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A Regulatory Science Initiative to Harmonize and Standardize Digital Pathology and Machine Learning Processes to Speed up Clinical Innovation to Patients

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Abstract

Unlocking the full potential of pathology data by gaining computational access to histological pixel data and metadata (digital pathology) is one of the key promises of computational pathology. Despite scientific progress and several regulatory approvals for primary diagnosis using whole-slide imaging, true clinical adoption at scale is slower than anticipated. In the U.S., advances in digital pathology are often siloed pursuits by individual stakeholders, and to our knowledge, there has not been a systematic approach to advance the field through a regulatory science initiative. The Alliance for Digital Pathology (the Alliance) is a recently established, volunteer, collaborative, regulatory science initiative to standardize digital pathology processes to speed up innovation to patients. The purpose is: (1) to account for the patient perspective by including patient advocacy; (2) to investigate and develop methods and tools for the evaluation of effectiveness, safety, and quality to specify risks and benefits in the precompetitive phase; (3) to help strategize the sequence of clinically meaningful deliverables; (4) to encourage and streamline the development of ground-truth data sets for machine learning model development and validation; and (5) to clarify regulatory pathways by investigating relevant regulatory science questions. The Alliance accepts participation from all stakeholders, and we solicit clinically relevant proposals that will benefit the field at large. The initiative will dissolve once a clinical, interoperable, modularized, integrated solution (from tissue acquisition to diagnostic algorithm) has been implemented. In times of rapidly evolving discoveries, scientific input from subject-matter experts is one essential element to inform regulatory guidance and decision-making. The Alliance aims to establish and promote synergistic regulatory science efforts that will leverage diverse inputs to move digital pathology forward and ultimately improve patient care.

Keywords: Artificial intelligence, digital pathology, machine learning, regulatory science, slide scanning

Introduction

“The scientist and science provide the means, the politician and politics decide the ends.”

-Alvin M. Weinberg[1]

Regulatory science is an established discipline that entails the application of the scientific method to support regulatory and other policy objectives.[2] Simply put, when medical
research provides a novel solution to a health need, regulatory
science applies the scientific method to assess benefits and
risks before marketing for clinical use. To assess benefits and
risks, regulatory scientists develop new tools, standards, and
approaches to evaluate the effectiveness, safety, and quality of
medical products. A primary challenge in the field of digital
pathology is the lack of understanding that strong relationships
between regulatory, basic, and translational scientists can
substantially improve clinical innovation.\(^2\)\(^3\)\(^4\)\(^5\)\(^6\) For example,
regulatory science is not restricted to regulatory agencies.\(^3\)\(^4\)\(^6\)
As a scientific discipline, regulatory science challenges current
concepts of benefit and risk assessments, submission and
approval strategies, patient involvement, and various ethical
aspects. Regulatory science includes the creation of a scientific
dialog for launching new ideas – not only derived from industry
and regulatory authorities but also by, for example, academies,
iclinicians, and patients.\(^7\) It has been recognized that regulatory
science can have a significant impact in bringing new devices
to patients in need.\(^7\)

Here, we outline a recently established, volunteer, collaborative
regulatory science initiative termed the Alliance for Digital
Pathology (the Alliance). To prevent confusion, our intent is to
familiarize the community with the aims, scope, and rationale
of the Alliance. The Alliance aims to move the field of digital
pathology forward by systematically assessing relevant aspects
and providing publicly available resources (e.g., data, tools,
and methods) to inform and improve the relevant regulatory
guidance landscape.\(^8\) Our premise (thesis) is that the Alliance
promotes regulatory science as a bridge between digital
pathology (the means) and moving the field of diagnostic
pathology forward (the ends). By promoting regulatory
science, the Alliance helps to unlock the potential of new
technologies and thereby overcomes the dichotomy illustrated
in the epigraph by Dr. Weinberg.\(^1\)

