



## Decision support systems for personalized and participative radiation oncology☆



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### ABSTRACT

A paradigm shift from current population based medicine to personalized and participative medicine is underway. This transition is being supported by the development of clinical decision support systems based on prediction models of treatment outcome. In radiation oncology, these models 'learn' using advanced and innovative information technologies (ideally in a distributed fashion – please watch the animation: <http://youtu.be/ZDJF0xpwqEA>) from all available/appropriate medical data (clinical, treatment, imaging, biological/genetic, etc.) to achieve the highest possible accuracy with respect to prediction of tumor response and normal tissue toxicity. In this position paper, we deliver an overview of the factors that are associated with outcome in radiation oncology and discuss the methodology behind the development of accurate prediction models, which is a multi-faceted process. Subsequent to initial development/validation and clinical introduction, decision support systems should be constantly re-evaluated (through quality assurance procedures) in different patient datasets in order to refine and re-optimize the models, ensuring the continuous utility of the models. In the reasonably near future, decision support systems will be fully integrated within the clinic, with data and knowledge being shared in a standardized, dynamic, and potentially global manner enabling truly personalized and participative medicine.

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## 1. Introduction

Several major advances in cancer care (including radiation oncology) have been made in the last 5–10 years, with many new diagnostic techniques and treatment modalities becoming available [1]. This wealth of choice, however, has brought with it new challenges. Attaining level I evidence is increasingly difficult given the copious disease, patient and treatment parameters that exist, resulting in ever-increasing data heterogeneity [2]. This new reality is somewhat at odds with traditional evidence based medicine, whereby randomized trials are designed for large populations of homogenous patients. Consequently, new approaches are required to build evidence for clinical decision making based upon this wealth of patient, disease and treatment characteristics [3].

The challenge can be exemplified as follows: For each patient, the physicians must consider biology (mutations, translations, etc.), pathology, state-of-the-art imaging (including guidance techniques), blood tests, drugs/hormones, improved radiotherapy planning systems, dose, fractionation, radiation type, and, in the near future, radiogenomic data [4]. Medical decisions should balance cure rate, median survival, toxicity, comorbidity, quality of life, patient preferences (inform and involve the patient) and (in most healthcare systems) cost effectiveness [5]. This myriad of factors renders clinical decision making a dauntingly complex, and perhaps inhuman, task as human cognitive capacity is limited to roughly five factors per decision [2]. Furthermore, dramatic genetic [6], epigenetic [7], transcriptomic [8], histological [9] and micro-environmental [10] heterogeneity exists within individual tumors, and even greater heterogeneity exists between patients [11]. In radiation oncology there is heterogeneity in dose prescription, treatment margins and plan quality (i.e., 3DCRT, IMRT, VMAT, etc.). Moreover, there is a growing availability of targeted agents and immunotherapy which also may affect outcome. Despite these enormous complexities, individualized cancer therapy is realizable. Indeed, intra- and inter-tumoral variability can be potentially exploited advantageously to maximize the therapeutic ratio, i.e. increasing the effects of therapy upon the tumor while decreasing those effects on healthy tissues [12–14].

The principal challenge is how best to collect and integrate diverse multimodal data sources (clinical, treatment, imaging, biological/genetic, etc.) in a quantitative fashion that can provide specific clinical predictions that accurately and robustly estimate outcomes as a function of the possible decisions [15,16]. Presently, numerous published prediction models are available that account for factors related to both disease and treatment, but lack standardized evaluation of their robustness, reproducibility and/or clinical utility [17]. Consequently, these models may not be suitable (let alone optimal) for clinical decision support systems.

In this position paper we highlight the recent advances in decision support systems (DSS) for personalized radiation oncology, with a focus on the methodological aspects of prediction model development/validation as well as the sophisticated and innovative information technologies which are fundamental to the implementation and success

of DSS. The benefits and accompanying challenges of DSS are also discussed as well as the steps required for the continued progression and wide spread acceptance of DSS within the clinic.

## 2. Rapid learning healthcare

### 2.1. The four phases of rapid learning healthcare

Rapid learning health care (RLHC) [2] (also known as: knowledge-driven medicine, computer assisted theragnostics, intelligent medical networks, etc.) is the (re)use of medical data (from both standard clinical practice and clinical trials) to aid in decision making with respect to new patients and/or to investigate novel hypotheses [18–22] (Fig. 1a). RLHC is comprised of four sequential infinitely reiterated phases [2] (Fig. 1b) that culminates in model development/validation which can be clinically implemented through DSS [23] (Fig. 1c). The Data phase handles the attainment and mining of prior data (e.g., patient, disease, treatment, outcome, etc.). The Knowledge phase utilizes sophisticated analytical methods, (e.g., machine learning), to harness knowledge from the aggregated data. The Application phase exploits this knowledge to improve clinical practice. The Evaluation phase assesses DSS performance with respect to outcomes, subsequently the initial phase commences once more. For each phase, current best practice coupled with the latest scientific understanding is used to optimize the process. The sections below describe each phase in detail.

### 2.2. The ‘4 Vs’ of ‘Big Data’

Perfect RLHC demands the ‘4 Vs’ of ‘Big Data’: veracity, velocity, variety, and volume of data (<http://www.ibmbigdatahub.com/infographic/four-vs-big-data>). The veracity of data is critical to the amount of trust that can be placed in the knowledge acquired. The velocity of data is essential to guarantee that knowledge is gathered as continuously and constantly as practicable. The variety of data (predominantly with respect to treatment modalities as well as patient and disease characteristics) is fundamental to ultimately conclude which treatment is optimal for an individual patient. The volume of data is key: A) to obtain enhanced knowledge (the fidelity of knowledge is directly related to the number of patients upon which that knowledge is founded); and B) to gain knowledge regarding rarer, less heterogeneous patient cohorts and/or to increase the number of variables in the knowledge phase.

Accessing data with adequate fidelity in relation to the ‘4 Vs’ is the largest obstacle in RLHC. It is recognized that both the clinical and research communities need to embrace a data sharing ethos [24], traversing institutional and national boundaries, so as to realize this goal [25]. One initiative to accomplish this goal is CancerLinQ [26] (<http://cancerlinq.org/>), of the American Society of Clinical Oncology (ASCO). It is a RLHC system designed to monitor, coordinate, and improve the quality of care provided to patients with cancer through the collection, aggregation, and analysis of data extracted from the electronic health records (EHRs) and practice management systems at

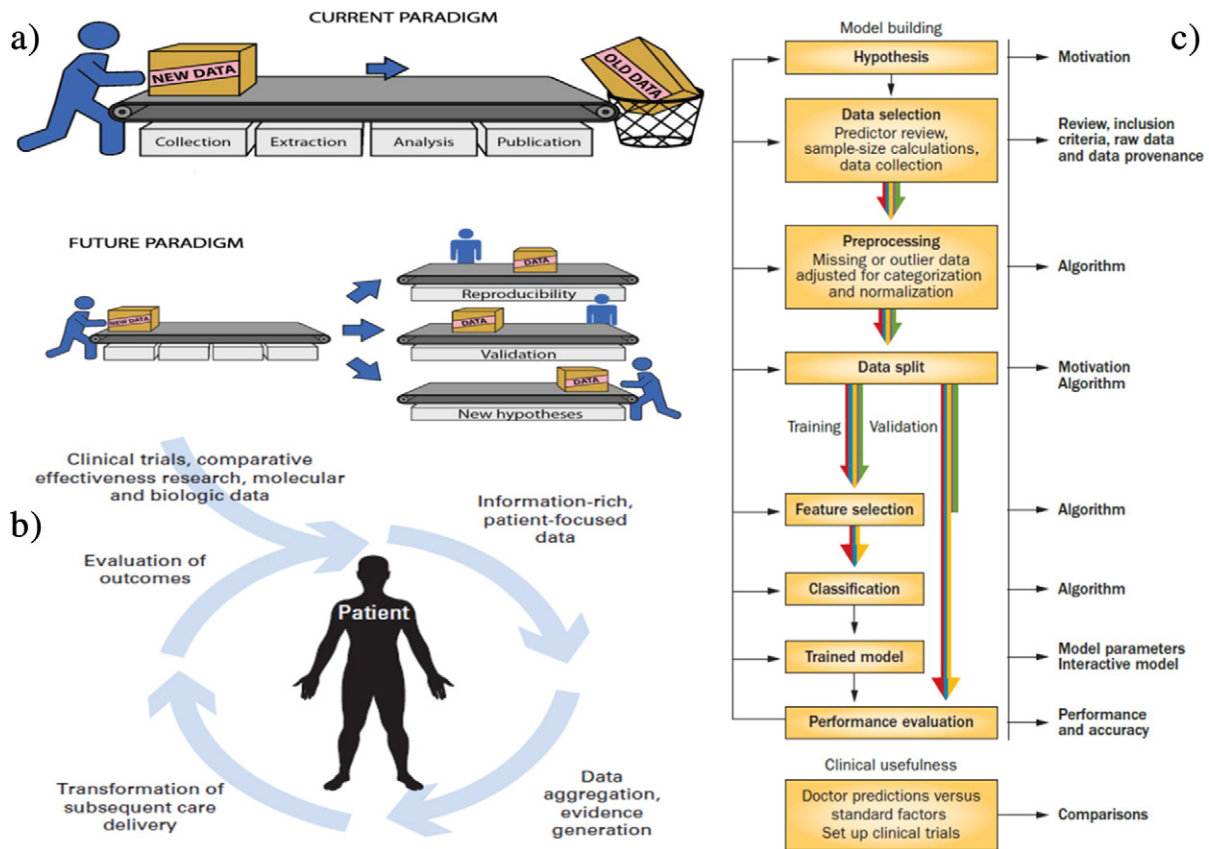


Fig. 1. Overview of the methodological aspects of clinical DSS development/validation, including assessment of clinical utility.

participating oncology practices. Unlike registries that collect pre-specified data elements from a defined cohort, CancerLinQ collects the complete EHR of all patients in a participating practice. This necessitates an established secure connection to CancerLinQ from the EHRs and practice management systems, to periodically transfer a range of information. The data proposed to be transferred includes; provider and patient demographics, appointments, billing codes, patient visit/encounter details, medical history and physical examination, family and social histories, consult reports, surgery reports, pathology and laboratory data, and medication administration and prescription history. Through the use of natural language processing, CancerLinQ will also be able to collect and process information from clinician notes. This traditional data centralization approach faces the following classical barriers to data sharing [27], which come in the form of: human resources or insufficient time; cultural and language difficulties along with data recording methods; the political and academic worth of data; hazards to reputation; legal and privacy issue, etc. These are all significant issues to address and are not easily overcome. However, a cooperative endeavor linking radiotherapy institutes in the Netherlands, Germany and Belgium (Fig. 2: now extended to the UK, Italy, Denmark, Australia, China, India, and the USA – Canada, South Africa and Ireland are currently prospective partners) successfully realized RLHC through a novel data federated approach in the euroCAT project ([www.eurocat.info](http://www.eurocat.info), please see the animation: <http://youtu.be/ZDJFOxpqwEA>). Novel applications for advanced information communication technologies were central to the realization of the endeavor (Fig. 3), facilitating synchronized RLHC in each center without any data needing to leave the institution (thus overcoming the classical barriers to data sharing aforementioned), known as ‘distributed learning’ (please see the animation: <https://www.youtube.com/watch?v=nQpqMluHyOk>). This forced the development of data with semantic interoperability

(also called ‘data with linguistic unity’ or ‘machine-readable data’), wherein local terms are matched to concepts from a well-defined ontology (e.g. NCI Thesaurus). Utilizing this technique, the ontology terms function as a common interface for the data at each institutional site, allowing a unified process for information retrieval and reasoning facilitated by a semantic gateway to the data. An advantage of such initiatives is that they encourage harmonization with regard to what data necessities collection and how (i.e., disease specific ‘umbrella’ protocols: NCT01855191 <https://www.cancerdata.org/protocols/eurocat-umbrella-protocol-nslc>) [28].

