Collaborative Community

for Digital Pathology

What is this now?

A collaborative community is more than the Alliance.

And many more

....

What is the promise?

tients.

Machine learning, conversely, approaches problems as a doctor progressing through residency might: by learning rules from data. Starting with patient-level observations, algorithms sift through vast numbers of variables, looking for combinations that reliably predict outcomes. In one sense, this process is similar to that of tra-

Machine learning has become ubiquitous and indispensable for solving complex problems in most sciences. The same methods will open up vast new possibilities in medicine.

Predicting the Future — Big Data, Machine Learning, and Clinical Medicine

Ziad Obermeyer, M.D., and Ezekiel J. Emanuel, M.D., Ph.D.

By now, it's almost old news: big data will transform medicine. It's essential to remember, however, that data by themselves are useless. To be useful, data must be analyzed, interpreted, and acted on. Thus, it is algorithms — not data sets — that will prove transformative. We believe, therefore, that attention has to shift to new statistical tools from the field of machine learning that will be critical for anyone practicing medicine in the 21st century.

First, it's important to understand what machine learning is not. Most computer-based algorithms in medicine are "expert systems" — rule sets encoding knowledge on a given topic, which are applied to draw conclusions

n engl j med 375;13 nejm.org September 29, 2016

What is the problem?

How current assay approval policies are leading to unintended imprecision medicine

Lancet Oncol 2020
Published Online
October 21, 2020
https://doi.org/10.1016/
S1470-2045(20)30592-1

Pathologists are responsible for selecting the assays for the optimal identification of patients for targeted therapy. The current paradigm of regulatory assay approval is that when a clinical trial involving a drug and a biomarker, using a specific assay to identify patients that might respond to the drug, meets its endpoint, the assay is approved concomitantly as a companion diagnostic. Private health insurance bodies or public health systems then decide on reimbursement of the assay when they decide on the reimbursement of the drug. Use of US Food and Drug Administration (FDA)-approved assays is obligatory in some countries, like the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA) and its combined positivity score-scoring system to assess PD-L1. Using more than one assay for the same biomarker is problematic because the assays have different positive prevalence rates. In the IMpassion130 trial, 46% of patients with triple-negative breast cancer were deemed to be positive using the Ventana PD-L1 (SP142) assay; when using other assays (eg, the PD-L1 IHC 22C3 pharmDx assay) in the same patients, the PD-L1 positive prevalence increased to nearly 80%.[3] The cause of these inconsistencies is multifactorial and includes reproducibility issues and

biomarker. For example, PD-L1 assay kits are approved by the FDA in 15 different cancer types but the PD-L1 staining patterns, scoring methods, and positivity thresholds are different in almost all of these cancer types. Moreover, the various assays and scoring systems are not equivalent, despite being matched to the same specific drug. There are at least five non-equivalent assays for PD-L1, each with its own scoring system and tumour site indications.

Absence of assay standardisation is an emerging issue for triple-negative breast cancer. In 2019, considering the results of the IMpassion130 trial, the FDA approved the Ventana PD-L1 (SP142) assay (Ventana Medical Systems, Tucson, AZ, USA) and cut-point (1% of tumour-infiltrating immune cells) to assess PD-L1 in patients with triple-negative breast cancer treated with atezolizumab.[1] However, following the Keynote 355 breast cancer trial,[2] the results of which were publicised in 2020, investigating pembrolizumab in the same patient population, the FDA is likely to approve the tests. A concerning situation is if patients underwent unnecessary toxicity and extra costs due to potentially false-positive tests. However, lower sensitivity of an assay, with potentially false-negative results, could lead to fewer patients receiving therapy and benefit. Some oncologists might prefer their pathologist to use an FDA-approved assay, despite being unaware of the analytical validity of the assay and the fact that many laboratory-developed tests can perform as well as FDA-approved companion diagnostics.[7] Others might prefer an assay with a higher positive prevalence to identify more patients that can be treated.

Different assays, different platforms, different positivity thresholds, and a divergent international approach to reimbursement of these assays suggest that patients are not well served by the current system. Industry, regulatory agencies, governments, clinicians, and patients also need to be aware that a positive phase 3 trial does not guarantee consistency, reproducibility, and practicality of the biomarker-specific assay used in

Idea (Salgado et al., 2020)

- Article focusses on one biomarker (PD-L1)
- Comment is intentionally written more generic
- Problem applies to TMB, ML-tools, and digital pathology
- **A new or revised regulatory framework is needed**
- A collaborative community on this topic is a very important step forward

CC: existing – and growing

The FDA currently participates as a member of the following collaborative communities, which have been established and are managed and controlled by external stakeholders.

