

# Enhancing Interoperability and Harmonisation of Nuclear Medicine Image Data and Associated Clinical Data

## Verbesserung der Interoperabilität und Harmonisierung von nuklearmedizinischen Bilddaten und zugehörigen klinischen Daten

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### ABSTRACT

Nuclear imaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) in combination with computed tomography (CT) are established imaging modalities in clinical practice, particularly for oncological problems. Due to a multitude of manufacturers, different measurement protocols, local demographic or clinical workflow variations as well as various available reconstruction and analysis software, very heterogeneous datasets are generated. This review article examines the current state of interoperability and harmonisation of image data and related clinical data in the field of nuclear medicine. Various approaches and standards to improve data compatibility and integration are discussed. These include, for example, structured clinical history, standardisation of image acquisition and reconstruction as well as standardised preparation of image data for evaluation. Approaches to improve data acquisition, storage and analysis will be presented. Furthermore, approaches are presented to prepare the datasets in such a way that they become usable for projects applying artificial intelligence (AI) (machine learning, deep learning, etc.). This review article concludes with an outlook on future developments and trends related to AI in nuclear medicine, including a brief research of commercial solutions.

### ZUSAMMENFASSUNG

Die Verwendung nuklearmedizinischer Bildgebungsverfahren wie der Positronen-Emissions-Tomografie (PET) und der Single-Photonen-Emissions-Computertomografie (SPECT) in Kombination mit der Computertomografie (CT) hat sich in der klinischen Praxis vor allem bei onkologischen Fragestellungen etabliert. Aufgrund einer Vielzahl an Herstellern, möglicher Messprotokolle sowie verfügbarer Rekonstruktions- und Auswertungssoftware werden dabei teils sehr heterogene Datensätze generiert. Der vorliegende Übersichtsartikel untersucht den aktuellen Stand der Interoperabilität und Harmonisierung von Bilddaten und der damit verbundenen klinischen Daten im Bereich der Nuklearmedizin. Es werden verschiedene Ansätze und Standards zur Verbesserung der Datenkompatibilität und -integration diskutiert. Dazu gehören beispielsweise die strukturierte klinische Anamnese, die

Vereinheitlichung der Bildakquisition und -rekonstruktion sowie eine standardisierte Aufbereitung der Bilddaten für die Auswertung. Es werden Lösungsansätze zur Verbesserung der Datenerfassung, -speicherung und -analyse aufgezeigt. Weiterhin werden Möglichkeiten vorgestellt, die Datensätze so vorzubereiten, dass sie für Projekte, die künstliche Intelli-

genz (KI) anwenden (Machine Learning, Deep Learning etc.), nutzbar werden. Der Übersichtsartikel schließt mit einem Ausblick auf zukünftige Entwicklungen und Trends im Zusammenhang mit KI in der Nuklearmedizin, inkl. einer kurzen Marktrecherche.

## Introduction

Nuclear medicine imaging techniques, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), produce highly informative images that offer valuable insights into physiological and molecular processes in the human body. This complements the information obtained from morphological imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI). Usually, either CT or MRI images are additionally acquired for attenuation correction and anatomical correlation as part of PET/CT, SPECT/CT or PET/MRI. Along with these imaging modalities, the integration of clinical data plays a vital role in advancing scientific research [1].

However, nuclear medicine research and clinical applications face a significant challenge: the heterogeneity of data across different imaging systems, acquisition protocols, institutions, and research studies. In particular, there are instances where imaging procedures have not been sufficiently harmonised, which can occur due to organisational reasons, differences in hardware and/or software or to achieve better image quality within the scope of personalised medicine (e.g., if a system has more advanced imaging hardware or software in comparison to other sites to be harmonised) [2].

