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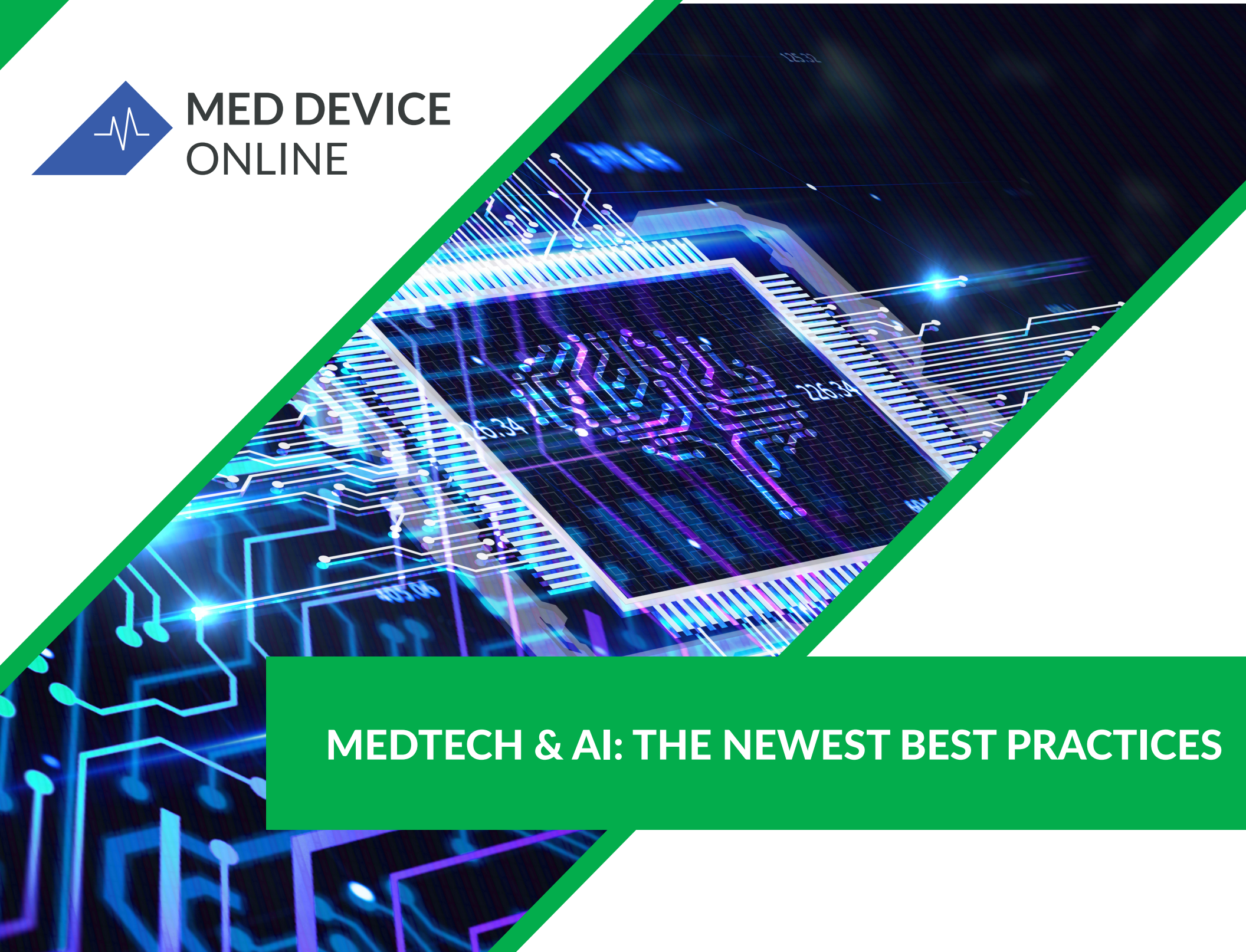
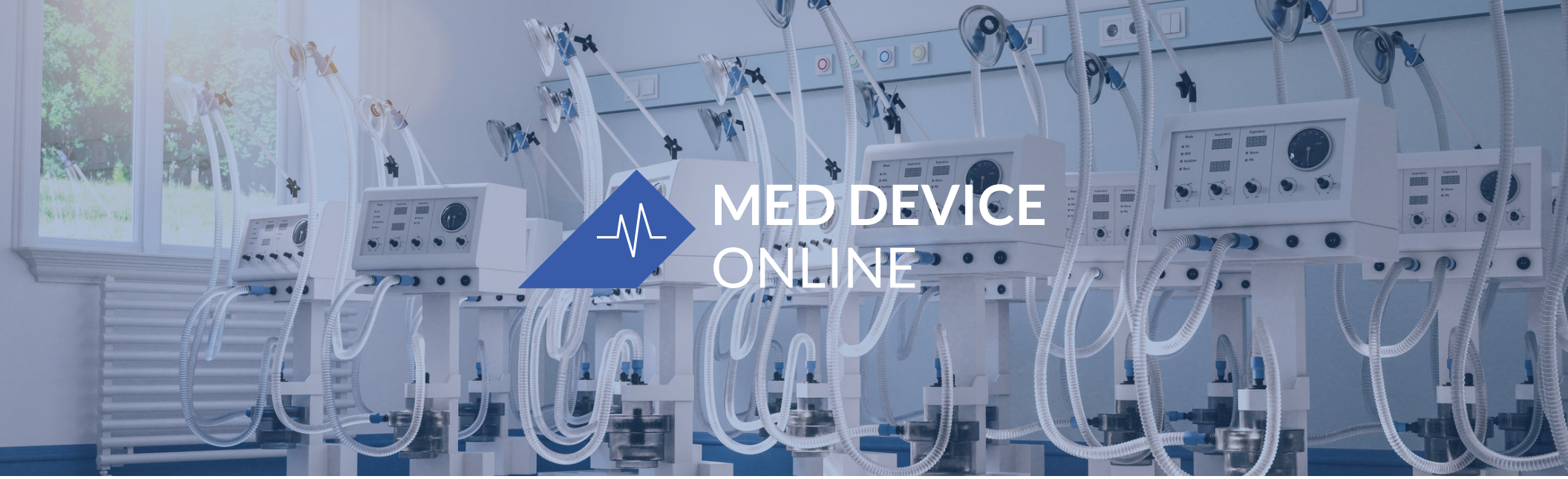


MEDTECH & AI: THE NEWEST BEST PRACTICES



MED DEVICE ONLINE

Artificial intelligence (AI) and machine learning (ML) are taking the life sciences world by storm. Do you know how to harness its power for your medical device?

In this e-Book, the first article examines how AI in medical devices is transforming multiple sclerosis (MS) diagnosis, monitoring, and treatment. Then, one of the physicists involved in helping advance breast health solutions through AI shares his very topical lessons learned from his experiences. Next, the e-Book delves into what AI and continuous validation have in common (hint: A lot!).

The last two articles in the e-Book examine regulatory requirements for AI: one article explains four topic areas to obtain global regulatory approval for your AI/ML-enabled medical device. The last article concludes by describing the upcoming “data effect” tsunami from the US FDA and the eight steps you should take to prepare for it. Are you ready?

