

FDA-2017-D-6569

**VIA ELECTRONIC SUBMISSION**

February 5, 2018

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852**Re: Docket No. FDA-2017-D-6569: Clinical and Patient Decision Support  
Software: Draft Guidance for Industry and FDA Staff**

Dear Sir or Madam:

The Clinical Decision Support Coalition (“CDS Coalition” or the “Coalition”) welcomes the opportunity to provide comments on FDA’s “Clinical and Patient Decision Support Software: Draft Guidance for Industry and FDA Staff” (“Draft Guidance”). The CDS Coalition is a diverse group of stakeholders consisting of software providers, IT infrastructure manufacturers, healthcare providers, medical device and pharmaceutical manufacturers, trade groups, and members of the clinical community. Focused on clinical decision support (“CDS”) software, the Coalition’s goal is to ensure a risk-based and clearly defined regulatory system for such software that appropriately balances the need for regulatory oversight with the need for innovation and access to new technology.

**Executive Summary**

If implemented, the Draft Guidance would substantially expand the scope of FDA regulation and force many sellers of existing CDS software to remove their products from the market. This is true for two different reasons.

First, the Draft Guidance fails to take an approach that is risk-based, and would sweep within the scope of FDA regulation software that, for example, guides a physician on how to treat an occasional headache, if the software is not transparent enough to be exempt under the 21<sup>st</sup> Century Cures Act (“Cures Act”). Just four years ago, FDA worked with the International Medical Device Regulators Forum (“IMDRF”) to develop a risk-based model for software as a medical device, including CDS. In that context, FDA and other regulators from around the world identified the two key factors that drive risk based on the intended use of software. Those two factors were the nature of the disease and the role of the software. Yet now, in proposing the U.S. policy for this topic, the Agency inexplicably abandons that international consensus.

In 2014, as a part of the international effort, FDA observed that the transparency issue did not serve as an appropriate basis for risk stratification. Further, in the Cures Act, Congress employed transparency not as a way to remove low risk products from FDA regulation, but rather as a means of delineating the dividing line between FDA jurisdiction and oversight by the state boards of medicine. Transparency is not a substitute for a risk-based model of regulation. We need a risk-based approach.

Second, the Draft Guidance would expand the scope of FDA regulation to include numerous CDS software products simply because they offer insights, for example, based on machine learning. Here, FDA is directly frustrating congressional intent and trying to limit the impact of the Cures Act. In the Draft Guidance, FDA proposes that software will only be exempt from regulation if the user is “able to reach the same recommendation on his or her own without relying primarily on the software function.” However, that is radically different from the statutory test, which exempts software if the user is able “to independently review the basis for such recommendations that such software presents so that it is not the intent that such healthcare professional rely primarily on any of such recommendations.” In no way does that mean that the user must be able to reach the same recommendation. Rather, it means that the user must be able to reach a recommendation on the same subject matter on his or her own. The difference is enormous.

FDA’s approach would basically extend regulation to any software that offers insights that the user might not be expected to come up with on his or her own. FDA would thus end up regulating any software that does not simply do mundane calculations that users could do themselves. Under the statute, however, the way it is supposed to work is that software that produces unique insights may be exempt from regulation as long as an informed professional user is able to access all of the underlying data and other information to reach his or her own conclusions; whether they would likely be the same or not is immaterial.

The resulting overregulation would be to the detriment of patient care. In Appendix A, we include a long list of, in most cases, existing software that FDA has not regulated in the past that now would be regulated under the Draft Guidance. Many software programs that have been on the market for years, if not decades, would have to be removed pending FDA compliance. In addition to those fundamental concerns, the Draft Guidance simply fails to add any real clarity to the scope of FDA regulation of CDS software.

In this comment letter, we propose several changes to address these concerns. Among other things, we recommend:

1. FDA incorporate the international criteria for stratifying risk of CDS software, and exempt low risk CDS software from FDA oversight.
2. FDA modify the Draft Guidance to follow the Cures Act, which allows for the possibility of unregulated software that provides unique insights that the healthcare professional might not have come up with on his or her own, so long as the user has access to the factual basis for the insights.

3. FDA do a better job of explaining the examples the Agency includes, so that the regulated industry can understand the basis for FDA's treatment of a given example.

Because these changes require that important new content be added to the guidance document, we request that FDA re-propose the guidance so that stakeholders will have an opportunity to comment on the new approach.

## **Background and Overview**

The Coalition has been eagerly awaiting the release of the Draft Guidance since 2011, when FDA first announced its intention to develop this document. After waiting over six years for it to be issued, we became particularly concerned about the fate of the document in early 2017, as there were rumors that FDA believed the enactment of the Cures Act in December 2016 rendered additional guidance on CDS software unnecessary. In light of this concern, on February 17, 2017, the Coalition sent a letter to CDRH Director, Dr. Jeffrey Shuren, urging FDA to release guidance on CDS software and detailing the key issues that such a guidance should address (i.e., issues not covered by the Cures Act). The letter concluded that:

“...FDA should proceed with the development of a guidance document on CDS, addressing:

1. A risk-based framework that defines CDS and the portion of CDS that FDA regulates.
2. The definition of the concept of transparency in the Cures Act, including how things like machine learning impact transparency.
3. Specific guidance on software used in conjunction with pharmaceutical products.
4. Guidance on how to treat CDS developed by collaboration among multiple parties.”

Although the Coalition finds certain portions of the Draft Guidance to be helpful, including the concept of patient decision support (“PDS”) software, the document does not address the Coalition's recommendations from our February 17, 2017 letter and, as a whole, fails to offer substantial new insight into FDA's plans for regulating CDS software. Instead, the Draft Guidance largely reiterates section 3060 of the Cures Act. And in sections where the Draft Guidance does go beyond the language of the statute, FDA seems to be veering off track from the risk-based approach that we believe should be the focus of CDS software regulation.

In particular, the Coalition believes that the Draft Guidance should be revised to:

- (1) Adopt the risk-based framework for medical device software developed by IMDRF, as set forth in its guidance entitled, “‘Software as a Medical Device’: Possible Framework for Risk Categorization and Corresponding Considerations” (“IMDRF Risk Categorization Document”).
- (2) Leave open the possibility that CDS software that employs machine learning can still satisfy the section 3060 transparency standard.

- (3) Reference the Coalition’s “Voluntary Industry Guidelines for the Design of Medium Risk Clinical Decision Support Software to Assure the Central Role of Healthcare Professionals in Clinical Decision-Making”<sup>1</sup> (“Coalition Industry Guidelines”) to provide CDS software developers with more detailed insight about how they might come into compliance with the Cures Act.

Without these changes, the Draft Guidance may force companies to remove many important, existing CDS software programs from the market, and, in the future, cause significant delays in the development of new, low risk CDS software – both of which will hinder access to products that can improve the quality of patient care.

In the sections that follow, we first highlight the positive aspects of the Draft Guidance. We then summarize the reasoning behind the three major recommended revisions listed above, and discuss how these revisions may be accomplished. Finally, we provide an overview of the regulatory and practical implications that the Draft Guidance would cause if left unchanged.