By harmonising data and combining them from multiple sources (e.g. practices and clinics), researchers are able to produce larger datasets that better represent a wide population and better depict statistical variations [3]. This process has the potential to uncover hidden patterns as well as relationships among features associated with disease progression, treatment efficiency, and patient outcomes that might not be apparent when analysing individual or single-institution datasets alone. This provides a deeper understanding of the mechanisms and dynamics of the system under investigation, which could lead to improved information-based decision-making in healthcare workflows [4]. Utilising data harmonisation, standardised workflows can be effectively implemented across multiple research sites, enabling distributed analyses, and fostering collaborations among clinicians. Moreover, it holds significant clinical and patient benefits by enabling the reliable training and application of artificial intelligence models across different centres, including smaller facilities, thus fostering advancements in personalised healthcare.

This review aims to comprehensively summarise the current state of interoperability and standardisation of nuclear medicine image data and associated clinical data to give an overview of improvements that might lead to even better data quality for machine learning (► Fig. 1). The focus of this work is on the entire data processing pathway, from the initial collection of medical his-

tory, through the acquisition of image data, to multi-centre evaluation using machine learning methods.

In this review, we define interoperability as the ability of different systems, tools, or datasets to work together seamlessly, enabling the exchange and utilisation of information without significant barriers. Standardisation refers to the establishment of uniform examination protocols and methods for data collection, measurement, and analysis within a single study or across multiple studies to minimise variability and enhance reliability of results. Harmonisation/normalisation is the process of reconciling and adjusting data from different sources to ensure compatibility and comparability.

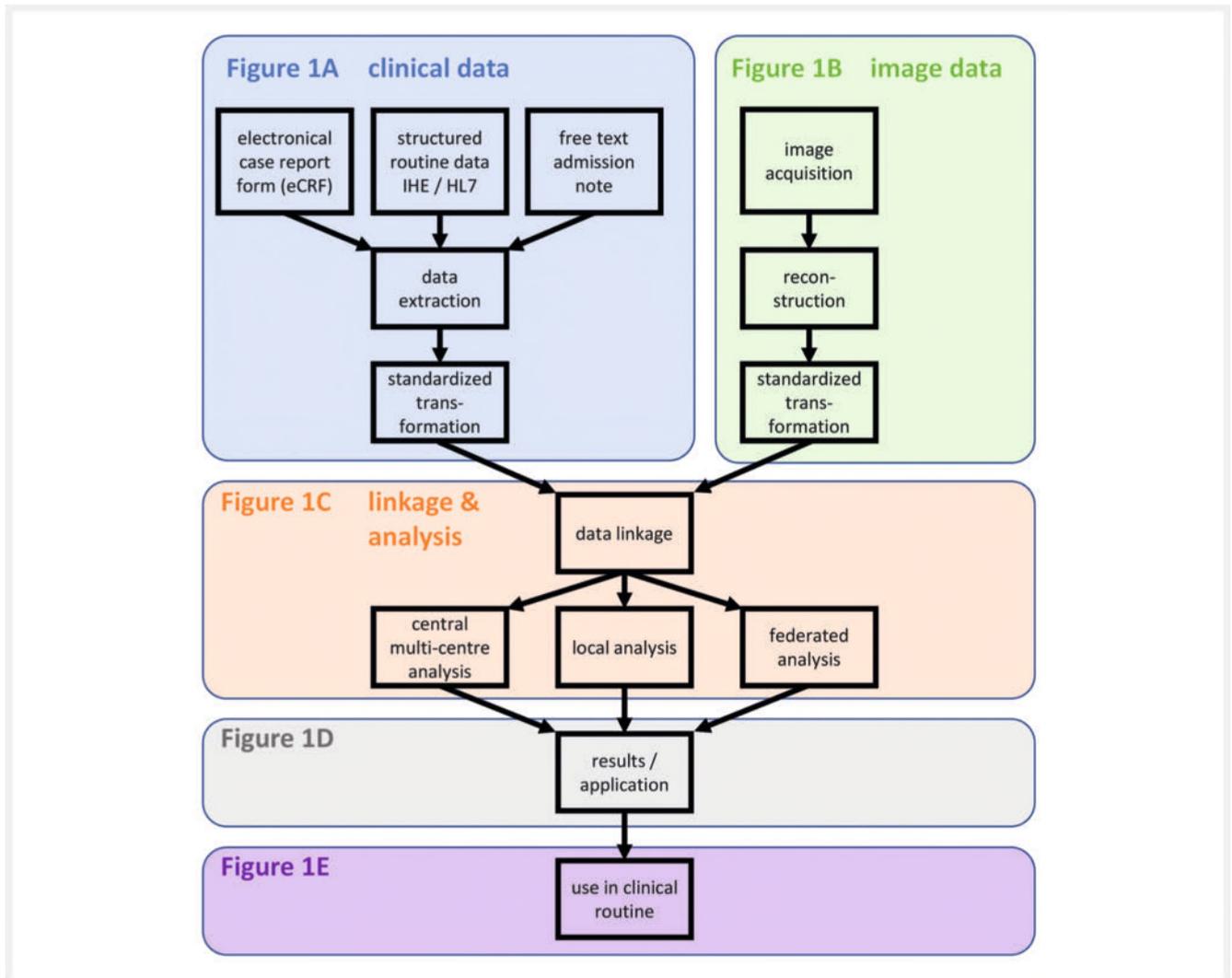
The subsequent sections of this paper will describe key aspects such as data formats and standards, integration of clinical data with nuclear medicine images, data harmonisation and normalisation techniques, interoperability frameworks, and emerging technologies that hold promise in overcoming existing barriers.

