# Radiomics Workflow Definition & Challenges - German Priority Program 2177
# Consensus Statement on Clinically Applied Radiomics
# ELECTRONIC SUPPLEMENTARY MATERIAL

Insights Imaging (2024) Floca R, Bohn J, Haux C, et al.

## Supplement 1

# SPP Radiomics – List of extracted step terms

A SPP Radiomics Workflow Definition Supplement

**Version:** 2024/03/09

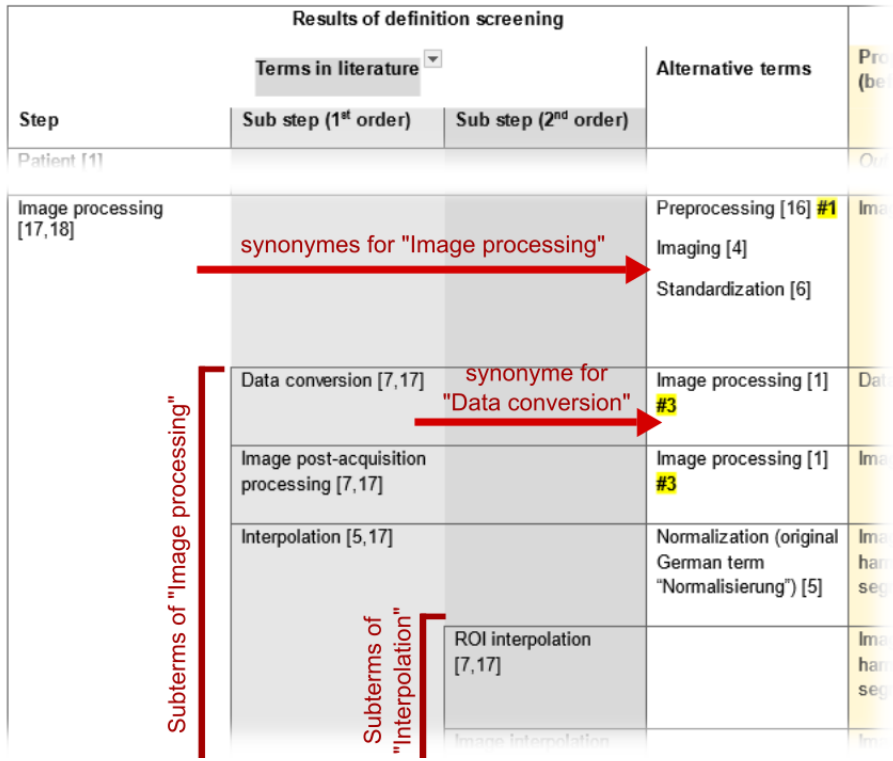
**Scope:** This is a supplement for the publication “Radiomics Workflow Definitions and Challenges of Implementation in Clinics: a Delphi-based Interdisciplinary Consensus” by the Scientific Priority Program Radiomics (DFG SPP2177) by the Germany Research Foundation. The supplement contains the list of step terms extracted from analyzed literature and used for compiling the baseline for the Delphi process described in the publication.

## Table of content

# Table instructions

Purpose of the provided table is to illustrate the terms, found in the analyzed literature, and their relation. Further this table documents which term was used to represent a certain definition for the Delphi process and the consensus term that was finally chosen for a definition.

**How to read the table**




The first four columns (heading “Results of definition screening”) are containing terms extracted from the analyzed literature. The first three columns (heading “Terms in literature”) are needed to depict the identified hierarchies between the terms. A cell of a higher order column can span over multiple rows of the lower order column (e.g. column 1 over column 2). This indicates that all rows of the lower order column contain sub terms. E.g. the “Image processing” cell spans over multiple rows of the 2nd column which indicates that e.g. “Data conversion” and “Interpolation” are sub terms of “Image processing” (see figure on the left). In the same way it is indicated that “ROI interpolation” is a sub term of “Interpolation” (whose cell spans over the “ROI interpolation” row). The fourth column (heading “Alternative terms”) contains all found synonyms for the term on the left side of the same row (e.g. “Preprocessing” is one found synonym for “Image processing”; see figure on the left).

The last two columns (heading “Delphi process”) indicate which terms were used in the therapy process after the analyzes. The fifth column (heading “Proposal (before Delphi)”) shows the terms that are used at the beginning of the process. The sixth column (heading “Workflow consensus (after Delphi)”) shows the respective consensus terms after the Delphi process.

Remark 1: The rows are ordered according to the analysis process that constructed the tree of step terms. Therefore, the order of the last column (“Workflow consensus (after Delphi)”) does not represent the structure/organization (phases and their aspects) of the consensus definition.

Remark 2: There is no dedicated meaning for the selection of which terms should be in the first three columns and which terms are declared their respective synonyms, as all synonymous terms are equivalent.

# Table of step terms

| Results of definition screening | | | | Delphi process | |
|---|---|---|---|---|---|
| | Terms in literature | | Alternative terms | **Proposal (before Delphi)** | **Workflow Consensus (after Delphi)** |
| **Step** | **Sub step (1st order)** | **Sub step (2nd order)** | | | |
| Patient [1] | | | | *Out of scope* | *Out of scope* |
| Data selection [2] | | | Creation of a dataset with appropriate clinical and radiological data [3] **#3** | Data selection | Study design<br>*(Merged into)* |
| | Choice of imaging protocol [2] **#3** | | | Choice of imaging protocol | Choice of imaging data |
| | Choice of prediction target [2] | | | Choice of prediction target | Choice of prediction target |
| | Choice of volume of interest [2] | | ROI definition [4] #1 | Choice of volume of interest | Choice of region of interest |

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|---|---|---|---|---|---|
| Data acquisition (original German term “Datenakquisition”) [5] | | | Creation of a dataset with appropriate clinical and radiological data [3] **#3**<br><br>Medical imaging [2]<br><br>MR Image acquisition with a standardization [6]<br><br>Medical imaging acquisition [7]<br><br>Image acquisition [3,7–12] | Data acquisition | Data acquisition |
| | Standardization [4,6] | | | Choice of imaging protocol | Choice of imaging data |
| | Imaging at multiple time points [2] | | Test-retest repeatability [1] | Test-retest imaging | Test-retest imaging |
| | Image acquisition [1,2,13–15] | | | Image acquisition | Image acquisition |
| | Reconstruction [1,13,15] | | | Reconstruction | Reconstruction |
| | Phantom studies [2] | | | Phantom studies | Phantom studies |

