanswered:

- Should an EHR be a physical centralization of data or a virtual data source?

- Should an EHR be a physical storage at all (regardless its centralized or distributed nature) or more be an infrastructure for just-in –time access of data to the original data sources (e.g. XDS for document sharing)?

- Does an EHR have read-only or read-write functionality?

- Who is the owner of the data, who is accountable for its content?

- How to resolve double entries, conflicting entries, delete operations?

- How to express different opinions (e.g. about a diagnosis)?

- How to keep track of the provenance of the data, and its evolution over time?

- How to reflect different data models, according to its usage?

- How to visualize data, adapted for the individual stakeholder (including patients)

- What is the relation between an EHR and the many specific repositories? Is it maintainable to keep on copying data? How does this influence ownership and accountability?
- How will the PHR and EMR interact with an EHR? Will they become one?
- How to limit data access on a "need to" basis?
- How to organize a global patient consent for accessing an EHR?
- Etc.

Scope

It becomes clear that apart from real implementation and deployments of an EHR, there is still need for a thorough investigation and debate on these topics. Basically the golden question is: "How can we let people work with health data, in their own environment and infrastructure, but seamlessly see the overall clinical (EHR) data with the adequate user interface, in the same environment, amending and correcting when needed or useful? This also calls for a solution for sharing and integrating multi-stakeholder workflows.
In other words: "How can an EMR/PHR evolve to an EHR or vice versa?"
Obviously there will be many ramifications to other technologies, discussed in this document (privacy & security, usability, connectivity and interoperability, semantics).

Healthcare providers more and more realize that there is a need to extend the clinical view on the patient beyond the scope of their own EMR/EPR. More and more systems consider building connectivity into the EMR/EPR to either import or view data from external systems. In turn, the data captured in the own EMR/EPR provides data to the external world. By "writing locally" and "reading globally" EMR/EPR's could grow to a de-facto EHR. On the other hand, we see more and more traditional EHR platform vendors adding interactive functionalities to their systems (scheduling, workflow support, decision support) and by doing this they evolve gradually to an EMR. The convergence between EMR/EPR and EHR is one of the most significant trends that will change the face of health ICT significantly.

Further research and innovation is needed in the following areas:

- The architecture of EMRs and EHRs and how they can converge;
- The components to allow data to be shared outside the boundaries of organizations: identity management, provenance, patient consent ownership;
- The solution to the questions and issues raised in the description of the specific challenges;

Expected deliverables

Projects should investigate the different approaches, make suggestions and prototypes and demonstrate the feasibility in terms of usability, integration, scalability, etc. It is important that theoretical discussions are substantiated with "commercializable" prototypes in order to keep "the feet on the ground" and deliver useable artifacts.

Expected Impact

- Better adoption of the EHR
- More effective sharing of information, resulting in better care coordination and quality
- Sharing of processes and workflow, resulting in better efficiency

3.3.4.2 TOPIC: STANDARDS

Specific Challenges

More and more systems are using standards to share clinical data. The existing standards are still lagging behind as they do not cover all use cases and have a poor support for semantics. This prevents the seamless collaboration between different initiatives, making them non sustainable at the end.

Standards and interoperability would support industrial scale but also improve the quality of care:

- While the healthcare industry has developed some standards, new systems still tend to be bespoke, provided by a single manufacturer and making minimal use of interoperable interfaces. Many companies and organizations invest large amounts of money and resources in the development and marketing of non-interoperable devices, services and data management tools, including electronic health record (EHR) systems. This is why there is an urgent need for core interoperable standards, to enable seamless care, encourage market development and to reduce fragmentation.

- Standardization is one way to foster security, accelerate innovation and lower costs. From an industrial standpoint, it allows for more efficient investment and gives industry the ability to quickly integrate innovation. From a patient's point of view, standards promote the improved quality and safety of medical solutions (since control is made easier); lower prices - thanks to scale - and benefits from the accelerated innovation. Some standards have been developed by industry consortia, although seemingly in an uncoordinated and intentionally competitive way. This is why it is important that authorities take a stand on which standards they wish to promote, validate or adopt. A clear position would encourage their adoption and use as a mandatory feature in public procurement (still too rarely the case in current requests for proposals (RFP) or tenders). While awareness of these issues has increased, for example in the EU eHealth interoperability framework in 2013, the scope of the framework is limited to cross-border eHealth services. For eHealth to gain momentum in the EU, it is important that such an approach be more systematic and coordinated with national, regional or project organizations. In this context, the Continua Health alliance has, within its work program on *personal connected health*, developed and published a set of interoperability design guidelines based on existing IEEE, IHE and HL7 standards.

