Artificial Intelligence Technologies and Their Applications in Healthcare Settings

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The Past

Surging Number of Medical AI Research

- Explosion of Medical AI Research

Source: Bertalan Meskó et al., npj Digital Medicine (2020), The Medical Futurist (2019)
First FDA Approved AI SaMD in 2017

Guidance for Industry and Food and Drug Administration Staff

Computer-Assisted Detection Devices
Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions

Document issued on: July 3, 2012

The draft of this document was issued on October 21, 2009.

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Division of Radiological Devices
Office of In Vitro Diagnostic Device Evaluation and Safety
The Past

Regulatory Approval of AI SaMD

- Regulatory Authorized Medical AI

How medical AI devices are evaluated: limitations and recommendations from an analysis of FDA approvals

A comprehensive overview of medical AI devices approved by the US Food and Drug Administration sheds new light on limitations of the evaluation process that can mask vulnerabilities of devices when they are deployed on patients.

Eric Wu, Kevin Wu, Roxana Daneshjou, David Ouyang, Daniel E. Ho and James Zou

Medical artificial intelligence (AI) algorithms are being increasingly proposed for the assessment and care of patients. Although the academic community has started to develop reporting guidelines for AI clinical trials, there are no established best practices for evaluating commercially available algorithms to ensure their reliability and safety. The path to safe and robust clinical AI requires that important regulatory questions be addressed. Are medical devices able to demonstrate performance that can be generalized to the entire intended population? Are commonly faced shortcomings of AI (overfitting to training data, vulnerability to data shifts, and bias against underrepresented patient subgroups) adequately quantified and addressed?

In the USA, the US Food and Drug Administration (FDA) is responsible for approving commercially marketed medical devices while European authorities have the corresponding role in Europe. Since the first approval of a machine learning (ML) algorithm-based medical device in 2015 – the Zephyrchest® – over 220 devices have been approved by the FDA. Over the same period, the EU has approved 240 medical devices that employ AI/ML-based technologies across 16 different categories. It should be noted that CE mark approval by the European Union is considered a surrogate for FDA approval in the USA. For further information, see the AI for Radiology website.

Source: Eric Wu et. al., Nature Medicine(2021), Urs JMuehlematter et. al., Lancet Digital Health(202)
Regulatory Authorized Medical AI

Original Research

FDA-regulated AI Algorithms: Trends, Strengths, and Gaps of Validation Studies

Shadi Ebrahimian, MD, Mannudeep K. Kalra, MD, Sheela Agarwal, MD, Bernardo C. Bizzó, MD, Mona Elkholy, MS, Christoph Wald, MD, Bibb Allen, MD, Keith J. Dreyer, DO, PhD

TABLE 1. Summary of FDA Regulated Software Across Different Function, CAD, and AI Groups. Some Algorithms Performed More Than One Functions. (NA- not applicable for non-AI-based software)

<table>
<thead>
<tr>
<th>Factors</th>
<th>FDA-regulated Software (Whether AI/ML-based)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functions</td>
<td>Characterization 13</td>
</tr>
<tr>
<td>CAD category</td>
<td>CADI 27</td>
</tr>
<tr>
<td>Al categories</td>
<td>AI-De 18</td>
</tr>
</tbody>
</table>

Figure 2. Summary of specific target findings evaluated by the FDA-regulated AI/ML algorithms. AI/ML, artificial intelligence/machine learning; FDA, Food and Drug Administration.

Source: Shadi et. al., Academic Radiology(2022)
First MFDS Approved AI SaMD in 2018
The Present

Medical AI is Nothing New

Source: 식약처(2020, 2021)
**Solution Overview**

**VUNO Med® - Chest X-Ray™**
- AI-based diagnostic support system for abnormalities in Chest X-Rays
- Detects five critical thoracic findings* 
- Displays abnormality areas and abnormality scores (%)
- Used 100% CT confirmed images taken with imaging equipment from 15+ global vendors
- 0.985 AUROC per-image, 0.943 JAFROC FOM per-lesion

* Nodule/Mass, Consolidation, Interstitial Opacity, Pleural Effusion, Pneumothorax