- Ophthalmic Imaging Collaborative Community
- National Evaluation System for health Technology Coordinating Center (NESTcc) Collaborative Community
- Standardizing Laboratory Practices in Pharmacogenomics Initiative (STRIPE) Collaborative Community
- International Liquid Biopsy Standardization Alliance (ILSA)
- Xavier Artificial Intelligence (AI) World Consortium
- Case for Quality Collaborative Community

NESTcc National Evaluation System for health Technology Coordinating Center (NESTcc) Collaborative Community

NESTcc has identified and selected **11 key demonstration projects to provide proof of concept for scalable approaches to evidence generation across device types** and across the total product life cycle.

Xavier AI World Consortium

XAVIER HEALTH | CONFERENCES | WORKSHOPS | INITIATIVES | ON DEMAND | NETWORKS | ABOUT

AI WORLD CONSORTIUM

- OVERVIEW
- AI WORLD TEAM
- AI SUMMIT
- AI WORKING TEAMS
- AI NETWORK
- AI RESOURCE MAP

AI World Team

The AI World Team, led by Xavier University, is a collaborative community passionate about advancing the responsible use of artificial intelligence to support improved success across the healthcare continuum, including healthcare diagnoses, product development, clinical trials, manufacturing operations, supply chain operations, and quality assurance.

Opportunity: The team recognizes that there is a plethora of artificial intelligence research, guidance, lessons learned and successful practices that currently reside in organizational silos around the world without a pathway for global awareness and access. Through the AI World Team community, we are driving the identification, access, gap analysis and development of artificial intelligence work to support successful adoption of AI across the healthcare space.

Mission

To enable the advancement of world health by expanding access to, and accelerating the development of, artificial intelligence solutions for the benefit of the global healthcare community.

Participating Members

Members from the following regulatory agencies, nonprofit organizations and industries are working collaboratively to advance the use of AI across the healthcare ecosphere.

AAMI, Abbott, AdvaMed, AMA, bigfinite, BIOINFORMATICS BARCELONA, bsi., CES Consumer Technology Association, ERS, U.S. FOOD & DRUG ADMINISTRATION, MHRA, MITA MEDICAL IMAGING & TECHNOLOGY ALLIANCE, PHILIPS, World Health Organization, XAVIER UNIVERSITY

CC: existing – and growing

The FDA currently participates as a member of the following collaborative communities, which have been established and are managed and controlled by external stakeholders.

- Ophthalmic Imaging Collaborative Community
- National Evaluation System for health Technology Coordinating Center (NESTcc) Collaborative Community
- Standardizing Laboratory Practices in Pharmacogenomics Initiative (STRIPE) Collaborative Community
- International Liquid Biopsy Standardization Alliance (ILSA)
- Xavier Artificial Intelligence (AI) World Consortium
- Case for Quality Collaborative Community

Example question:
How are we different from the ML/AI CC?
Answer:
Pathology-specific issues (pre-analytics, scanners, standards, workflows, patient care relationship…)

The Alliance is one player
...digital pathology needs more

- Input in regulatory decision making
  - Along with many others
- Regulatory initiatives
- That's why we are here
- Who – if not us ?
- Not providing input is a missed opportunity

First meeting July 2019 – first talk

THE ALLIANCE FOR DIGITAL PATHOLOGY

MGH-MDIC-DPAF-FDA

A successful initial meeting was held at the FDA on July 18, 2019.

Over 50 attendees from various entities were in attendance. Attendees shared an interest to encourage innovation and commercialization by developing evaluation tools, methods and standards, and clarifying regulatory pathways in digital pathology and specifically in the AI space were present. A temporary alliance has been established between the different participating entities with the intent to grow the alliance to incorporate additional stakeholders.

Below are four of the key presentations by FDA, MDIC, DPA, and The Alliance for Digital Pathology Proposal.

MICHELLE TARVER, FDA, COLLABORATVIE COMMUNICATIONS

The presentation outlines best practices for establishing and maintaining collaborative communities.
Specifically, a collaborative community may be appropriate when challenges are ill-defined and there is interrelatedness of the partners.
The presentation outlines also some potential deliverables.

▷ VIEW PRESENTATION

Idea

- Process through which parties who see different aspects of a problem can constructively explore their differences...
- Mutually beneficial relationship...

