User Manual for LIBRA

1) Build and Run

This section explains the procedure of building and deploying LIBRA from the github source files.

There will be many code snippets that explain the building process. Each snippet has the following format:

- First the github repository has to be obtained.

```
$ git clone https://github.com/projectlibra/projectlibra.git
```

- Once you clone the repository, you will encounter a file structure like the following:

```
/projectlibra
├── README.md
├── libra-backend
└── libra-frontend
```

Building the Client

The client is written in React JS and the build procedure is fairly simple.

Install React JS

If React JS is not currently installed on your system, we consult you to the official React JS documentation for the installation process.

Install dependencies

You can install all dependencies required for the client using the following snippet:

```
$ cd libra-frontend
$ npm install
```

Setting up the HOST IP

You must change the host IP embedded in the file **host.js** for the backend server that you are running:

```
var host = 'Backend Server IP:PORT'
```

Running the client

You can run the client via npm and the landing page will be displayed in the default browser:

```
$ npm start
```

Building the Server

Since the server has many dependencies in Python, we suggest using a virtual environment:

```
$ pip install virtualenv
$ virtualenv libra
$ source libra/bin/activate
# For deactivating virtualenv
$ deactivate
```

Installing dependencies

```
$ cd libra-backend
$ pip install -r requirements.txt
```

Setting up a PostgreSQL Server

We consult you to PostgreSQL server setup tutorial from digitalocean.

After the setup, the configuration line under **app.py** has to be changed with the following information:

```
postgres://user_name:password@db_server_ip:port/db_name
```

Setting up SnpEff

We consult you to SnpEff installation manual

In addition to the installation procedure, we need GRCh38.86 database.

```
$ java -jar snpEff.jar download -v GRCh38.86
```

Running the Server

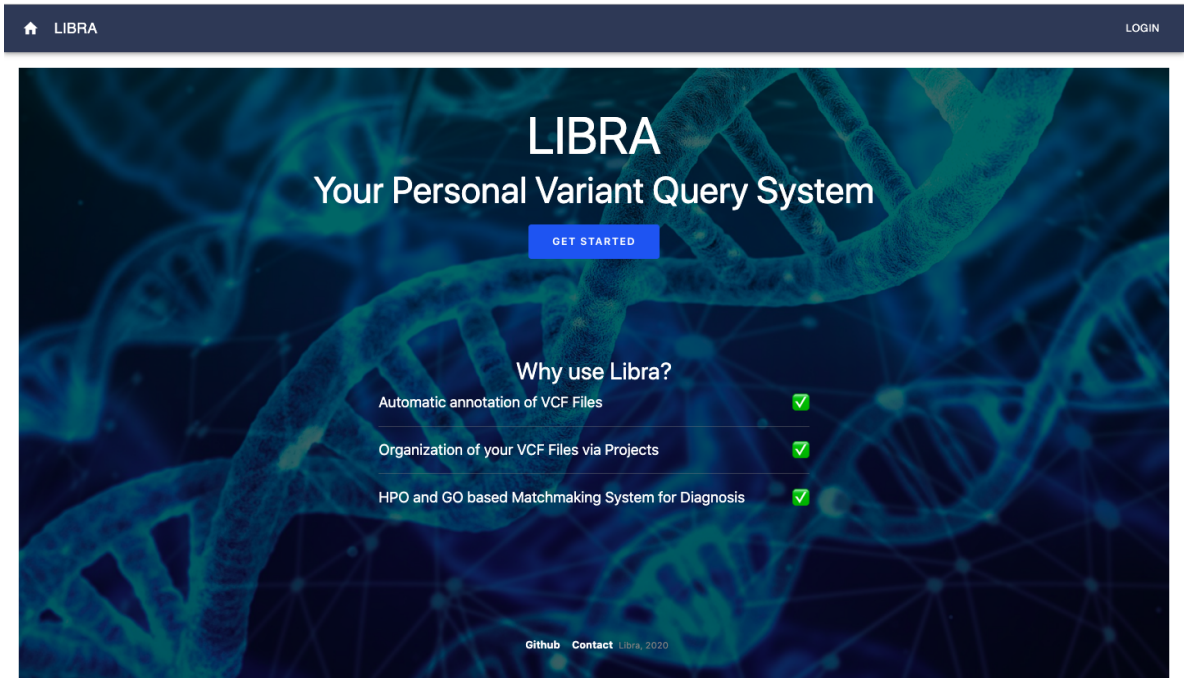
The following will run the back-end server with the specified **PORT** on the server's IP address accepting all connections.

```
$ cd libra-backend
$ flask run --host 0.0.0.0 --port PORT
```

2) Usage of LIBRA: Registration and Profile

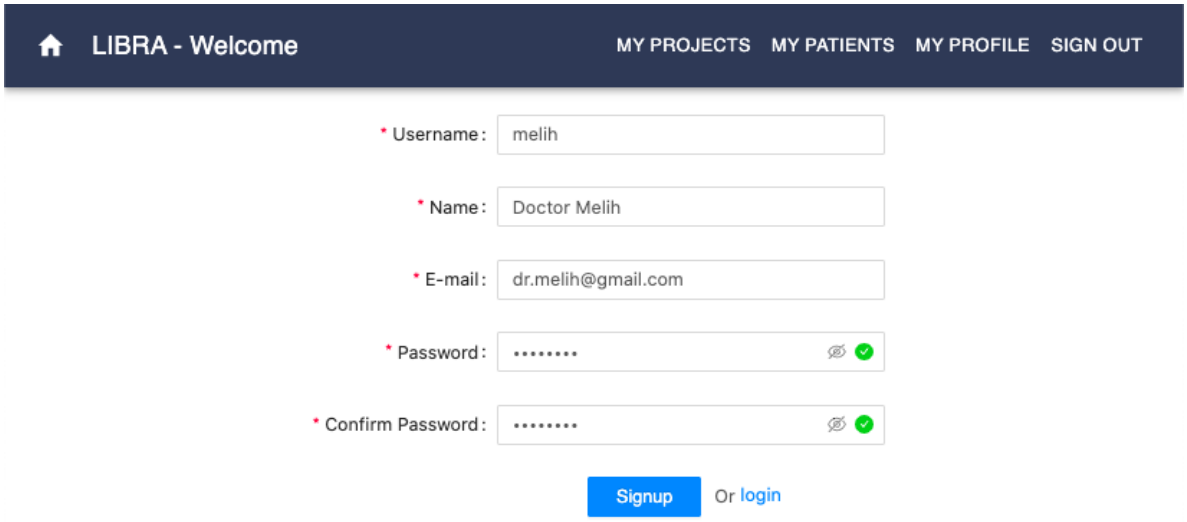
Homepage

This is the landing page potential users will be greeted with when they click on our website on a web browser. Visitors can proceed to sign up by pressing the Get Started button in the center.