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CONTENTS

HARNESSING THE POWER OF AI IN MS DIAGNOSIS, MONITORING, AND TREATMENT

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EXPERT NETWORK

Applications of artificial intelligence (AI) are rapidly expanding in healthcare, including the handling of administrative logistics at hospitals, assessment of patient health data, and analysis of novel molecules in drug discovery. A prime example of the future potential of AI is in revolutionizing the way we diagnose, monitor, and treat multiple sclerosis (MS), thereby advancing our understanding of the disease course. Today, MS continues to be a difficult disease to diagnose and treat because the underlying etiology remains unknown. Persistent challenges in the current treatment approach to MS include a lack of reliable biomarkers, making patient diagnosis, disease monitoring, and drug discovery challenging. To maximize the utility of AI in MS, drug developers and medtech manufacturers must strategically incorporate AI solutions into their approach to MS drug development and commercialization.

LEVERAGING AI TO ENHANCE THE DIAGNOSIS OF MS

Recent breakthroughs in AI research have demonstrated that computer-aided diagnosis can facilitate the early detection of MS via classification, quantification, and identification of diagnostic patterns in medical images. These enable earlier treatment interventions to reduce long-term MS-related disability. Data generated using AI techniques are analyzed automatically, taking the place of labor-intensive and time-consuming manual methods.

Diagnosis Disruption Factors: AI platforms may allow for diagnosis of MS through identification of indolent clinical characteristics that a physician may not otherwise notice. Earlier detection of MS has been shown to result in improved clinical outcomes and a reduced burden on the healthcare system.[1] Developing these platforms requires the compilation of large clinical data sets to power the detection

of MS patients. The ability to reference large reservoirs of clinical data can be used to power precision-based medicine, tailored to each patient, as MS subpopulations become evident.[2] Accurate, cost-effective AI diagnostic tools for MS may allow physicians to treat more patients more effectively in the future, but it will be critical to understand where these streams of patient data are sourced and who manages them to effectively capture the required "building blocks" of AI from integrated health networks or large payer systems. These capabilities hinge on access to large patient databases, a potential barrier to development, as access to sensitive data remains a challenge for data privacy.

DIAGNOSIS CASE STUDIES

AI's utility in specific applications shows how it can be employed to improve the diagnostic approach to MS:

- ***Machine Learning Diagnostic Tools for MS Proof of Concept:*** S. Sharifmousavi and M. Borhani (2020) recently demonstrated that a support vector machine algorithm can accurately diagnose MS using patients' plasma selenium, vitamin B12, and vitamin D3 counts.[3] Aberrations in these vitamin levels are associated with a risk of developing MS and disease activity. The AI developed by these researchers was able to accurately differentiate between patients previously diagnosed with MS and control subjects, using only data on the blood levels of these biomarkers. This proof of concept establishes the potential of AI to elevate clinicians' approach to diagnosing patients with MS.[4]
- ***Eye Detection and AI Technology Potential to Identify MS:*** C Light Technologies, a neurotech and AI company, has developed an eye-tracking technology paired with machine learning that can be used to detect MS. C Light's machine learning algorithms and instruments have potential to allow for earlier and more accurate prognosis of MS, leading to better patient outcomes and reduced overall healthcare costs.[5]

BETTER MONITORING OF MS PATIENTS USING AI

Innovations in digital disease tracking technology may allow for the accumulation of real-world (RW) patient data in real time that can be integrated into burgeoning machine learning databases such as those being developed for MS. Advances in data collection technology, such as developments in biosensors and disease tracking applications for smartphones, unlock access to an unprecedented wealth of disease data. Using AI technology to sift through and derive meaningful patient care implications will be essential to capitalizing on these novel databases.

Disease Monitoring Disruption Factors: Physicians may use digital disease tracking technology to monitor their patients remotely, requiring in-office consultations only at precise milestones during disease progression and allowing for improved patient clinical outcomes and satisfaction. Another potential disruption factor of integrating AI into MS disease monitoring is the potential to broaden clinical understanding of the disease. In-office clinical consultations capture a snapshot of patients' disease etiology, limiting the current treatment approach. Evolving toward the use of remote monitoring AI devices elevates the potential for superior clinical outcomes by capturing a patient's comprehensive clinical profile, which may be leveraged for a more tailored treatment approach.

MONITORING CASE STUDIES

Combined with advances in data tracking technology, specific developments in AI indicate future changes in MS disease monitoring:

- ***Use of Biosensors and AI to Track Patient Disease Progression:*** Researchers from AbbVie and the University of California San Francisco used biosensors to track MS disease progression in Phase 2 clinical trials for patients receiving elezanumab, a monoclonal antibody currently under investigation to treat MS. The researchers believe that this RW data, gathered through patients wearing biosensors, could be leveraged to better capture patient prognosis, track their disease progression, and select appropriate clinical intervention.[6]
- ***Remote AI Monitoring Device for MS:*** Outside of the academic setting, remote AI monitoring technology is beginning to gain traction among large drug manufacturers. Tools such as FLOODLIGHT MS, a smartphone-based digital assessment suite for MS in development by Roche and Genentech, are attracting attention for the way they can deliver novel measures to help detect if, and how, the underlying causes and symptoms of the disease are evolving.[7]

IMPROVED DRUG DISCOVERY PLATFORMS

Integration of AI approaches into pharmaceutical and biotech drug discovery platforms has the potential to expedite the identification of novel biologic therapies for challenging diseases like MS. ***Drug Discovery Disruption Factors:*** AI is set to disrupt the drug discovery process across multiple disease spaces, including MS, because of its ability to enable a rapid and less labor-intensive drug discovery platform.

DRUG DISCOVERY CASE STUDIES

Specific advances in AI technology illustrate the potential for integration of this technology into current drug discovery platforms:

- ***Use of AI with an In Vitro Model to Power MS Drug Discovery:*** AxoSim's NerveSim, powered by Nerve-on-a-Chip, allows for the identification of neurological therapies for diseases like MS by leveraging an in vitro model to monitor the impact of drug candidates on the electrophysiological properties and cell-cell interaction of Schwann cells. This drug discovery platform more accurately represents human physiology, with the potential to reduce clinical failures and enable companies to develop effective drugs rapidly and at lower costs.[8]

- ***AI Model to Identify Novel Biologic Drug Candidates:*** Another development has been the Alphafold 2 model from Google Deepmind, which recently demonstrated its ability to predict a protein's 3D structure based on amino acid sequence at the Critical Assessment of Structure Prediction (CASP) challenge. During the CASP challenge, the Alphafold 2 model was found to be nearly as accurate as gold-standard experimental techniques, like cryo-electron microscopy, which are laborious and expensive.[9]

CONCLUSION

AI has the potential to revolutionize the ways in which we diagnose, monitor, and treat MS. Effective application of these technologies could lead to improved clinical outcomes at reduced costs, provide a platform for precision-based medicine, and expedite the development of the next generation of MS treatments. Drug developers and medtech companies must understand how to incorporate AI into their drug discovery platforms and approaches to developing diagnostic tools, especially in nuanced disease areas like MS. To do so, the sources of required patient and market data must be accessible to all stakeholders as the building blocks of AI. If these data can be consolidated and accessed across the value chain, AI technology can become the focal point of the drug discovery process and the treatment paradigm for MS. While it is clear that AI will be a critical factor in drug development and treatment of MS, the integration of AI into healthcare is not limited to MS. Drug developers operating in other diseases, particularly those with high unmet needs, poorly characterized underlying pathways, and expensive and burdensome drug discovery approaches, must be able to understand and harness the utility of AI to be successful in the coming years.