The individual aspects of this review article are shown in ► Fig. 1. At the beginning, section 2 of this article (► Fig. 1A) deals with the collection and processing of clinical data. Section 3 (► Fig. 1B) then focuses is on image data acquisition and processing. Section 4 goes deeper into harmonisation of image data and associated clinical data and their preparation for different machine learning options (► Fig. 1C). Section 5 presents different use cases and software tools (► Fig. 1C and 1D). Section 6 gives a brief overview of the current state of harmonisation in routine clinical practice (► Fig. 1E), including a market review.

## Data acquisition and organisation

To standardise and harmonise patient data for matters of patient care or clinical research, a standardised collection of patient data that is consistent for each hospital and department is necessary (► Fig. 1A). Therefore, it is crucial to use standardised forms or documents to help clinical personnel to obtain the same type of information for each patient. Information collected from the patient's medical history, including procedures and imaging studies [5], have been shown to be of great added value. These roughly structured documents contain information for patients, such as the need for and the performance of the procedure, alternatives to the preferred strategy, as well as risks and possible complications of the approach. The medical staff also gather information about the patients and their conditions.

To enable the use of this information in clinical research, a storage system is needed that stores the information in a standardised and structured way and makes it available for later use in a format that can be used for analysis (statistics, machine learning



► **Fig. 1** Overview of the process of data collection, processing, and evaluation for medical research with nuclear medicine image data and associated clinical data. This is subdivided into the collection and preparation of clinical data (Figure 1A) as well as image data (Figure 1B), data linkage and analysis (Figure 1C), the development of applications (Figure 1D) and their use in clinical routine (Figure 1E).

algorithms, deep learning, etc.). For this purpose, electronic case report forms (eCRFs) are a valuable resource [5]. The eCRF forms are built into electronic data capture (EDC) systems that allow researchers to design individual forms for each study. Researchers and clinical staff can use them to manually enter data into the system. These systems not only offer an effective way to collect data for clinical and research purposes, but also facilitate collaborative data sharing among different research sites and hospitals. Advantages include early detection of protocol violations, reducing unnecessary work, and improving the data quality of clinical trials. These types of data can be integrated into electronic health records very easily. Also, installation, maintenance, and support of such software applications are difficult to provide and often lack funding. There are also concerns about initial installation costs and patient privacy. As the data usually have to be transferred manually, this creates additional workload for the staff. Therefore, to reduce the time-consuming and labour-intensive activity of manually copying the data from the paper forms into eCRFs, an

automated extraction from the primary clinical systems would be helpful [6]. This could lead to a reduction of transfer errors and workload and increase data quality and security.

The reuse of electronic health record (EHR) data, as obtained from eCRFs, is not only desirable for medical staff but also for the patients, as it could prevent duplication of patient examinations and thus reduce time and study costs. Studies have also shown that the automatic transfer of data from EHRs [7] into eCRFs can reduce data latency, transcription errors, missing data, the number of necessary database queries as well as staff time and effort [8, 9].