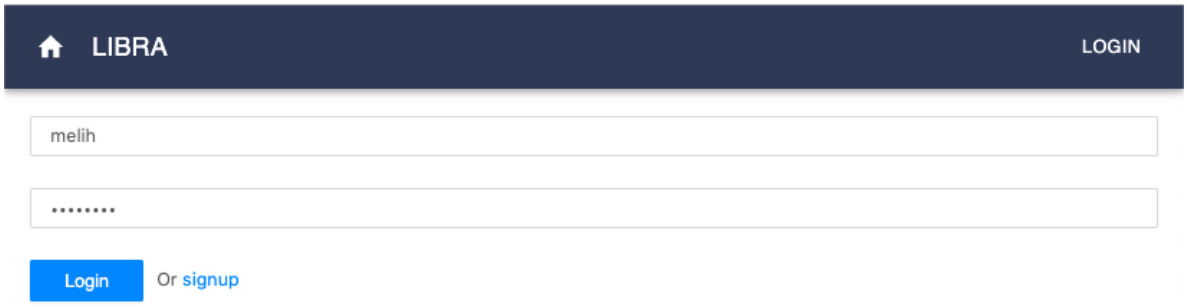
Sign Up

In this page, to create a new users visitors will have to fill in the required input fields. These fields are username, name, email address, password and password confirmation. After clicking sign up, users will be redirected to the index page to login their accounts.



Login

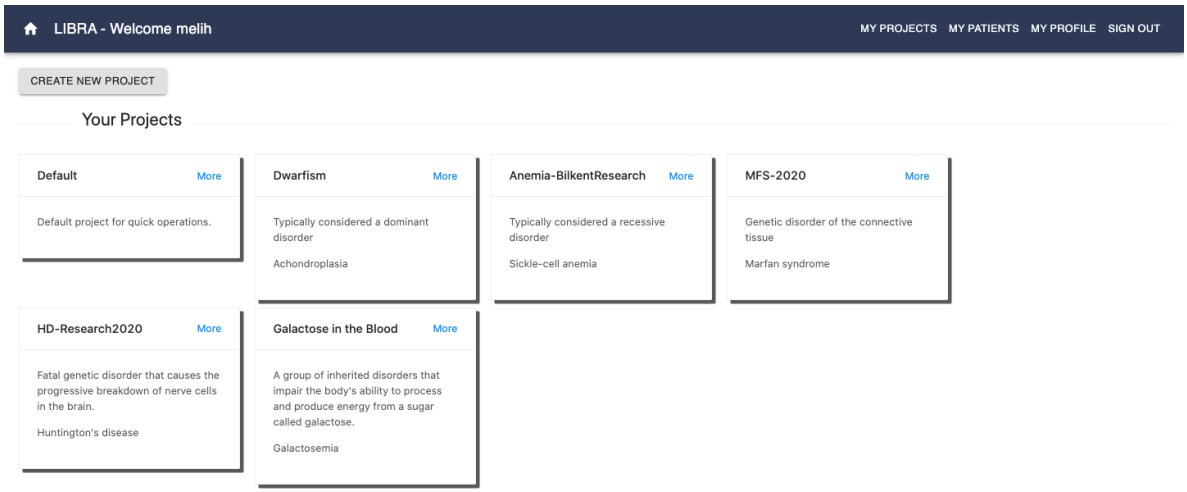
In this page visitors will be presented with two options: If the visitor has an account they can proceed to log in by entering their username and password or if they do not have an account they can choose to create one by clicking on the sign up button.



