AI IN MOBILE MEDICAL APPS: A LOOK AT CURRENT AI HEALTHCARE INNOVATION AND REGULATION

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Executive Summary

In this paper the influence of mobile medical apps (MMAs) on healthcare, and artificial intelligence's (AI's) influence on MMAs, is researched. The three main case studies, Gauss Surgical, AliveCor, and Viz.AI provide clear evidence that mobile apps will increasingly deliver artificial intelligence based diagnostics and solutions to patients and medical professionals. While some firms, like Gauss Surgical, have focused on artificial intelligence capabilities from the outset, others, like AliveCor, have rapidly integrated AI into their applications to exponentially increase their capabilities and remain market leaders. The application of AI in mobile health applications does not necessarily dictate price or reimbursement strategy and large differences in both are observed between MMAs with AI functionality.

Introduction and Background

Introduction of Mobile Apps Into Healthcare

Software regulations began in 1986 with "FDA Policy for the Regulation of Computer Products (Draft)", an overarching informal policy for computer programs. It wasn't until 2005 that they codified a more fluid regulatory stance stating a single policy for such a diversity and complexity of softwares. It wasn't until July 2011 that draft guidance for MMAs was released. Under this guidance MMAs meet the definition of classical medical devices and is intended to either be used as an accessory to a regulated medical device, or to transform a mobile platform into a regulated medical device. [1] Figure 1 shows the incredible rise of avaiable MMAs on the market. Interestingly, following the release of the FDA's 2011 draft guidance, there was a rapid increase in MMA development.

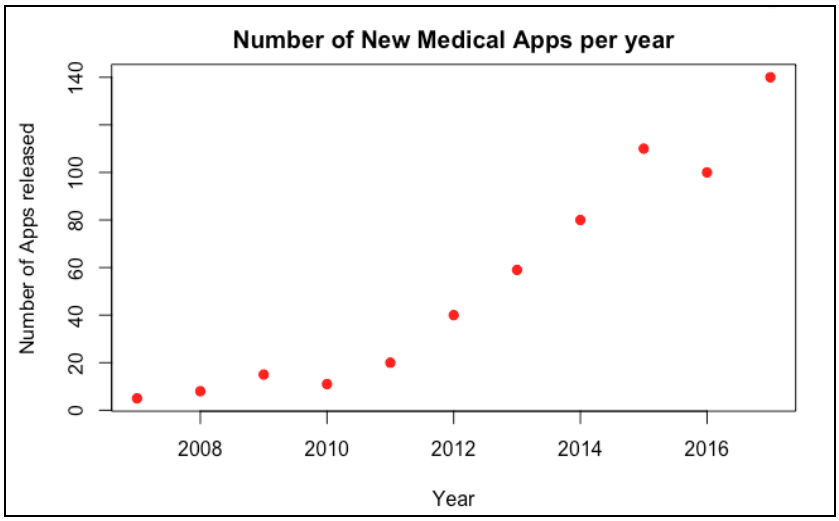

Figure 1: The number of MMAs released from the creation of the iPhone in 2007 to 2017

Three broad classes of MMAs exist [2]:

1. *Basic clinical analysis programs*
   The category encompasses passive measurement of various health metrics (i.e. heart rate, blood pressure, body temperature).
2. *Basic disease management analysis programs*
   This is considered a low risk category that considers patient-specific data to aid in disease management in conjunction with well established clinical guidelines and healthcare professionals. This would, for example, be a nutrition or diet management system for patients suffering from heart disease.
3. *Programs that use data downloaded from medical devices for disease management*
   The FDA recognizes apps that perform analysis and trend finding algorithms of data derived from connected medical devices as MMAs. This would include apps that analyze glucose levels, for example, in diabetic patients using a separate glucose monitoring device.

The common trend in these classes and a continuing trend for MMAs that will incorporate AI is that their analysis and diagnostic capabilities typically do not replace professional care and input—they are meant as a supplement.

Introduction of AI Into Healthcare

AI, which aims to copy or simulate human cognitive processes, is making a major impact in healthcare and is enabling new, previously unexplored, functionalities and areas of research. Due to the recent increase in data, resources, and most importantly technology, scientists are now able to apply AI to both structured and unstructured healthcare data. [3]

Current techniques used in AI include machine learning, classical support vector, neural networks, modern deep learning and natural language processing. All of these different methods are being used in healthcare to detect, diagnose and treat a variety of medical conditions. [3]

Additionally, AI allows researchers to create new treatments for conditions that would have otherwise been impossible to create and the ubiquity of smartphones and tablets allow the awesome power of AI to be accessed by almost everyone. Thus, AI has become one of the most important research focuses of the decade.

Beginning in early 2013, there was a great push towards training AI models by using the data that is generated from clinical activities such as patient questionnaires, diagnostics, passive data collection, and clinical trial data. All of these data sources are grouped into smaller subsections

and correlations and associations between different features and outcomes are observed. In line with this the number of journal articles relating to healthcare increased drastically from 2013 to 2016 and this trend is expected to continue. [3]

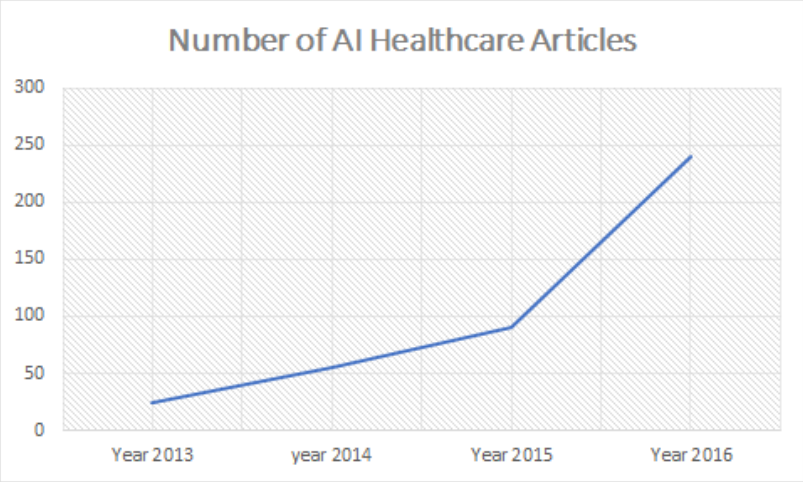

Figure 2 : Estimated number of AI healthcare Articles from 2013 to 2016

This brings us to an important point: it is crucial that a clear framework to regulate the massive influx of AI based healthcare solutions be created. A clear framework will serve to contain and organize the development of these AI based solutions and protect the patients and society in general.

The Food and Drug Administration (FDA) is currently developing multiple frameworks to regulate AI products that are actively used in medicine and is continuously adjusting its approach based on new and upcoming data. This turned out to be very challenging given that the performance of AI constantly changes based on the exposure to new clinical data, where the approach needs to constantly change with the model used, so the regulatory framework has to be as flexible as AI changes.

The FDA's proposed frameworks will examine the performance of the product's algorithms and any future plans that the manufacturer might have, according to the FDA it is a more tailored fit than the existing regulatory paradigm for software as a medical device. [4]

The FDA also needs a regulatory framework that should have support for adaptive AI systems that learn and change overtime, the FDA already approved different medical devices that are based on algorithms that do not change over time which require frequent interval updates from the manufacturer, such as devices used to diagnose strokes and diabetes. Those approved systems have the crucial responsibility of not only performing very well but also ensuring accurate and precise information that helps doctors make important decisions. However, those systems have

increased importance as they set the precedence on what and how the FDA can regulate and monitor such developments.