## I. The Draft Guidance Provides Some Helpful Policy

The Coalition found the following features of the Draft Guidance to be helpful:

- **The Draft Guidance addresses software used by patients and non-healthcare professional caregivers.** FDA seems to be open to exempting certain PDS software from its regulatory requirements. However, the exact test for transparency (i.e., whether the software enables the patient or caregiver to independently review the basis for the recommendation presented by the software) requires additional clarification. Further, additional examples of regulated versus unregulated PDS software would be useful.
- **The Draft Guidance includes CDER’s signature.** CDER signing the Draft Guidance is important because, in the past, CDER has declined to sign on to software guidance documents developed by CDRH (e.g., the Mobile Medical Applications Guidance). CDER’s signature appears to evidence its agreement to abide by the Cures Act and its support for the policies in the Draft Guidance surrounding PDS software. Yet, CDER’s signature may largely be ceremonial as there is very little content within the Draft Guidance that is directly relevant to drugs, and the document explicitly states: “This guidance does not address other FDA statutory or regulatory requirements that may apply to certain decision support software, including software disseminated by or on behalf of a sponsor, for use with one or more of its drugs or biologics, such as requirements applicable to drug or biologic labeling or combination products.”

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<sup>1</sup> CDS Coalition, *Voluntary Industry Guidelines for the Design of Medium Risk Clinical Decision Support Software to Assure the Central Role of Healthcare Professionals in Clinical Decision-Making* (Aug. 30, 2017), <http://cdscoalition.org/wp-content/uploads/2017/08/CDS-3060-Guidelines-Final-2.pdf> [attached as Appendix B].

FDA's regulation of software used with drugs has been an important focus for the Coalition in recent years. In fact, we filed a citizen petition in August 2016 urging FDA to address this precise issue. As the Agency has avoided addressing this issue in the Draft Guidance, we continue to await this important feedback.

- **The Draft Guidance refrains from being overly prescriptive with respect to how CDS content is displayed.** FDA should not include specific requirements for how certain content (e.g., transparency-related information) is made available to clinicians. Software usability is a complex issue and vendors and healthcare organizations are constantly refining their approaches to minimize problems like alert fatigue, information overload, etc. We believe that FDA should continue to provide vendors and healthcare organizations with significant flexibility in this area.

Despite these positive features, we found the Draft Guidance to be lacking in several fundamental and essential respects.

## **II. The Draft Guidance Does Not Employ a Risk-Based Approach and Therefore Violates Federal Law and Policy**

### *A. The Draft Guidance Does Not Adopt a Risk-Based Approach*

#### 1. The Importance of a Risk-Based Approach

A risk-based regulatory approach is a foundational feature of Agency law and policy. Indeed in 2018, over 40 years since the enactment of the Medical Device Amendments of 1976, this should be well-accepted. As is the case with other medical device products, there is a continuum of risk associated with CDS software.

At the high risk end of the spectrum, for example, there is CDS software that provides radiation treatment planning. If this type of software makes the wrong recommendation, and if the software is not transparent, there is a reasonable likelihood that patient harm – or even death – could result.

There are also many low risk CDS applications, such as:

- Software that uses data from individuals and commonly accepted, but unidentified formulas for predicting risk score for developing stroke or heart disease for creating prevention or interventional strategies; and
- Software that uses data from individuals for predicting risk score in healthy populations for developing the risk of myopia, to be used in medical counseling (see additional examples in Appendix A).

These software functions are low risk based on their limited role and the non-seriousness of the healthcare situation in which they are used. For instance, with respect to the software in the first example, the formulas for predicting risk scores simply inform clinical management with regard to creating prevention or interventional strategies for a disease or condition. Similarly, the

software in the second example uses data that simply informs clinical management of healthy individuals with regard to a non-serious healthcare condition (myopia).

Under the Draft Guidance, all CDS software – regardless of risk – is subject to FDA regulatory requirements unless the software is transparent under section 3060. The Draft Guidance fails to incorporate accepted, international risk-based principles into FDA’s assessment of CDS products. Thus, FDA will regulate software that tells a doctor how to treat a hangnail unless the developer abides by the special section 3060 transparency principles. In other words, according to the FDA Draft Guidance, no CDS software is too trivial to be regulated.

There are several reasons why low risk CDS software may not be transparent. For example, a company might have a proprietary algorithm that works very well and does not wish to disclose it to competitors for competitive reasons. Further, for some use cases, because they are so trivial, trying to create transparency would frankly only make the user interface more complicated. It does not follow that such non-transparent software should necessarily warrant FDA regulatory oversight. But because the Draft Guidance does not include a broader assessment of product risk, CDS software that is not transparent will be regulated by FDA even if: (1) the role of the software is very benign, and (2) the seriousness of the disease is very low. This is bad policy.

Failing to follow a risk-based approach to determine whether a particular CDS software program warrants regulation will create problems for both industry and the public health. Requiring companies to meet FDA regulatory requirements in developing low risk CDS software imposes unnecessary costs, which in turn, drive up the costs of new products and delays patient access to these products. In addition, regulating low risk CDS software distracts the Agency from focusing its limited resources on those high risk products that should really be the focus of its regulatory attention. We would expect that, in 2018, these basic principles would be well-accepted.

## 2. FDA Identified Two Key Factors that Drive the Risk of CDS Software

While much has been written about the risk of health information technology generally, one of the most relevant outputs related to the assessment of risk in the context of medical device software was produced by IMDRF – the IMDRF Risk Categorization Document.<sup>2</sup> IMDRF is a group composed of leading medical device regulators from across the world that come together to harmonize international medical device regulation. FDA has been (and continues to be) an active IMDRF participant, and had a particularly integral role in shaping the final IMDRF Risk Categorization Document. Bakul Patel of FDA led the IMDRF workgroup and CDRH Director Dr. Shuren even signed the document as the “IMDRF Chair.”

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<sup>2</sup> IMDRF, “*Software as a Medical Device*”: Possible Framework for Risk Categorization and Corresponding Considerations (Sept. 18, 2014), <http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-140918-samd-framework-risk-categorization-141013.pdf>.

The IMDRF Risk Categorization Document analyzed a wide range of factors related to the use of software as a medical device (“SaMD”) that could potentially produce public health risk. Specifically, the group analyzed the following:

- The type of disease or condition
- Fragility of the patient with respect to the disease or condition
- Progression of the disease or the stage of the disease/condition
- Usability of the application
- Designed towards a specific user type
- Level of dependence or reliance by the user upon the output information
- Ability of the user to detect an erroneous output information
- Transparency of the inputs, outputs and methods to the user
- Level of clinical evidence available and the confidence on the evidence
- The type of output information and the level of influence on the clinical intervention
- Complexity of the clinical model used to derive the output information
- Known specificity of the output information
- Maturity of clinical basis of the software and confidence in the output
- Benefit of the output information vs. baseline
- Technological characteristics of the platform the software are intended to operate on
- Method of distribution of the software.