However, the exchange of medical data remains limited due to a lack of interoperability of data between healthcare providers. This may be due to outdated infrastructure or inconsistent data formats. Employing a harmonised data format would facilitate the exchange of medical data and enable both nationwide and international collaborations. Data interoperability requires EHR data to be structured in a common format and standardised terminol-

ogies. To this end, the Health Level 7 Fast Healthcare Interoperability Resources (FHIR) model was adopted [10, 11]. FHIR is an international standard that integrates diverse datasets into well-defined interchangeable segments of information called FHIR resources. This format facilitates interoperability and enables the harmonisation of data, which allows standardised data processing. Also, the rollout of artificial intelligence (AI) applications is possible across clinics and hospitals regardless of which information system is used there. Making such clinical data from the primary clinical information systems available to medical research in a standardised and harmonised way is the main goal of the German Medical Informatics Initiative (Medizininformatik-Initiative) [12].

In conclusion, standardisation and harmonisation of patient data are crucial for effective clinical research. The use of standardised forms and electronic data capture systems streamlines data collection and promotes consistency across hospitals and departments. Despite the advantages, challenges such as incomplete or incorrect data and difficulties with maintenance have been identified. Automated data extraction from primary clinical systems holds promise in reducing errors and workload. The adoption of Health Level 7 FHIR models supports data exchange and standardised processing, and promotes collaboration. This clinical data, along with the image data, the harmonisation and standardisation of which will be discussed in the next section, can then be used for collaborative research.

## Prospective harmonisation of image-derived parameters

In addition to the organisation and availability of the data, the content of the stored data is of course also a decisive factor for multiparametric or multicentre evaluations in medical research. Here, imaging data often form the basis or at least an important part. A thorough calibration of the imaging systems forms the basis for any multi-centre analysis. The basic requirement is that the imaging system has been commissioned and that a regular quality control (QC) protocol is in place to ensure that the system reliably provides qualitative clinical images (i. e., the distribution of counts in the subject). Once these conditions are met, an ideal prospective harmonisation of image-based parameters requires careful calibration (i. e., conversion of counts to activity) and a certain level of standardisation of the resolution between systems or sites. These two aspects will be described in this chapter (► Fig. 1B).

### Calibration of imaging systems

In nuclear medicine imaging such as PET/CT or SPECT/CT, tomographic reconstructions yield the number of counts measured by the detectors, typically corrected for the reduction in count rate caused by photon attenuation or scatter effects. In quantitative imaging, this count rate is typically converted to activity or activity concentration using an image-based calibration factor.

For SPECT/CT, this calibration factor is usually determined by scanning a phantom filled with a known activity. Ideally, the radionuclide calibrator used to measure the activity injected into the

phantom should be traceable to a primary standard of activity, providing harmonisation of activity measurements and thus the image-derived activity concentration across sites [13, 14, 15].

In PET/CT, the activity concentration is typically converted to the standardised uptake value (SUV), a semiquantitative measure of uptake in tissue. It is calculated as the ratio of the image-derived activity concentration (based on the calibrated imaging system) and the whole-body activity concentration of the injected radiopharmaceutical (the radionuclide calibrator-based activity administered to the patient divided by the patient weight). Most PET/CT systems are calibrated by cross-calibration with a traceable  $^{68}\text{Ge}/^{68}\text{Ga}$  source. For large phantoms (i. e., when minimising the partial volume effect [16]) this can lead to very accurate image-derived activities with a relative standard uncertainty of down to 1% [17]. To avoid systematic errors in SUVs between sites, care should be taken that a traceable radionuclide calibrator is used to measure the activity administered to the patient. The same applies to the weight of the patient, which should be automatically determined by a calibrated balance instead of, as is common practice, asking the patient, as this can also lead to substantial errors in SUV [18]. Finally, it should be ensured that the injected radioactivity as well as the times of activity measurement (administration of the therapeutic activity as well as start of imaging) are entered correctly in order to avoid unnecessary errors in SUV.

