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Design and Development of Hemogram,  
a Web Application for a Remote Examination of  
Peripheral Blood Smears from Resource-Limited Clinics in  
Nepal

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**Abstract**

Design and Development of Hemogram,  
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Examination of peripheral blood smears is a simple medical laboratory test that can provide significant diagnostic information. Nevertheless, this test is manual, time-consuming, and demands highly experienced medical technologists and/or pathologists. The gravity of this test is far more significant in resource-limited clinics in developing countries where advanced laboratory testing is beyond their capacity. Hemogram, a web application, is developed as a prototype project that aims at providing a user-friendly yet robust platform to remotely examine peripheral blood smears by experienced laboratory professionals. Implementing Hemogram to resource-limited clinics can provide added laboratory support in diagnosing hematologic disorders and alleviate the problem of shortage of laboratory professionals. This thesis presents various facets of Hemogram, including the design and development of its database schema, user interface, and application logic.

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## **DEDICATION**

to my dear grandfather, Permananda Bhandari

## Chapter 1

# INTRODUCTION

### *1.1 Introduction and Scope*

The microscopic examination of peripheral blood smears (PBS) is one of the oldest and most commonly performed tests in the hospital laboratory. The examination includes White Blood Cell (WBC) classification and morphological evaluation of WBCs, Red Blood Cells (RBC) and platelets. PBS can provide valuable guidance to physicians in the diagnosis of blood and bone marrow related disorders. Despite being a common laboratory test, it requires highly trained and experienced laboratory technologists and pathologists to read the smear manually and can be a time-consuming procedure[1].

In Nepal, a developing country, where laboratory medicine is still in its infancy, there are very few laboratories and most of them are owned and operated by private hospitals[2]. Since these private laboratories are offering more lucrative opportunities, small clinics and community hospitals are struggling to hire and retain laboratory professionals with higher qualifications and experience[3]. Because of the scarcity of trained laboratory technologists, most of the small clinics and community hospital laboratories do not offer the microscopic examination of PBS as part of routine laboratory testing.

With the advancement in the field of information technology infrastructure in recent years, telepathology has become a reality today. It can be applied to review digitized images of PBS, collected at small clinics and community hospital laboratories in Nepal, by experienced technologists from remote locations. However, the existing telepathology system is predominantly used in histology and anatomical pathology, which requires users to have a private server, install the company's software and process digital images at the local laboratory. In this project, I looked upon existing telepathology technology and implemented

a proof of concept to explore the design and development of a web application to remotely evaluate PBS.

## **1.2 Related Work**

There have been a few web-based technologies aimed at remote consultation of smears, specifically histological and anatomical smears. The primary objectives of such applications are to address the issue of shortage of medical professionals in the field of pathology. iPath, a web and email-based application, was introduced at the University of Basel, Switzerland for telepathology. This platform brings pathologists from all over the globe to provide telepathology support for diagnostic consultation and provides education to centers with limited resources[4]. In 2011, the Pathology Quality Control Center of China and the Ministry of Health introduced a website based telepathology platform for community hospitals to send digital images of histology slides to make pathology diagnosis, assess the quality of pathology slides or offer second opinions[5].

These existing applications do provide a solution for remote diagnostic consultation and education. Unfortunately, due to the high volume and manual complexity involved in the examination of PBS, no application offers a platform to provide this test as part of routine laboratory testing in resource-limited laboratories in developing countries.

## Chapter 2

### BACKGROUND

In this chapter, I will present a general background on blood cell types seen in PBS and how classification and evaluation of cells are performed in a laboratory settings. Additionally, I will also provide a background on hematology services in resource-limited clinics in Nepal and introduce the concept of tele-hematology to provide remote smear evaluation service to those clinics.

#### **2.1 Blood Cells in PBS**

##### *2.1.1 WBC*

WBC, also known as leukocytes, are the central component of the human immune defense system. They are small nucleated cells that defend the body from harmful foreign bodies and mutated cells. The family of the WBC includes neutrophils, lymphocytes, monocytes, eosinophils, and basophils. These are mature WBCs that circulate in our peripheral blood. Each of them has distinct morphological features and different responsibilities in the immune defense system. Neutrophils phagocytose and kill bacteria that are considered harmful by the immune system. Lymphocytes are complex cells that identify foreign antigens and initiate antibody and cell-mediated antagonistic responses. Monocytes identify and phagocytose foreign particles and help lymphocytes in initiating antibody response. Eosinophils are primarily involved in allergy or parasitic infections. Basophils boost the inflammatory response. Basophilia, an elevated basophil count, often signals a hematologic disease, such as leukemia[6]. Differentiating the types of WBCs found in the blood and identifying their morphological abnormalities are very crucial in determining the cause of blood and bone marrow related illness. Figure 2.1 displays the family of WBCs, RBCs, and platelets.

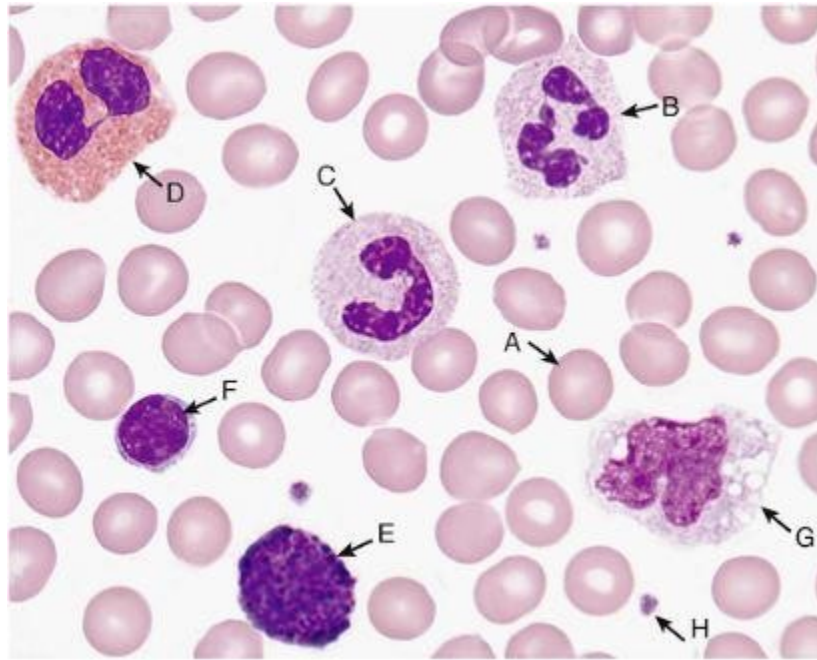


Figure 2.1: PBS with 100X magnification. A. Erythrocyte (RBC), B. Segmented Neutrophil, C. Band Neutrophil, D. Eosinophil, E. Basophil, F. Lymphocyte, G. Monocyte, H. Platelet[7].

### 2.1.2 RBC

RBCs, also known as erythrocytes, are anucleate biconcave cells that mature in the bone marrow before entering the peripheral blood. The average size is 7 to 8 microns. RBC contains hemoglobin that transports oxygen and carbon dioxide from the lungs to the tissues. Qualitative evaluations of RBCs abnormalities such as sickle cells, spherocytes, malarial parasites, and other RBC inclusions can be clinically significant in diagnosing RBC disorders[6]. These abnormal findings are only possible through careful evaluation of PBS.

### 2.1.3 Platelets

Platelets, also known as thrombocytes, are blood cells that are smaller in size than RBC. They are 2 to 4 microns in diameter. They are very crucial in maintaining hemostasis, a

series of cellular and plasma-based mechanisms that prevent blood loss during vessel injury. An injured blood vessel sends a signal and platelets respond to the signal by traveling to the site of injury. At the injury site, platelets adhere together to form a plug to stop the bleeding[6]. Microscopic examination of the platelet morphology can provide significant value in identifying the cause of platelet disorders.

## ***2.2 PBS Evaluation and its Significance in Diagnostic Medicine***

As discussed in the previous section, WBC, RBC, and platelets are cellular blood products that circulate throughout the bloodstream. Each of these blood cells has its own primary function. Microscopic examination of these blood cells is known as PBS evaluation and can be the first indicator of infections, inflammations, myelodysplastic syndrome, leukemia, lymphoma, and myeloproliferative disorder. This test could also be used to monitor the effectiveness of medication[8].

Despite the recent advancement in the field of complex laboratory technologies, such as flow cytometry, chromosomal studies, and molecular testing, the simple microscopic examination of PBS is still a very important diagnostic test to the hematologist[9]. This test is relatively straight-forward, yet effective not only in providing significant information in detecting early-stage blood and bone marrow related disorders but also in rapid diagnosis of infectious diseases[10]. The importance of this test is more significant for resource-limited clinics where clinicians do not have the luxury to order more advanced diagnostic tests like the ones mentioned above.

## ***2.3 Preparation of PBS***

In order to prepare a PBS, a drop of blood from the Ethylene Diamine Tetra-acetic Acid (EDTA) tube is placed at one end of the slide. Using a second slide, known as a pusher slide, the drop of blood is pushed toward the other end of the slide creating a wedge smear. Figure 2.2(a) shows the wedge technique to make a PBS and figure 2.2(b) depicts a PBS made using such a technique. After the smear is made, it is fixed using methanol and stained

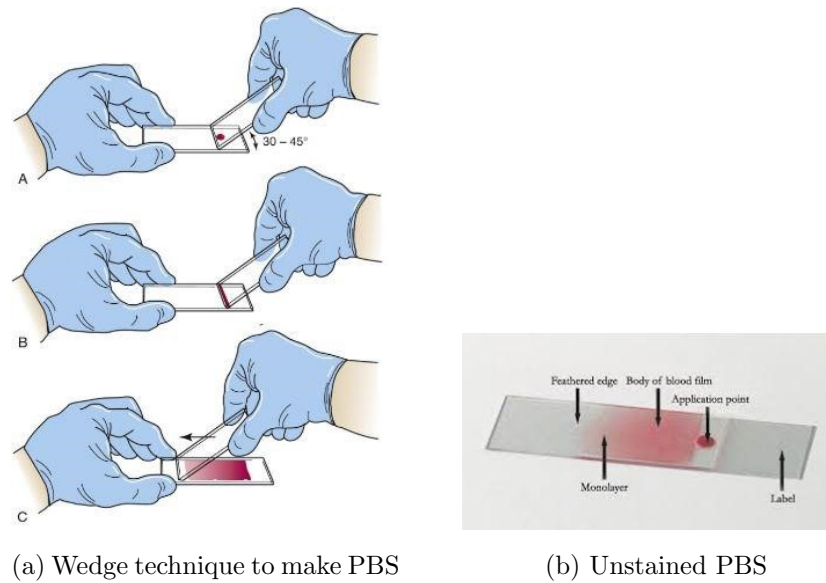


Figure 2.2: Wedge technique to make a smear[7]

with Wright's stain[6].

## 2.4 Evaluation of PBS

After the smear is made and stained, it is ready to be evaluated by qualified technologists and/or pathologists. Evaluation of the PBS begins by scanning the entire slide under low magnification and locating an ideal area to examine blood cells. After the ideal spot is identified, the evaluation process begins, and that is discussed in sections below.

### 2.4.1 White Blood Cells Differential Count

The family of WBC, i.e., neutrophils, lymphocytes, monocytes, eosinophils, and basophils, plays an important role in protecting the host body from foreign pathogens as well as from mutated cells. The first part of the evaluation of PBS is a differential count that measures the relative percentage of each type of WBC. A smear is placed under the microscope at 50X oil-immersion magnification to perform the differential count. This includes counting

and classifying 100 consecutive WBCs and reporting these classes as percentages. Immature WBCs are usually not present in the peripheral blood; therefore, their presence might indicate infections or malignancies. Thus, the presence of young WBCs is also reported in the differential count. The count is performed in a systematic manner using the “battlement” track, which minimizes WBCs distribution error[11]. Figure 2.3 shows the pattern used in reading a PBS.