Gauss Surgical: Triton Case Study

For decades operating rooms have been afflicted by the challenge of accurate intraoperative blood, or hemoglobin, loss measurements. Blood loss assessment is of critical importance both in standard operating procedures and during labor where 1-5% of women experience postpartum hemorrhaging [5], which should be accurately and closely monitored for effective intervention.

Quantification of Blood Loss

Current methods for measuring blood loss include visual estimation, which is rudimentary and subjective, and the gravimetric method, which uses weight differences between dry and blood-soaked items to determine blood loss. Though the gravimetric method is considered the gold standard, it is notoriously inaccurate and difficult to carry out in a busy clinical setting [6].

The primary sources of inaccuracies using the gravimetric method are the confounding weights of non-sanguineous fluids (i.e. saline, amniotic fluid), and the assumption of constant hemoglobin concentration in blood which is false due to increased dilution by IV fluids [7]. These inaccurate quantifications of blood loss manifest themselves in the cost of unnecessary transfusions when blood loss is overestimated or, at the other extreme, life threatening conditions for a patient when blood loss is underestimated.

Hence, Gauss Surgical Inc. was founded in 2011 by Mark L. Gonzalgo and Siddarth Satish to address the unmet need of accurate, real-time monitoring of blood (hemoglobin) loss. Based out of Menlo Park, CA, Gauss Surgical developed the Triton system, an AI-enabled platform for monitoring blood loss during surgery. Currently, Gauss Surgical develops two embodiments of the Triton system: Triton OR for the surgery, and Triton L&D for the labor room. The Triton OR system uses vision-based AI for real-time monitoring of hemoglobin loss.

Figure 3: A clinician holds up a bloodied absorbent item up to an iPad where the Triton app indicates the region of soaked blood and provides a determination of blood loss volume.

Blood captured on surgical sponges and suction canisters is visually analyzed, and a readout of estimated hemoglobin mass lost is provided to clinicians. The Triton L&D system calculates hemoglobin loss based on weight of blood-soaked items using known dry-weight measurements of absorbent items and provides a metric for hemorrhage status. The Triton Systems also logs blood loss and provides real-time announcements to the room, serving an important role in status updates where there is potential for lost information in changeovers between clinicians during a procedure.

Mobile App Component

The primary component of the Triton OR system is a vision-based AI that determines regions of blood-stained absorbent items, and the Triton L&D system also incorporates elements of machine learning in providing hemorrhage risk updates. Hence, their primary technology is software-based, which is meant to operate on a standard iPad. They provide their various versions of the Triton systems as apps on the Apple iStore: Triton Sponge, Triton Canister, and Triton L&D. Supplementary hardware components interface with the app via Bluetooth. These include a scale to weigh blood captured on absorbent substrates and a foot pedal to interact with the app.

FDA Regulatory Pathways

The items in the Triton suite are classified as medical devices as they are consistent with the FDA's definition. Specifically, they represent a class of instrument/apparatus or implementation that is intended for the diagnosis of hemorrhaging and the mitigation of excessive blood loss. Up to its most recent embodiment, the Triton system has undergone three separate rounds of FDA classification: one De Novo classification [8] and two Class II 510(k) approvals.

De Novo Classification

Triton's story with the FDA began with a De Novo classification of their Pixel 3 System in February 2013 which would go on to become the first-generation Triton OR app. This system represents the software that would go on to function as the backbone current forms of the technology. The FDA identified the generic type of request as an image processing device for estimation of external blood loss, and due to the absence of prior equivalence the filling fell under this De Novo classification.

Limitations identified include warnings indicating incompatibilities with an MR environment and the presence of non-sterile iPads. The documentation also stresses that the Pixel 3 should not be used as a standalone trigger for clinical action; conventional vital signs (i.e. blood pressure, heart rate, respiratory rate) should be considered alongside Pixel 3 output in determining clinical decisions. Limitations also outline some operational ranges. In particular, the system has only

been validated for patient hemoglobin levels from 5 to 17 g/dL and sponges containing 6 g of hemoglobin. In addition, this section outlines compatible surgical materials and accessories (i.e. iPad, four types of blood absorbent sponges).

Results of non-clinical studies demonstrate that the Pixel 3 System would perform as anticipated. In an increasingly noisy wireless environment, the system demonstrated functionality in the presence of five separate wireless signals. Benchtop testing demonstrated 95% agreement between the Pixel 3 and known volumes/contents of blood soaked onto sponges. Figure 4 shows the frequencies of differences between three methods of blood loss determination (including the Pixel 3) and known amounts of blood adsorbed. Furthermore, bright, medium, and dark lightning conditions were also demonstrated to have negligible effect on the determination of blood loss. Konig et al. went on to publish this result. [9]

Additionally, Gauss Surgical sought to demonstrate the effectiveness of the device design, or UI, in a human factor assessment. Endpoints were evaluated on operational task pass/fail criteria, with 94% completion by eight users on the first pass and 100% completion by the second pass. Gauss Surgical also conducted two IRB approved clinical studies: a preliminary clinical test (46 patients, 758 sponges), and a confirmatory clinical test (50 patients, 791 sponges). In both trials, the Pixel 3 System proved its safety and effectiveness in being more accurate than conventional visual and gravimetric methods.

In conclusion, the benefits are summarized as sponge counting functionality to assure additional accountability, estimated blood loss on validated sponges which outperforms conventional practices and streamlined collection of inputted information. The De Novo is granted on the basis that these benefits outweigh the risks of potential inaccuracies in estimations, user error, or incompatibilities with wireless environments.

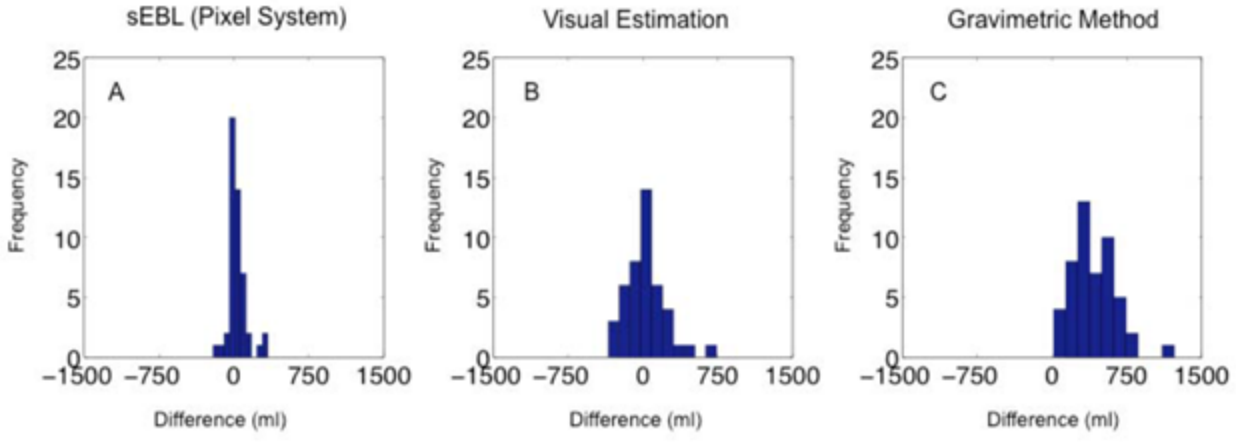

Figure 4: Comparison of the Pixel 3 System's calculation of blood loss and the conventional visual and gravimetric methods. The difference considered is between the method calculation and known volumes of blood absorbed onto substrates.