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|---|---|---|---|---|---|
| Data management (original German term “Datenmanagmement”) [5] | | | | Data management | Data management |
| | Export of DICOM images from PACS to the computer software that will be used to perform the radiomics analysis [3] **#3** | | | PACS export | Export of Imaging Data |
| Image processing [17,18] | | | Preprocessing [16] **#1**<br>Imaging [4]<br>Standardization [6]<br>Computation of radiomics features [7] #3<br>Data preprocessing (original German term “Datenvorverarbeitung”) [5] | Image processing | Image processing and segmentation<br>*(Merged into)* |
| | Data conversion [7,17] | | Image processing [1] **#3** | Data conversion | Data conversion |
| | Image post-acquisition processing [7,17] | | Image processing [1] **#3** | Image filtering | Image filtering |

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|---|---|---|---|---|---|
| | Interpolation [5,17] | | Normalization (original German term “Normalisierung”) [5] | Image geometry harmonization (pre segmentation) | Image geometry harmonization and resampling<br>*(Merged into / unified as)* |
| | | ROI interpolation [7,17] | | Image geometry harmonization (post segmentation) | Image geometry harmonization and resampling<br>*(Merged into / unified as)* |
| | | Image interpolation [7,17] | | Image geometry harmonization (post segmentation) | Image geometry harmonization and resampling<br>*(Merged into / unified as)* |
| | Analysis of outliers (original German term “Analyse von Ausreißern”) [5] | | | Outlier analysis | Image quality assessment |

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|---|---|---|---|---|---|
| Segmentation [1,2,4,8,9,11–13,17] | | | Image segmentation [3,18–20]<br><br>Nodule volume segmentation [10]<br><br>Segmentation (original German term “Segmentierung”) [5]<br><br>ROI Extraction (original German term “Extraktion der ROI”) [5] **#1**<br><br>Region of interest segmentation [15,16]<br><br>Tumor labeling [6]<br><br>Specification of ROIs [14]<br><br>ROI segmentation [7]<br><br>ROI definition [6] **#1**<br><br>Computation of radiomics features [7] #3 | Segmentation | Segmentation/ annotation<br><br>*(Merged into Image processing and segmentation as)* |
| | Re-segmentation [17] | | ROI resegmentation [7] | Re-segmentation | Quality control of segmentation |

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|---|---|---|---|---|---|
| Feature extraction [2,3,6,9–14,16,18,20] | | | Feature extraction and quantification [15]<br>Feature selection and extraction [8]<br>Radiomics feature extraction [19]<br>Calculation of the radiomics characteristics (original German term “Berrechnung der Radiomics-Merkmale”) [5]<br>Computation of image biomarker [1]<br>Generation of radiomics features [4]<br>Computation of radiomics features [7] #3 | Feature extraction | Feature extraction |
| | Feature calculation [17] | | | | Feature calculation |
| | ROI extraction [7,17] **#1** | | | ROI extraction | ROI extraction |
| | Intensity discretization [17] | | Discretisation [7] | Intensity discretization | Intensity discretization |

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|---|---|---|---|---|---|
| | Preprocessing [12,13] **#1** | | | Preprocessing | Preprocessing |
| Development of database [4] | | | Data handling [16] | Multimodal data integration | Multi disciplinary data curation and integration<br>*(+ moved to Data management)* |
| Modeling [1,2,21] | | | Statistical analysis and machine learning [7]<br>Analysis [10,11,13,16]<br>Model building [9] **#2**<br>Building predictive and prognostic models [15]<br>Statistical analysis [6,16]<br>Machine learning for building radiomics classifiers [9]<br>Analysis of database [4] | Modeling | Modeling |
| | Feature harmonization [22] | | | Feature harmonization | Feature harmonization |

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|---|---|---|---|---|---|
| | Feature selection [2,3,9,11,12,14,15,18, 22] | | Feature selection and extraction [8]<br>Radiomic feature selection [19]<br>Selection of radiomics characteristics (original German term “Auswahl von Radiomics-Merkmalen”) [5]<br>Radiomics signature modeling [20] | Feature selection | Feature selection |
| | | Dimensionality reduction [22] | Dimension reduction [18] | Dimensionality Reduction | Dimensionality Reduction |
| | | Exploratory analysis [2] | | Exploratory analysis | Exploratory analysis |
| | Choice of modeling methodology [2] | | | Choice of modeling methodology | *Splitted into*<br>Definition of the analysis and modeling strategy<br>*and*<br>Adaption of the analysis and modeling strategy |

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|---|---|---|---|---|---|
| | Model building [12,14,19] **#2** | | Creation and application of the radiomics model (original German term “Erstellung und Anwendung des Radiomics-Modells”) [5]<br><br>Model development (original German term “Modellentwicklung”) [5]<br><br>Model construction [22]<br><br>Model training [18]<br><br>Radiomics signature modeling [20]<br><br>Multivariate Analysis and Model Building [6] | Model building | Model building |
| | | Classification [15,22] | | Classification | *Merged into* Modeling *as it is just one of several specific task types (e.g. also detection)* |
| | Validation [2,3,9,12,16,22] | | Model analysis [20]<br><br>Performance evaluation [12] | Validation | Testing<br><br>*(renamed as validation in ML normally means the optimization of the architectural model/hyperparameter and* |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | *Testing is semantically covering what the publication wanted to express)* |
| | | MVI Prediction Model Evaluation [19] | | Validation | Testing |
| | | Nomogram Construction and Evaluation [19] | | Validation | Testing |
| Reporting open-access scientific data [2] | | | | Reporting | Reporting |
| Clinical application of radiomics [7] | | | Deployment (original German term “Bereitstellung”) [5] | *Out of scope* | *Out of scope* |
| | Prospective evaluation of model [7] | | | *Out of scope* | *Out of scope* |
| | Personalized treatment [7] | | | *Out of scope* | *Out of scope* |
| Radiomics signature [4] | | | | *Out of scope* | *Out of scope* |

**Legend:**

(x): Reference to the publication using that term

#1: Term involved in a conflict of type “Homonym”

#2: Term involved in a conflict of type “Hierarchy conflict”

#3: Term involved in a conflict of type “Semantic ambiguity”

## Terminology conflicts

Explanation of all conflicts found while screening the workflow definitions in literature.

**Synonyms:** This type of conflict is indicated if a cell in column “Alternative names in literature” is not empty; each alternative term, not indicated as another type of conflict, is a synonym. The cell then contains all found synonyms for the respective term in the same row (e.g. term “Choice of volume of interest” has the synonymous term “ROI definition”). Remark: Synonyms are regarded as conflicts in this context, as it makes the “interoperability” between different publications harder as the reader has to translate between different terms.