After considering these factors, the group, with FDA at the helm, settled on two key factors (which could be identified by the intended use of SaMD) that define the level of risk for SaMD. IMDRF stated: “Although many of these aspects may affect the importance of the output information from SaMD, only some of these aspects can be identified by the intended use of SaMD. Generally these aspects can be grouped into the following two major factors that provide adequate description of the intended use of SaMD:

- Significance of the information provided by the SaMD to the healthcare decision, and
- State of the healthcare situation or condition.”<sup>3</sup>

Significantly, IMDRF rejected the use of certain factors, such as transparency, in determining risk categorization because such factors are specific to a given product and manufacturer, and are not applicable to a broad category of software. IMDRF explained: “Other aspects that are not included in the two major factors (e.g., transparency of the inputs used, technological characteristics used by particular SaMD, etc.), although still important, do not influence the determination of the category of SaMD [(i.e., the risk-based categorization of the software)]. These other aspects influence the identification of considerations that are unique to a specific approach/method used by the manufacturer of a particular category of SaMD.”<sup>4</sup>

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<sup>3</sup> *Id.* at 10.

<sup>4</sup> *Id.*

The IMDRF Risk Categorization Document represents a consensus among the international medical device regulatory community, which specifically included FDA, that there are two key factors that drive the risk level in medical device software, including CDS software. Those two factors are: (1) the significance of the information provided by the SaMD to the healthcare decision (i.e., whether the information is critical to decision-making or more peripheral), and (2) the state of the healthcare situation or condition (i.e., how urgent the condition is/whether the patient could die). To accord with this international policy, which FDA had a pivotal role in developing (and which the CDRH Director signed as the “IMDRF Chair”), the Draft Guidance should similarly set forth a risk-based approach for CDS regulation, relying on the two factors above as the primary determinants of risk.

### 3. FDA Failed to Incorporate Its Own Risk Factors

The Draft Guidance completely ignores the two factors identified in the IMDRF Risk Categorization Document. As such, FDA appears to have walked away from a risk-based approach for CDS software regulation. While this is an incredibly important point, it is frankly not very complicated. FDA identified two risk factors for CDS software. FDA then did not use either of them when developing the Draft Guidance.

The Agency has offered no explanation for why it did not use the risk factors the Agency itself identified. While the exact dividing line between FDA oversight and unregulated territory could be subject to some interesting discussions, employing the Agency’s own risk factors to identify the appropriate low end of the risk scale for exemption from FDA oversight would seem to be uncontroversial. We cannot understand the omission.

### 4. Transparency Is Not a Substitute for Employing Appropriate Risk Factors

The bottom line is that the Draft Guidance cannot be called risk-based. As discussed more in the next section, FDA periodically publicly suggested – prior to publication – that its guidance would be risk-based. We are not sure why FDA would say that, but we wonder if it has something to do with the Agency’s implementation of section 3060 through the transparency provision.

Although the transparency of software is incidentally related to its risk (making sure that the healthcare professional user has information to double check the recommendations of the software may help prevent a bad decision that would otherwise be made in reliance on the software), the primary purpose of the transparency standard is to draw a line between activity subject to FDA regulation and activity falling under the practice of medicine, and thus subject to state board of medicine oversight. In this regard, it may be helpful if we share a paper we wrote in support of section 3060. We reproduce that below. After observing that there was a need for more than just the risk-based framework for CDS that FDA was already promising in response to the Food and Drug Administration Safety and Innovation Act (“FDASIA”), we urged Congress to adopt the transparency principle to clarify the dividing line between FDA’s jurisdiction and the practice of medicine.

“Federal regulation in this area should be risk-based. But there is another dimension the government should consider – the source of the risk.

Why? Because the source determines the appropriate regulatory jurisdiction as between two complementary regulatory systems: FDA and the state boards of medicine.

FDA's mission is not to regulate any and all high risk in medicine, regardless of the source. Instead, the statute FDA operates under specifically excludes the practice of medicine from FDA oversight. By law, FDA concentrates on regulating risk that flows directly from a medical device, leaving to the state boards of medicine risk that comes from any inept doctors.

So how do we discern the source of the risk? Actually, that's pretty easy. Over the years, the CDS industry has developed a concept called transparency, or the ability of the end user to see past the software to examine for herself the underlying data and clinical logic the software is using. If the software is transparent, the user does not have to depend on the software to reach her decision. Rather, through examining the same information the software considers, she can apply her own expertise to determine whether she agrees with what the software recommends.

The result: if software is transparent, the risk of a bad decision comes from the user, not the software. On the other hand, if the software is not transparent and the user must blindly follow its recommendation or courageously ignore it, the software is the source of the risk.

There is no profession – be it doctors, lawyers, accountants or engineers-- that cannot be joined, at least occasionally, by an incompetent person. It is possible to find a doctor who is both relatively unintelligent and lazy, at least compared to what we expect from doctors. And this doctor might, for example, simply accept a recommendation from software without even thinking about it. That would be bad, and risky. But the risk intrinsically comes from the doctor. And that's for the state boards of medicine to oversee. In fact, that is exactly what they do.

A doctor could use any product wrong. A hurried doctor could use a scalpel to remove the wrong kidney. But it would be folly to try to regulate that risk through FDA.

The downside here is that if FDA intrudes in software development where the true risk comes from the practice of medicine, they might discourage some very useful software. From the patient perspective, that's a problem because rather than protecting patients, that regulatory oversight may actually cause harm.

Incompetent doctors are going to hurt people whether they have software or not, especially if the alternative is expecting, for example, a relatively lazy doctor to rigorously review a patient's health record and think carefully about the range of diagnostic and treatment possibilities. Removing software from their toolkit will not make them safer doctors. The risk will remain, and indeed likely be worse.”

We need to speak plainly. Following the congressional directive that distinguishes between FDA regulation and the practice of medicine does not make FDA’s approach risk-based. FDA’s approach to regulation is only risk-based if the Agency takes into account the primary, recognized risk factors in defining the scope of its oversight. Here, in the international context, FDA defined the two primary drivers of risk. But when it came to defining the scope of its oversight of CDS software, the Agency completely ignored those two primary risk factors.

In fact, as noted above, the IMDRF Risk Categorization Document expressly recognized that transparency was *not* an appropriate factor to use in categorizing software by risk. Therefore, it is difficult to understand why FDA, who was active in authoring the IMDRF Risk Categorization Document, would later issue guidance that is not only out of alignment with the international document, but also proposes a fundamentally different regulatory approach.

The Draft Guidance is simply not risk-based.

5. FDA’s Reference to the MMA Guidance Is Not a Substitute for Stratifying CDS Based on Risk

The Draft Guidance’s reference to FDA’s Mobile Medical Applications Guidance (“MMA Guidance”) does not exempt low-risk CDS software. In lines 332-340, the Draft Guidance makes a cryptic reference to enforcement discretion being previously applied to certain healthcare professional support software in the MMA Guidance, e.g., mobile apps that perform simple calculations routinely used in clinical practice.<sup>5</sup> The Draft Guidance states that such software is not affected by the Cures Act or the Draft Guidance. However, because only a few very low risk CDS examples are even included in the MMA Guidance, this reference does not address low risk CDS more broadly. In addition, the MMA Guidance specifically states that it does not apply to “software that performs patient-specific analysis to aid or support clinical decision-making,” which would encompass many CDS products.

