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Subject: MDDT PROPOSAL

Submission Type: Q-SUBMISSION: INFORMATIONAL MEETING REQUEST

Office: **Office of In-Vitro Diagnostics and Radiological Health**

Division: **DIVISION OF MOLECULAR GENETICS & PATHOLOGY**

Branch ((if known; in bold print):

Lead reviewer (if known; in bold print):

MDDT Name: TILs Annotated Dataset

MDDT Type: NONCLINICAL ASSESSMENT MODEL

Context of Use: This tool is a dataset of slides, images, and annotations that may be used for the analytical validation of a sponsor's artificial intelligence or machine learning algorithm that quantifies tumor-infiltrating lymphocytes in images from whole slide imaging systems of hematoxylin and eosin stained slides containing breast cancer. The tool includes a statistical analysis plan and software to carry out the statistical analyses.

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1. Name and Address of Investigator-Sponsor

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2. Proposal Phase Goal

The goal of the Proposal Phase submission is to assess agency interest in a dataset as an MDDT and discuss opportunities for standardization of algorithm validation.

Appendix A lists key questions needing to be addressed. Via an informational meeting with the agency, we wish to begin answering these questions with your regulatory team.

3. Category of Development Tool

The TILs dataset fits most closely with a non-clinical assessment model (NAM) in that it provides data for the testing of algorithms in order to measure device performance.

4. Medical Device Clearance or Approval

The dataset is not a cleared or approved medical device. It will be used as a standardized validation dataset for algorithm submissions to the agency, which fit the context of use.

5. Abbreviations

- AI: Artificial Intelligence
- BC: Breast cancer
- CTA: Computational assessment of tumor-infiltrating lymphocytes
- HTT: High-throughput truthing
- H&E: Hematoxylin and Eosin
- ML: Machine Learning
- ROI: Region of interest
- sTIL: tumor-infiltrating lymphocyte in tumor-associated stroma
- TIL: Tumor-infiltrating lymphocyte
- VTA: Visual assessment of tumor-infiltrating lymphocytes
- WSI: Whole slide imaging
- WSI system: Whole slide imaging system
- WSI image: Image from whole slide imaging systems

6. Context of Use

This tool is a dataset of slides, images, and annotations that may be used for the analytical validation of a sponsor's artificial intelligence or machine learning (AI/ML) algorithm that quantifies tumor infiltrating lymphocytes (TILs) in images from whole slide imaging systems (WSI images) of hematoxylin and eosin (H&E) stained slides containing breast cancer (BC). The tool includes a statistical analysis plan and software to carry out the statistical analyses.

The images will be scanned on currently cleared WSI systems.

The annotations in this dataset are the percent of tumor-infiltrating lymphocytes in tumor-associated stroma (sTILs) in regions of interest (ROIs) collected from multiple pathologists using the gold-standard technology, the microscope. We call these annotations Visual TIL Assessments (VTAs). Briefly, a VTA in an ROI equals the area occupied by sTILs divided by the area of tumor-associated stroma. This is referred to as sTILs density or the percent sTILs when multiplied by 100. For more details on VTA, please refer to guidelines published by the International TILs Working group (Salgado, R. et al, 2014).

Using eeDAP, an evaluation environment for digital and analog pathology, VTAs will be collected on the microscope and mapped onto the images. This mapping is possible because eeDAP is a software and hardware platform for designing and executing digital and analog pathology studies where evaluation of ROIs in the digital image are registered to the real-time view on the microscope.

The MDDT data will allow an investigator to conduct an analytical validation of an AI/ML algorithm as outlined in the "SaMD guidance", FDA's document titled "Software as a Medical Device (SaMD): Clinical Evaluation - Guidance for Industry and Food and Drug Administration Staff" (FDA CDRH, 2017). The investigator will not have to design or execute the study. The investigator will not have to source slides or recruit pathologists. The investigator will not have to plan statistical analyses. The investigator will be able to run their algorithm on the images to produce a computational assessment of TILs (CTA) that can be compared with VTAs from pathologists. The comparison will follow the MDDT statistical analysis plan using the MDDT statistical analysis software. The investigator will be able to report the results in the analytical validation component of the device submission. Both the data and the software components of the MDDT will be made available to the public.