Occurrences: 55 (including 9 synonymous usages that are also involved in other conflicts)

**Homonyms:** Homonyms were found when identically named steps were defined differently. This type of conflict is indicated by a term being present in multiple rows of the first 4 columns (“Result definition screening” columns).

Occurrences:

1. ROI Extraction: Used as synonym for “Segmentation” [5] and as its own term [1].
2. Preprocessing: Used as synonym for “Image processing” [16] and as its own term [12, 13] as a sub step of “Feature extraction”.
3. ROI Definition: Used as synonym for “Choice of volume of interest” [4] and as synonym for “Segmentation” [6].

**Hierarchy conflicts**: This type of conflict is a subclass of Homonyms. They occurred when a step was mentioned as a step in one publication, while it was a sub step in another publication. It is indicated by the same term occurring on multiple levels (nth order sub steps) of the same step term.

Occurrences:

1. Model building: Used as synonym for “Modelling” [9] and as its sub step [12,14,19].

**Semantic ambiguity:** Semantic ambiguities occurred where definitions of a publication could not be clearly assigned to one step, but to multiple main steps.

Occurrences:

1. Choice of imaging protocol [2]: Could be partly a sub step of “Data selection” (planning part) and partly of “Data acquisition” (execution).
2. Image processing [1]: Could be partly sub step “Data conversion” [17] or sub step “Image post-acquisition processing” [17].
3. Export of DICOM Images from PACS [3]: Could be partly a sub step of “Development of database” [4] or sub step of “Data management” [5].
4. Creation of a dataset with appropriate clinical and radiological data [3]: Could partly be “Data selection” [2] or partly “Data acquisition” [5].
5. Computation of radiomics features [7]: Could partly be “Image Processing” [17], partly “Segmentation” [1] and partly “Feature Extraction” [2].

## Literature

List of literature that was analyzed in the definition screening.

1. Zwanenburg A. Radiomics in nuclear medicine: Robustness, reproducibility, standardization, and how to avoid data analysis traps and replication crisis. Eur J Nucl Med Mol Imaging. 2019;46(13):2638. doi: 10.1007/s00259-019-04391-8

2. Lambin P, Leijenaar RTH, Deist TM, et al. Radiomics: The bridge between medical imaging and personalized medicine. Nat Rev Clin Oncol. 2017;14(12):749. doi: 10.1038/nrclinonc.2017.141

3. Horvat N, Bates DDB, Petkovska I. Novel imaging techniques of rectal cancer: What do radiomics and radiogenomics have to offer? A literature review. Abdom Radiol (NY). 2019;44(11):3764. doi: 10.1007/s00261-019-02042-y

4. Scheckenbach K. Radiomics: Big data instead of biopsies in the future Laryngorhinootologie. 2018;97(S 01):S114. doi: 10.1055/s-0043-121964

5. Murray JM, Kaissis G, Braren R, Kleesiek J. Wie funktioniert radiomics. Radiologe. 2020;60(1):32. doi: 10.1007/s00117-019-00617-w

6. Chaddad A, Kucharczyk MJ, Daniel P, et al. Radiomics in glioblastoma: Current status and challenges facing clinical implementation. Front Oncol. 2019;9:374. doi: 10.3389/fonc.2019.00374

7. Vallières M, Zwanenburg A, Badic B, Cheze Le Rest C, Visvikis D, Hatt M. Responsible radiomics research for faster clinical translation. J Nucl Med. 2018;59(2):189. doi: 10.2967/jnumed.117.200501

8. Hassani C, Varghese BA, Nieva J, Duddalwar V. Radiomics in pulmonary lesion imaging. AJR Am J Roentgenol. 2019;212(3):497. doi: 10.2214/AJR.18.20623

9. Avanzo M, Stancanello J, El Naqa I. Beyond imaging: The promise of radiomics. Phys Med. 2017;38:122. doi: 10.1016/j.ejmp.2017.05.071

10. Wilson R, Devaraj A. Radiomics of pulmonary nodules and lung cancer. Transl Lung Cancer Res. 2017;6(1):86. doi: 10.21037/tlcr.2017.01.04

11. Lambin P, Rios-Velazquez E, Leijenaar R, et al. Radiomics: Extracting more information from medical images using advanced feature analysis. Eur J Cancer. 2012;48(4):441. doi: 10.1016/j.ejca.2011.11.036

12. Ibrahim A, Vallières M, Woodruff H, et al. Radiomics analysis for clinical decision support in nuclear medicine. Semin Nucl Med. 2019;49(5):438. doi: 10.1053/j.semnuclmed.2019.06.005

13. Fornacon-Wood I, Faivre-Finn C, O'Connor JPB, Price GJ. Radiomics as a personalized medicine tool in lung cancer: Separating the hope from the hype. Lung Cancer. 2020;146:197. doi: 10.1016/j.lungcan.2020.05.028

14. Lee S-H, Park H, Ko ES. Radiomics in breast imaging from techniques to clinical applications: A review. Korean J Radiol. 2020;21(7):779. doi: 10.3348/kjr.2019.0855

15. Thawani R, McLane M, Beig N, et al. Radiomics and radiogenomics in lung cancer: A review for the clinician Lung Cancer. 2018;115:34. doi: 10.1016/j.lungcan.2017.10.015

16. Machicado JD, Koay EJ, Krishna SG. Radiomics for the diagnosis and differentiation of pancreatic cystic lesions. Diagnostics (Basel). 2020;10(7):505. doi: 10.3390/diagnostics10070505

17. Zwanenburg A, Vallières M, Abdalah M, et al. The image biomarker standardization initiative: Standardized quantitative radiomics for high-throughput image-based phenotyping. Radiology. 2020;295(2):328. doi: 10.1148/radiol.2020191145

18. van Timmeren JEs, Cester D, Tanadini-Lang S, Alkadhi H, Baessler B. Radiomics in medical imaging—“how-to” guide and critical reflection. Insights Imaging. 2020;11(1):91. doi: 10.1186/s13244-020-00887-2

19. Yang L, Gu D, Wei J, et al. A radiomics nomogram for preoperative prediction of microvascular invasion in hepatocellular carcinoma. Liver Cancer. 2019;8(5):373. doi: 10.1159/000494099

20. Gu D, Hu Y, Ding H, et al. CT radiomics may predict the grade of pancreatic neuroendocrine tumors: A multicenter study. Eur Radiol. 2019;29(12):6880. doi: 10.1007/s00330-019-06176-x