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4 LESSONS FOR AI IN MEDTECH: CASE STUDIES FROM BREAST CANCER DETECTION

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The detection and prevention of breast cancer has come a long way in the past 20 years, thanks to advances in digital mammography and 3D mammography. Radiology diagnostic performance is improving, death rates are declining, and more individuals in the United States and around the world are getting access to state-of-the-art screenings. Now, recent advances in machine learning, especially deep learning, are poised to help further advance the detection and diagnosis of breast cancer.

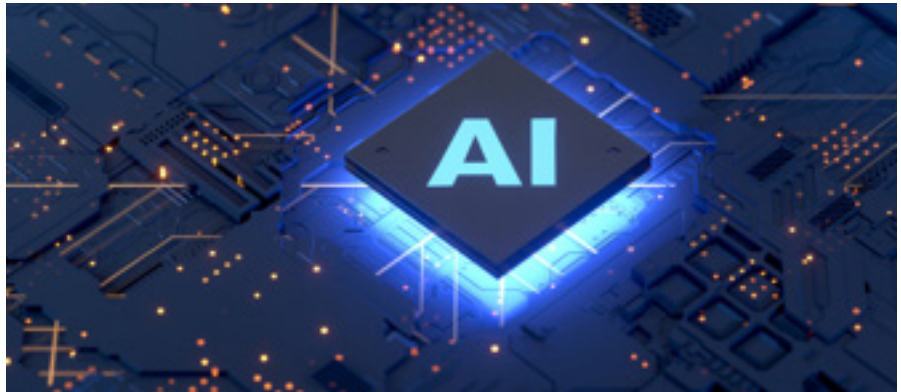
As one of the physicists involved in helping advance breast health solutions through this inspiring artificial intelligence (AI) evolution, I'm at once very pleased with our progress and acutely aware of how we got here and how much further we will go. Across the medical industry, research and development teams are working diligently to bring new AI-fueled innovations to life. However, as promising as this advancing technology is for bringing greater certainty and peace of mind to the patients and healthcare professionals who care for them, many challenges must be overcome, especially as regulators wrestle with how to assess these increasingly complex technologies.

Leveraging the development of the mammography technology, this article shares lessons learned and key considerations for successfully bringing the AI medical devices reliably to life – from concept through development, approval, launch, and adoption.

QUICK OVERVIEW OF REFERENCED TECHNOLOGIES

Before jumping right in, let's define our terms. For reference:

- AI is a broad term used to describe machines or computers that mimic functions of human cognition.
- Machine learning (ML) technology is a subset of AI. It uses statistical models that can be trained using known data samples to perform a task at hand, such as detection of specified features from images.



- Deep learning (DL) is the next generation of machine learning. It uses the massive computational power offered by graphical processing units (GPUs) to train very complex statistical models that contain hundreds of layers of parameters and are therefore referred to as "deep."

LESSON 1: AVOID UNINTENDED CONSEQUENCES

In screening, trained radiologists read mammogram images of the general population to identify potential abnormalities. Even the best performing radiologists find some cancers, miss some cancers, and falsely identify non-cancers. Typically, a radiologist reviews four digital image sets per individual, two per breast, on a computer screen. While this takes time and produces some errors, it is a vast improvement in efficiency and accuracy over the old days of relying on manual exams and/or reviewing X-ray films on light boxes. The latest technology, 3D mammography, requires the radiologist to review hundreds of images per individual.

About 20 years ago, radiologists began using computer-aided detection (CAD) as a virtual second opinion for breast cancer screenings.

The original CAD algorithms worked by searching mammograms for characteristics of breast cancer. AI scientists programmed software to detect these "features," and then modified and trained the algorithms to maximize their performance. In clinical use, the CAD system scans mammogram images, searching for and marking potential abnormalities for human review. This breakthrough technology was designed to improve detection accuracy by helping radiologists avoid overlooking pathologies.

It went through clinical trials and studies, gained regulatory approval, and quickly found its way into the real world. So far, so good.

Eventually, however, clinicians in the field identified limitations. One limitation was the CAD algorithm missed many cancers. And more importantly, in the real world, where only about five in every 1,000 U.S. women has cancer that can be detected using mammograms, the algorithm generated marks on nearly every study, necessitating review of each of the "false" marks, so as to avoid missing cancers.

This was a significant lesson learned. That product aimed to help radiologists avoid missing a cancer they may have overlooked. In the real world, it probably did make a small positive difference in cancer detection, but it certainly also increased the radiologist's workload in reviewing and dismissing all the false marks.

It is important to be super diligent in thinking through all the implications of an AI product, including its initial purpose and all the ways the product might change users' behavior.

LESSON 2: RECOGNIZE THAT AI ALGORITHMS WORK BEST USING OBJECTIVE TRUTH

The next tough lesson comes from a product developed to measure breast density. For reference, breast density is the amount of fibrous and glandular (heavier) tissue compared with the amount of fatty (lighter) tissue. In mammography, this is important for two main reasons: 1) dense breasts have a higher risk of getting breast cancer, and 2) mammograms of dense breasts are less accurate. In the U.S. radiologists routinely report on breast density and, in some states, clinicians must notify patients found to have high density breasts because of the risks cited above. With this purpose, an algorithm was programmed to read a mammogram and provide an assessment of breast density. These original algorithms were determining objective breast density for which an algorithmic approach was available, so AI was not needed in this initial product.

However, once in use on market, some radiologists objected, because the product, even though calculating breast density in a "true" manner, often disagreed with their subjective assessments. Additionally, during this time, the actual clinical definition of breast density that a radiologist would use changed to a more subjective measure. State-of-the-art breast density algorithms use machine learning, not to more accurately determine actual breast density, but rather to more closely mimic how a radiologist will assess breast density, regardless of the "truth" of the radiologist's assessment.

Machine learning requires objectively factual data be input in order for the algorithm to learn what the truth is and to train to identify it. However, with breast density, the quality of the training data is not precise.

Therein lies the lesson. Breast density is a subjective measure based on the radiologist's assessment – no single truth exists. In fact, oftentimes two radiologists reviewing the same mammogram will rate breast density differently

(known as inter-reader variability), just as the same radiologist might if some time has lapsed between assessments of the same mammogram (known as intra-reader variability). The lack of established real truth of breast density is a challenging application for AI. How can one design an algorithm that will agree with all radiologists if they don't agree amongst themselves?

LESSON 3: DEFINE THE QUESTION YOU WANT TO ANSWER, & DON'T BE AFRAID TO PIVOT IN YOUR END GOALS

There are several areas where clinical performance in mammography can be improved. One is improving cancer detection by helping radiologists avoid missing cancers. This was the goal for the original CAD product. Another goal is to help reduce false positives, which limits unnecessary additional imaging and reduces healthcare costs. Yet another is to address the radiologist's workload, which has only become worse with the introduction of 3D mammography and its hundreds of images. Each of these are useful goals for an AI product.

