MEDIDATA / Rave

WHITE PAPER

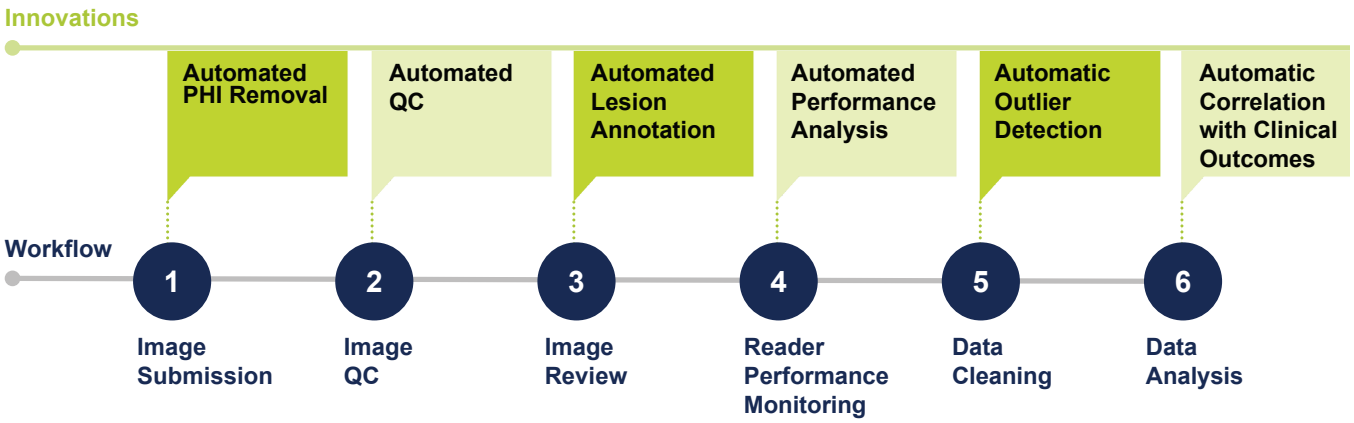
Innovations in Clinical Trial Imaging – Today and Beyond

Table of Contents

For the first 125 years of medical imaging, technological advances focused primarily on new modes of imaging as we progressed from the discovery of the X-ray in 1895 to ultrasounds, MRIs, PET, and CT scans in the late 20th century. Now, arguably, the most notable advances are being made in how images from those technologies are securely shared, managed, stored, and assessed.

These advancements are largely due to the application of Artificial Intelligence (AI) and Machine Learning (ML) to imaging systems and data platforms. Automation is improving virtually every stage of the imaging workflow, as seen in Figure 1. Sponsors can benefit from improved compliance with privacy regulations, stronger data quality controls, more accurate and efficient imaging reads, and advanced data analysis for improved decision making. The following paper outlines some of these advancements that are in various stages of development, some of which are available today and others expected to be in operation in the near future.

Figure 1: Automated Touchpoints in the Imaging Workflow



Advances in Image Data Privacy, Collection, Acquisition and Interpretation

PROTECTING PERSONAL HEALTH INFORMATION

Data privacy regulations in the US Health Insurance Portability and Accountability Act (HIPAA) and in the EU (GDPR), require that personal health information (PHI) be redacted from clinical trial data. If all identifiers are stripped from health information and an individual cannot be identified from it, HIPAA privacy rules no longer apply.[1] In the EU, the General Data Protection Regulation (GDPR) prohibits the collection, processing and sharing of personal data unless certain exceptions apply.[2]

Clearly, PHI must be stripped from medical image files before they can be transferred from clinical trial sites to a central lab, Contract Research Organization (CRO), or Sponsor. While investigator sites are required to do this, their approaches are not always fool proof, and it is possible for some PHI to slip through, and oftentimes, it does so without warning. Such incoming data thus needs to be double-checked and scrubbed of any PHI that was not caught by the site. Traditionally, this second review has been done manually by an imaging core lab or other designee. However, it is possible for an algorithm to automatically detect and remove PHI from Digital Imaging and Communications in Medicine (DICOM tags) and pixel data before it's transmitted to other users. See example in Figure 2. It will be important for clinical trial imaging software and AI algorithms to support these practical use cases. The application of such an algorithm will help ensure compliance with all data privacy regulations and remove any opportunity for human error in the review step.