The TILs MDDT dataset is limited to use by algorithms meant to evaluate sTIL density in breast cancer.

7. Development Tool Description

Study Prep: Glass slides of H&E stained BC will be scanned on an FDA-cleared WSI system. Multiple pathologists will evaluate the WSI images to create ROIs that are 500x500 um (1000x1000 pixels at 0.5 um/pixel: 20X equivalent). ROIs will be placed

within the tumor, along the tumor margin, external to the tumor, and in regions labeled as, “other.”

Data Collection: Using eeDAP, the ROI boxes created on the digital image will drive the microscope to the same locations on the corresponding glass slides. The study pathologists will evaluate the ROIs using the microscope, delineated by a marker within the microscope reticle. The pathologists will provide their VTA (percent sTILs) and it will be recorded digitally within the eeDAP system software.

The ROI approach to image evaluation allows for a location-specific evaluation of the algorithm. The ROI approach also directs the collection of multiple truthing annotations from different pathologists to allow for a location-specific accounting of the variation in the pathologist VTAs. Once it is established that the algorithm CTAs adequately agree with the pathologist VTAs on square ROIs, this agreement is expected to generalize to ROIs of different sizes and shapes and ROIs defined by tissue features. For example, ROIs could be irregular regions defined by the tumor or tumor boundary. Please refer to the VTA guidelines published by the International TILs Working group (Salgado, R. et al, 2014).

Dataset collection plan is demonstrated in Figure 1 below.