### Harmonisation of the image resolution

In addition to image calibration, which typically refers to the cross-calibration between the radionuclide calibrator and the imaging system, the harmonisation of image resolution and thus quantitative parameters that are spatially confined to smaller areas also plays a major role. This includes, for example, parameters derived from the SUV in spatially delineated volumes of interest such as SUVmax (voxel with the highest SUV), SUVpeak (mean SUV in a subregion around SUVmax), or SUVmean (mean SUV in the entire volume of interest). Adequate comparability between SUV-derived parameters can be achieved by harmonising patient preparation as well as acquisition and reconstruction parameters, as recommended, e. g., by the European Association of Nuclear Medicine Research Ltd (EARL) accreditation program for  $^{18}\text{F}$ fluorodeoxyglucose-PET/CT tumour imaging, which was launched in 2010, and updated in 2019 [19]. By setting limits of acceptability for recovery coefficients (SUV) of participating systems, the program has since helped to successfully harmonise the spatial SUV parameters of more than 200 PET/CT systems at more than 150 sites, located mostly in Europe [20, 21]. In the context of multicentre studies, which are likely to become increasingly important in the future, it is strongly advised that participation in such harmonisation programmes is given serious consideration.

Overall, the success of multi-centric research with image data heavily relies on the harmonisation of image parameters. To achieve accurate and standardised measurements across different imaging systems, standardised calibration procedures and effective quality control are required. The calibration of imaging systems through traceable radionuclide calibrators and cross-calibration methods ensures consistency in activity measurements.

Additionally, harmonising image resolution by aligning patient preparation, acquisition, and reconstruction parameters significantly enhances comparability. How these image data can be further harmonised and processed for use in machine learning models is described in the next section.

## Data preparation and harmonisation for multi-centre applications

The validity of Radiomics- and deep learning-based models relies on the reproducibility of image data including test-retest reliability [22, 23, 24] and comparability of image acquisition and reconstruction across different imaging systems and protocols [25, 26, 27, 28]. While variability in post-processing (e. g., volume segmentation, feature extraction, etc.) can be avoided by standardisation of procedures, variability in raw image data needs to be corrected (e. g., by retrospectively filtering the data to achieve a similar resolution across systems) [29, 30, 31, 32, 33].

To enable the multi-centric application of machine learning models (► **Fig. 1C**), one of the following approaches should be considered:

1. Aligning input data using harmonisation methods. These methods encompass not only prospective standardisation of image generation and processing techniques but also strategies for retrospectively assimilating image data.
2. Employing transfer learning. This involves leveraging knowledge gained from pre-trained models using data from one centre to improve performance when dealing with data from another centre.
3. Including information on machine/vendor/centre as additional model input. This is done by incorporating categorical features indicating the source of data in the machine learning model.

While harmonisation of input data must be performed before the training of clinical models, multi-centric information is considered in approaches (2) and (3) during the training of clinical models. For transfer learning, no central pooling of patient data is required. To enable a straightforward application of machine learning models to new centres without central pooling of patient data for methods (1) and (3), federated learning is highly relevant. Federated learning allows training of a model in several independent runs at each centre without the need for central data pooling. Considering that the most promising harmonisation methods themselves require training on patient data from different centres, this could be solved in the future either also by federated learning approaches or centralised processing of benchmark data generated using 3D-printed radioactive phantoms [34, 35, 36] in combination with PET data simulations adapted for each individual scanning device. While the concept of federated learning is methodologically sound – especially in light of the aforementioned harmonisation approaches –, a major bottleneck may prevent its widescale adoption: local patient demographics and the way patients approach or voluntarily delay contacting their healthcare providers, have profound implications for when and at which stage of the disease patients enter the loop of the respective clinical screening processes. In addition, local variations

in how those patients are treated have a major impact on the clinical outcome, and therefore, also on the clinical endpoint any multi-centric AI approach takes as input. In this regard, the incorporation of all locality-specific metadata (i. e., demographics, healthcare availability, clinical screening and treatment decision processes, etc.) in the AI analysis is a potential way to further enhance data quality and hence the ability to leverage multi-centric AI approaches such as federated learning. Extensive reviews on harmonisation strategies have been published [37, 38, 39]. These methods can be applied directly in the image domain or, for radiomics applications, also after feature extraction in the feature domain.