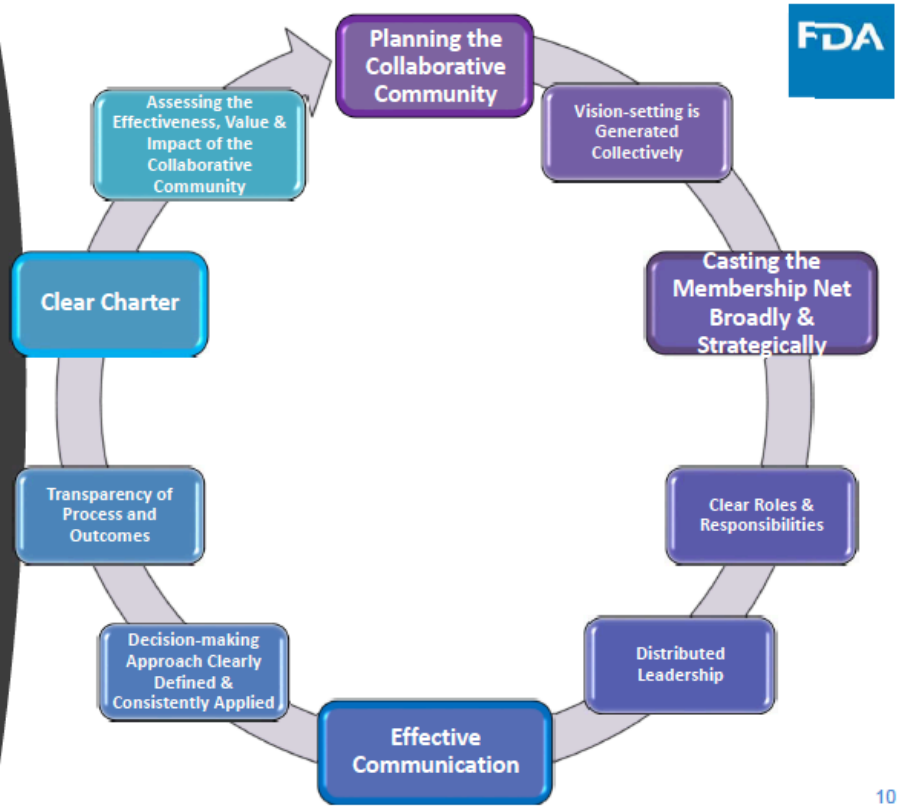
Goal (FDA)

Establish 10 new Collaborative Communities by end of 2020

=> Timeline (let's dicuss)

What have we been tasked with?

Best Practices for Establishing & Maintaining Collaborative Communities

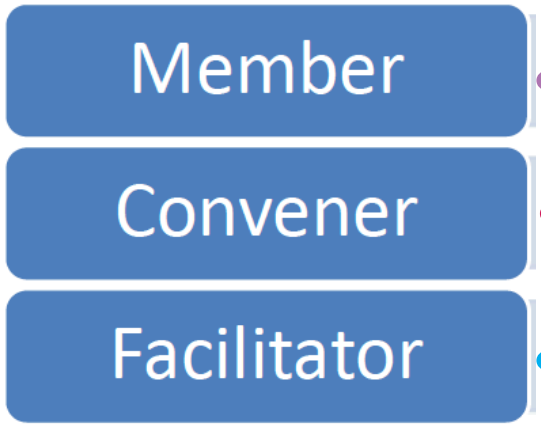


Sector for Potential Members

Sector for Potential Members

Patient & Consumer Advocacy Organizations FOCR, PCORI	Academia Many	Hospital Systems Yes	Trade Associations …
Device Manufacturers Many, MDIC	Medical Device Distributors several	Professional Societies/ Associations/ DPA, CAP, ACR	Payers …
Research Institutions Yes	State, Federal and International Organizations FDA, IARC, WHO, NIH(NCI), CDC	Foundations DPAF	Public-Private Partnerships …

Facts, Roles, and Responsibilities



- **We (the field)** are helping to create a collaborative community
- **MDIC** will be the convener (Jithesh, John, Pamela, ...)
- **FDA** cannot be a voting member and cannot be listed on the steering committee.
  - Acknowledge FDA's role (via a) liaison with advisory capacity
- Other **stakeholders (including the Alliance)** = facilitator
- Current charter needs input and revisions

What we (can) aim to deliver

- Guidance and Standards
- White paper (peer reviewed publication)
- Research agenda and projects
- Proposed regulation and proposed legislation
- Best practices and tool developments
- Culture change = paradigm shift in digital pathology

Charter is a means to get to these points

Tasks at hand

- Charter
- Steering Committee
- Finalize charter
- Establish the community
- Start working on projects

Charter

- Website + 2 upcoming meetings
- Open to the public
- Drafting sessions
  - **Nov 10th at 3PM (EST)**
  - **Nov 13 at 10AM (EST)**
- Everything is on the table
  - E.g. name, structure, etc.
- Open to the public

The ~~Alliance for~~ Digital Pathology – Collaborative Community

~~"Alliance~~-CC"

–Charter–

I: Preamble

Section 1: Name

The Alliance for Digital Pathology – Collaborative Community (~~Alliance-~~CC) is a regulatory science initiative with members from academia, industry, regulators, health care providers, and advocacy groups.