3) Usage of LIBRA: VCF Upload, Annotation and Filtering

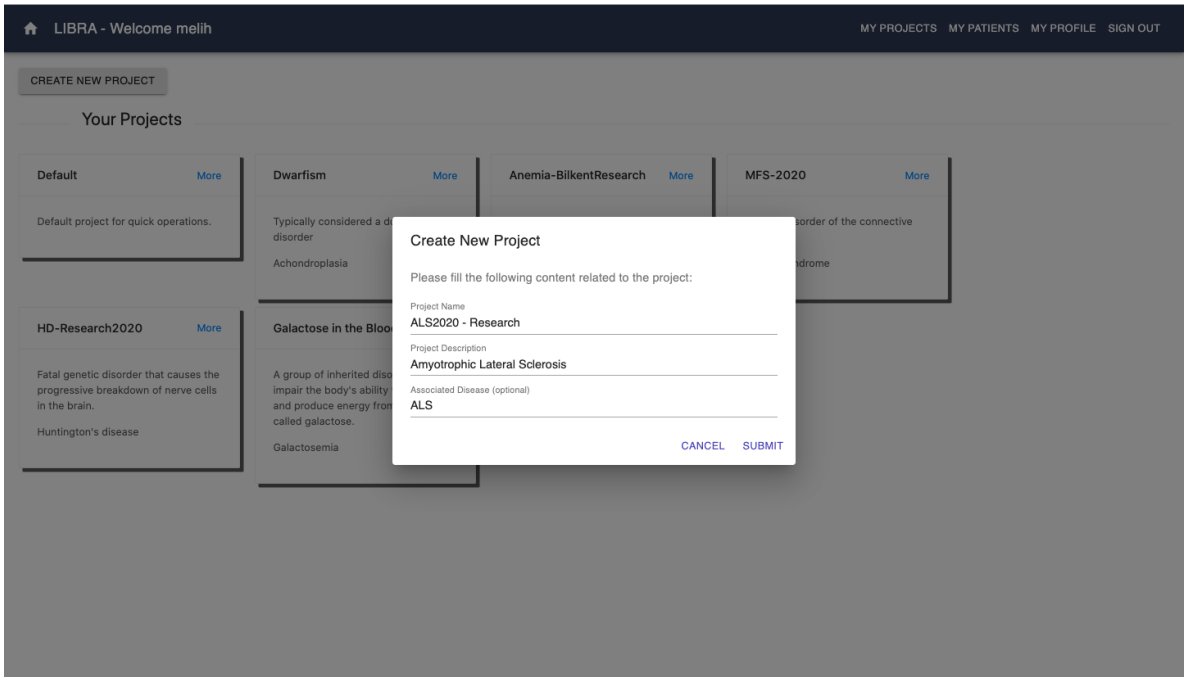
My Projects

After logging in, users will be directed to the projects page. In this page they will have one project by default for quick start on a random project. Additionally, users can create their custom projects.



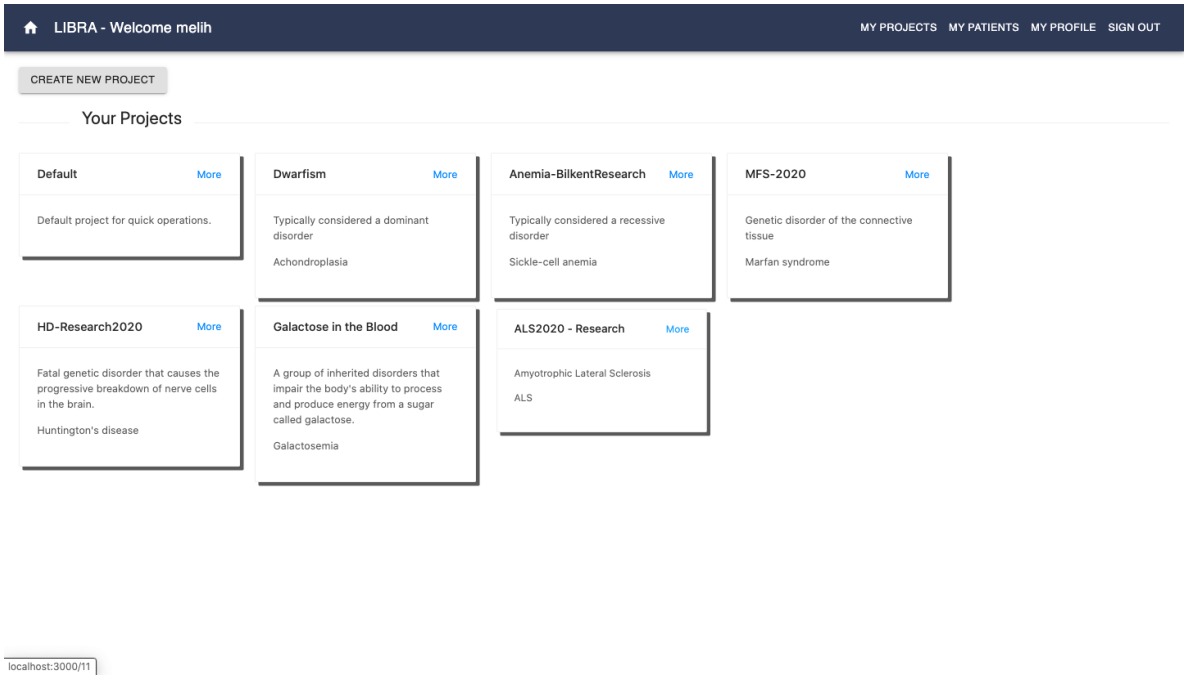
Create a New Project

When the users press the "CREATE NEW PROJECT" button, a dialog will pop up which will ask the user to fill in the Project Name, Project Description and optionally the disease associated with the project.



Project Details

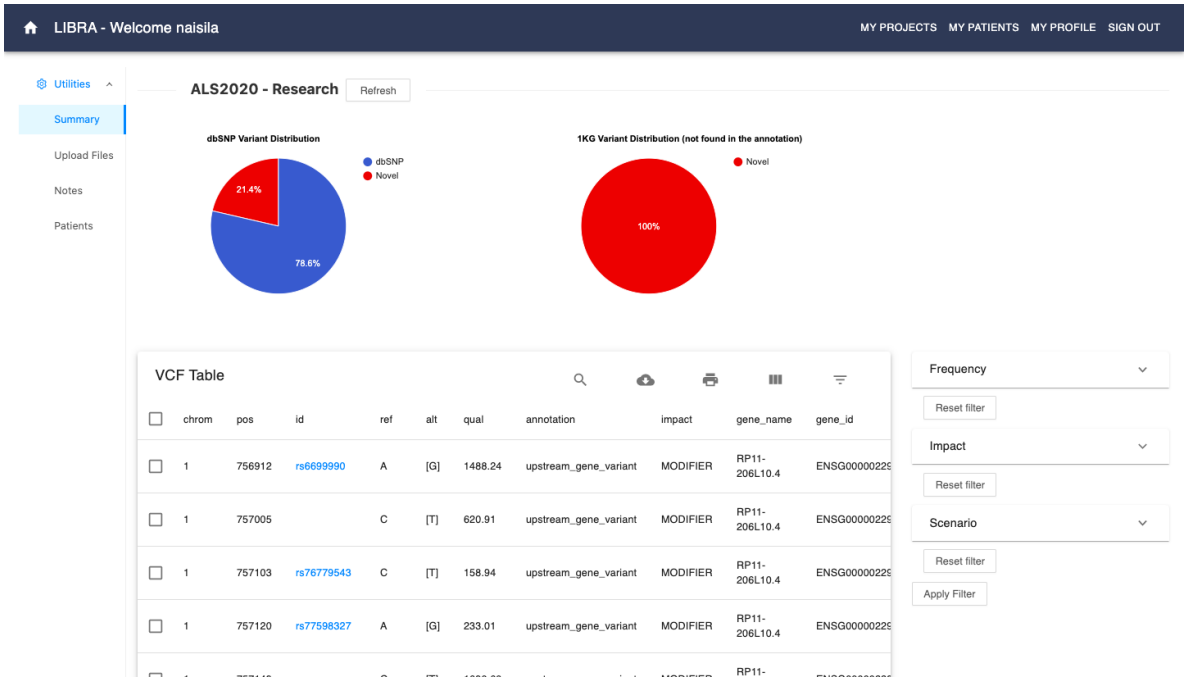
By clicking "More" at the top right corner of the project box, the user can redirect to project details page. On the right side of this page, there is a menu that contains summary, upload, notes and patients items.