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<sup>5</sup> Per the MMA Guidance, these apps are generally tailored for clinical use, but retain functionality that is similar to simple general purpose tools such as paper charts, spreadsheets, timers or generic mathematical calculators. Examples include medical calculators for, e.g., Body Mass Index (“BMI”), Total Body Water / Urea Volume of Distribution, Mean Arterial Pressure, NIH Stroke Scale, etc. FDA, *Mobile Medical Applications: Guidance for Industry and FDA Staff* (Feb. 9, 2015), <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf>.

*B. The Draft Guidance's Approach Runs Afoul of Both Agency Policy and Federal Law*

As already observed, the Draft Guidance does not provide insight into how the Agency makes determinations of risk with respect to CDS software, including the factors that distinguish high and low risk products (which the Agency actively helped develop in its IMDRF leadership role). Not only does the Draft Guidance fail to do that, but it also provides little indication that FDA is interested in drawing that line. We believe that this approach is inconsistent with FDA's own policy, and further, does not comply with federal law.

1. FDA Has Not Followed its Own Policy Directives

The Draft Guidance's failure to promote a risk-based approach to CDS software regulation is at odds with statements made by FDA Commissioner Dr. Scott Gottlieb over the past year. For example, on June 15, 2017, Dr. Gottlieb published a blog post entitled, "Fostering Digital Innovation: A Plan for Digital Health Devices," in which he indicated that FDA will take a risk-based approach to digital health regulation. Referencing the need to encourage innovation, but also the need to ensure products are safe and effective, Dr. Gottlieb observed: "By taking an efficient, risk-based approach to our regulation, FDA can promote health through the creation of more new and beneficial medical technologies."<sup>6</sup>

Additionally, in a recent CNBC interview, Dr. Gottlieb noted the following with regard to digital health products: "From a regulatory perspective, we are trying to take a risk-based approach. Some of these products are low risk and we'll think differently about them (than medical devices) and take some out of pre-market review process."<sup>7</sup> The Draft Guidance certainly does not reflect the risk-based thinking that Dr. Gottlieb has repeatedly referenced. Plus, the references above are just a few examples of instances in the recent past where an FDA official has touted the benefits of a risk-based regulatory approach in the medical device space.

2. FDA Has Not Complied with FDASIA

The Draft Guidance similarly ignores the recommended risk-based approach to CDS software regulation embodied in the report FDA submitted to Congress as required by FDASIA.<sup>8</sup> Under section 618 of FDASIA, the Agency, in consultation with the Office of the National Coordinator for Health Information Technology ("ONC") and the Federal Communications

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<sup>6</sup> Dr. Scott Gottlieb, *Fostering Digital Innovation: A Plan for Digital Health Devices*, FDA Voice (June 15, 2017), <https://blogs.fda.gov/fdavoices/index.php/2017/06/fostering-medical-innovation-a-plan-for-digital-health-devices/>.

<sup>7</sup> Christina Farr, *FDA Chief: I'm Surprised it Took Big Tech This Long to Get into Health Care*, CNBC (Dec. 30, 2017), <https://www.cnbc.com/2017/12/30/fda-chief-im-surprised-it-took-big-tech-this-long-to-get-into-health-care.html>.

<sup>8</sup> FDA, FCC & ONC, *FDASIA Health IT Report: Proposed Strategy and Recommendations for a Risk-Based Framework* (April 2014), <https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM391521.pdf>.

Commission (“FCC”), was required to prepare “a report that contains a proposed strategy and recommendations on an appropriate, risk-based regulatory framework pertaining to health information technology, including mobile medical applications, that promotes innovation, protects patient safety, and avoids regulatory duplication.”<sup>9</sup>

The resulting report, the FDASIA Health IT Report, specifically acknowledged the potential value of CDS software in enhancing patient care and recommended clarification of FDA’s regulation of CDS software through the guidance process. The report also provided a high-level overview of the principles that FDA would address in such a guidance. The report noted: “In applying a risk-based approach, FDA does not intend to focus its regulatory oversight on [the following list of] products/functionalities, even if they meet the statutory definition of a medical device;” it then went on to list several examples, including software that offers “[s]uggestions for possible diagnoses based on patient-specific information retrieved from a patient’s EHR.” Despite the clear language found in the FDASIA Health IT Report stating that the Agency plans to take a risk-based approach, FDA made absolutely no attempt to stratify CDS software based on risk in the Draft Guidance. FDA walked away from its promise to Congress.

*C. The Cures Act Did Not Obviate the Need for FDA to Carry Through on the Agency’s Promise to Develop a Detailed, Risk-Based Approach to CDS Software Regulation*

Congress never intended for the Cures Act to provide FDA’s risk-based approach to CDS software regulation. Rather, as the Agency itself promised in the FDASIA Health IT Report, FDA was supposed to develop and adopt such an approach through guidance. Congress deliberately left the development of a risk-based approach to the Agency because the Agency already promised it was developing such an approach, and the approach required a level of specificity that Congress generally tries to avoid in legislation. The lengthy IMDRF Risk Categorization Document is evidence of the level of specificity necessary to implement a risk-based approach.

In other guidance documents, the Agency has taken a clear risk-based regulatory approach, focusing squarely on whether products are low risk (e.g., FDA’s General Wellness Guidance). Here, however, FDA has clearly departed from that approach. The problematic result is that CDS software that does not meet the statutory standard for transparency will always be subject to FDA regulation, regardless of risk. So if, for example, software uses a complicated machine learning algorithm to discern whether patients have the common cold, it will be regulated simply because it uses a complicated algorithm that the physician user cannot mentally duplicate even though the risk of injury is minuscule. The Draft Guidance does not adequately account for the risk of the software.

*D. Recommendations*

To address the concerns detailed above, we recommend that FDA formally adopt the IMDRF risk stratification model outlined in the IMDRF Risk Categorization Document that it

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<sup>9</sup> *Id.* at 3.

itself had a hand in developing. Specifically, in a new section VI to the Draft Guidance, inserted right before the existing section VI on line 402, FDA should add in an in-depth discussion of the IMDRF Risk Categorization Document, explaining the two key factors that IMDRF identified as the primary drivers of software risk (i.e., (1) the significance of the information provided by the software to the healthcare decision, and (2) the state of the healthcare situation or condition).

This new section should explain that FDA intends to exercise enforcement discretion over those CDS software products that fit within Category I based on the IMDRF model. Examples of such Category I products, which may include those listed in Appendix A, should also be provided in this section. In addition, FDA should make clear that this risk stratification approach applies to both professional use CDS software as well as PDS software.

### **III. The Draft Guidance Unnecessarily Clouds the Future of CDS Software Based on Machine Learning**

Much of the CDS software of the future will be based on machine learning and other similar technologies. However, the Draft Guidance seems to preclude any CDS software that uses machine learning from falling outside of FDA's regulatory purview. In this respect, the Draft Guidance appears to go beyond the Cures Act and extends FDA regulation to certain software that should be exempt under the statute.