Section 2: Preamble

Several categories of documents will govern Alliance-CC activities, duties, and responsibilities. The Alliance-CC documents may include but may not be limited to: (1) Alliance-CC Charter (this document) and (2) Standard Operating Procedures (if applicable). If there is any perceived inconsistency between (1) and (2), this document governs.

Section 3: Mission and Vision

The Mission and Vision of the Alliance-CC are:

Mission: To accelerate the development and delivery of regulatory science initiatives in the pre-competitive space that advance the field of digital pathology, including but not limited to machine-learning and artificial intelligence. This may be accomplished through collaborative initiatives using various health technologies, leveraging real-world data, and innovative research.

Collaborative Communities: Addressing Health Care Challenges Together

In the medical device ecosystem, collaborative communities bring together stakeholders to achieve common outcomes, solve shared challenges, and leverage collective opportunities. CDRH believes collaborative communities can contribute to improvements in areas affecting patients and health care in the United States. Accordingly, participation in collaborative communities is one of CDRH's strategic priorities for 2018-2020.

CDRH encourages interested stakeholders to learn more about collaborative communities and review the toolkit, which provides a collection of helpful ideas to foster strong collaborative communities that are well-prepared to take on health care challenges.

Content current as of:
09/30/2020

Value proposition

- Patient Impact
- Public health impact
- Improved patient services (access)
- Improved patient management (workflows)
- Improved diagnosis (quality)
- Improved diagnosis (quantity)
- Etc...

Assessing Impact and Ouctome of the CC

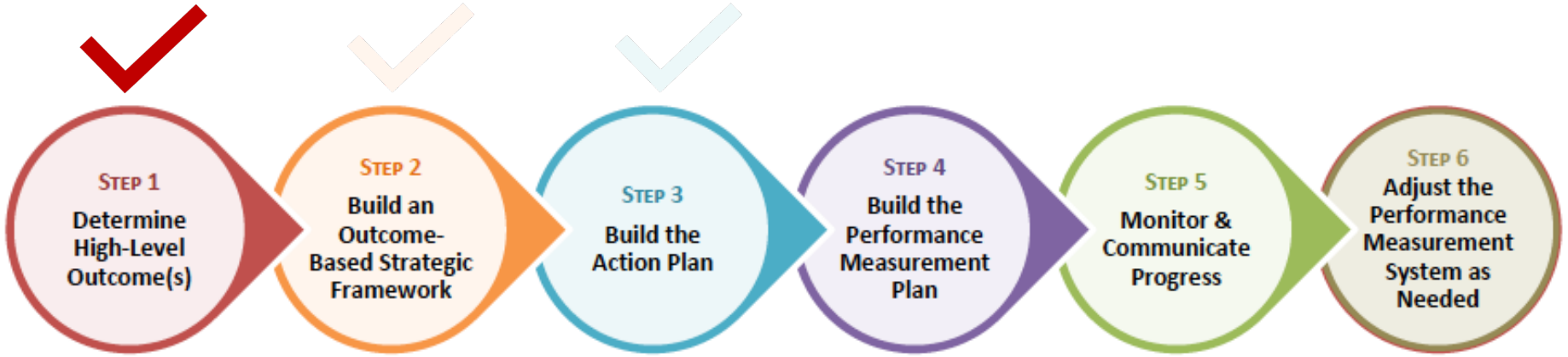


Figure 1. Process from Determining the High-Level Outcome to Implementing the Performance Management System.

How can you help?

Practical = projects

Collaborative Community

1. Read the FDA toolkit
2. Review M. Tarvers presentation
3. Study existing communities
4. Read the draft Charter
5. Consider assuming a role
6. Join the meetings – and help craft the structure of the community

Download a PDF of the toolkit (5 MB)

Summary

- Collaborative Communities (CC) are an existing way to engage with “us” and (formally) with the FDA (regulator)
- We need to form a Collaborative Community
- It will enable (via various stakeholders) to directly provide input into creating or improving the regulatory framework
- The FDA is interested and will likely engage with us