21. Moons KGM, Altman DG, Reitsma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): Explanation and elaboration. Ann Intern Med. 2015;162(1):W1. doi: 10.7326/M14-0698

22. Mayerhoefer ME, Materka A, Langs G, et al. Introduction to radiomics. J Nucl Med. 2020;61(4):488. doi: 10.2967/jnumed.118.222893

## Supplement 2

# SPP Radiomics – Consensus Radiomics Workflow Definition

A SPP Radiomics Workflow Definition Supplement

**Version:** 1.0 – 2024/03/15

**Scope:** This is a supplement for the publication “Radiomics Workflow Definitions and Challenges of Implementation in Clinics: a Delphi-based Interdisciplinary Consensus” by the Scientific Priority Program Radiomics (DFG SPP2177) by the Germany Research Foundation. The supplement contains the consensus definition after the delphi process described in the publication. It also reflects all accepted additions and refinements proposed by the expert panel as well as the aspects that remain controversial. In addition it provides a mapping table between the consensus definition and analyzed literature.

## Legend

**Consensus color encoding:**

| | |
|---|---|
| Consensus:<br>>75% agreement (Agree or Strongly Agree) | |
| Minor controversy<br>>55% / <75% agreement (Agree or Strongly Agree) | |
| Major controversy<br><55% agreement (Agree or Strongly Agree) | |

Phases: ***Are printed italic and bold.***

Aspects: Are printed in normal text.

## Terminology

- Workflow: A workflow is structured in phases and their aspects and comprises any activity/step, to plan, to conduct and to report the building of an image feature-based prediction model.
- Phase: Phases represent different fundamental workflow steps and therefore can be found to a certain extent in every Radiomics workflow. A phase may contain one or more aspects. Between phases there is a logical dependency and therefore the order is not arbitrary.
- Aspects: Aspects are activities that take place within a phase. Aspects are often optional and they have per se no fixed order (sorting in this document is alphabetically by the English name of the aspect). As an effect of this ambiguity, the literature partially strongly differs on the aspects and their sequence. In some cases aspects are arranged in hierarchies (e.g. because we found sub aspects in the literature).

## Remarks

- Mandatory/optional workflow elements: As a default, aspects of a workflow can be regarded as optional (in occurrence, order or number). The list below compiles aspects that are documented in literature and are commonly found in Radiomics workflows. Nevertheless, we think that some aspects are crucial in the Radiomics workflow to ensure the validity and reliability of its results. Those “mandatory” aspects are indicated in the column “Mandatory”. Workflow phases that have at least one mandatory aspect are also mandatory.
- Machine learning / Deep learning: Deep learning techniques are increasingly applied also in the context of Radiomics workflows. They are (potentially) applicable at many aspects of the workflow; from simply replacing single aspects (like doing the annotation) up to replacing large parts of the workflow (e.g. end-to-end approaches). Therefore, the usage of deep learning techniques in the context of the workflow definition is not represented by additional optional aspects (which would be highly redundant) but by indicating which aspects can be replaced/covered by a deep learning technique (indicated by the column “ML”).

## Workflow Definition

| English Name | German Name | Definition (English) | Mandatory | ML |
|---|---|---|---|---|
| ***Study design*** | ***Studiendesign*** | ***Definition of the (clinical) research question, the imaging data and other data required as well as the analysis strategy. The definition should precede the analysis and always serves to ensure a reproducible and representative analysis.*** | **X** | |
| Choice of imaging data | Definition der Bildgebungsdaten | Definition of image data / standardization of the imaging protocol to ensure the feasibility and reproducibility of the analysis. | **X** | |
| Choice of prediction target | Definition des Prädiktionsziels | Definition of the prediction goal of the model. (e.g. stratification with respect to progression-free survival). | **X** | |
| Choice of region of interest | Definition der Zielstruktur | Definition of the structures (ROI) to be analyzed incl. the segmentation protocol. | **X** | |
| Definition of further data (non-imaging) | Definition weiterer Daten (keine Bildgebungsdaten) | Specification of the non-imaging data used for modeling. The data can be both modeling features and data on relevant endpoints. Due to the often low standardization of many non-imaging data, the formats and terminologies used should also be defined in advance and the widest possible/established options for coding should be used. | | |
| Definition of the analysis and modeling strategy | Definition der Analysestrategie | Definition of the analysis and modeling strategy to answer the defined research question with the selected data. | | |
| Definition of the clinical added value or the expected benefit | Definitionen des klinischen Mehrwertes (Motivation) und des erwarteten Nutzens | Definition of the added clinical value or the expected benefit, which should be achieved by the created model. | | |

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|---|---|---|---|---|
| ***Data acquisition*** | ***Datenakquisition*** | ***Summary of all activities necessary for prospective image data collection/standardization including associated metadata.*** | | |
| Image acquisition | Bildaufnahme | This aspect refers solely to the image acquisition and the associated acquisition parameters. | | |
| Phantom studies | Phantomstudien | Use of phantom studies to calibrate imaging systems for a prospective study; especially for multi-center studies. Furthermore, phantom studies can be used to investigate differences between scanners and segmentation methods (inter-observer variability). | | |
| Reconstruction | Rekonstruktion | Use of a reconstruction algorithm to reconstruct the image volume from the raw data. | | **X** |
| Test-retest imaging | Test-Retest-Bildgebung | Experimental reproducibility assessment by repeating recordings with temporal delay to detect normal variations in the image signal (test retest). | | |
| ***Data management*** | ***Datenmanagement*** | ***This phase contains all the actions necessary to compile the study data for the analysis and make it available for processing in the radiomics pipeline.*** | **X** | |
| Data archiving | Datenarchivierung | Archiving / Storage of data for potential re-analysis, subsequent validation or further research.<br><br>FAIR principles should be regarded/supported by the chosen archiving strategy. | | |
| Data format conversion | Datenformat-Konvertierung | Conversion of the data into other data formats (e.g. from DICOM to NIFTI). This is solely the transformation of the format (in the case of a lossless conversion). The conversion of the actual data takes place in the "Data conversion" aspect in the "Image processing and segmentation" phase. | | |

