AAPM 2022
JULY 10–14 | WASHINGTON, DC
64TH ANNUAL MEETING & EXHIBITION
CELEBRATING MEDICAL PHYSICS
TRANSFORMING HUMAN HEALTH

Integrating Omics in the Era of AI for Better Patient Specific Outcomes

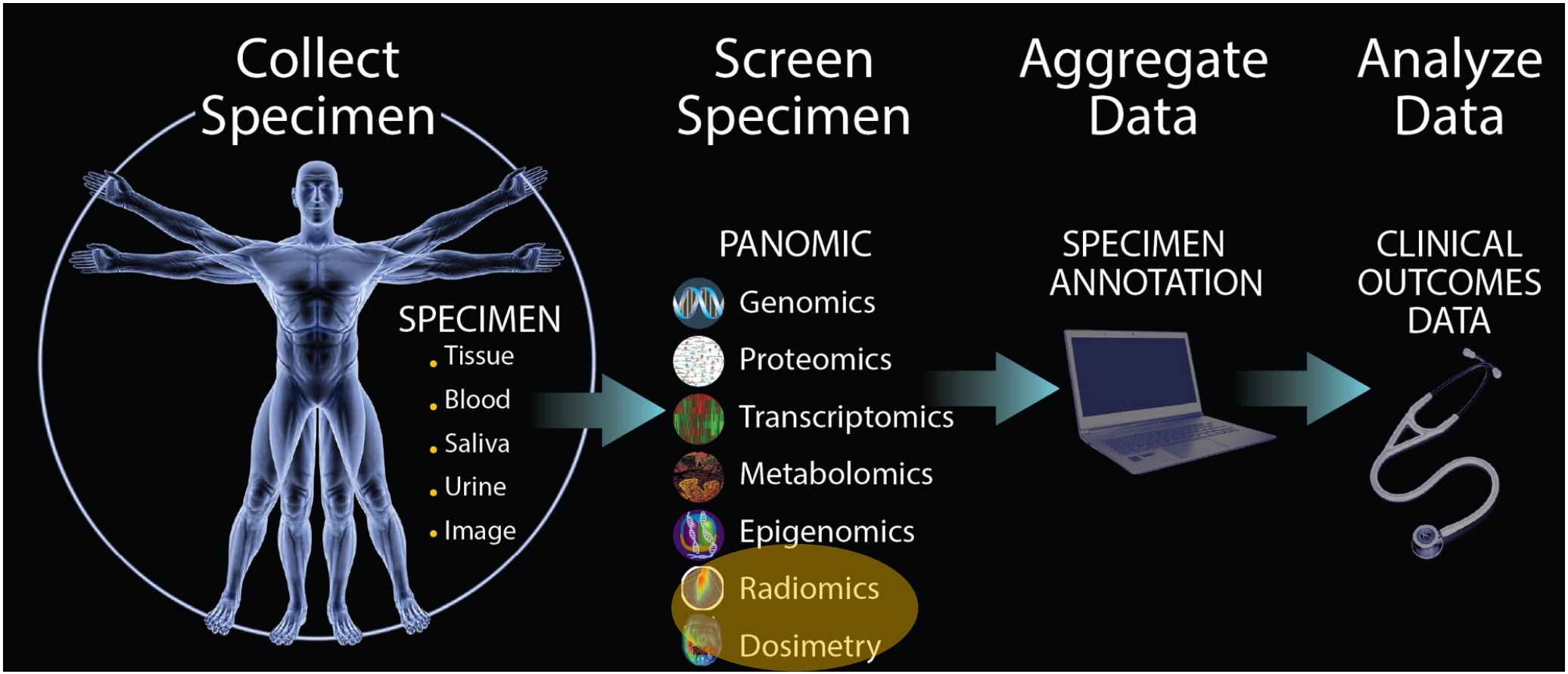
Issam El Naqa, Sarah Mattonen, Lise Wei, Sunan Cui, Rachel Ger

Learning Objectives

- Review concepts of multi-omics
- Discuss role of AI in multi-omics
- Explain How to build robust models of multi-omics using AI
- Show example applications in clinical decision support:
  - Managing and quantifying tumor response
  - Managing and quantifying normal tissue toxicities

- **Sarah Mattonen**, PhD, Western University
  - *Radiomics for supportive care interventions in head and neck cancer*
- **Lise Wei**, PhD, University of Michigan
  - *The Effect of Stereotactic Body Radiation Therapy for Hepatocellular Cancer on Regional Hepatic Liver Function*
- **Sunan Cui**, PhD, Stanford University
  - *Utilizing multi-omics data to improve the prediction of toxicities*
- **Rachel Ger**, PhD, John Hopkins University
  - *Challenges in the Omics Landscape*