For example, if the goal is breast cancer detection, then the AI must learn to identify all signs of potential abnormalities, even faint ones. The trade-off is the AI likely also generates more false positives. But this may be a trade-off that customers are willing and able to make.

Consider another example where we want to reduce false positives. In the United States, to find the on average five cancers per 1,000 women, a full 10%, or 100 women are called in for follow-up exams, and being called back in often causes emotional stress to the patient, as well as financial strain (e.g., taking work off, arranging for childcare, paying deductible, etc.) and physical discomfort. It also increases the total cost of care. If AI can help reduce a fraction of these false positives up front, it can improve healthcare and reduce costs. However, unless the AI is totally accurate, the risk is reducing false positives might also mean that, hopefully rarely, a cancer is overlooked. But this eventuality needs to be considered and weighed.

If the population of 1,000 women only has five cancers, then 995 mammograms do not show disease. Can we use AI to find these? If AI can help identify even a fraction of these disease-free mammograms, then potentially these mammograms will not need to be carefully read by radiologists, as they are today. In such a scenario, the physician's workload is reduced without adversely affecting patient care.

In these three examples, regardless of the problem you aim to solve, the AI is trained on the same data, i.e., verified mammogram images, but programmed differently. For the reasons described above, each algorithm is created to serve a specific purpose in solving a stated problem. But each successfully reached AI goal carries trade-offs.

The takeaway here for product developers is to know the questions you can train AI to answer and anticipate and understand the trade-offs whenever it does. That way, you can consider whether and how to address them with additional algorithms or product innovations. For example, in lesson #2 above, the product proved of value for another purpose. Every time the algorithm assessed a mammogram for breast density, it generated the same ratings. Its human counterparts did not. Hence, the AI offered clinical settings consistency in care, and this became one of the product's main selling points. Perhaps, in retrospect, this should have been the goal in the first place, rather than asserting that the algorithm determined real "truth" when no such truth existed.

LESSON 4: MOVING FORWARD, BE PREPARED FOR "SHOW," NOT "TELL"

Knowing the main role of a regulatory body is to assess the safety and effectiveness of the product under review, you need to be able to explain how your product works and answer regulators' detailed questions related to efficacy and safety. As with the full spectrum of medical products, the better you can articulate how your AI works and why, the more comfortable regulators will be.

Machine learning-based AI algorithms are easy to explain, because they are trained in the same manner as a human would be: "If I'm a radiologist who is an expert in reading mammograms and I have a new resident who wants to read them, I'd show her what breast cancer signs look like and what false positives look like, and teach her what to look for. For example, breasts are usually symmetric, if you see something on one and not the other, that's suspicious. If you see a round mass that has irregular borders, that's suspicious…" So, for ML algorithms, we can state that the algorithm searches for rounded masses with irregular borders, and it searches for asymmetries in breasts, and so on.

With deep learning (DL), however, explaining how the algorithm works is easier said than done, because it uses a completely different method of training and programming. With DL, the AI is given a comprehensive series of mammograms

and trains itself. The model is not trained to directly look for features of cancers as was done with conventional ML algorithms. How it succeeds, what it is flagging, no one knows. Also, nobody knows under what circumstances the algorithm will make mistakes. This technological riddle makes regulators less comfortable during review and approval processes. The upside is DL AI is showing superior performance to older ML AI, and so this is well worth pursuing.

Still, DL-driven medical products recently have been approved, including the early breast cancer detection medical technology that finds cancers with improved accuracy. DL solutions also are showing promise in being able to identify mammograms that are clearly benign. So, a precedent for approval is being set, which is, while you cannot explain the inexplicable, you can demonstrate performance through tests and studies. This brings us to our final lesson learned: For the most advanced AI products in development, plan ahead in terms of program management and resources to do more showing than telling.

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Andrew Smith, Ph.D., is the vice president of image research for Hologic, Inc. He has been involved in medical imaging research and development for over 30 years, with his current focus on advanced breast imaging technologies such as 3D tomosynthesis. He lectures widely around the world on breast imaging and is a named author on over 100 U.S. patents. Prior to Hologic, he co-founded Digital Scintigraphics, a company that developed high-resolution nuclear medicine neuroimaging systems. He received his B.S. and Ph.D. degrees in physics from MIT in Cambridge, MA.

WHAT DO ARTIFICIAL INTELLIGENCE AND CONTINUOUS VALIDATION HAVE IN COMMON?

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In 2011, the Center for Devices and Radiological Health (CDRH) initiated the *Case for Quality*, which provided guidance on how software validation processes can be improved and streamlined for the medical device, pharmaceutical, and biotech industries. By refocusing on patient and product safety, quality assurance, and data integrity, some suggest that validation documentation can be reduced (between 20% and 40%, in my experience) by applying automated testing and deployment. The benefits are accurate code, faster development processes, and reduced validation documentation.

This article is part one of a three-part series and continues the discussion on computer software assurance (CSA), introduces new technologies and methods to achieve continuous software development, provides insight into new standards (e.g., ISO 9001 and ISO 13485-2016), and concludes with a few good reasons to join the growing number of medical device, pharma, and biotech companies with software specialists (or companies that work with software development organizations) who are creating and/or using test automation tools and applying them throughout the software development life cycle (SDLC) phases: inception, design, implementation, maintenance and monitoring, audit, and disposal.

As we await FDA's communication on the CSA guidance, we have an opportunity to reevaluate the phases of the SDLC and start to think about using new software development methods, such as a combination of artificial intelligence (AI) and adaptive machine language (ML) to provide human-like instructions for automated testing. Challenges include how to evaluate your SDLC phases and make the transition to continuous test automation. What is most puzzling to many is the impact of making this transition from traditional computer system validation (CSV), effectively and efficiently, to a continuous validation life cycle, while applying the tenets of CSA: critical thinking, risk management, patient and product safety, quality assurance, and data integrity.

ISO STANDARDS ADDRESS RISK MANAGEMENT

For those in the medical device industry, your software development team (or your software supplier that you work with) are required to comply with medical device regulations and standards, such as ISPE GAMP 5, ISO 9001, and ISO 13485-2016 – Medical Devices. The regulations and standards include a risk-based assessment (RBA) for all computerized software systems. ISO 9001 requires this assessment during the initial phase of the SDLC; ISO 13485-2016, however, requires that a risk-based assessment be updated at every stage of the SDLC to determine the level of risk and the validation and/or change control actions required to be compliant.

Applying the Agile methodology enables you to find opportunities to improve, implement, and comply with the regulations and standards since it uses an iterative approach to ensure quality: continuous code reviews, continuous testing, continuous deployment, continuous monitoring and maintenance, and continuous audit and disposal. Many software development organizations are already performing automated testing and updating their SDLC. Agile testing methods, such as behavior-driven development (BDD), test-driven development (TDD), and acceptance test-driven development (ATDD), are all different approaches to validating code and may be used for automated testing. With the Agile method and progress in development of intelligent technologies, manual testing and/or unscripted testing for low-risk features may become obsolete.