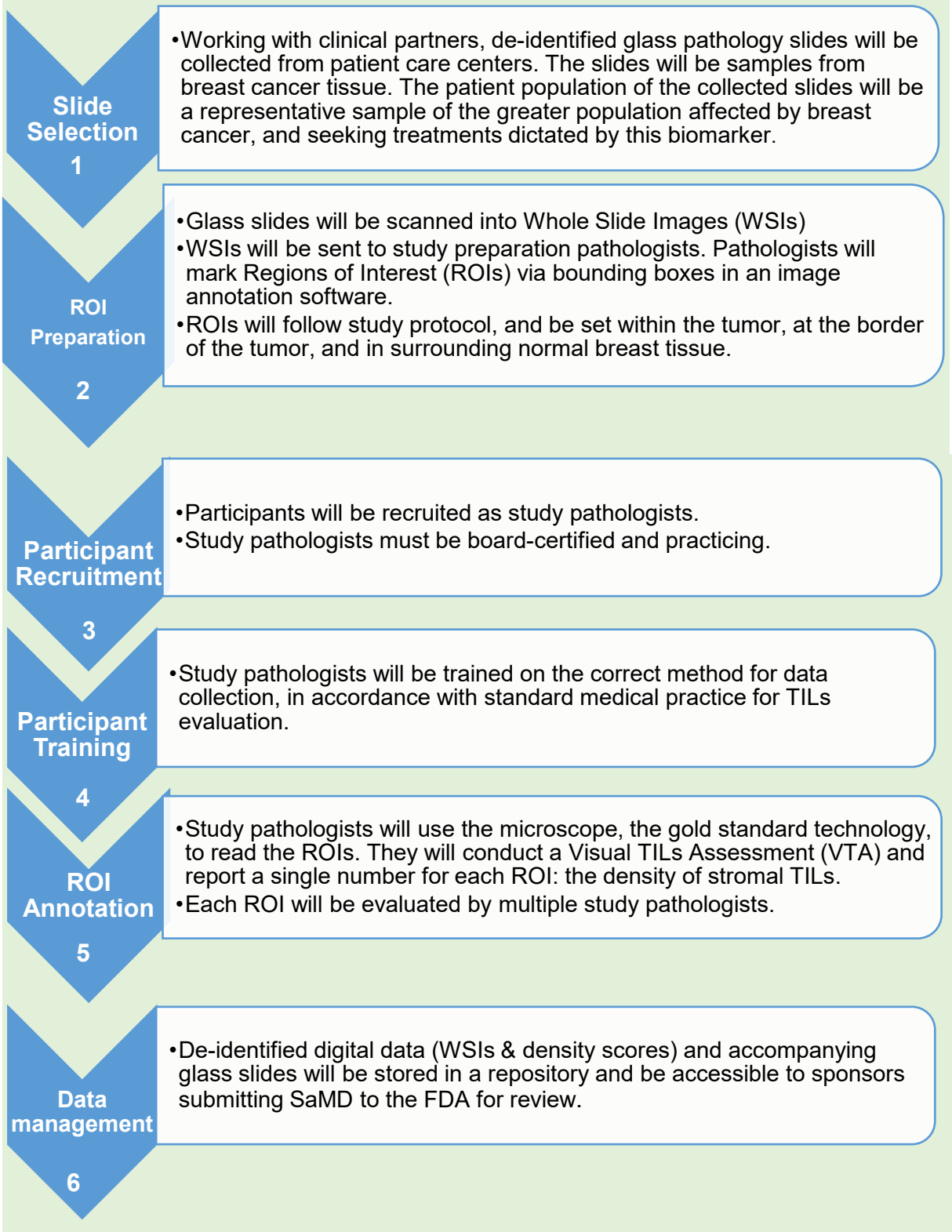


Figure 1: demonstration of pipeline for MDDT data creation.

Why TILs?

In March of 2019 at the 16th St Gallen International Breast Cancer Conference, the Expert Committee concluded that characterizing and reporting of TILs in triple-negative breast cancer (TNBC) should be routinely included in pathology reports. As a promising new biomarker in the prognostic and treatment space, several teams are working on new products and challenges to design machine learning algorithms for their evaluation.

The Focus Group in AI for Health (FG-AI4H), in association with the World Health Organization (WHO) and the International Telecommunications Union (ITU), has chosen TILs in Breast Cancer as their primary use case for the evaluation of AI for Health. They have chosen TILs due to its recent classification as described above and the morphologic variance represented in the pathology slides. Breast Cancer slides for TIL evaluations contain multiple tissue compartments such as glands, tumor, stroma, and necrosis, as well as a myriad of different cell types. The WHO and ITU believe that this morphologic variance presents an ideal use case for the stress testing of AI algorithms as it is both challenging and an exciting new addition to the field of cancer evaluation.

The association between TILs and outcome in BC was first reported by Aaltomaa and colleagues in the early 1990s (Aaltomaa et al., 1992). Since this report, many other investigators have studied and, very recently, validated the prognostic and predictive value of TILs using material collected from several randomized clinical trials including thousands of patients (Savas et al., 2016). While association is established via multitudes of studies, the association is possibly underestimated due to inconsistent measurement.

In 2010, Denkert and colleagues demonstrated that the lymphocytic infiltrate on pre-therapeutic core biopsies predicted pCR in response to anthracycline/taxanes neoadjuvant chemotherapy (Denkert et al., 2010). The association between response to neoadjuvant chemotherapy and TILs has been confirmed in numerous other reports (Issa-Nummer et al. 2013; Ali et al. 2016; Ono et al. 2012; Solinas et al. 2017).

In the adjuvant setting, the prognostic value of TILs was investigated retrospectively using material from a phase III trial (BIG 2-98) including more than 2,000 patients. In this study, stromal and intratumoral TILs were more abundant in ER-negative/HER2-negative and HER2-positive tumors than in ER-positive/HER2-negative tumors. TILs were shown to be associated with a better prognosis in ER-negative/HER2-negative BC (Loi et al. 2013). The prognostic impact in this BC subtype was later confirmed in two other reports from phase III adjuvant chemotherapy trials involving anthracycline-containing regimens, supporting TILs as an independent prognostic biomarker in TNBC (Adams et al., 2014; Loi et al., 2014). TILs were evaluated as a continuous variable, and each 10% increment was associated with a reduction in the risk of distant recurrence varying between 13% to 18%, depending on the study. Tumors with the highest TIL infiltration (50% lymphocytic infiltration of either tumor epithelium or stroma) were categorized as lymphocytic-predominant BC (LPBC). Although this subgroup included a

lower number of patients, it was associated with the best outcome, highlighting the very good prognosis for patients with extensive TIL infiltration. The association between TILs and a better outcome after anthracycline-based chemotherapy supports the hypothesis that a pre-existing host immune response might enhance the effect of immunogenic chemotherapy such as anthracyclines (Galluzzi et al. 2016). TILs may also be associated with PD-1/PD-L1 cellular interactions. In a study by Kitano et al. (2017), expression of PD-L1 and PD-1 is associated with higher TIL densities and pCR. Anti PD-L1 treatment has already been approved with promising results in treating metastatic TNBC.