Two 510(k) Rounds of Approval

Gauss Surgical obtained an additional class II FDA approval in March 2015 for the Triton Canister Image Processing Device for Estimation of External Blood Loss in Surgical Canisters.[12] This fell under the classification that was previously predicted in the De Novo classification. Herein, a second version of software, Triton Canister App, was evaluated in conjunction with two added accessories: a canister specific insert and canister scanning label. This approval process followed much of the same scrutiny that was seen in the De Novo application but with the use of canisters in place of sponges. A notable addition was human factor testing to qualify the usage of the added accessories; all users passed the pass/fail criteria set forth demonstrating appropriate device design and labeling.

The most recent class II approval from the FDA came in August 2016.[13] Gauss Surgical sought to have their second-generation Triton OR app approved with the added functionality of automatic sponge-capture via infrared 3D sensors and a Bluetooth scale to weighing additional blood components. [10] This 510(k) document is brief due to the strong prediction by the previous classifications, demonstrating equivalence, and no changes to the overall effectiveness.

Health Economics and Reimbursement

The Triton apps are licensed out to hospitals at a rate of $96,000 per year. This cost falls on the hospital and there is no healthcare reimbursement involved given that the use of the Triton systems is not an optional service that the patient can opt into. The cost to the hospital, however, was shown to be an expense-cutting investment. In a study by Hackensack University Medical Center, Triton saved the hospital over $1 million in correctly identifying hemorrhaging and reducing the number of unnecessary transfusions [10].

Concluding Comments on the Triton System

Safety and Effectiveness

The classification documents provide in-depth assessments of safety and effectiveness, which are summarized above, but it is worthwhile to further comment on the potential impact the Triton systems can have on healthcare. The utility of the Triton systems is apparent in the vast number of peer-reviewed journal articles citing the use of the Triton systems. Both clinical experience and accuracy of measurements have been studied in at least 13 journal articles [11]. Its effectiveness is also evident in the adoption of Triton into more than 50 hospitals since 2017 [12].

On AI Implementation

Both Gauss Surgical Inc. and market experts consider AI as the cornerstone of the company's technology. Because AI is a computationally expensive process, Triton apps rely on cloud-based computation to seamlessly provide blood loss metrics to clinicians. We would like to note that as extensive as the approval process is, there is no mention in the documentation on cybersecurity measures surrounding medical mobile devices.

Future of Gauss Surgical Inc.

Gauss Surgical, Inc. has gained high praise throughout the medical and tech community. In 2019 they were regarded by FierceHealthcare as one of the top 15 most promising healthcare companies, and in 2018 they went onto raise $20 million in Series C funding. We expect to see continued growth and adoption of this technology in more ORs around the world and potentially in emergency vehicles.

AliveCor: Case Study

While some mobile medical devices, like the Gauss Surgical Triton system, have used AI as a core part of their device from the beginning others, like AliveCor's suit of mobile ECG's, have arrived at using artificial intelligence later in their lifecycle. These companies began with a product that met their primary objectives and then extended their device's capability by adding artificial intelligence capabilities once it became technically feasible to use artificial intelligence in a commercial setting.

Background on ECGs

According to the American Heart Association "An electrocardiogram — abbreviated as EKG or ECG — is a test that measures the electrical activity of the heartbeat. With each beat, an electrical impulse (or "wave") travels through the heart. This wave causes the muscle to squeeze and pump blood from the heart. A normal heartbeat on ECG will show the timing of the top and lower chambers." ECG's come in three main forms. The first is the standard hospital ECG which is usually a large device with a monitor and ten electrode leads that are attached to the patient around their heart. The ECG records the electric pulse that travels through the heart and produces the diagram that reflects this electrical signal (Fig 6). A hospital's ECG produces a diagram that shows the patient's heartbeat in real time allowing doctors to analyze the shape of the beat to see if the patient has any abnormal heart conditions. Doctors and medical professionals will look at the shape of the ECG as well as the timing and speed of the ECG to screen the patient for a

variety of medical issues. [14] The industry leading General Electric MAC 5500 ECG is larger than a laptop and very bulky (Fig 5).

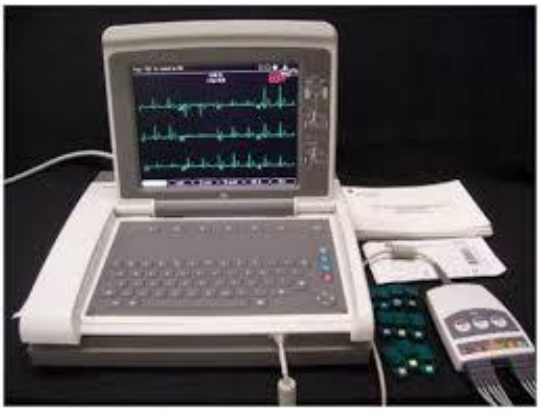

Figure 5 : A typical Hospital, MAC 5500 ECG Machine made by General Electric [15]

ECG's in hospitals are used to actively monitor a patient recovering from surgery or recovering from an acute traumatic incident, as well as on patients who have become severely ill or have just suffered a heart attack. EMT's will sometimes administer ECG's while in an ambulance to monitor a patient as transportation to a hospital occurs. In certain health systems, like Tokyo's ECG data recorded in the ambulance is automatically sent to the hospital in order for the emergency room to better diagnosis the patient and prepare treatment.[16] ECGs are also used in a clinical setting to detect ailments such as Long QT syndrome, Atrial Fibrillation, Bradycardia, Tachycardia. [17]

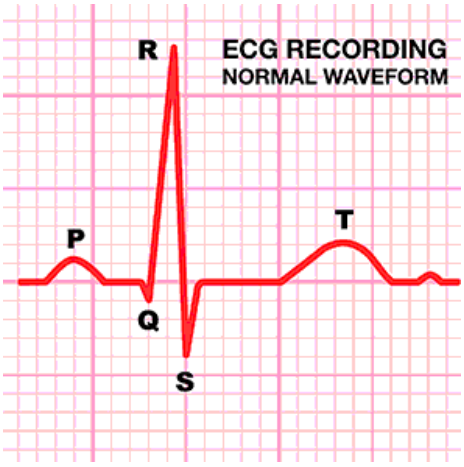

Figure 6: A typical ECG waveform

The second most common form of ECG is the ambulatory ECG. Not to be confused with ECG's found in ambulances to monitor patients as they travel to a hospital (these machines are fundamentally the same as the ones found in the hospitals themselves) ambulatory ECG's are ECG's that are placed in a holster and worn by a patient throughout their day in order to study

their heart in a regular environment with varying stress levels. Ambulatory ECG's are particularly helpful when finding heart problems that occur in scenarios that are not likely to happen at a hospital or physicians office like eating, sleeping or sex.[17] ECG's third form, small mobile ECG's (Fig. 7), are now becoming more common. This is in large part thanks to Dr. David Albert and the AliveCor KardiaMobile ECG.