**Upcoming Updates**
- Additional Thoracic Abnormal Findings (11)
  - Nodule/Mass, Consolidation, Interstitial Opacity, Pleural Effusion, Pneumothorax, Atelectasis, Calcification, Rib Fracture, Mediastinal Widening, Pneumoperitoneum, Cardiomegaly
- Disease Diagnosis (2)
- Trained on +100K images

**VUNO Med® - LungCT AI™**
- AI-based detection solution for pulmonary nodules in chest CT scans with nodule RADS score and malignancy prediction capabilities
- Detects nodules between 4mm ~ 30mm within 1 minute with high sensitivity
- Provides volumetric data of nodules and data on the types of nodules
- Provides baseline scans and follow-up data for nodule growth assessment (Can match the scans pixel to pixel)
VUNO Med® - BoneAge™

Solution Overview
- Korea’s 1st AI-based medical device approved by MFDS
- Assesses the skeletal age of a child and compares it against his chronological age
- Enhances clinical efficiency by improving reading time and accuracy
- Deep-learning based automatic Bone Age Assessment software that supports both GP and TW3 methods
- Provides a comprehensive patient report including growth charts and expected adult height using actual age, current height and gender
- Used 50,000+ images collected from Korea and US to ensure stable performance across races

VUNO Med® - DeepBrain™

Solution Overview
- Deep-learning based brain parcellation for the quantification of brain atrophy and diagnosis of neurodegenerative diseases
- Segments the brain into over 100 parts to provide information of brain atrophy
- Provides volumetric information on areas, cortical thickness data of cortex area from 0mm, ICV ratio, and WMH (White Matter Hyperintensities) associated with degenerative brain diseases
- A comprehensive report with atrophy information in comparison with normal group
- Processing time is less than 1 minute per case
VUNO Med® - PROMISE-I

Solution Overview

- AI-based image analysis solution that automatically analyzes associated regions for prostate cancer in MR images
- Consistency rate above 90% compared to radiologists
- Solution is intended to help medical professionals diagnose prostate cancer and determine the target biopsy areas

VUNO Med® - FundusAI™

Solution Overview

- Korea’s 1st “Breakthrough medical device” and non-radiology AI medical software obtained Class III approval
- Detects and locates 12 fundus abnormalities associated with retinal disease within 2 seconds
- Adjust the sensitivity of each findings based on clinical needs: Low (75%), Mid (85%), High (95%)
- Trained on 103,262 fundus images with 57 Ophthalmologists participated in the research: 16 Retina specialists, 9 Glaucoma specialists, 3 Corneal specialists
- Report provided to patient for further consultation

User Interface

Clinical Validation

User Interface

Report
Solution Overview

- Provides the number and ratio of cells expressed in immunohistochemistry (IHC), which is widely used for the diagnosis of various types of cancer, for biomarker analysis which shortens the reading time and provides consistent quality analysis
- Accuracy above 90 percent in detecting cells compared to that of clinical pathologists

Clinical Validation

- VUNO Med DeepCARS™ measures and predicts the real-time risk of cardiac arrest of patients in the general wards through 4 vital sign (blood pressure, HR, respiratory rate, body temperature) observation, and provides a risk score from zero to 100.
- The first AI-based SaMD waived for new health technology track in Korea
Emerging Technologies in Healthcare

- Hype Cycle of Emerging Digital Health Trends

Source: The Medical Futurist (2021)
### Diagnostic Imaging Workflow

- **Patient Record**
  - Decision to image
  - Best use criteria

- **Scheduling**
  - Inpatient scheduling
  - Appointment booking

- **Acquisition**
  - Automated acquisition
  - Dose reduction
  - Scan time reduction

- **Processing**
  - Post processing
  - Registration

- **Perception**
  - Segmentation
  - Detection
  - Quantification

- **Reasoning**
  - Diagnostic inference
  - Decision making

- **Reporting**
  - Documentation
  - Synoptic reporting

- **Communication**
  - Results communication
  - Actioning
  - Patient information

Source: Hugh Harvey (2018)
AI-enabled Medicine

Hyper Competition

- Cheaper, Connected, and AI-Enabled Medical Devices

Source: Butterfly, Hyperfine, Tesseract, Nanox (2021)
Making Existing Medical Devices Smarter using AI

Source: VUNO, Huvits, Rayence (2021)
AI-enabled Medicine

### Intelligent Imaging Acquisition

#### Making Imaging Acquisition Smarter with Quality

**Scan with Confidence**

Caption AI emulates the expertise of a sonographer by providing real-time guidance that prompts users to make specific transducer movements to optimize and capture a diagnostic-quality ultrasound image.