**TOWARD AN OPERATIONAL DEFINITION OF A CLINICAL,
INTEROPERABLE, INTEGRATED SOLUTION FOR DIGITAL
PATHOLOGY**

The key aim of the Alliance is to help convert the
existing (traditional) pathology technologies and workflows
into interoperable, digitally enhanced solutions by contributing
regulatory science deliverables that can be used to inform
and improve the applicable regulatory guidance landscape.
Numerous groups have attempted to specify the relevant
components of digital pathology solutions;\(^9\)\(^10\)\(^11\) however,
given the modularized nature of diagnostic pathology,
defining the specific scope of a digital pathology solution
is highly context dependent. For example, the variability
of a stain (e.g., hematoxylin and eosin across or within
laboratories) may influence the performance of a downstream
mutation prediction algorithm.\(^19\)\(^20\)\(^21\) In this example, one may
consider drawing an arbitrary boundary before the staining
step; however, the fixation and processing method (e.g.,
formalin fixed, paraffin embedded) or even the tissue
acquisition, handling, or image acquisition\(^22\) may influence
the performance of the predictor as well. Thus, for the
purpose of the Alliance, we considered three descriptors for
the solution. First, we aim toward a clinical (as opposed to
a research-based) solution. Second, due to the modularized
nature of the various subprocesses within the main workflows
in pathology, we aim for interoperability of systems. Third,
to account for the various and arbitrary boundaries of
workflow steps (modules) and technologies relevant for a
given task (intended use), we consider every step, from the
medical procedure acquiring the cell or tissue sample all the
way to the fully integrated diagnostic output (e.g., report
or model output), as relevant. As opposed to an end-to-end
solution, where the supplier of an application or system will
provide all the hardware and/or software to meet specific
requirements, we are aiming for modularized solutions
within the main workflow. We refer to these three solution
descriptors (clinical, interoperable, and modularized) as an
“integrated solution” for digital pathology. We acknowledge
that this definition is operational and arguably incomplete yet
represents a technique that enables flexible modeling to solve
challenging problems.\(^23\)\(^24\)\(^25\)\(^26\)

**THE MULTIFACETED NATURE OF DIGITAL PATHOLOGY
NEEDS INCREASED REGULATORY CLARITY**

Digital pathology has grown into a multimillion-dollar
vendor landscape,\(^27\) and the application of machine learning
algorithms holds big promise for improving diagnostics
in numerous ways.\(^28\)\(^29\)\(^30\) Despite this active and promising
research, the Food and Drug Administration (FDA) has
only recently authorized two digital pathology whole-slide
imaging (WSI) systems for primary diagnosis.\(^9\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\) Even
with the authorization of two WSI systems and numerous
use cases,\(^12\)\(^14\)\(^18\)\(^33\)–\(^38\) in the U.S., we see few hospitals
changing their daily clinical operations to integrate WSI for
primary diagnosis.\(^19\)\(^43\) Clinical laboratories face additional
challenges when implementing high complexity and/or
high-risk medical devices coupled with software solutions
as laboratory-developed tests (LDTs).\(^44\)\(^45\) For example,
even when using an FDA-authorized whole-slide imaging
device, the approval or clearance does not eliminate the need
for an individual laboratory to verify the performance of
these systems for the specific intended diagnostic purpose.
Specifically, Clinical Laboratory Improvement Amendments
of 1988 or CLIA ’88 in the US requires at least verification\(^47\)
and substantial adaptation to implement.\(^48\)\(^52\)

One value proposition for digital pathology is to take advantage
of the digital nature of WSI and use artificial intelligence/
machine learning (AI/ML) algorithms to support clinical
decisions.\(^11\)\(^53\) In fact, several groups have proposed that AI/ML
will unlock the full potential of digital pathology.\(^53\)\(^54\)

To examine the current regulatory guidance landscape related
to digital pathology and AI, four authors (HDM, RH, EA, and
JKL) performed a review of pertinent documents from the FDA.
We noted the official release dates and assigned each document to one of five dimensions [Figure 1 and Supplemental Table 1]. By plotting these documents and dimensions over time, we show how the regulatory guidance landscape evolves. A novice in the field may look for one comprehensive guidance document for digital pathology and may be discouraged by the initial complexity; however, we hope that Figure 1 provides a reasonable starting point for learning the current regulatory guidance landscape. As we show [Figure 1, arrows], the regulatory guidance landscape adapts over time as technologies and the associated regulatory science matures. One key element in the multistep process to improve the regulatory guidance landscape is critical scientific input from subject-matter experts.3-5,10,11,15,53 We strongly believe that “watching and waiting” will not help the case of digital pathology. Similarly, workarounds turn into long and winding roads that ultimately end at the FDA and within the FDA’s regulatory framework.83 The Alliance intends to organize subject-matter experts and provide scientific input.