Scope

Further research and innovation is needed in the following areas:

- Endorse standards but push them beyond what they are now. The lack of underpinning by formal semantics and model theory of the current communication standards (HL7, Open EHR, archetypes, …);
- Mapping between terminologies and ontologies;
- Knowledge morphing;

Expected deliverables

- Interoperability (of health information systems);
- Standards (common interfaces and formats);

Expected Impact

Standards and interoperability would support the scaling up of key digital healthcare services, and improve the quality and efficiency of care.

3.3.4.3 TOPIC: IT SERVICE ECOSYSTEM FOR PRIMARY AND SECONDARY USE: OPEN MARKETPLACE

Specific Challenges

Integrated Care, linked data, workflow sharing and decision support will require procuring IT infrastructure services, reaching outside the walls of the institution, the GP practice and the home of the patient. On one side, we will need to build, deploy and maintain the necessary infrastructure frameworks and, on the other side, more and more content will need to be generated, made available and kept up to date.

This will require efforts of IT companies, technical and clinical experts, consumption of connection lines and hosting of computer power. This doesn't come for free and therefore, it will be necessary to create a transactional platform to invoke the necessary IT services but also to automate the business/commercial side of these transactions.

While being open from the technical side, security and privacy measures should be implemented and an effective governance process over such platforms must be organized.

Scope

Projects should work on infrastructural and organizational solutions for IT service platform with support for financial and business transactional services along with the technical and medical services. Different business models should be investigated and proposed (e.g. pay per use, subscription based). Stakeholders can be a consumer of services or a producer or services and some stakeholders will be both. Note, that also the patient has a role in such a platform by making his data available but also consuming services. There could/should be connections to other forms of e-commerce and inclusion in non-health infrastructures such as e-government, smart-cities, transportation, home automation, wellness, coaching, etc.

Expected deliverables

- E-commerce based prototypes, able to automate the invocation and consequent billing of consumed services;
- Guidelines for making and deploying services;
- Business models;
- Government guidelines;
- Actual implementations and prototypes;
- Collaboration between different infrastructures (network of the networks);
- Deployment and real life usage (in pilot mode or beyond);

Expected Impact

An **open service oriented IT platform** for deploying and consuming ICT services, creating a new type of clinical IT service marketplace with the following challenges:
- Respect for privacy;
- Respect for governance, while still being an open platform;
- E-commerce support with automatic billing of complex and user specific usage patterns and just in time service composition;

A new type of commerce, a new marketplace and collaboration paradigm, enabling the sustainable deployment of infrastructural and content services, necessary for establishing Integrated Care and the Digital (Health) Agenda.

3.3.5 THEME 4:
REMOTE HEALTH SERVICES & SOCIAL CARE SUPPORT

Specific Challenges

For healthcare organizations to fully embrace the Remote Health concept, there are specific challenges that need to be overcome. Besides providing new technologies which are ready-to-use, the human aspect of this transformation must be carefully addressed. Currently, most healthcare providers are not ready for this transformation and many new skills will be necessary. Change Management and new medical practices and tools should be seriously taken into account in this critical transition. Partnering with industry and academia will also be necessary.

Additionally, remote health solutions should seek to provide a response to existing unmet user needs in order to make this change successful and to break down the barriers between organizations and professions.

In remote health, patients/citizens are put in the center and we should engage them in maintaining their health and managing their conditions and independent living with the assistance of technology, supported mostly by mobile health technologies.

Likewise, standards are necessary to secure three crucial aspects of remote health services and social care: interoperability (as well as interoperable care records), patient safety and privacy. Standards are prerequisites to reach economies of scale for companies which offer eHealth-related goods and services. This in turn leads to lower costs for users, and a more rapid take-up of eHealth solutions as experience is transmitted faster between different countries.