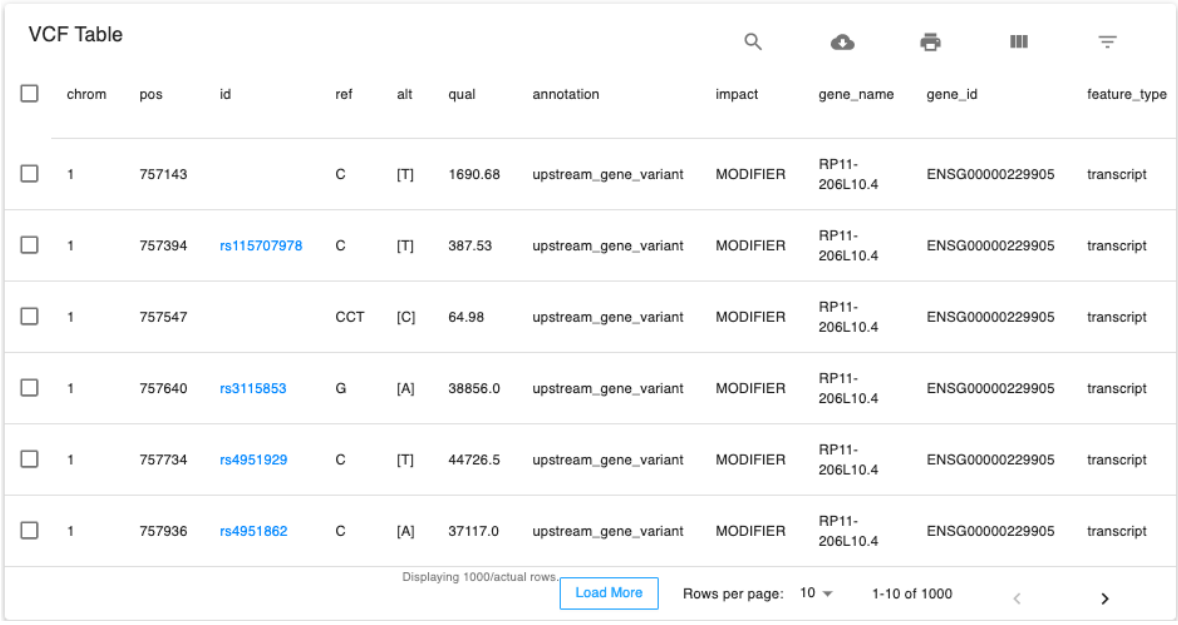
localhost:3000/11

Project summary

User is redirected to this page after clicking on a specific project on the "Projects Page." User will first be presented the VCF table. If there are no VCF files uploaded to the project instead of seeing the VCF table the user will see "You haven't uploaded any files yet." If there is a VCF file uploaded to the project, however, they will see two pie charts indicating the presence of variants in the 1000 Genomes and dbsnp databases, the annotated VCF file presented in a table and a filter to select certain tuples of the VCF table based on frequency, scenario and impact of the variants, as shown in the following image:

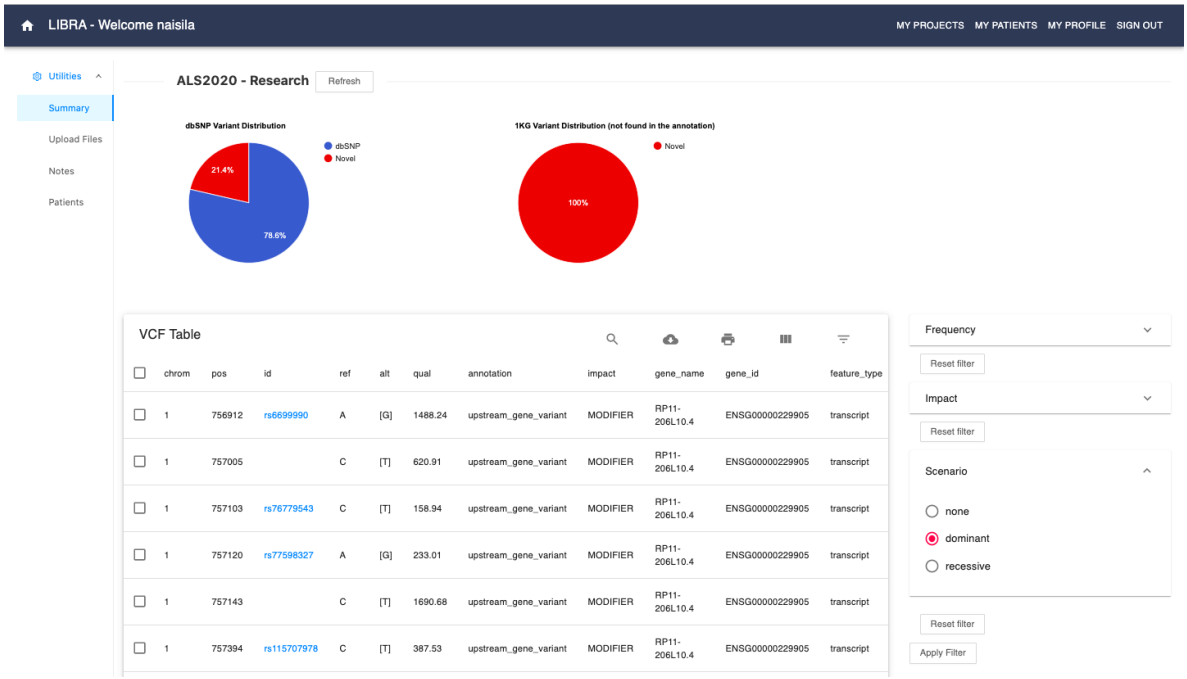


Because of the immense size of VCF files, initially only 1000 elements of the table will be uploaded to the UI. The user can select to add another 1000 tuples to UI table by pressing on the "Load More" button. They can repeat this operation as many times as they want until the entire file is uploaded to the UI.