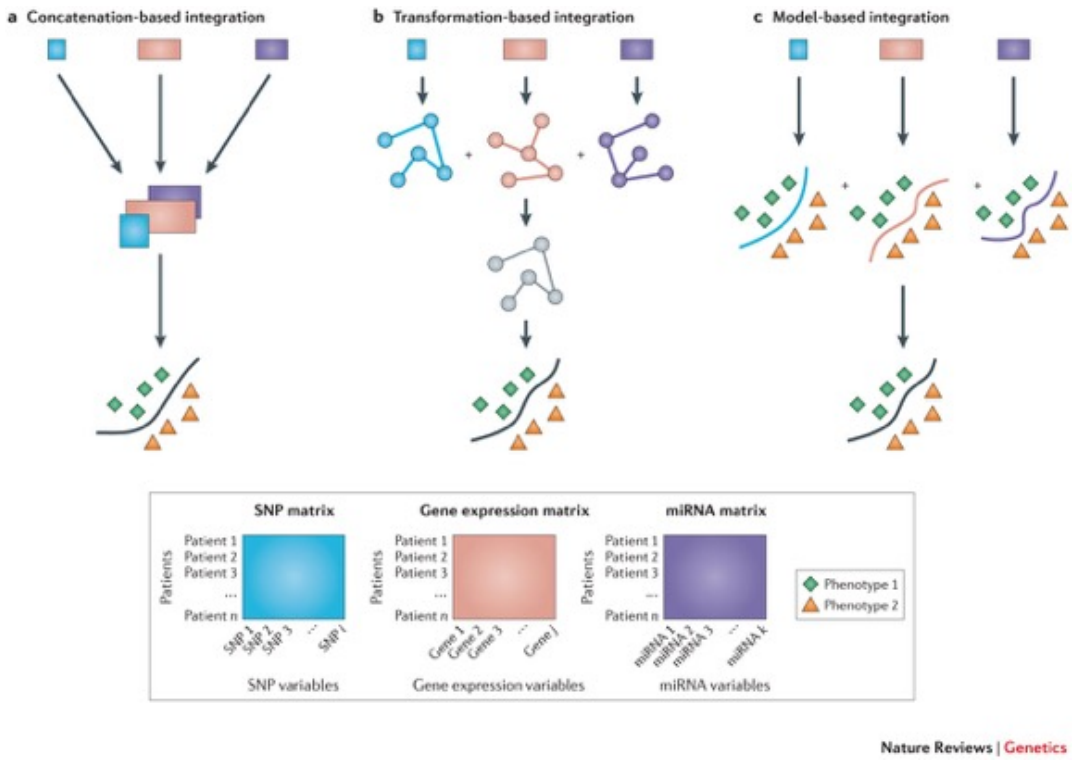
The multi-omics of Oncology



El Naqa et al, PMB, 2017

Data Integration for Modeling Response

- Purpose
  - To enable detection of underlying themes by relating patient-specific 'omics' to outcomes (e.g., treatment response to radiation)
- Common types
  - Concatenation
  - Transformation
  - Modeling

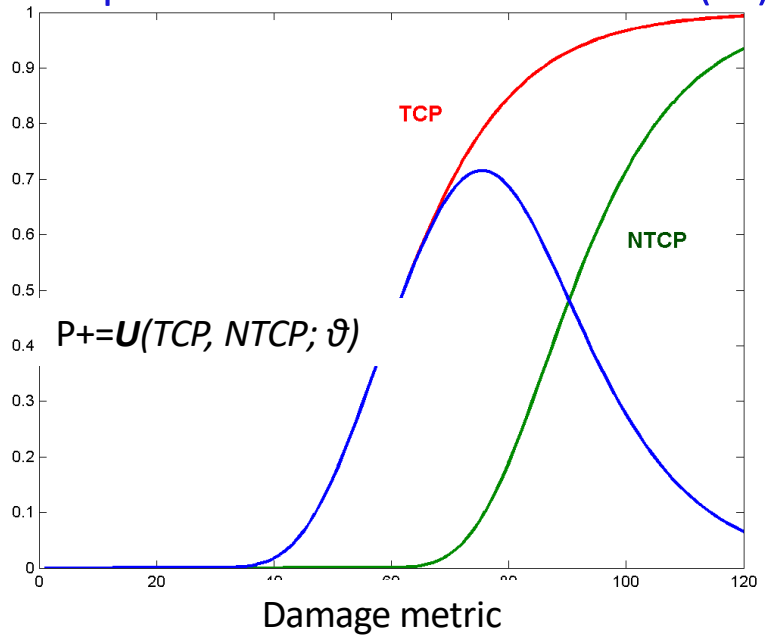


Ritchie, Nature Reviews Genetics, 2015

Modeling Response in Radiotherapy

- Tumor control (TCP)/Normal tissue complication (NTCP) are multi-factorial and depend: radiation dose and patients' genomic (radiogenomics) and imaging (radiomics) characteristics before & during radiotherapy

Complication-free tumor control (P^+)



