6.S897/HST.956 Machine Learning for Healthcare

Lecture 22: Regulation of ML/AI in the US

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1 Lecture Overview

Lecture 22 was taught by guest lecturers, Andy Coravos and Mark Shervey. Andy Coravos is CEO of Elektra Labs, which is building a digital biomarker atlas, backed by the National Science Foundation I-Corps program. Mark Shervey is a data engineer at the Institute for Next Generation Healthcare (INGH) at Mount Sinai. In his lecture, they covered the following topics:

- Overview of US Regulatory Agencies
- How to Submit a Public Comment
- Institutional Review Board (IRBs)

2 Overview of US Regulatory Agencies

2.1 Healthcare Products

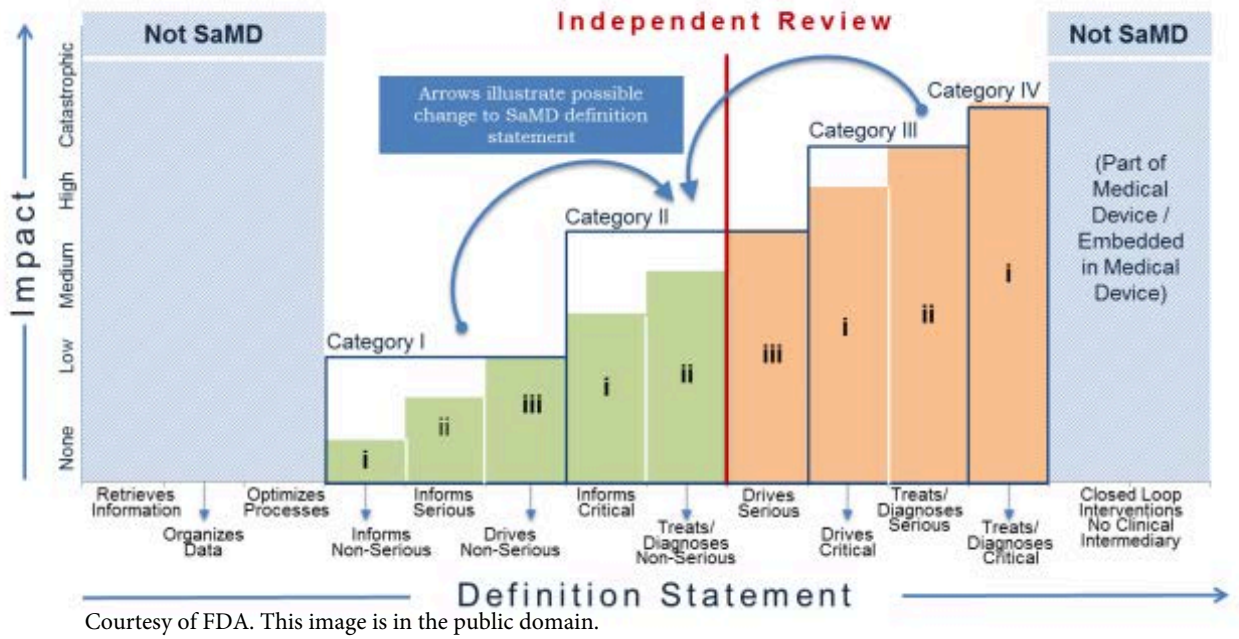
Software and algorithms have a wide range of applications that fall under one of the following categories:

Measure	Diagnose	Treat
With sensors + algorithms to create objective measurements	With advanced algorithms to support clinician	With novel software-based therapies that may augment or substitute a drug
e.g. *Digital biomarkers, clinical decision support*	e.g. *Digital diagnostics*	e.g. *Digital therapeutics*

Some examples:
Developing these products requires building safe and clinically-validated algorithms.

The BEST framework was created in 2016 by an NIH-FDA Working Group as a glossary of terminology and uses of biomarkers and endpoints in biomedical research, medical product development and clinical care. Although not explicitly listed in the BEST framework, a digital biomarker is defined as a biomarker collected through digital means, often used in a remote (at-home) setting. BEST outlines the seven types of biomarkers:

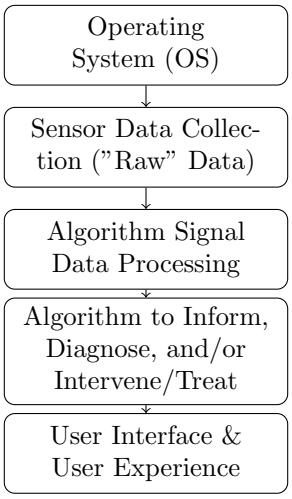
1. Diagnostic Biomarker
2. Monitoring Biomarker
3. Pharmacodynamic / Response Biomarker
4. Predictive Biomarker
5. Safety Biomarker
6. Susceptibility / Risk Biomarker



Courtesy of FDA. This image is in the public domain.

Figure 1: Types of software as medical devices

We then discussed the modularity of software and sensor products to detect atrial fibrillation through connected technologies, by dividing products into (1) software built and maintained by listed manufacturer, and (2) software built and maintained by third party. The general workflow of technologies was outlined as follows, and we categorized products based on the workflow modules they well-embodied:



The FDA cleared multiple SaMDs (Software-as-a-medical-device) after the EKG machine, borught by AliveCor in 2014, which delivers medical-grade EKG in just 30 seconds right to your smartphone.

A game called NEURORACER, developed in a lab at UCSF to address pediatric ADHD, proposed a 30-day protocol that enhances cognitive control in older adults. The work was published in Nature in 2013 and became technology licensed to Akili Interactive Labs, working to commercialize the product in a way

that mimicked drug companies (rather than tech companies). Four years later, the therapy video game hit its goal in a pivotal ADHD trial and showed better long term effects in reducing ADHD symptoms.