Figure 1 below provides an example diagram of the continuous phases for automated testing: integration, delivery, and deployment.

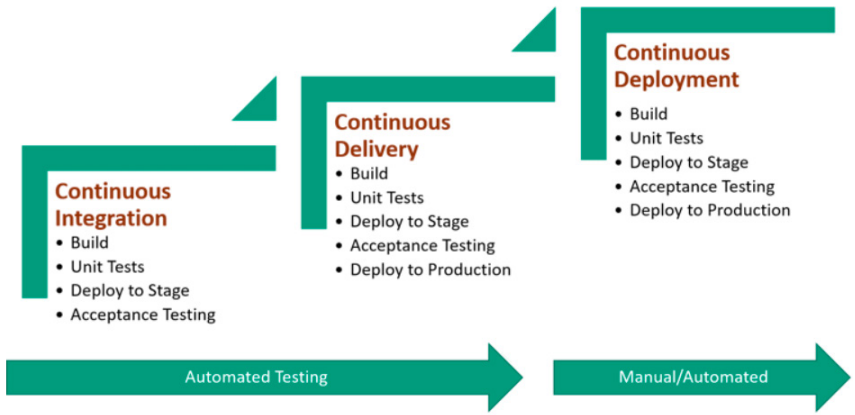

Figure 1: Automated Testing Strategy

As demonstrated above, the software engineering/development team lead will need to develop a test framework, identify the test phases, and choose the testing tools (i.e., open source or proprietary) for the various tests, such as regression, cross-browser, smoke, etc., and design the test for re-useability according to the testing phase or technology stack.

INFORMATION TECHNOLOGY ALIGNMENT WITH SOFTWARE ENGINEERING

Intelligent systems require IT and DevOps personnel, along with software developers, programmers, and software engineers, to acquire new skills and knowledge while applying the principles of software engineering. The ability to get back to basics and skills in software engineering principles, mathematics, and machine language will continue to be highly desired. Making the transition to continuous validation and continuous testing will not be an easy task, especially for mature companies that have been performing traditional validation since 2003 or earlier. Typically, the quality organization has been responsible for ensuring that the software application(s) are compliant and meet all required regulations for software validation. The process seemed straightforward: inception, design (analyze) implementation (build, test, deploy), maintenance and monitoring, audit, and disposal.

Quality assurance's (QA) role was to oversee the validation effort by reviewing all computer system validation processes and documentation to ensure that they followed the company's policies and standard operating procedures (SOPs) for compliance and met the associated regulations and standards. Deviations were documented, errors were corrected, and final documentation was reviewed, approved, and stored following 21 CFR Part 11 regulations. With continuous life cycle management for software development, QA's focus will be on patient and product safety rather than manual testing and documentation, which will be replaced by test automation to enable continuous validation.

OPPORTUNITIES FOR CONTINUOUS LIFE CYCLE MANAGEMENT

By applying the concept of *continuous* life cycle management for software development, advantages such as the ability to address risk (critical, high, medium, etc.) during each stage of the development process are feasible.

Performing iterative code reviews and automated testing enables early detection of errors, resulting in error-free code that can be shared with other software developers and programmers, minimizing change control actions after software is released. Organizations that will need to reinvent themselves include, but are not limited to, the following:

- DevOps groups have developed a set of practices for software development (Dev) and IT operations (Ops). The purpose is to streamline the SDLC, applying validation methodologies, such as Agile, to software development, and providing continuous delivery.
- Quality groups will need to change as intelligent technologies replace repetitive and mundane validation tasks by providing automated assurance that the software is performing as it was intended and according to the user requirements specifications.
- Intelligent technologies and methods (e.g., AI and ML) will replace traditional/legacy technologies and methods that will over time become obsolete.
- SDLC needs to be modernized and get back to basics by applying software engineering discipline and principles to new applications that enable continuous life cycle management.

AI AND ADVANCED TECHNOLOGY AND RESEARCH

AI presents a modern way for quality organizations to be compliant using test automation. AI is also a method used to advance technology and research by directing computers to perform automated tasks (using algorithms) through the application and translation of machine language. AI can teach machines to learn for themselves and find new avenues for learning.

As the life sciences industry starts taking advantage of AI and ML, its leaders will be known as future thought leaders, visionaries, and influencers. When we think of AI, some examples that come to mind are: adaptive (i.e., robust, efficient, and agile), prescriptive, and actionable data analytics; machine learning, automated administrative tasks (i.e., for patients, doctors, and healthcare personnel), as well as intelligent medical devices; and machines that can be designed to help and assist humans. Some of the top uses include, but are not limited to, diagnostic imaging, surgical robots, and faster, smarter, and secure tools. In fact, when looking at the world of robotics, machines can be designed in such a way as to imitate humans. By integrating engineering fields (i.e., mechanical engineering with computer engineering), software engineers can now develop programs in human-like language.

Some new challenges for software developers and software validation leads may include, but are not limited to, how do you test code when the outcome of the prescribed code potentially provides different results each time you test it? How do you test code when the inputs vary and the outputs are based upon other factors? How do you leverage the extensive work of the software developer/software engineer without duplicating the code? Answers to these and other questions will be discussed as we do a deeper dive into AI and ML.

CONCEPTS FOR INTELLIGENT TECHNOLOGIES

Concepts that enable intelligent technologies include, but are not limited to, the following:

- ***AML:*** ACPI Machine Language (AML) is platform independent code.
- ***Machine learning:*** Can machines learn by themselves? Maybe, if machines were coded to think like humans, learn to read text, and figure out the purpose of the text and/or understand music.
- ***Neural networks*** are computer systems that simulate the human brain and can be taught to understand things based on their structure. Applied intelligence is AI services coupled with analytics and automation to create a strategy for your organization.
- ***Predictive analytics*** uses data, statistical algorithms, and ML techniques to predict trends, human behaviors, and patterns based on current and historical data.

CONCLUSION

Biopharma, medical device, and pharmaceutical companies understand the benefits of test automation and many have already included continuous integration (CI) and continuous development and deployment (CDD) into their SDLC, while others are waiting for the new CSA guidance from FDA on how continuous testing will impact current validation regulations. Either

way, intelligent, automated systems (e.g., AI and ML) are already here and will continue to be the future direction of technology development. The impact on these industries' software and on the validation life cycle will be huge. The next article in this three-part series will continue to expand on validation challenges and next-generation intelligent technologies.