Figure 2: Example of Redaction on Image

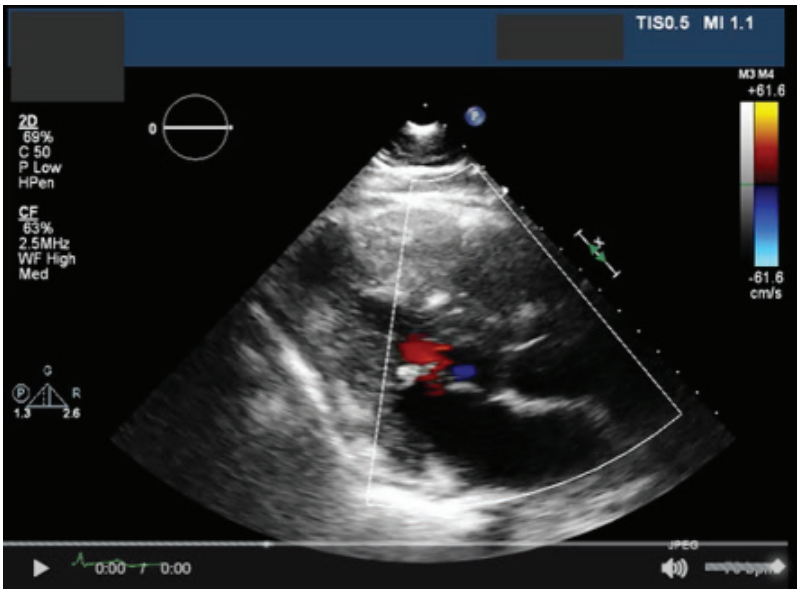


IMAGE QUALITY CONTROL

The standard quality control process for medical images generated in a clinical trial is for incoming images from trial sites to be reviewed against a variety of quality control parameters. For example, in a standard oncology trial, the following parameters are typically confirmed: anatomical coverage, contrast enhancement, scan parameters, field of view, and patient consistency over time. All are critical to ensuring a subsequent accurate assessment by a radiologist and to collecting clinical trial endpoints of good quality and avoiding unevaluable data.

Traditionally, this quality check has been performed by a technician or imaging specialist trained in the imaging modality. This step not only takes time, but involves some subjective judgement on the part of the reviewer. In the near future, it will be possible for a computer program to perform this step automatically, using AI and ML. In essence, the program would scan the image and evaluate it objectively against specific quality measures and determine if it meets the required standards. Any shortcoming would be identified and presented to the user. This would not only speed the process of providing feedback to sites, but would remove a level of subjectivity in quality control, helping to ensure that all images meet the required standards and are evaluable.