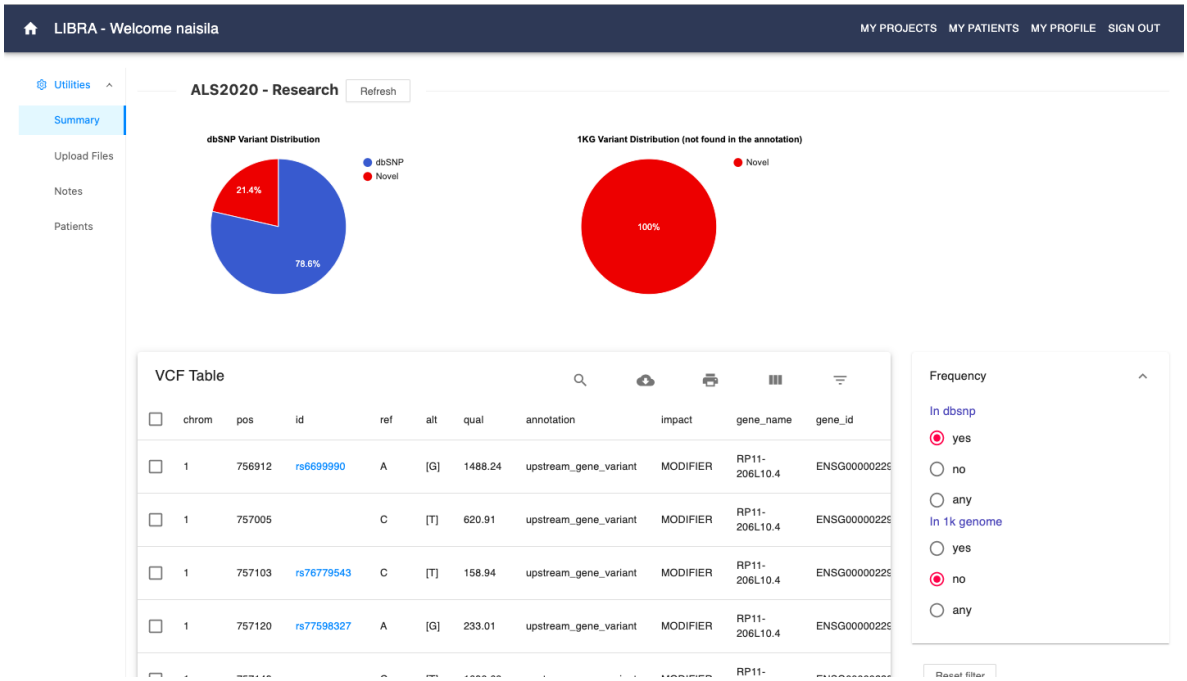


To the left of the VCF table there are three filters. These filters are scenario, frequency and impact filters. Users can select the options presented in the filters and when they are done selecting the options they can press on the "Apply Filters" button to view tuples on the VCF table that fit into the selected options.

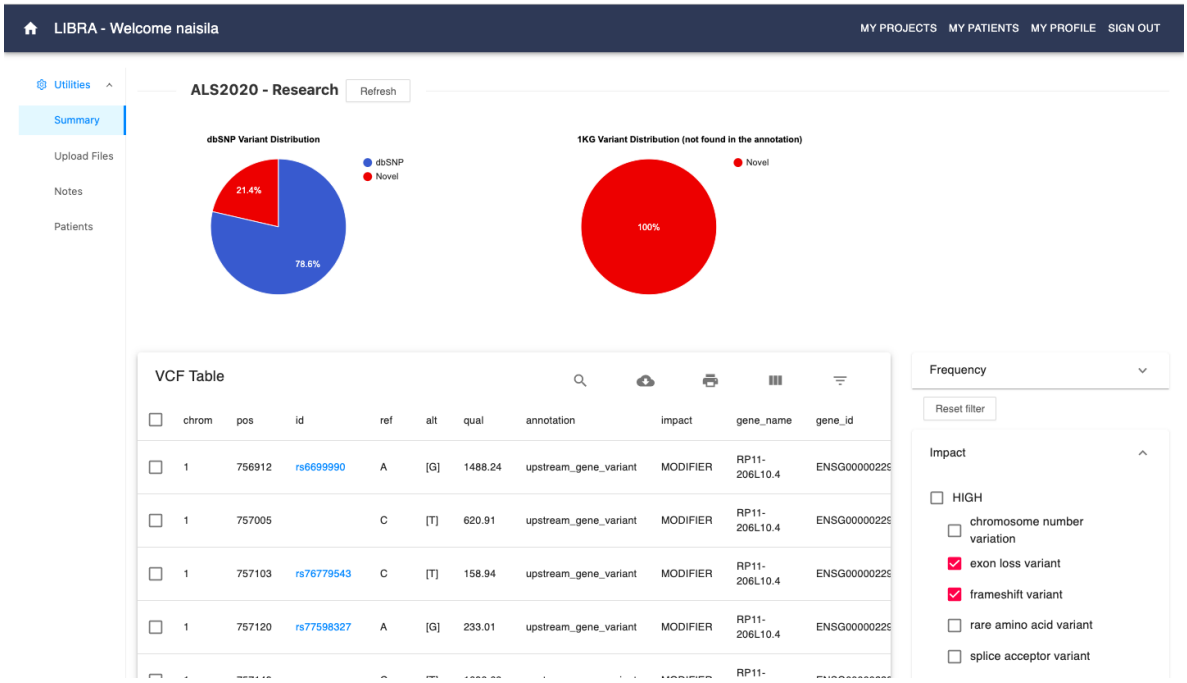
The scenario filters select dominant or recessive variants.