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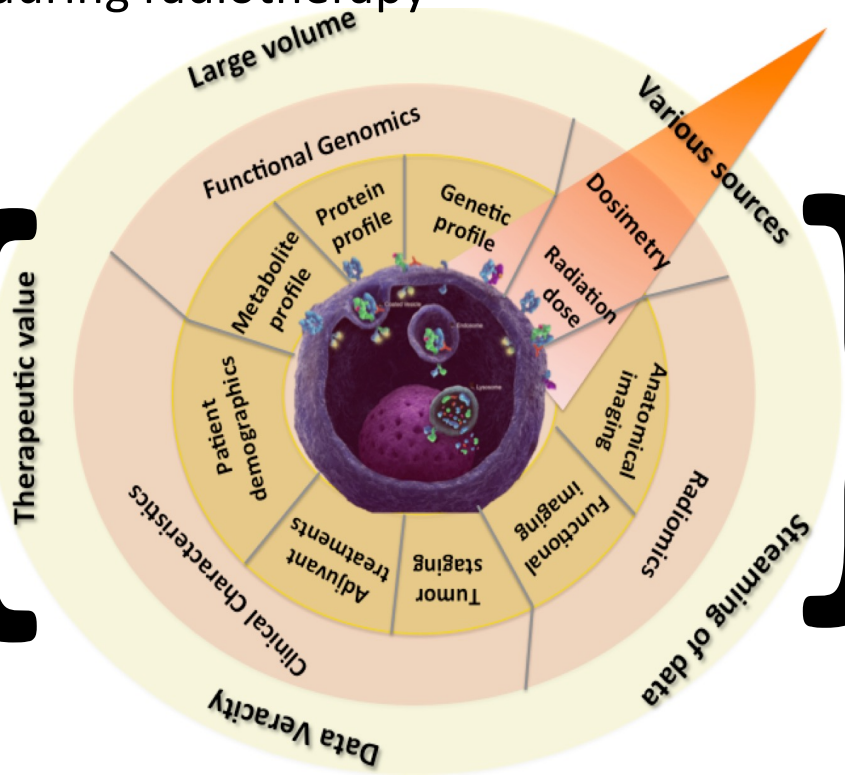

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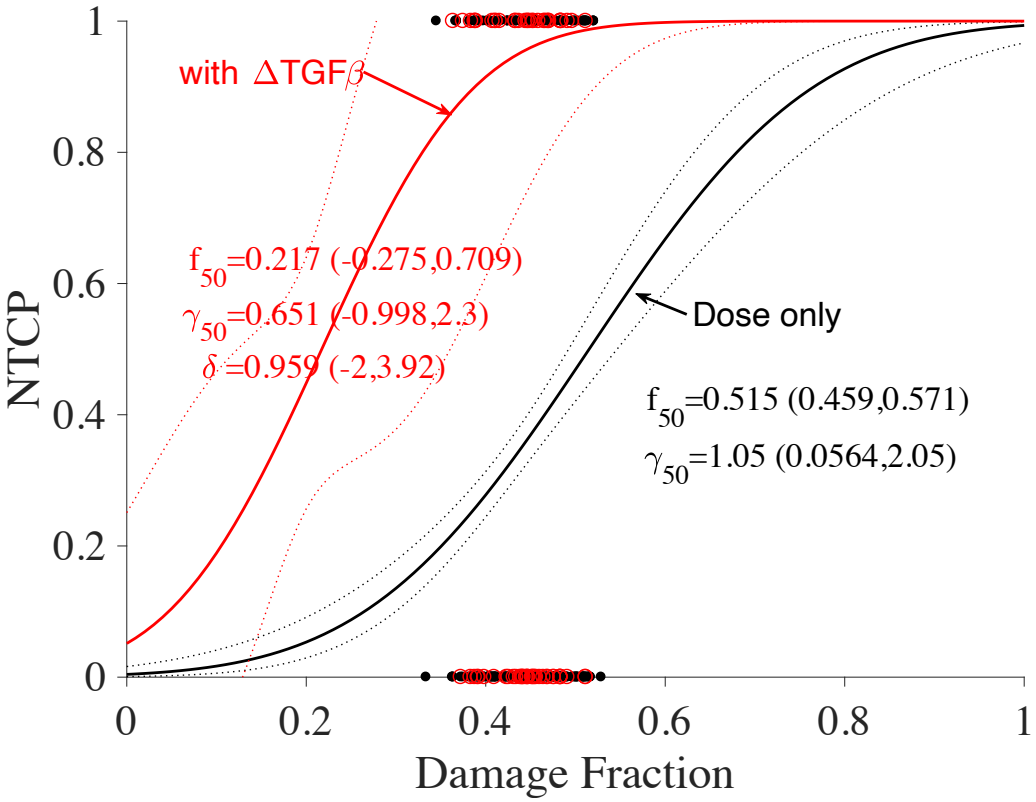
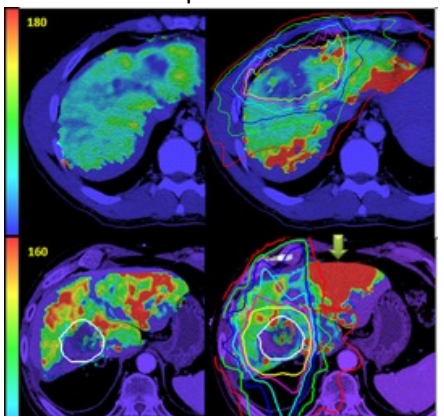
El Naqa, Methods, 2016