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AI/ML-ENABLED MEDICAL DEVICES — 4 KEYS TO OBTAIN GLOBAL REGULATORY APPROVAL

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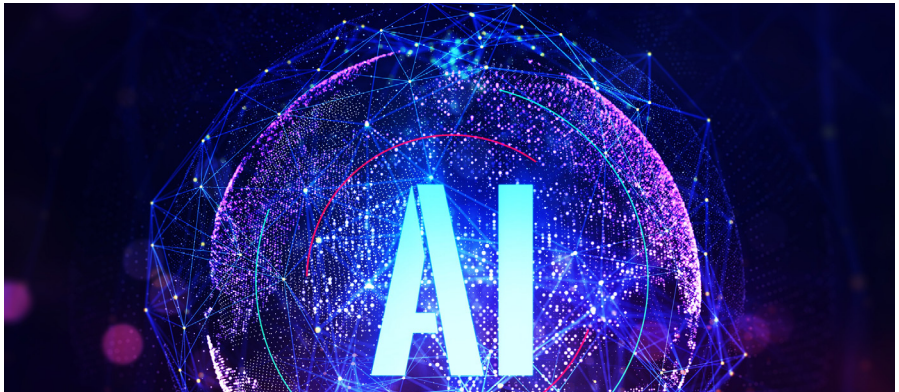
Artificial intelligence (AI) and machine learning (ML) are disrupting and improving our world. With intelligent machines capable of high-level cognitive processes like thinking, perceiving, learning, problem-solving, and decision-making, coupled with advances in data collection and aggregation, analytics, and computer processing power, AI and ML present opportunities to complement and supplement human intelligence. Application of AI and ML in medical devices is making possible AI/ML-driven diagnostics and personalized treatments.

Artificial intelligence has the potential to provide incremental value to medical device designers and manufacturers and is expected to be the key source of competitive advantage for firms that adopt it. Global regulators have understood that AI and ML models do not fit well within the current medical device regulatory framework and are feverishly working to achieve a harmonized approach to the management of AI medical devices. The International Medical Device Regulators Forum is attempting to standardize oversight of AI- and ML-based medical devices, and the terminology associated with those devices, among its members. Nonetheless, aside from the regulatory submission and review process, which as of right now is very different from jurisdiction to jurisdiction, medical device companies must realize that data is one of the primary drivers of AI/ML solutions and, thus, appropriate handling of data to ensure privacy and security is of prime importance. Challenges include data usage without consent, risk of identification of individuals through data, data selection bias and the resulting discriminatory nature of AI/ML models, and asymmetry in data aggregation.

By digesting the different jurisdictional AI/ML regulatory frameworks that have been released (draft or enforceable), along with our own experience with the different agencies, we have identified the common denominators that, if properly implemented and operationalized, would enable medical device companies to mount a compelling approach to global commercialization of AI/ML medical devices.



We have distilled the four common enablers that would accelerate regulatory review, approval, and subsequent commercialization:

- Software Risk Management
- Algorithm Design
- Quality of Data
- Security

1. SOFTWARE RISK MANAGEMENT

Considering that one of the most widely used standards (IEC 62304) for applying a risk-based approach to software development and maintenance throughout the product life cycle does not consider artificial intelligence or machine learning, any firm's software risk management activities should be updated based on:

- the intended use of the software (target disease, clinical use, importance, urgency)
- usage scenarios (applicable population, target users, places of use, clinical processes)
- core functions (processing objects, data compatibility, functional types) throughout the software life cycle process.

The risk of clinical use of software should also include false negatives and false positives, where a false negative is a missed diagnosis, which may lead to delay in follow-up diagnosis and treatment activities, especially in evaluating the risk of delay in diagnosis and treatment of rapidly progressing diseases.

2. ALGORITHM DESIGN

Consider algorithm selection, algorithm training, network security protection, and algorithm performance evaluation in the algorithm design. Design data-driven and knowledge-driven algorithms to improve the explanatory nature of the algorithms. Algorithm selection should specify the name, structure (e.g., number of layers, parameter size), flowchart, out-of-the-box framework (e.g., TensorFlow, Caffe, PyTorch), input and output, operating environment, and algorithm source basis. At the same time, clarify the principles, methods, and risk considerations of algorithm selection and design, such as quantitative error, gradient disappearance, overfit, and white boxing. If you are using migration learning techniques, supplement those with summary information such as data set construction, validation, and validation of pre-trained models.

Base the algorithmic training on the training set, tuning set training, and tuning, with clearly evaluated indicators, training methods, training objectives, tuning methods, and training data volume such as the evaluation indicator curve. Base the evaluation indicators on clinical needs, such as sensitivity, specificity, etc. Training methods include, but are not limited to, the set-aside method and the cross-validation method. Training objectives should meet clinical requirements and be supported by evidence such as ROC curves. The tuning method should clarify the algorithm optimization strategy and implementation method. The evaluation indicator curve should be able to confirm the advent and effectiveness of algorithmic training.

3. QUALITY OF DATA

Data collection should consider compliance and diversity of data sources, epidemiological characteristics of targeted diseases, and data quality control requirements. Data sources should ensure data diversity on a compliance basis to improve the ability to generalize algorithms, such as representative clinical institutions from as many different geographies and levels as possible and as many devices acquiring data as possible. Use acquisition parameters that maximize your data acquisition.

Epidemiological characteristics of the target disease include, but are not limited to, disease composition (e.g., classification, station), population distribution (e.g., health, patient's sex, age, occupation, geography, lifestyle), statistical indicators (e.g., morbidity, prevalence, cure rate, mortality rate, survival rate), and the impact of complications and similar diseases of the target disease.

It is important that the acquisition equipment clarify the compatibility requirements and its acquisition requirements. Base the compatibility requirements on data generation methods (direct generation, indirect generation) to provide a list of acquisition equipment compatibility or technical requirements, clear acquisition equipment manufacturers, model specifications, performance indicators, and other requirements, if there are no specific requirements for acquisition equipment that provide appropriate

support information. Acquisition requirements should specify the acquisition method (e.g., regular imaging, enhanced imaging), acquisition protocol (e.g., MRI imaging sequence), acquisition parameters (e.g., CT load voltage, load current, load time, layer thickness), acquisition accuracy (e.g., resolution, sample rate), and other requirements.

The training set shall ensure that the sample distribution is balanced, and the test set and the tuning set shall ensure that the sample distribution conforms to the actual clinical situation. The training set needs to include the samples of the training set, the tuning set, or the two intersections of those sets.

4. SECURITY

The intended use of the software, usage scenarios, and core functions, based on confidentiality, integrity, availability, and other network security characteristics should determine the software network security capacity-building requirements to deal with network threats such as cyberattacks and data theft. Common network threats to this type of software include, but are not limited to, framework vulnerability attacks (the use of algorithms to exploit the out-of-the-frame framework itself), vulnerabilities for network attacks, and data pollution (network attacks through the pollution of input data). A helpful ENISA report considers the different stages of the AI life cycle from requirements analysis to deployment and the ecosystem of AI systems and applications; it also provides the identification of assets of the AI ecosystem as a fundamental step in pinpointing what needs to be protected and what could possibly go wrong in terms of security of the AI ecosystem.

CONCLUSION

Regulators have recognized that AI and ML technologies pose several challenges from a regulatory perspective. They will be asking questions about how to determine when changes to an algorithm are so significant that they merit reevaluation of the medical device and its safety and effectiveness. There is a flurry of activity to address the gaps in technological and regulatory perspective, such as ISO/IEC 22989 Artificial Intelligence – Concepts and terminology, ISO/IEC 23053 Framework for Artificial Intelligence (AI) Systems Using Machine Learning (ML), and ISO/IEC 23894 Information Technology – Artificial Intelligence – Risk Management, among others.