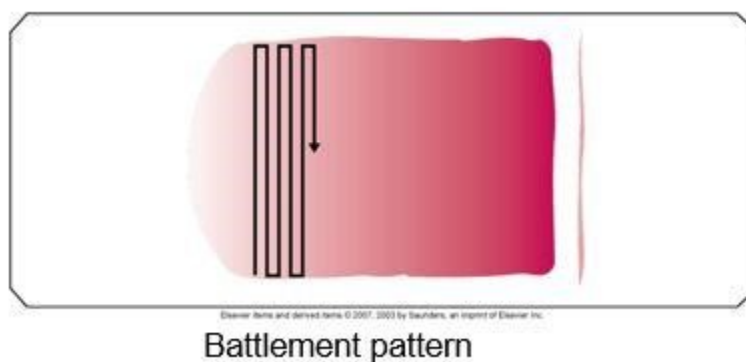


Figure 2.3: Battlement pattern to read a smear[11]

#### 2.4.2 Blood Cell Morphology

Cell morphology evaluation is a crucial part of the PBS examination. Morphological changes in the shape, size, and color of the BC [abnormal cells] and the presence of immature cells in the PBS are often indicators of the disease state. The abnormal and immature cells are differentiated from normal cells by their morphological features. Therefore, the recognition and reporting of the morphological abnormalities of all three types of blood cells are crucial in diagnosing and treating diseases.

#### *2.4.2.1 WBC Morphology*

In WBC morphology, primarily the maturity and morphological abnormality are reported. These findings provide significant information to assess hematopoietic pathologies as simple as bacterial infection to a complex disease like leukemia. For instance, the presence of the myeloblasts, immature WBC with distinct morphological features, suggests an underlying malignant hematologic disorder[12]. In some instances, WBC morphology can provide enough information for the diagnosis of leukemia or lymphoma, and in other instances, it can indicate which additional tests should be performed.

#### *2.4.2.2 RBC Morphology*

For RBC morphology, abnormalities include size, shape, inclusions, immaturity, color, and arrangements. These morphological abnormalities can provide diagnostic information about anemia, hemoglobinopathies such as sickle cell and infection of RBCs by parasites such as Malaria, Babesia and Ehrlichia[6].

RBC count, hemoglobin value, mean cell volume (MCV) and mean cell hemoglobin (MCH) are automated laboratory test values that can provide enough information to diagnose some forms of anemia, such as microcytic anemia. But other cases of anemia, such as hemolytic, macrocytic or sickle cell, require RBC morphologic information to differentiate them. The finding of RBC fragments is one of the most important morphologic findings since it can signify a life-threatening condition such as Disseminated Intravascular Coagulation (DIC), Hemolytic Uremic Syndrome (HUS) or Thrombotic Thrombocytopenic Purpura (TTP). Such findings are only possible through the manual evaluation of PBS[12]. Figure 2.4 depicts the presence of RBC fragments/Schistocytes, an abnormal RBC morphology.

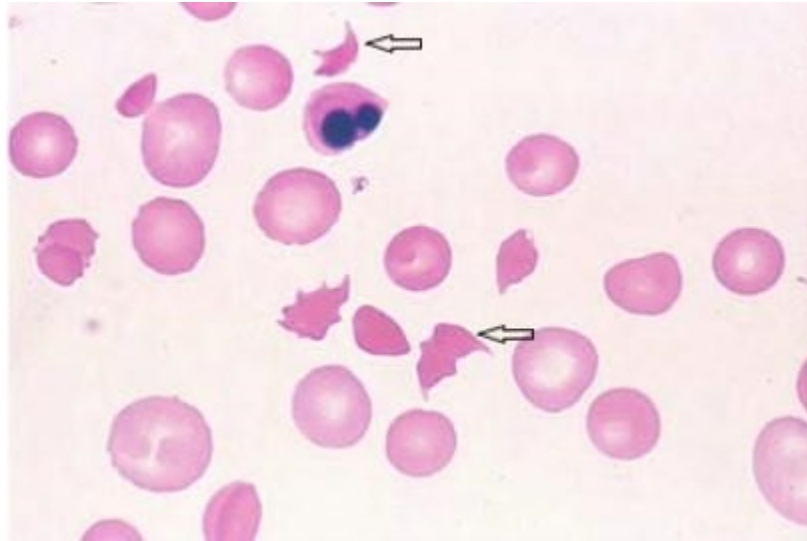


Figure 2.4: RBC fragments/Schistocytes[7]

#### 2.4.2.3 Platelets Morphology

Platelet morphology includes the size, arrangement, and granularity. Abnormalities can be found in hematopoietic pathologies such as leukemia or some bleeding disorders[7]. Large platelets, also known as giant platelets, signify increased bone marrow production due to destruction processes found in diseases such as immune thrombocytopenia. In the above sections, some of the abnormalities within different blood cells were discussed. By no means, it is a complete list of all morphological findings. Several publications have been dedicated to this subject. To identify these abnormalities a careful evaluation of the PBS is a requirement. These findings along with patient's clinical data can provide rapid and reliable information to establish a diagnosis.

#### 2.4.3 Digital PBS Evaluation

Manual microscopic evaluation is considered a gold standard procedure in evaluating PBS[13]. However, this evaluation method is highly demanding and labor-intensive work in the med-

ical laboratory setting. Recent advancements in the field of the robotic digital microscope and Machine Learning (ML), a branch of Artificial Intelligence (AI), automation has been used in the classification of blood cells using digital images in the modern laboratory. Currently, in the United States (US) the Food and Drug Administration (FDA) has approved systems such as CellaVision DM (CellaVision, AB, Lund, SWE) (Figure 2.5(a)) and Medica EasyCell Assistant (Medica, Bedford, MA) (Figure 2.5(b)) for clinical uses in hospital laboratory settings. These instruments use PBS to scan, capture, and store images of BC for classification and morphological evaluation. Several published studies have shown digital PBS evaluation to have a higher degree of accuracy for classifying WBC; however, the FDA still requires a licensed medical technologist (MT) to review the classification before generating the final laboratory report[1]. These platforms also have advanced algorithms to identify cells' morphological abnormalities but are not yet cleared by the FDA, therefore rely on MT's input on morphological evaluation of blood cells.

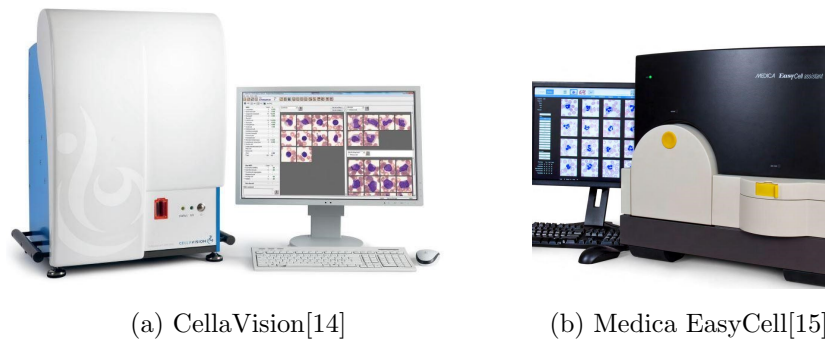


Figure 2.5: Digital Microscopy Systems

#### 2.4.4 *CellaVision DM9600*

CellaVision DI9600 is an automated digital microscope design and developed by CellaVision Corporation based in Lund, Sweden. This instrument consists of three main components - a robotic-armed microscope that scans the PBS, a digital camera that captures BC images and

artificial neural network technology to classify cells. It has a loading capacity of 96 slides and has a throughput of 30 slides per hour. When a slide is fed into the instrument, it scans the slide bar-code and automatically identified a mono-layer to locate blood cells and capture high-quality digital images. After the processing of the slide is completed, captured images are presented to trained professionals for review and verification[16]. In this project, I am using DM9600 as a primary device to collect BC images from PBS. DM9600 is used primarily for convenience in this proof of concept: generation of images in the resource-limited clinics is an unsolved problem.

## ***2.5 Healthcare and Laboratory Services in Nepal***

Nepal is one of the developing countries in South Asia. The population of Nepal is 29.9 million, and about twenty-one percent of its population lives below the poverty line. Working adults who live below the poverty rate make an average of three US dollars a day[17]. Poverty continues to be one of the major obstacles Nepal is facing in providing affordable healthcare. Most of the healthcare expenses are self-paid, therefore, illness can be a financial burden to the patient and their family. To avoid the financial burden, many people choose to live with an underlying disease than seek medical attention[18].

Along with the issue of affordability, there is also a severe shortage of medical professionals in Nepal. There are 2.1 physicians, 2.2 nurses, 2.4 midwives and 0.1 pharmacists per 10,000 people[18]. The number is much lower for laboratory professionals. Nepal Health Professional Council (NHPC), which manages the laboratory science and its related occupations, data shows that there are 37 Medical Laboratory Technologists (specialist), 725 Medical Technologists and 576 Laboratory Technicians in Nepal[19].

The annual report published by the Department of Health Services of 2018 shows that there 123 public hospitals, 200 primary health care clinics and 1,715 private hospitals and clinics in Nepal[20]. Since most of the healthcare cost is self-paid, private hospitals only provide care to patients who have the means to pay. People who are living below the poverty rate generally seek medical needs at primary health care clinics because they are compara-

tively inexpensive. But many of these clinics do not have the infrastructure such as medical professionals and technical capabilities to support laboratory testing[21]. Therefore, many clinicians/nurses in these resource-limited clinics diagnose disease primarily based on patient's clinical signs and symptoms. Diagnosis of diseases primarily established from clinical signs and symptoms, rather than an evidence-based diagnosis, can be unreliable and misdiagnosis may occur. For instance, in Tanzania, out of 4670 patients who were diagnosed with malaria based on clinical symptoms, the laboratory blood smear microscopy showed that only 2062 (46.1%) of the admitted patients were positive for malaria[22]. Diagnosis based exclusively on the patient's clinical symptoms, without diagnostic testing, can lead to the inappropriate treatment, additional financial burden, and the development of disease complications.

In recent years, due to the support of foreign and non-governmental organizations (NGO), some of the resource-limited clinics are providing additional healthcare services including laboratory testing[23]. With additional financial support, these clinics are providing some automated laboratory tests such as Complete Cell Counts (CBC), Basic Metabolic Panels (BMP) and Urinalysis (UA) to their patients. Such funding has provided additional support to the resource-limited clinics but it has not fixed the problem of shortage of laboratory professionals. Having tools and instruments alone is not enough to provide full laboratory service. There is still a severe shortage of skilled laboratory professionals. According to a collaborative study by the World Health Organization and NHPC from 2010 to 2011, most of the technicians employed in the laboratory in several major cities in Nepal were unskilled[19].

Tests like PBS evaluation, which is a time-consuming manual test, require highly knowledgeable and experienced medical technologists and pathologists. Until the problem of scarcity of qualified laboratory professionals is solved, manual laboratory tests are less likely to be performed by resource-limited clinics in Nepal.

## 2.6 Telemedicine and Telepathology

Telemedicine is the use of Information and Communication Technology (ICT) by medical professionals to provide medical and educational services to patients across all geographical locations. The World Health Organization (WHO) has adopted the following definition of telemedicine.

*“The delivery of health care services, where distance is a critical factor, by all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities[24].”*

As our information technology infrastructure is rapidly advancing, the use of telemedicine has become more prominent than ever before and new possibilities are emerging for healthcare service and delivery.

Telepathology, a branch of telemedicine, is the practice of pathology at a distance. It consists of collecting digital microscopic images of cells or tissues and uploading them to the server and making them available to certified off-site professionals for interpretation, consultation and/or for educational purposes[25].

Although telepathology is gaining popularity in the space of telemedicine, it is not a new technology. The first case involving telepathology was documented in the late 1960s, when Massachusetts General Hospital (MGH) and Logan Airport Medical Station in Boston, Massachusetts established a real-time “television microscopy” service. Since then, the field of telepathology has evolved. The most recent technology developed in this field is virtual slide telepathology, also known as Whole-Slide Imaging (WSI). This system has the capability to scan the slide and capture high-resolution digital images. Because of such innovative technology, many potential uses of telepathology are evolving. One of the branches of pathology that can benefit from this technology is tele-hematology[25].

Tele-hematology is a practice of clinical hematology which involves collecting digital im-

ages of cells from PBS and transmitting it to the server for remote interpretations of cells by certified medical technologists and pathologists.

## ***2.7 Remote PBS Evaluation for Resource-Limited Clinics in Nepal***

Telepathology has been proven to be a great source for providing exceptional pathology services to distant locations where there is a shortage of pathology service or where the shipment of the specimens is too expensive or not feasible. In developing countries like Nepal where there is a severe shortage of medical laboratory technologists, tele-hematology service could provide an efficient way to solve the problem of the shortage of skilled laboratory professionals. In the following section, I discuss some of the benefits as well as the challenges in implementing tele-hematology.