Finally, other barriers hinder the development of the remote health services and social care market including lack of legal clarity and the local market specificities e.g. data privacy laws.

Scope

The use of remote health services depends more on setting of a favorable environment, rather than designing specific technology solutions, since these already exist.

In other words, to make the use of remote health services and social care effective, strategies need to address the user's unmet needs, including aspects of interoperability, patient safety, and data security and privacy. The security of data and the protection of privacy are fundamental issues for digital healthcare innovators, practitioners, legislators and patients Indeed, medical data have particular security needs: Medical eHealth data, including data acquired and transferred through mobile devices, have a particular need to be kept secure. Thus secure hosting, traceability of access, and authentication should be mandatory for obvious reasons. the SIM card can be a very secure means of authentication. In France, health professionals use a combination of their professional card (CPS) and their SIM to authenticate themselves. As for the Data hosting, a secured environment is recommended - as already in place in the US (HIPAA) and some European countries, France and the Netherland for instance – as well as technical guidelines to simplify security checks (access, confidentiality, integrity and availability).

Expected deliverables

- Adoption of an EU wide Health Data Hosting Policy, aiming at overcoming security challenges of data hosting in the current fragmentation, and creating a real European industrial platform;
- Adoption of an EU methodology for assessing the medico-economic benefits of any e-/m-Health project, that include all dimensions;
- Safety and privacy;
- Interoperability (of health information systems);
- Standards (common interfaces and formats);

Expected Impact

eHealth technologies help to transform healthcare as delivered today into an outcome-based healthcare tomorrow, but some of the above challenges need to be overcome. The industries call for the creation of a single, leading and competitive eHealth market in Europe. This can only be achieved by creating the same market conditions across Europe.

4. REGULATORY AND HEALTH ECONOMY ASPECTS

Regulatory and health economy aspects are crucial for the success of innovations in medical imaging and healthcare IT, because under the common healthcare systems, industry cannot receive a return on its investment until after (a) regulatory approval is in place and (b) reimbursement becomes available. Innovation depends on a large number of systemic factors, that include incentives and obstacles set by the existing regulatory framework. The regulatory environment matters at all stages of the innovation process, from R&D to the market access.

With this context, a favorable regulatory framework would enhance the impact of Horizon 2020 financing instruments, supporting initiatives to tackle societal challenges and ensure industrial development, innovation and competitiveness in Europe.

While the EU has no mandate to interfere with the reimbursement of healthcare in Member States, it is important for innovators to learn about the respective Member State Policies.

4.1. REGULATORY ASPECTS

The research programs proposed in this strategic research agenda will eventually lead to commercial products on the market that may be considered as medical devices according to the current definitions. It is well known that the current regulatory framework for medical devices is under revision. Most of the research described in this paper will lead to products (well) beyond that time. It is expected in the context of recent political debates that the regulatory framework may change substantially.

It can be stated that in the current climate, manufacturers might be expected to more and more demonstrate through clinical evaluation and clinical studies, that their products are not only safe and effective, but also have incremental clinical value in comparison to currently-available solutions. While this is certainly to be appreciated from the perspective of optimizing healthcare delivery, it may lead to a reduction in the number of beneficial innovations that reach the market as the burden of gathering clinical evidence may become excessive. The projects, therefore, will have to include provisions that allow such extensive clinical investigations.

A further complication may be that some of the research could lead to products that are rather complex in the regulatory context. For example, combinations of contrast media, inert metal particles either with protein coating or not, microcapsules for medicine delivery, etc. These combination products may prove to be more effective than traditional products, yet may give rise to regulatory complications through being on the boundary between two (or more) regulatory regimes. The research programs should therefore also contain sufficient regulatory competence, if and where needed, to be in a dialogue with those developing and interpreting regulatory regimes.

4.1.1 REGULATORY ASPECTS FOR MEDICAL IMAGING SYSTEMS

Increasingly, medical imaging systems are used beyond diagnosis, and become integrated into clinical solutions for image-guided therapy delivery, in which their performance is linked to tracers as well as particles and drugs to be delivered under image guidance. In Magnetic Particle Imaging, for example, the spatial resolution of the imaging method depends on properties of the used tracer. And Image-guided, targeted drug delivery may be associated with novel drug-device combinations. This call for new methodologies for and approaches to regulatory approval processes.