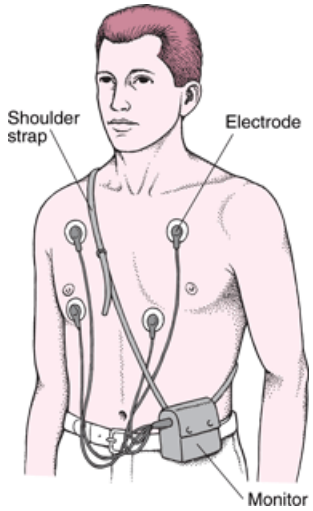

Figure 7: Diagram of a patient wearing an Ambulatory ECG. [18]

Mobile ECG

Before the first version of the AliveCor ECG, the KardiaMobile, was created there were multiple predicate devices on the market which allowed the AliveCor to file a 510(k) Premarket Notification. Specifically, AliveCor referenced the iRhythm Technologies, Inc. Event Card, CardioNet, Inc. Ambulatory ECG Monitor with Arrhythmia Detection, Card Guard Scientific Survival, LTD. King of Hearts Express + AF Monitor, and the Heart Check Pen Handheld Heart Rhythm with GEMS Home. The Heart Check Pen was the device which was referenced most

consistently and throughout the 510(k).[17]

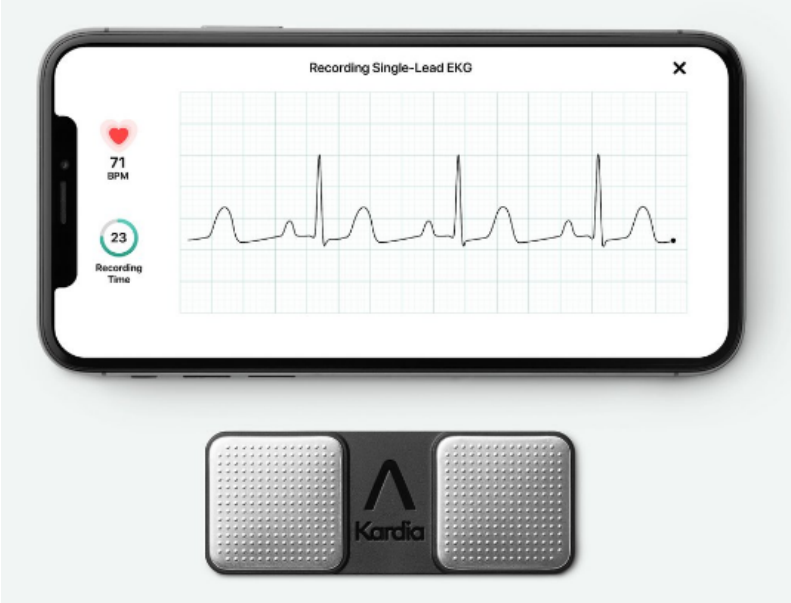

Figure 8: The current AliveCor Kardia Mobile with ECG Nodes detached from the case. Patients usually will press their left and right thumbs on the two pads respectively. Retail price: $99(www.alivecor.com)

AliveCor: Origins

Well before founding AliveCor, Dr. David Albert was working on bringing mobile ECG's to the earliest handheld computers and smartphones and developing new ways for ECG's to collect information. Dr. Albert received a patent for a handheld ECG IN 1994 which he received a 510(k) for in 1997. In an interview Dr. Albert said, "In 1997 I got a 510(k) on a product called Rhythm Stat XL which displayed ECGs on a Scion PDA". This was one of the first devices where an object not produced by the device manufacture itself (i.e. the phone or handheld computer which the ECG is connected to) had to be regulated and approved for use alongside the device. One worry that the FDA had during the review process was that the device relied on a wireless connection to send data to a computer. Dr. Albert and his partners made the case that "defibrillator monitors have all kinds of cellular, WiFi or Bluetooth embedded in them." This defense proved sufficient. [8]

AliveCor's first prototype was put together before the company was actually founded. In 2010 cofounder Dr. David Albert put a YouTube video online showing an iPhone displaying Dr. Albert's real time ECG reading. Dr. Albert shows the two places on the case where patients can hold the device and shows that they have the ability to record the data in real time and save it on the iPhone's memory. The video quickly went viral, Dr. Albert went on a media tour and appeared on multiple news programs including Good Morning America, and after going to the Consumer Electronics Show, he received 3 million dollars to start and grow the company. Previously Dr. Albert had worked on making ECG's that could be used with laptops. Since the

first prototype was already constructed the approval process for the AliveCor occurred relatively quickly and the first AliveCor phone case was released and it was approved to be sold to the public in 2012.[18]

The considerable attention given to Dr. Alberts' ECG initially caught the attention of the FDA in a negative light. After attending the Consumer Electronics Show, the FDA contacted Dr. Albert because it appeared that he was marketing an unapproved medical device. However, Dr. Albert claims that he explained to the head of the FDA's Division of Cardiovascular and Respiratory Devices at the Office of Device Evaluation that he had genuinely not anticipated the amount of coverage which his device received and that he understood that he needed to get the device approved before returning to the press. [18]

Initial Device Classification and Approvals

Approval Process

The FDA received the Premarket Notification for the AliveCor in October of 2012. The application identified the AliveCor as a class II medical device. When filling the PMA AliveCor applied for the most rudimentary form of the device. The iPhone case (the KardiaMobile) and AliveCor app, and the iPhone itself were all factored into the FDA's approval process. From the onset, AliveCor did *not* attempt to get the device approved in a way that would allow patients to analyze their own ECG's neither would the app itself attempt to diagnose the patient. According to the PMA itself the first version of the AliveCor ECG for iphone was: [17]

1. Use by licensed medical professionals or patients to obtain single‐lead electrocardiogram (ECG) rhythms.
2. Recording the patient ECG so that later a qualified physician can review the data for analysis.

The first prototype in the video shown by Doctor Albert showed him being able to see a full ECG on his iPhone screen in real time. However, in remaining consistent with the first claim the Alivecor ECG app first version did not actually show a detailed version of the patient's ECG to the patient, this data was only accessible by a medical professional, and real time data was only viewable when a physician or medical professional (registered with Alivecor) is using the app. Crucially this meant that the ECG was not something that patients were able to buy directly; the first version had to be prescribed by a physician.

Proving Substantial Equivalency

Oftentimes, when a marketing department is trying to sell a new medical device they go to great lengths to demonstrate how new and different the device is from the incumbents. [19] However, when proving substantial equivalency to the FDA the opposite is usually the best practice; demonstrate to the FDA that the device is merely a small yet useful deviation from past products. In order to do this Alivecor chose the "HeartCheck Pen Handheld Heart Rhythm" made by CardioComm.

Figure 9: The Heart Check device: a mobile ECG without mobile phone integration. [17]

The device (Fig. 9) essentially looks like a long stick with two pads for the patients thumbs . The device records the patient's ECG and while doing so displays the ECG on a tiny low resolution screen in the center of the device. The device itself then stores the ECG readouts with a maximum of 20 recordings. Once the recording limit is reached, the patient must manually download the memory of the device via USB or Bluetooth to their computer and wipe the memory of the device so another 20 recordings can be taken. In comparing their "indications for use" Alivecor notes that the HeartPen, "is an over-the-counter device intended to record, store, transfer single channel HeartRhythm signals and, for users under a physician's care, display Heart Rhythm waveforms." In comparison Alivecor writes that the KaridaMobile device is to be used by "licensed medical professionals." Thus, patients will not be able to self diagnose themselves in a way that only a medical professional should. In doing this Alivecor is attempting

to show that because their device is going to be used by someone who has more skill and medical knowledge than the average patient, the KardiaMobile is not only equivalent to the predicate device, but it is also operating in a way that has less chance for user error than the predicate device. Later in the PMA Alivecor specifically states that they believe that with resubmission their device can be approved for OTC use.