### *2.7.1 Benefits*

- Hematology support: Due to the severe shortage of laboratory professionals, resource-limited clinics do not offer the evaluation of PBS as part of routine laboratory testing to their patients. Tele-hematology has the potential to provide these clinics with additional medical technologist support to review PBS. Thus, making this test a part of routine medical laboratory testing.
- Informed clinical decisions: PBS can provide a definitive diagnosis of a disease, or, more often, can be an important indicator for additional testing[26]. With this added service, a physician from these clinics can make informed clinical decisions in treating their patients.
- Socio-economic benefits: Even though it is quite difficult to evaluate the direct socio-economic benefits from the tele-hematology service, several researchers have found that specific telehealth applications have been shown to offer significant socio-economic benefits to patients and families, health-care providers and the health-care system[27].

### 2.7.2 Challenges

While tele-hematology has the potential to provide excellent benefits to the patients in Nepal, there are numerous hindrances in the implementation of such services.

- **Equipment:** Previously discussed equipment such as CellaVision or Medica EasyCell Assistant, which have the capability to scan the smear and captures images of BCs, are highly expensive. Without considerable funding resources, attaining those instruments is not possible.
- **Internet connection:** Nepal is still in the process of building internet infrastructures; internet connectivity could be an issue. Slow or no internet connection will be a barrier in transferring images from the clinic to the server as well as accessing the laboratory results.
- **Maintenance:** Regular maintenance and repair of the instruments can be expensive. System engineers who are trained and certified to fix instruments are usually outside the country. Getting an engineer to the site could be a lengthy and expensive process.
- **Privacy:** The privacy and security of patient's data is the biggest hindrance to tele-hematology, especially in a situation when two different countries are involved. In the US, a healthcare organization must comply with the Health Insurance Portability and Accountability Act (HIPAA) to protect individual's medical records and other personal health information[28], whereas in Nepal there is no strict regulation that governs patient privacy and confidentiality.
- **Regulation:** All blood cells' image datasets need to be analyzed and reviewed by licensed medical technologists or pathologists before generating the laboratory report. Since the licensing and accreditation regulations differ in Nepal and the US, establishing and maintaining regulation can be cumbersome.

## Chapter 3

# WEB APPLICATION DESIGN AND DEVELOPMENT

In this chapter, I am discussing the methodology used in the design and development of the tele-hematology web application - Hemogram. I will also layout various technologies that I implemented in order to support wide range of application functions.

### ***3.1 What is a Web Application?***

A web application is software that can be easily accessed through a web browser such as Internet Explorer, Firefox, Safari, and Opera using an internet connection. One of the main reasons for its popularity is that users do not need to download and install software. The application and its data are stored on a server; therefore, users can access web applications from anywhere provided they have access to a web browser and the internet[29]. A web application not only makes the accessibility of the software easy but also simplifies software maintenance and ongoing development. A newer version of the software can be instantly delivered to all users by simply uploading a newer version of software to the server.

### ***3.2 Web Application Design Process***

The process of designing a web application involves determining and understanding the objectives and requirements of the project. In the following section, I will layout the core objective of the Hemogram application and various design principles used in this project.

#### *3.2.1 Hemogram Application Goal*

Hemogram is a web application with a primary goal to support a tele-hematology service. In this proof of concept project, CellaVision DM9600 is used for collecting digital images of

PBS and uploaded those images along with patient demographic data to a cloud-based server. After upload, those digital images are accessed by technologists and pathologists in a remote location via a web browser with an internet connection. These laboratory professionals can analyze those digital images using a web interface to classify blood cells and generate a full PBS evaluation report. After the report is generated, it is accessible to the clinics that ordered the test.

### *3.2.2 Identifying Users*

Users of the Hemogram application are medical professionals such as Doctors, Pathologists, Medical Laboratory Technologists, Laboratory Technicians, and Laboratory Assistants. Since all the users are medical professionals, most of the content and the functionality of the application can be mastered with little training. Standard Operating Procedures (SOP) describing various components of the application and step-by-step instructions on how to complete tasks will be provided in the training section.

### *3.2.3 Functional Requirements*

In designing a web application, it is crucial to understand and document functions that the application can perform. In this section I am going to outline Various functions of Hemogram application.

1. User Registration and Authentication - In the previous section, I identified potential users of this application. One of the functions of the application is to allow the Hemogram administrator to register users. Once registered, users can authenticate their accounts using the login credentials to perform tasks authorized by their role.
2. Assign Roles - Based on the users' profession, they can assume a certain role. Hemogram database stores sensitive patient data; therefore, assigning a role and granting the least privilege to perform their task, will limit the accessibility to data and protects it from unauthorized modification.

3. Patients, Orders, and Samples Registration- This module will allow users to add new patients, laboratory test orders, and samples. In order to prevent duplicate patient registration, this module provides search functionality. If no record is found on a search query, the module will prompt to add a new patient.
4. Provider and Clinic Registration - Each laboratory test ordered on a patient must have a provider's information along with clinic information. This module will permit administrators to enter information regarding providers and clinics.
5. Pending Display - Samples that are yet to be analyzed must be brought to the attention of users periodically. The Pending Display module will asynchronously alert users with the number of samples to be analyzed at a constant interval.
6. Analyze Samples and Generate Laboratory Reports - The module will allow medical technologists or pathologists to analyze the images collected from PBS and generate a final laboratory report.
7. Display Laboratory Reports - After the samples are analyzed, the final report must be provided to the ordering physician in a readable format. This module will gather sample data from the database and render it for the provider to view it.
8. Search Patient - A lookup functionality will provide application users to search patient data via various parameters such as first name, last name, and date of birth.
9. Post and Display Standard Operating Procedures (SOP) - To provide a higher standard of laboratory testing by all medical professionals, a comprehensive set of guidelines need to be established. This module will permit the administrator to establish SOP and upload them to the database, which is accessible to all users.

### **3.3 Design Principles**

With the intention of delivering a higher quality application functionality and enhanced user experience, I followed three simple design principles, which are discussed below.

#### *3.3.1 Simplicity*

Even though Hemogram users are medical professionals, it is very difficult to predict the user's experience in using computers, particularly in Nepal. Therefore, it is crucial to design a simple yet fully functional application. The application should be very straightforward and simple to navigate from one page to another. The objective of simplicity in this project is to minimize the noise and maximize the signal. Consistency in design, a visually pleasing composition, a logical and sequential ordering and the presentation of the proper amount of information will help us reduce the noise and achieve clarity and simplicity to the application[30].

#### *3.3.2 Consistency*

In conjunction with simplicity, consistency is also pivotal to the design principles. Ozok and Salverdy have found in their research that consistency in an application can significantly help users commit fewer errors[31]. With consistency in visual elements and functionality, users of this application will be able to transfer information to new contexts. A layout that flows easily will help gain familiarity, contributing to overall usability and participation.

#### *3.3.3 Scalability*

In addition to simplicity and consistency, a well-designed application should be able to scale to various workloads. Workload could be defined as simultaneous users, storage capacity, the frequent database transactions that would push the application beyond its original capacity[32]. In short-run, scalability can be a time-consuming and expensive process but in the long run, it can save time and money.

### 3.4 Web Application System Architecture

Hemogram application utilizes the 3-tier application architecture framework. The primary advantage of this architecture is that it separates production and development environments by compartmentalizing data storage, application logic, and user interface into different modules. This provides great flexibility to the application developer to upgrade one module without interfering with other ones. The 3-tier architecture consists of a database tier, client tier, and logic tier. The database tier is comprised of a database management system (DBMS) and a database. It manages and stores the entire data that is applicable to this application. The client tier provides a user interface to enhance the user's experience. Finally, the logic tier is the core mechanics of the application[33]. It facilitates the user's requests such as login, logout, patient data, search function, etc. Figure 3.1 shows the 3-tier architecture used in this project.

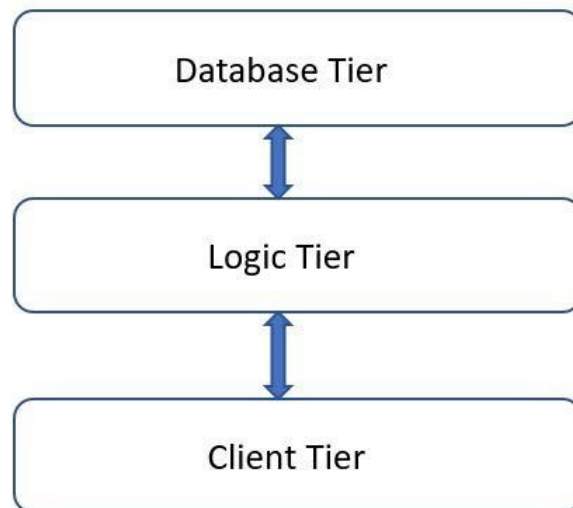


Figure 3.1: 3-Tier application architecture

### **3.5 Technology Choices**

This section provides a brief summary of web technologies used on each tier of Hemogram application architecture. The primary objective of this project was to provide a proof of concept to determine the feasibility of web application to support tele-hematology, therefore, all of the software technologies that I used are open-source or free-tier packages which provide non-restrictive licensing.

#### *3.5.1 Database Tier*

Hemogram is a data-driven application, therefore it very pivotal to use a robust database system to manage the data storage, retrieval, and integrity of data at all times. This section covers the database software I used in the Hemogram application.

##### *3.5.1.1 PostgreSQL*

For the database management, Hemogram application is taking full advantage of PostgreSQL, which is an open-source relational database management system. It was first developed at the University of California at Berkeley in 1977. It is one of the best and most advanced open-source database systems in the world[34]. It has many enterprise-class features that are typically available with commercial level DBMS. It is well designed for applications such as Hemogram where data is frequently uploaded, retrieved and updated.

##### *3.5.1.2 SQLAlchemy*

SQLAlchemy, a Python library, provides a high-level interface to PostgreSQL, the DBMS implemented to the Hemogram application. It includes a database server-independent Structured Query Language (SQL) and an object-relational mapper (ORM) that lets us use SQL to persist our application objects automatically[35]. ORM makes it simple to create database tables and columns. Table names are defined using classes and column names are defined

using class attributes. ORM specifies the database schema and allows us access databases using pythonic like an object rather than writing complex raw SQL queries[36].

### *3.5.2 Client Tier*

Hemogram is only accessible through the web browser. The users, also known clients, make requests to the application via a web browser. In turn, the browser makes a request to the logic-tier of the application to retrieve data. After retrieval, the browser renders data on the user's device. Several client-side technologies used in client tier are discussed below.

#### *3.5.2.1 HTML*

HTML stands for Hypertext Markup Language. It is the core language for creating web applications. It is a common language all the web browsers such as Google Chrome, Internet, etc.can understand[37]. It defines the structure of the web pages to the browser. The web browser takes the HTML content and arranges it as defined to display it on the screen.

#### *3.5.2.2 CSS*

Cascading Style Sheets (CSS) is a language that adds visual appearance to web pages and applications[37]. It is a simple yet very powerful language in the world of web development. It provides the web browser styling rules on how each HTML element should look. In simple terms, it defines the color, size, and position of text and other HTML elements.

#### *3.5.2.3 Bootstrap Framework*

Bootstrap is an open-source front-end framework that was originally built by Twitter, a social media network, to help ease the design process of web pages and applications. The framework uses HTML and CSS for templates, typography, forms, navigations, buttons, tables and more. One of the biggest advantages of using bootstrap is that it allows the web

application to have a responsive layout in order to render web content on various devices or screen sizes[38].

#### *3.5.2.4 JavaScript*

JavaScript is a programming language designed to dynamically control the web content on the browser. With this language, the web application can provide an enhanced user interface by allowing the manipulation of the behavior of HTML elements displayed on the web pages[39]. In this application, the JavaScript is primarily used for some data handling and automatically updating some of its content.

#### *3.5.2.5 Ajax*

Ajax stands for Asynchronous JavaScript and XML. The primary function of Ajax is to allow web applications to work behind the scenes to access data and display as needed[40]. In Hemogram, Ajax is used for asynchronously updating sample counts that are yet to be analyzed.

#### *3.5.2.6 jQuery and jQuery UI*

jQuery is a JavaScript library. It offers a simple way to achieve a variety of common JavaScript tasks quickly and consistently, across all web browsers[41]. It makes handling HTML elements and events very simple and easy.

jQuery UI is another JavaScript library built on top of jQuery. This library allows us to provide some animation, effects and web control to build an interactive web application. This library has been intensively used in the BC image classification section of the Hemogram application.

### *3.5.3 Logic Tier*

Logic Tier processes the functional logic of the application. It handles activities like account authentication, image processing, laboratory report generation, etc. Programming language and framework used in the logic tier are discussed below.

#### *3.5.3.1 Python*

Python is one of the most common and popular programming languages. It is a powerful programming language to build just about anything. It has efficient high-level data structures and a simple but effective approach to object-oriented programming. Python standard library is very extensive and provides significant documentation[42].