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| Data transfer and import | Datentransfer und -import | Transfer and import of the data into a target system which is required for the execution of the workflow (e.g. the evaluation is not conducted in the same facility or is conducted in a non-integrated system). | | |
| Ethics and data protection | Ethik und Datenschutz | Display of ethical vote, detailing on data protection means (anonymisation/ pseudonymisation) also for secondary use of the employed data. | **X** | |
| Export of Imaging Data | Export der Bilddaten | Export of Imaging Data (e.g. DICOM images) from the data archive (e.g. PACS) to be able to use them in the Radiomics pipeline. | **X** | |
| Multi disciplinary data curation and integration | Multidisziplinäre Datenkuratierung und -Integration | Optional inclusion of non image data (e.g. clinical data, genetic data) that should be used for the modeling. | | |
| Record linkage (of multi disciplinary data) | Verknüpfung der Datensätze (multidisziplinär) | Linking/merging of data (from different primary sources; e.g. multidisciplinary data with different IDs) of a subject. | | |
| ***Image processing and segmentation*** | ***Bildverarbeitung und Segmentierung*** | ***This phase contains all actions necessary to create the segmentations and prepare images as well as segmentations for feature calculation.*** | | **X** |
| Data conversion | Datenkonvertierung | Conversion of the image signal (image data) into another representation (e.g. conversion of PET signal image into Standardized Uptake Values (SUV)). | | **X** |
| Image filtering | Bildfilterung | Processing of the image signal with filters (e.g. noise reduction, gray value normalization,...). | | **X** |

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|---|---|---|---|---|
| Image geometry harmonization and resampling | Harmonisierung der Bildgeometrie und Resampling | Step to convert all images in the evaluation into an identical image geometry, in order to make voxel size-dependent features comparable. The harmonization can be done before the segmentation (the segmentation is thus performed on the harmonized geometries) or after the segmentation (The segmentation must therefore also be harmonized and resegmentation may be necessary). | | **X** |
| Image registration | Bildregistrierung | Transfer of images to target geometries with a given mapping rule (e.g. to compensate for motion artifacts, to spatially align multimodal images or to normalize to a reference anatomy). | | **X** |
| Quality control of segmentation | Qualitätskontrolle der Segmentierung | Checking and correction of segmentation (especially at its edges) to correct errors that were e.g. introduced by the segmentation or by "harmonization of image geometry" (post segmentation). | | **X** |
| Segmentation/annotation | Segmentierung/Annotation | Segmentation/annotation of the defined region of interest based on the defined protocol. | | **X** |
| Image quality assessment | Qualitätsbewertung der Bilddaten | The analysis of outliers is used to evaluate the quality of the used image material. For the assessment general criteria (e.g. correct modality or right body part) as well as study specific criteria (e.g. need minimal resolution, absence of artifacts) can be used. The assessment can be implemented by expert decision as well as automated quality control (to support scalability and reproducibility, it is adviseable to implement a process that is as quantitative and automated as possible. | **X** | **X** |
| ***Feature extraction*** | ***Merkmalsextraktion*** | ***In this phase, all aspects are summarized that are necessary/relevant for feature extraction, i.e. the derivation of quantitative information from the segmented images using mathematical formulas.*** | **X** | **X** |

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|---|---|---|---|---|
| Feature calculation | Merkmalsberechnung | The actual process of calculating individual features based on the input data, the formula/algorithm and their parameterization. | **X** | **X** |
| Intensity discretization | Intensitätsdiskretisierung | A discretization/binning of intensities within the ROI is performed to make the calculation of texture features comprehensible and to suppress noise. Binning can be performed for all features or adapted for specific features. | | **X** |
| Preprocessing | Vorverarbeitung | The preprocessing steps in this phase are used to prepare the images before feature extraction. In contrast to the aspect "Image Processing" (Phase Image Processing & Segmentation), "Preprocessing" only includes preprocessing steps that are needed for specific features (e.g. a Fourier transformation) but have no general relevance or validity. In the works studied, the preprocessing steps named were i.a. filtering in general, edge reduction or smoothing. | | **X** |
| Quality control of calculated features | Qualitätskontrolle der berechneten Merkmale | Quality control (e.g. through automatic plausibility check or random checks) of the calculated features. | | **X** |
| ROI extraction | ROI-Extraktion | Isolation of one or more of the ROIs from the rest of the image (e.g. by replacing excluded pixels/voxels with NaN). This step depends on the feature and the implementation of the extraction method. | | **X** |
| ***Modeling*** | ***Modellierung*** | ***This phase contains all aspects that are necessary to establish a model that, based on given input data (radiomic features, clinical features, etc.), allows prediction in terms of the defined prediction goal.*** | **X** | |

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|---|---|---|---|---|
| Adaption of the analysis and modeling strategy | Anpassung der Analyse- und Modellierungsstrategie | Sometimes it can be necessary to adapt the analysis strategy of the study in order to achieve the research goal with the given study data. This aspect covers this necessity, but should be avoided if possible. If one has to adapt the strategy and diverge from the original study design, it should be handled very carefully and statistically double-checked to ensure the validity and integrity of the results. As later changes can introduce bias, over fitting or statistical errors and alike, the results could otherwise be compromised. | **X** | |
| Dimensionality Reduction | Dimensionsreduktion | Combination of several features into a new feature (e.g. by Principal Component Analysis). | | |
| Exploratory analysis | Explorative Analyse | Interactive analysis on the predictive power of different combinations of radiomic features and non-radiomic features. This can be used to perform more targeted feature selection and reduction. It is important that this aspect is not done with the data for testing. | | |
| Feature harmonization | Merkmalsharmonisierung | Mathematical method to correct batch effects (e.g. location-dependent variations during the image acquisition). In contrast to a harmonization of the gray values (e.g. also by phantom studies, see above), here the harmonization takes place only after the extraction of the features. | | |
| Feature selection | Auswahl von radiomischen Merkmalen | Selection of radiomic features that are relevant and informative for the planned task, from the extracted radiomic features (e.g. mRMR). Another criterion is the exclusion of non-reproducible radiomic features. | | |

| | | | | |
|---|---|---|---|---|
| Model building | Modellentwicklung | The optimization of a model, to ensure a best possible prediction of the prediction targets based on the selected features. This includes i.a. the parameter optimization of parameterized models (Training) or architectural model/ hyperparameter optimization (Validation). | **X** | |
| Testing | Testen | Testing using dedicated data, which is not used for model training, serves the final evaluation of the suitability of the radiomics model (e.g. with regard to robustness/generalizability, predictive quality/accuracy...). Ideally, this is done by means of an independent test set. The testing can also be done by means of cross-validation (whereby it must then be ensured that all aspects mentioned above must be cross-validated, including e.g. nested cross-validation for hyperparameter optimization).<br>Remark: The term “Testing” was preferred over often found “Validation” because validation in ML normally means the optimization of the architectural model/hyperparameter and “Testing” is semantically fitting term in ML. | **X** | |
| ***Reporting*** | ***Report*** | ***Report of the results including all necessary metadata (data provenance, data source, processing steps, data quality) as part of publications or the enablement of subsequent usage . The FAIR principles should be regarded/implemented in the report.*** | **X** | |
| Open source publication of methods and tools | Open source Publikation der Methoden und Werkzeuge | Publication (e.g. via public code repositories) of the used program source codes and analysis scripts to support reproducibility of the study setup and reuse of the published methodology. ***The FAIR principles should be regarded/implemented in the code publication.*** | | |