## Retrospective harmonisation of image data

As described in the previous section, a simple strategy to harmonise image properties is the standardisation of image acquisition and reconstruction protocols before data collection [40]. Although proactive harmonisation reduces information loss and should therefore always be performed, if possible, a study using 3D printed phantoms scanned on different devices has shown that even this approach could not eliminate all differences in radiomic features [33]. In the context of multi-centre studies, there is also the difficulty that the data are [mostly] collected and analysed retrospectively, but the raw data have already been deleted and thus harmonisation can no longer take place in this data processing step. In contrast, standardisation of image post-processing can always be performed. In the image domain, this comprises the interpolation of images to a specific voxel size and the standardisation of quantification procedures such as image normalisation or voxel-wise extraction of tracer kinetics. For example, it has been shown that even the choice of interpolation algorithm can affect feature comparability [41]. Moreover, filtering techniques can be applied to equalise image resolution and noise characteristics. This, however, results in a reduction of available image information. For example, texture properties can be smoothed out when wide filters (i. e., with large full width at half maximum) are required for sufficient image harmonisation [42].

Another recent approach is deep learning-based image harmonisation [43, 44, 45, 46, 47, 48]. These methods aim to generate harmonised images using deep networks such as convolutional neural networks (CNNs) or generative adversarial networks (GANs). Choe et al. [44] found a reduced effect of different CT image reconstruction kernels when applying CNN-based image conversion. Hognon et al. [43] first artificially generated a paired MRI dataset by applying unpaired image-to-image translation (CycleGAN [49]) to transform a multicentric MRI dataset into a standard domain. In a second step, they used these paired data to train a second network for paired image-to-image translation (pix2pix [50]). The second network then allowed to reduce the variability between domains while preserving the within-domain variability. Another group by Modanwal et al. [45] tackled the task of preserving the structure while harmonising MRI image properties (intensity and noise distribution) by introducing a CycleGAN that uses small patches of the input image. Zhong et al. [46] successfully employed a dual GAN approach to harmonise features derived from diffusion tensor images. Another architecture called

StarGAN v2 consisting of a style encoder, content encoder, generator, and discriminator was evaluated by Bashyam et al. [48] for the harmonisation of MRI images to improve cross-site generalisability of deep learning age prediction. Very recently, diffusion models have gained increasing interest in various tasks including image-to-image translation [51]. For example, it has already been applied for translation between multiple modalities [52, 53].

### Retrospective harmonisation of image-derived features

When radiomics are used for medical predictions, harmonisation can also be applied to the feature extraction process or the extracted features themselves. This includes the discretisation of intensity values (fixed bin width or the number of bins) [33, 54] and the application of standardised feature extraction methods as defined by the imaging biomarker standardisation initiative (IBSI) [55]. In case of volume-based radiomics, the choice of a standard procedure for tumour segmentation is essential [29, 56, 57]. When new radiomic features are established, availability of the methods and algorithms is required for final standardisation, which ideally is guaranteed through open access code or free software. Such methods comprise, e. g., dynamic radiomics [58], delta radiomics [59, 60], multi-modal radiomics [61], the application of voxel-wise texture information [62, 63, 64], or so-called deep features [65].

One approach to ensure the reliability of radiomic features is to select features for which statistical measures demonstrate high test-retest reliability and robustness between different machines, vendors, and centres, or to even design new features for specific purposes. However, this can result in the exclusion of clinically relevant features and thus unnecessarily reduce the clinical performance of models [66].

The ComBat harmonisation method has proven to be highly effective in removing the batch effects, i. e., variations in feature distributions obtained for different centres. This is achieved by estimating the shift and spread of feature value distributions [67, 68, 69, 70, 71]. One advantage compared to a simple z-score normalisation is that ComBat allows to consider variable frequencies of certain patient groups at different centres using a subcategory covariate [70]. Some variants of ComBat have been proposed [68, 72], the performance of which is yet to be validated by independent groups.