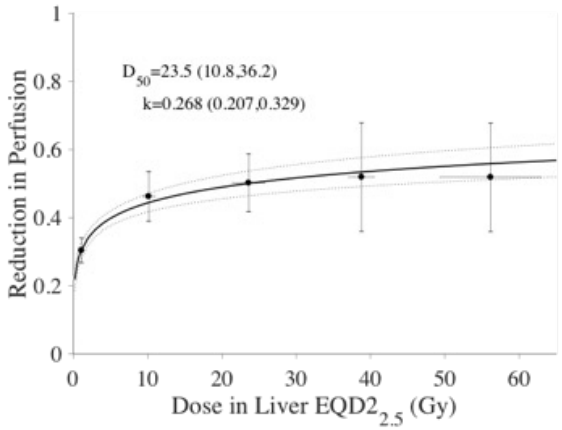
Non-AI Methods: Modeling of Liver Function

Dose modifying effect of imaging + cytokines



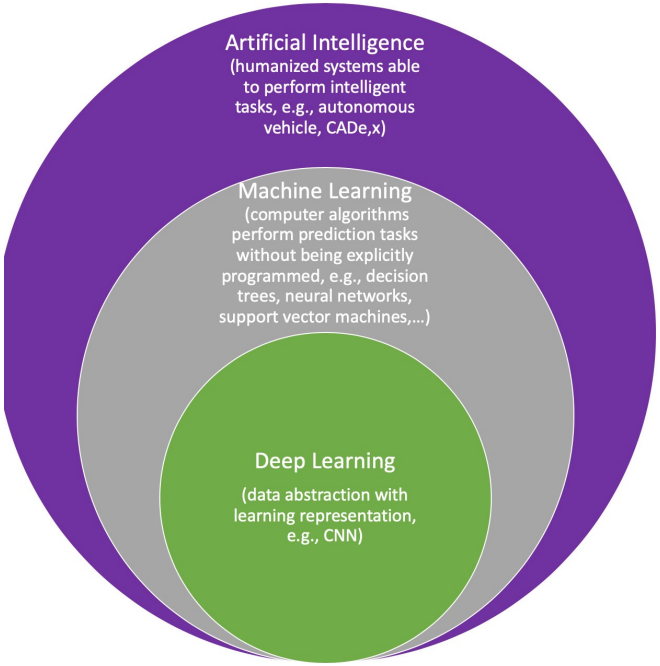
MRI-DCE perfusion





El Naqa et al, IJROBP, 2018 (CME article)

AI/ML Primer



El Naqa, BJR 125th Annv., 2020

Artificial Intelligence

Originated in the 1950s

Build machines that think like humans

Machine Learning

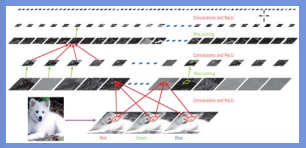
Originated in the 1960s

Computer algorithms that learn from data

Deep Learning

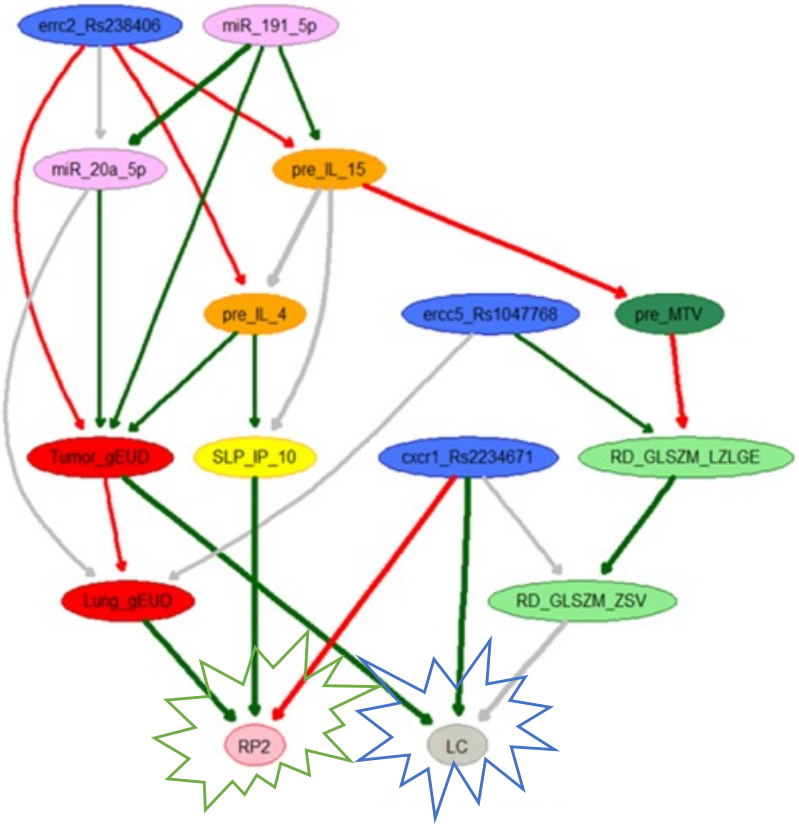
Originated in the 1970s

Based on neural networks that learn features

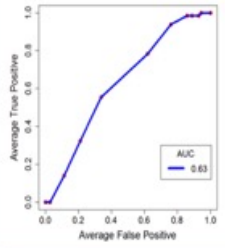
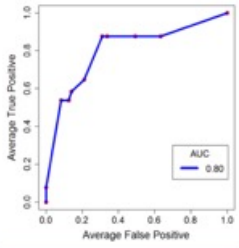
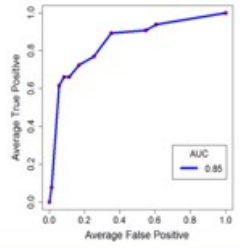