The prognostic value of immune signatures has been shown in systemically untreated ER-negative/HER2-negative and HER2-positive tumors from several gene expression datasets (Desmedt et al., 2008; Bense et al., 2017). The prognostic role of TILs in untreated patients shows in TNBC that early stage patients with high TILs have >98% 5-year survival (Park et al., Annals of Oncology). This has now been investigated in an additional study aiming to assess the prognostic value of TILs in adjuvant chemotherapy-treated (anthracycline-based regimen) and this shows exactly the same, namely >98% 5-year survival if an early stage patients has high number of TILs (unpublished data, but available at request). These observations are the trigger to include TILs in daily practice and clinical trial designs.

In HER2-positive BC, higher sTILs predicted benefit of anthracycline-only adjuvant chemotherapy in the BIG2-98 trial, and to trastuzumab in the FinHER trial (Loi et al. 2013; Loi et al. 2014). This latter observation suggested that an immune response contributes to trastuzumab's anti-tumor effect (Bianchini et al. 2014), also supported by gene-expression analysis (Perez et al., 2015). A recent large phase III adjuvant trial including women with HER2-positive BC patients confirmed the prognostic value of sTILs, but did not observe trastuzumab benefit in patients with high TIL levels (Perez et al., 2016). These conflicting results could be due to the low number of events in the trastuzumab arm in Perez et al., which was therefore likely to be underpowered to confirm the results of the FinHER trial (Loi et al., 2014; Perez et al., 2016). The presence of increased sTILs has was recently reported to be associated with increased overall survival in HER2-positive metastatic BC, suggesting the prognostic value of TILs assessed in primary tumors extends to the advanced setting (Luen et al., 2016).

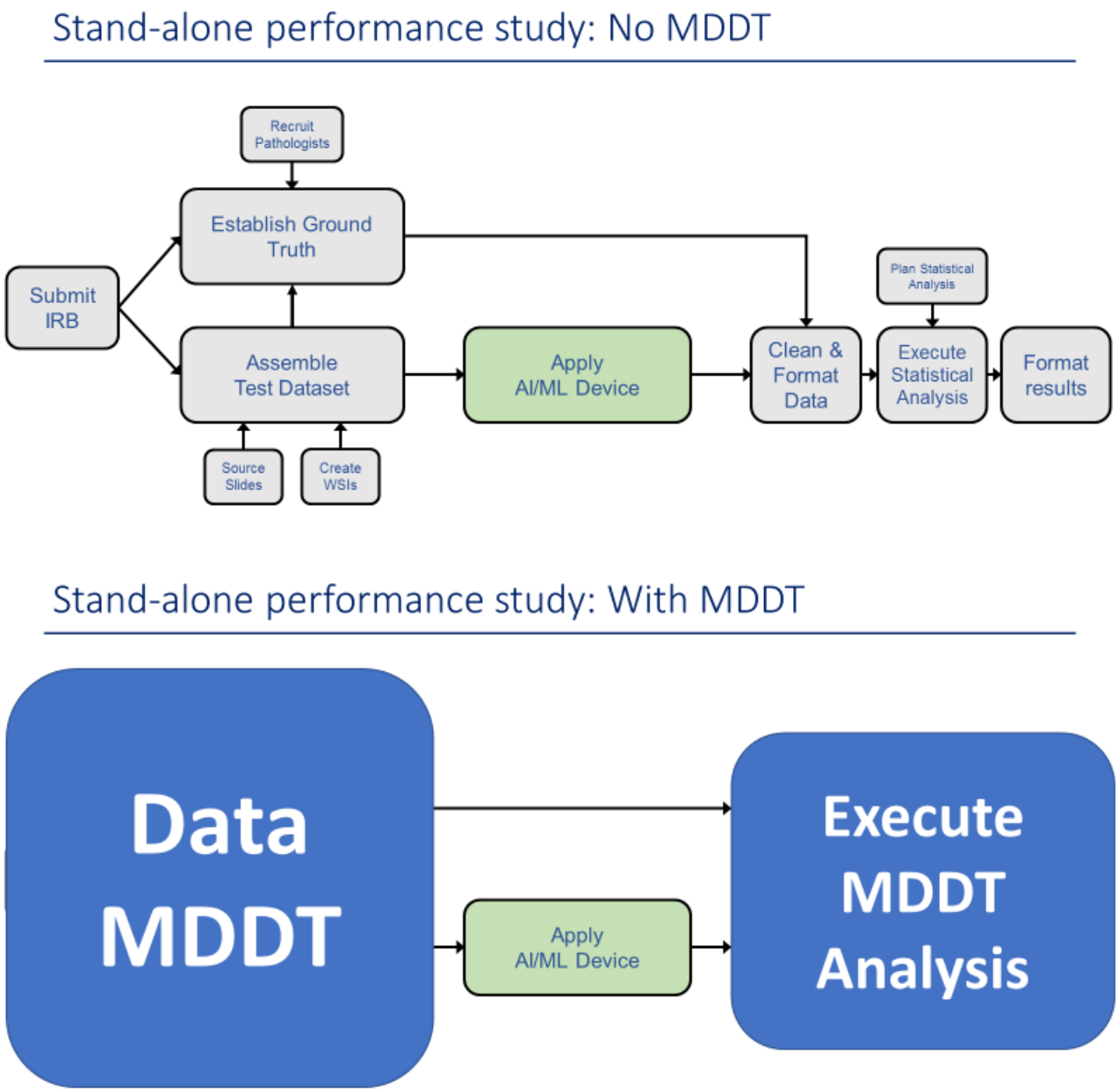
Describe an example medical device which would use this tool