**Capture with Quality**

The Quality Meter shows users in real-time how close they are to capturing a diagnostic-quality ultrasound image. The meter rises as the user gets closer to the optimal view, turning green when the image is deemed diagnostic. AutoCapture then records the clip, hands-free.

**Never Lose the Best**

Caption AI continuously keeps track of the best images seen during each scanning session so the best image from each view is automatically captured. Users have the freedom to explore each view with the reassurance that they can always access the best two-second clip seen during their scan at the touch of a button.

**Automate Interpretation**

Caption AI automatically calculates ejection fraction while scanning from any combination of up to three cardiac views commonly acquired at the point of care: apical 4-chamber (AP4), apical 2-chamber (AP2), and an industry-first—parasternal long-axis (PLAX). It’s as quick as a visual assessment, with comparable performance to an expert.

**Scan your Way**

Caption AI gives users the flexibility to create and follow a customizable indication-based or workflow-based protocol of ultrasound views. While scanning, users can easily skip to the view they need.

**Start Smart**

Begin every exam with a probe positioning diagram indicating where to place the ultrasound transducer. A reference image provides a visual example of what to look for while scanning.

Source: Caption Health (2021)
Introducing a new era of image reconstruction.

Training Phase in Factory
Using high-quality images, Advanced Intelligent Clear Engine (AICE) learns to differentiate between signal and noise in low-quality images.

Operational Phase in Clinic
Using the intelligence from the Training phase, AICE has the potential to aid in fast and confident clinical results by providing high-quality images.

Source: GE, Cannon (2021)
Making Existing Medical Devices Faster or Safer using AI

Source: Subtle Medical, AIRS Medical (2021)
Medical AI for Population Health

In a landmark approval, the American Medical Association (AMA) issued a specific CPT code for AI-based automatic analysis of VCFs, an early sign of osteoporosis. This is an important step in proper risk-adjustment of populations towards widespread preventative care, and a game changer in the long-term management of this terrible disease.

*Effective January 1, 2022.

“The CPT is named “Cat III-Accurate Augmented Intelligence Analysis,” and defined as “Accepted addition of code 00367 to report an automated analysis of an existing computed tomography study for vertebral fractures.”

Source: Zebra Medical Vision(2021)
Medical AI for Cancer Risk Stratification

PRESS RELEASE: CMS assigns new technology payment classification for Optellum’s Lung Cancer Prediction score

Rhiannon Lassiter - June 28, 2022 - Medical / News & PR / Regulatory

How to compute the score for one or more nodules of interest

- **Patient scan**
  - The CT and any prior scans are automatically uploaded in Virtual Nodule Clinic.

- **Identify nodule**
  - Easily review any available CT and mark the nodule(s) of interest.

- **Optellum Lung Cancer Prediction score**
  - Within seconds, the Optellum Lung Cancer Prediction analyzes the 3D image region around the nodule to compute the score.

- **Optimal clinical decisions**
  - With the support of the Optellum LCP score, make the optimal clinical management decision for the patient.

Source: Optellum(2022)
Digital Pathology Workflow with Advanced Analytics

**Analogue to digital conversion**
The renal biopsy glass slide (input) is converted into a digital WSI (output).

**Knowledge extraction**
The WSI input is transformed into meaningful knowledge (output) using AI and visual assessment.

**Knowledge integration**
Fused knowledge from WSI and other domains (input) becomes actionable intelligence for patient care (output).

**Discovering pathomics**
Convolution and activation
Pooling
Up-sampling

**Hand-crafted pathomics**
Whole slide image
Kidney biopsy procurement

**Clinical knowledge**
Machine learning models
Data transcription
Data translation

**Digital pathology-derived knowledge**
Pathomic feature space
Data transcription
Data translation
Visual assessment

**Other omics knowledge**

Source: Laura Barisoni et al., *Precision Medicine in Nephrology*, 2020,
Andrew Janowczyk et al., *Journal of Pathology Informatics*, 2015
Clinical applications of basic and advanced deep-learning (DL) image analysis in histopathology.