Medical device manufacturers can still design, develop, and commercialize while the streamlining of global regulations and the harmonization of international standards are taking place by understanding the privacy framework in the applicable jurisdiction and being able to demonstrate adherence to the local jurisdictional expectations.

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ARE YOU READY FOR THE FDA'S "DATA EFFECT" TSUNAMI? 8 STEPS TO PREPARE

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The FDA is moving forward with its Data Modernization Action Plan (DMAP), the next leg of the Technology Modernization Action Plan (TMAP). Announced on March 3, 2021, DMAP is the agency's overhaul of technology and data with the objective of bringing together increasingly disparate and diverse data sources to help understand and pinpoint emerging public health threats.

This sounds very noble, and using data as the basis of the FDA's regulatory decision-making seems to be an improvement. So, why would this be a tsunami for biotechnology, pharmaceutical, and medical device manufacturers? Do not misunderstand, data turned into knowledge improves understanding, decision-making, and, ultimately, outcomes. Businesses have learned this and are continuously improving their use of analytics as a competitive differentiator. However, what makes data valuable and informative can also be dangerous when wielded by a novice or used without proper verification and governance. On paper, the DMAP outlines several aspirational efforts to bring together a massive number of disparate data sources. What DMAP fails to address are the associated risks that come with predictive algorithms and poor modeling.

Predictive analytics and modeling are a form of artificial intelligence (AI). Predictive analytics uses machine learning to predict outcomes using historical data. Machine learning is an AI technology that finds patterns at scale with data sets. With machine learning, the models used to create predictions can act as black boxes. This means that how the predictions came to be is not fully understood. And while there are many instances of positive experiences with black-box algorithms, there are cautionary tales of algorithms gone bad. Let's be honest, the FDA does not always take an innocent until proven guilty approach with manufacturing firms.

The time is now for manufacturers to prepare themselves for the influx of questions, audits, observations, warning letters, and more with this new proclaimed approached to maintain data-driven regulatory decision-making.

Before we outline a road map to prepare for the incoming storm, we must discuss how social media will influence the FDA's modernization of information. OpenFDA is an excellent source of FDA data accessible to the public (note the warning to avoid using this information in making medical decisions). The goal of providing data access to all puts manufacturers in the driver's seat to better control their destiny. What is missing? There are over a quintillion bytes of data generated daily with social media outlets.1 Most social media information (e.g., Twitter, TikTok, Instagram, reviews on Amazon, etc.) does not apply to manufacturers. However, there is a small percentage of this information that significantly impacts your business. Guess what? The FDA plans to monitor and assess this information under the umbrella of protecting public health. To prepare for this broad sweep of informational overload, manufacturers need to expand their post-market system capabilities by creating their own manufacturer Data Modernization Action Plan (mDMAP). Here's the eight-step method to create your own mDMAP.

1. WALK THE WALK WITH PREDICTIVE ANALYTICS

Many manufacturers proclaim they have predictive capabilities, but instead they outline archaic approaches toward demonstrating state-of-the-art devices, made under state-of-the-art conditions, with state-of-the-art outcomes. Repetitive descriptive statistics only tell the history and remain a passive approach to post-market monitoring of signals. Descriptive analytics does not facilitate the much-needed dynamic monitoring. Without dynamic monitoring, manufacturers cannot proactively respond to information and prevent significant business disruption. The FDA is going predictive. Manufacturers need to prepare themselves to stay ahead of the curve. Instituting mDMAP can be a source of competitive advantage and significantly decrease the time spent writing fiction as to why your devices remain the best of the best.

2. INSTITUTE NEW CAPABILITIES INTO YOUR POST-MARKET SURVEILLANCE LISTENING SYSTEMS

This will bolster your ability to respond to user experiences with your competitive devices (your opportunity to make quality a competitive advantage). As your mDMAP program evolves, your business vernacular will need to standardize around machine learning, predictive algorithms, and predictive intelligence. mDMAP is your way to get intimate with new data sources and new ways of seeing the information. Avoiding this intimacy increases your risk of "for cause" audits (we all know these audits go well!).

The bulk of new data is unstructured, which means the data is not conveniently in the form of a table with structured rows and columns. It is textual, video, pictures, etc. This lack of structure makes it difficult for the quality professional to understand, evaluate, and use it to support prevention. However, anything worth having is typically difficult at first. Unstructured data represents your new gold mine for post-market enlightenment. Anyone connected to the internet can voice their opinions. The ability to listen means manufacturers need to optimize their listening systems.

3. USE THE A+B=C FORMULA

Given that we understand A (your current post-market listening system state) and C (the future post-market listening system state), we can solve for B (what you need to do to stay ahead). The same thing goes for our ability to transform our post-market listening systems and predictive analytics program. The first step of a great mDMAP approach is to outline your targeted future state (or variable C). To create a targeted future state, paint a picture of the destination (what you want to accomplish). Next, define your current state (or where you are currently sitting, variable A). Painting a realistic picture of the current state is difficult for many manufacturers, as it requires a lot of arduous self-reflection and realizations. What are your current capabilities, what are your current data sources, do you have a quality warehouse or data lake? By outlining the current post-market state and painting a picture of the destination, you effectively can solve for B – how to achieve your new mDMAP realities.

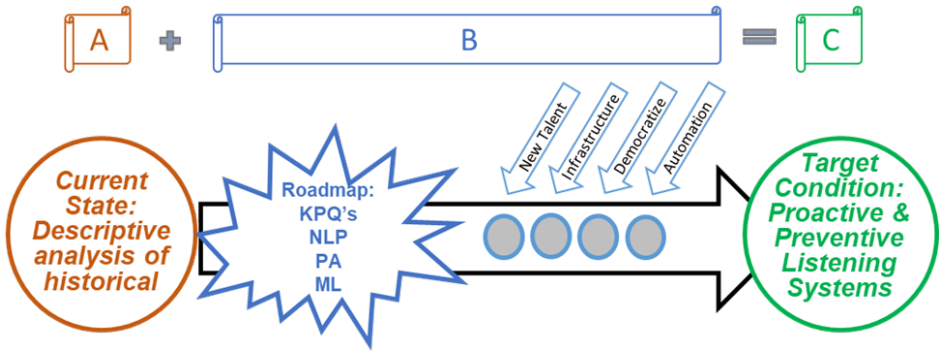


Figure 1. Road map to mDMAP

Variable B represents the road map from your current condition to the mighty target condition. Transforming your post-market listening systems and predictive capabilities requires investment in your infrastructure and some sweat equity. Before you begin building, the path to enlightened post-market and predictive systems begins with a cross-functional assessment of key performance questions (KPQs). Many people and businesses jump right to KPIs (key performance indicators), but the rocket fuel in any analytics program begins with KPQs.

4. DEVELOP YOUR KEY PERFORMANCE QUESTIONS

Your ideal KPQs will allow you to develop a customized suite of information that delivers exactly what you need and avoid the traditional report on everything where you learn nothing. KPQs need to be open-ended (as they are questions) so that the team can determine:

- Which KPI answers the question?
- What type of data is necessary to create the KPI?
- Where does this data reside?
- Do we have access to such data?