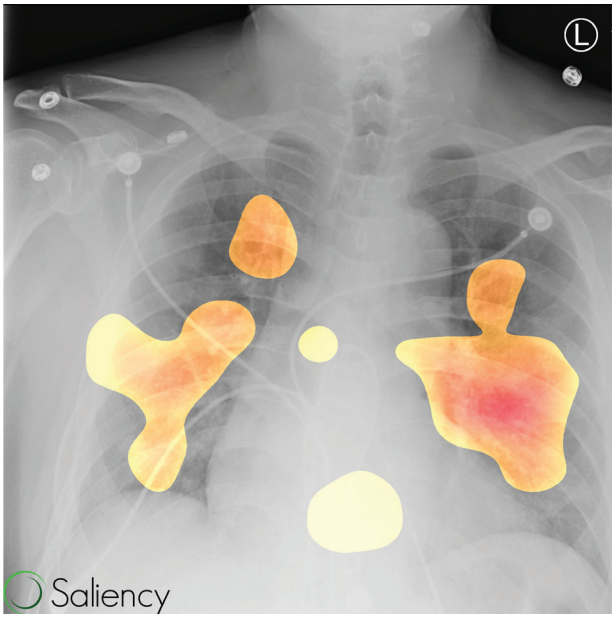
SUPPORTING RADIOLOGIST ASSESSMENT

AI/ML algorithms are being developed and perfected to aid radiologists in their assessments by performing automated measurements according to the relevant assessment criteria (for example, RECIST, Lugano, RANO, etc. for oncology assessments). In the envisioned ideal capability, the software will identify, premeasure, and categorize anatomy for presentation to the radiologist in Medidata's web-based viewer. The radiologist would then review the algorithm's work and either approve it or modify it as he/she sees fit. This would obviously save time and money, as radiologists can be one of the trial's most expensive resources. Just as important, it would also reduce the variability between readers by presenting them with consistent lesion identification for oncology assessments.

The FDA supports computer-assisted image interpretation, stating that it "may form an important component of the read process." See Figure 3 for an example of how algorithmic results are used in diagnosis. The agency requires that the extent of computer assistance be described within the project specific imaging charter in a manner that clearly documents the roles of the reader and the reading tool.[3]

Figure 3: Sample of Algorithm Results(AI)

For an input X-ray, the neural network-based algorithm outputs the probability of each potential diagnosis. It also highlights the regions of the image that are indicative of the most likely diagnosis (shown here).[4]



REMOTE IMAGE REVIEWS

Radiologists use a variety of viewers to analyze medical images – some core labs may need to maintain several different software tools in order to accommodate the different trials they're involved in and each tool is very expensive! Many of these viewing tools today must be physically installed on a workstation, which limits where reviews can be performed and limits the reader pool that can be used to perform image analysis. Viewers that can be accessed remotely offer limited options and may require users to use a virtual private network (VPN) or some other remote connection tool. We foresee that image analysis tools will transition to cloud-based solutions so that they can be accessed from any device, anywhere, by any reader.

ANALYZING IMAGES WITH RADIOMICS

One of the latest developments in imaging is the field of radiomics which uses high-throughput technology "…to extract minable, high-dimensional data from clinical images" whereby the software finds associations between qualitative and quantitative information extracted.[5] Through the use of algorithms, the process is capable of finding clinically essential information that is not detectable by the human eye to objectively describe the tumor phenotype.[6] Algorithms can automatically extract tumor feature information and can make clinical outcome assumptions and correlations based on that detail. For example, they can, through the spatial arrangement of the intensity values at the voxel level, characterize the texture of a tumor.[7] Radiomics is currently being studied in CT-scan and MRI imagery.

The radiomic data extracted from digital images can be integrated with genomic data to guide a highly personalized course of treatment for a patient.

Future applications of radiomics include:

- Predicting tumor stage;
- Distinguishing between healthy and pathological tissue, thus eliminating the need for invasive biopsies, e.g., Nonalcoholic steatohepatitis (NASH);
- Detecting genetic characteristics; and
- Predicting response to treatment, patient survival, and drug side effects.[8]

Extracting radiomic data from imaging is possible today, however the challenge is in operationalizing it for use in clinical trials. Medidata's cloud-based imaging workflow management and viewing tools available within Rave Imaging, as well as our ability to integrate with our Rave EDC and Mediadta Detect products, uniquely position Rave Imaging to serve as a tool that can effectively analyze and extract radiomic data from clinical trial images and then automatically correlate it with clinical outcomes.

Advances in Image and Data Quality Control and Analysis

AUTOMATIC OUTLIER DETECTION IN IMAGING DATA

Using sophisticated statistical algorithms and machine learning analytics, it is possible to interrogate imaging data for outliers, data anomalies, and trends. The system automatically learns the proper ranges for all data fields and detects outliers and flags any data outside of the acceptable parameters. This can be used to:

- Uncover data entry errors
- Identify patterns in reader assessments (for instance if adjudicated cases always support one reader over another)
- Spot a lack of standardization of applied read criteria

Such algorithms can help detect these issues early on, allowing sponsors, CROs and/or core labs the ability to remediate these issues before there is a large impact to the data.