Frequency filter selects tuples in dbsnp or 1k Genome database.



Impact filters select tuples with high, moderate, low or modifier putative impacts.



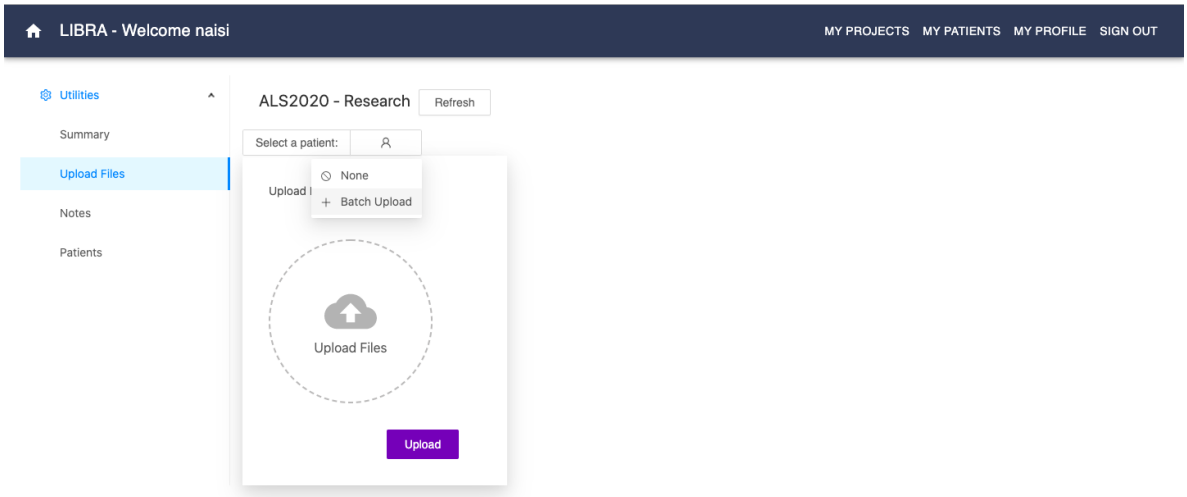
Scenario and frequency filters are radio button groups, so, the user will be able to only pick one of the options presented there for each filter. Impact filter is a checkbox group, so, the user can select a combination of the impacts.

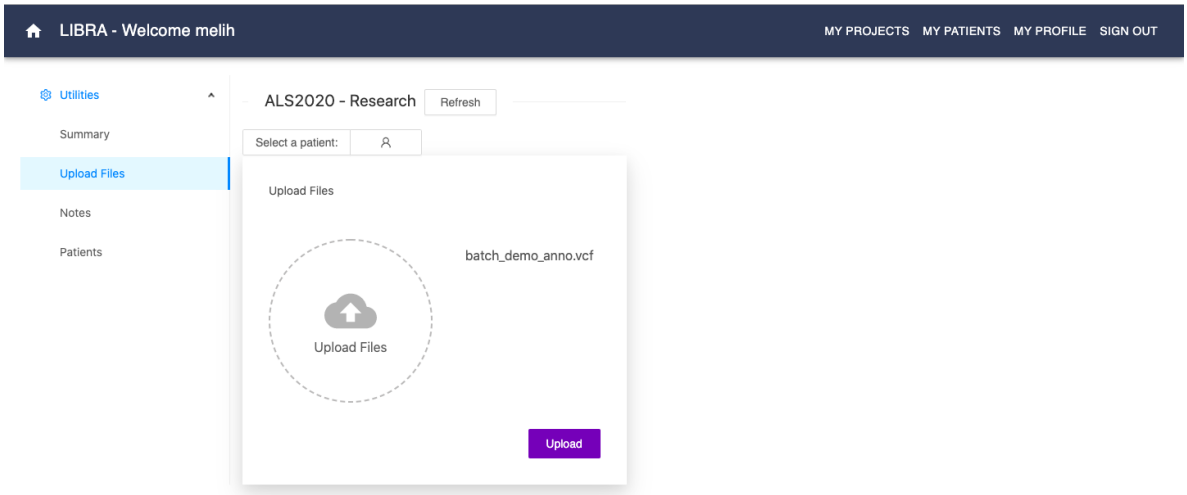
VCF upload

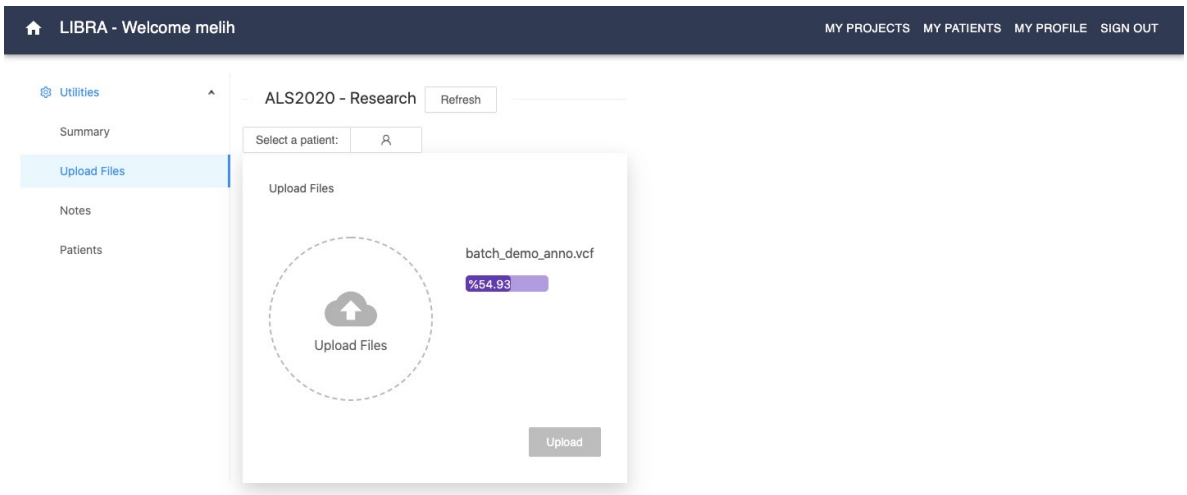
This page is where the user uploads the VCF files. On the top of the page there is a dropdown menu that has the options none, batch upload or specific patients. Below that is the dropzone for the file upload. The users can drag and drop one or more VCF files into the dropzone. Based on the option selected on the dropdown menu the upload procedure will work differently:

- If the user selected none option, then the uploaded VCF will not be related to any patient. It will be used for statistical purposes only.
- If the user selected the batch upload option, the uploaded VCF has two or more patients inside, and they all will have automatically created profiles in the system.
- If the user selected a specific patient, data would be imported for that patient from another project to the current one.