# Supplement 3

| Consensus definition | Zwanenburg 2019 [1] | RQS Lambin 2017 [2] | Horvat 2019 [3] | Scheckenbach 2018 [4] | Murray 2020 [5] | Chaddad 2019 [6] |
|---|---|---|---|---|---|---|
| ***Study design*** | | | ***Creation of a dataset with appropriate clinical and radiological data #1*** | | | |
| Choice of imaging data | | Choice of imaging data #2 | | Standardization | | Standardization |
| Choice of prediction target | | Choice of prediction target | | | | |
| Choice of region of interest | | Choice of region of interest | | ROI definition | | |
| Definition of further data (non-imaging) | | | | | | |
| Definition of the analysis and modeling strategy | | Choice of modeling methodolog | | | | |
| Definition of the clinical added value or the expected benefit | | | | | | |
| ***Data acquisition*** | | ***Medical Imaging*** | ***Creation of a dataset with appropriate clinical and radiological data #1; Image acquisition*** | | ***Datenakquisition*** | ***MR Image acquisition with a standardization*** |

| | | | | | | |
|---|---|---|---|---|---|---|
| Image acquisition | Image acquisition | Image acquisition | | | | |
| Phantom studies | | Phantom studies | | | | |
| Reconstruction | Reconstruction | | | | | |
| Test-retest imaging | Standardization | Imaging at multiple time points | | | | |
| ***Data management*** | | ***Creation of databases; Data management*** | | | ***Datenmanagement*** | |
| Data archiving | | | | | | |
| Data format conversion | | | | | | |
| Data transfer and import | | | | | | |
| Ethics and data protection | | | | | | |
| Export of Imaging Data | | | Export of DICOM images from PACS to the computer software that will be used to perform the radiomics analysis #3 | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Multi disciplinary data curation and integration | | Radiogenomics | Export of DICOM images from PACS to the computer software that will be used to perform the radiomics analysis #3 | Development of database | | |
| Record linkage (of multi disciplinary data) | | | | | | |
| ***Image processing and segmentation*** | | ***Data selection*** | | ***Imaging*** | ***Datenverarbeitung*** | ***Standardization*** |
| Data conversion | Image processing #5 | | | | | |
| Image filtering | Image processing #5 | | | | | |
| Image geometry harmonization and resampling | | | | | Interpolation; Normalisierung | |
| Image registration | | | | | | |
| Quality control of segmentation | | | | | | |
| Segmentation/annotation | Segmentation | Segmentation | Image segmentation | Segmentation | Segmentierung Extraktion der ROI | Tumor labeling ROI definition |
| Image quality assessment | | | | | Analyse von Ausreißern | |
| ***Feature extraction*** | ***Computation of image biomarker*** | ***Feature extraction*** | ***Feature extraction*** | ***Generation of radiomics features*** | ***Berrechnung der Radiomics-Merkmale*** | ***Feature extraction*** |

| | | | | | | |
|---|---|---|---|---|---|---|
| Feature calculation | | | | | | |
| Intensity discretization | | | | | | |
| Preprocessing | | | | | | |
| Quality control of calculated features | | | | | | |
| ROI extraction | | | | | | |
| ***Modeling*** | ***Modeling*** | ***Modeling; Radiomics Modeling*** | | ***Analysis of database*** | | ***Statistical analysis*** |
| Adaption of the analysis and modeling strategy | | Choice of modeling methodolog | | | | |
| Dimensionality Reduction | | Dimensionalty Reduction | | | | |
| Exploratory analysis | | Exploratory analysis | | | | |
| Feature harmonization | | | | | | |
| Feature selection | | Feature selection | Feature selection | | Auswahl von Radiomics-Merkmalen | |
| Model building | | | | | Erstellung und Anwendung des Radiomics-Modells; Modellentwicklung | Multivariate Analysis and Model Building |

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|---|---|---|---|---|---|---|
| Testing | | Validation | Validation | | | |
| ***Reporting*** | | ***Reporting open-access scientific data*** | | | | |
| Open source publication of methods and tools | | | | | | |

| **Consensus definition** | **Vallières 2018 [7]** | **Hassani 2019 [8]** | **Avanzo 2017 [9]** | **Wilson 2017 [10]** | **Lambin 2012 [11]** | **Ibrahim 2019 [12]** |
|---|---|---|---|---|---|---|
| ***Study design*** | | | | | | |
| Choice of imaging data | | | | | | |
| Choice of prediction target | | | | | | |
| Choice of region of interest | | | | | | |
| Definition of further data (non-imaging) | | | | | | |
| Definition of the analysis and modeling strategy | | | | | | |
| Definition of the clinical added value or the expected benefit | | | | | | |

| ***Data acquisition*** | ***Medical imaging acquisition; Image acquisition*** | | ***Image acquisition*** | ***Image acquisition*** | ***Image acquisition*** | ***Image acquisition*** |
|---|---|---|---|---|---|---|
| Image acquisition | | | | | | |
| Phantom studies | | | | | | |
| Reconstruction | | | | | | |
| Test-retest imaging | | | | | | |
| ***Data management*** | | | | | | |
| Data archiving | | | | | | |
| Data format conversion | | | | | | |
| Data transfer and import | | | | | | |
| Ethics and data protection | | | | | | |
| Export of Imaging Data | | | | | | |
| Multi disciplinary data curation and integration | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Record linkage (of multi disciplinary data) | | | | | | |
| ***Image processing and segmentation*** | ***Computation of radiomics features #4*** | | | | | |
| Data conversion | Data conversion | | | | | |
| Image filtering | Image post-acquisition processing | | | | | |
| Image geometry harmonization and resampling | Image interpolation; ROI Interpolation | | | | | |
| Image registration | | | | | | |
| Quality control of segmentation | | | | | | |
| Segmentation/annotation | Computation of radiomics features #4; ROI segmentation | Segmentation | Segmentation | Nodule volume segmentation | Segmentation | Segmentation |
| Image quality assessment | | | | | | |
| ***Feature extraction*** | ***Computation of radiomics features #4*** | ***Feature extraction and selection*** | ***Feature extraction*** | ***Feature extraction*** | ***Feature extraction*** | ***Feature extraction*** |
| Feature calculation | | | | | | |
| Intensity discretization | Discretization | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Preprocessing | | | | | | Preprocessing |
| Quality control of calculated features | | | | | | |
| ROI extraction | ROI extraction | | | | | |
| ***Modeling*** | ***Statistical analysis and machine learning*** | | ***Model building; Machine learning for building radiomics classifiers*** | ***Analysis*** | ***Analysis*** | |
| Adaption of the analysis and modeling strategy | | | | | | |
| Dimensionality Reduction | | | | | | |
| Exploratory analysis | | | | | | |
| Feature harmonization | | | | | | |
| Feature selection | | Feature selection and extraction | Feature selection | | Feature selection | Feature selection |
| Model building | | | | | | Model building |
| Testing | | | Validation | | | Performance evaluation; Validation |
| ***Reporting*** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Open source publication of methods and tools | | | | | | |

