Diagnostic smartphone application for anemia in developing countries

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Abstract
Anemia is one of the most prevalent blood conditions worldwide. The reason for such high incidence percentages is due to the vast variety of types and causes of anemia. Anemia, in short, is when the is not enough hemoglobin in the body, or oxygen cannot properly bond to the hemoglobin. In both cases, oxygen is not able to get to where it needs to be in order for the body to function at a level necessary for healthy living. The good part about anemia is that is most cases, it is easily treated. However, in many countries, they do not have implementation of the proper technology in order to treat those who have this condition. Because of the lack of resources in such areas of the world, anemia goes from being a relatively manageable condition to being the leading cause of preventable death.
The fact that countless preventable deaths could be drastically cut down by providing these countries with some sort of inexpensive, portable, and user friendly device is the driving force behind this project. The goal of this project is to design an application for a smartphone that will integrate some of the most important aspects of existing devices and combine them into one full-package anemia diagnostic device. The first and most important aspect of the application is that it will be able to say whether or not a person is anemic. The application will run an interface with a pulse oximeter in order to perform its function. The second aspect of the application is that it will be able to classify the type of anemia a person has based on their mean corpuscular volume (MCV). While an ultimate decision has not yet been made on how this value will be determined, it is very likely that we will utilize a magnification attachment for the phone that will compare a peripheral smear of the patient's blood with a database, using an algorithm programmed into the app. The third aspect of the app. analyze the patient's cells and determine if there is any abnormal morphology. The fourth and final aspect of the app. is to put together all of the information from steps one through three and set up a patient-specific treatment plan to help them control this very controllable condition. While steps three and four are very important, the focus of the project for the time being is on the first two steps. Once those are smoothed out proven to be effective, the remaining steps may be conquered too.
Due to the fact that the driving force behind this project is to make something that is cost effective and can be used in a place with extremely limited resources, every aspect of the device, from the way it is powered to specifics of the external hardware have been considered to meet that criteria. Everything that is being used is relatively inexpensive and would be very easy to acquire, transport, and use for a person who is interested in helping with this cause. However, because it is smaller and uses a less advanced technology than some existing methods, does not mean it will not be accurate. The device will go through many test, aided by supplies from the client, in order to assure all information that is presented by the device is accurate and could never put any person at risk for further harm.

Introduction
Problem statement
The problem statement of this project is made up of four phases.
Phase 1. To develop a smartphone application that will incorporate hardware with the purpose of diagnosing anemia in developing countries (i.e. Ghana) by measuring hemoglobin concentration.
Phase 2. To classify and differentiate the type of anemia by using a magnifying lens attached to the camera to measure cell size mean corpuscular volume (MCV).
Phase 3. To improve classification of the anemia based on abnormal cell morphology or shape through the use of magnified images of the cells that will be analyzed by the designed program

in order to compare abnormal blood cell morphology or shapes to an archived library of blood cell anomalies.
Phase 4. To expand on the developed application that will further analyze the data using a programming algorithm to provide treatment recommendations for the various types of anemia observed.

Background

The Biology behind Anemia and its Diagnosis

Anemia is a condition in which a person has a lowered hemoglobin concentration due to a low red blood cell count or improper binding of oxygen to hemoglobin. This results in low oxygen levels in body tissues which can cause symptoms ranging from minor issues such as headaches, fatigue, and shortness of breath to more critical symptoms such as seizures, coma, and death. Anemia is a relatively common condition due to the fact that there are many causes: inherited abnormalities in red blood cell shape, lowered red blood cell concentration due to internal blood loss or decreased blood cell production, low levels of folic acid , vitamin B12, and iron deficiency. Because there is such a wide variety of causes, there are also a variety of common treatment plans. While there are some treatments that are more universal, such as iron and folic acid supplements, there are also some treatments that are geared to treat specific types of anemia.

The Biology behind the Applications Design

Currently, the diagnosis of anemia can be performed through invasive and noninvasive means. Invasive means can be performed with a finger prick providing a blood sample that is then analyzed through the use of laboratory devices such as the Coulter Counter and CASY or through handheld devices such as in the Hemocue. Non-invasive diagnosis of anemia is currently done through the use of advanced pulse oximeters.