### 2.3. Knowledge

Machine learning is a method to transform data into knowledge. In machine learning, models/algorithms are utilized to optimally characterize data and generate knowledge which can be exploited to make predictions with respect to new, unobserved data. Models trained on past data can be employed to predict the outcomes (e.g., control, toxicity, quality of life, etc.) of numerous treatments using data from a new patient. With evermore patient characteristics becoming available (clinical, treatment, imaging, biological/genetic, etc.) there is more heterogeneity in the data and consequently greater opportunity to garner superior knowledge. However, an un-validated model is of highly limited worth and it is thus essential that models are properly validated. The TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) statement is an excellent template for this – exemplifying increased model accuracy and robustness stemming from proper data management [29–33]; Therefore, a validation dataset must be readily obtainable, if possible from an external institute(s) dissimilar (but not inappropriately different) than that from which the data was used to train the model.



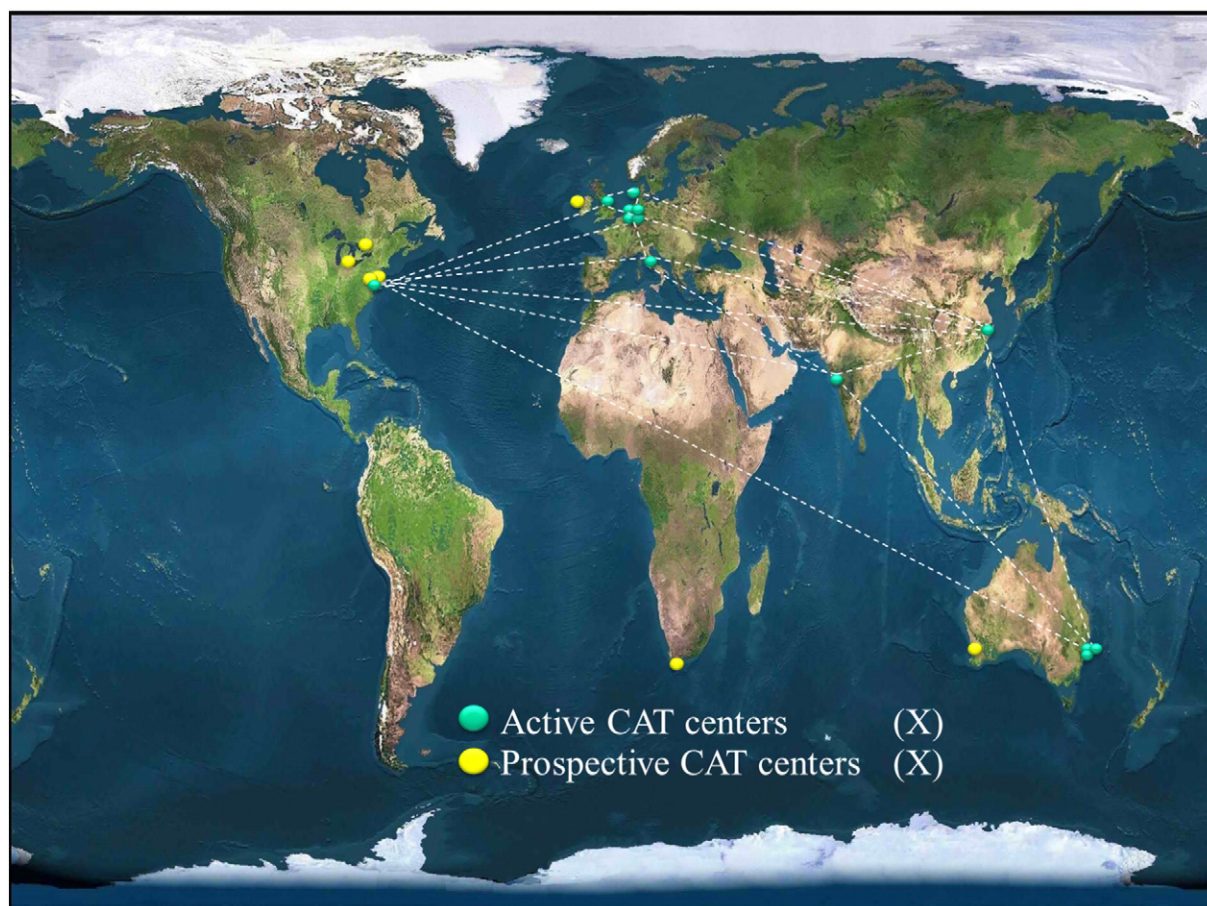


Fig. 2. Overview of the current 'worldCAT' network: Active and prospective partner sites.

Examples of radiotherapy models (on the basis of both clinical trials and routine clinical care data) are available for non-small cell lung, rectal and head-and-neck cancer on <http://www.predictcancer.org>, breast cancer on <http://research.nki.nl/ibr/>, prostate cancer on <https://www.mskcc.org/nomograms/prostate>, and glioblastoma on <http://www.eortc.be/tools/gbmcalculator/>.

#### 2.4. Application

Clinical trials are vital in informing routine clinical care; however, current designs have considerable deficiencies, such as selection bias (e.g. under-representation of elderly patients) [34–37]. RLHC helps meet this challenge as the knowledge gained from RLHC is drawn directly from the routine clinical care population. This knowledge is applied with the aid of DSS. These are archetypally software applications that may be utilized to apply RLHC in practice. Examples include nomograms (Fig. 4) [38–40], recursive partitioning analysis models [41], and websites, such as those given above. DSS are proposed to support the physician and the patient in taking the most knowledgeable decision possible with respect to treatment options (they are neither proposed nor appropriate as a substitute to the physician). Healthcare professionals leveraging computer models in radiation oncology are not novel. Physics-based models for dose calculation along with radiobiology-based normal tissue complication probability (NTCP) [42] and tumor control probability (TCP) [43] models to link dose with toxicity and tumor control, are all accepted within the radiotherapy community. The emergent models from RLHC [44] are a natural evolution of this practice. An important attribute of RLHC models is their 'holistic' and multifactorial structure, integrating the current physics- and/or radiobiology-based models,

along with accounting for patient, tumor and non-radiotherapy factors [23]. For instance, a RLHC model of radiation-induced esophagitis predicts that the risk for this toxicity depends not simply on just the dose to which the esophagus is exposed, but also significantly increases if concomitant chemotherapy is delivered [45]. Another example is that for non-metastatic unresectable non-small cell lung carcinoma, the prognostic value in relation to survival is inferiorly predicted by tumor-node-metastasis (TNM) classification than a multifactorial model built upon clinical, imaging and biomarkers variables [46].

#### 2.5. Evaluation

The primary idea in RLHC is that the utilization of knowledge obtained from clinical data results in comprehensive understanding and subsequently improved predictability of treatment outcomes, suggesting that these outcomes can be improved both in terms of effectiveness (attaining the desired outcome) and efficiency (the resources needed to attain the outcome). While adding features may result in enhanced outcome prediction, this is not always the case and therefore critical appraisal of complex multifactorial models with comparatively simple generally accepted models is crucial to define the precise worth of added features [32]. Indeed, RLHC models ought to be repeatedly (re-)evaluated, fixed on the questions 'Is the outcome of treatment as expected, and if so, how does this relate to consensus and/or evidence based guideline knowledge?'. This appraisal ought to if possible be performed with (meta-analysis of) robust data that is independently interpreted by multiple interested stakeholders (researchers, physicians, economists and patients/representatives).

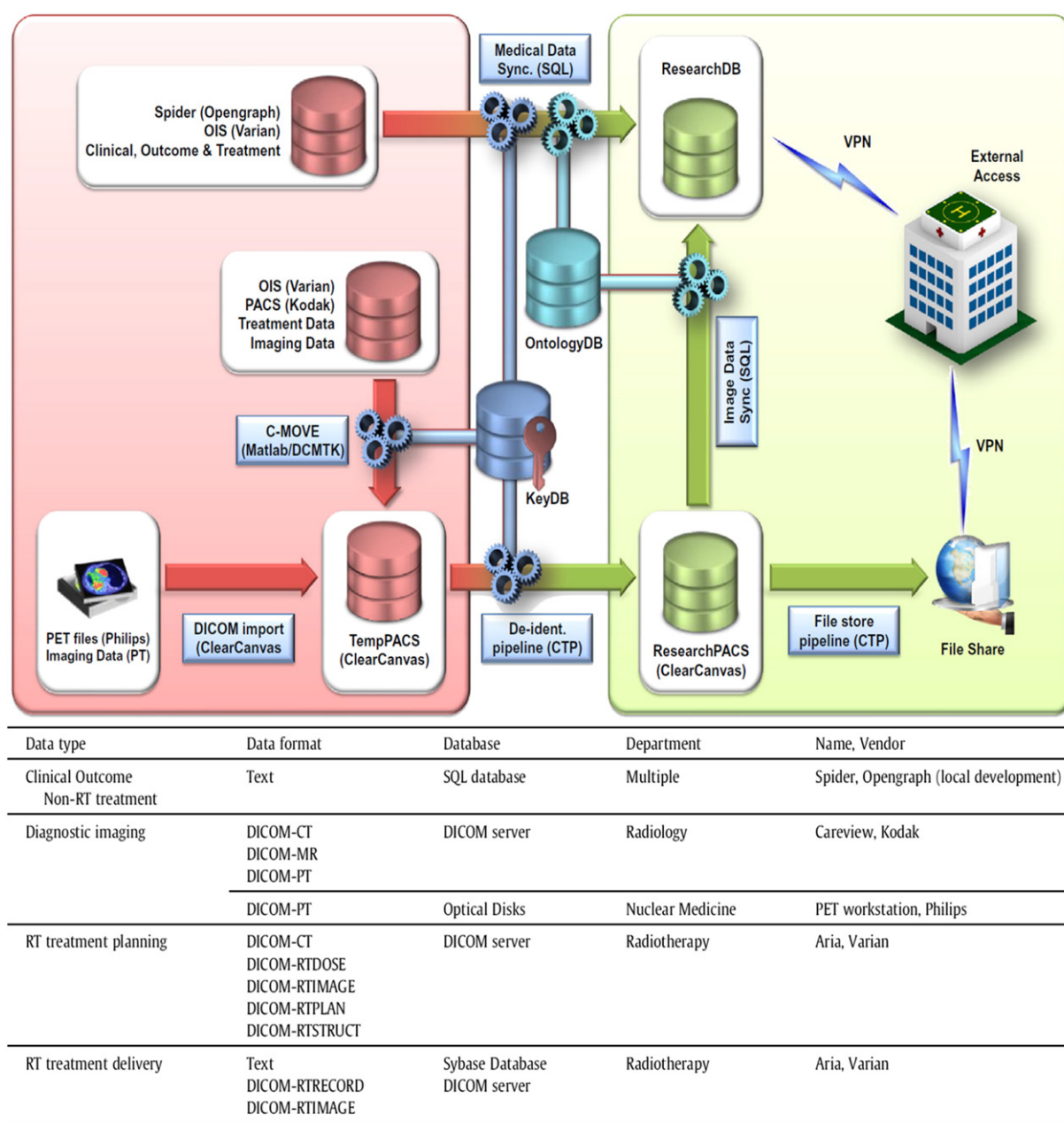


Fig. 3. Overview of data sources, flow and external access of the current network infrastructure installed at each partner site within 'worldCAT'.