| Consensus definition | Fornacon-Wood 2020 [13] | Lee 2019 [14] | Thawani 2017 [15] | Macchicado 2020 [16] | IBSI Zwanenburg 2020 [17] | van Timmeren 2020 [18] |
|---|---|---|---|---|---|---|
| ***Study design*** | | | | | | |
| Choice of imaging data | | | | | | |
| Choice of prediction target | | | | | | |
| Choice of region of interest | | | | | | |
| Definition of further data (non-imaging) | | | | | | |
| Definition of the analysis and modeling strategy | | | | | | |
| Definition of the clinical added value or the expected benefit | | | | | | |
| ***Data acquisition*** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Image acquisition | Image acquisition | Image acquisition | Image acquisition | | | |
| Phantom studies | | | | | | |
| Reconstruction | Reconstruction | | Reconstruction | | | |
| Test-retest imaging | | | | | | |
| ***Data management*** | | | | | | |
| Data archiving | | | | | | |
| Data format conversion | | | | | | |
| Data transfer and import | | | | | | |
| Ethics and data protection | | | | | | |
| Export of Imaging Data | | | | | | |
| Multi disciplinary data curation and integration | | | | Data handling | | |
| Record linkage (of multi disciplinary data) | | | | | | |

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|---|---|---|---|---|---|---|
| ***Image processing and segmentation*** | | | | ***Preprocessing*** | ***Image processing*** | ***Image processing*** |
| Data conversion | | | | | Data conversion | |
| Image filtering | | | | | Image post-acquisition processing | |
| Image geometry harmonization and resampling | | | | | Interpolation; Image interpolation; ROI interpolation | |
| Image registration | | | | | | |
| Quality control of segmentation | | | | | Re-segmentation | |
| Segmentation/annotation | Segmentation | Specification of ROIs | Region of interest segmentation | | Segmentation | Image segmentation |
| Image quality assessment | | | | | | |
| ***Feature extraction*** | ***Feature extraction*** | ***Feature extraction*** | ***Feature extraction and quantification*** | ***Feature extraction*** | | ***Feature extraction*** |
| Feature calculation | | | | | Feature calculation | |
| Intensity discretization | | | | | Intensity discretization | |
| Preprocessing | Preprocessing | | | | | |

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|---|---|---|---|---|---|---|
| Quality control of calculated features | | | | | | |
| ROI extraction | | | | | ROI extraction | |
| ***Modeling*** | ***Analysis*** | | ***Building predictive and prognostic models; Classification*** | ***Analysis; Statistical analysis*** | | |
| Adaption of the analysis and modeling strategy | | | | | | |
| Dimensionality Reduction | | | | | | Dimension reduction |
| Exploratory analysis | | | | | | |
| Feature harmonization | | | | | | |
| Feature selection | | Feature selection | Feature selection | | | Feature selection |
| Model building | | Model building | | | | Model training |
| Testing | | | | Validation | | |
| ***Reporting*** | | | | | | |
| Open source publication of methods and tools | | | | | | |

| Consensus definition | Yang 2019 [19] | Gu 2019 [20] | TRIPOD Moons 2015 [21] | Mayerhoefer 2020 [22] | CLEAR Kocak 2023 [23] | ARISE Kocak 2023 [24] |
|---|---|---|---|---|---|---|
| Study design | | | | | Study design | Design |
| Choice of imaging data | | | | | Selection of imaging modality | |
| Choice of prediction target | | | | | | |
| Choice of region of interest | | | | | | |
| Definition of further data (non-imaging) | | | | | | |
| Definition of the analysis and modeling strategy | | | | | | |
| Definition of the clinical added value or the expected benefit | | | | | | |
| Data acquisition | | | | | Data acquisition | |
| Image acquisition | | | | | Image acquisition | |
| Phantom studies | | | | | Phantom studies | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Reconstruction | | | | | | |
| Test-retest imaging | | | | | | |
| Data management | | | | | Data preperation | |
| Data archiving | | | | | | |
| Data format conversion | | | | | | |
| Data transfer and import | | | | | | |
| Ethics and data protection | | | | | Ethics and data protection | |
| Export of Imaging Data | | | | | | |
| Multi disciplinary data curation and integration | | | | | | |
| Record linkage (of multi disciplinary data) | | | | | | |
| Image processing and segmentation | | | | | Segmentation strategy and Preprocessing | |
| Data conversion | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Image filtering | | | | | Image types | |
| Image geometry harmonization and resampling | | | | | | |
| Image registration | | | | | | |
| Quality control of segmentation | | | | | | |
| Segmentation/annotation | Image segmentation | Image segmentation | | | Segmentation | |
| Image quality assessment | | | | | | |
| Feature extraction | Radiomics feature extraction | Feature extraction | | | Feature extraction | Feature extraction/ Radiomics methodology |
| Feature calculation | | | | | | |
| Intensity discretization | | | | | | |
| Preprocessing | | | | | Preprocessing | Preprocessing |
| Quality control of calculated features | | | | | | |
| ROI extraction | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Modeling | | | Modeling | Classification | Modeling | |
| Adaption of the analysis and modeling strategy | | | | | | |
| Dimensionality Reduction | | | | Dimensionality Reduction | | |
| Exploratory analysis | | | | | | |
| Feature harmonization | | | | Feature harmonization | | |
| Feature selection | Radiomics feature selection | Radiomics signature modeling | | Feature selection | | |
| Model building | Model building | Radiomics signature modeling | | Model construction | Training and tuning | |
| Testing | MVI Prediction Model Evaluation; Nomogram Construction and Evaluation | Model analysis | | Validation | Testing | Internal and external testing |
| Reporting | | | | | Reporting | Metrics and reporting |
| Open source publication of methods and tools | | | | | Open science | |

Legend:
#1: Semantic ambiguity: Could be part of “Study design” or partly “Data acquisition”.
#2: Semantic ambiguity: Could partly be a sub step of “Study design” (planning part) and partly of “Data acquisition” (execution).
#3: Semantic ambiguity: Could partly be “Export of imaging data” and partly “Multi disciplinary data curation”.
#4: Semantic ambiguity: Could partly be “Image processing and Segmentation” and partly “Feature Extraction”.
#5: Semantic ambiguity: Could partly be “Data conversion” and partly “Image filtering”.