#### *3.5.3.2 Flask*

Hemogram uses Flask, a python based micro-framework built for web applications. It is based on Werkzeug and Jinja2 template engine and only comes with basic services. It does not have native support for databases, validating web forms, authenticating users, or other high-level tasks[43]. Therefore, to build a web application, several extensions and libraries must be imported to achieve certain application features. At a glance, getting extensions for each additional feature may feel cumbersome, but this provides the flexibility to test out several libraries and pick the best library that fits the application's needs the most. Thus, the flask has been gaining popularity among web application developers. Flask also has extensive documentation and community support online.

## Chapter 4

### DEVELOPMENT OF WEB APPLICATION

The development of the Hemogram application consists of three phases based on the architecture explained in chapter 3. Our discussions in this section focus on three phases of application development. Figure 4.1 depicts three phases of development.

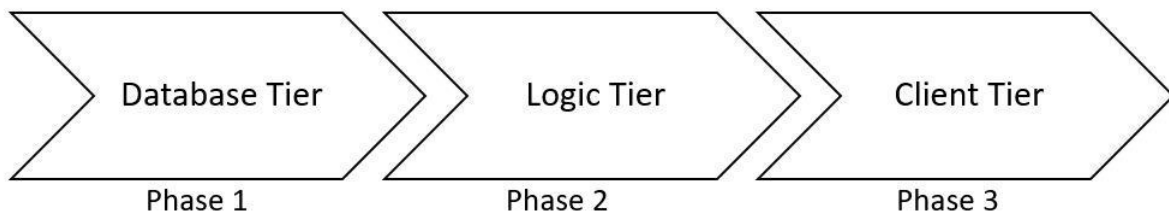


Figure 4.1: Three phases of the development process

#### **4.1 Database Tier**

As discussed in the previous chapter, Hemogram is a database-driven application. Hence, understanding data and their relationship with each other is very important in building a successful database. In this section, I focused on identifying data that I want to store and manage the relationship between them.

##### *4.1.1 Relational Database*

A relational database stores data in tables and manage the relationship between them - for example, in Hemogram application, patients visit the clinic, laboratory tests are ordered on patients, or samples are collected from patients. In a relational database, each table has a unique name and is composed of columns and rows. Columns in the table represent the data

attributes whereas rows represent the data pertaining to each item or record. Each row in the table is identified by a unique value[44].

#### *4.1.2 Flask-SQLAlchemy*

SQLAlchemy allows us to work with the database in python like objects. To support SQLAlchemy in Flask, I needed to configure the Flask-SQLAlchemy library with the Hemogram application. This library was primarily built for Flask to support and configure SQLAlchemy to web applications.

#### *4.1.3 Identifying Entities*

The first step in designing our database was to identify the data that I wanted to store. In this section, I carefully listed application functions to establish a framework to identify entities. Following list summaries, I underlined unique subjects to identify entities.

1. Add new hemogram user
2. Assign a role to the user
3. Have procedures to guide users on how to use the application
4. Add clinic, provider/doctor
5. Add patient, order requisition and sample
6. Keep track of events associated with orders
7. Add BC images from patient's smear
8. Add additional comments associated with the patient's sample
9. Add morphological findings to the smear

10. Add pathologist review if required to the patient's sample

From the above list, taking out all the subjects generated a preliminary table list applicable to Hemogram application. Table 4.1 shows the database tables list created based on the identified entities.

Database Table Names	
	Name
1	Users
2	Roles
3	Procedures
4	Clinics
5	Providers
6	Patients
7	Orders
8	Events
9	Samples
10	Smears
11	Images
12	Comments
13	Morphs
14	Path Reviews

Table 4.1: Hemogram database tables

#### 4.1.3.1 Data Model

Based on the requirements gathered in the previous section, now we can start defining the data model. In SQLAlchemy, the python class name is used for representing the tables whereas, class attributes are used for representing each column in the table. Each model must inherit from a declarative base class `db.Model`, which provides a Hemogram database instance with a set of helper classes and functions. In figure 4.2, the class name represents a table, class variable `__tablename__` defines the name of the table and each class attribute is a column in the table.

```
class User(UserMixin, db.Model): ← A
    __tablename__ = 'users' ← B
    id = db.Column(db.Integer, primary_key=True, index=True) ← C
    username = db.Column(db.String(64), unique=True)
    user_first_name = db.Column(db.String(64), nullable=False)
    user_last_name = db.Column(db.String(64), nullable=False)
    email = db.Column(db.String(120), unique=True, nullable=False)
    password_hash = db.Column(db.String(128), nullable=False)
```

Figure 4.2: Python class representing users table. A. class name; B. table name; C. class attribute.

After carefully gathering information in the previous section, fourteen tables were identified and a brief description of each table is discussed below.

1. Users - All the users of the Hemogram application. The data in this table is important to authenticate and authorize users.
2. Roles - We need roles to grant privileges to the user. Table stores predefined roles that a user can assume.
3. Procedures - Standard Operating Procedures (SOP) are vital to a Hemogram application because it allows users to get familiarized with the application.

4. Clinics - Different resource-limited clinics in Nepal may participate in tele-hematology service. This table holds information regarding those clinics.
5. Providers - The providers' table is for storing the information of each doctor who is ordering the laboratory test.
6. Patients - Each patient demographic data is stored in this table. Unlike the US, Nepal does not have a Social Security Number (SSN) system in place to uniquely identify each individual. In order to overcome this challenge, the Hemogram application uses 'Father's Full name' as a unique identifier for a patient. This is a common practice in Nepal to uniquely identify an individual.
7. Orders - Table to store each laboratory test order received for a patient. Each order needs to have a clinic and provider information as well.
8. Events - To track progress in laboratory testing for each order, a timestamp for each action is recorded in the events table.
9. Samples - Patient blood samples are recorded in this table.
10. Smears - After the smear is made from a blood sample, it is loaded to an instrument to scan and capture images of blood cells. This table stores the name of the instrument and sample identification number.
11. Images - All images of the BC captured by the instrument on each smear are stored in the 'images' table. Each row contains the name of the image file, smear ID, BC classification type.
12. Comments - In certain circumstances, additional information may be added to the sample. The 'comments' table stores additional information, sample ID and the user ID who generated the comment.

13. Reviews - Patients with severe hematopoietic disorder and certain parasitic infections tend to have abnormal BC morphologies. In these situations, smears may need additional review by a pathologist. The table stores report generated by pathologists.
14. Morphs - This table stores predefined blood cell morphologies that can be added to the PBS evaluation report.
15. Blood-Morphologies - In Hemogram database, many-to-many relationship exists between ‘morphs’ and ‘smears’ tables, therefore a new table is required to decompose the many-to-many relationship into two one-to-many relationships making it easy to associate data from one table to another. The ‘blood-morphologies’ table is added to the database list depicted in table 2 as a linking table to establish the many-to-many relationship.

#### *4.1.4 Table Relationships*

A relationship between two tables exists when data on a first table is associated with the data in the second table. Such a relationship is established by using a primary and foreign key. There are three types of relationships that can exist between a pair of tables.

##### *4.1.4.1 One-to-One Relationships*

When a single row in the first table is related to only a single row in the second table, a one-to-one relationship is established. In this type of relationship, one table serves as “parent” and the second tables serve as “child” table. In order to record a relationship, the primary key in a row of a parent table is recorded in a single row of the child table[44]. For example, in the Hemogram database, a relationship between tables “orders” and “samples” is a one-to-one relationship because an order can be related to only one sample. Figure 4.3 shows illustrate the relationship between the two tables.

Orders		
Order ID	Clinic ID	Patient ID
1000	1	13456
1001	1	13468

Samples		
Sample ID	WBC	Order ID
100	10.20	1000
101	16.85	1001

Figure 4.3: One-to-One Relationship - Establishing the one-to-one relationship between orders and samples tables

#### 4.1.4.2 One-to-Many Relationships

A one-to-many relationship between a pair of tables exists when a single row in the parent table is related to multiple rows in the child table. In the Hemogram database, a “patients” table has a one-to-many relationship with the “orders” table, because one patient can have multiple test orders. Following figure 4.4 illustrates the relationship between “patients” and “orders” table.

Patients		
Patient ID	First Name	Last Name
1000	John	Doe
1001	Mary	Jane

Orders		
Order ID	Patient ID	Collection Time
100	1000	1300
101	1000	2000

Figure 4.4: One-to-Many Relationship - Establishing the one-to-many relationship between patients and orders tables

#### 4.1.4.3 Many-to-Many Relationships

When a single row in the first table can relate to multiple rows in a second table and a single row in a second table can relate to multiple rows in the first table, a special relationship between these tables exists known as a many-to-many relationship. However, to establish this relationship a separate table known as association or linking table is needed. The association table makes it easy to relate rows from one table to those of the other table[44]. In the hemogram database, there is one instance of a many-to-many relationship between “smears” and “morphs” tables. The association table “blood\_morphologies” links both “smears” and “morphs” table by taking copies of the primary key of both tables. Following figure 4.5 depicts the relationship between the tables.

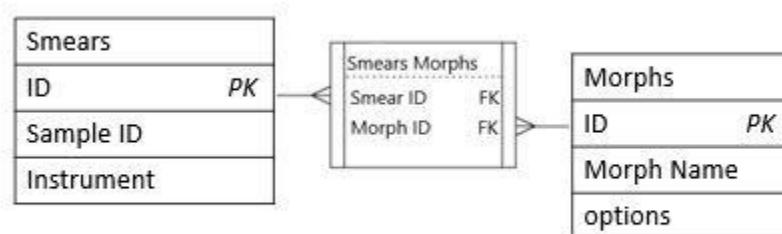


Figure 4.5: Many-to-Many Relationship - Establishing the many-to-many relationship between smears and morphs tables

#### 4.1.4.4 Entity-Relationship (ER) Diagram

A graphical representation of the relationships between entities/tables is known as an ER diagram. It illustrates how database entities interconnect with one another. The diagram provides a visual representation of the database architecture. Figure 4.6 shows the relationship between tables in a Hemogram database.

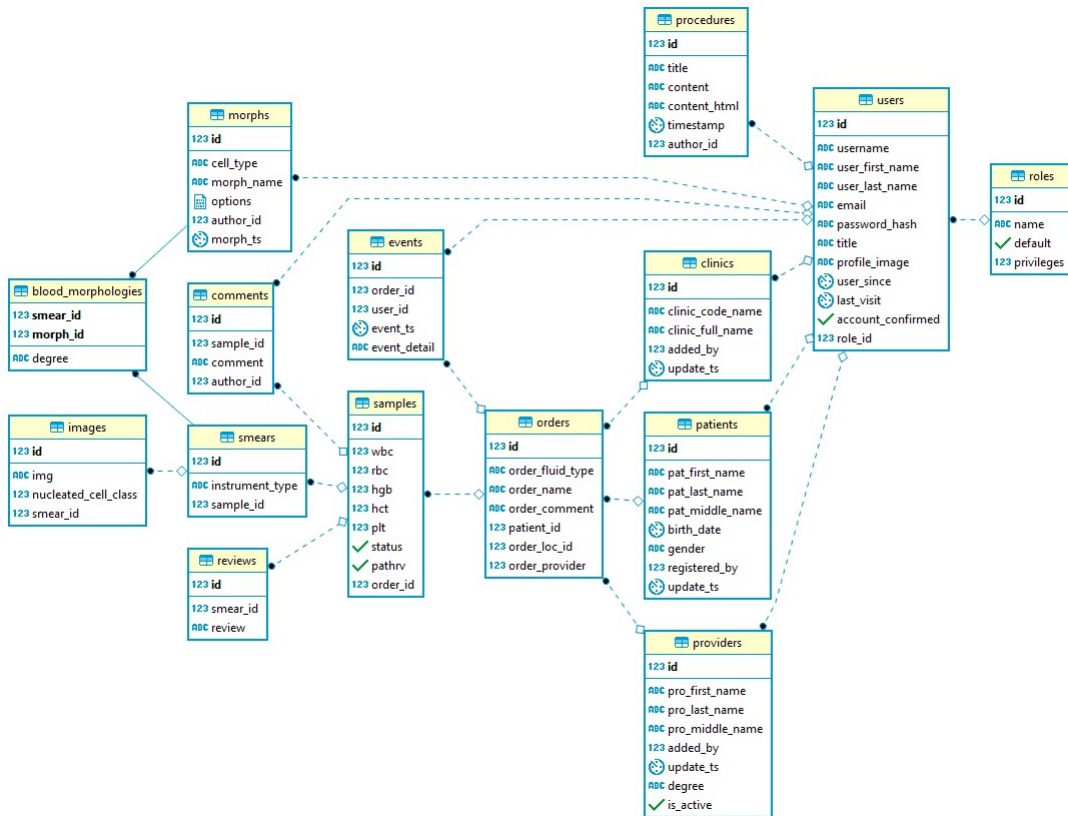


Figure 4.6: ER Diagram - The complete ER diagram for Hemogram database

## 4.2 Logic Tier

Logic tier is responsible for handling all requests made by the users. Based on the request, application logic will have to extract data from the database, manipulate it and provide it the user through the user interface. In this section, I will briefly discuss various steps in setting up the application logic.