AI/ML Methods: Modeling of Lung Cancer Outcomes

A multi-objective Bayesian network (MO-BN) is used to predict multiple radiation outcomes simultaneously from multi-omics data, which provides opportunities of finding appropriate treatment plans to solve the trade-off between competing risks in non-small lung cancer



Legend
Pre-treatment Cytokines
During-treatment Cytokines
SNPs
microRNAs
Dosimetry
Pre-treatment Pet Information
During-treatment Pet Information
Positive Association
Negative Association
Mixed Association

	Lung_gEUD and Tumor_gEUD	Pre-Treatment BN for joint prediction of LC and RP2	During-Treatment BN for joint prediction of LC and RP2
AU-FROC	0.63	0.8	0.85
95% CI	0.53-0.77	0.66-0.85	0.71-0.89
FROC			

Luo et al, Med Phys, 2018 (Editor's Choice)

Challenges for Multi-omics in Radiotherapy

International Journal of Radiation Oncology biology • physics

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EDITORIAL

Radiation Therapy Outcomes Models in the Era of Radiomics and Radiogenomics: Uncertainties and Validation

Issam El Naqa, PhD,* Gaurav Pandey, PhD,† Hugo Aerts, PhD,‡,§ Jen-Tzung Chien, PhD,‖,¶ Christian Nicolaj Andreassen, MD, PhD,# Andrzej Niemierko, PhD,** and Randall K. Ten Haken, PhD*

Check List for AI/ML in Medical Physics (CLAMP)

- Purpose and justification of AI/ML algorithm selection
- Dataset characteristics (acquisition, size, partitioning [3Ts: training, tuning, testing])
- ML methods
  - Optimization, loss function, augmentation, regularization
  - Performance metrics and evaluations (internal, external)
- Significance of results
  - Interpretation of ML performance
  - Clinical translation and actionability

TABLE 1 Checklist for AI in *Medical Physics* (CLAMP)

Indicate whether each section clearly summarizes or describes:	Checkboxes		
1. Abstract	**Yes**	**No**	**N/A**
a. Purpose, rationale, novelty or significance			
b. AI/ML methods and data type, dataset partitioning into training, validation (tuning), and test sets (include numbers used in training, validation, and test sets)			
c. Main results, including statistical analyses			
2. Introduction			
a. Purpose and justification of using AI/ML algorithm approach			
b. Contribution(s) of AI/ML to medical physics application			
c. Stage of development (e.g., pilot study, mature study)			
3. Materials			
a. Dataset characteristics including sample size and clinical acquisition sites			
b. Device(s) used for data acquisition (e.g., scanner makes), start-end dates of acquisition (or equivalent means with biotechnology generated data), and any data harmonization, augmentation, and enrichment strategies, or pre-processing are clearly described			
c. For imaging data: image or data acquisition modality, acquisition protocol, or parameter ranges are detailed			
d. For patient data: method to obtain the sample, representativeness of the population for the purpose of the study, IRB approval (or equivalent), and relevant patient demographics plus clinical variables such as prevalence(s) of disease(s) or lesion characteristics			
e. For phantom data: Type of phantom and method for generating phantom data			
f. Data composition appropriateness for AI/ML application			
g. Description of the "ground truth," that is, the reference standard, including the annotation process, level of subjectivity, and uncertainty			
h. Data partitioning into training, validation (tuning), and test sets including any criteria to mitigate bias and justification of sample sizes			
i. Final validation using public dataset or study dataset to be shared/made publicly available (desirable but not required).			
4.1 Methods: Machine learning algorithm			
a. Methodology in sufficient detail to allow replication, including model architecture, hyperparameters, inputs, dimensionality of the input (e.g., 2D or 3D images), pre-processing, output type and definition, and discretization/binning, if any.			
b. Training/optimization method including loss function, regularization approach, data imbalance mitigation process (if needed), measures to minimize overfitting and bias, and ablation studies, if any.			
c. AI/ML software code to be shared/made publicly available (desirable but not required).			
4.2 Methods: Performance and statistics			
a. Performance metric(s) including any postprocessing (such as scoring criteria, decision threshold, binning) of the AI/ML output.			
b. Method(s) to estimate the uncertainty (such as 95% confidence intervals) of the performance metric(s).			
c. Significance of the obtained results compared to the null hypothesis (if applicable) or compared to a suitable benchmark metric.			
d. Subgroup analyses for important subgroups (e.g., by age, lesion size).			
e. Demonstrative results for the training, validation (tuning), and test sets.			
5. Discussion			
a. Conclusions as supported by the results.			
b. Limitations of the study.			
c. Discussion/summary of innovation (algorithm or application), significance (clinical or scientific), and/or contributions to the field of medical physics.			