Challenges

Challenges to be addressed in this area relate to novel methods and concepts supporting regulatory approval for medical imaging systems, in particular in the context of image-guided therapy.

In addition, the new technologies must be consistent with the general initiatives at International, European and National level, aiming at reducing the dose exposure of the public and the patients. Industry, under the MITA umbrella, has already initiated dose reduction initiatives through new features in their products and training on the use of devices emitting ionizing radiations.

Activities

Activities in order to address these challenges are required in the following areas:

- For Medical Imaging using tracers: Guidelines clarifying what is expected for the validation of the joint use of a tracer and a medical imaging device: Clinical data needed, specific tests and studies, answer to essential requirements, identification of adverse effects, claims to be included in the user instructions;

- For Image-guided therapy delivery: Guidelines on Hazard and Risk evaluation, Classification of combined products, answer to essential requirements

- For radiation dose reduction: Novel features for measuring, controlling and optimizing dose in the medical devices emitting ionizing radiations, training for users on dose control and optimization. Manufacturers are required by regulators to standardize on common methods for optimization;

- New methods for regulatory approval of systems for therapy based on the quantitative imaging and image-guided delivery of labeled drugs and therapeutic cells; clear rules and criteria for regulatory approaches towards drugs versus drug-device combinations used in imaging procedures;

- New investigations into patient safety for novel imaging methods, e.g. for the assessment of patient hazards associated with Magnetic Particle Imaging;

- Investigation into whether alternative applications or therapy delivery schemes are within the original approval of existing systems and products, for example the use of existing Gadolinium agents for MRI in the context of spectral CT;

- Investigations into regulatory approaches aiming to avoid / ban hazardous materials from being used in imaging systems or systems for image-guided therapy;

Expected deliverables

Expected deliverables are European guidelines on the validation of the joint use of a tracer and medical imaging devices, on Image-guided therapy delivery, and on features allowing dose optimization; improved regulatory processes, providing proper guidance to innovators regarding regulatory requirements and pathways.

Expected Impact

Expected impact will be safer association of imaging devices and tracer, better validation and risk assessment of new technologies and products, optimization of dose in imaging technologies, and, as a result, faster time to market for innovative imaging-related products.

4.1.2 REGULATORY ASPECTS FOR INTERVENTIONAL DEVICES

As interventional devices become increasingly "intelligent" through integrated sensors, and potentially through actuators, and as implants are being equipped with wireless communication capabilities, a need for new methodologies for and approaches to regulatory approval processes arises.

Challenges

Challenges to be addressed in this area relate to novel methods and concepts supporting regulatory approval for "intelligent" interventional devices.

Activities

Activities in order to address these challenges are required in the following areas:

- Investigations into safety and efficacy for intelligent interventional devices, assuring that their functioning is not intermitted, disturbed or otherwise perturbed while in their interventional stage - e.g. for the integration of –short range- communication technology, and exhaustive test of electromagnetic immunity and biological compatibility;

- Investigations of regulatory requirements regarding risk mitigation and supervision procedures for interventional devices, as well as environmental protection aspects (avoidance of hazardous materials);

- Development of regulatory guidelines regarding intelligent devices (e.g. smart stents), their positioning accuracy and quantification error for imaging of functional parameters such as blood pressure or blood flow speed;

Expected deliverables

Expected deliverables are improved regulatory approaches and guidelines for novel intelligent devices.

Expected Impact

Expected impact will be more effective regulatory processes.

4.1.3 REGULATORY ASPECTS FOR HEALTHCARE IT

As care providers increasingly depend on complex healthcare IT for data and workflow management as well as clinical decision support, new methodologies for and approaches to regulatory approval processes will be required. Especially for clinical decision support systems, new liability aspects may arise as care providers follow recommendations provided by the respective algorithms, and mechanisms must be created to assure quality and maintenance of the underlying knowledge which is used to derive those recommendations. In algorithms for computer-assisted diagnosis, one of the problems, the acquisition of "ground truth", deserves special attention and an early dialog between manufacturers and regulatory authorities in order to properly design the creation of the respective data.