### 4.2.1 Initialization and Configuration

To run a flask application an instance of the Flask class needs to instantiate. Once the application is instantiated, a Python object hemogram is created. This object is responsible to

handle all requests that are received from the web server using the WSGI protocol. Following figure 4.7 illustrates how a hemogram object is created in a flask.

```
from flask import Flask
hemogram = Flask(__name__)
```

Figure 4.7: Creating an instance of hemogram application

After the application is initialized, configuration variables such as secret key, database address, S3 bucket key, email server credential, etc. need to be configured to meet the application's needs. I created a python class "Config" to handle configuration variables. Nonetheless, these configuration variables are sensitive data and should not be included as plain text in the application code. Therefore, I stored these variables in the operating system (OS) and imported them as environment variables. Configuration variables are displayed in Figure 4.8.

```
"""
Common configuration settings
"""
# general config
SECRET_KEY = os.environ.get('SECRET_KEY')
LAB_ADMIN = os.environ.get('LAB_ADMIN')
SQLALCHEMY_TRACK_MODIFICATIONS = False

# smtp/email config
MAIL_USERNAME = os.environ.get('MAIL_USERNAME')
MAIL_PASSWORD = os.environ.get('MAIL_PASSWORD')
MAIL_SERVER = os.environ.get('MAIL_SERVER')
MAIL_PORT = int(os.environ.get('MAIL_PORT'))
MAIL_USE_TLS = True
MAIL_SUBJECT = os.environ.get('MAIL_SUBJECT_HEMOGRAM')
MAIL_SENDER = os.environ.get('MAIL_SENDER_HEMOGRAM')

#AWS S3 config
AWS_ACCESS_KEY_ID = os.environ.get('AWS_ACCESS_KEY_ID')
AWS_SECRET_ACCESS_KEY = os.environ.get('AWS_SECRET_ACCESS_KEY')
AWS_STORAGE_BUCKET_NAME = os.environ.get('AWS_STORAGE_BUCKET_NAME')
S3_LOCATION = 'https://s3.amazonaws.com/{}'.format(AWS_STORAGE_BUCKET_NAME)
```

Figure 4.8: Configuration variables

### 4.2.2 Composition of Routes and Links

After the Hemogram application is initialized and configured, routes need to be set up so that the application knows what code to run for each Uniform Resource Locator (URL) request. In a flask, a special decorator function called a route() maps a URL request to the python function[43]. Figure 4.9 depicts a route to a login page

```
@main.route('/login')
def login():
    return render_template('main/login.html')
```

Figure 4.9: Login route

The route basically maps the URL request to the Python callable. To connect the application from one URL to another, I used a helper function called url\_for() to generate links for each webpage. For example, a URL link to the Hemogram login page can be defined by url\_for('main.login') function. This function returns the absolute URL link [http://hemogram.labmed.uw.edu/login] for the login page.

### 4.2.3 Application Structure and Requirements Files

As the Hemogram application started to become complex, it became quite evident to me to organize a file structure to make it more manageable. I wanted to organize the application into a smaller and reusable module by putting related files together. To organize files in modular form, Flask uses a concept of Blueprints. It helped me redistribute application code into several organized distinct components by putting related files together. Blueprints represent subsets of the application in a modular form and can include template filters, static files, templates and other utilities such as routes, form, etc. Figure 4.10 depicts the admin blueprint structure.

```

hemogram/
  admin/                                <-- blueprint module
    __init__.py                          <-- blueprint initialization
    forms.py                              <-- forms
    routes.py                             <-- routes handlers
  templates/
    admin/                                <-- admin templates
      add_user.html
      edit_user.html

```

Figure 4.10: Admin blueprint file structure

After refactoring application code based on their distinct function, I was able to modularize the application into five distinct blueprints.

1. Main Blueprint - This blueprint encapsulates the support for primary functions such as login, logout, account confirmation, etc.
2. Admin Blueprint - This blueprint handles administration related functions such as user registration, define a role to users, etc.
3. Lab Blueprint - Lab module handles functions such as adding patients, orders and samples. Analyzing PBS, generating laboratory results, display pending samples, etc. are also encapsulated by lab blueprint.
4. Users Blueprint - Functions that are specific to the users, for instance, user login or logout functions, are supported by this blueprint.
5. Errors Blueprint - There are times when certain errors will cause the application to fail. This module will provide support for error handlers.

#### 4.2.4 Flask extensions and libraries

As discussed in the previous chapter, the Flask framework only provides basic utilities to build an application. It does not provide intrinsic support for high-level functions such

as validating forms, authenticating users, or SQL queries. Applications can perform these high-level functions by using flask extensions and libraries. In the process of developing this application, I tested and picked extensions and libraries that worked best for the hemogram project. Table 4.2 lists all flask extension and libraries

Flask Libraries			
alembic	asn1crypto	bcrypt	bleach
blinker	boto3	botocore	certifi
cff	Click	cryptography	docutils
dominate	Flask	Flask-Bootstrap	Flask-Logging
Flask-Login	Flask-Mail	Flask-Markdown	Flask-Migrate
Flask-Moment	Flask-PageDown	Flask-SQLAlchemy	Flask-Testing
Flask-WTF	gunicorn	itsdangerous	Jinja2
jmespath	Mako	Markdown	MarkupSafe
paramiko	Pillow	psycpg2	psycpg2-binary
pyasn1	pycparser	PyNaCl	python-dateutil
python-editor	pytz	PyYAML	s3transfer
six	SQLAlchemy	tzlocal	urllib3
virtualenv	visitor	webencodings	Werkzeug
wincertstore	WTForms		

Table 4.2: List of imported libraries

### 4.3 Client Tier

From the Hemogram user's perspective, this is the most crucial part of the application. Client tier, also known as presentation tier, permits users to communicate with the other

two tiers of the hemogram application to perform their tasks. Keeping this connection as smooth as possible is one of Hemogram design principles. Various web-based technologies that offer seamless interaction between the users and the application are discussed in the section below.

#### *4.3.1 Templates*

Templates are used to separate codes between those two client and logic tiers. Templates are basically files that store the HTML codes and a placeholder for some dynamic content. A rendering function converts the template files into an HTML page. In Flask, a template engine called Jinja2 allows us to render web pages. As shown in figure 20, calling a `render_template()` function will trigger the Jinja2 template engine and render the filename given as its argument. Rendering a webpage that is visible to the user consists of parsing the Jinja2 code, inserting any dynamic content and creating HTML code[45].

#### *4.3.2 User Interface*

User Interface (UI) is a visual element of the application that defines how the user interacts with the application. Designing a UI for a web application from scratch requires an extensive amount of time. However, Bootstrap, a free and open-source CSS and JavaScript framework, provides an efficient way to create simple, attractive yet fully functional UI. Some of the Bootstrap interface elements used in Hemogram application are as follows -

1. Input Controls - Buttons, switch, dropdown lists, toggles, text fields
2. Informational Components - cards, icons, tables, Forms
3. Navigational Components - navbar, breadcrumb

## 4.4 Application Deployment

The final step of the development process is the deployment of the application. Deployment involves packing up the application and moving it to the live server to make the application available to its users.

In recent years, hosting applications on the cloud has gained a tremendous amount of popularity due to its flexibility, high scalability, manageability, and cost-effectiveness. Platform as a service (PaaS) is one of the cloud computing services that provide a fully managed platform on which applications can run. Through their services, an application can be deployed to the server with just a few lines of code[43].

### 4.4.1 Heroku

Heroku is one of the PaaS platforms to host a web application in the cloud. It is an ideal platform where applications need to be deployed often and quickly. Git, a source control management system, is used for pushing Hemogram code to Heroku. With git, it is very straightforward to continuously deploy the newer version of an application or to roll back to an earlier version, if the application did not perform as intended. Heroku also supports an add-on for PostgreSQL to back the Hemogram database. After setting up the application configuration variables on the Heroku environment, the deployment of the Hemogram application was just a few lines of code[46].

### 4.4.2 Amazon Simple Cloud Storage Service (Amazon S3)

Heroku provides an excellent platform to deploy an application with very minimal effort. But Heroku filesystem is ephemeral - that means we can make changes to the filesystem, but as soon as the server restarts, all changes are gone[47]. For this reason, Heroku is not an ideal solution to store images in their server. Since the Hemogram application holds many digital images of PBS, I needed a different platform that provides persistent storage. Amazon Web Services (AWS) provides a highly scalable and reliable storage solution called Simple Storage

Solution (S3)[48]. It provides unlimited online storage and is accessible through an internet connection, therefore I decided to use Amazon S3 to store and manage digital images for Hemogram application.

## Chapter 5

### LIMITATIONS OF THE HEMOGRAM APPLICATION

The Hemogram application was designed to support tele-hematology service to the resource-limited clinics in Nepal. This application provides key features to read PBS and generate a full laboratory report. However, the Hemogram application presented here is a proof of concept, and has limitations that are discussed below.

#### **5.1 Functional Limitation**

1. Manual Upload - Hemogram application does not have a machine-to-machine (M2M) interface capacity to upload digital images directly from CellaVision DM9600 to the server. Therefore, digital PBS images (regardless of the source) are manually uploaded to the server. This practice has the potential for a labeling error.
2. Lacks mobile optimization - Hemogram is a desktop application. Even though the best techniques have been implemented to provide an effective user interface to the application user, Hemogram does not provide functional properties and layout for small size devices like smartphones and tablets. Performing PBS evaluation requires action such as drag-n-drop and/or context menu. These actions are not available in small devices. Nevertheless, simple function such as result retrieval,login, logout can be performed in mobile devices.
3. Limited to one test - Currently, the Hemogram application can only handle the evaluation of PBS. With further research, more tests such as Bone Marrow (BM), Cerebral Spinal Fluid (CSF), and other Body Fluid (BF) slides evaluation could be added to the application.

4. Instrument limitation - Hemogram application was tested with PSB images generated by CellaVision image technology. Therefore, it is optimized to process images captured by CellaVision Instrument. In the past few years, smartphone camera technology has become so advanced that there could be a possibility of attaching a smartphone to a microscope to capture BC images and analyze them using the Hemogram application. However, to be able to process digital images of PBS from the non-CellaVision devices, it will require additional design and development of the application.
5. File lock not supported - Hemogram application does not support a file lock system to restrict a single user to evaluate a smear at a time. Without this feature, multiple users can concurrently analyze a smear from multiple locations. Thus, there is no way to prevent other users from editing and overwriting the content of the PBS report. This may lead to inconsistency in a laboratory report.

## **5.2 Compliance Limitation**

Data Protection Compliance - In the US, securing and protecting Patient Health Information (PHI) is an utmost priority for the healthcare organization. It is mandatory to comply with the legislation guidelines to keep PHI private and protected by following HIPAA standards. There are several layers of rules outlined by HIPAA that a business entity must comply with to protect the privacy and security of PHI. For a web application that stores and processes PHI must follow Technical Safeguards, Physical Safeguards and Administrative Safeguards rules outlined by HIPAA to make it compliant with these standards. The Technical Safeguards outline guidelines on access controls, audit controls, data integrity, authentication, and data transmission security. The Physical Safeguards state the guidelines of storage, maintenance and backup of the physical servers that stores the patient data. Finally, Administrative safeguards describe the policies and protocols that govern security measures[49].

Hemogram application is intended to process and store patient data but no measures were

taken to make this application HIPAA compliant. Therefore, additional work is required to make it HIPAA complaint.

### **5.3 System Limiation**

1. No Database Backup – Hemogram application stores a significant amount of data pertaining to users, patients, clinics, etc. No backup system has been configured to periodically backup the database. If the database system crashes, the application would lose all the data causing significant service interruption.
2. No Secure Sockets Layer (SSL) Certificate – SSL is an industry-standard security technology that initiates an encrypted link between the server and the web browser. SSL encrypts all the data that is being transferred through an application using public-key cryptography[43]. This adds a layer of protection to the web application. The hemogram application does not have an SSL certificate.