Issam El Naqa[1]
John M. Boone[2]
Stanley H. Benedict[3]
Mitchell M. Goodsitt[4]
Heang-Ping Chan[4]
Karen Drukker[5]
Lubomir Hadjiiski[4]
Dan Ruan[6]
Berkman Sahiner[7]

Quality assurance for AI application in the clinic

- **Acceptance Testing**
  - To ensure that the ML tool meets all applicable safety and performance standards (prediction) and that it meets contractual specifications
  - Manufacturer includes an acceptance test procedure with the ML tool
    - Selection of evaluation endpoint and definition of performance criteria (e.g., AUC);
    - Selection of a benchmark data
- **Commissioning**
  - The process whereby the needed tool-specific data/parameters are acquired and operational procedures are defined
  - May include:
    - Training data collection
    - Developing procedures
    - User training before first use
- **Quality Assurance (QA)**
  - Effort to ensure treatments are given accurately, safely and efficiently according to established tests and evaluations
- **Continuing Quality Improvement (CQI)**
  - Effort that seeks to make treatments and operations better by recognizing current weaknesses in the program, anticipating problems before they happen, streamlining tasks and responding to changes in practice

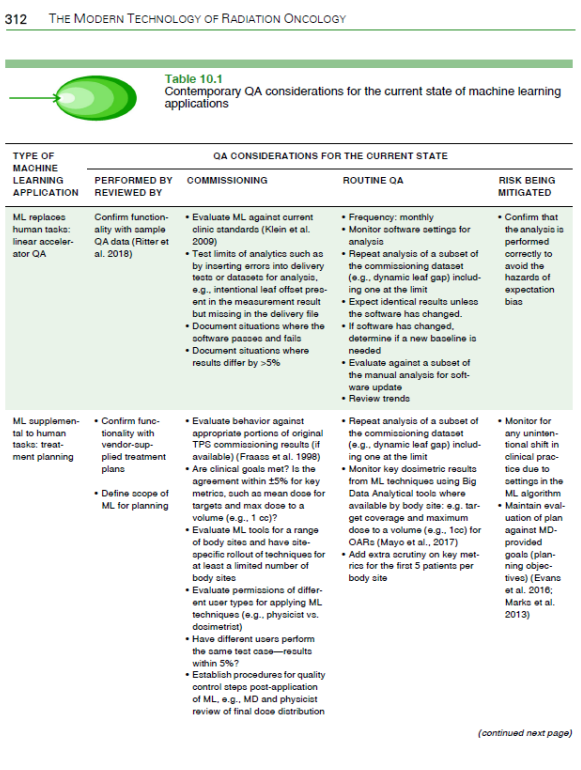

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Table 10.1
Contemporary QA considerations for the current state of machine learning applications

TYPE OF MACHINE LEARNING APPLICATION	QA CONSIDERATIONS FOR THE CURRENT STATE			
	PERFORMED BY REVIEWED BY	COMMISSIONING	ROUTINE QA	RISK BEING MITIGATED
ML replaces human tasks: linear accelerator QA	Confirm functionality with sample QA data (Ritter et al. 2018)	• Evaluate ML against current clinic standards (Klein et al. 2009) • Test limits of analytics such as by inserting errors into delivery tests or datasets for analysis, e.g., intentional leaf offset present in the measurement result but missing in the delivery file • Document situations where the software passes and fails • Document situations where results differ by >5%	• Frequency: monthly • Monitor software settings for analysis • Repeat analysis of a subset of the commissioning dataset (e.g., dynamic leaf gap) including one at the limit • Expect identical results unless the software has changed. • If software has changed, determine if a new baseline is needed • Evaluate against a subset of the manual analysis for software update • Review trends	• Confirm that the analysis is performed correctly to avoid the hazards of expectation bias
ML supplemental to human tasks: treatment planning	• Confirm functionality with vendor-supplied treatment plans • Define scope of ML for planning	• Evaluate behavior against appropriate portions of original TPS commissioning results (if available) (Fraass et al. 1998) • Are clinical goals met? Is the agreement within ±5% for key metrics, such as mean dose for targets and max dose to a volume (e.g., 1 cc)? • Evaluate ML tools for a range of body sites and have site-specific rollout of techniques for at least a limited number of body sites • Evaluate permissions of different user types for applying ML techniques (e.g., physicist vs. dosimetrist) • Have different users perform the same test case—results within 5%? • Establish procedures for quality control steps post-application of ML, e.g., MD and physicist review of final dose distribution	• Repeat analysis of a subset of the commissioning dataset (e.g., dynamic leaf gap) including one at the limit • Monitor key dosimetric results from ML techniques using Big Data Analytical tools where available by body site: e.g. target coverage and maximum dose to a volume (e.g., 1cc) for OARs (Mayo et al., 2017) • Add extra scrutiny on key metrics for the first 5 patients per body site	• Monitor for any unintentional shift in clinical practice due to settings in the ML algorithm • Maintain evaluation of plan against MD-provided goals (planning objectives) (Evans et al. 2016; Marks et al. 2013)