After detailing the Coalition's position on machine learning in the context of CDS software, this section explains how the Draft Guidance has created uncertainty in this area, and makes recommendations for revisions to the Draft Guidance.

#### *A. The Coalition's Approach to Machine Learning in CDS Software*

In August 2017, we published our Coalition Industry Guidelines with the intention of guiding developers in the design of medium risk CDS software (as defined in the document) that assures healthcare professionals remain in charge of the clinical decision (the Coalition Industry Guidelines are attached as Appendix B). In developing these guidelines, the Coalition carefully considered machine learning to identify ways in which companies could employ complex algorithms and still safely proceed to market without regulatory oversight. The Coalition even met with FDA to share our thinking on the topic, as well as the public comments that the Coalition had collected. Based on our investigation into this topic, we believe there is a pathway through which enough information can be communicated to the healthcare professional user about the machine learning software that would give the user a reasonable opportunity to review the basis for the recommendation – and, therefore, satisfy the statutory transparency test.

This, of course, is an emerging area, and we recognize that many people are studiously working to figure out a way to make machine learning software less of a black box. For example, biomedical research scientists are working to address the challenge of articulating machine learning models in a clear and concise manner. In the meantime, as outlined in the Introductory Memorandum to the Coalition Industry Guidelines, there are five key steps that developers can take that we believe create enough transparency to meet the requirements of the Cures Act standard:

1. **Explain what can be explained.** Don't make the problem bigger than it has to be. If the software is actually a blend of expert systems and machine learning, and if a particular recommendation is based on expert systems, such as simply looking up the drug allergy in the patient's EHR, following a simple computational model or recommending a treatment because it is cheaper, the recommendation ought to reveal that reason.
2. **Communicate the quality of the machine learning algorithms.** When the source is truly machine learning, the software needs to reveal that source, along with information that will help the user gauge the quality and reliability of the machine learning algorithm. Through a page in the user interface that can be periodically updated, the developer could explain to the user the extent to which the system has been validated and the historical batting average of the software. That context helps the user understand the reliability of the software in general.
3. **Describe the data sources used for learning.** Providing a thorough explanation of the data sets used to feed and test the machine can provide important context and assurance to the clinician.
4. **State the association as precisely as possible.** With machine learning, really what we are seeing is an association – something in the patient-specific information triggers an association to what the software has seen in other cases. Even though the software cannot articulate exactly what it is about the data that triggers the association or even what features it looked at, that does not make it any different than a radiologist who points to a place on an image and says, "I've seen that before, and it's been malignant." Much of what we "know" in medicine is really just associations without a deeper understanding of a causal relationship. Software built on machine learning needs to explain that it has spotted an association, and state as precisely as it can the details of that association.
5. **Convey the confidence level.** While software based on machine learning does a miserable job of explaining the clinical logic it follows, machine learning excels at communicating its confidence level in reaching a particular recommendation. And that is quite valuable. That information helps the user decide how much deference the user should give a particular recommendation.

If these guidelines are followed by CDS software developers, the healthcare professional user should be equipped to independently review the basis for the recommendations provided by the CDS software, thereby allowing the software to satisfy the statutory transparency standard and avoid FDA's regulatory requirements.

*B. The Draft Guidance Creates Uncertainty for CDS Software Incorporating Machine Learning*

As detailed above, the Coalition believes that CDS software incorporating machine learning should be able to avoid FDA regulation if certain steps are taken to ensure transparency. The Draft Guidance, however, casts doubt on this scenario. At best, the Draft Guidance creates

substantial confusion with regard to how the Agency will treat software based on machine learning. At worst, the Draft Guidance simply precludes the use of machine learning in unregulated CDS software.

Lines 223-225 of the Draft Guidance state: “In order for the software function to be excluded from the definition of device, the intended user should be able to reach the same recommendation on his or her own without relying primarily on the software function.” The core problem is FDA’s use of the phrase “the same recommendation.” If software is using machine learning on a large data set, it is unclear what exactly this language means. Must the human user be able to reach the same conclusion that the machine learning produces, or is it acceptable for the human user to merely be able to reach a professionally justifiable conclusion on the same question?

We believe that the Draft Guidance language referenced in the paragraph above oversteps and misinterprets what is included in the Cures Act. Nowhere in the statute is there a requirement that the healthcare professional user be able to reach the *same recommendation presented by the software on his or her own* (in order for software to be excluded from the device definition). Instead, the statute simply requires that healthcare professionals be able to independently review the basis for recommendations presented by software so that they are not relying primarily on such recommendations to make diagnoses or treatment decisions.

The Cures Act does not support barring CDS software incorporating machine learning from falling within the scope of medical software excluded from FDA regulation, provided that the statutory transparency standard is satisfied. If a company follows the transparency-related guidelines that we developed for CDS software incorporating machine learning (as set forth in the Coalition Industry Guidelines), the software should be considered exempt under the Cures Act.

### C. *Recommendations*

There is non-low risk CDS software that should be permitted to use machine learning without FDA oversight. As discussed above, we believe that such software can meet the exemption under the Cures Act (despite the language in the Draft Guidance), as long as the relevant portions of our Coalition Industry Guidelines are followed. As these guidelines went through substantial public vetting and appear to have broad consensus support, we believe that, if followed, they will adequately assure that the healthcare professional user retains the central role in clinical decision-making, thus allowing software to satisfy the Cures Act transparency standard.

To ensure that the Draft Guidance does not automatically preclude CDS software that uses machine learning from avoiding regulation, we recommend that FDA revise the Draft Guidance to clarify that the user does not need to be able to do what the software does in the way the software does it, but the user instead needs to be fully capable of making the decision on which the software advises. Specifically, we recommend the following three changes:

1. Lines 223- 225 should be revised to say: “In order for the software function to be excluded from the definition of device, the intended user should be able to ~~reach the~~

~~same recommendation~~ make the required decision on his or her own without relying primarily on the software function.”

2. The sentence that follows the one above (on line 225) should be revised to read: “In addition, ~~the~~ sources...” This added language makes it clear that the sentences which follow that first sentence add additional dimensions, and are separate from the first sentence. The following sentences impose additional requirements, such as making sure that the underlying clinical evidence is available to the user, and is understandable to the user.
3. FDA should add a sentence explaining that the Agency is interested in figuring out ways to encourage the adoption of machine learning, and will issue guidance on that topic in the future. Such a sentence would make it clear that FDA has not reached a conclusion about the best way to treat CDS software that employs machine learning.

#### **IV. Portions of the Draft Guidance Require Clarification or Further Explanation**

In general, the principles articulated in the Draft Guidance are briefly and broadly stated, with very little elaboration beyond what the statute already provides. To give a high-level sense of the difference in detail between the Draft Guidance and the Coalition Industry Guidelines, the latter covers in 40 pages what the Draft Guidance covers between lines 218-231. The Draft Guidance’s cursory style does little to assist CDS software developers in understanding when FDA will apply (or not apply) its regulatory requirements. To provide more meaningful guidance to industry, and resolve existing ambiguities, additional explanatory language should be added throughout the Draft Guidance.