Hemocue

The Hemocue devices utilize a spectrophotometer to test concentrations of hemoglobin in the blood stream. This is accomplished in two ways: the first uses a reaction cuvette to isolate a product of a breakdown of hemoglobin to measure, and the other directly measures the light absorbance of hemoglobin. The reaction method in the microcuvette is a modified azidemethemoglobin reaction. The erythrocyte membranes are disintegrated by sodium deoxycholate, releasing the hemoglobin. Sodium nitrite converts the hemoglobin iron from the ferrous to the ferric state to form methemoglobin, which then combines with azide to form azidmethemoglobin (Board). The concentration of azidmethemoglobin is then measured using the spectrophotometer. In the second form, utilized in the Hemocue Hb 301, the hemoglobin concentration is measured directly using the absorbance of whole blood at an isobestic point of oxygenated and deoxygenated hemoglobin.

Coulter Counter

In the use of a Coulter Counter, a tube with an aperture (small hole) is placed in an electrolytic solution containing containing suspended particles. An electric field is applied between an electrode inside the tube and an electrode outside the tube but inside the solution. As particles are directed through the aperture, they displace a certain amount of electrolyte, causing a change in the impedence across the aperture and creating a measurable pulse in the voltage and current of the system. Using the height amount of these pulses, one can count the number of, the size of, and determine the identity of the particles. (Beckman)

Pulse Oximetery

Standard pulse oximeters are clips that can be put on a finger or earlobe (foot or hand in infants) which sends two wavelengths of light, red and infrared through the site. Oxygenated and deoxygenated hemoglobin absorb different amounts of light at these wavelengths and a ratio between oxygenated and deoxygenated hemoglobin can be obtained from these absorbances. This data is useful in diagnosing hypoxia, a lack of adequate oxygen supply to parts of the body, but offers little in terms of total hemoglobin concentration and the diagnosis of anemia. However, since the invention of the pulse oximeter, various others have been created that use three or more wavelengths of light to establish a value for the total hemoglobin concentration. (Pulse)

Project Motivation

The motivation for this project stems from the need for a point of care diagnostic tool that can diagnose anemia, classify the type and provide a possible course of treatment. Currently, devices are available that can do one of these steps, but having each step available at the point of care would make this device ideal for use in a developing country. This is due to the fact that many people cannot go to a hospital or clinic frequently, and a return trip for test results is extremely unlikely. A lack of recording a medical history couples with this, making effective treatment difficult. Offering a test, diagnosis, and treatment at the point of care is then a necessity for effective medical treatment in a developing country.

Project Design Specification (PDS)

Design Requirements

The design must be able effectively and accurately diagnose anemia as well as determine the mean corpuscular volume of the blood and abnormally shaped cells in a patient and suggest an appropriate treatment plan for the patient. This must be done in a short amount of time and all parts must be able to be carried in a small pack by an individual. All reusable parts of the device must be able to be wiped down and all non-reusable parts of the device must be able to be disposed of. All peripherals will transmit data to the android phone and display results in a manner that can be understood by an individual with little understanding of the biology behind anemia.

Safety concerns

Safety concerns associated with this device include the possibility of misdiagnosis, failure due to water exposure, patient privacy, and concerns associated with sterility. The risk associated with misdiagnosis is not severe due to the fact that most treatments for anemia are supplements such as iron and folic acid which may already be found in the body. Health concerns only arise when extremely large doses of these supplements are taken which will not be advised by our device. Testing will have to be done to understand the effects of water on the device if it is possibly submerged in water or gets rained on. Patient privacy will be preserved by not asking for a name to be associated with the data. Data will be recorded with only the location and time stamp associated with the results. This will assure that the patient will remain anonymous. The pulse oximeter will be wiped down after each use to ensure the sterility of that device while the user will be required to wear gloves while taking a blood smear, disposing of the slide after use. There must also be no contact between the blood on the slide and the cell phone.