Simply put, the practical dilemma in digital pathology is that developers are challenged to create an FDA submission following the evolving and complex regulatory guidance landscape, and the adoption of WSI by pathologists is slowed because they cannot realize the full potential and utility of digital pathology and AI/ML without full clinical integration. The field of digital pathology is looking for broader guidance, practical advice, and streamlined regulatory pathways to help navigate this uncharted and exciting territory.

**Regulatory Science, the Precompetitive Space, and Real-World Evidence**

FDA clearance of a medical device offers a vendor market access. Once introduced, market forces tend not to encourage the vendor to make the device or its subsystems interoperable.55-61 We like to emphasize that routine diagnostic pathology is highly modularized and the practice does not lend itself easily to nonmodular, locked down solutions.3,9-11,27,50,51,54-62 The Alliance believes that it can promote interoperability and innovation by launching initiatives and creating deliverables (data, standards, tools, and methods) in the precompetitive space. Organizing industry to work collaboratively in the precompetitive space will eliminate unnecessary or duplicative (proprietary) efforts and thereby save all parties’ time, money, and resources when pursuing device authorizations.63 The Alliance initiatives and deliverables will speed clinical integration and carry mutual benefit to all stakeholders, including regulators, clinicians, manufacturers, and most importantly, patients.

Real-world evidence (RWE) comes from the competitive, postmarket space. RWE can identify trends in adverse events, summarize where resources are being spent, and track the impact of a new diagnostic device or therapy in terms of patient outcomes. RWE can support clinical practice guidelines and decisions about reimbursement and policy. Furthermore, RWE can inform regulatory decision making, as effectively demonstrated by the Medical Device Innovation Consortium,64,65 the National Evaluation System for health...
Figure 2: Concept, process, role, and proposed benefits of the Alliance. (a) The approach of the Alliance is to deliver tools via precompetitive FDA programs and use the gained experience to support effective FDA review. The concept also includes a predetermined exit strategy (i.e., one fully integrated solution for digital pathology). (b) The process of moving Alliance projects forward is essentially a two-step, multidisciplinary peer review by subject-matter experts. First, projects are reviewed, and after a multidisciplinary selection process that emphasizes the patient perspective and relevance for patient care, the steering committee (jointly with relevant partners) attempts to allocate resources. (c) Role and proposed benefits of the Alliance exemplified using the high-throughput truthing project for tumor-infiltrating lymphocytes as a biomarker in breast cancer. AMCs: Academic medical centers; MDDT: Medical Device Development Tools (precompetitive FDA submission program); Mock: mock submission program (precompetitive FDA submission program); OIR: Office of In vitro Diagnostics and Radiological Health; OPEQ: Office of Product Evaluation and Quality; OSEL: Office of Science and Engineering Laboratories; FDA: Food and Drug Administration

Technology Coordinating Center, the Patient-Centered Outcomes Research Institute, Friends of Cancer Research, and others.

FROM KEY MISSION ELEMENTS TO A DELIVERY PROCESS

Accomplishing mutual benefit to multiple stakeholders is a daunting value proposition that requires a unique regulatory science approach and stakeholder involvement for selection and prioritization of deliverables. The approach of the Alliance [Figure 2a] is to deliver tools by harnessing existing, precompetitive FDA programs and use the gained experience to inform effective regulation. The approach thereby aims to streamline precompetitive and eventually competitive submissions that enable faster time to market to improve patient care. Regulatory science deliverables, including tools and the experience from precompetitive submissions, will be shared, and when one integrated solution has been enabled, the Alliance can dissolve [Figure 2a]. The key mission elements of the Alliance are summarized in Table 1.

To align stakeholder interests, initiatives and deliverables need to be prioritized and prioritization requires a process. We conceptualized an approach that is composed of synergistic review, project components, and resource allocation [Figure 2b]. The process starts with synergizing various stakeholder interests into concise individual projects. An Alliance project may consist of a clinically relevant intended use case, a data set (e.g., pixel and metadata), and an applicable regulatory science pathway [e.g., Figure 2b, triangle]. The Alliance membership, composed of subject-matter experts from various domains, will have the opportunity to review, contribute, and potentially modify these projects through free and voluntary feedback to the project owner. Over time, individual effort and maturation of
Table 1: Key mission elements of the Alliance