In particular, we recommend adding a sentence starting on line 231 that references the Coalition Industry Guidelines and recommends that CDS software developers use these guidelines to identify practices to help them design software in such a manner that healthcare professional users will be able to independently review the basis for the recommendations that the software produces (as required by the Cures Act exemption, and in line with the Draft Guidance). Alternatively, FDA may consider incorporating the more detailed analysis contained within the Coalition Industry Guidelines directly into the Draft Guidance to more effectively guide industry in Cures Act compliance.

Beyond the need to generally expand the level of detail in the document, we discuss below specific areas within the Draft Guidance that require clarification or further explanation.

##### *A. Ambiguities Requiring Clarification*

We have identified the following specific ambiguities:

1. Lines 223-225: “In order for the software function to be excluded from the definition of device, the intended user should be able to reach the same recommendation on his or her own without relying primarily on the software function.”
  - a) The words “able” and “same” create ambiguity. We assume that rather than the word “recommendation,” FDA really means “decision.” Does the word

“able” mean that, in fact, if the professional user did not have the software, the professional user would always or at least likely reach the same decision as the software? If so, does that mean that the only software that will meet this test is software that is merely used to speed up the calculation? If true, this interpretation is problematic as many CDS products are intended to help physicians think of things that they would not have considered or may have forgotten.

- b) Does this sentence mean that the intended user must, in some sense, know everything that the software knows, having absorbed all of the same clinical knowledge regardless of its source? What if the database includes clinical information that the user is not familiar with and has not read, such as recent or obscure journal articles?
  - c) Does it mean that the intended user must be able to answer the question as reliably and correctly as the software? What if there is lots of math, and conceptually the intended users can do the math, but human users are much more prone to mathematical errors?
  - d) What if the user can conceptually do all of the math, but it would simply take way too long for the user to do so? Taking way too long means either from an efficiency standpoint, or due to the need to make a decision more quickly. Among other things, software often can speed up necessary calculations.
2. Lines 225-231: “The sources supporting the recommendation or underlying the rationale for the recommendation should be identified and easily accessible to the intended user, understandable by the intended user (e.g., data points whose meaning is well understood by the intended user), and publicly available (e.g., clinical practice guidelines, published literature). A practitioner would be unable to independently evaluate the basis of a recommendation if the recommendation were based on non-public information or information whose meaning could not be expected to be independently understood by the intended health care professional user.”
- a) What if the underlying rationale is found in a simple statistical analysis performed by the software of a large data set? Does this mean that, so long as the enormous data set is available to the intended user to analyze, this criterion is met?
  - b) What if the underlying clinical knowledge is found in a large data set that is analyzed by complex machine learning algorithms? Is the data set the source of clinical knowledge, or are the machine learning algorithms the source of support?
  - c) What does it mean for the source to be easily accessible? If the source is clinical guidelines that can be purchased for a significant amount of money from a medical society, is that “easily accessible?”

- d) With regard to the requirement that sources be “publicly available,” FDA should clarify that such information need not be “generally publicly available” (in other words, the requirement should be met if the relevant information is available to the healthcare professional user; the information need not be available to the general public).

*B. Examples Requiring Further Explanation*

1. Regulated v. Unregulated Software Examples

Although it is helpful that the Draft Guidance provides examples of CDS software products that are regulated versus those that are unregulated, these examples provide limited insight into FDA’s thinking because there is no explanation provided as to why a given functionality is regulated or not. The Draft Guidance simply lists the intended use of software falling under either the unregulated or regulated category, without any accompanying analysis.

In the examples provided of unregulated software, we (apparently) are supposed to assume that the underlying bases for the recommendations provided by the software are completely available to the user. However, this is not clearly articulated in the example descriptions. Overall, the examples tend to create more questions than answers. For instance, one listed example of unregulated software is “[s]oftware that provides healthcare professionals with recommendations on the use of a prescription drug that are consistent with the FDA-required labeling.” This begs the question of when a recommendation is “consistent” with drug labeling. Drug labeling provides high level parameters for the use of a drug. Software might very well work within those broad parameters – with respect to dosage, for example – but, based on machine learning, may identify nuances aimed at ensuring that a particular patient gets the exact right dose of the drug at the right time. It is unclear whether such software would still qualify as unregulated. And what if the software is not inconsistent with the labeling, but goes deeper than the labeling? Would it still qualify as unregulated?

In the IMDRF Risk Categorization Document, a brief explanation is included after each provided example to clarify why the particular example falls within a given category. We recommend that FDA adopt this same format in providing examples of software that is regulated versus unregulated. This added detail would greatly enhance the value of the Draft Guidance to industry.

2. Conflicts between Examples

In addition to lacking detail, some of the examples provided in the Draft Guidance are difficult to interpret because they seem to contradict one another. Consider FDA’s statements regarding the interpretation of genomic data. Lines 178-186 state: “Technologies that analyze those physiological signals and that are intended to provide diagnostic, prognostic and predictive functionalities are devices[:];...examples include algorithms that...analyze and interpret genomic data (such as genetic variations to determine a patient’s risk for a particular disease).” Yet, the Draft Guidance later provides the following as an example of unregulated software (lines 255-258): “Software that makes chemotherapeutic suggestions to a health care professional based on patient history, test results, and patient characteristics, including, for example, software

suggesting a platinum-based chemotherapy for BRCA-positive individuals that is consistent with the drug labeling.” In this example, “BRCA-positivity” is an interpretation of genomic data. Thus, this example seems to contradict the earlier statement provided in lines 178-186.

To resolve this conflict, FDA should delete the example provided in lines 185-186 and retain the example in lines 255-258. We believe software that interprets genomic data is low risk because it provides information that is otherwise available to the healthcare professional, and supports treatment/diagnostic decisions in a non-critical situation where there is plenty of time for the healthcare professional to evaluate the basis of a recommendation and make an informed clinical decision. The risk of misinterpretation is low because the outcome of computer analysis is not a treatment/diagnostic verdict, but summarized information that presents clear options relevant for the individual patient to help the healthcare professional make better-informed clinical decisions. In addition, genomic data is analyzed using transparent and validated computer algorithms that are based on publicly available clinical and scientific data (that is curated and referenced).

## **V. Impact of Leaving the Draft Guidance Unchanged**

Despite FDA policy, federal law, and IMDRF guidance paving the way for the Agency to adopt a risk-based regulatory approach for regulating CDS software, the Draft Guidance veers in a different direction. As described further below, if left unchanged, the Draft Guidance would: (1) subject low risk CDS software to regulation if it is not transparent, and (2) subject CDS software incorporating machine learning to regulation even if it otherwise meets the statutory exemption. Not only would this increase the number of CDS software products regulated by FDA, it would also hinder software innovation and impede patient access to important software products.

### *A. Low Risk CDS Software Will Be Regulated Simply Because it is Not Transparent*

Over the last six years, the Coalition has spoken to dozens upon dozens of CDS software developers. In those conversations, virtually everyone assumed that FDA’s guidance on CDS software would be risk-based. This assumption was based on the FDASIA Health IT Report, which discussed a risk-based approach, as well as the IMDRF Risk Categorization Document, which called for consideration of the significance of the information provided by the software and the state of the relevant healthcare situation or condition as the two key factors for stratifying the risk of software. Even though FDA was actively involved in authoring the FDASIA Health IT Report and the IMDRF Risk Categorization Document, the Draft Guidance walks away from the principles embodied in those documents in a significant way.