### **5.4 Reporting Limitation**

Reference Ranges – Reference Ranges, also known as “normal ranges” provide the range of values for a laboratory test in a healthy person[6]. These ranges are established by the local laboratories based on their population and it is a general practice to provide reference ranges with laboratory reports. In this project, I simply wanted to assess the viability of Hemogram application, I decided not to provide reference ranges with the laboratory report.

## Chapter 6

# APPLICATION WALKTHROUGH

In this chapter, I am going to walk you through the various sections of Hemogram application via screenshots. Throughout this project, I have adhered to the design principles of simplicity and consistency, to make an intuitive user interface to facilitate users with basic computer skills.

### 6.1 Login Page View

The contents of the Hemogram are private, thus accessible only to authorized users. Figure 6.1 displays the application's login page.

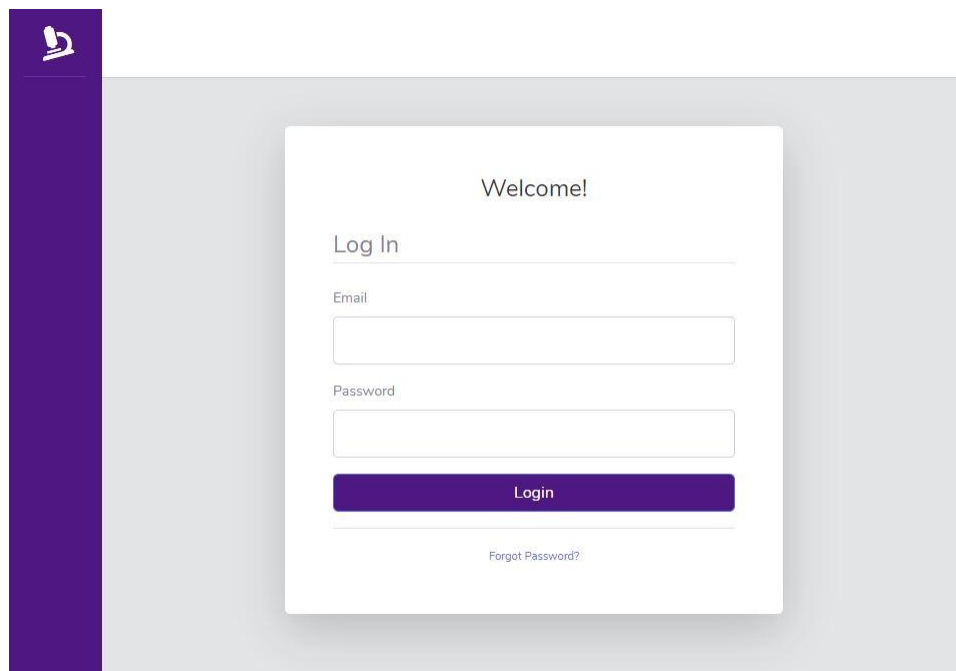


Figure 6.1: Login Page View

## 6.2 Dashboard View

After a successful login, users are routed to the dashboard page. The Dashboard provides current laboratory metrics such as the number of patients, samples, clinics, and smears. The dashboard also provides navigation menus to other sections of the application. Figure 6.2 illustrates the administrative dashboard page.

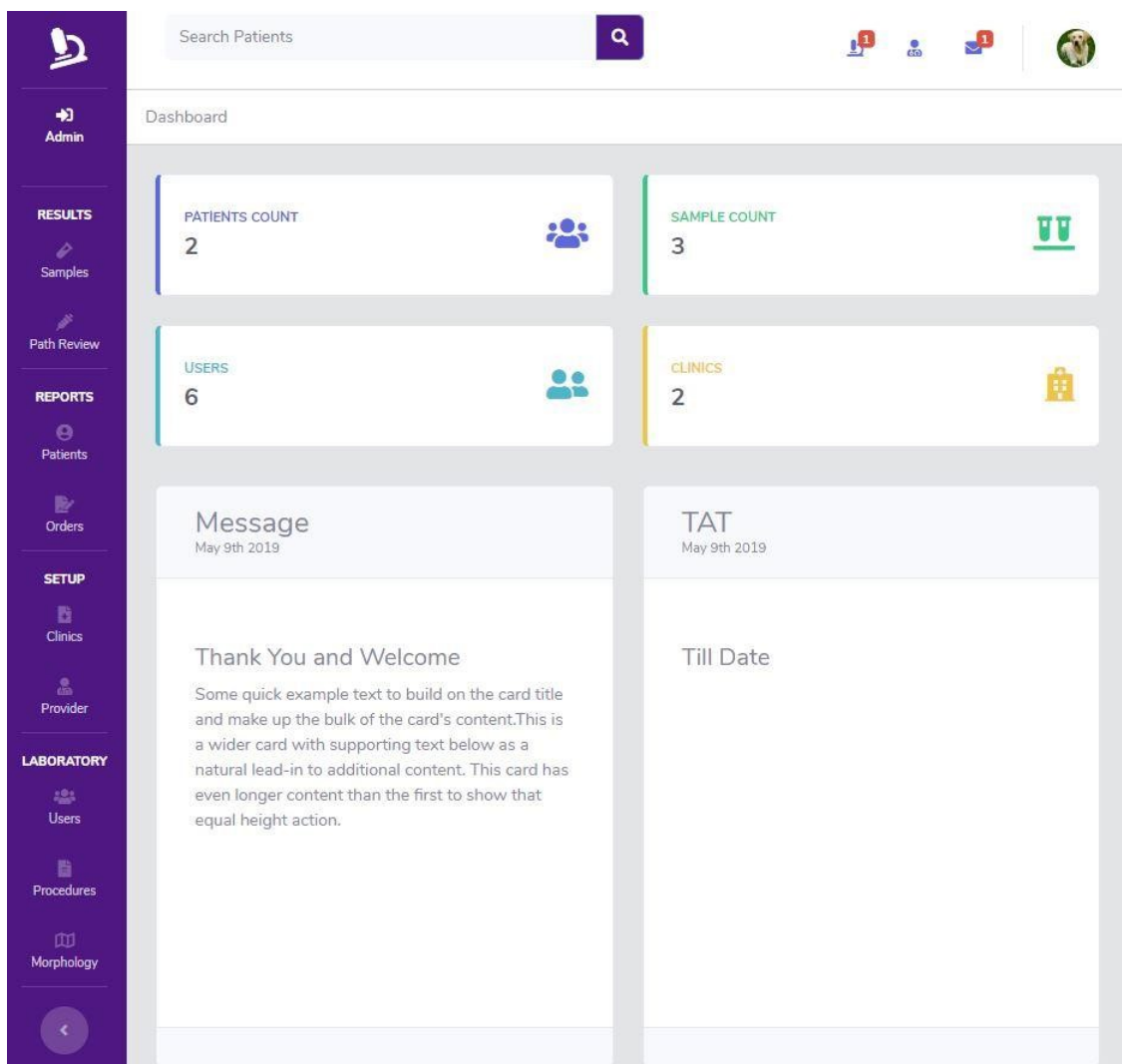


Figure 6.2: Admin Dashboard View

### 6.3 User Registration View

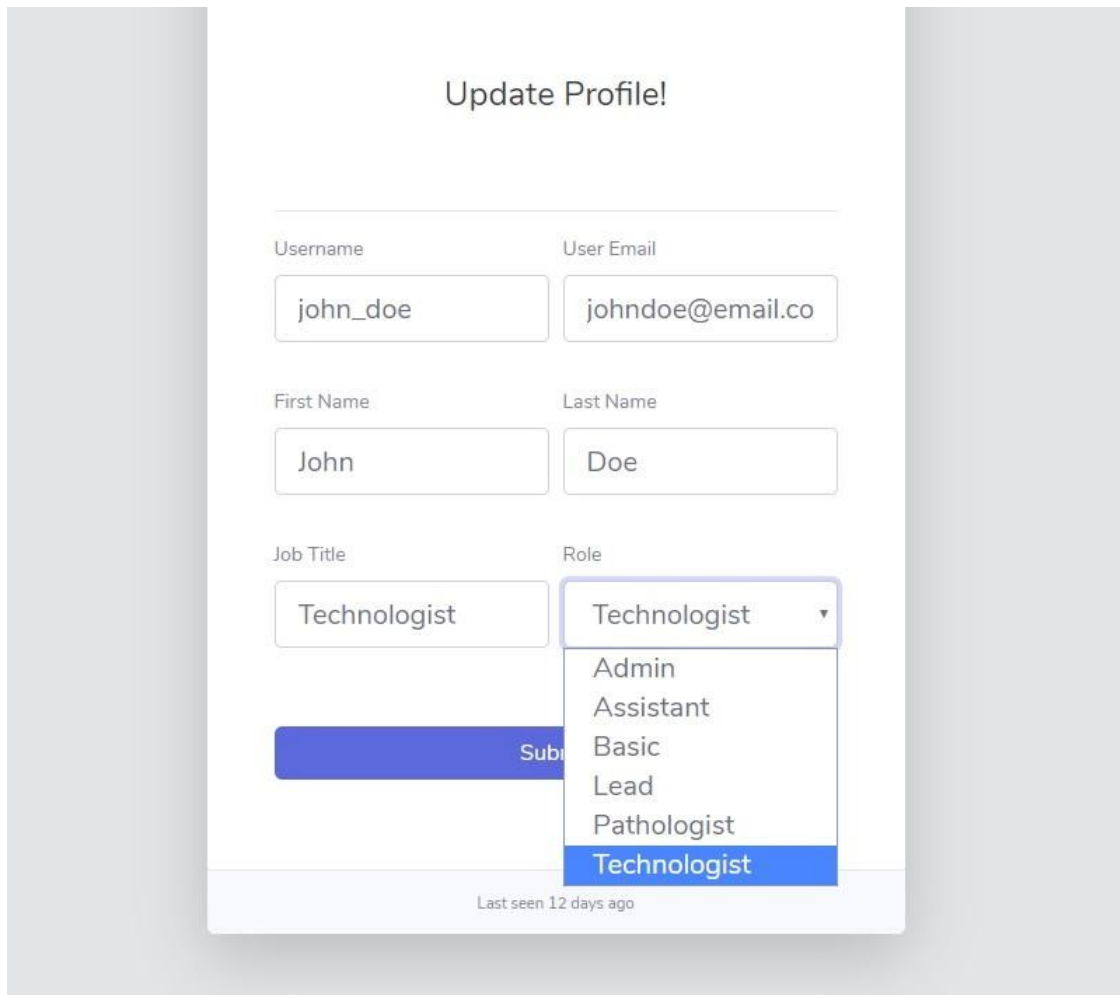
To protect patient data, the Hemogram application does not allow self-registration for new users. The administrator of the application has the privilege to add new users. Thus, this page is only accessible to the administrator. Figure 6.3 shows the new user registration page.

The screenshot displays the 'Add User' registration page. On the left is a vertical purple sidebar with icons and labels for various application sections: Admin, RESULTS (Samples, Path Review), REPORTS (Patients, Orders), SETUP (Clinics, Provider), and LABORATORY (Users, Procedures, Morphology). The main content area is white and contains a form titled 'User Information' with the heading 'Add User!' and the instruction 'Please enter all fields.' The form has five input fields: 'First Name', 'Last Name', 'User Email', 'Confirm User Email', and 'Job Title'. A purple 'Register' button is positioned at the bottom of the form. At the top of the page, there is a search bar labeled 'Search Patients' and a breadcrumb trail: 'Dashboard > Admin > Users > Add User.'

Figure 6.3: New User Registration Page

## 6.4 Role Assignment View

Role assignment grants users the least amount of privilege to perform their job. Administrators assign a role to users based on their job titles. Currently, there are six roles - basic, assistant, technologist, lead, pathologist, and admin. Figure 6.4 depicts how an admin can assign a role to a user from the dropdown select menu.



The screenshot displays a web form titled "Update Profile!". The form is organized into several sections:

- Username:** A text input field containing "john\_doe".
- User Email:** A text input field containing "johndoe@email.co".
- First Name:** A text input field containing "John".
- Last Name:** A text input field containing "Doe".
- Job Title:** A text input field containing "Technologist".
- Role:** A dropdown menu with "Technologist" selected. The dropdown list is open, showing the following options: Admin, Assistant, Basic, Lead, Pathologist, and Technologist. The "Technologist" option is highlighted with a blue background.

At the bottom of the form, there is a blue "Submit" button and a status indicator that reads "Last seen 12 days ago".

Figure 6.4: User's Role Assignment Page

## 6.5 Patient Profile View

The patient profile page provides the patient's demographic data. It also displays the patient's laboratory test history. Figure 6.5 shows a patient information page.