### 3. Producing a clinical decision support system

#### 3.1. Factors for prediction

The primary goal of producing DSS is to discover, based upon the available information, a combination of factors that accurately and robustly predict an individual patient's outcome [47] (e.g., clinical, treatment, imaging, biological/genetic, etc.). Outcomes can be categorized coarsely as either control (rates of local recurrence, evolution to metastatic disease, overall survival, etc.) or toxicity (acute, late, moderate, severe toxicity induction, etc.), or a combination of these end points (cost effectiveness can also be considered [48]). Although predictive factors (i.e., factors that influence response to certain treatments) are essential for DSS, prognostic factors (i.e., factors that influence response without treatment) [49] are equally significant in illuminating the complex relationship with outcome. Henceforth, we refer to both of these

terms commonly as 'features' because for a predictive model correlation with outcome must be demonstrable.

#### 3.2. Model development

The process of feature selection for model development is comparable to that of biomarker assays [50]. In that framework, we can distinguish qualification and validation. Qualification demonstrates that the data is predictive of an end point, while validation establishes that a combination of features is both reliable and suitable for the envisioned purpose. i.e., features must be identified and tested in independent datasets to determine if treatment decisions made based upon these features would improve outcomes. The complete cycle of model development entails several stages (Fig. 1c).

In the hypothesis-generation stage, the end point to predict must be considered along with the timing of the treatment decision and the

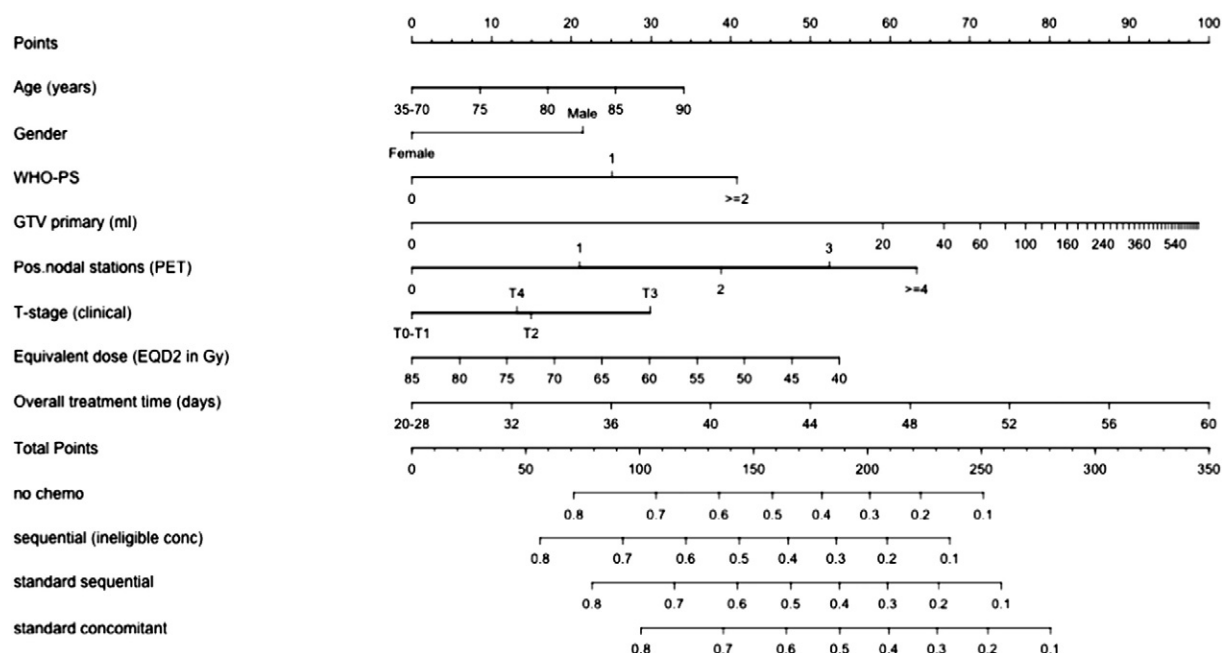


Fig. 4. A nomogram for prediction of 2 year overall survival for stage III non small cell lung cancer patients treated with (chemo) radiotherapy (<http://www.predictcancer.org/Main.php?page=LungSurvivalModel3>).

available data at these time points. In the data-selection stage, a review of possible features is performed, by either expert panel or by mathematical approaches such as a Bayesian network (which has been shown to be superior to expert panels [51]). Sample-size calculations are recommended, particularly for the validation phase [52,53]. Data from both clinical trials (high quality, low quantity, controlled/biased selection) and clinical practice (low quality, high quantity, uncontrolled/unbiased selection) are useful, however selection biases should be accounted for in both instances and inclusion criteria ought to be equivalent. For all features, data heterogeneity is a key requirement to identify predictive features which enable the personalization of treatment.

Preprocessing manages various issues such as missing data (imputation) [54], incorrectly measured or entered data (sanity checks) [55] as well as discretizing and normalizing data (if applicable) to avoid sensitivity for different orders of data scales [56]. If an external, independent dataset is not available for validation, the available data must be split (in a separate stage) into a model training dataset and a validation dataset. In the feature selection stage, the ratio of the number of evaluated features to number of outcome events must be kept as low as possible to avoid overfitting [57–59]. When a model is overfitted, it is specifically and exclusively trained for the training data (including its data noise) and consequently performs poorly on new data. Data-driven preselection of features is therefore recommended [60]. Univariate analyses are commonly used to prioritize the features – that is, testing each feature individually and ranking them on their strength of correlation with outcome. Next, performance measures for the model are determined on both the training and validation datasets. These measures are typically the area under the receiver operating characteristic curve (AUC) or the c-index for censored data [32]. The AUC and c-index quantify the sensitivity and specificity of the model and have values between 0 and 1 (with 1 denoting a perfect model, 0.5 randomness, and 0 the inverse of a perfect model).

### 3.3. Predicting outcomes

Training data is employed to train a model, classifying all potential outcomes. Classical statistical [61] as well as machine-learning models [62] can be considered. For two or more classes (e.g., survival vs death), logistic regression, support vector machines, decision trees, Bayesian networks or Naive Bayes algorithms can all be utilized [63,

64]. For time-to-event outcomes (irrespective of censorship), Cox proportional hazards models or the Fine and Gray model [65] of competing risks are typical. Model selection is dependent on the nature of the outcome (e.g., logistic regression for two or more outcomes, or Cox regression for survival-type data) and the nature of the training data (e.g., Bayesian networks necessitate categorized data, while support-vector machines are appropriate for continuous data). As a general rule, several models should be evaluated to ascertain which model is optimal for the available data. This also includes investigation of non-linear associations and interactions. Akaike's information criterion can be used to deal with the trade-off between goodness of fit and model complexity [66] (i.e., a simpler model is expected to be more robust than a more complex model to a wider range of data).

Performance in the training dataset is always upwards-biased because the features were selected from the training dataset. Therefore, a validation dataset is essential to establish the likely performance in the clinic. Preferably, validation data should come from an external independent institution or trial. When data is scarce, internal validation can be conducted using random split, temporal split or k-fold cross-validation techniques [67]. The developed model should demonstrate a clear benefit with respect to decision making, and must be evaluated prospectively in the clinic in the penultimate stage of model development. Predictions forecast by the model and clinicians must be compared [45,68] along with standard prognostic and predictive factors [69]. Application of models in clinical practice often requires an extra step in the development process. While most models provide a predicted probability for an outcome, clinical decision making usually relies on threshold values for treatment choices. Depending on the consequences a threshold value is chosen to minimize either false positives or false negatives. So a wide range of tools exist, ranging from informative, by providing a probability, to prescriptive tools, that use a fixed threshold, and even tools that are capable of identifying patient-specific thresholds. Irrespective of their nature, it is crucial to confirm improvements in patient outcome, quality of life and/or reduced toxicity [70], by performing clinical trials and impact studies whereby the random allocation of patients is predicated by the model. Satisfying this requisite will produce the ultimate evidence that the model is enhancing health care by comparing, in a controlled way, the personalized therapy with standard therapy in the clinic.



Lastly, the prediction models and development data can be published, allowing the broader oncological community to assess them. Full transparency of the data as well as methodology is vital to the global implementation of the model within DSS. This proposition is analogous to clinical 'omics' publications for which the raw data, the code used to analyze the data, evidence for data provenance (the procedure that led to a piece of data) and a written report of nonscriptable analysis steps are customarily made available [71].

### 3.4. Clinical features

Decision making in radiotherapy is largely built on clinical features, such as the patient performance status, organ function and grade of the cancer based on histologic assessment, the extent of the tumor (defined by the TNM system), age, comorbidity of the patient, etc. Such features have been repeatedly found to be prognostic for survival and toxicity [72,73]. Accordingly, such features should be assessed/incorporated when developing robust and clinically acceptable models for DSS. Measurement of some clinical features can be captured with minimal effort (e.g., performance status). Even a simple questionnaire should be validated as is the case for laboratory measurements of organ function or parameters measured from blood [74,75].

A standardized protocol should be established (e.g., the 'Umbrella' protocol NCT01855191 <https://www.cancerdata.org/protocols/eurocat-umbrella-protocol-nscl> [28]) to guarantee that comparisons are possible and appropriate between centers and questionnaires over time [76]. Additionally, why particular features were selected for measurement should be clearly explained (e.g., if hemoglobin measurements were only recorded for patients with fatigue, the subsequent bias would dictate caution when including and interpreting the measurements). Only when clinical parameters are recorded prospectively with a level of scrutiny equivalent to laboratory measurements will observational studies become as trustworthy as randomized trials [77,78].

Toxicity measurements and grading should also be based upon validated systems, such as the common terminology criteria for adverse events (CTCAE: [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)) [79], which can be reported by the physician or patient [80,81]. Indeed, a recent meta-analysis revealed that high-quality toxicity assessments from observational trials are comparable to those of randomized trials [82,83]. However, a prospective protocol must clarify which system was used and how changes in toxicity grade over time with respect to treatment were managed.

Finally, to ensure standardized interpretation, the reporting of clinical and toxicity data and their analyses should be conducted in line with the STROBE (strengthening the reporting of observational studies in epidemiology) statement for observational studies and genetic-association studies, which is essentially a checklist of items

that should be addressed in reports to simplify critical appraisal and interpretation of these type of studies [84–86].