Challenges

Challenges to be addressed in this area relate to the creation of guidance for the regulation of innovative technologies in the areas of knowledge based clinical decision support, computer assistance, and access to and use of registries.

Activities

Activities in order to address these challenges are required in the following areas:

- Investigation of and guidance for liability aspects for clinical decision support systems;
- Development of guidelines regarding the need for and collection of ground truth for computer-assisted diagnosis software;
- Evaluation of risks and risk mitigation regarding self-learning systems;
- Investigation into patient data bases and registries which could support regulatory approval processes for healthcare IT;
- Investigation of regulatory implications of software only products in the current MDD (Medical Device Directive), generation of improved classification schemes and improved guidance regarding potentially 'risky' SW-only products;

Expected deliverables

Expected deliverables are improved guidance documents and regulatory processes for healthcare IT.

Expected impact

Expected impact will be better regulatory processes, improved understanding of regulatory requirements between manufacturers and authorities.

4.2. HEALTH ECONOMY ASPECTS

Considering socio-economic changes across the EU countries, and the budgets for healthcare shrinking, or at least not growing in line with increasing demand, healthcare systems in the developed markets have been 'declared' unsustainable. For policy-making authorities in the years to come, the key question is how to serve more citizens and patients with more complex medical conditions (e.g. multiple chronic illnesses), with more convenience, better quality and at lower public costs.

Within this context, public authorities often use the Health Technology Assessment approach to assess the medical, economic, social and ethical implications of a health intervention. HTA helps determine whether an innovative procedure or device is a cost-effective solution compared to current practice. While this is to be appreciated from the perspective of the healthcare decision maker, it will add to the burden of the manufacturer. Apart from ethical considerations –more clinical trials, more patients- it adds to the cost and timeline of developing new products and procedures.

Challenges

Challenges to be addressed in this area relate to the avoidance of additional obstacles in terms of cost or "time to patient". Authorities need to cooperate constructively to support the introduction of innovative technology that demonstrably brings clinical benefits and/or adds to quality of life, as quickly as possible within the context of the economic environment; perhaps initially restricted and conditionally.

Activities

Activities in order to address these challenges are required in the following areas:

- Multi-stakeholder studies and workshops involving regulatory bodies, HTA groups, payers (public and private), care providers and patient advocacy groups alongside medical technology industry representatives with the aim of creating the right boundary conditions and defining commercialization perspectives for innovative products at an early stage.

Expected deliverables

Expected deliverables are guidance documents regarding stakeholder policies and considerations for the market access of innovative medical technologies.

Expected impact

Expected impact will be improved health economic planning ability for all stakeholders

4.3. HEALTH TECHNOLOGY ASSESSMENT METHODOLOGY AND INFRASTRUCTURE

Policy and decision makers in the organizations involved in approval and reimbursement discussions increasingly rely on Health Technology Assessment (HTA). HTA is a "multi-disciplinary field of policy analysis that examines the medical, economic, social and ethical implications of the incremental value, diffusion and use of a medical technology in health care[32]. It is intended to provide a bridge between the world of research and the world of decision-making[33]. ….. Health policy decisions are becoming increasingly important as the opportunity costs from making wrong decisions continue to grow[34]."

In its position paper on Health Technology Assessment[35], COCIR has stated the following:

> "*COCIR believes that the innovative solutions developed by the Medical Technology, Devices and IT industry sectors have a key role in addressing the increasing and unsustainable productivity, accessibility and affordability gaps. However, at the same time, Public Authorities, which are understandably prudent in the administration of scarce healthcare resources while facing increasing cost pressures, often view innovative medical and information technology as a cost, rather than an opportunity to improve quality, efficacy and the efficiency of healthcare. In an effort to better understand and reconcile these contradictory views it is essential that all stakeholders participate in developing appropriate processes to better evaluate the role Medical Technology, Devices and IT plays in the continuum of care.*"

Challenges

The price and reimbursement of healthcare interventions, including medical devices, are largely defined by the health technology assessment (HTA) process that is performed by independent, national agencies. HTA analyses the medical, economic, social and ethical implications of the value, effectiveness, costs and impact of a health intervention.