| Definition | Explanation |
|------------|-------------|
| Aim        | To move the field of digital pathology, AI/ML and computational pathology, forward |
| Focus      | Key emphasis on regulatory science (“how to get to the next step”); inform regulatory guidance and decision-making; explore new regulatory programs |
| Deliverables | The Alliance focuses on concrete practical deliverables, such as projects or practical guidelines, that can be used to inform and improve the regulatory guidance landscape (regulatory science) |
| Collaboration | We seek participation from all stakeholders |
| Participatory | We aim to sustain and expand the existing collaborative infrastructure of the Alliance |
| Market strategy | Focus on the precompetitive space with an emphasis on clinical deliverables towards financial sustainability for all stakeholders |
| Patient perspective | Make the patient perspective and clinical relevance an integral part of the deliverables |
| Temporary | Exit strategy: Once an end-to-end solution has been clinically integrated, the Alliance ends |
| Free | No membership fees |

AI: Artificial intelligence; ML: Machine learning

ideas will result in optimized projects (“big ideas”). To help realize the proposed deliverables and/or allocate additional resources, we established the Alliance Steering Committee, a flexible organizational structure, and a code of conduct [Supplemental Table 2].

An example project is illustrated in Figure 2c. A subset of members in the Alliance are studying the relevance of tumor-infiltrating lymphocytes (TILs) as a prognostic and predictive biomarker. The interest in this clinical use case led to a collaborative project that includes members from the FDA, academic medical centers (AMCs), and industry. The project, referred to as the high-throughput truthing (HTT) project, aims to demonstrate the collection and use of pathologist annotations for the purpose of evaluating AI/ML algorithms and other digital pathology initiatives. The project also aims to qualify the glass slides, whole-slide images, and pathologist annotations for evaluating AI/ML algorithms through the precompetitive FDA’s Medical Device Development Tools (MDDT) program. If qualified, the “ground-truth” materials can serve as a publicly available, standardized evaluation “tool” for algorithm evaluation that can be used in submissions to the FDA.

In relation to the Alliance, the HTT project was submitted to the Alliance and discussed in November 2019. The Alliance can contribute in multiple ways to accelerate the realization of this and similar projects. First, the Alliance confirmed that the aims of the project could benefit many stakeholders.

The discussions provided useful feedback from subject-matter experts regarding the clinical use case, sourcing slides from multiple sites, agreements for sharing materials within the project, and issues related to sharing materials publicly.

The discussions also identified future work that could build on the lessons, methods, infrastructure, and relationships created while pursuing the current aims. Important future work identified in the discussions included scaling the effort to address generalizability across sites and generalizability across use cases.

The Alliance has since provided help with the project [Figure 2b, triangle 01, relevant intended use case; Figure 2c, 01] by disseminating the project needs. This networking through the Alliance has yielded volunteers for sourcing and scanning slides, pathologists to annotate slides and images, and opportunities to collect data. Connections have been created that are expected to help in the development of the statistical analyses and the future hosting of slides, images, and annotations. Currently, the project is developing the strategy and materials for the FDA’s MDDT program [Figure 2b, triangle, MDDT; Figure 2c, 03]. The development is a learning
experience for all involved, with contributions from project and Alliance subject-matter and regulatory affairs experts. The learning experience is expected to continue through official interactions with the FDA related to the MDDT submission. Thus, aside from helping to create the ground-truth data set, the Alliance aims to understand regulatory issues and processes for future streamlining of other projects and submissions. As demonstrated here, a qualified data set may result in time-savings when preparing submissions, generating additional tools, and streamlining regulatory review, resulting in faster time to market and improved patient care.

**Who Is the Alliance?**

The Alliance is composed of a diverse and interdisciplinary group of stakeholders who contribute to various aspects of diagnostic pathology, from tissue acquisition to reporting and data analytics. When deconstructing the clinical digital pathology and AI/ML pipeline into its component parts, numerous workflow steps have to function in unison [Figure 3a]. Aside from the modular nature and operational complexity, these components emphasize the importance of involving various stakeholders with each module. Given the novelty of pursuing a collaborative regulatory science effort to solve the challenge of clinical adoption of digital pathology, we noted a lack of concrete data on interested stakeholders and their priorities. In September 2019, we conducted an internal survey [n = 42; Supplemental Table 3]. At that time, the survey respondents stated that the top 3 deliverables/workflow steps to focus on should be the DICOM standard, AI/ML test validation, and pixel and metadata capture [Figure 3b]. By self-reported primary affiliation, the Alliance encompasses representation from academia (32%), industry (50%), government regulators and nongovernment organizations (12%), and patient advocacy groups (6%) [Figure 3c].