In showing that the device, while similar, does have some advantages over the predicate, Alivecor pointed to the limited number of recordings possible with the HeartPen, the slow pace of transmission from the device to a physician (the Alivecor allows for nearly instantly transmission via a PDF format whereas the HeartPen require users to download the data to a computer before it can be sent via email .) The Alivecor is also takes higher fidelity readings of the electrical signals the heart produces (300 per second vs 250) per second.[13]

Public Response to Initial Product

While the tech world was fascinated with the Alivecor and the media covered its release extensively, there was a certain level of ire levied at the FDA for withholding patient data from the users. In 2012, right after the PMA was approved Fast Company wrote a widely shared article celebrating the device and its potential but asked serious question about patient rights. In its initial release the Alivecor would only show an abstraction of what the patient's waveform looks like to the patient and would only show the full detailed ECG to a physician. This was a tenant of the 510K presumably so that patients would not be self-diagnosing themselves with serious conditions or using the device to self-certify that they do not have a particular condition.

The author makes the case that while certain drugs should not be administered by patients without a physician and many medical devices require proper insertion or instruction from a physician (no one is going to buy an over the counter pacemaker) how can the FDA prevent Americans from being able to passively view their own heartbeat? Anyone can sit down and take their own pulse so how can you prohibit someone from passively seeing their own waveform? As medical apps continue to become more prevalent questions of a patient's liberty to access their own data versus the security of withholding their data from them will continue to become more prevalent and more complicated. [20]

Subsequent Approvals

Since 2012 the Alivecor has been substantially updated as has the competitive landscape which it operates in. When the Alivecor was first released it was only an iPhone case, it had to be prescribed by a physician and it was unable to diagnose patients. Fast forwards to 2019 and all of this has changed. The FDA approved the OTC sale of the Alive core in 2014 and allowed patients to see their full ECG if they want to, ending the debate over patients freedom to access

their own information. They then introduced a snap on version that can be placed on any iPhone with or without a case. Overtime they began building a convolutional neural network in order to diagnose Atrial Fibrillation, Tachycardia and Bradycardia without physician input. In the IPEDS trial, which looked at the diagnosis of AFIB and other indications using the KardiaMobile compared to hospital treatment they found surprisingly high levels of efficacy. The KardiaMobile managed to diagnose 56 percent of patients in 9.5 days on average compared to standard physician based measurements which diagnosed 10% were diagnosed in an average of 43 days. they succeeded in doing this and they were approved to give people warnings if the system detects that the patient may be suffering from one of these conditions. When the apple iWatch was released AliveCor began working on a wristband which operated in a similar way to the original Alivecor phone case but with a different shape. Also in 2019 they received approval for a far more advanced "medical grade" ECG that produces an ECG which rivals a hospitals ECG in terms of accuracy. It will be the subject of further clinical trials. [21]

Reimbursement

From the beginning, the AliveCor ECG was not covered by insurance and patients had to pay the full out pocket cost. However, the device was extremely inexpensive compared to most ECG machines. When it was first released in 2012 Doctors could pre order the KardiaMobile for a price of $199. Once the OTC approval occurred the price was slashed to $99 where it remains today. As an upsell, Alivecor provides cloud data storage, medical reports and medication tracking for $99/year. The iWatch wristband is also priced at $99 and the new ultra-accurate Kardia Mobile is available to pre order for $199. In comparison to the industry leading General Electric ECG that was available when AliveCor's first product was released the Kardia mobile was quite cheap: the GE's retail price was over $12,750.00. [15]

Once the KardiaMobile was approved to diagnose patients rather than just passively monitor them it became possible to compare the cost of the KardiaMobile's use versus standard physician based diagnosis. In the IPEDS study it was concluded that on average the KardiaMobile reduces the cost per patient by $1,200. [21]

AI in Alivecor

Artificial Intelligence was not a large part of the Alivecor family of products until the firm began to focus on creating products that could diagnose a patient without the help of a physician. According to an Alivecor representative, Alivecor's journey to implement artificial intelligence in their products began in 2013 with the collection and analysis of thousands of ECG readouts. This was particularly challenging as even a slight mistake could lead to missing a disease, a misdiagnosis or a product that over diagnosis people with a serious heart disease. Overtime the

ECG's were analyzed until it was possible to create a neural network. To prove out the model three large clinical trials were conducted with the goals of diagnosing four separate issues:

1. Bradycardia: Bradycardia is a heart rate that is considered to be too slow. A proper diagnosis of Bradycardia has to evaluate the patient's age, weight, height and other factors. [22]
2. Tachycardia: Tachycardia is where a patient consistently has a heart rate that is considered to fast (usually a resting heart rate of over 100BPM) like Bradycardia a proper diagnosis of Bradycardia has to evaluate the patient's age, weight, height and other factors. [23]
3. Atrial Fibrillation: AFib is a quivering/irregular heartbeat. Often, it results in too fast a heartbeat, making differing between it and Tachycardia a challenge for AliveCor's neural network. [24]
4. Long QT syndrome: Long QT syndrome is where it takes the patient's heart longer than it should to repolarize. And the Q and T interval of the heartbeat appear to be longer on an ECG as a result. The Alivecor neural network is able to evaluate the ECG reading and determine whether or not the patient has Long QT syndrome. [24]

Diagnostics for the aforementioned indications were approved by the FDA throughout late 2017 to early 2019. Because of how quickly Alivecor built out a sophisticated artificial intelligence system and how the product directly helps patients Alivecor received first place in Fast Companies annual ranking of artificial intelligence startups. [21]

Future of AI in Healthcare

There are many speculations as to what AI will be able to accomplish in the area of healthcare in the future given the critical nature of healthcare and the low margin of error that is typically expected in healthcare technologies, however as shown in the figure below AI is already being considered to help with many disease types. The current data is very promising and as a result investors have deployed capital into many healthcare arenas. We will look at few of the major areas that AI currently plays and, within three years, "is expected to play" a major role in:

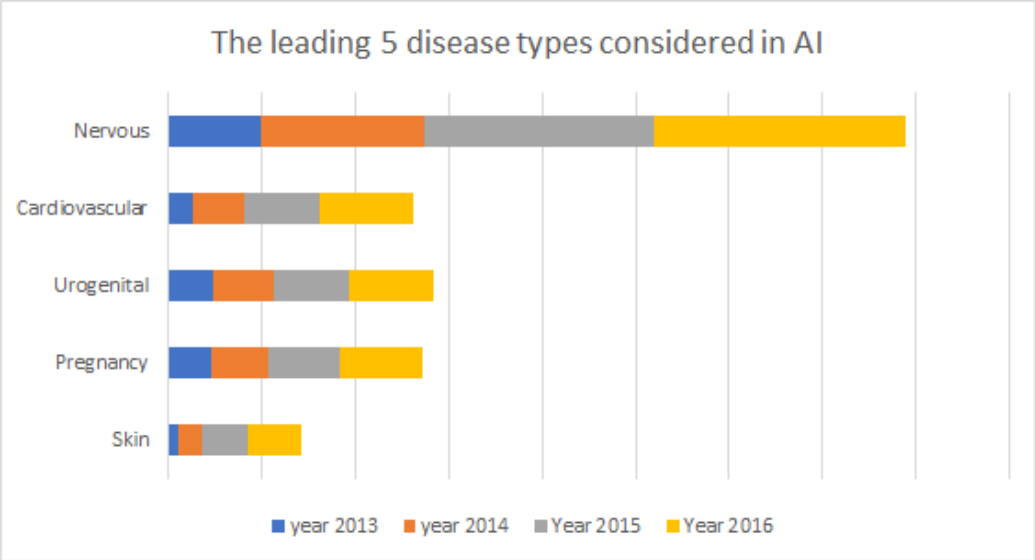

Figure 10 : The leading 5 disease types considered in the artificial intelligence (AI) estimated literature from 2013-2016.