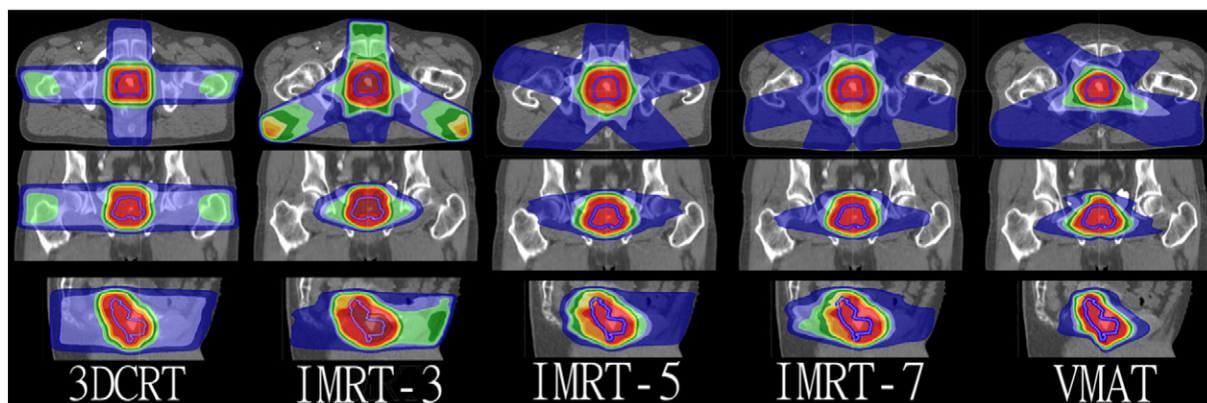
### 3.5. Treatment features

A delicate balance exists between tumor control and treatment-related toxicity. Presently, image-guided radiotherapy (IGRT) is a highly precise cancer treatment modality in delivering its agent (radiation) to the tumor [87]. Additionally, broad knowledge of the effects of radiation upon normal tissue has been obtained [88–90]. Utilizing modern radiotherapy techniques – such as Brachytherapy (low dose or High dose rate), intensity-modulated radiotherapy (IMRT), volumetric arc therapy (VMAT) or particle-beam therapy – the treatment dose can be sculpted around the target volume with dosimetric accuracy of a few percentage points delivering millimeter precision to spare as much as possible the organs at risk [91] (Fig. 5).

For modeling purposes, features that are derived from planned spatial and temporal dose distributions are significant. Furthermore, a description of the efforts undertaken during treatment to safeguard that the prescribed dose is in fact delivered as planned (e.g., in-vivo dosimetry) is also required [92]. Additional therapies, such as hormonal therapy, chemotherapy, targeted agents and surgery, and their respective features must also be detailed because these also influence to varying degrees outcome. A prime example of this is concurrent versus sequential chemoradiation, which has a major impact on the incidence of acute esophagitis and induces dysphagia [93].

With respect to the spatial dimension of radiotherapy, how to combine information about the spatially variable dose distribution for every subvolume of the tumor or organ remains an open question. Dose–response relationships for tumor and healthy tissues are frequently reported as mean dose, though voxel-based measures have also been reported [94]. Mean doses or point doses (e.g., max/min dose) inside the tumor or healthy tissue are easily quantified and are sufficient for numerous applications. However, spatial characteristics might be more relevant in personalized approaches to ensure radioresistant/sensitive areas of the tumor or healthy tissue receive higher/lower doses [95].

Clinical dose volume histogram analysis was first described in 1991 for radiation pneumonitis and proctitis after treatments for non-small-cell lung and prostate cancers [96]. In 2010, a series of comprehensive reviews of all commonly irradiated organs (the QUANTEC project) was published [89], illustrating that, similar to the tumor, care must be taken when assessing dose at the organ level. For example, in some organs the volume receiving a certain dose is important (such as the esophagus or lung [97,98]), while in other organs it is the maximum dose which is most important (such as for the spinal cord [99]). Predicting toxicity in healthy tissues is an active research area with ongoing, large, prospective multicenter studies [100–107].



**Fig. 5.** Example of the variety of dose distributions (calculated on the same patient for several established external beam treatment modalities) which are available within radiation oncology for the treatment of prostate cancer. The number following IMRT-3/5/7 refers to the number of beams.

Though significant, relying solely on dose-based predictions is ill-advised due to the large variability in toxicity which patients' exhibit. The cause of this variability includes several recognized clinical and biological/genetic-based features as well as the quality of the treatment execution (i.e., planned vs delivered dose [108]). The overemphasis on the planned radiotherapy dose distribution as the primary factor of outcome is possibly the most common hazard in prediction modeling as substantial deviations from the original plan during treatment often occur [109]. The accuracy of prediction models is anticipated to improve when measured dose is used, as this quantity reveals the effect of radiotherapy most truthfully. Delivered dose reconstructions (2D and 3D [110]), Gamma-Index calculations and dose volume histograms (DVH) aid identification of increasingly accurate dose-related features [111, 112], such as radiation pneumonitis and esophagitis [98,113].

When considering dose as a treatment feature, it is important to be aware of the concept of biologically effective dose (BED) [114,115]. The BED concept is an inherent part of the linear quadratic (LQ) model which is derived from sound biophysical principles of radiation effect [116], with the consequence that BED is accurate and robust in a reasonably wide range of scenarios and can be expressed as:

$$\text{BED} = nd \left( 1 + \frac{d}{\alpha/\beta} \right)$$

where  $\alpha$  and  $\beta$  are the radiosensitivity coefficients associated with lethal (linear) cell damage and potentially lethal/repairable (quadratic) cell damage respectively,  $n$  the number of fractions and  $d$  the dose per fraction, such that the total treatment dose is equivalent to  $nd$ . BED is viewed as an important biological measure of the physical dose delivered to tissue (characterized by the  $\alpha/\beta$  ratio). Therefore, nearby tissues with different  $\alpha/\beta$  ratio values (e.g., bladder, prostate, rectum), each receiving identical dose and fractionation, will be associated with different BEDs. It follows that, for a specified value of the  $\alpha/\beta$  ratio, a particular BED can be attained by numerous different (yet isoeffective) fractionation schedules. Thus, BED is a powerful comparator of competing fractionation schedules. A limitation of this concept is that precise values for  $\alpha/\beta$  ratios (of both the tumor(s) and healthy tissues) are seldom known in individual patients.

The temporal properties of fractionated treatment are also a vibrant field of research. Treatment dose is rarely increased to compensate for increases in treatment course duration (especially outside of squamous cell carcinoma of the head-and-neck or cervix), however, there is a growing body of evidence which advocates that reduced treatment times, while delivering the same total dose, improve outcome [117, 118]. A multicenter head-and-neck cancer study of patients treated with radiotherapy alone showed that the potential doubling time of the tumor prior to treatment was not predictive of local control [119]. Classic processes such as accelerated repopulation [120], fluctuations in cell loss, hypoxia and radioresistant tumor stem cells have each been advocated as the principal origins of this observation, the potential implications of which include shorter overall treatment times with increased doses per fraction and the avoidance of treatment gaps [121, 122]. Generally, treatment time is an available feature that is associated with local failure in numerous tumor sites [123–125].

In the ideal scenario, both the spatial and temporal properties of radiotherapy would be leveraged by monitoring/knowing the cumulative/fractional dose distribution in a tumor and/or healthy tissue (i.e., a radioresistance/sensitivity map that is continuously updated during treatment). Regrettably, such a comprehensive maps of radioresistance/sensitivity do not yet exist, although progress is being made [126,127]. With the provision of such a map, DSS would support the planning and adaptation of the spatial and temporal dose distribution in such a manner as to conserve or improve the therapeutic ratio continuously during treatment, as opposed to the present method that attempts to deliver the dose to the tumor

as planned. Currently, a randomized phase II trial (RTOG 1106/ACRIN 6697) of individualized adaptive radiotherapy using during-treatment 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) and modern technology in locally advanced non-small cell lung cancer is underway to answer important questions with respect to realizing this goal. The hypothesis of the trial is that the during-radiotherapy FDG-PET/CT-based adaptive therapy will allow increased daily dose to the reduced target volume for the remainder of the treatment in the majority of patients and meet the dose limits of organs at risk (OARs), thus improving loco-regional control without increasing normal tissue toxicity.

### 3.6. Imaging features: from tumor size to radiomics

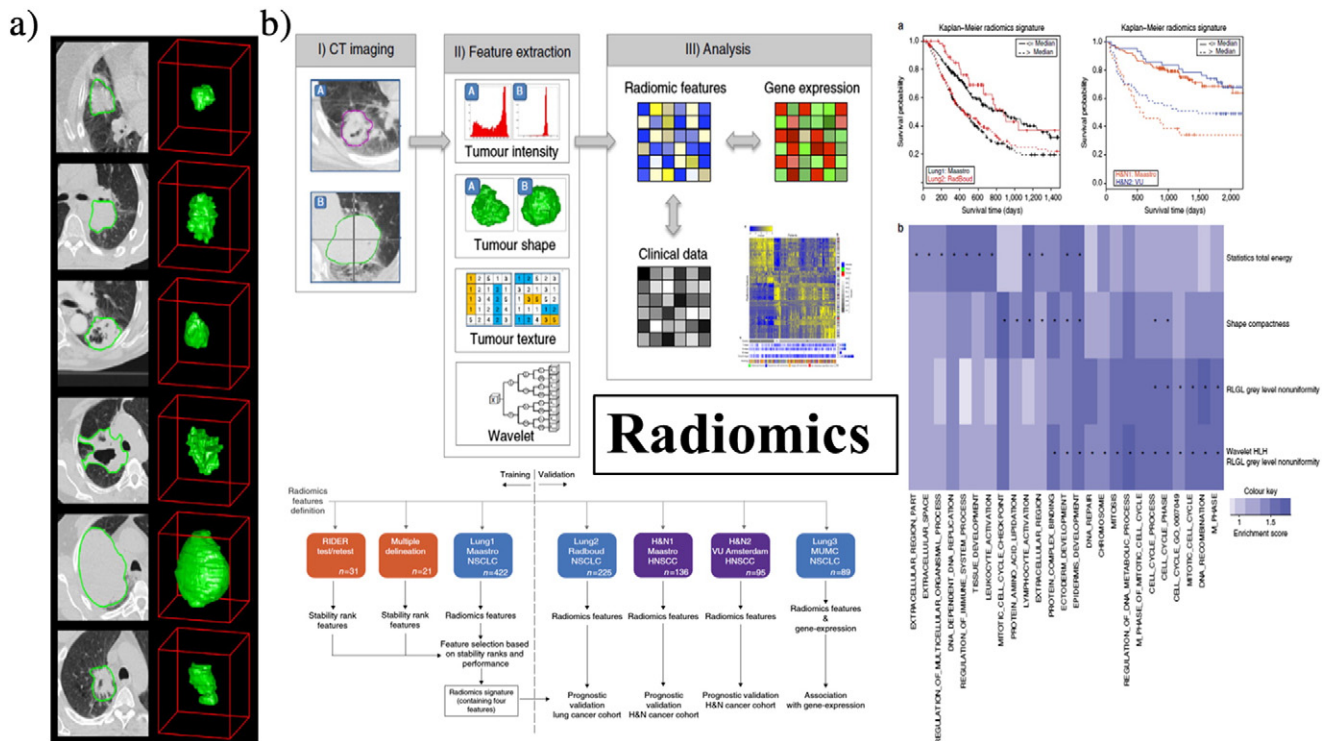
Imaging plays a pivotal role in oncology, especially in radiotherapy it dominates treatment planning and response monitoring roles [128, 129]. Technological progress in imaging – including enhanced temporal and spatial resolution, faster scanners and protocol standardization – has rapidly advanced the area towards the identification of quantitative noninvasive imaging biomarkers, also known as “Radiomics”. [21,130, 131] (Fig. 6).