The screenshot displays a patient profile page with a purple sidebar on the left containing navigation options: Admin, RESULTS (Samples, Path Review), REPORTS (Patients, Orders), SETUP (Clinics, Provider), and LABORATORY (Users, Procedures, Morphology). The main content area shows the patient's profile for 'Patient One' (Patient ID: 1). The profile includes a search bar at the top, a breadcrumb trail (Dashboard > Patients > Patient One), and a grid of demographic and visit information. Below this is a table of laboratory orders.

AGE   DOB	GENDER
16Y   Dec-22nd-2002	Male

FIRST VISIT	LAB ORDER COUNT
a month ago   April 1, 2019	2

#	Order ID	Originate Date	Last Update	Clinic	Action
1	1	CREATED 2019-Apr-01 10:16	SMEAR_ANALYZED 2019-Apr-07 19:12	Clinic One	

Figure 6.5: Patient Profile Page

## 6.6 Patient List View

A full list of patients is displayed on this page. A search box is added to give users an option to query patients based on first name, last name, or date of birth. This page also allows

the user, if authorized, to access the detailed information or to add new laboratory testing. Figure 6.6 depicts the patients' list page.

Dashboard > Patients

**Patients**
+

Show  entries
Search:

	Patient ID	Full Name	DOB	Age	Gender	Registration Date
<div style="display: flex; flex-direction: column; gap: 5px;"> <span style="background-color: #007bff; color: white; padding: 2px 5px; border-radius: 4px;">👁</span> <span style="background-color: #28a745; color: white; padding: 2px 5px; border-radius: 4px;">+</span> </div>	1	Patient O One	Sunday 22. December 2002	16Y	MALE	Apr 1st 2019
<div style="display: flex; flex-direction: column; gap: 5px;"> <span style="background-color: #007bff; color: white; padding: 2px 5px; border-radius: 4px;">👁</span> <span style="background-color: #28a745; color: white; padding: 2px 5px; border-radius: 4px;">+</span> </div>	2	Patient T Two	Friday 05. May 1995	24Y	FEMALE	Apr 7th 2019
	Patient ID	Full Name	DOB	Age	Gender	Registration Date

Showing 1 to 2 of 2 entries

Previous
1
Next

Figure 6.6: Patients List View

## 6.7 Clinic Profile View

The clinic profile page provides detailed information about the clinics who are registered to the Hemogram application. This page also lists all the patients who are currently being treated at the clinic and have PBS evaluation done through hemogram. Figure 6.7 shows the clinic's detail information.

The screenshot displays the 'Clinic Profile View' for 'Clinic One'. The interface includes a purple sidebar with navigation options: Admin, RESULTS (Samples, Path Review), REPORTS (Patients, Orders), SETUP (Clinics, Provider), and LABORATORY (Users, Procedures, Morphology). The main content area shows the clinic's name, a contact person info section, and two summary cards: 'PATIENT COUNT' (1) and 'ORDER COUNT' (2). Below these is a table listing patient information.

#	Patient ID	Patient Full Name	Age	Birth Date	View Detail
1	1	Patient O One	16Y	Dec-22nd-2002	

Figure 6.7: Clinic Profile View

## 6.8 New Test Order View

Once the patient is registered to the Hemogram application, a new test can be added to the patient record. Figure 6.8 displays a screenshot of a new test. Currently, Hemogram application can only accept a Complete Blood Count with differential (CBD) test.

The screenshot shows the 'New Order' form for Patient One. The patient information is 16Y | Dec-22nd-2020 | MALE. The form contains the following fields:

- Order Location:** CONE
- Provider:** Doctor Smith
- Fluid Type:** Whole blood
- Order Name:** CBD
- Comment:** (Empty text box)
- Action:** Add Order (Purple button)

The left sidebar contains navigation options: Admin, RESULTS (Samples, Path Review), REPORTS (Patients, Orders), SETUP (Clinics, Provider), and LABORATORY (Users, Procedures). The top navigation bar shows the breadcrumb: Dashboard > Patients > Patient One > Create Order Req.

Figure 6.8: Add a new PBS test

## 6.9 Pending Alert View

The pending alert displays the current number of PBS that are yet to be analyzed by the laboratory professionals. The alert function makes an asynchronous call to the database at a regular interval. Therefore, the user always sees the most recent PBS pending status without refreshing the web browser. Figure 6.9 shows the location of the alert box in the navigation bar of the application. The navigation bar is visible in all pages of the Hemogram application. A mouse click on the pending alert will provide additional information about the current pending status and a URL link to the pending PBS list. Figure 6.10 displays

the additional information box on the mouse click.

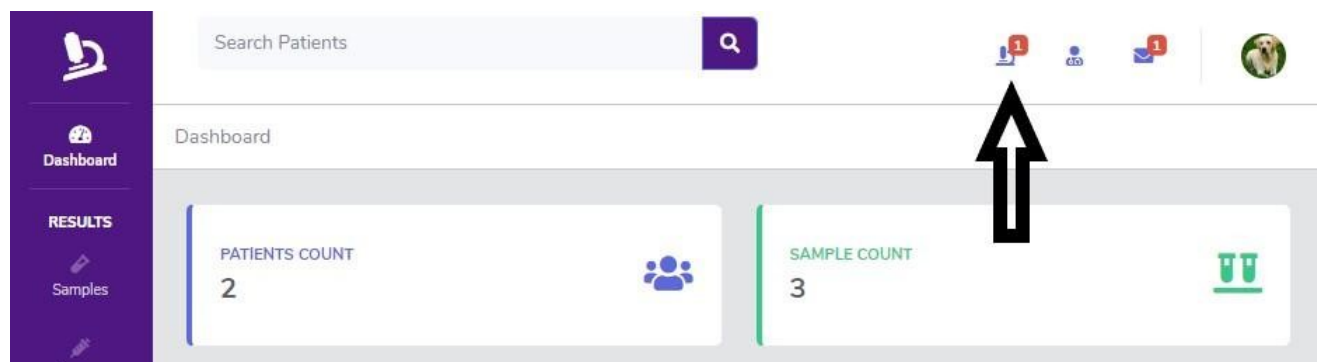


Figure 6.9: Pending alert on the navigation bar

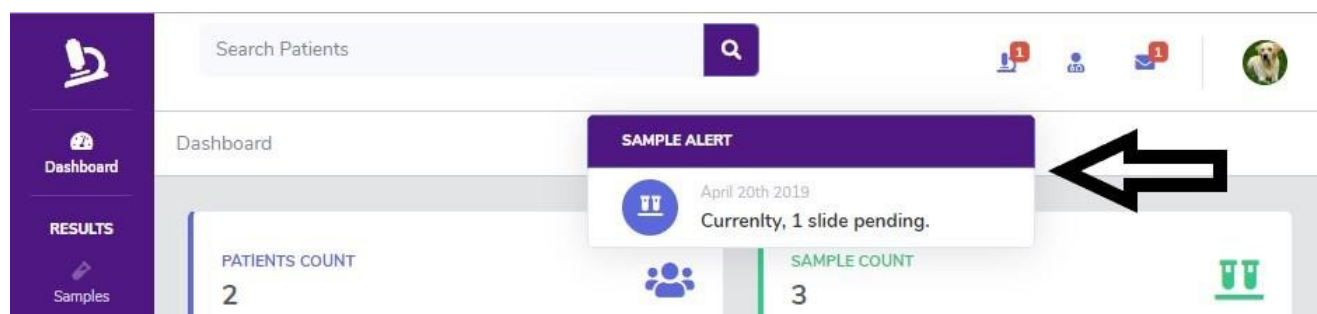


Figure 6.10: Additional information on mouse click

### ***6.10 PBS Evaluation and Final Report View***

The primary function of the Hemogram application is evaluating PBS and generating a final report on it. PBS evaluation is a three-step process.

### 6.10.1 Classification of WBC

The first step in the PBS evaluation is the classification of the WBC. Generally, 100 to 115 images of WBCs are displayed on the screen. Initially, all images are classified as unidentified cells. Figure 6.11 displays the WBC classification page. Technologists can use two different

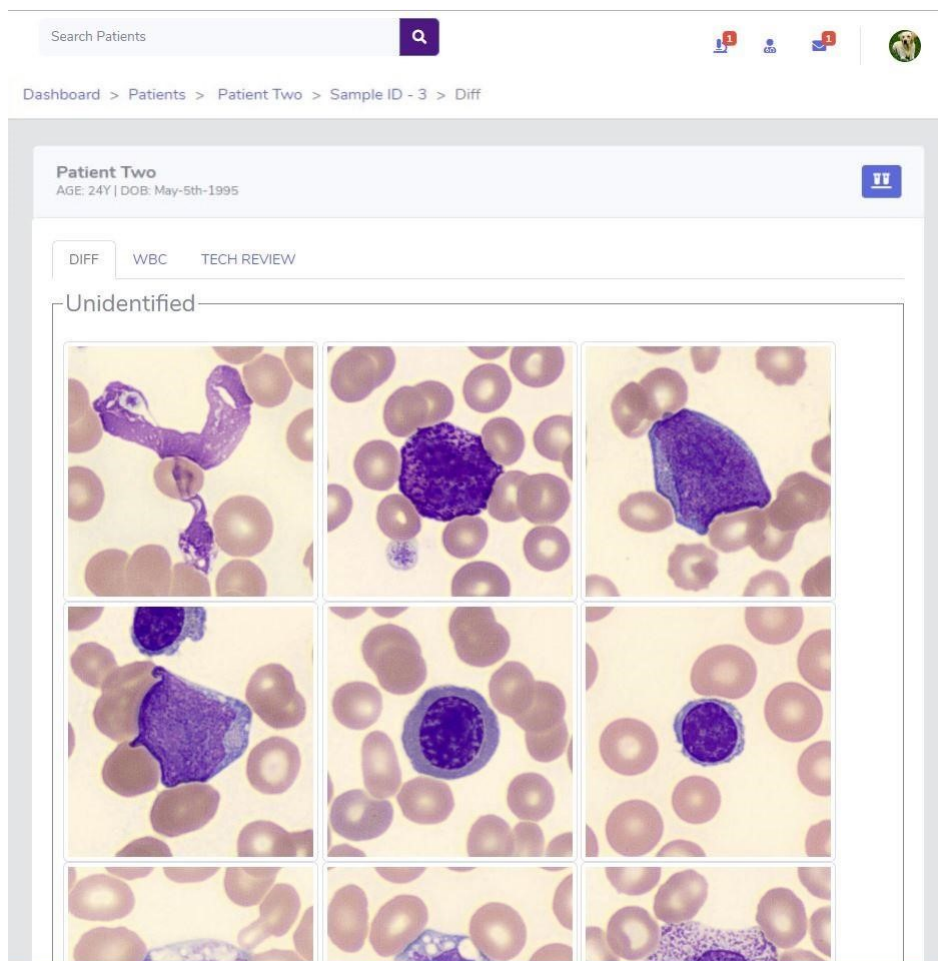


Figure 6.11: WBC classification page

UI configurations to classify these WBCs. The following section briefly describes the two different ways to classify cells.

### 6.10.1.1 Context Menu

The context menu is a special type of Graphical User Interface (GUI) menu that is visible when the user activates it. The right-click of the mouse is an example of a context menu. In the Hemogram application, a context menu is activated by right-clicking on the mouse while hovering over the image of the WBC. When activated, all possible options are displayed for users to select. After the selection is made, the image of the WBC moves to the selected WBC box and the database is updated asynchronously with the new WBC class. Figure 6.12 displays an activate context menu.