1. *Durg organization*
   Many AI solutions are being planning to identify new drugs or reorganizing and reevaluating the effectiveness of current drugs using multiple large databases of information which will accelerate the process for developing new drugs and make existing drugs more efficient and probably cheaper as well.[25]

2. *Primary care*
   AI and chat base systems are becoming more and more "smart" where they tell patients basic information such as their history, clinic information as well as schedule appointments and set up reminders. This advancement is an area of potential growth where systems become better and better and eventually get to a point where they diagnosis simple symptoms and suggest treatment options.[25]

3. *Medical Imaging*
   Given the new and innovative AI systems especially in the area of image processing and analysis they are expected to become a crucial part of the screening process, identify abnormalities and early detection as well as many new scenarios are currently being worked especially in the area of cardiology and brain scans. [25]

Further Applications of AI

IDx-DR

The FDA permitted the marketing of a medical device that is used to detect high levels of diabetic retinopathy in adults with diabetes. Diabetic retinopathy happens when high levels of blood sugar damage the blood vessels of the retina, it is the most common cause of vision loss among diabetic people.IDx-DR is a software program that depends on AI algorithm to analyze images of the eye taken with a retinal camera "Topcon NW 400" where the doctor will provide the patient's images and the software will detect a "more than mild" diabetic retinopathy. [26]

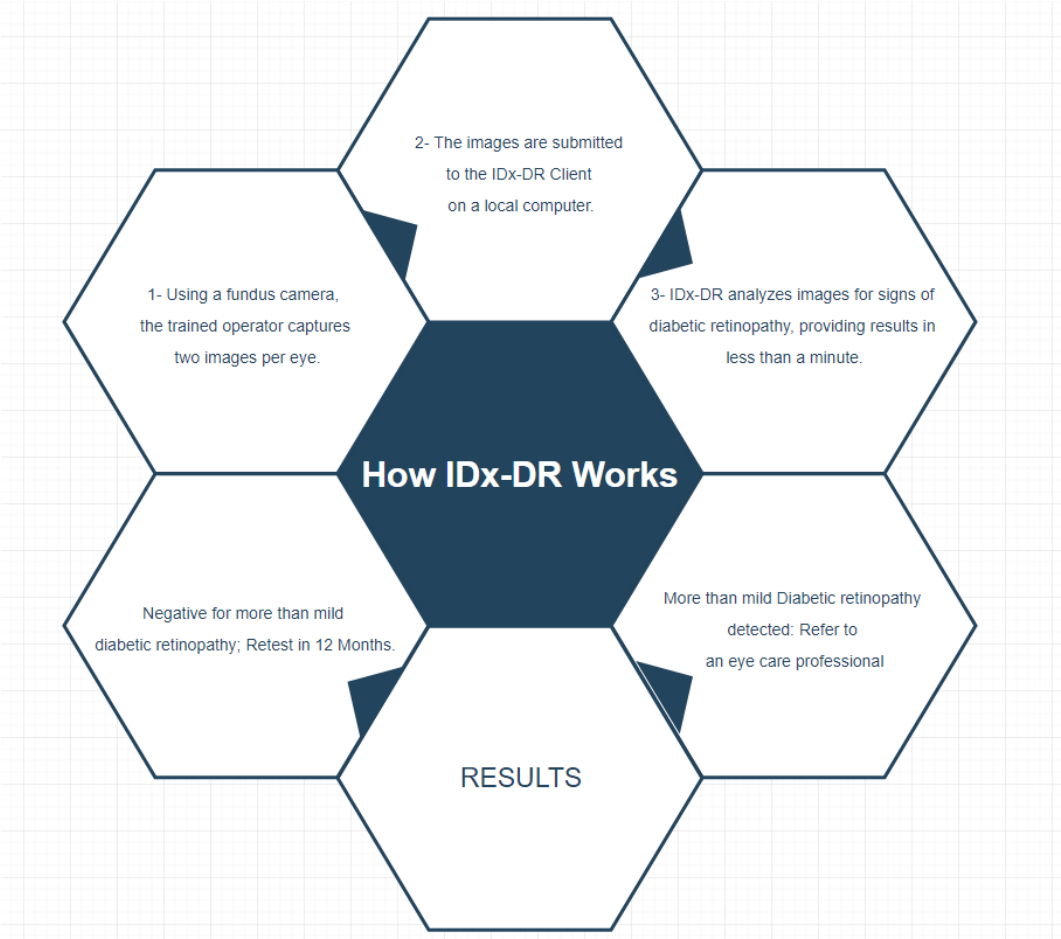

Fig. 11: Representation of IDx-DR functionality and determination of results

The FDA used a clinical study that would assess the performance of the IDx-DR software and how often it would correctly identify 'more than mild' diabetic retinopathy, according to the study the acurecenty percentage was in the upper 80s for both negative and positive detection. [26]

Viz.AI Contact Application

According to the FDA Viz.AI is a "type of clinical decision support software designed to analyze computed tomography (CT) results that may notify providers of a potential stroke in their patients." [27]

What is a Stroke ? A stroke is the blockage of blood to any portion of the brain, which can cause short and long term brain damage, disability or in some cases even death. Stroke is one of the leading causes of death in the U.S.

"Strokes can cause serious and irreversible damage to patients. The software device could benefit patients by notifying a specialist earlier thereby decreasing the time to treatment. Faster treatment may lessen the extent or progression of a stroke," said Robert Ochs, Ph.D., acting deputy director for radiological health, Office of In Vitro Diagnostics and Radiological Health in the FDA's Center for Devices and Radiological Health. [27]

How does Viz.AI Contract application help diagnose and treat strokes?

The Viz.AI Contact application is a software that relies on AI algorithms to analyze CT images of the brain, then notifies a neurovascular specialist in case the software identifies a blockage of a large vessage, the software also enhances the normal process of identifying stakeholders where it notifies the first-line providers and also can be sent to a mobile device which speeds the process significantly.

The FDA is actively working on creating a regulatory framework for such devices and have recently done the following: [28]

(1) Created a Digital Health Innovation Action Plan
According to that FDA's Center for Devices and Radiological Health (CDRH) "This Digital Health Innovation Action Plan outlines the efforts to reimagine FDA's approach for assuring that all Americans, including patients, consumers and other health care customers have timely access to high-quality, safe and effective digital health products. This plan lays out the CDRH's vision for fostering digital health innovation while continuing to protect and promote the public health" [29] this plan includes the following:

- Guidance to provide clarity on the medical software provisions
- Innovative pilot precertification program to work with our customers to develop a new approach to digital health technology oversight
- Building FDA's bench strength and expertise in CDRH's digital health unit.

(2) Published the first draft guidance - "Clinical and Patient Decision Support Software," According to the FDA, The purpose of the draft is to help organize regulating software functionality by identifying the types of decision support software functionalities that:

- Do not meet the definition of a device as amended by the Cures Act; [30]
- May meet the definition of a device but for which FDA does not intend to enforce compliance with applicable requirements of the FD&C Act, including, but not limited to, premarket clearance and premarket 120 approval requirements; [30]

Future Challenges

Data and Privacy Concerns

Given that AI is dependent on data, especially during the system's training process, data privacy and patient information become a huge concern and a complicated obstacle in the process of regulating systems. Critical AI systems are usually developed by a large number of engineers and those developers, testers and supervisors need access to all of that data which complicates the process of regulation and can inhibit the development process and approaches taken by tech companies.