In the clinic, patients that are TNBC by immunohistochemical testing (negative for human epidermal growth factor receptor 2, estrogen receptor, and progesterone receptor) will undergo a biopsy or resection of the affected tissue. H&E stained slides will be prepared and digitally scanned to generate WSI images. A pathologist reviewing the slides is expected to report his or her VTA. The pathologist marks ROIs given various tumor boundary assessments according to the VTA clinical guidelines (Salgado, R. et al, 2014). The medical device in this case is an algorithm which is activated to produce estimates of the percent sTILs in the ROIs. The sTIL percentage can then be reported in the patient's pathology report.

Example use of the tool in an Analytical Study
The tool will be used to simplify the submission of the device evaluation from the sponsor to the FDA. This streamlined submission will additionally ease the burden of review by the FDA. Figures 2 and 3 highlight the use of the tool.

In Figure 2 we show an example stand-alone performance study. This study has burdensome data-collection elements: Submitting IRB, Sourcing slides & Creating WSI images for Assembly of test dataset, and Recruiting pathologists for Establishment of ground truth. In Figure 2 we also see burdensome data-analysis elements: Cleaning & formatting data, Planning and executing statistical analyses, and the Formatting of results. In Figure 3, we show how the MDDT data and statistical analysis plan can be used to reduce the burden to the sponsor.

Within FDA's document titled "The Least Burdensome Provisions: Concepts and Principles", the FDA defines "least burdensome" to be "the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time." This MDDT is created in the spirit of those guiding principles.



Figures 2 & 3: diagrams of example analytical (i.e. standalone performance) studies submitted to the FDA both with and without the proposed MDDT. Note that in Figure 2, the sponsor doesn't need to recruit readers, source any slides, or design the statistical analyses.

8. Justification: How the Tool Meets a Public Health Need

How the tool supports the Patient

The primary impact expected is innovation. The MDDT dataset will encourage sponsors to create algorithms for the TILs clinical use case. Additionally, this MDDT will also help

develop non-TILs-counting algorithms as it will establish best practices and development methods for clinical trials for AI in the space.

This MDDT addresses a topic of high clinical relevance. In March of 2019, TIL analysis was added to the standard of care for breast cancer diagnosis by the St. Gallen Commission. TILs are a topic of interest to physicians and point of care specialists who will be seeking aids in this space as there is a current dearth of TIL validation resources.