Design

Design Alternatives

This project was originally presented as an application compatible with the iPhone. However, after further analysis it became more feasible to design an Andriod application due to larger market share of the system and ease of start up programming. On a similar note, one of the primary concern with Apple is the fact the majority of source files to create an original application are not easily obtained for first time programmers. Also, the students working on this design have only been primarily exposed to Java programming - the language which Andriod executes. Each phase of this process presents design options. The first phase was measuring hemoglobin, and a pulse oximeter was chosen as the diagnostic tool . The other options for analyzing the hemoglobin concentration of a patients included using a hemocue or a chemical indicator. Currently, the hemocue was too expensive and used largely the same method as a pulse oximeter, while the chemical indicator does not exist. While a Hemocue is slightly more accurate than a pulse oximeter in determining hemoglobin concentration, we decided on using a pulse oximeter. The Hemocue would require a prick of blood, introducing the transmission of bloodborne diseases from patient to analyzer or vice versa. The Hemocue would also require a new reaction microcuvette for each patient which represent a recurring cost and must be contained in a freezer while not in use. This limits the use of the device to regions with refrigeration technology readily available. Basic training would be required to teach an individual how to draw blood from the patient as well as handle the microcuvette in a way that did not sacrifice accuracy. For the next phases, designs are still currently being determined. The choices to measure MCV in phase two are a Coulter Counter or CASY system or a peripheral blood smear analyzed by the smartphone utilizing a program in our application. For phase three, the design alternatives will determine how we compare images of a blood smear to a library with the location of the library being the main source of choice. These are all the current design alternatives, our brainstorming of options for further phases.

Current Design

It was decided to create a cell phone application for the android network due to a larger market and easier access to previously written code. A pulse oximeter was also the input device of choice in order to measure total hemoglobin concentration primarily due to safety factors and its cost effectiveness in terms of the scope of this project. Compared to the alternative Hemocue device, a pulse oximeter is noninvasive, lower in cost, and safer for both the user and patient in terms of the transmission of disease. The pulse oximeter will be specifically used to determine the MCV of the patient. A mobile version of a coulter counter could be created to carry out this function. However, due to increased hardware and complexity of this design idea, it is more feasible to develop an algorithm that could analyze a magnified picture of a slide and determine the size of the cells, particularly due to the necessary traveling that will occur.

Methods/Testing

Testing

Due to the fact that our project is a four-phase process, each step will need to be thoroughly tested in order to determine the accuracy, precision and reliability of the application output is held to a high standard, eventually following US FDA standards. The developed algorithm must be tested with all possible input values to ensure that it will run properly even under abnormal conditions such has hot, cold or dusty locations.

One phase of the testing procedure will be to create an application user interface that will correctly transition through all phases of the design and corresponding algorithm of the diagnostic procedure. Aside from correctly carrying out all application functions consistently, the application will need to be able to recognize and store an input value from our external devices and run another algorithm to display the calculated output value. This will need to be tested repeatedly by running the application to ensure it is consistently working correctly. It will also be necessary to determine the percent error of the pulse oximeter that may occur due to nail fungus, think skin, constricted blood vessels, and other factors that may occur depending on location or local factors.

A second phase of testing will be the accuracy of the output value determined from the algorithm in the first phase of the design, which is the determination of the hemoglobin concentration. The external device will need to be calibrated correctly and interface correctly with the application to give the correct output value with a high degree of precision and accuracy. For this step, patients at Dr. Bain's clinic will be asked to sign a release form so the application can be tested on a human subject. The patient will then go through the current and accepted way of diagnosing anemia and the results will be compared. The release form will also ask for permission to take a blood sample to test Phase Two and Three - the external magnification hardware and cell morphology libraries. All data obtained from this testing method will then be compared to the data observed after the device is implemented. From repeated trials and comparisons to accepted values, accuracy of the device will be able to be determined.