**Meetings, Growth, and Working Groups**

Since its inception in May 2019, the Alliance hosted numerous teleconferences, web meetings, and three, in-person, national meetings [Figure 4a]. Over this period (May 2019–January 2020), the Alliance membership grew from an initial n = 37 (July 2019) to n = 322 individuals [May 2020; Figure 4a]. Each of these in-person meetings solicited collaborative input from stakeholders toward execution of concrete regulatory science deliverables. Figure 4a also includes the number of participants and frequency of steering committee web meetings. By July 2019, it became clear that various stakeholders worked on or had interest in distinct topics that the Alliance subsequently organized into 8 working groups by autumn 2019 [Figure 4b]. These group topics are intended to align stakeholders with subject-matter expertise and interest. Clearly, some functional requirements are relevant for multiple groups. However, we hope to minimize such redundancies by providing clear documentation of projects through appropriate project management and frequent content updates. The names of the founding and current working group leaders are provided in Figure 4b. One example of a regulatory science deliverable is also provided per group [Figure 4b]. For further updates or details on the various topics, please visit the Alliance website or to become a member and get involved.

**The Alliance Facilitates Regulatory Submissions**

As a first key regulatory science deliverable, in late 2019, members of the Alliance submitted an MDDT proposal to the FDA for review (HTT project described above). The experience gained through this submission will create a starting point and testing ground for the proposed approach of the Alliance. In contrast to the largely confidential submission owned by the submitting entity (typically represented through a consulting firm and/or a regulatory affairs division), gaining and sharing the submission experience may inform subsequent submissions, and Alliance members can draw from the experience of these submissions. This particular concept is new to digital pathology. Similarly, we consider several precompetitive submission programs by the FDA[^78][^79] a paradigm shift that enables different ways to engage with regulatory entities. Importantly, the Alliance intends to create
a repository of submission documents as a resource to bolster subsequent submissions with the collective experience of previous submitters. We propose that the field, and in particular patients, will ultimately benefit from sharing the experiences of Alliance members who have submitted to regulatory agencies.

**Conclusion**

In the current environment of sparse and dispersed regulatory guidance for digital pathology and AI/ML, with siloed pursuits by diverse stakeholders, the Alliance saw an opportunity to establish an important missing element: a precompetitive regulatory science collaboration. We believe that for patients to benefit from highly complex new technologies, benefit and risk assessments are essential. The Alliance helps tackle this daunting task (i.e., benefit and risk assessment for digital pathology and AI/ML) through regulatory sciences with the hope of successful clinical integration and improved patient care. That said, there are numerous issues that we need to address. For example, we want to investigate and develop protocols and definitions for continuous performance assessments of continuously learning ML algorithms. Similarly, approaching financial sustainability will require clear demonstration of clinical utility. However, the fact that numerous unanswered questions persist represents an opportunity for other agencies, regulatory entities, professional groups, and collaborative movements (like the Alliance) to step up and drive developments toward comprehensive risk and safety assessments. It is important to emphasize the crucial importance of funding for regulatory and implementation science projects, in particular those that aim to inform technically appropriate and efficient science-based regulatory decision-making processes. Such funding is needed to advance cutting-edge innovations into clinical practice. In summary, the Alliance aims to advance the field of digital pathology and we hope that synergistic efforts between various stakeholders and regulatory scientists will ultimately speed the improvement of patient care. This begs the question: Who, if not us?

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**Conflicts of interest**

There are no conflicts of interest.