Performance and Quality

AI is improving rapidly and is currently becoming better and better on a daily basis but the more AI gets evolves into more critical areas in medicine that higher the bar will get in terms of error margins and quality assurance. In terms of monitoring the performance and quality of AI and machine learning approaches, attention should be given to the adaptive and autonomous nature of AI applications. The FDA has identified both the utility and complexity of AI based medical devices with commentary on adjustments to the approval process following an initial review. It is critical to actively question any changes in input or performance in subsequent approval processes. [1] AI machines, especially complex implementations of AI, are considered a black box in that they take some inputs and provide useful outputs through a decision process that cannot be interrogated (i.e. multi-layer convolutional neural networks). Due to the fundamentally poorly understood nature of these iterative, autonomous, and self-improving AI tools, outcome- based FDA approval criteria should be appropriately adapted to encompass these uncertainties and to define the conditions inputs that conclude certain outcomes.

AI models can be powerful tools but they are only as effective as model training data can allow them to be. As such, AI model training must consider a range vast amounts of training data, considering multiple subpopulations of patients (i.e. by age, gender, underlying health status).

Furthermore, an AI model should only make determinations based on the limitations dictated by the training data. For example, consider a hypothetical MMA that utilizes AI for classification of skin lesions from images taken by a smartphone camera. If this AI was trained on sets of images from patient populations of >50 years old, limitations should be set forth that restrict use of this app on younger patients. Subsequent FDA approvals should be granted only on the basis of expanded data-sets.

Conclusions

With growing complexity and prevalence of AI and machine learning in healthcare, we can expect to see the introduction of highly accurate and streamlined medical devices accomplishing a range of useful tasks and determinations. We predict that MMAs will be the primary carrier of such AI software due to the growing ubiquity and practicality of mobile apps in healthcare. Hence, we must consider the marriage of AI and MMAs as a new front in medical device development and implementation. The FDA's regulation efforts should reflect the challenges associated with AI software. De Novo approvals will likely drive the introduction of new AI driven MMAs as new applications of AI will likely lack prediction due to inherent novelty. Thus, FDA approval efforts and guidance documents should consider the potential for evolution of a given AI capability.

Appendix

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Figures

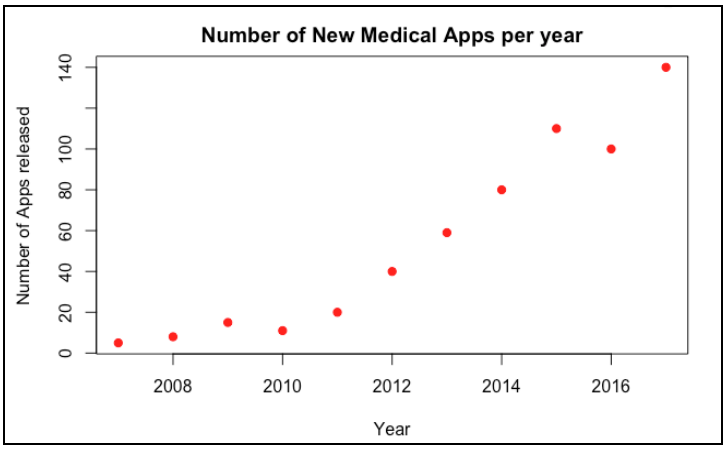

Figure 1: The number of MMAs released from the creation of the iPhone in 2007 to 2017

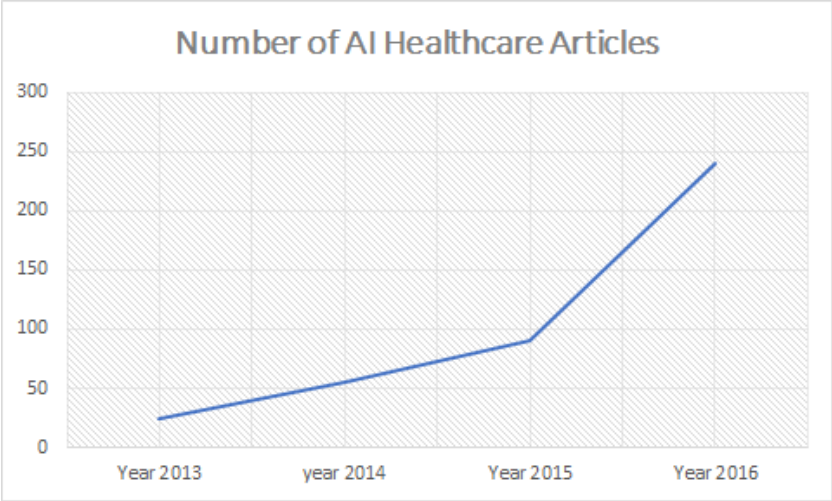

Figure 2 : Estimated number of AI healthcare Articles from 2013 to 2016

Figure 3: A clinician holds up a bloodied absorbent item up to an iPad where the Triton app indicates the region of soaked blood and provides a determination of blood loss volume.

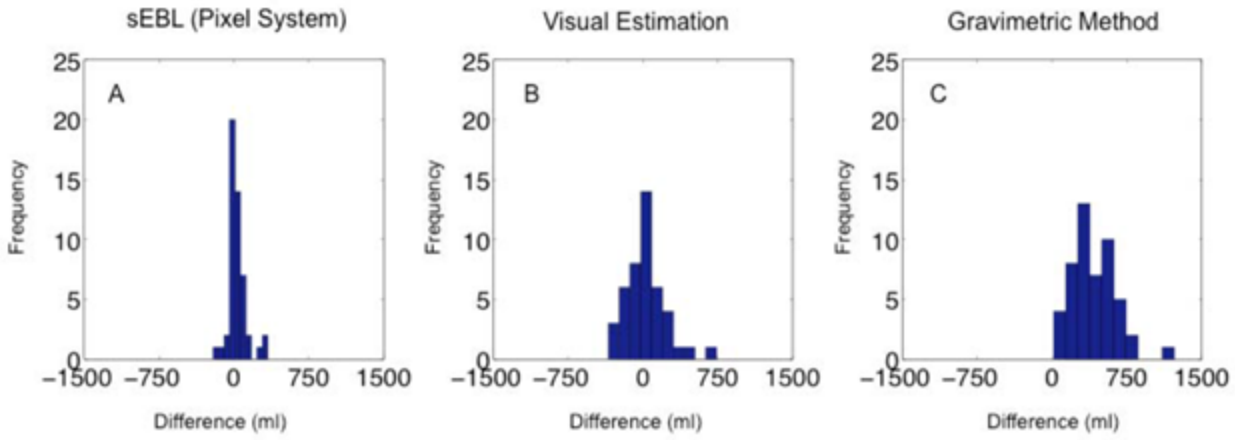

Figure 4: Comparison of the Pixel 3 System's calculation of blood loss and the conventional visual and gravimetric methods. The difference considered is between the method calculation and known volumes of blood absorbed onto substrates.