The FDA approvals for AI in medicine are accelerating, with 12 healthcare algorithms cleared by the FDA and an increasing number of software offerings pursuing 501(k) and De Novo approvals.

Mobile technologies are enabling new clinical investigation designs like **Decentralized Clnical Trials (DCTs)** which are fully virtual and remote. Digital tools are not making it easy to adhere to historical distinctions between the intervention and measurement/endpoint collection; in effect, digital tools are blurring the line between measuring, diagnosing, and intervening.

2.2 List of US Regulatory Agencies

The following agencies are the ways in which the US ensures that the products brought to market are safe and effective.

US Food and Drug Administration (FDA)

- Assure safety and effectiveness of medical products (e.g., drugs, devices)
- Facilitate medical product innovation
- Expedite patient access to high quality medical products
- Promote and adopt consensus standards

Office of the National Coordinator (ONC)

- Adopt standards, administer certification programs for health information technology (HIT)
- Promote electronic health information exchange
- Promote HIT policy
- Coordinate HHS HIT policy with other relevant federal agencies

Federal Communications Commission (FCC)

- Regulate interstate and international communications by radio, television, wire, satellite and cable
- Establish technical regulations, administer authorizations for equipment to minimize interference potential

Federal Trade Commission (FTC)

- Prevent business practices that are anticompetitive or deceptive or unfair to consumers
- Enhance informed consumer choice

National Institute of Standards and Technology (NIST)

- Non-regulatory federal agency
- Mission: promote innovation & industrial competitiveness
- Involvement in the form of standards for mobile products and software

Both the FTC and FDA oversight is focused on consumer protection, which is achieved by overseeing promotion and advertising. The FDA further takes protection to a public health perspective.

The FDA has multiple Centers:

- **Center for Drug Evaluation and Research (CDER)**
- **Center for Devices and Radiological Health (CDHR)**

Regulatory Pathway	510k	De Novo	Premarket Approval
Product risk levels	Class I and II	Class I and II	Class III
FDA decision type	Cleared	Granted	Approved
Requires a predicate	Yes	No	No
Decision criteria	Product demonstrates 'substantial equivalence' to a predicate (e.g., no independent assessment of the product required)	Probable benefits of the product outweigh probable risks	Requires independent assessment of the product's safety and effectiveness

Figure 2: Regulatory Pathways for Device Development

- **Center for Biological Evaluation and Research (CBER)**
- Center for Food Safety and Applied Nutrition
- Center for Veterinary Medicine
- Center for Tobacco Products
- National Center for Toxicological Research

The 21st Century Cures Act (December 2016) spurred and authorized FDA innovation around software regulation. It was designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently. This act also changed the definitions and regulations around what it means to be a "device", which we then discussed at depth. The FDA defines a medical device as:

- "an 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 is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Is my product a device? – it's about what the manufacturer claims the product can do: the same product can be developed/marketed as a "device" (regulated) or not a device simply through a change of words, and no change in hardware or code. The better question to ask is, **"What is the intended use of the product?"**

FDA-Cleared $\neq$ FDA-Approved

3 How to Submit a Public Comment

Whenever an agency is proposing either brand-new regulations or changes to existing ones, they must do it in two phases.

1. The agency will post a draft and ask the public to comment on it
2. The agency will read and digest the comments and draft a final version

You should participate in this process by submitting comments because:

- **Anyone can comment,** including experts in the field, startups, corporations, lobbying groups, concerned citizens.
- **You will be heard.** Legally, the agency is required to address all comments in the final rule.
- **Be a voice from the people.** Major industry players and trade groups almost always submit comments. Meanwhile, there are unfortunately lots of groups who rarely do, like startups, individual doctors, engineers, product managers, security experts, user researchers, and people from families who struggle with the exact scenarios being discussed.

To actually submit a public comment, you can visit regulations.gov to find the regulation of interest. Once you find the regulation, you click on the "Comment Now!" button and add your feedback.

For more details, on this process, the U.S. Department of Health and Human Services (HHS) published a more detailed guide on this here.

4 Institutional Review Board (IRBs)

The IRB determines whether your project is ethically sound. Researchers' responsibility to make sure everything is done to ensure a respectful and just experience for participants, avoiding any aspects that could be ethically questionable or overly manipulative. Human subjects research is when data is collected through intervention or interaction, usually private and identifiable.

- Inclusion ex: coded or identifiable elctronic health record (EHR) data; any protected health information (PHI)
- Exclusion ex: publicly available, anonymous data

4.1 Brief History

Nuremberg Code (1947)

- Rules for permissible medical experiments
- Result of cruel, brutal WWII experimentation on war prisoners that resulted in death sometimes

National Research Act (1974)

- Result of Tuskegee (and other experiments)
  - Assess natural progression of syphilis in untreated black men without informed consent
  - Participants were told they were being treated for "bad blood"
  - 40 years instead of 6 months (1932-1972, Mason Country Alabama)
  - Did not treat even when penicillin was deemed an effective treatment
- Established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

    - To identify basic ethical principles for research on humans
    - Developed guidelines for ensuring principles were adhered to ('75-'78)
  - Required establishment of IRB at organizations receiving Public Health Service (PHS) support for human research

4.2 Digital Research Studies

- **Project Activities** (worldwide audience) - collection of essays about historical cases regarding a project on the project website or social media
- Social media or emails about science news
- content about other research happening in similar subject matter
- **Study Activities** (enrolled participants) - electronic informed consent of prospective participants in research
- Administration of study questionnaires in the app, with data sharing or withdrawal process

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