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| Date               | n* | Title                                                                 | Issuer                                                                 |
|--------------------|----|----------------------------------------------------------------------|------------------------------------------------------------------------|
| January 11, 2002   | 16 | General Principles of Software Validation                           | CDRH and OPEQ                                                          |
|                     |    | [https://www.fda.gov/media/73141/download](https://www.fda.gov/media/73141/download) |                                                                        |
| January 14, 2005   | 10 | Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software | CDRH and OPEQ                                                          |
|                     |    | [https://www.fda.gov/media/72154/download](https://www.fda.gov/media/72154/download) |                                                                        |
| August 17, 2011    | 1  | Advancing Regulatory Science at FDA                                  | FDA                                                                    |
|                     |    | [https://www.fda.gov/media/81109/download](https://www.fda.gov/media/81109/download) |                                                                        |
| July 02, 2012      | 12 | Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions | CDRH, OSEL, and OPEQ                                                  |
|                     |    | [https://www.fda.gov/media/77635/download](https://www.fda.gov/media/77635/download) |                                                                        |
| July 02, 2012      | 13 | Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions | CDRH, OSEL, and OPEQ                                                  |
|                     |    | [https://www.fda.gov/media/77642/download](https://www.fda.gov/media/77642/download) |                                                                        |
| December 09, 2013  | 17 | Software as a Medical Device (SaMD): Key Definitions                 | IMDRF and SaMD WG                                                      |
|                     |    | [http://www.imdrf.org/docs/imdrf/final/technical/imdrf-technical-131209-samd-key-definitions-140901.pdf](http://www.imdrf.org/docs/imdrf/final/technical/imdrf-technical-131209-samd-key-definitions-140901.pdf) |                                                                        |
| September 18, 2014 | 18 | Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations | IMDRF and SaMD WG                                                      |
|                     |    | [http://www.imdrf.org/docs/imdrf/final/technical/imdrf-technical-140918-samd-framework-risk-categorization-141013.pdf](http://www.imdrf.org/docs/imdrf/final/technical/imdrf-technical-140918-samd-framework-risk-categorization-141013.pdf) |                                                                        |
| February 09, 2015  | 27*| Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices | CDRH and CBER                                                          |
|                     |    | [https://www.fda.gov/media/88572/download](https://www.fda.gov/media/88572/download) |                                                                        |
| October 02, 2015   | 19 | Software as a Medical Device (SaMD): Application of Quality Management System | IMDRF and SaMD WG                                                      |
|                     |    | [http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-151002-samd-qms.pdf](http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-151002-samd-qms.pdf) |                                                                        |
| April 20, 2016     | 6  | Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices | CDRH, OPEQ, OHT7, and DMGP                                           |
|                     |    | [https://www.fda.gov/media/90791/download](https://www.fda.gov/media/90791/download) |                                                                        |
| August 24, 2016    | 2  | Patient Preference Information - Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling | CDRH and OCD                                                          |
|                     |    | [https://www.fda.gov/media/92593/download](https://www.fda.gov/media/92593/download) |                                                                        |
| October 24, 2016   | 3  | Parallel Review with Centers for Medicare and Medicaid Services (CMS) | FDA and CMS                                                            |
|                     |    | [https://www.federalregister.gov/documents/2016/10/24/2016-25659/program-for-parallel-review-of-medical-devices](https://www.federalregister.gov/documents/2016/10/24/2016-25659/program-for-parallel-review-of-medical-devices) |                                                                        |
| August 10, 2017    | 4  | Qualification of Medical Device Development Tools                   | CDRH                                                                   |
|                     |    | [https://www.fda.gov/media/87134/download](https://www.fda.gov/media/87134/download) |                                                                        |
| August 31, 2017    | 7  | Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices | CDRH and OPEQ                                                          |
|                     |    | [https://www.fda.gov/media/99447/download](https://www.fda.gov/media/99447/download) |                                                                        |
| September 06, 2017 | 14 | Design Considerations and Premarket Submission Recommendations for Interoperable Medical Devices | CDRH, OSPTI, DDH,                                                      |
|                     |    | [https://www.fda.gov/media/95636/download](https://www.fda.gov/media/95636/download) |                                                                        |
| September 21, 2017 | 20 | Software as a Medical Device (SaMD): Clinical Evaluation            | IMDRF, and SaMD WG                                                      |
|                     |    | [http://www.imdrf.org/docs/imdrf/final/technical/imdrf-technical-170921-samd-n41-clinical-evaluation_1.pdf](http://www.imdrf.org/docs/imdrf/final/technical/imdrf-technical-170921-samd-n41-clinical-evaluation_1.pdf) |                                                                        |
| October 25, 2017   | 8  | Deciding When to Submit a 510(k) for a Change to an Existing Device | CDRH and OPEQ                                                          |
|                     |    | [https://www.fda.gov/media/99812/download](https://www.fda.gov/media/99812/download) |                                                                        |
| October 25, 2017   | 21 | Deciding When to Submit a 510(k) for a Software Change to an Existing Device | CDRH and OPEQ                                                          |
|                     |    | [https://www.fda.gov/media/99785/download](https://www.fda.gov/media/99785/download) |                                                                        |
| December 08, 2017  | 22 | Software as a Medical Device (SAMD): Clinical Evaluation            | CDRH, OSPTI, and DDH                                                    |
|                     |    | [https://www.fda.gov/media/100714/download](https://www.fda.gov/media/100714/download) |                                                                        |
| October 18, 2018   | 11 | Content of Premarket Submissions for Management of Cybersecurity in Medical Devices | CDRH and OCD                                                            |
|                     |    | [https://www.fda.gov/media/119933/download](https://www.fda.gov/media/119933/download) |                                                                        |
| January 08, 2019   | 23 | Developing a Software Precertification Program, A Working Model (v1.0 January 2019) | CDRH, OSPTI, and DDH                                                    |
|                     |    | [https://www.fda.gov/media/119722/download](https://www.fda.gov/media/119722/download) |                                                                        |