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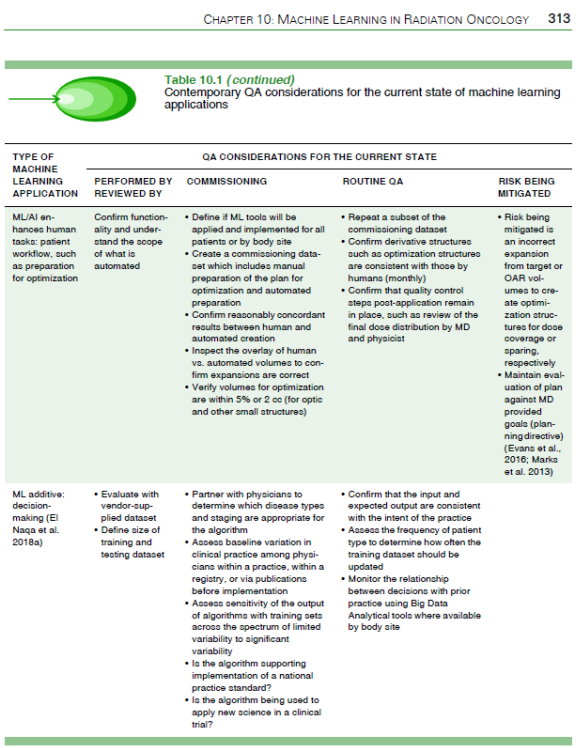


CHAPTER 10: MACHINE LEARNING IN RADIATION ONCOLOGY 313

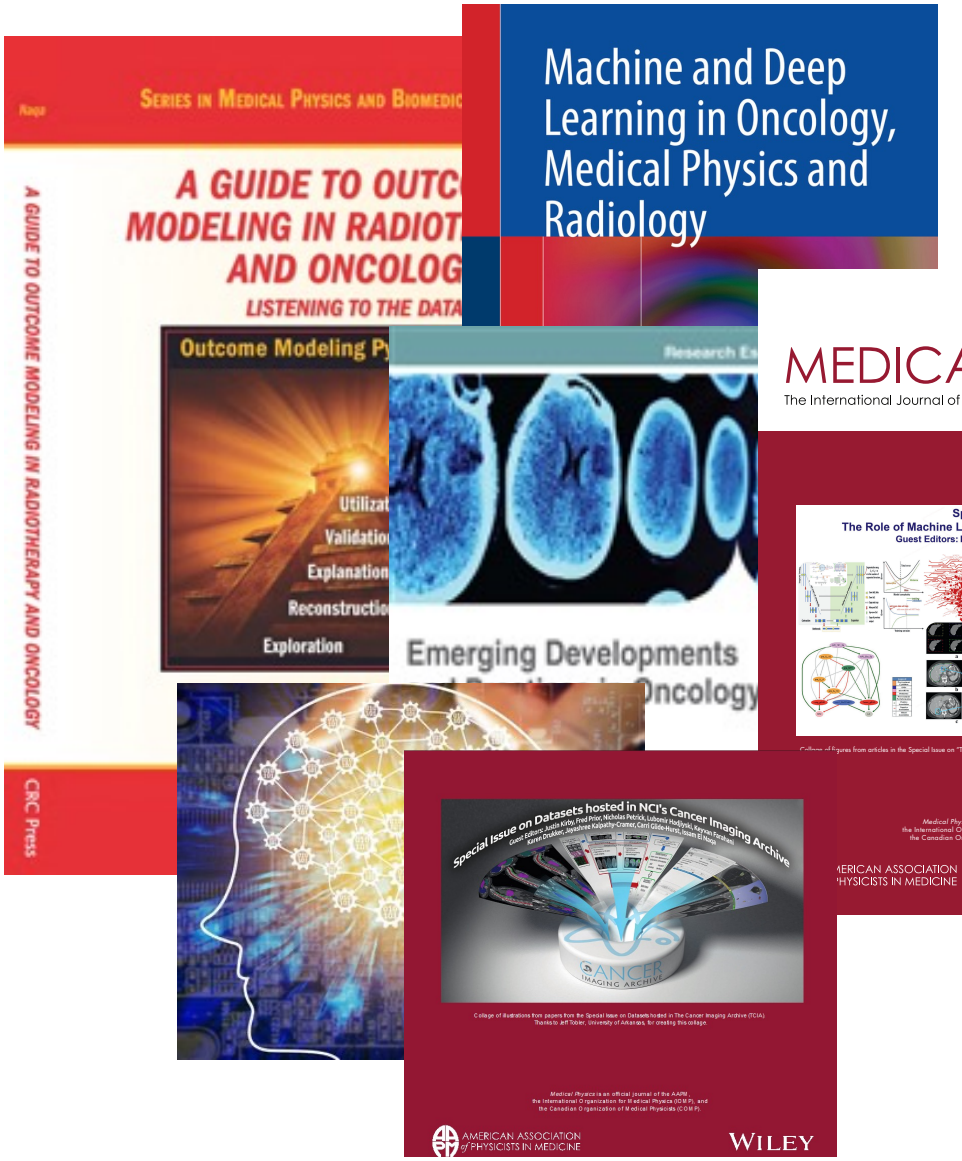
Table 10.1 *(continued)*
Contemporary QA considerations for the current state of machine learning applications