It is possible to harness algorithms, such as the ones which will use this MDDT dataset for validation, to increase patient impact. The primary method of patient impact is accessibility. Assessment of TILs can take place in geographically remote locations where specialists are scarce. Algorithms have the opportunity to bring life-saving medical solutions to those who currently cannot receive access to care. Additionally, the algorithms expected to use the MDDT dataset will be the first in this domain, a necessary first step to algorithms that have more impactful outputs, like prognosing survival or predicting therapy outcomes. There are plans to expand the dataset in the future to incorporate patient outcomes, this will allow for more impact on patient management.

The proposed MDDT can also ensure that a validated ML-tool is used for drug trials.

How the tool supports the FDA

The proposed MDDT can be a roadmap for medical device sponsors to follow as they plan their own algorithm evaluations for other clinical use cases. This MDDT can also be a roadmap for other stakeholders (clinical societies, collaborative initiatives, or patient advocacy groups) to follow as they might want to create similar datasets to support the field in bringing algorithms to market and to monitor algorithms on the market. Having the community follow a common roadmap will lead to better submissions, faster reviews, and more capacity and experience to consider algorithms with broader impact (adaptive algorithms and automatic diagnosis algorithms), all cycling back to faster patient access to life-saving technologies.

There is currently no common “apples to apples” evaluation metric amongst all quantitative imaging AI devices which evaluate the same clinical use case. This poses a significant problem for reviewers, and the potential for an impact in safety for the patient. We propose this MDDT to offer such equivalent comparison for all algorithms given this clinical use case.

The proposed MDDT is meant to simplify a reviewer’s evaluation of a sponsor’s analytical validation. Reviewers will not need to evaluate the study design and statistical analysis, just the performance results. This will leave more time to evaluate alternate submission sections, or faster turn-around time for decision summaries. Furthermore, when comparing various devices with similar use cases, reviewers could evaluate devices on an equal playing field, via the standardized validation dataset.

Particularly when addressing adaptive algorithms, the TILs MDDT is a roadmap for collecting more data after qualification that may be used (in part or in total) to explore questions about generalizability, algorithm change protocols, monitoring, and ensuring non-inferiority between later versions of the medical device and its initial submission.

How the tool supports Industry
The dataset tool offers industry decreased clinical trial efforts and expenditures and increased submission clarity. This MDDT additionally increases sponsor accessibility to FDA approval, prompting increased innovation in the space, with particular benefit to startups and other teams with limited funding for clinical research and access to well curated datasets**.** All above reasons will create a feedback loop into increased patient access to better technology, and potentially better patient outcomes.

9. Readiness of Tool and Timeline

The HTT Project Leadership has convened to address ongoing discussions over final protocol selection. They wish to ensure that the data-collection methods are in line with FDA current thinking. Acceptance into the MDDT program will ensure protocol questions are answered before expensive data collection begins. The team has begun testing the data-collection tools and will prepare technical infrastructure before the end of 2019. We have multiple sites interested in sharing slide data and access to their pathology team. We are working on the research collaboration agreements that will govern this work. We plan to visit collaborating organizations to collect data in the first quarter of 2020 and will continue until a complete dataset is obtained. The size of the complete dataset (and the number of data source sites) will be determined via statistical simulation data and analysis, and in consultation with the FDA during the MDDT pre-qualification phase. The team will then begin collecting data from pathologists.

During the pre-qualification phase, the HTT team will develop the statistical analysis plan that users of the MDDT data may follow. The statistical analysis development will incorporate simulated data, early collection data from real pathologists, and consultation with the FDA. The HTT team will then establish an appropriate storage environment for the MDDT dataset. The team will also establish appropriate sharing mechanisms (controlled or free release), in consultation with the FDA, mindful of human subjects data and assurance of use only after algorithm training is complete.

10. Questions

1. As we explore sizing our study, we would like to hear FDA's thoughts on the number of sites to use to source slides, the number of slides per site, and the number of readers per slide.
2. As we begin sourcing slides, we would like to know FDA's thoughts on sourcing breast cancer cases without and with triple-negative IHC status. We feel that cases without TNBC status could be used to effectively evaluate algorithms and would be more readily available

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