Source: Amelie Echle et al., British Journal of Cancer, 2020
FDA Authorizes Software that Can Help Identify Prostate Cancer

For Immediate Release: September 21, 2021

Today, the U.S. Food and Drug Administration authorized marketing of software to assist medical professionals who examine body tissues (pathologists) in the detection of areas that are suspicious for cancer as an adjunct (supplement) to the review of digitally-scanned slide images from prostate biopsies (tissue removed from the body). The software, called Paige Prostate, is the first artificial intelligence (AI)-based software designed to identify an area of interest on the prostate biopsy image with the highest likelihood of harboring cancer so it can be reviewed further by the pathologist if the area of concern has not been identified on initial review.

“Pathologists examine biopsies of tissue suspected for diseases, such as prostate cancer, every day. Identifying areas of concern on the biopsy image can help pathologists make a diagnosis that informs the appropriate treatment,” said Tim Stenzel, M.D., Ph.D., director of the Office of In Vitro Diagnostics and Radiological Health in the FDA’s Center for Devices and Radiological Health. “The authorization of this AI-based software can help increase the number of identified prostate biopsy samples with cancerous tissue, which can ultimately save lives.”

Source: paige.ai, FDA(2021)
### Regulatory Approved/Certified Solutions for Precision Pathology

**Bjorn, Digital pathology certified AI software validation**

Source: 식약처(2020), 청년의사(2021), FDA(2021)
Toward Integrated/Predictive Modeling using Multi-modal/Multi-omic Data

Source: Nathaniel Braman et. al., MICCAI (2021)
Virtualized Medicine
Virtualized Patient

- Enhanced diagnosis and personalized treatments through virtual testing and optimization of treatment prior to the actual delivery using digital twin of patient

Towards Personalized Cardiology: Multi-Scale Modeling of the Failing Heart

Elham Kayvanpour1,2,*, Tommaso Mansi1,2, Farbod Sedaghat-Hamedani1,2,*, Ali Amy1,2, Dominik Neumann1,2, Bogdan Georgescu1,2, Philipp Seegerer1,2, Ali Kamen1,2, Jan Haas1,2,*, Karen S. Frese1,3, Maria Irawati1, Emir Wirasz1, Vanessa King1, Sebastian Buss1, Derliz Mareles1, Edgar Zitron1, Andreas Kellner1, Hugo A. Katus1,2,*, Dorin Comaniciu1, Benjamin Meder1,2,*,

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v-Patients by Virtonomy is a library of common variations to help medical equipment makers test conduct studies on how these variations may affect the performance and safety of new devices.
• Identify maintenance needs before they arise using a virtual representation of a device

The challenge is to identify potential problems before they occur, so you can schedule maintenance at a time when the equipment is not in use.

By running simulations on virtual prototypes of the device, we were able to perform tests that would have taken months and several iterations if we had to build physical prototypes first.

The four components of a digital twin of a device

1. Device data
2. AI / Data analytics
3. Device knowledge
4. Physics-based device modeling

Source: Philips (2018)
Virtualized Medicine

Virtualized Hospital

- Virtual hospital models help to plan the beds, schedules of staff, and operating rooms to maximize the care to patients while keeping a check on the costs.

Source: GE Healthcare (2017),
Conclusion

Level of Evidences for New Diagnostic Technology

- QUALITY = OUTCOMES + PATIENT EXPERIENCE
- COST = DIRECT COSTS + INDIRECT COSTS

Source: RAS LLS (2019)

Source: G. Scott Gazelle et al., Radiology (2011)
Conclusion

Future Direction in AIMD/Digital Healthcare

**Convergent/Translational Medical Device/Digital Healthcare Research**

**Trustworthy SaMD**
- Explainable Prediction
- Uncertainty Quantification
- Calibrated Output
- Fairness/Bias Awareness

**Integrative Medicine**
- Multi-modal Fusion
- Multi-omics Approach
- Prognostic Biomarker
- Therapeutic Support

**Virtualized Medicine**
- Virtualized Patient
- Virtualized Devices
- Virtualized Hospital
- Virtualized Treatment

**Medical/Healthcare Data**
- Medical Image
- Electronic Medical Records
- Genomic Data
- Patient Generated Health Data

**Data-driven Analytics**
- Nonlinear Optimization
- Data Mining
- Machine/Deep Learning
- Artificial Intelligence
Thank you!

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