### Statistical measures of similarity

Various statistical measures have been applied to evaluate and compare the different image and feature harmonisation techniques. For example, ComBat has been shown to successfully improve feature similarity according to Friedman/Wilcoxon testing for paired data [67, 73] and ANOVA for unpaired data [68]. However, ComBat was not able to remove changes in the ranking of patients according to feature values arising, e. g., from different reconstruction settings. In other words, the correlation of features obtained for different settings could not be improved. It remains to be investigated if, for example, deep learning-based image harmonisation can be used to correct for both the batch effects and patient ranks simultaneously. Further frequently employed statistical measures for evaluating the robustness of radio-

mic features include the coefficient of variation (CV) and the intra-class correlation coefficient (ICC) [41, 74, 75]. This huge variety of statistical measures and their implications shows how important the correct choice of statistical metrics is for the assessment and optimisation of harmonisation techniques [33, 71]. Additionally, it is essential to conduct the final benchmarking of harmonisation strategies by evaluating their performance enhancement on specific clinical tasks using real patient data [68, 76, 77, 78, 79, 80].

In summary, ensuring the reliability and comparability of image data is paramount for the effectiveness of radiomics and machine learning in multi-centre applications. Approaches like data harmonisation, transfer learning, and integration of centre-specific information aim to enable robust model performance across different centres. Retrospective harmonisation methods, both in the image domain and in the feature domain, hold promise for aligning input data. While various statistical measures are used to evaluate these techniques, comprehensive benchmarking in clinical tasks using actual patient data is essential to validate their effectiveness. The challenge of harmonising data in the context of complex patient demographics and treatment processes requires the integration of site-specific metadata that could drive multi-centre AI. The corresponding projects and software tools are presented in the following chapter.

## Analysis projects with harmonised data

In the field of medical data science, data harmonisation facilitates the development of visualisations that provide an intuitive and comprehensive representation of complex interacting systems from multiple sources and sites.

When analysing multi-centric data (► **Fig. 1D**), a distinction can be made between a centralised collection of the data with subsequent analysis or a federated analysis, with the latter involving higher technical hurdles. In centralised analysis, on the other hand, there may be limitations due to data protection. Here, explicit consent may be required, but there are also initiatives, such as the German Medical Informatics Initiative, which promotes a large-scale collection of broad consent [81].

As an example, the Molecular Tumor Board Platform (Cancer Core Europe) started setting up a promising harmonised infrastructure in Europe for the exchange and use of next-generation sequencing data, automating the interpretation of results, promoting consistent decision-making, and enabling precision oncology [82]. Regarding distributed analysis, the ongoing project RACOON (Radiological Cooperative Network) in Germany established a nationwide infrastructure for structured reporting of COVID-19 related radiological data [4]. The harmonised data in this project enabled decentralised as well as centralised data analysis, resulting in various novel research findings [83, 84] and facilitating the development of powerful tools such as imaging-based severity predictors. Such tools, which rely on harmonised data (e. g., structured diagnosis), have proven crucial to improve data accessibility and interpretability and addressing the challenges and opportunities presented by the exponential growth of healthcare data today [4, 82, 85].

► **Table 1** FDA-registered medical devices with a focus on cancer-suspected lesions or image optimisation (as of July 2023).

FDA CFR Title 21 Section	FDA Product Code	Name	Number of registrations
892.2050	QKB	Radiological image processing software for radiation therapy	15
892.2060	POK	Radiological computer-assisted diagnostic software for lesions suspicious of cancer.	5
892.2080	QFM	Radiological Computer-assisted Prioritisation Software For Lesions	15
892.2090	QDQ	Radiological Computer Assisted Detection/diagnosis Software for Lesions Suspicious for Cancer	15
892.2100	QJU	Image Acquisition And/or Optimisation Guided By Artificial Intelligence	2

The availability of standardised clinical data also enables the utilisation of artificial intelligence models for clinical decision support. Machine learning and deep learning techniques play an increasingly important role in modern medicine. In the field of medical image analysis, standardised workflows based on deep learning, such as nnU-Net [86] and AUCMEDI [87], are becoming increasingly popular in radiomics as they provide automated artificial intelligence solutions to improve disease diagnosis, risk stratification, and – potentially – treatment recommendations. Standardised and harmonised clinical data not only facilitate the development of robust and strong predictors, but also enable the use and application of models across multiple sites [10].