Contd...
| Date              | n* | Title                                                                 | Issuer                      |
|-------------------|----|----------------------------------------------------------------------|-----------------------------|
| April 02, 2019    | 24 | Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback | CDRH, OSPTI, and DDH        |
| April 19, 2019    | 9  | Technical Performance Assessment of Quantitative Imaging in Device Premarket Submissions | CDRH and OPEQ               |
| May 07, 2019      | 5  | Requests for Feedback and Meetings for Medical Device Submission: The Q-Submission Program | CDRH, OPEQ, ORP, and DRP1   |
| September 27, 2019| 25 | Off-The-Shelf Software Use in Medical Devices                         | CDRH, OSPTI, and DDH        |
| September 27, 2019| 15 | Clinical Decision Support Software                                     | CDRH, OSPTI, and DDH        |
| September 27, 2019| 26 | Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act | CDRH and CBER               |
| February 09, 2019 | 27 | Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices | CDRH and CBER               |
| January 28, 2020  | 24b| Artificial Intelligence and Machine Learning in Software as a Medical Device - update to: Proposed Regulatory Framework for Modifications to Artificial Intelligence/ Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback | CDRH and CBER               |
| April 24, 2020    | 28 | Enforcement Policy for Remote Digital Pathology Devices During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency | CDRH and OPEQ               |

No* refers to numbering in main Figure 1; a,b Refers to updated guidance documents. CBER: Center for Biologies Evaluation and Research; CDRH: Center for Devices and Radiological Health; CMS: Centers for Medicare and Medicaid Services; DDH: Division of Digital Health; DMGP: Division of Molecular Genetics and Pathology; DRP1: Division of Submission Support; FDA: Food and Drug Administration; IMDRF: International Medical Device Regulators Forum; OCD: Office of the Center Director; OHT7: Office of Health Technology 7; OPEQ: Office of Product Evaluation and Quality; ORP: Office of Regulatory Programs; OSEL: Office of Science and Engineering Laboratories; OSPTI: Office of Strategic Partnerships and Technology Innovation; SaMD WG: Software as a Medical Device Working Group
## Supplemental Table 2: The Alliance Steering Committee and Membership by Sector

| Founders | Affiliation | Sector |
|----------|-------------|--------|
| Jochen K. Lennerz, MD, PhD | Medical Director, Center for Integrated Diagnostics, Massachusetts General Hospital/Harvard Medical School | Academia |
| Esther Abels, MSc | Vice President of Regulatory Affairs, Clinical Affairs and Strategic Business Development, PathAI | Industry |
| Brandon D. Gallas, PhD | Mathematician, FDA/CDRH/OSEL/Division of Imaging, Diagnostics, and Software Reliability | Government |