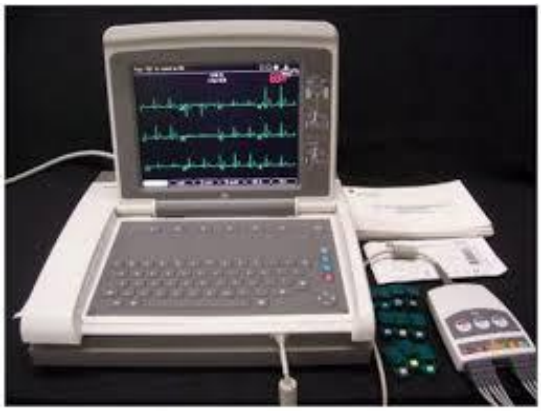

Figure 5 : A typical Hospital, MAC 5500 ECG Machine made by General Electric

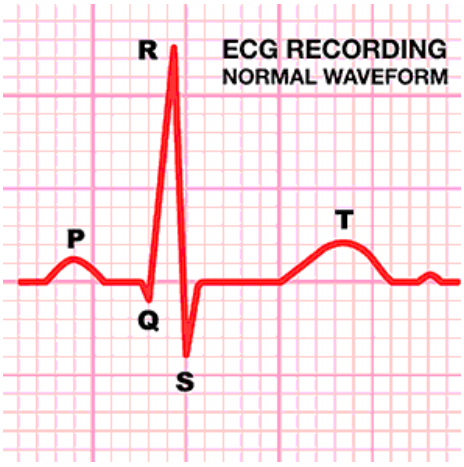

Figure 6: A typical ECG waveform

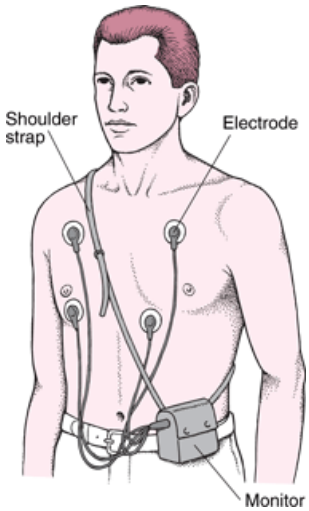

Figure 7: Diagram of a patient wearing an Ambulatory ECG

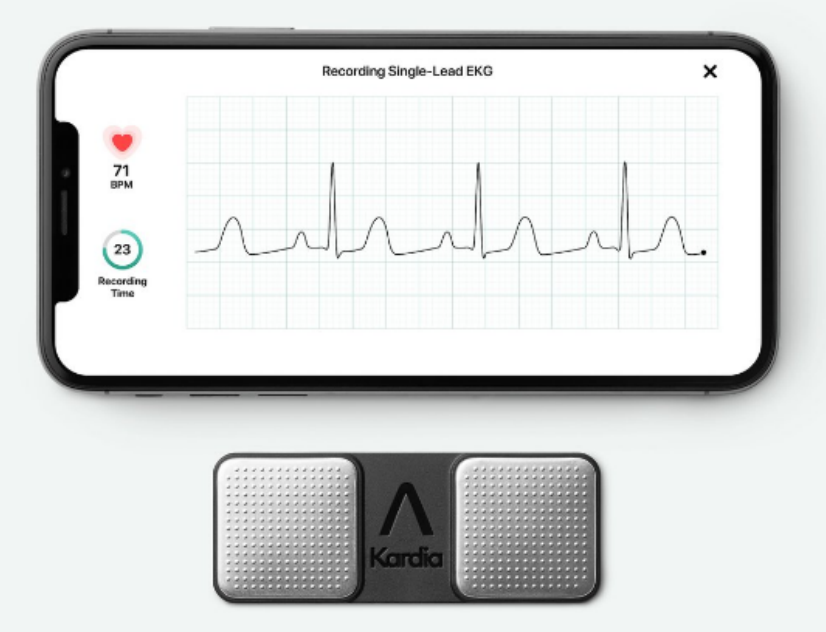

Figure 8: The current AliveCor Kardia Mobile with ECG Nodes detached from the case. Patients usually will press their left and right thumbs on the two pads respectively. Retail price: $99

Figure 9: The Heart Check device: a mobile ECG without mobile phone integration

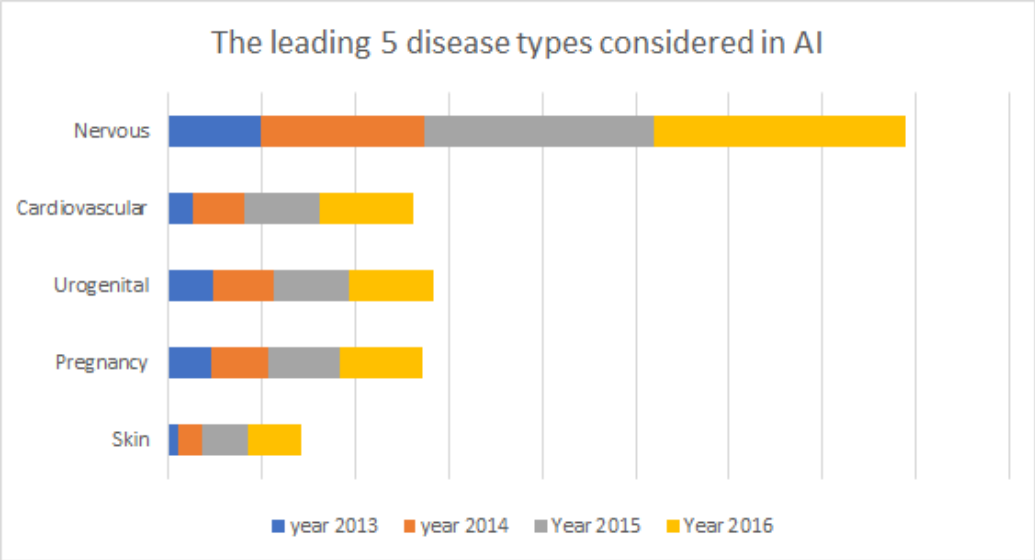

Figure 10 : The leading 5 disease types considered in the artificial intelligence (AI) estimated literature from 2013-2016.

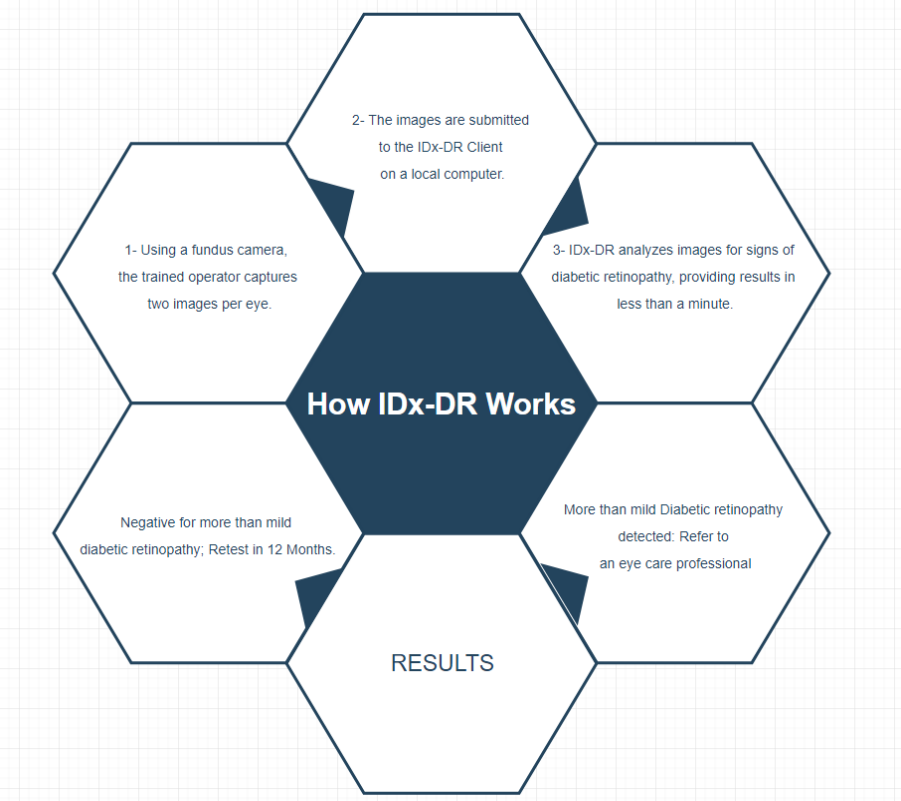

Fig. 11: Representation of IDx-DR functionality and determination of results.