Metrics built on tumor volume and location are the most frequently employed image derived features of tumor response to therapy and survival [132–139], and utilize CT or magnetic resonance imaging (MRI) technology for 3D measurement [140–142]. Although used in clinical practice, tumor volume and location are subject to inter-observer variability that can be ascribed to variances in tumor delineations [143, 144]. Furthermore, the optimal techniques for measurement and definitions of appropriate response criteria are still to be definitely determined [145–149]. In addition, tumor motion and image artifacts are further sources of uncertainty [150,151]. To meet these challenges, computerized tumor delineation algorithms have been developed [152–155] based upon image properties such as the range of Hounsfield units (which characterize the linear attenuation coefficient of the tissue) on the CT which represent a specific tissue type, or calculation of the gradient across the CT (mathematical filter) to reveal the borders between tissue types. Thorough assessment, however, is required before these approaches can be routinely used in the clinic [156–158].

A typical tracer for the metabolic uptake of the tumor is FDG for PET imaging [159,160]. The pretreatment maximum standardized uptake value (SUV, which is the normalized FDG uptake for an injected dose according to the patient's body weight) is strongly linked with tumor recurrence as well as overall survival in a number of tumor sites, such as the lung, head and neck, rectum, esophagus and cervix [161–167]. Additionally, numerous studies have revealed that variations in SUV during and after treatment are initial predictors of tumor recurrence [168–171]. However, FDG-PET measurements are dependent on a several factors, including injected dose, FDG clearance, baseline glucose concentration, image reconstruction methods used and partial-volume effects [172,173]. Global standardization of these factors is therefore essential to enable comparisons and validation of data from FDG-PET imaging across institutions [174–178].

Multiple studies have demonstrated that diffusion-weighted MRI parameters, such as the apparent diffusion coefficient (ADC), which quantifies water mobility in tissues, can accurately predict response and survival in multiple tumor sites [179–182]. However, issues concerning reproducibility of ADC measurements – which can be attributed to the dearth of standardization of instrumentation among vendors and of internationally recognized calibration protocols – remain a challenge for these kinds of investigations [183]. Assessments of varying time points in dynamic contrast-enhanced MRI have also been employed to quantify tumor perfusion [184–186]. Indeed, hypothesis-driven preclinical and xenograft studies support these clinical studies [187–189]. An example of this is that assessment of





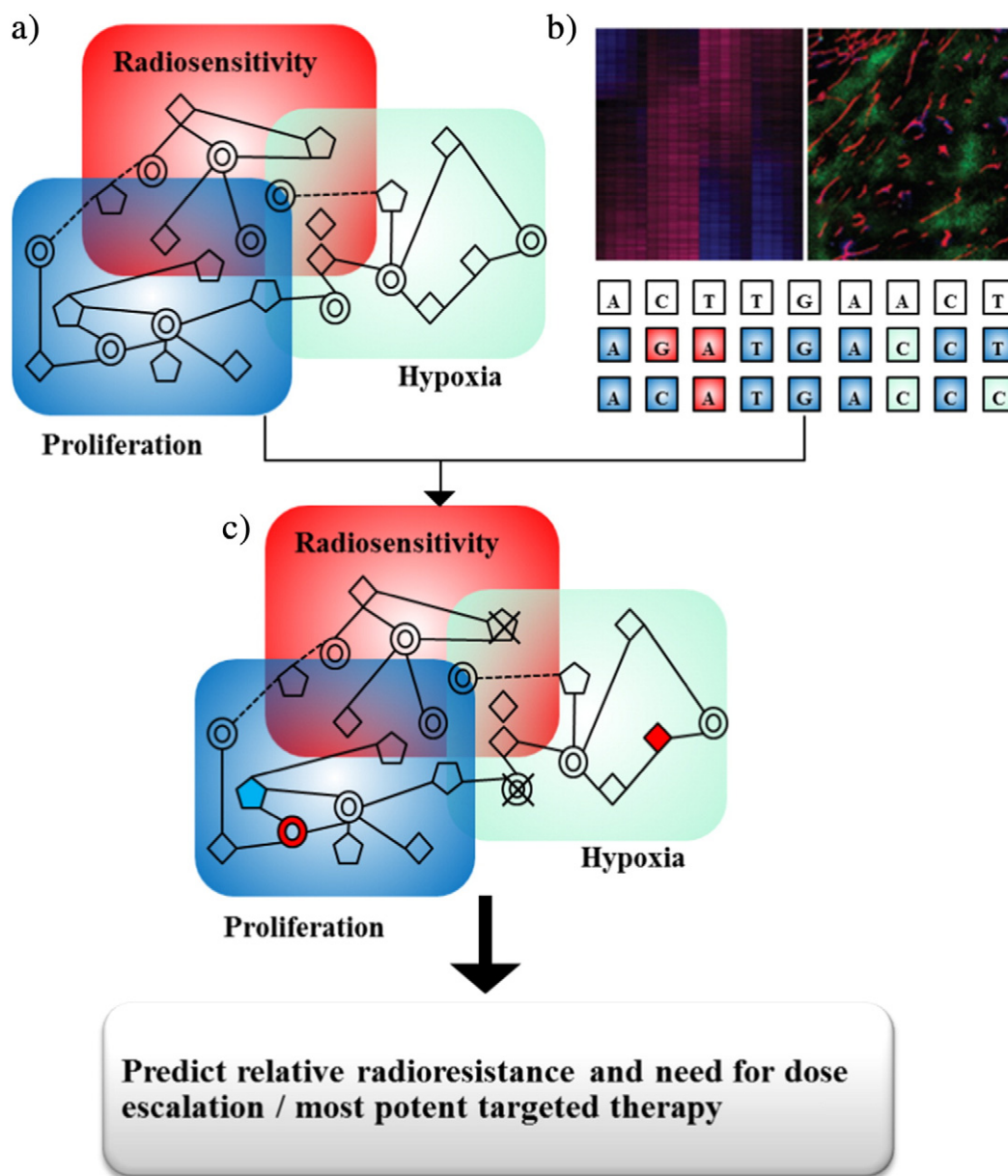
the correlation of features from imaging, such as the extent of reoxygenation and lactate level, with tumor control is possible.

Increasingly sophisticated image derived features are presently being explored. It is currently possible with routine clinical imaging to capture both tumor heterogeneity and post-treatment changes, which can be processed to detect functional biomarkers. For instance, a surrogate for tumor perfusion can be directly related between variations in Hounsfield units in contrast-enhanced CT and the quantity of contrast agent present in the tissue [190,191] (corresponding perfusion defects can be detected by dual energy CT [192]). Indeed, decreasing magnitude of CT Hounsfield units after treatment has been used to assess treatment response in pulmonary, hepatic and rectal cancers [193,194].

Standardization of image analysis to obtain a large number of features derived from imaging is now being considered for novel imaging biomarker approaches [21] with innovative image processing techniques, descriptors of tumor heterogeneity (such as variance or entropy of the voxel values) and the relationship of the tumor with adjacent tissues can be objectively quantified [195–197]. These systematic methods facilitate high-throughput assessment of imaging features which can be correlated with treatment outcome and, potentially, with biological data [198].

As a proof-of-concept it was shown that underlying genetic changes and early treatment responses influenced image derived radiomic features in a preclinical study [199]. In glioblastoma patients, MR imaging features have strongly corresponded to cancer related and drug targetable mutational status [200]. Indeed, qualitative imaging features from CT and MRI images have successfully predicted mRNA abundance variation in hepatocellular carcinomas and brain tumors [201–203]. Additionally, a composite of anatomical, functional and metabolic imaging may capture pathophysiological/morphological tumor characteristics in a noninvasive fashion, quantifying intra-tumoral heterogeneity [204–206].

The arrival of radiomics has increased the scope, purpose and potential for medical imaging within oncology. Radiomics mines and deciphers numerous medical imaging features. The hypothesis being that these imaging features are augmented with critical and interchangeable information regarding tumor phenotype [207]. Additionally, radiomic features provide a complete and full representation of the entire tumor and hence adeptly capture intra-tumor heterogeneity. It is thought that intra-tumor heterogeneity has potentially profound implications for clinical predictions (i.e., treatment response, survival outcomes, disease progression, etc.) and consequently it is deemed to be an essential element of precision oncology (i.e., a subset of the larger concept of precision medicine — prevention and treatment strategies that take individual variability into account) and related research [208–211]. The concept of precision medicine [212] is not new (e.g., a century of blood typing to guide blood transfusions), however, the prospect of applying this concept broadly has been radically enhanced with the modern development of powerful methods for characterizing patients, such as radiomics together with large-scale/interconnected databases and computational tools for analyzing large complex datasets. Several studies have reported the significant predictive/prognostic power of radiomic features. It has been demonstrated that radiomic features are related to tumor histology, tumor grade/stage, patient survival, metabolism, and several additional clinical outcomes [213–218]. Furthermore, some radiogenomic studies have reported the associations between radiomic features and the underlying gene expression patterns [219]. Different radiomic features have been evaluated in various cancer types with respect to diverse imaging technologies [220–224] and the reproducibility/variability of radiomic features in disparate clinical settings has also been examined [225–227]. These results suggest that radiomics can enhance individualized treatment selection and monitoring. Furthermore, unlike genomics



**Fig. 7.** Overview of a simplified schematic representation of systems biology applied to radiotherapy. a) On the basis of in-vitro, in-vivo and patient data, modules representing the three biological categories (gene expression, immunohistochemical data and mutation data) important for radiotherapy response can be created. b) For an individual patient, appropriate molecular data will be accumulated. c) Combining the individual patient data with the modules will provide knowledge on specific module alterations (such as a deletion, upregulation [red] or downregulation [blue]), which can be translated to information on relative radioresistance and the molecular 'weak' spots of the tumor. This information will subsequently indicate whether dose escalation is necessary and which targeted drug is most effective for the patient.

based approaches, radiomics is non-invasive and comparatively cost effective. Radiomics is an innovative and encouraging breakthrough towards the realization of precision oncology.

### 3.7. Biological/genetic features

Biological/genetic features provide valuable biomarkers for DSS [228–231]; these include prognostic and predictive factors for outcomes [232], such as tumor response and normal-tissue tolerance. Notwithstanding these virtues, trials of biological/genetic biomarkers are susceptible to experimental inconsistency; therefore standardization of assay criteria, trial design as well as analysis is vital if biological/genetic biomarkers are to be effective prognostic/predictive tools in oncology [50] (Fig. 7).