# Supplement 4
# SPP Radiomics – List of challenges

A SPP Radiomics Workflow Definition Supplement

**Version**: 2024/03/13

**Scope**: This is a supplement for the publication “Radiomics Workflow Definitions and Challenges of Implementation in Clinics: a Delphi-based Interdisciplinary Consensus” by the Scientific Priority Program Radiomics (DFG SPP2177) by the Germany Research Foundation. The supplement contains a list of all challenges regarding the translation and clinical application of radiomics extracted from literature or proposed by experts. The challenges proposed by the experts have an index marked with *.X*) and were collected in the third round of the Delphi process described in the publication.

**Remark**: Challenge F.1 “Lack of reproducibility of biomarkers” was merged into C.5 “Problems related to reproducibility /generalizability” for round 5 of the Delphi process as on this abstraction level F.1 can be seen as a subset of C.5.

## A Lack of guidelines

*This category contains challenges that originate in a lack of guidelines for important/relevant steps in the workflow.*

A.1 Lack of processing guidelines

A.2 Lack of reporting guidelines

A.X1 Lack of quality ensuring guidelines for reviewers (and editors)
*(e.g. stricter guidelines to ensure scientific quality and manage the increasing number of radiomics; preventing quantity rather than quality (which is pushed by “publish and perish))*

## B Lack of standardization

*This category contains challenges that originate in a lack of standardization of aspects in the workflow .*

B.1 Lack of homogenous evaluation criteria
*(e.g. the way evaluations are conducted (i.a. metrics to use, baselines) is not standardized; reporting guidelines not applied)*

B.2 Lack of standardized computation methods
*(e.g. the feature computation is not conducted in a standardized way)*

## C Problems related to radiomics studies

*This category contains challenges that originate in problems with the study design or the way the study is conducted.*

C.1 Lack of definition of a "good" radiomics study

C.2 Problems related to use of routine data
*(e.g. the routine data proofs not to be suitable to answer the research question (i.a. due to problems with quantity, quality or contained information); other problems with the data not covered elsewhere)*

C.3 Problems related to study design
*(e.g. Insufficient size of patient cohorts, Lack of statistical significance, Non-consistent conduct of radiomics studies, High false-positive rates, Class imbalance; Insufficient / irrelevant clinical contribution (problem addressed is not relevant in clinical routine, e.g. radiomics prediction of IDH mutation status in gliomas))*

C.4 Problems related to study results
*(e.g. Lack of validation of studies, Causality difficult to establish, Overly optimistic results, Problems related to reporting of studies, Insufficient reporting about patient data, Insufficient reporting about prediction models, Insufficient reporting about methodological information)*

C.5 Problems related to reproducibility /generalizability
*(e.g. Lack repeatability, Lack of generalizability, Lack of reproducibility of studies)*

C.X1 Lack of evidence gained by prospective evaluation
*(e.g. performances of retrospective results cannot be reproduced in a prospective setting)*

## D Problems related to radiomics pipelines

*This category contains challenges that originate in problems with the way the processing is done or the used tooling.*

D.1 Problems related to image acquisition
*(e.g. Imaging inconsistency, Imaging at multiple time points, Use of not standardized image acquisition protocols, Differences between imaging modalities, Lack of standardization of acquisition parameters, Heterogeneity caused by variations in acquisition parameters, different sequences (MRT), Contrast agent application protocol, used reconstruction kernels)*

D.2 Problems related to prediction models
*(e.g. Choosing a suitable algorithm for model building, Underfitting, Overfitting, Lack of generalizability of Radiomics Models, Lack of clinical utility, Lack of reproducibility of prediction models, Lack of standardized performance evaluation)*

D.3 Problems related to image processing methods
*(e.g. Number of subsets, Gaussian filter width for post reconstruction smoothing, unspecified hyperparameters)*

D.5 Problems related to segmentations
*(e.g. Differences in segmentation methods / software, Intra-/ Interobservervariability of segmentation, Reproducibility of segmentation methods)*

D.6 Inconsistent processing schemes

D.7 Inconsistent radiomic methods

D.8 Variations in mathematical definitions

D.9 Differences in radiomics toolboxes

D.10 Differences between observers

D.11 Experimental inconsistency

D.X1 Problem related to uncertainty/trustability of models
*(e.g. Workflows are not use because the uncertainty of their results can not be investigated; Workflows cannot detect that input is OOD and react/escalate accordingly)*

D.X2 Lacking workflow integration
*(e.g. Workflows are not well integrated in current workflows; imposing extra steps or systems that hinder normal workflow; too much time consumption by needed interactions)*

## E Problems related to data management

*This category contains challenges that originate in problems with handling the data used in the study (e.g. including additional data not to the correct samples).*

E.1 Complex data management

E.2 Difficulties integrating other data sources

## F Problems related to radiomics features

*This category contains challenges that originate in problems with the used radiomics features (e.g. use different radiomics extraction pipelines that have different names for the same features).*

F.1 Lack of reproducibility of biomarkers

F.2 Variations in feature nomenclature

F.3 Lack of standardized radiomic features

F.4 Variability in radiomic feature generation

## G Problems related to data sharing

*This category contains challenges that originate in problems with sharing or reusing data for a study (e.g. not sharing data of private data sources makes studies not reproducible).*

G.1 Legal and privacy problems
*(e.g. open questions regarding model training/sharing and GPDR; Data sharing and GPDR/(broad)consent management; implications of Medical Device Directive if research software is applied prospectively (often not bearable from research groups))*

G.2 Political and academic value of data

G.3 Hazards to reputation

G.4 Data recording methods

G.5 Cultural and language difficulties

G.6 Insufficient time

G.7 Insufficient human resources