| Steering Committee | Affiliation | Sector |
|---------------------|-------------|--------|
| Alain C. Borczuk, MD | Professor of Pathology and Laboratory Medicine, Weill Cornell Medicine | Academia |
| Amanda Lowe | Managing Director of Americas, Visiopharm Corporation | Industry |
| Ashish Sharma, PhD | Associate Professor, Department of Biomedical Informatics, Emory University School of Medicine | Academia |
| Clive R. Taylor, MD, DPhil | Professor Emeritus, University Southern California | Academia |
| David A. Clunie, MBBS | Owner, PixelMed Publishing, LLC | Industry |
| Frank R. Dookie, MBA | CEO and President, Sales Management Operations Consulting, Inc.; Strategic Consultant, JAV Advisors Corp. | Industry |
| Gina Giannini, MS | Manager of Regulatory Affairs, Digital Pathology, Roche Tissue Diagnostics | Industry |
| Hetal D. Marble, PhD | Program Manager of Biomarker Development and CDx, Center for Integrated Diagnostics, Massachusetts General Hospital/Harvard Medical School | Academia |
| Jithesh Veetil, PhD | Program Director of Data Science and Technology, Medical Device Innovation Consortium | Nonprofit |
| Joachim H. Schmid, PhD | Vice President of Research and Development, Digital Pathology, Roche Tissue Diagnostics | Industry |
| Jon Hunt, PhD | Vice President of Clinical Science and Technology, Medical Device Innovation Consortium | Nonprofit |
| Keyvan Farahani, PhD | Program Director, National Cancer Institute | Government |
| Lakshman Ramamurthy, PhD | Head of Regulatory Affairs, Precision Medicine and Digital Health, GlaxoSmithKline Inc. | Industry |
| Laura Lasiter, PhD | Director of Health Policy, Friends Of Cancer Research | Nonprofit |
| Mark D. Zarella, PhD | Deputy Director of Informatics, Department of Pathology, Johns Hopkins University | Academia |
| Markus D. Herrmann, MD, PhD | Director of Computational Pathology, Massachusetts General Hospital/Harvard Medical School | Academia |
| Matthew G. Hanna, MD | Director of Digital Pathology Informatics, Assistant Attending Pathologist, Memorial Sloan Kettering Cancer Center | Academia |
| Matthew O. Leavitt, MD | Chairman, Founder, and Chief Medical Officer, LUMEA | Industry |
| Mike Bonham, MD, PhD | Chief Medical Officer, Proscia Inc. | Industry |
| Michael Isaacs | Director of Clinical Informatics and Business Development, Washington University School of Medicine | Industry |
| Pamela W. Goldberg, MBA | President and Chief Executive Officer, Medical Device Innovation Consortium | Nonprofit |
| Richard Huang, MD | Clinical Informatics Fellow, Massachusetts General Hospital/Harvard Medical School | Academia |
| S. Joseph Sirintrapun, MD | Director of Pathology Informatics, Associate Attending Pathologist, Memorial Sloan Kettering Cancer Center | Academia |
| Sarah N. Dudgeon, MPH | Research Fellow, FDA/CDRH/OSEL/Division of Imaging, Diagnostics, and Software Reliability | Government |
| Scott M. Blakely | Business Development Manager of Whole Slide Imaging and Digital Pathology, Hamamatsu Corporation USA | Industry |
| Steven Barbee | President, JAV Advisors Corp | Industry |

### Overall Membership By Sector (Total: 320)

- **Academia:** 102 Members
- **Industry:** 128 Members
- **Government:** 76 Members
- **Nonprofit:** 14 Members

CDRH: Center for Devices and Radiological Health; OSEL: Office of Science and Engineering Laboratories; FDA: Food and Drug Administration
| Question number | Question                                                                 | Answer choices                                                                 |
|-----------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| 1               | How long have you been involved with digital pathology?                  | <1 year<br>1-5 years<br>5-10 years<br>&gt;10 years                             |
| 2               | How many papers have you published about digital pathology?              | Open ended                                                                     |
| 3               | What sector do you represent?                                            | Academia<br>Industry<br>Government<br>Nongovernmental organization<br>Other     |
| 4               | Are you familiar with the MDIC?                                          | Yes<br>No                                                                        |
| 5               | Should patient advocacy groups be a part of the Alliance?                | Yes<br>No                                                                        |
| 6               | FDA regulatory oversight of digital pathology is:                        | Too simple<br>Adequate<br>Too complex                                           |
| 7               | Should the Alliance focus on slide generation as a preanalytical factor? | Yes<br>No                                                                        |
| 8               | Should the Alliance focus on metadata capture?                           | Yes<br>No                                                                        |
| 9               | Which workflow steps should the Alliance focus on?                      | Archive retrieval<br>Preanalytics<br>Slide scan<br>Pixel data<br>Electronic health record<br>Laboratory inventory management system<br>Metadata<br>DICOM<br>Storage<br>Computation<br>Modeling<br>Test validation<br>Deployment<br>Utilization |

DICOM: Digital Imaging and Communications in Medicine (here referring to an interoperable file format for digital pathology); FDA: Food and Drug Administration; MDIC: Medical Device Innovation Consortium