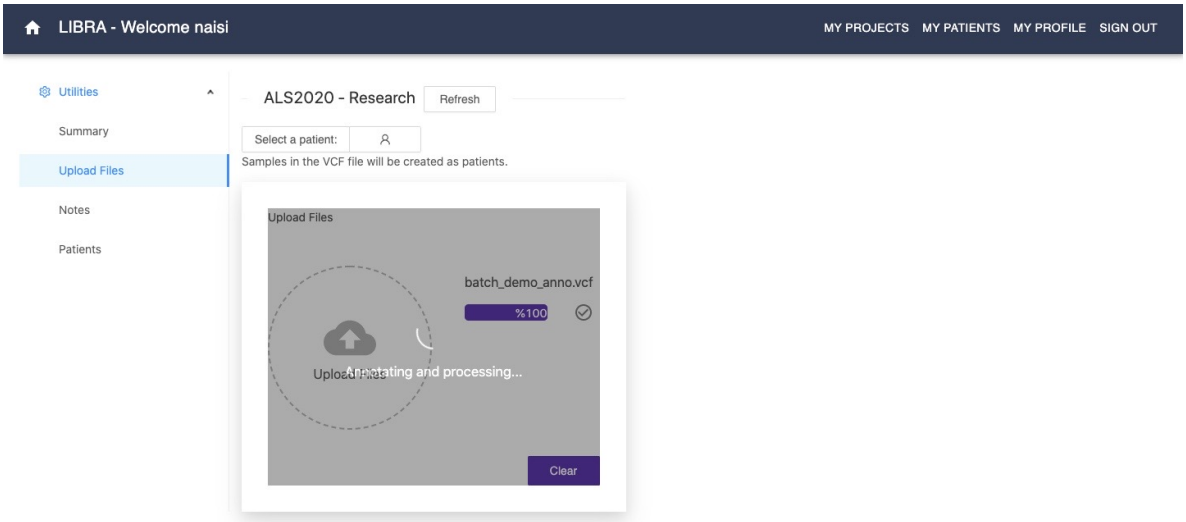
We show the procedure for batch upload:





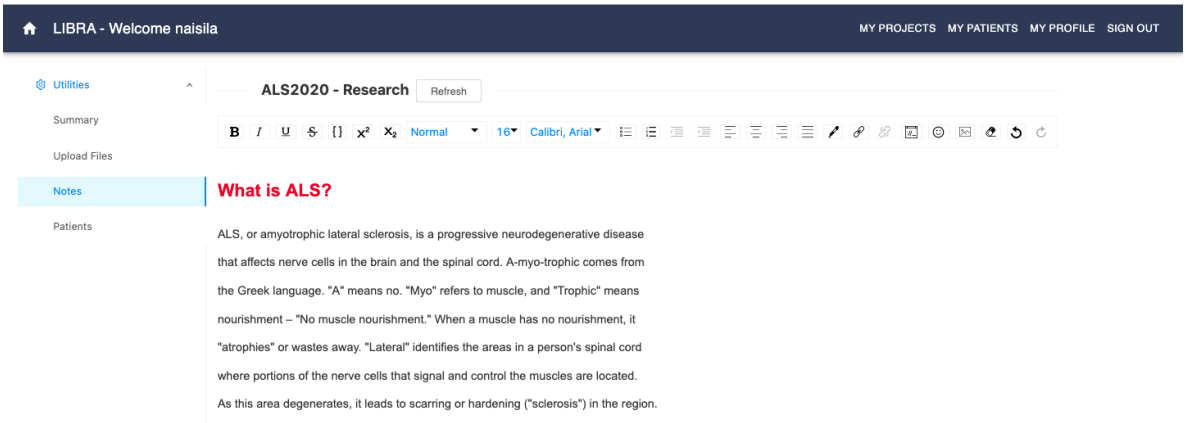


After the files are successfully uploaded the annotation process will take place in the backend and the users will be unable to interact with the dropzone.