Results

Data from Experiments (Tables)

Statistics (Graphs)

Discussion

Phase One

Phase One established the brainstorming process and determined the overall scope of this project. Foremost, the primary decision that directed the design of this application was the idea to pursue a smartphone application compared to an iPhone application as discussed in "Design Matrices" and "Current Design." Further analysis of programming skills and accessibility to Apple source files confirmed this decision.

The input method also served as a key motivator for the direction of this project. It was determined an noninvasive procedure would be safer and more sterile for both the user and patient because of the high risk of the transfer of AIDS/HIV and other blood-borne diseases in the countries. Sterility issues may also influence the percent error of the data collected because of the alcohol used to clean the device and contaminating the blood sample. Cost effectiveness is one of the most critical influences of this decision to continue with a noninvasive procedure due to the fact a Hemocue - the invasive device of interest - can cost up to $10,000 plus the cost of equipment to ensure sterility.

The biggest challenge of Phase One is creating an interface for an application and algorithm that can accurately be executed to determine if the patient has anemia or not. This interface then must be easily edited to continue on to Phase Two. Due to the challenge of programming, Phase one has been a challenge; however, to date, an outline of the algorithm has been created (Appendix B).

Phase Two

The obstacle of Phase Two will be determining the specific hardware needed to appropriately magnify the slide in order to measure cell size and obtain MCV. These observations are critical because they will allow the user to accurately diagnose the patient with either normocytic, microcytic, and macrocytic to help lead to a more accurate treatment option in Phase Four.

The current work being done with Phase Two is determining how to obtain MCV. The current idea that is favored is using a magnified blood sample that is examined using the camera's sensor to determine dimensions of red blood cells and therefore be able to calculate MCV. The alternative would be finding a way to downsize a Coulter Counter or CASY while decreasing the price to make it useful to our project. The classification of anemia is a vital step in the process because it narrows the possible causes and plays a large role in determining an effective treatment course.

Phase Three

In terms of Phase Three, the design direction is moving towards creating an algorithm that would serve as a library which pictures from a blood smear can be compared. The challenges of this design is connecting the device to a library of images due to the limited resource memory capacity of the phone. This could create a necessity to have the device plugged into a computer to compare memory. The issue with have a procedure such as this is that this will take time. Because clinics operate for approximately eight hours a day, it is important to see as many patients as possible so they can be accurately diagnosed, but also enough data is collected to understand more about the area of interest. This will also cause more hardware to be transported to such areas initially affecting cost and ease of transportation.

As of now, the first future plans for Phase Three include real life observations of blood smears at Dr. Bain's clinic so "left shifts" of red blood cells is more understandable. Then importing the pictures taken during a similar visit and from other doctors with the same interests as Dr. Bain in to the library created. Next will be creating an input algorithm so the computer can accurately read the picture transferred from the smartphone to compare red blood cell shape and size with the pictures in the library. The challenge that will arise from this step is ensure the pictures taken on the smartphone are of correct magnitude and clarity that the pictures in the algorithm are comparable. Finally, an output message will then need to be created to then be sent back to the smartphone of treatment analysis.

Phase Four

In order to successfully continue in a direction that remains in the scope of this project, background research regarding the treatment methods currently used in developed countries to treat anemia was conducted. The application will be designed to apply these methods in a cost effective and portable way that is compatible with the data collected in phases one through three. The vision for the treatment interface will include lists of treatments options tabulated by various MCV and abnormal cell values. All treatment options will be searchable to the user. However, when the application is being used for the complete diagnostic procedure, treatment options will be displayed based on the observed MCV and abnormal cell values of the specific patient allowing users to create an individualized treatment plan for each patient.

The original concerns that controlled to focus of the conducted background research for the treatment interface were primarily focused on the possibility of the wrong treatment plan due to misdiagnosis. This was dismissed because it all treatment options were deemed not fatal. Overall, the primary struggle that may be encountered during this phase is determining the appropriate amount of treatment options so the application can be applied to all developing countries and still be individualized.

The plan of action to implement the treatment interface to conduct more research about treatment options while also interview UW-Madison staff and contact points provided by Dr. Bain to determine what options are suitable for the areas where the application will be used.