TYPE OF MACHINE LEARNING APPLICATION	QA CONSIDERATIONS FOR THE CURRENT STATE			
	PERFORMED BY REVIEWED BY	COMMISSIONING	ROUTINE QA	RISK BEING MITIGATED
ML/AI enhances human tasks: patient workflow, such as preparation for optimization	Confirm functionality and understand the scope of what is automated	• Define if ML tools will be applied and implemented for all patients or by body site • Create a commissioning dataset which includes manual preparation of the plan for optimization and automated preparation • Confirm reasonably concordant results between human and automated creation • Inspect the overlay of human vs. automated volumes to confirm expansions are correct • Verify volumes for optimization are within 5% or 2 cc (for optic and other small structures)	• Repeat a subset of the commissioning dataset • Confirm derivative structures such as optimization structures are consistent with those by humans (monthly) • Confirm that quality control steps post-application remain in place, such as review of the final dose distribution by MD and physicist	• Risk being mitigated is an incorrect expansion from target or OAR volumes to create optimization structures for dose coverage or sparing, respectively • Maintain evaluation of plan against MD provided goals (planning directive) (Evans et al., 2016; Marks et al. 2013)
ML additive: decision-making (El Naqa et al. 2018a)	• Evaluate with vendor-supplied dataset • Define size of training and testing dataset	• Partner with physicians to determine which disease types and staging are appropriate for the algorithm • Assess baseline variation in clinical practice among physicians within a practice, within a registry, or via publications before implementation • Assess sensitivity of the output of algorithms with training sets across the spectrum of limited variability to significant variability • Is the algorithm supporting implementation of a national practice standard? • Is the algorithm being used to apply new science in a clinical trial?	• Confirm that the input and expected output are consistent with the intent of the practice • Assess the frequency of patient type to determine how often the training dataset should be updated • Monitor the relationship between decisions with prior practice using Big Data Analytical tools where available by body site	

El Naqa, Moran, Ten Haken, The Modern Technology of Radiation Oncology, V4, Van Dyke

Take Home Messages

- Multi-omics offers new opportunities to develop better understanding of radiation oncology processes and for personalizing therapy
- AI techniques (Machine/deep learning) can improve feature selection and statistical learning in multi-omics analytics and outcome modeling
- Main challenges for multi-omics with AI methods
  - Proper integration of various multi-omics data
  - Building robust models with AI methods from multi-omics data
  - Validation and evaluation of AI-based multi-omics models across independent datasets
  - Better interpretation of AI models is still lagging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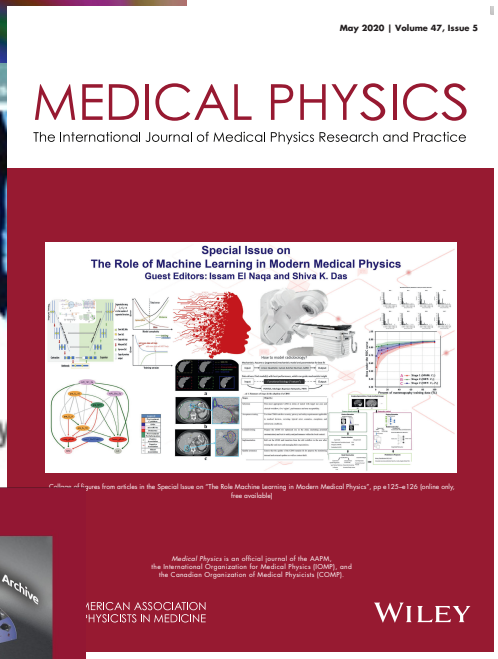
May 2020 | Volume 47, Issue 5
MEDICAL PHYSICS
The International Journal of Medical Physics Research and Practice
Special Issue on
The Role of Machine Learning in Modern Medical Physics
Guest Editors: Issam El Naqa and Shiva K. Das
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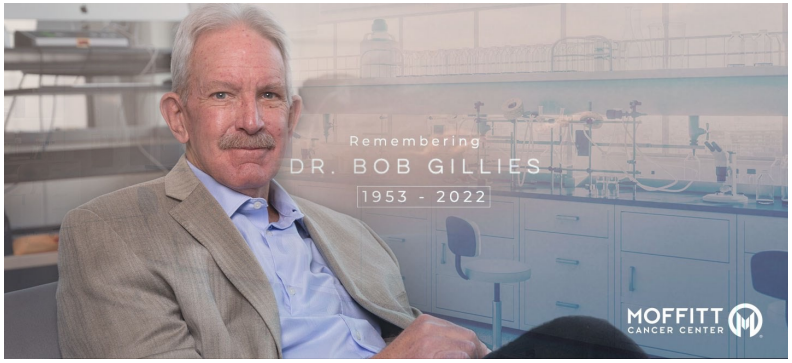
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DR. BOB GILLIES
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Thank YOU!