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Regulatory Implications of AI Model Sharing and Transfer Learning

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Background

- Imaging AI as an FDA-regulated device
- Types of imaging AI
- FDA's approach to AI-based image analysis
- Challenges with the current regulatory paradigm
- Moving forward with imaging AI

Imaging AI as Medical Device

- Broad definition of a medical device:

  [A]n instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

  - recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
  - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
  - intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and

  which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o).

- No exemptions under the 21st Century Cures Act: Image analysis specifically excluded
- Does not qualify as a PACS device or medical device data system (MDDS)

Imaging AI as Medical Device

- Requirement for FDA regulation: Interstate commerce
  - Federal regulatory authority based on commerce among the states
  - Liberally interpreted
- Development at a local institution
  - FDA regulatory authority may be questioned
  - Viable argument that use within a given institution does not qualify as interstate commerce
  - FDA position on use within a given institution is mixed
- Caveats
  - Transfer outside of a given institution
  - Adverse events

Imaging AI as Medical Device: Regulatory Paradigms

- 510(k) pathway
  - Must be substantially equivalent to existing, 510(k)-cleared device (known as a "predicate") in terms of indications for use and technological characteristics
  - Preferred pathway by the Division of Radiological Health for computer-assisted image analysis (CAD)
- De novo reclassification
  - Appropriate for low to moderate risk devices for which there is no predicate
  - Frequently used by FDA for CAD products that lack a predicate
- Premarket market approval (FDA)
  - Applied to high risk devices
  - Current trend is to move away from the PMA pathway for CAD devices

Imaging AI as Medical Device: Supporting Data

- Software documentation consistent with FDA's May 2005 Software Guidance
  - Typically moderate level of concern
- Standalone performance testing
  - Required supporting data for all types of CAD devices
  - Involves running a CAD algorithm past a database of "truthed" cases for which a diagnosis has been established
  - Performance typically expressed in terms of sensitivity and specificity
- Clinical performance testing: Reader study
  - Typically required where there is some interpretation of results, i.e., marks on images
  - Involves multiple readers reviewing truthed cases before and after application of the algorithm
  - Seeks to demonstrate improvement in results, typically in terms of improved area under an ROC curve

Imaging AI as Medical Device: FDA Expectations

- Algorithm is frozen at time of the marketing submission
  - AI can be used to evolve the algorithm during development
  - Consistent with long-standing FDA policy that final, finished devices are cleared or approved, and not concepts
  - Reflects the need for FDA to evaluate existing performance
- Final pivotal testing is conducted on a dedication validation dataset(s)
  - Cannot mix training and final validation data
- All relevant testing must be completed with the frozen algorithm at the time that a marketing submission is filed
  - FDA will not conditionally clear or approve medical device
  - Concern that products reach the market only to have subsequent data demonstrate a lack of safety or effectiveness

Approach to AI: Computer Assisted Triage (CADt)

- Alerts a radiologist or other professional to the potential presence of an abnormality in a study prior to any review of the images
  - New type of CAD technology
- Does not mark the image
  - Can provide a non-diagnostic “preview” image(s) that displays images that triggered the alert
- Can be supported by standalone performance testing alone
- Examples: Viz.ai, Aidoc, MaxQ

Approach to AI: Computer Assisted Detection (CADe)

- Marks images with potential areas of abnormality for professional interpretation
  - Often positioned as “second read”
  - Represents traditional CAD technology
- Typically requires standalone performance testing and a reader study
- Example: Mammography CADe, CTC CAD

Approach to AI: Computer Assisted Diagnosis (CADx)

- Variable output but typically includes a diagnosis and/or confidence level in that diagnosis
  - May mark images as well with potential areas of abnormality, heat maps, etc.
  - May or may not involve review of the results by a professional
- Always requires standalone performance testing
  - Depending on the indication, this may be considerably more involved than CADt standalone performance testing
- May require a reader study if images are marked
- Example: QuantX

Challenges to the Current Paradigm: Supporting Data

- FDA's current approach is indication-specific
  - This means that each condition evaluated requires a specific data set and dedicated study
  - Based in the belief that multiple conditions can bias results
- Example: Head CT conditions
  - Seeking intracranial hemorrhage (ICH) and large vessel occlusion (LVO) indications
  - Separate studies with separate datasets required for each condition
- Issue: Clearing a large number of conditions or declaring a study to be "normal" can require multiple studies
  - Time and resource-intensive, particularly if reader studies are involved

Challenges to the Current Paradigm: Supporting Data

- Standalone performance testing is typically manageable
  - Number of conditions being evaluated can conceivably become a burden
- Reader studies are a major issue
  - Resource-intensive in terms of design, number of readers, and cost
  - Typically beyond the reach of young companies
  - Lower data requirements has driven the popularity of CADt
- FDA initiatives
  - Established truthed datasets for reader studies

Challenges to the Current Paradigm: Post-Clearance Changes

- Intrinsic value of AI is the ability of the algorithm to refine performance
- Applicable FDA regulations are inconsistent with the evolving nature of AI
- Indications for use: Any major change to the indications requires a new marketing submission
- Technological characteristics: Any change that could significantly affect safety or effectiveness requires a new marketing submission

Challenges to the Current Paradigm: Post-Clearance Changes

- Many 510(k) holders seek to expand cleared indications for use
- Currently, every new indication(s) requires a new marketing submission (traditional 510(k) notice or PMA supplement) supported by dedicated testing for that indication
- Leads to multiple submissions
  - Typically must be done sequentially
  - Considerable burden in terms of administrative requirements and lost time

Challenges to the Current Paradigm: Post-Clearance Changes

- Significant algorithm changes may well implicate FDA requirements for a new submission, i.e., could the change significantly affect safety or efficacy
  - Applied in an absolute sense, i.e., even improvement in performance can trigger the need for a new submission
  - Threshold determination is quite subjective and entirely up to the agency with essentially no practical way to appeal
- Can lead to multiple new submissions
  - Must be supported by appropriate data
  - Considerable administrative and regulatory burden

Moving Forward with Imaging AI: Current Efforts

- Leveraging companies' quality systems
  - Pre-certification program
  - Unclear as to the boundaries or ultimate value of the program
- Allowing streamlined submissions with faster review
  - At the discretion of the reviewing Branch
  - Leverages similarity to existing, cleared devices
- Avoiding submissions altogether in certain defined circumstances
  - FDA review of scope of changes, validation protocol
  - Allows internal documentation as opposed to formal submissions

Moving Forward with Imaging AI: The Future

- FDA is learning as is the industry
  - Working with the agency through trade association, academic and stakeholder efforts will be crucial
- Regulatory implications of development and use at an individual institution is unclear
- Legislation may ultimately be necessary
  - Exceedingly difficult in today's environment
- Regulation always lags behind innovation

Questions

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