Conclusion

This application will have the ability to diagnose anemia through the use of an attached pulse oximeter as well as subclassify the type of anemia based on the mean corpuscular volume found in the patient and the presence of cell abnormalities through the use of a magnified lens for the phones camera as well as an analysis algorithm. These peripherals will optimize cost, efficiency, and ease of use. The application will also suggest a course of treatment for the patient. This will allow point of care diagnosis and treatment of anemia worldwide, particularly in developing countries who lack access to adequate diagnostic tools.

Future Work

There is immense potential for future work in this project. A wireless capabilii ty of any required hardware would be the first possible upgrade for this project. Our future work also currently includes finishing our whole problem statement. After that is complete, the potential of the device comes into play and it has the possibility to be expanded because it will have the capability to do blood measurements as well as examine blood smears. Iwt has the ability to be an effective diagnostic tool for diseases outside of our scope of anemia. The output values could be changed with upgraded algorithms and more diagnostic values could be determined to aid in the treatment of a multitude of diseases.

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Appendix

Appendix A - Product Design Specification
Appendix B - Code Outline
Appendix C - Device Sketches
Appendix D - Design Matrices

Appendix A

The Product Design Specification (PDS)*

Definition and Purpose: The PDS sets out in as much detail as possible the requirements that must be met to achieve a successful product. It is the basic reference source and should be used throughout the entire design process.
Preparation and Evolution of the PDS: The PDS is a **comprehensive** document, which contains all the facts relating to the product outcome, and should contain all the realistic constraints to be imposed upon the design by the client.
Items in the PDS should be as **quantitative** as possible. (e.g., the device must weigh less than 2 lbs.; the device must fit in a 3 ft x 3 ft x 2 ft space), and ranked in order of importance.
The PDS is a **dynamic** document that should evolve as the project scope develops. This is because frequently at the start of a project it is not always clear what is achievable and to what extent certain parameters are essential.

CONTENTS OF PDS

Title: Diagnostic smartphone application for anemia in developing countries

Team Members: Allison Benna, Colin Dunn, Scott Schulz, and Tim Abbott

Project Need: Anemia is one of the leading causes of preventable death worldwide. Screening is largely unavailable in impoverished areas such as Ghana due to the lack of availability, limited resources, and high cost of screening devices and supplies.

Project Goals: The goals of this project are fourfold.

The first goal is to create a smartphone application that incorporates hardware that will diagnose anemia by measuring hemoglobin concentration.

The second goal is to classify the type of anemia by using a magnifying lens attached to the camera to measure cell size mean corpuscular volume- MCV) to help differentiate the types of anemia.

The third goal is to classify the anemia based on abnormal cell morphology or shape. The magnified images of the cells will be analyzed by a program that will compare abnormal blood cell morphology (shapes) to a library of blood cell anomalies

The fourth and final goal is to create an application that will analyze the data using a programming algorithm and provide treatment recommendations for the various types of anemia encountered.

CLIENT REQUIREMENTS

Design requirements: This device description should be followed by list of all relevant constraints, with the following list serving as a guideline.

1. Physical and Operational Characteristics

a. *Performance requirements*:

- Specific phone brand and model to support app - TBD
- Target user - volunteers traveling to developing countries with none or limited professional medical experience or training
- Patient - local citizens in developing countries (i.e. Ghana)
- Usage/Day - 8 hours days
    - Number of Patients - 200?
- Usage/Day MAX - TDB
- Memory - TBD
- Accuracy -
    - Overall Diagnosis - TBD
    - Overall Programming - TBD
    - Interface - Easy to read and use

b. *Safety*: Due to it being very common for target populations to be misdiagnosed, safety concerns to keep in mind while using this app include:

- Misdiagnosis
- Water exposure
- User privacy
- Patient privacy
- Sterility
    - HIV/AID transfer

Understand any safety aspects, safety standards, and legislation covering the product type. This includes the need for labeling, safety warnings, etc. Consider various safety aspects relating to mechanical, chemical, electrical, thermal, etc.

c. *Accuracy and Reliability*:

- Blood Reading - TBD
- Overall Diagnosis - TBD
- Treatment Suggestions - TBD
- Overall Programming - TBD
- Data Transitions - TBD
- Data Transfer - TBD
- Errors - TBD
- Data Loss - TBD
- Interface - Easy to read and use

Limits for precision (repeatability) and accuracy (how close to the "true" value) and the range over which this is true of the device.

d. *Life in Service*:

- Establish resources available in or to countries of use
    - Electricity

    - Number of Volunteers
    - Treatments
- Length of Exam - TBD
- Usage/Day - 8 hours/day
- Updates required

e. *Shelf Life*:

- Battery Life

f. *Operating Environment*:

- Water Exposure
- Heat Exposure
- Dust Exposure
- Vibrations
- Dropping of phone (or hardware)

g. *Ergonomics*:

- Overall – (Efficient)
- Interface – TBD
- User – No Formal Medical Training

h. *Size*:

- Memory
- Application Size
- Applications Updates and Maintance
- Hardware Dimension
- Hardware Maintance
- Portability for Traveling Purposes
    - Weight
    - Material
    - Safety

j. *Materials*: NEED RESTRICTIONS

- Cell Phone - Model, Brand
- Hardware (TBD)

k. *Aesthetics*, *Appearance, and Finish*: TBD
(Simple, easy to read, organized, and understandable by user with little to no prior knowledge.)

2. Production Characteristics
a. *Quantity*:

- 1 smartphone application with hardware set

    - Smartphone may be included

b. *Target Product Cost*:

- Testing Costs - TBD
- Hardware Manufacturing Costs - TBD
- Competitors Costs -
    - HemoGlobe: $10 - 20

- Final Cost of Application - TBD
- Final Cost of Hardware

3. Miscellaneous

a. *Standards and Specifications*:

- Cultural Acceptance
- Travel Requirements and Safety
    - Country Expectations
    - Device Expectations

b. *Customer Expectations*: Volunteers to Developing Countries

- Easy to Use Interface and Procedure
- Easy to Understand Procedure and Acquired Data
- Easy to Explain Procedure to Patient
- Confidentiality of both User and Patient
- Ability to Archive Information Observed for Future Analysis

c. *Patient-related concerns*:

- Sterility - possiblity of HIV/AIDS, Viruses, STDs, etc.
    - Pulse oximeter
    - Finger Pricks/Blood Retrieving Devices
    - Gloves while
- Confidentiality
    - No Name Included during Visit - include only Sex, Age Range, Date, Time

d. *Competition*:

- HemoGlobe
- Lifelens
- Hemocue

Appendix B

Code Outline

Menu Screen
New Patient
Previous patients
Treatments

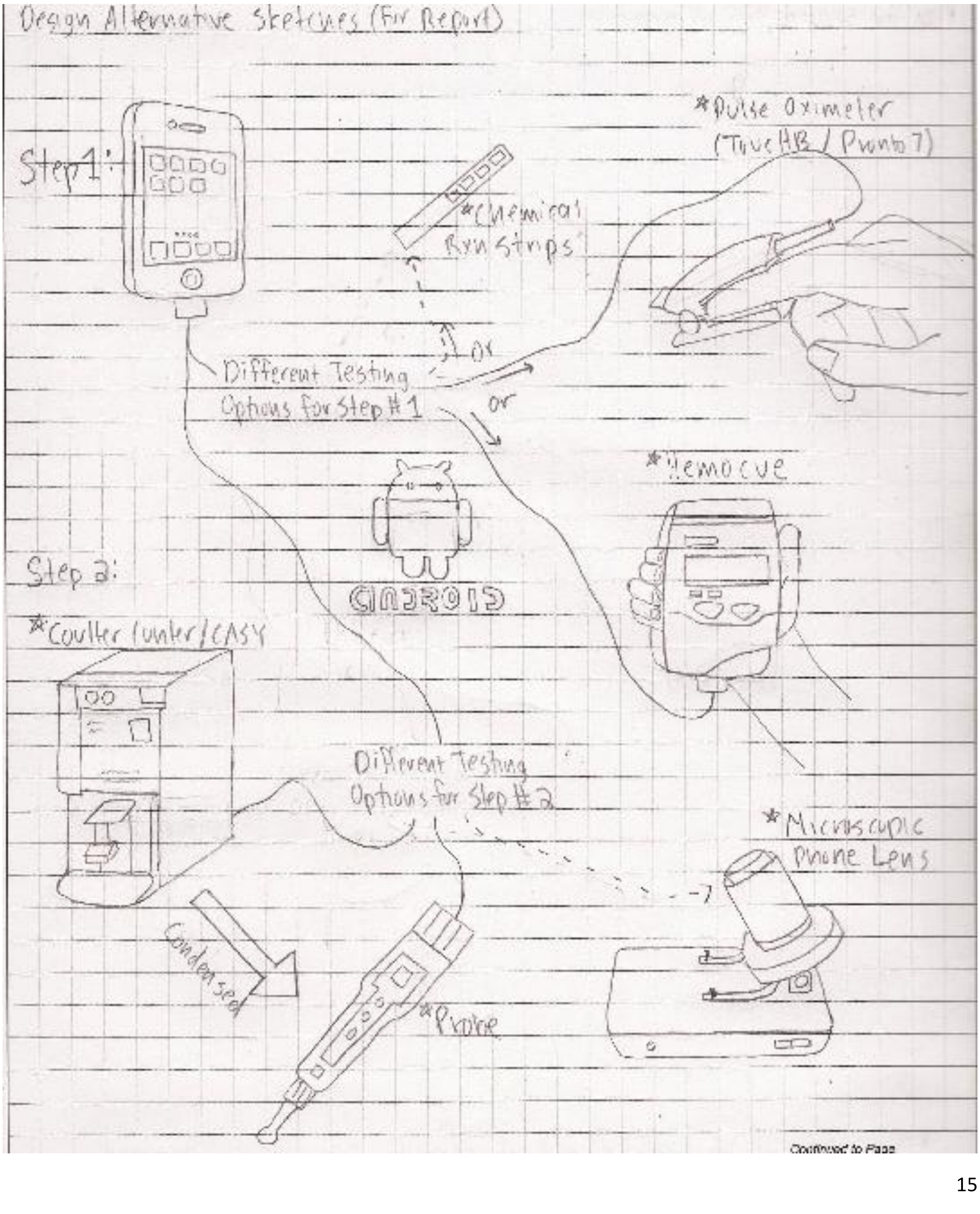
New Patient (allow user input of all data values and skipping of any step)
record time, date, and prompt for location (automatic if GPS)
take hemoglobin count from data collector, assign to HGcount
if HGcount >= 11
    display that patient does not have anemia
else
    display that they have anemia
button to continue to next step
(algorithm for collecting and analyzing data from blood smear)
take MCV from data collector, assign to MCV
if MCV<80
    display microcytic
elseif MCV>=80 & MCV<=100
    display normocytic
elseif MCV>100
    display macrocytic
button to continue
take data from abnormal cell analysis (for user input display buttons of various cell abnormalities)
button to continue
redirect to tab of "Treatments" section corresponding to data collected

Previous Patients
list of previous patients distinguished by time and date
clicking on patient shows HGcount, MCV, abnormal cells and treatment
ability to "flag" important patients/ add comments to patients
ability to delete patient file (delete all, mark to not be deleted)

Treatment
lists of treatments options tabulated by various MCV and abnormal cell values.

Appendix C

Device Sketches



Appendix D

Design Matrices

	Programming Difficulty (10)	Source Files (8)	Cost (5)	Target Audience (5)	**Totals (Weighted Average out of 10)**
iPhone	4	3	3	3	3.36
Andriod	8	7	3	4	6.11

	Safety (8)	Efficacy in diagnosis (10)	Training (7)	Cost (8)	Mobility (7)	**Total (Weighted Average out of 10)**
Hemocue	5	8	3	2	6	4.98
Pulse Oximeter	8	7	6	6	7	6.83
Chemical Indicator	?	?	?	?	?	?