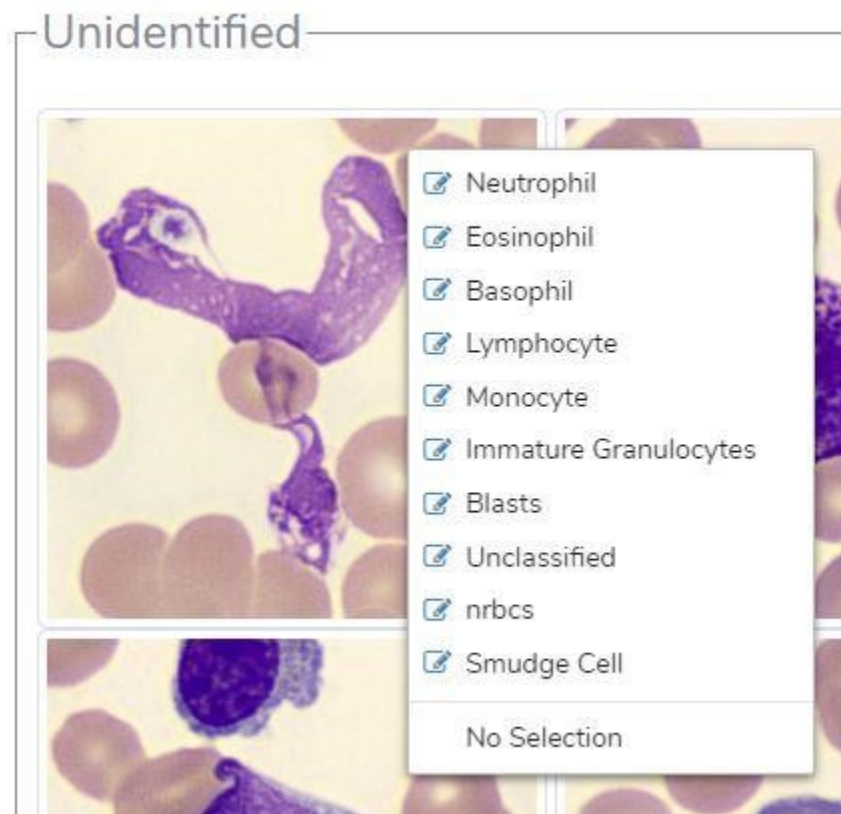


Figure 6.12: Activated context menu

### 6.10.1.2 Drag and Drop

Another way to classify the images of WBCs is by drag and drop function. The user can simply drag an image of WBC and drop it on a predefined WBC class. Figure 6.13 shows the WBC dragged from an unidentified class to the Neutrophil class. After the image is dropped the database is updated asynchronously.

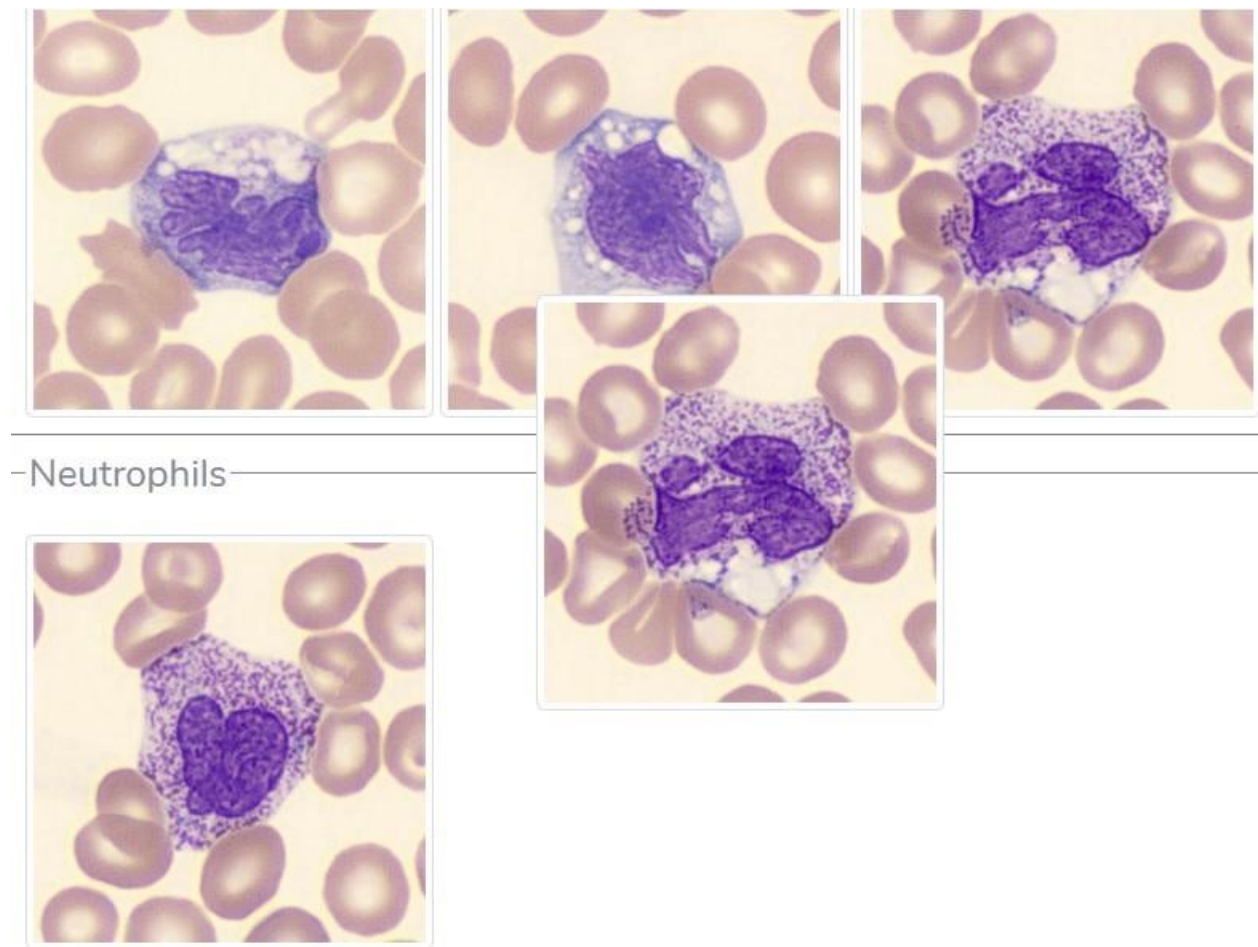


Figure 6.13: Drag and drop for WBC classification

### 6.10.2 Morphological Evaluation

After all the images of WBC are classified, the second step in the process of PBS evaluation is selection the morphological findings. Morphological findings listed on Hemogram application are based on clinical significance and can be customized as needed. Figure 6.14 displays a switch for different WBC morphologies. The user can select all possible findings by using bootstrap switch functions. When the switch is clicked, the morphological finding is recorded on the database asynchronously.

DIFF	WBC	TECH REVIEW
<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/> Auer Rods
<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/> Blasts
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Dohle Bodies
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Hyper-segmented Neutrophils
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Hypo-granulated Neutrophils
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Hypo-segmented Neutrophils
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Immature Granulocytes
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Increased Bands
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Neoplastic Lymphocytes
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> No Neutrophil
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> No Significant Morphology
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Nucleated Red Blood Cells
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Platelet Satellitism
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Reactive Lymphocytes
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Smear to be reviewed by Pathologist
<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/> Toxic Granulation

Figure 6.14: Morphology switches

### 6.10.3 Final Review of the PBS Evaluation

The final step in the PBS evaluation is the review of the report. This step allows the laboratory professionals to review the report before it is finalized. If the WBC classification or the morphological evaluation is incomplete, the application will not allow the user to finalize the report. Figure 6.15 shows a warning if steps 1 and 2 are incomplete.

The screenshot shows a laboratory report interface with three tabs: DIFF, WBC, and TECH REVIEW. The WBC tab is active, displaying the following values:

- CBC -
- WBC -  $6.98 \times 10^3 / \mu\text{L}$
- RBC -  $4.5 \times 10^6 / \mu\text{L}$
- HGB - 14.2 g/dL
- HCT - 41 %
- MCV - 91 fL
- MCH - 32.0 pg
- MCHC - 35 g/dL
- PLT -  $350 \times 10^3 / \mu\text{L}$

Below the WBC tab, there are three columns of data with warning flags:

- DIFF - Absolute:** unidentified cells present, please finish diff. A black arrow points to this text.
- DIFF - Relative:** (Empty)
- Morphology -** No morph selected. A black arrow points to this text.

A purple button labeled "Validate" is located at the bottom right of the interface.

Figure 6.15: Incomplete report with flags

After the completion of step 1 and 2 in PBS evaluation, a summary of the report is displayed for the users to verify the report. Figure 6.16 displays a complete report that can be finalized by clicking on validate button.

### 6.10.4 PBS Evaluation Report

After the PBS evaluation is finalized by the laboratory professionals. The report is now available for clinicians to view. Figure 6.17 depicts the report visible to the clinicians.

DIFF	WBC	TECH REVIEW	
CBC -			
WBC - $6.98 \times 10^3 / \mu\text{L}$		DIFF - Absolute	DIFF - Relative
RBC - $4.5 \times 10^6 / \mu\text{L}$		neutrophils--1.55	neutrophils--22.22%
HGB - 14.2 g / dL		lymphocytes--0.78	lymphocytes--11.11%
HCT - 41 %		monocytes--1.55	monocytes--22.22%
MCV - 91 fL		basophils--0.78	basophils--11.11%
MCH - 32.0 pg		eosinophils--0.00	eosinophils--0.00%
MCHC - 35 g/dL		* immature_granulocytes--0.78	* immature_granulocytes--11.11%
PLT - $350 \times 10^3 / \mu\text{L}$		* blasts--1.55	* blasts--22.22%
		* nrbc--0.78	* nrbc--11.11%
			Morphology -
			Blasts Present
			Nucleated Red Blood Cells Present
			Toxic Granulation Present
			<a href="#">Validate</a>

Figure 6.16: Final review page before validation



Sample ID: 1		Complete  	
<b>Patient One</b>			
Patient ID: 1			
Age: 16Y	DOB: Dec-22nd-2002	Gender: Male	
Received Date: Apr-01-2019 17:17	Status: Completed	Completed Date: Apr-08-2019 02:12	Completed By: 1
Hemogram	Results	Reference Range	Flags
WBC	10.2 X 10 <sup>3</sup> / uL		
RBC	4.0 X 10 <sup>6</sup> / uL		
HGB	13.1 g / dL		
HCT	35 %		
MCV	88 fL		
MCH	33.0 pg		
MCHC	37 g/dL		
PLT	300 X 10 <sup>3</sup> / uL		
Differentials			
% Neutrophils	65%		
% Lymphocytes	18%		
% Monocytes	6%		
% Basophils	12%		
% Eosinophils	0%		
Neutrophils	6.63 X 10 <sup>3</sup> / uL		
Lymphocytes	1.84 X 10 <sup>3</sup> / uL		
Monocytes	0.61 X 10 <sup>3</sup> / uL		
Basophils	1.22 X 10 <sup>3</sup> / uL		
Eosinophils	0.0 X 10 <sup>3</sup> / uL		
Morphology			
WBC Morphology	No Significant Morphology		

Figure 6.17: Final PBS evaluation report

## Chapter 7

### CONCLUSION AND FUTURE WORK

In this chapter, I am going to summarize the design and development process of the Hemogram application and layout some perspective points for future work.

#### **7.1 Conclusion**

With recent advancements in information technology, telepathology is becoming part of the regular laboratory medicine system in developed countries. The implication of such technology in the field of hematology can have a higher degree of signification in reducing the barrier to laboratory service in the resource-limited clinics in developing countries. In resource-limited clinics where clinicians do not have the luxury to order advanced molecular testing, evaluation of PBS can provide information with significant diagnostic value to their patients. Despite being simple, it is a time-consuming manual test that requires highly trained laboratory professionals. Hemogram was designed and developed with the premise of providing a remote evaluation of PBS service to the resource-limited clinics in Nepal.

In order to design the Hemogram application, an enormous amount of time was spent to carefully evaluate its potential users and the functional requirements. Simplicity and consistency have been the core design principle to facilitate users with different levels of computer skills. The development process was divided into three phases to carefully study the system architecture required to build a web application. Powerful programming technologies such as Flask for logic tier and PostgreSQL for database tier are used to provide robustness and functionality to the application. JavaScript, Ajax, and jQuery were used to create and control the dynamic content of the application while HTML, CSS, and Bootstrap were used for rendering the pages.

## **7.2 Looking Forward**

In this project, I designed and developed a proof-of-concept web application, Hemogram, with essential functions to remotely evaluate PBS. Other functions such as SSL certificate, data encryption, load balancing etc., can be added to make the application more secure and robust. Real-world implementation of this application can play a significant role in the field of tele-hematology in providing continuous hematology support to resource-limited clinics in Nepal.

While the aim of the project was to build a platform for remote evaluation of PBS, I do believe that this platform is admissible to other possibilities as well. With further testing and customization of the Hemogram, I believe the application can be used for the online training of laboratory professionals in developing countries to bridge the disparity gap in hematology training and education. Additionally, Hemogram's blood cells image dataset can be used to train a machine-learning algorithm to create a pattern recognition model, which can automate the identification of blood cells and alleviate the laboratory professional shortage in developing countries. Despite many possibilities of Hemogram, there are telemedicine and informatics challenges such as patient data protection, regulations, liabilities, and costs that also need to be addressed before implementing.

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