## Applications of artificial intelligence in routine clinical care

The procedures described in the previous sections for standardisation and harmonisation of image data and associated clinical data, and the subsequent training of machine learning models, result in useful tools that need to be transferred from research to routine clinical practice. AI has the potential to revolutionise the interpretation and analysis of medical images, leading to better accuracy, efficiency, and patient care (► **Fig. 1E**) [88, 89]. These imaging and radiomics data could, for example, support clinicians in the diagnosis of cancer [90]. However, any software designed to diagnose, prevent, monitor, predict, or treat a disease is considered a medical device and must be approved as such [91]. This approval process requires a high level of accountability for the software to minimise the risks of false results, which can be achieved through extensive risk mitigation. One potential way to mitigate usability-related risks is investing efforts into explainable AI [92] and the widescale utilisation of domain experts in both the development as well as the independent validation phases of medical devices [93]. Uncertainty analysis can help to provide insights into the reliability of predictions and foster trust in the technology's outcomes [94]. Various AI-driven medical devices have been recently approved that can be used in routine clinical care [95]. These software products are typically classified as class 2 medical devices by the United States Food and Drug Administration (FDA). The product groups with a focus on cancer-suspected lesions or image optimisation are listed in ► **Table 1**. Since the legal situa-

tion in Europe regarding the use of AI in medical devices is not yet as advanced as in the United States, market research is difficult, but it can be assumed that AI-based evaluation tools that are approved by the FDA will eventually also be approved for the European market. In this regard, endeavours to approve medical devices by European notified bodies have increasingly become a challenge for two main reasons. On the one hand, the number of approval requests has been sharply increasing, which has prevented notified bodies from reacting adequately. As a result, the ever-increasing backlog of European notified bodies may leave any medical device manufacturer with a straight refusal due to time constraints. On the other hand, the applicable laws within Europe are becoming more and more tightened, while the FDA is making significant efforts to continuously update and properly guide and ease certain approval processes within the USA [96].

A large proportion of approved products are used in radiology with a focus on oncology [97]. However, for artificial intelligence, appropriate training and validation data are needed, which can be provided through the harmonisation and interoperability methods presented here. With the support of software tools in diagnosis and therapy, a minimum standard independent of the physician's experience or other local factors that influence the quality of medical care can be achieved and thus health equity can be approached [98]. Regarding the occurrence of different medical software categories, a clear trend is visible towards detecting and characterising suspicious lesions, as well as supporting radiotherapy planning, while AI-driven image acquisition approaches are to date underrepresented, giving an obvious priority to AI-driven clinical decision support.

## Conclusion

By establishing standardised protocols, formats, and data structures, harmonisation enables research between different devices, institutions, and research facilities. This promotes collaboration, facilitates data sharing, and supports the development of advanced analytical techniques, leading to improved patient care, better research outcomes, and overall advancement in nuclear medicine. Harmonisation also improves the accuracy, consistency, and reliability of data, enabling more effective diagnosis, treatment planning, and patient monitoring. Therefore, investing in initiatives and technologies that promote the harmonisation of

nuclear medicine image data and associated clinical data is paramount to driving innovation to realise the full potential of nuclear medicine in modern healthcare. In addition to the above endeavours, properly handling significant local demographics-based variations across different centres that attempt to harmonise their data for multi-centric evaluations remains a major challenge. Beyond technological or local demographic variations, the reaction time gap between FDA and European notified bodies is a major disadvantage for European medical device manufacturers and patients warranting a fundamental overhaul of European medical regulatory processes for the benefit of patients.

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## Conflict of Interest

L. Papp is co-founder of Dedicaid GmbH, Austria (wholly-owned by Telix Pharmaceuticals Ltd)

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