With currently about 50 national and/or regional HTA agencies across Europe, fragmentation is very high slowing the access of medical devices in the European market. For instance, the average time to market access for selected medical devices was estimated at 26 months in France and at 30 months in Italy, compared to 15 months in the USA[36]. The limited standardization and coordination of the HTA process in Europe requires that healthcare manufacturers address multiple stakeholders and systems which apply varying

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32 INAHTA (International Network of Agencies for Health Technology Assessment). (May 15, 2009). "HTA resources."
33 Battista, RN: *The scientific basis of health services.* BMJ Publishing Group, 1996
34 Menon D.; Marshall, D (1996). "The internationalization of heath technology assessment.". IJTAHC 12 (1): 45–51.
35 COCIR Position Paper: "Measuring the value of Medical Technology, Devices and Healthcare IT - The role of Health Technology Assessment (HTA)", 6 October 2010
36 Sheptarsi Basu M.P.A. et al. N Engl J Med 2012; 367:485-488

requirements to secure access to their products for patients in the different Member State markets. Challenges to be addressed in this innovation area relate to the development of a 'unified EU approach to HTA in order to allow medical technology and IT companies to develop innovative products with more clarity, consistency and predictability.

- Current HTA processes vary widely across nations within the EU, with different processes, stakeholder involvement levels, methods and implications. Current methods of assessing the full value of medical devices are not fit for purpose in many jurisdictions. HTA methods almost without exception, do not assess the full value of medical devices. They have primarily been developed to support pharmaceutical evaluation which is not necessarily appropriate for medical technologies and healthcare IT which have very different IP, regulatory data requirements and product life-cycles Any attempts to use HTA as a pre-requisite for public procurement or reimbursement of medical device technologies would have a significant delaying effect on market access i.e. patients' access to the benefits of new technologies would be severely compromised.

- Current reimbursement processes for innovative medical devices cause delays or deny access to many of the benefits (clinical, economic, etc) of innovative medical devices. Hence, there is a need for clear criteria on the standard/type of evidence required to support a unified EU HTA evaluation process. How are products to be selected, what outcomes are needed to support decision-making, what quality of evidence on outcomes are required, how will national differences be considered; different patient pathways and costs. Until very clear rules of engagement have been defined the success of a unified EU HTA will be minimal as it will be too difficult and potentially risky for industry to participate.

Activities

Activities in order to address these challenges are required in the following areas:

- for **HTA Assessment Methodologies and Processes**: research on and assessment of methodologies and processes across all participating nations to identify what works in order to gain a consensus on what methodologies and processes might be optimal for a unified EU evaluation. This could include activities such as:

  > full review of existing recommendations from current HTA bodies, both negative and positive to help clarify the type, quality and quantity of evidence that is more likely to support a positive recommendation to guide future clinical evidence generation.

  > Full review of current methodologies for evaluating innovative products in real terms (without years of clinical evaluation studies / data being available) to allow an assessment of whether current methodologies are actually fit for purpose.

- for **HTA Assessment Infrastructure**: perform research and derive consensus on what bodies will be involved in the HTA process from the early identification of relevant technologies through to the evaluation and then the final recommendations.

Expected deliverables

Standardized, predictable and transparent methods and criteria upon which appraisals for new medical technology, processes and devices are based.

Expected Impact

An appropriate HTA assessment of innovative technologies to support rapid adoption across the EU with impact on improved quality, efficacy and efficiency of healthcare.

GENERAL INFORMATION ABOUT COCIR

COCIR is the European Trade Association representing the medical imaging, radiotherapy, health ICT and electromedical industries.

Founded in 1959, COCIR is a non-profit association headquartered in Brussels (Belgium) with a China Desk based in Beijing since 2007. COCIR is unique as it brings together the healthcare, IT and telecommunications industries.

Our focus is to open markets for COCIR members in Europe and beyond. We provide a range of services in the areas of regulatory, technical, market intelligence, environmental, standardisation, international and legal affairs.

COCIR is also a founding member of DITTA, the Global Diagnostic Imaging, Healthcare IT and Radiation Therapy Trade Association (*www.globalditta.org*).

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