Tumor control following treatment is largely determined by the criteria: the number of cancer stem cells (as often reflected by tumor volume prior to treatment) and their intrinsic radiosensitivity, the hypoxic fraction, repopulation and reoxygenation capacity during the course of radiotherapy [233–235]. Numerous methods have been developed to quantify the additional features which are predictive of tumor response.

Tumors exhibit large variability in intrinsic radiosensitivity, including among tumors of similar origin and histological type [236–238]. Efforts to measure the radiosensitivity of human tumors are currently based upon the ex-vivo tumor survival fraction, detection of unrepaired DNA double strand breaks, e.g. using phosphorylated histone  $\gamma$ H2AX [239,240]. These investigations have established that tumor cell radiosensitivity is a major feature for radiotherapy outcome in prostate, lung, brain, cervical, and head-and-neck

carcinomas [241–245]. However, these colony assays suffer from technical drawbacks which include a low success rate (<70%) for human tumors and the time required to produce data, which can be up to several weeks. Studies have shown promising results that immunohistochemically staining  $\gamma$ -histone H2AX, a marker of DNA damage, can potentially gauge intrinsic radiosensitivity very early after commencement of treatment [246,247]. Double-stranded breaks are produced when cells are exposed to ionizing radiation or DNA-damaging chemotherapeutic agents, which swiftly results in the phosphorylation of  $\gamma$ -histone H2AX.  $\gamma$ -Histone H2AX is the most sensitive marker that can be employed to examine the DNA damage and its ensuing repair, and it can be identified by immunoblotting and immunostaining using microscopic or flow cytometric detection. Clinically, two biopsies (prior to and after treatment) are required to evaluate the  $\gamma$ -histone H2AX status, which can be difficult to implement in practice.

Previous research has also assessed chromosome damage, DNA damage, genetic and epigenetic alterations, mitochondrial DNA abnormalities, glutathione levels, and apoptosis [248,249]. Indeed, some clinical studies using such assays have demonstrated correlations with radiotherapy outcome, whereas others have not [250,251]. Despite the ability to quantify a feature that is fundamental to the response of tumors to radiotherapy, these cell-based functional assays have restricted clinical utility as a predictive tool.

Hypoxia is the key feature in assessing likely radioresistance and malignant progression; it is a negative prognostic factor after treatment with radiotherapy, chemotherapy and surgery [252,253]. Indeed, data exists which not only demonstrates the requirement of oxygen for radiation-induced cytotoxic DNA damage or decreased proliferation of hypoxic cells limiting cytotoxicity of many chemotherapeutic agents but also suggests that hypoxia stimulates both angiogenesis and metastasis and therefore plays a crucial role in tumor progression [254]. While a strong correlation has been shown between pimonidazole (a chemical probe of hypoxia) staining and outcome after radiotherapy in head-and-neck cancer [255], the same relationship has not been confirmed in cervical cancer [256]. One hypothesis put forward to reconcile these contrasting results is that hypoxia tolerance is more important than hypoxia itself [257].

The use of fluorinated derivatives of such chemical probes also enables their detection by noninvasive PET [258–261]. While this method does require the administration of a drug, it benefits from sampling the entire tumor and not just a subvolume of it. An additional potential surrogate marker of tumor hypoxia is vasculature; the predictive worth of tumor vascularity has been quantified by both intercapillary distance (assumed to reflect tumor oxygenation) and microvessel density (the 'hotspot' technique that offers a histological evaluation of tumor angiogenesis). Studies have shown positive correlations with outcome – largely using microvessel density in cervical cancer – although others have demonstrated negative correlations [262]. Reservations have been expressed regarding the degree to which biopsies (random sampling of tissue) correctly characterize the typically large, heterogeneous tumors [263].

When the overall treatment time is protracted, (e.g., equipment malfunction or poor tolerance by the patient), an increase in the prescription dose is necessary to compensate for the effect of tumor proliferation [264]. While proliferation during fractionated radiotherapy is evidently a significant factor in determining outcome, accurate measurement methods are currently unavailable [265]. A deeper comprehension of the response at both the cellular and molecular level is required along with an answer to the question of why radiation induces accelerated repopulation response in some but not all tumors [266].

Innate differences in cellular radiosensitivity (within the patient population) govern normal tissue reactions toxicity more than any other causal factor [267]. The implication being that the majority of prescribed doses may in fact be too conservative (i.e., because 5–10% of patients are highly sensitive; they skew what is 'optimal' treatment

towards the lower tier of the tolerance spectrum, to the detriment of most patients whom are less sensitive). Future DSS should accurately identify highly sensitive patients and classify them accordingly so they receive appropriate treatments, facilitating improved/escalated treatments for the less sensitive patients.

Several small and large in vitro studies reported a correlation between severity of toxicity and radiosensitivity (e.g., radiation-induced fibrosis of the breast) [268,269], however these studies contain inconsistencies due to a lack of standardized quality assurance for in-vivo radiotherapy [270,271]. Corresponding results have also been reported through rapid assays which quantify chromosomal damage, DNA damage and clonogenic cell survival [272–274]. The lymphocyte apoptosis assay has been utilized within a prospective breast cancer trial to stratify patients and assess late toxicity using letrozole as a radiosensitizer [275]. Cytokines such as TGF- $\beta$ , which influence fibroblast proliferation and differentiation, are known to play an important role in fibrosis and senescence [276,277]. However presently, the relationship between late complications and the lymphocyte predictive assay, TGF- $\beta$  is strictly correlative and a mechanistic molecular explanation is missing. Analyses of single nucleotide polymorphisms (SNPs) and genome-wide association studies (GWAS) in candidate genes have demonstrated capacity in classification of normal tissue toxicity [278–284], identifying possible SNPs associated with the development of late radiation-induced toxicity. Recently, the identification of the TANC1 risk allele (SNP rs264663) suggesting that carriers of this allele have 6 times greater risk of developing late toxicity, underscores the potential of adding these features to predictive models. However, validation of SNP or GWAS studies has turned out to be difficult emphasizing the complex mechanisms behind radiation-induced toxicity in normal tissue [285,286]. In general, the weakness of all these approaches has been the large experimental variability as opposed to the inter-patient variations in radiosensitivity. Normal tissue toxicity is the dose-limiting factor in the field radiation oncology; therefore, a comprehensive DSS should be built upon predictors of tumor control and normal tissue toxicity.

An additional important and promising development in the field of radiation oncology is that of biomarkers for immunotherapy. It is recognized that ionizing radiation provokes an anti-tumor immune response and that the clinical potential of these immunogenic effects in combination with different immunotherapies is substantial [287]. For a durable and vigorous immune response, activation of T-cells, endowed with antigen specificity and memory effects, is generally a prerequisite [288]. In such a response several factors are of key importance. Paramount, the tumor must contain antigens which are different from the healthy tissue, in order to be recognizable to the immune system. Such neoantigens are derived from mutated proteins from a tumor cell. Recent data shows that the success rate of immunotherapies is dependent on the presence of neoantigen-specific T-cells [289]. Consistently, it is shown that the mutational load of a large series of human tumors correlates with the cytolytic activity of natural killer cells and T-cells [290].

When a tumor has the potential to be recognized by the immune system, an adequate immune response can be orchestrated. In this process it is of essential importance that neoantigens are taken up by antigen presenting cells (APCs) or dendritic cells (DCs) and subsequently cross-presented to naïve T-cells [291]. The latter is then transformed into tumor killing cytotoxic T-cells. In this context the ability of radiation to boost immune responses seems to be critically dependent on the quantity and quality of DCs present [292,293].

Tumors have variable ways to protect them from adequate cytotoxic T-cell responses, such as interfering with various immune checkpoints. Depending on the type of interference several specific molecules have biomarker potential. One example of this is the expression of PD-1L. PD-1L binds PD-1 on the cytotoxic T-cell, preventing it to conduct its cytolytic action. Regarding the effects of anti-PD-1 mediated immunotherapy, not only the mutational load shows a strong correlation with clinical responses but also the expression of PD-1L in non-small lung cancer patients [294,295].



Such biological/genetic features hold great potential and will undoubtedly be included in future DSS.

### 3.8. Visualization of clinical decision support systems

The process of developing a predictive model defines the characteristics of the DSS (e.g., features selection, overall prediction accuracy, robustness, etc.). However, the success/appeal of the DSS depends on other dynamics, such as its utility, availability, interactivity, adaptability, etc. which increases the acceptability. Even DSS with models developed in large patient populations, with appropriate external validation, may fail to be accepted within the health-care community if the DSS is difficult to interpret, if there is little opportunity for application of the DSS or if the clinical usefulness has not been clearly demonstrated [296]. While some DSS (e.g., decision trees, nomograms, Bayesian networks) fundamentally have a visual representation that is readily comprehensible, many DSS do not. Another method of increasing the acceptability of DSS for personalized medicine is to make peer-reviewed DSS interactively available online (with sufficient background information); clinicians can subsequently scrutinize them using their own patient data. Such an approach affords retrospective validation of the DSS by the broader community, as well as providing a gauge of the clinical utility of the DSS. A website that focuses on DSS for radiotherapy has been established: [www.predictcancer.org](http://www.predictcancer.org). The purpose of this website is to enable clinicians, researchers, and patients to utilize, develop, and validate the DSS for cancer patients treated with radiotherapy. This contributes to DSS advancement in general by showing the potential and limitations of these predictions as well as raising awareness

### 3.9. Cost effectiveness for decision support systems

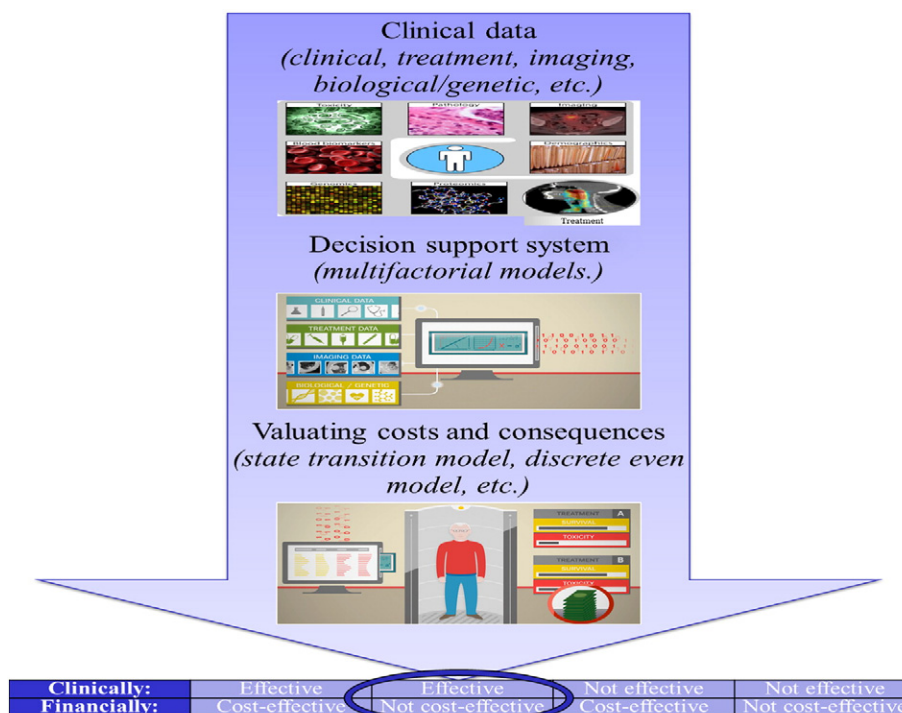
Traditionally, DSS have been focused on clinical endpoints. However, considering the almost exponential rising costs of healthcare, it is increasingly important to consider cost and cost-effectiveness in clinical

decision making. Consequently, future DSS should include cost and/or cost-effectiveness as supplementary endpoints (Fig. 8).