Capturing the answers to these questions through a simple matrix helps to archive the knowledge, aligns the organization, and, most importantly, allows a new person to understand the intelligence behind the data analysis. You will be amazed at how powerful such a simple document becomes with immediate improvement to an existing post-market intelligence system. Having a prepared, yet simple and solid starting point, succinctly aligns the organization on your impending journey toward mDMAP bliss. Additionally, put this matrix in an existing procedure and be amazed at your ability to tame outside regulatory authorities.

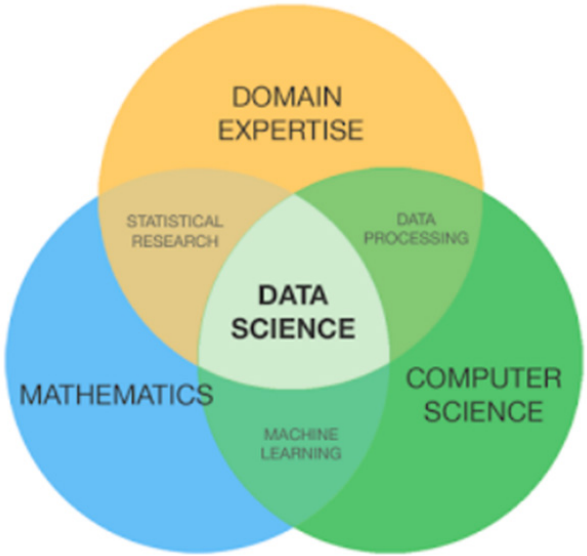
5. BRING IN NEW SKILLS AND CAPABILITIES (PEOPLE TALENT)

As people leave the organization or the business grows, the organization must focus on different skills and capabilities. As people exit the organization, we typically replace them with others with a similar skillset. Our mDMAP journey requires a more thoughtful approach to new employees. Use these opportunities to look for the skills needed to drive your future state. An excellent method to support skill requirements is to draw three circles and outline three high-level skills required. As an example:

- Circle 1 = Domain expertise (e.g., quality, regulatory, technical, etc.)
- Circle 2 = Computer hacking (e.g., programing skills such as Python, R, or data analysis skills with Power BI or Tableau)
- Circle 3 = Math and statistics (e.g., multivariate, uni and bivariate, etc.)

Once you have your three main topics, you can add subcategories within the circles. Why use three circles? It is easier to digest how to think about the future skills needed using such an approach. Jumping into a job description makes it easy to fall into the trap of using what currently exists (or simply plagiarizing some other company's description from Indeed or another job site). Upon completion of the three circles, you intersect them for your own personal Venn diagram. At the center of the intersection is the unicorn you are looking to hire. Figure 2 provides an example of a Venn diagram for a data scientist. Do not allow this simple diagram to limit your thoughts on skills and capabilities. Three circles are not a limit but are a tool. Be thoughtful; as the number of circles grows, so will your difficulty in acquiring a unicorn. If you begin to find you require more than four circles, chances are you have two different jobs you need to fill.

Figure 2. Venn diagram of a data science unicorn.



6. LEVERAGE EXISTING INFRASTRUCTURE OR LOOK INTO NEW INFRASTRUCTURE

By new infrastructure, I do not mean significant capital investment. Remember, this is a journey that will take multiple years. Initially, most companies are using an office suite (e.g., Microsoft, Google, Salesforce, etc.) that they can leverage. If your company currently uses Microsoft, PowerBI is a simple tool that integrates easily for a minimal monthly fee. Don't get caught in the big, expensive solution. Start simple, and as the company begins to reap the benefits of their initial investment, evolution will continue.

How can this be accomplished? First, leadership must break the barriers on access to information and data. Many organizations create significant barriers to accessing data. IT must become a shepherd for sharing data and access. This does not mean being irresponsible with security; it means training and facilitating read-only access to data sources (one-way streets to pull but not write information) and creating data warehouses and data lakes that can be accessed by all (real-time financial information notwithstanding, some information must stay protected to avoid insider trading). Through a combination of access and training using free sources and in-house experts, learning and institutional knowledge will begin to blossom.

7. DEMOCRATIZE YOUR INFORMATION

Democratization of your information – driving the training and tech into all organizational ranks – requires a lot of focus and effort. Through democratization, the exponential growth of knowledge and improvement will rise like a phoenix. There are plenty of free tools available on the web or at edx.org to help with this effort. Heavy dollar investment is not required, only heavy investment in your sweat equity.

Democratization serves two significant purposes. It grows the institutional knowledge and keeps your workforce learning. A business can only grow if its people are growing (learning is the foundation of people growth). Democratization is a form of visual cues that provides a strong and robust safety net capable of seeing information and issues previously unnoticed. Think of it like this: Would fans attend a baseball game if they could not see the score? By driving the information into all ranks, the score is known by all and, more importantly, quality is seen as more than a function; it becomes transformed into an institutional capability embraced by all.

8. AUTOMATE — BUT NOT YET

Many companies want to jump to automation. Avoid this urge. Technology accelerators have their place; however, technology-induced change without proper process or relevancy is a program killer and money pit all in one. People become enamored with the flashing lights and new technological toys. Smart businesses have learned to run, but you must first walk, and to walk you must crawl. The reality is that focusing on finding the right future talent and initial infrastructure and democratizing your information will serve to move your program from a crawl to a walk. Once these elements are going well, you can begin the next phase of leveraging better prediction through automation and machine learning.

Now that you have the right talent, a simple to understand infrastructure, and a well-versed organization, you are primed to use technology to help accelerate good processes and begin to converge with more expansive data sets. Applying the right set of machine learning tools allows a business to create a more informed analysis of existing data for deeper insights and statistical patterns.

Our historical data sets can be used to train algorithms to understand behavioral patterns, anticipate problems, and effectively allow for timely and prepared action. Additionally, these learning algorithms can actively monitor the many different disparate data sources that generate new information daily. Doing so will facilitate the development of early warning signals or, better yet, outline things that are going well. Understanding what works well allows a business to exploit a competitive advantage within its quality program.

Another benefit is that these predictive algorithms can be used to monitor industry trends, including with regulatory agencies and competitive businesses. This monitoring effectively helps you see the winds of change and stay away from oncoming obstacles.

An effective method to determine your automation road map is to evaluate what is working well; this is a candidate to automate and evolve through machine learning. Start with a new set of KPQs and create three circles for your automation Venn diagram. Each circle wraps around an automation concept. For

example, what drives customer behaviors around the quality of your products, what issues are your customers passionate about, what type of data exists, and what types of algorithms can be used to explore the data? Combine the three circles into your Venn diagram. The overlap will help shine the spotlight on how to attack and automate your next steps toward an automated predictive program.

CONCLUSION

The FDA's initiative could have significant and costly ramifications for manufacturers, whether in biotechnology, digital health, pharmaceuticals, and anywhere in between. However, by following mDMAP we can mitigate the likelihood of regulatory scrutiny. Starting your mDMAP integration voyage now allows you to stay ahead of the data management curve and protects your business. More importantly, your mDMAP journey will provide greater understanding and help you proactively pivot using the voice of your customers. The proactive capability drives your ultimate goal of doing well by doing good. Or, said another way, we ensure safe and effective outcomes through measured and consistent approaches.

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ABOUT US

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