MONITORING READER PERFORMANCE

Despite the application of standardized criteria on how images should be interpreted, many measures require radiologists to make some subjective judgements. Thus, there is always some level of variability in assessments from one reader to the next. These variations can be mitigated by introducing a third reader to adjudicate differences between the two primary readers, however even in these situations, reader performance needs to be monitored carefully to ensure that readers are accurately applying the chosen criteria.

Algorithms can be developed that can automatically identify patterns that suggest a deviation from the imaging criteria, allowing early remediation of these issues. Ideally, the results are presented in a dashboard and updated in real time, proactively to identifying anomalies before they become systemic issues.

CORRELATING IMAGING DATA WITH CLINICAL DATA

Because historically, imaging data and clinical data reside in two different systems that are not integrated, it has been onerous for Sponsors to analyze both data sets together. Even when imaging and EDC systems are integrated, as is the case with Rave Imaging and Rave EDC, data managers and statisticians still have to sift through the data to identify meaningful correlations. We predict that in the very near future, AI/ML algorithms will be developed that can automatically discern meaningful correlations and present them to sponsors. This will give Sponsors the ability to identify correlations that may have otherwise been missed, for example, being able to identify clinical similarities in patient subsets that can provide more information as to why they may or may not be responding to treatment.

Summary

The advances discussed here have the potential to transform not only how imaging data for clinical trials is collected, processed and analyzed, but also how the imaging data is cleaned and correlated with clinical outcomes. Some of these products are available now in a limited capacity and others are longer- term goals for the industry. However, given Medidata's integrated cloud-based clinical trial solutions, we are well positioned to operationalize these offerings in a way that is simple and scalable. It will be important for Sponsors to work with vendors who not only offer the latest appropriate technology, but the wherewithal to operationalize it… to apply it to scale in a compliant way that is reproducible.

RAVE IMAGING HAS RE-ENGINEERED CLINICAL TRIAL MANAGEMENT

Medidata Rave Imaging is changing the way the industry thinks about imaging in clinical trials. Our system's intelligent workflows simplify image and data collection and are configured to immediately perform edit checks and de-identification during the image upload process. It then automates the distribution and review process after upload, per the protocol design to ensure that the most accurate data is distributed to the right users at the right time.

This automated and structured approach helps study managers meet their study goals by:

- Reducing the query rate, dramatically
- Supporting on-time completion of all image-related steps in the clinical trial
- Minimizing the risk, error-rate, and complexity of medical image management
- Minimizing data entry and workflow steps

Rave Imaging works with any network, any image format, and any data set, making it a truly scalable system.

For more information on how Rave Imaging can transform image management in clinical trials, visit our website, www.medidata.com.

Endnotes

1. https://www.hipaajournal.com/what-is-considered-protected-health-information-under-hipaa/

2. https://gdpr-info.eu/art-4-gdpr/

3. "Clinical Trial Imaging Endpoint Process Standards: Guidance for Industry," US Food and Drug Administration, April, 2018.

4. Assessment results performed by Saliency Algorithm.

5. Rizzo S, Botta F, Raimondi S, et al. Radiomics: the facts and the challenges of image analysis. Eur Radiol Exp. 2018;2(1):36. Published 2018 Nov 14.

6. Meng, Yiming et al., "Application of Radiomics for Personalized Treatment of Cancer Patients, " Cancer Management and Research, 2019:11 10851 – 10858.

7. Rizzo S, Botta F, Raimondi S, et al. Radiomics: the facts and the challenges of image analysis. Eur Radiol Exp. 2018;2(1):36. Published 2018 Nov 14.

8. Meng, Yiming et al., "Application of Radiomics for Personalized Treatment of Cancer Patients, "Cancer Management and Research, 2019:11 10851 – 10858.