### 3.10. Shared decision making

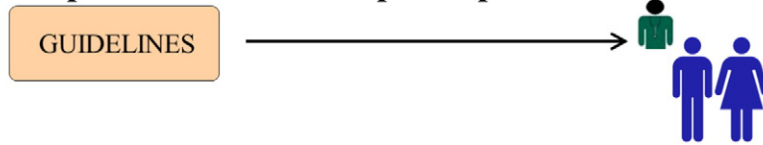
DSS can greatly assist in the choice of the most appropriate therapeutic and/or diagnostic modality. Yet, deciding the most appropriate care pathway for each patient is a very complex process which is dependent upon unique personal patient characteristics and preferences. However, hitherto now, DSS do not take patient preferences and personal values explicitly into account. This stems from the traditional healthcare approach, which is more paternalistic than participative. Clinicians may utilize DSS to determine treatment without considering the distinctive and important personal predilections of patients, as patients will seldom question or challenge the clinician's opinion. However recently, this paternalistic approach is more and more shifting towards a more participative patient-centered approach. The ramifications of this shift are that clinicians should proactively provide additional, appropriate, and relevant information to patients thereby realizing shared decision making (SDM) practice (Fig. 9).

SDM is an interactive process in which patients and practitioners collaborate in choosing healthcare [297], based upon the best available evidence [298,299] (e.g., radical or palliative treatment, brachytherapy or surgery, etc.). Several studies have demonstrated that patients involved decision making, experience less decisional conflict, improved compliance with treatment and greater quality of life [300]. A significant barrier to the implementation of SDM comes in the form of effective patient-clinician communication. Clinicians often unintentionally use difficult language (from the patient's perspective) and may dominate the conversation, while patients may lack the courage to ask questions. To involve patients in SDM it is crucial to communicate effectively with them by providing information and encouraging substantial feedback. Another important obstacle is that some patients may not be receptive to the information provided as anxiety or emotional distress can impair the patient's ability to coherently process information [301]. To help

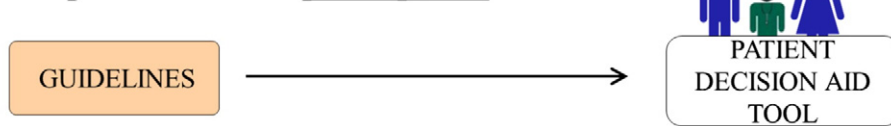


**Fig. 8.** An illustration of Cost-effectiveness analysis. Comparative effectiveness research is often scarcely available for innovative therapy techniques, making it challenging to examine cost-effectiveness. Quality of life in terms of utility scores can be utilized as an outcome measure. The benefit of such analysis is that it provides clinicians, insurers, and policy makers with quantitative estimates of the financial impact of therapy and therefore greatly facilitates budgeting and allocation of resources.

## CONVENTIONAL DECISION MAKING: non-personalized & non-participative



## TRADITIONAL SHARED DECISION MAKING: non-personalized & participative



## NOVEL SHARED DECISION MAKING: personalized & participative



**Fig. 9.** Overview of the evolution and development of decision making within medicine. a) Illustrates the conventional dictatorial clinician driven decision making process. b) Displays progression towards inclusion of patients within the decision making process. c) Demonstrates the advancement of the decision making process to achieve truly personalized and participative components.

overcome these challenges patient decision aids (PDAs) have been developed [302,303]. PDAs provide patients with disease-specific information and treatment options, through various multimedia, helping patients to recognize and clarify their personal values [304–306] (Fig. 10).

PDAs do not promote one option over another, nor are they meant to replace clinician consultation. Instead, they prepare patients to make informed, values-based decisions with clinicians (<http://ipdas.ohri.ca/>). A recent Cochrane review [307] reported level I evidence that PDAs improve patient's knowledge about



**Fig. 10.** An example and overview of an interactive PDA for prostate cancer (<http://www.treatmentchoice.info/>). The PDA is intended to assist the patient in making an informed decision about which treatment is most appropriate. The PDA provides information on the available treatments, helps identify what is important to the patient, compares the available treatments and offers advice based upon the information provided by the patient. It is keenly stressed that the PDA is simply meant to inform the patient, a final decision should always be taken together with the clinician.

treatments, involvement in the decision process, and accurate risk perceptions. Appropriate SDM within modern medicine requires the integration of PDAs and DSS. This will genuinely deliver personalized and participative therapy that supports both clinicians and patients.

### 3.11. An example of personalized therapy in radiation oncology

With deeper knowledge of the complexities of cancer, a realization that optimal cancer therapy most likely requires increasingly personalized treatment has taken hold. Personalized therapy has huge potential in cancer care. Within medical oncology the search for personalized therapy has produced many targeted agents. New medications have revealed substantial activity within subsets of tumors harboring particular targetable mutations. Trastuzumab is well recognized for HER2-positive breast cancer, and recent novel targeted agents such as crizotinib and vemurafenib have been successful in increasing survival in anaplastic lymphoma kinase rearranged lung cancers and BRAF (V600E) mutationpositive melanomas, respectively. This underscores the significance of the individual patients' biology, enabling correct patient and tumor stratification. The progress of genetic assays has enabled improved prediction of patient sensitivity to different chemotherapy agents, and there is mounting clinical validation of these models. An OncotypeDX21-gene assay has been validated to predict both the recurrence risk and the magnitude of adjuvant chemotherapy benefit for breast cancer [308]. However, an OncotypeDX21-gene assay for stage II colon cancer has been found to be prognostic but not predictive of an adjuvant chemotherapeutic benefit [309].

The central issues regarding the personalization of radiotherapy are those of dose, fractionation and target volumes. A type of personalized therapy is presently ongoing in the form of de-escalating dose for human papillomavirus positive oropharyngeal cancers. Contrastingly, considerable research efforts into dose escalation are also underway, despite negative phase III dose escalation trials for several malignancies. These efforts could be significantly augmented by genetic analysis, providing superior selection of the target population, and therefore increasing the likelihood of success. At the vanguard to personalized therapy within radiation oncology is the development of a radiation sensitivity index (RSI), a multigene expression model proposed to predict radiation responsiveness (a high RSI indicates radioresistance) [310–313]. The RSI signature has been previously validated [313], and was recently applied to primary and metastatic colon cancer samples [310]. Large differences in RSI based on anatomical site of metastases ( $P < .0001$ ) were observed, which persisted when the analysis was restricted to lesions from the same patient ( $P < .0001$ ). Initial clinical validation in a cohort of 29 liver and lung metastases patients treated with stereotactic body radiation therapy confirmed these results [310]. Appreciation of the strengths and weaknesses of the RSI is essential when evaluating these results and the implications. The surviving fraction following 2 Gy (SF2) was ascertained in breast, central nervous system, colon, melanoma, non-small cell lung cancer, ovarian, prostate, renal, and leukemia cell lines [311]. Linear regression analysis correlated ten hub genes with SF2, and the relative expression of these genes forms the basis of the RSI. An important point of consideration here is that SF2 experiments are typically conducted under normoxic conditions, dissimilarities in local environments of metastatic sites may produce variances in radiosensitivity undetected in the current assay. Furthermore, the clinical applicability of the RSI model to differing fractionation regimes (e.g., hypofractionation) is uncertain. Data supporting clinical validation of the RSI model is provided in the form of 14 rectal and 12 esophageal cancer patients treated with neoadjuvant chemoradiation and 92 head and neck cancer patients treated with definitive chemoradiation [313]. Potential caveats to accepting this as RSI substantiation include small cohort sizes and the contribution of concurrent chemotherapy. Additional data supporting clinical validation of the RSI model is provided in the form of 503 breast cancer patients, reporting that radiosensitive

patients had improved 5-year relapse free-survival and distant metastasis free survival rates than radioresistant patients, when treated with radiotherapy and surgery [312]. Differences in outcome vanished for (radiosensitive/radioresistant) patients only receiving surgery, suggesting that the RSI is a radiotherapy biomarker. The most recent data supporting clinical validation of the RSI model is provided by the differences in radiosensitivity between colon primaries (704 patients) and sites of metastases (1362 patients), in a further demonstration of the potential to personalize therapy [310]. RSI ranking by anatomic site revealed large differences: ovary (0.48), abdomen (0.47), liver (0.43), brain (0.42), lung (0.32), and lymph nodes (0.31);  $P < .001$  (Recall that a high RSI indicates radioresistance). These results were substantiated in analyses restricted to lesions within the same patient. The conclusion being that in the treatment of oligometastatic disease, prescribed doses should be contingent on the metastatic site, with lung (the second most frequent site of metastases) being more radio-sensitive than liver (the most frequent site of metastases). Finally, data supporting indirect clinical validation of the RSI model is provided in the form of clinical outcomes for lung (9 patients) and liver (14 patients) metastases patients (RSI data unavailable) treated with stereotactic body radiotherapy (SBRT) to 60 Gy in 5 fractions. The rate of 2-year local control was noted to be significantly higher for lung than for liver metastases (100% vs 73%, respectively,  $P = .026$ ). While these results demonstrate real progress in terms of personalized therapy, clinical applicability of the RSI model as DSS is hampered by the critical limitations in both the lack of clinical and treatment characteristics and the treatment-related outcomes available to correlate with the RSI analysis and the low patient numbers. These initial results warrant validation in a larger clinical cohort. Ultimately, notwithstanding these criticisms, the RSI represents a significant and important advance towards further personalizing radiotherapy [314].

### 3.12. A vision of decision support systems for personalized and participative radiation oncology in practice

In a clinic two patients diagnosed with non-small cell lung cancer stage IIIB receive an appointment for a consultation in the same week. In the year 2010, these two patients would probably have gone through the same diagnostic procedure receiving identical treatment. With RLHC these two patients can potentially receive personalized and participative treatment resulting in two different care paths.

**Case A).** A 75-year-old male patient has an inoperable squamous cell carcinoma of the lung stage IIIB. The patient is a heavy smoker and has limited lung function as well as angina pectoris. His principal wish is to be able to celebrate, in a reasonable condition, his 40th wedding anniversary, which is scheduled to take place in 6 months. Long term survival is not a priority for him; he does not want to stop smoking and refuses any heavy treatment which might induce hair loss.