FDA seems to have decided to draw the line between regulated and unregulated CDS software based solely on the concept of transparency – the standard under section 3060 of the Cures Act that exempts software from FDA regulation if it allows the user a reasonable basis for reviewing the recommendation provided by the software. Of course, FDA had to adopt the statutory standard, but that did not foreclose the use of a risk-based standard as well. By failing to adopt a risk-based standard, and only excluding from regulatory oversight CDS software that is transparent, FDA ensnares many more products within its regulatory net, including low risk products such as the following (among other examples set forth in Appendix A):

- Software that identifies drug-drug interactions and drug-allergy contraindication alerts to avert adverse drug events done based on machine learning analysis of collected data.
- Triage software that asks patients online a series of structured questions to help discern which common disease or ailment a patient might have such as sinusitis and muscle ache. The software then presents the physician with the answers to those questions as well as the proposed diagnosis and treatment plan. The physician can decide whether additional information is necessary, or whether an in-person checkup is required. The software does not present the physician with the underlying logic or clinical guidelines that the software is applying.

Notably, many of the examples included in Appendix A were found through general Internet searches. This means that many of these example products are currently on the market today, and would need to come into compliance with FDA requirements should the Draft Guidance be finalized without revision. Coming into compliance may well require removing these CDS products from the market.

In passing the Cures Act, which formally deregulates various types of medical device software, Congress did not intend to expand the scope of FDA’s regulation to cover categories of CDS software that FDA did not previously regulate. Many CDS products have been on the market for decades, and it would cause a significant disruption in patient care if these products had to be removed from the market pending compliance with FDA regulatory requirements.

*B. CDS Software that Otherwise Complies with the Cures Act Exemption Will Be Regulated Simply Because it Employs Machine Learning*

FDA only exempts from regulation simple, expert system software that implements clinical guidelines and other established medical knowledge. In order to be exempt, according to the Draft Guidance, the professional user has to “be able to reach the same recommendation on his or her own without relying primarily on the software function.” Further, “[t]he sources supporting the recommendation or underlying the rationale for the recommendation should be identified and easily accessible to the intended user, understandable by the intended user...[,] and publicly available....” As discussed above, this language effectively precludes CDS software that uses machine learning from meeting the exemption. In contrast, as discussed above, the CDS Coalition has interpreted the statute to allow certain CDS software that uses machine learning to still satisfy the exemption, as long as it meets the statutory transparency standard.

FDA’s interpretation here looks backwards at popular, simple software over the last couple of decades and exempts them, but, frankly, is completely silent as to artificial intelligence going forward. And with that silence, FDA extends its reach to even low risk software that uses machine learning; an interpretation that is likely to impede innovation and delay patient access to new CDS software programs going forward.

\* \* \* \*

**Conclusion**

Based on the significant changes we recommend to the Draft Guidance, we ask that FDA re-issue the guidance in draft once revised. If the CDS Coalition can assist in developing revised draft guidance on this topic, please do not hesitate to contact us.

Yours truly,

A handwritten signature in black ink, appearing to read "Bradley Merrill Thompson". The signature is fluid and cursive, with the first name being the most prominent.

Bradley Merrill Thompson  
On Behalf of the Clinical Decision Support Coalition

## Appendix A

### Category I CDS Software Using IMDRF Risk Stratification Model

The list of software products in this appendix was created mostly by summarizing software already available on the market today. In reviewing these, let's assume that none of them are designed to be transparent enough to qualify for exemption under section 3060 of the 21<sup>st</sup> Century Cures Act.

These nontransparent software programs should nonetheless be exempt under FDA enforcement discretion because they meet the following criteria:

1. SaMD that provides information to drive clinical management of a disease or conditions in a non-serious situation or condition is a Category I and is considered to be of low impact.
2. SaMD that provides information to inform clinical management for a disease or conditions in a serious situation or condition is a Category I and is considered to be of low impact.
3. SaMD that provides information to inform clinical management for a disease or conditions in a non-serious situation or condition is a Category I and is considered to be of low impact.

Examples are followed by the explanation as to which particular criteria apply. This list is organized based on the three criteria.

#### Criteria 1

1. Software that applies a series of mathematical equations to analyze clinical, administrative, and physiological data, then feeds the results into a computer model that simulates actual healthcare processes and human physiology. The software takes patient-specific data from more than 30 different variables to create "individualized guidelines" based on each person's unique risk factors, history, treatments, and, when available, biomarkers across multiple morbidities. The system can recommend patient-specific care plans for better disease management for common, low risk illnesses.
  - a. *Under criteria 1 above, this analytics software provides information to drive clinical management of a disease or conditions in a non-serious situation or condition.*
2. Software that uses advanced Natural Language Processing to extract key clinical features including lab test results, vital signs and social factors from the EMR, analyzes those features and then produces a differential diagnosis for the clinician within the EMR workflow. The software uses a specially designed medical database built from continually updated medical textbooks and journals structured around 3 separate and proprietary taxonomies to apply advanced pattern-matching techniques (non-linear adaptive digital signal processing), that enable identification of the patterns that naturally occur in text, based on the usage and frequency of words or terms that correspond to

specific concepts. The data entry and system outputs are further processed by a complex interplay of approximately 40 proprietary algorithms in order to ensure that the end results are highly accurate and relevant. The focus of the software is common, low risk diseases and conditions.

- a. Under criteria 1 above, the differential diagnosis calculations provide information to drive clinical management of a disease or conditions in a non-serious situation or condition.*
3. Triage software that asks patients online a series of structured questions to help discern which common disease or ailment a patient might have such as sinusitis and muscle ache. The software then presents the physician with the answers to those questions as well as the proposed diagnosis and treatment plan. The physician can decide whether additional information is necessary, or whether an in person checkup is required. The software does not present the physician with the underlying logic or clinical guidelines that the software is applying.
  - a. Under criteria 1 above, the proposed diagnosis and treatment plan provide information to drive clinical management of a disease or conditions in a non-serious situation or condition.*

## Criteria 2

4. Software that computes an established acuity score (APACHE, MEWS, SOFA, Sepsis risk, etc.) and uses that score for risk stratification, for example, displaying a list of patients sorted by decreasing acuity.
  - a. Under criteria 2 above, these established acuity scores merely inform clinical management for disease or condition, which in some cases might be serious.*
5. Software that calculates the risk that an inherited disease that is present in a family will recur in that family, by blending three commonly-accepted but unidentified methodologies, for the purpose of informing physician decision-making.
  - a. Under criteria 2 above, these methodologies for calculating inherited disease risk merely inform clinical management for disease or condition, which in some cases might be serious.*
6. Software that analyzes patient history, presenting symptoms, and physician knowledge, looking for patterns in the data to produce a checklist, with statistical probabilities, for physicians to go through while making a differential diagnosis.
  - a. Under criteria 2 above, these search and pattern recognition capabilities merely inform clinical management for disease or condition, which in some cases might be serious.*
7. Software that uses data from individuals and commonly accepted but unidentified formulas for predicting risk score for developing stroke or heart disease for creating prevention or interventional strategies.
  - a. Under criteria 2 above, these formulas for predicting risk scores merely inform clinical management with regard to creating prevention and interventional strategies for disease or condition, which in some cases might be serious.*
8. Software that identifies possible diagnoses based on patient-specific information retrieved from a patient's EHR.