**Case B).** A 55-year-old female patient, non-smoker, has an adenocarcinoma of the lung stage IIIB. She is of Asian origin and has 4 children (between 11 and 18 years). She is a company director and wishes to be cured at all costs. She insists on the most accurate information on her prognosis, as she wants to schedule her absence and quality time with her company and children, respectively. Assuming a fully mature RLHC network (access to more than 20,000 lung cancer patients' clinical, treatment, imaging, biological/genetic, records as well as a follow-up data documenting complications and scoring based on the CTCAE system of the NCI) with integrated DSS and PDAs, the following care paths are feasible: first advanced computer vision and pattern recognition tools localize, segment and characterize the thorax images (lung, tumors and heart) of the patients (CT and FDG-PET). Second, DSS aid in the selection of the most beneficial diagnostic procedure (the most likely procedure to improve prognosis and/or prediction and/or cost efficiency). Third, DSS with PDAs help the clinician and patient



determine the most appropriate treatment (the most probable treatment to achieve the desired survival, toxicity, and/or cost efficiency). Both patients receive a full history/anamnesis, a physical examination, CT-thorax and a CT-abdomen, a blood sample, and a bronchoscopy with biopsy. For *Cases A* and *B*) a PET scan with FDG is recommended by the DSS. After the patients have received a FDG–PET–CT, the DSS then suggest the following: For *Case A*) a blood marker for tumor hypoxia, which demonstrates elevated levels. Thus, a PET–CT scan with FMISO as the tracer for hypoxia is performed which visualizes a limited zone of hypoxia in 3 cm<sup>3</sup> within the tumor. For *Case B*) a mutation analysis of the EGFR gene, a SNP analysis and a gene expression array. The analyses reveal a mutation of the tyrosine kinase domain of the EGFR, no polymorphism of the TGF beta gene and a rapidly proliferating tumor without hypoxia. The missing polymorphism predicts no increased risk for a radiation induced pneumonitis. The DSS suggests a Thymidine PET–CT scan, enabling visualization of the heterogeneity of the tumor proliferation, which might suggest a radiation boost of a sub-volume of the tumor. Before treatment begins the various outcomes for each treatment, based on the pretreatment prediction module, are discussed with the patient. *Case A*) after discussion with his doctor he decides to accept a high dose radiotherapy treatment including a concomitant boost of the hypoxic region within the tumor but refuses the addition of chemotherapy drugs. The polymorphism analysis of the TGF beta gene reveals an increased risk for radiation-induced pneumonitis. The DSS therefore advise an early follow-up extensive vaccination program against influenza and pneumonia. As a consequence of this care pathway, the patient decides to move into an apartment on the ground floor without stairs. Finally, he and his wife are able to celebrate their 40th wedding anniversary with no major toxicity. One and a half years later, the patient passes away due to progressive liver metastases. *Case B*) after discussion with her doctor, she agrees to undergo a concomitant accelerated chemo-radiotherapy treatment together with the combined adjuvant treatment of an anti-EGFR drug (due to the positive EGFR mutation analysis). Two weeks into treatment, the risk of esophagitis together with weight loss (taking into account neutropenia) is re-evaluated. Using the pre-treatment DSS it is suggested that the risk for the development of severe esophagitis is higher than 70%. Consequently, an esophageal feeding tube is transiently positioned. A second post-treatment DSS prediction of survival and pneumonitis is then performed which takes into account the quality of treatment (set-up error, in vivo dosimetry, treatment duration, drug effectively given) and the metabolic response at 3 months (based on a FDG–PET). In this particular case, the probability of survival at 2 years is predicted to be 85%. Consequently, the patient decides not to sell her company. The follow-up DSS identify her case as high risk for the development of brain metastases and advise either regular repeated brain MRI or preventive total brain irradiation, which in this case was favored by the patient. Five years later, the patient remains free of disease. An update of the system integrating new data on cancer risk and gene polymorphisms reveals an increased risk for the development of breast cancer together with her thorax irradiation. This convinced her to begin yearly mammography screening.

The above treatments described are not the standard of care and are hypothetically the optimal treatments with the goal of personalizing care (e.g., concurrent treatment with an anti-EGFR drug is currently under investigation (RTOG 1306) and is not routinely performed in all patients with a mutation.).

#### 4. Future prospects

Enthusiasm for the great potential of the future must be tempered by the pragmatic reality of the present. Currently, most of the 'eHealth' analytics effort is focused on monitoring and improving hospital costs, quality of healthcare management, and productivity. The initial impact and widespread adoption of RLHC together with DSS will probably be

felt first in an administrative/business sense rather than a scientific/clinical sense within institutions. When RLHC together with DSS eventually do make it to the clinical setting, there is the potential risk of the misuse of such technologies/tools (e.g., generation of artifacts, false signals, data corruption, etc.). These genuine concerns can be averted by implementing and adherence to stringent universal data-quality assurance programs and semantic interoperability harmonization, coupled with automated data correction, imputation and/or rejection procedures.

The need for very complex DSS should be relativized as recently approved novel anti-cancer therapies, such as immunologics, are yielding major therapeutic gains which massively outweigh the small gains of former anti-cancer approaches. Thus the need for complex DSS when the gains of treatment A versus B differ massively, does not have the same implication for the decision making process as with classical 4–7% gains.

The primary focus of this position paper has been model development/validation for DSS along with the cutting-edge information technologies which are essential for the realization of such DSS. While an accurate model forms the foundation of a DSS, further concerns must be addressed prior to a new DSS being utilized in routine clinical practice.

Foremost, all decisions taken by a physician (or patient) can be distilled into a balance between harm (toxic effects, complications, quality of life and financial cost) and benefit (survival, local control and quality of life). For instance, larger dose typically results in a greater probability of normal tissue toxicity, but also a parallel greater probability of tumor control. Determining the correct balance between harm and benefit is a profoundly personal choice that varies considerably among patients. Therefore, an ideal DSS should comprehensively predict local control, survival, toxicity, quality of life and cost. The DSS should present these estimates and the balance between them in a manner that is easily interpreted by both the physician and the patient, enabling shared decision making.

Furthermore, all predictions made by a DSS must include confidence intervals. Correctly estimating confidence intervals is a dynamic and challenging field of research due to the unique uncertainties associated with the process e.g., feature noise, missing features, size and quality of the training dataset, as well as the inherent uncertainty of cancer; must all be combined to specify the uncertainty in the prediction for any given individual patient. DSS are deficient when deprived of certainty with respect to potential choices that may or may not have a statistically significant and/or clinically meaningful difference in outcome. Distributed learning of appropriate data upon which the model was developed is a key ingredient to achieve sufficient certainty in DSS. Despite the ethical, administrative, political and technical boundaries, the continuing development, interconnection, and growth of RLHC networks towards full maturity are of vital importance to modern medicine, as the future performance of DSS is dependent upon both the number and heterogeneity of available patients to learn from. However, there are still difficulties to be addressed with regard to distributed learning within RLHC networks. For example, model developers cannot access and curate all available data within a RLHC network, consequently stringent quality assurance protocols coupled with automated data correction, imputation and/or rejection procedures need to be developed and standardized.

Notwithstanding these challenges, the dream of accurate robust patient specific predictive models leading to DSS that are dynamically updated through global RLHC networks is becoming an ever increasingly tangible reality, and many important milestones have already been reached. These include the aforementioned universal data-quality assurance programs and semantic interoperability harmonization. Indeed, investment is already underway in research and innovation for health-informatics systems (Apple, Google, IBM, etc.), which indicates that 'eHealth' will be among the major health-care innovations of the coming decades.

It is our firm belief that this genuinely innovative approach will lead to urgently necessary improvements in both healthcare effectiveness and efficiency.

This position paper has thus far focused on the predictive, personalized, and participative elements of medicine, however, medicine will transition (even farther) from a reactive to a proactive discipline over the coming decade — a discipline that is predictive, personalized, participative and preventive (P4) [315–317]. P4 medicine will be driven by system approaches to disease/health, utilizing emerging technologies and analytical tools. Preventive medicine can become a reality as fully matured RLHC networks expose the opportunity to apply therapies intended to prevent or halt disease progression. Importantly, invoking the P4 medicine concept will enable a paradigm-shift in health care from an emphasis on disease to a focus on health — with vast associated cost savings for society resulting in a decreased absenteeism from work and a parallel increase in productivity. P4 medicine is a potentially catalyzing revolution of modern medicine that offers solutions to manage the heretofore overwhelming obstacles of incredible complexities of disease/health via systems approaches, innovative technologies and sophisticated analytical tools. The ultimate goal is that the emphasis of medicine will be lifted from disease and placed onto health. In the not too distant future, there is the very real possibility that billions of data points for each individual within fully matured RLHC networks will define with exquisite exactitude the precise nature of their health — and any transitions into disease.

## 5. Conclusions

Truly personalized cancer therapy is the goal in modern oncology. However, personalized cancer therapy is also a colossal challenge. The immense diversity of both cancer patients and therapy choices makes it tremendously problematic to decide which choices are best for the individual patient. Nevertheless, DSS produced by RLHC can contribute to the realization of this goal. Accurate robust validated prediction models are being swiftly developed, whereby multiple features related to the patient, disease, and treatment are combined into an integrated prediction. The key, however, is standardization — mainly in data acquisition across all areas (clinical, treatment, imaging, biological/genetic, etc.). Standardization requires harmonized clinical guidelines, regulated image acquisition and analysis parameters, validated biomarker assay criteria and data-sharing methods that use identical ontologies. Assessing the clinical utility of any DSS is just as important as standardizing the development of externally validated accurate and robust prediction models with high-quality data, preferably by standardizing the design of clinical trials. These crucial steps are the basis of validating DSS, which in turn, will stimulate developments in RLHC and will enable the next major advances in personalized and participative medicine.

## Disclosures of potential conflicts of interest

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## Abbreviations

3D	Three dimensional
3DCRT	Three dimensional conformal radiotherapy
4 Vs	Velocity, veracity, volume, and variety of data
ACRIN	American College of Radiology Imaging Network
ADC	Apparent diffusion coefficient
ASCO	The American Society of Clinical Oncology
AUC	Area under the curve
BRAF	Serine/threonine-protein kinase

CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DC	Dendritic cell
DNA	Deoxyribonucleic acid
DSS	Decision supports systems
DVH	Dose volume histogram
EGFR	Epidermal growth factor receptor
EHR	Electronic health record
FDG	Fluorodeoxyglucose - 18F
FMISO	Fluoromisonidazole - 18F
GWAS	Genome-wide association studies
H2AX	H2A histone family, member X
HER2	Human epidermal growth factor receptor 2
IGRT	Image guided radiotherapy
IMRT	Intensity modulated radiotherapy
MR	Magnetic resonance
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NCI	National cancer institute
NTCP	Normal tissue complication probability
P4	Predictive, personalized, participative and preventive medicine
PD-1L	Programmed death-ligand 1
PDA	Patient decision aid
PET	Positron emission tomography
QUANTEC	Quantitative analysis of normal tissue effects in the clinic
RLHC	Rapid learning health care
RSI	Radiation sensitivity index
RTOG	The Radiation Therapy Oncology Group
SBRT	Stereotactic body radiotherapy
SDM	Shared decision making
SF2	Surviving fraction following 2 Gy
SNP	Single nucleotide polymorphisms
STROBE	Strengthening the reporting of observational studies in epidemiology
SUV	Standardized uptake value
TCP	Tumor control probability
TGF-β	Transforming growth factor beta
TNM	Tumor-node-metastasis
TRIPOD	Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis
VMAT	Volumetric arc therapy

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