- a. Under criteria 2 above, these matching functions merely inform clinical management for diseases or conditions, which in some cases might be serious.*
9. A software management system based upon the principles of disease management and standardized nursing processes that map out common disease categories. The system highlights abnormal findings and changes in condition and provides the nursing team with appropriate interventions and physician communication.
  - a. Under criteria 2 above, these mapping and highlighting functions merely inform clinical management for diseases or conditions, which in some cases might be serious.*
10. Software that offers oncologists actionable insights based on molecular profile data, in the context of a patient's clinical history. In particular, the software allows an oncologist to review the patients' molecular & clinical history, order molecular testing and select molecularly targeted therapies.
  - a. Under criteria 2 above, these matching functions merely inform clinical management for diseases or conditions, which in some cases might be serious.*
11. Drug selection software that physicians used to pick the right drug for a given set of symptoms. The software is based on drug formulary guidelines and professional society treatment guidelines, but does not disclose the specific source of its recommendations.
  - a. Under criteria 2 above, these drug matching functions merely inform clinical management for diseases or conditions, which in some cases might be serious.*
12. Software that identifies drug-drug interactions and drug-allergy contraindication alerts to avert adverse drug events done based on machine learning analysis of collected data.
  - a. Under criteria 2 above, these drug matching functions merely inform clinical management for diseases or conditions, which in some cases might be serious.*
13. Software that embodies an antimicrobial stewardship initiative that helps identify, for a particular patient, drug bug mismatches, redundant therapies and unnecessary double coverage of pathogens.
  - a. Under criteria 2 above, these drug matching functions merely inform clinical management for diseases or conditions, which in some cases might be serious.*
14. Software that serves as a broad symptom checker that uses a huge, proprietary database of symptoms and diseases (e.g. diabetes, CVD, oncology, osteoporosis, allergy, etc.) assembled manually by a large group of medical advisors.
  - a. Under criteria 2 above, these matching functions merely inform clinical management for diseases or conditions, which in some cases might be serious.*
15. Software that uses machine learning to calculate, using a patient's medical record, a Behavioral Health Impairment Index (BHI) to identify each patient's behavioral health status, surface patients with behavioral health issues, notify key care team members in real-time, and energize therapeutic interventions with actionable insights.
  - a. Under criteria 2 above, calculation of the BHI merely informs clinical management for diseases or conditions, which in some cases might be serious.*
16. Software that applies predictive analytics algorithms using data in the enterprise data warehouse to offer insight into each patient's risk of a positive or negative outcome of interest, as well as the factors contributing to that patient's level of risk. This is most often delivered as a worklist. For example, machine learning can predict which patients to monitor more closely for central line-associated blood stream infection (CLABSI), because they are exhibiting similar patterns or characteristics to past patients who had

higher incidences of CLABSI. These machine learning insights can be presented in an actionable dashboard for clinicians at the point of care.

- a. Under criteria 2 above, the predictive analytics algorithms merely inform clinical management for diseases or conditions, which in some cases might be serious.*
17. Software that searches through hundreds of thousands of patient data records to calculate likely diagnoses for a list of symptoms. The software uses machine learning algorithms to calculate disease frequency and likelihood based on patient data. The database is comprised of data shared by individual users.
  - a. Under criteria 2 above, the differential diagnosis calculations merely inform clinical management for diseases or conditions, which in some cases might be serious.*
18. Software that uses machine learning in conjunction with natural language processing to go through a patient's entire medical history in the EHR, looking for hundreds to thousands of different crucial facts, to inform an emergency department physician. Over time, these decisions can be captured to "learn" what clinicians find relevant in the course of care to improve accuracy and utility.
  - a. Background. The average patient visiting the emergency department has around 60 documents in his or her medical history, and each document can take up to a minute to read. With clinicians seeing two patients every hour, it is neither feasible nor practical to comprehensively identify relevant and crucial facts in the patient history for informing care decisions. In such time-constrained settings, clinicians can spend more than half their time with the patient conducting a review of his or her medical history in the EHR and still risk missing relevant facts.
  - b. Under criteria 2 above, flagging pertinent facts merely informs clinical management for diseases or conditions, which in some cases might be serious.*
19. Software that continuously collects and analyzes complex data across 1,200 health monitored events and based on more than 9,000 clinical rules and guidelines flags conditions that require the physician's attention.
  - a. Under criteria 2 above, flagging pertinent facts merely informs clinical management for diseases or conditions, which in some cases might be serious.*
20. Software that uses machine learning algorithms and models to deliver more accurate predictions of disease occurrence, allowing for early intervention to prevent disease.
  - a. Background. Traditionally, physicians or doctors use a risk calculator to assess the possibility of disease development. These calculators use fundamental information such as demographics, medical conditions, life routines, and more to calculate the probability of developing a certain disease. Such calculations are done using equation-based mathematical methods and tools. Unfortunately, they often have very low accuracy. For an example, the Framingham Study can predict the hospitalization with only 56% accuracy for a long-term cardiovascular disease. Machine learning has been shown to produce higher accuracy than these historical formulas.
  - b. Under criteria 2 above, these machine learning based models that deliver predictions of disease occurrence merely inform clinical management for diseases or conditions, which in some cases might be serious.*

21. Software that helps physicians and other healthcare professionals determine the most likely diagnosis of a disease quickly and accurately based on patient symptoms and lab results, by searching for diagnostic similarities between the patient's clinical features and master maps contained in the program's database. The software presents several possible diagnoses along with the percentage of similarity between the clinical features and the underlying indications forming the diagnosis. The software provides current consensus on disease treatment; Suggested tests to document the disease; Image and biopsy displays; and a disease bibliography from PubMed. The software constructs a map containing all the bits of information that comprise the characteristics of a particular disease. Information with respect to these characteristics is first gathered by specialists from well-recognized publications, medical texts, journals, as well as their own experience. The information is then converted into key words. Patterns among these words are identified which the software converts into a master map. Each disease has a unique, proprietary master map. Information in the patient's medical record is then scanned. The bits of information contained in the standard medical file – patient history, physical exam, and laboratory data – written as usual by the physician, comprises the user map. The user map is then compared to the master map and the similarities are computed allowing the physician to review the best diagnosis and disease management for a particular patient.
- a. Under criteria 2 above, this mapping exercise merely informs clinical management for diseases or conditions, which in some cases might be serious.*

### Criteria 3

22. Software that uses data from individuals for predicting risk score in healthy populations for developing the risk of myopia, to be used in medical counseling.
- a. Under criteria 3 above, this data merely informs the clinical management of healthy people with regard to myopia, a non-serious condition.*