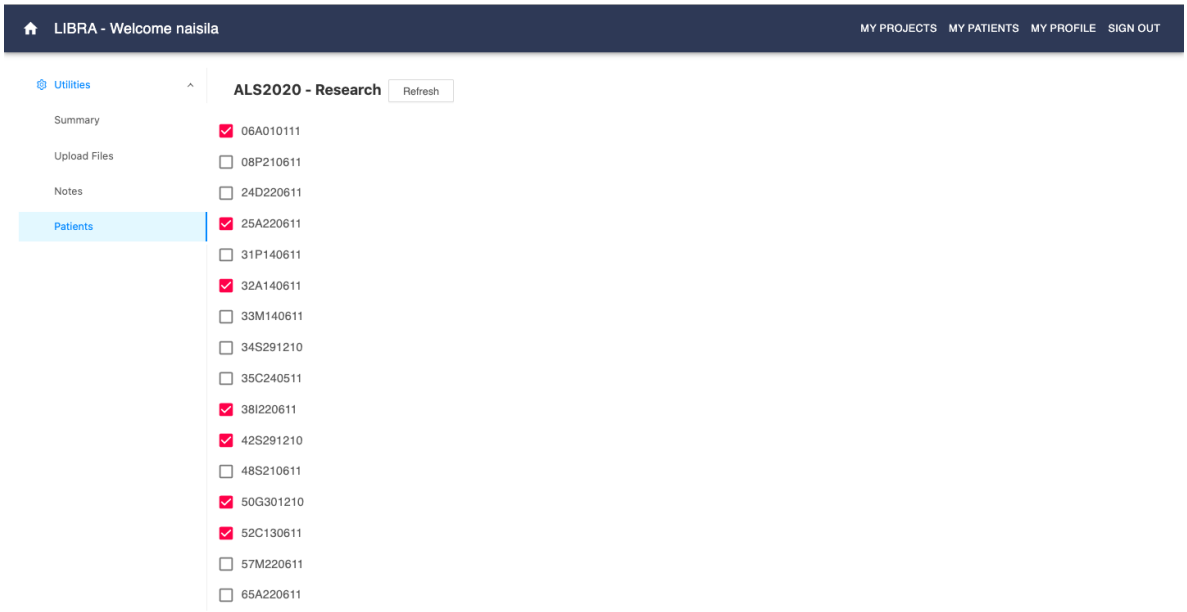
Project Notes

The user can add any notes related to the project in this tab. The notes are provided with cool formatting as well.



ProjectPatients

After uploading a batch vcf file, the patients will be automatically created, and the user can choose whether the patients have the associated disease of the project as well, by clicking on the checkboxes, as shown in the figure. In this example, the case is on ALS disease.

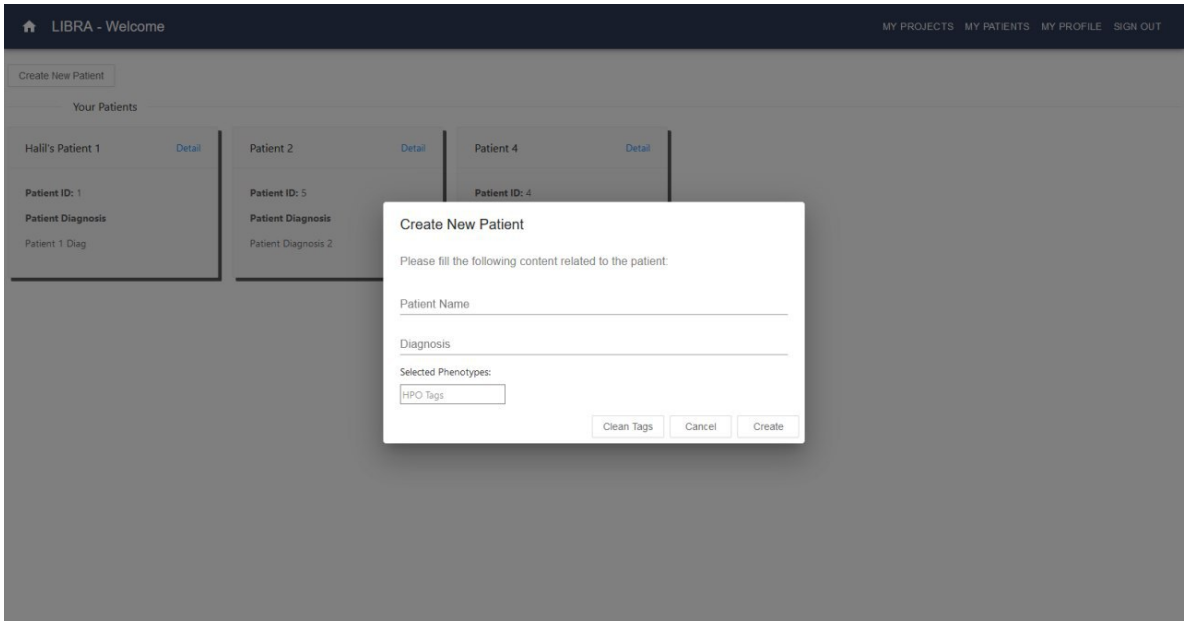


4) Usage of LIBRA: Match Maker

Match maker contains facilities which are: creating a patient with diagnosis and human phenotype ontology(HPO) terms, showing over all view for patients, showing detailed view for a patient, getting gene ontology similarity from VCF annotation, accessing HPO traverser, accessing automated similarity notification system, accessing manual similarity notification system, and changing similarity threshold configuration.

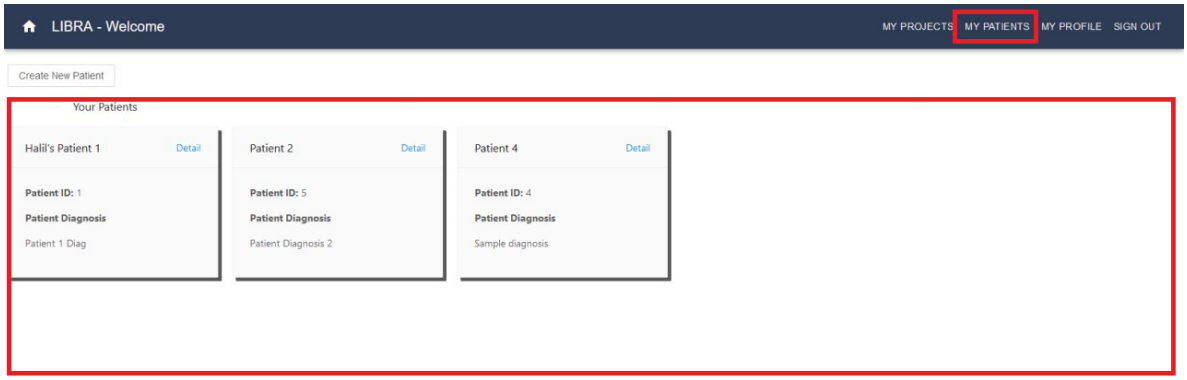
Create New Patient

To create a new patient click "My Project" button on the navigator. After that, press "Create New Patient" button. Fill "Patient Name" and "Diagnosis". Type HPO Tags via search bar and select from dropdown menu. You can delete tags by pressing "Clean Tags" button. After adding all phenotypes, click "Create" button.



See Overall View for Patients

Click "My Project" button on the navigator. Below "Your Patient", you see all patients. For each patient you see patient name, patient id and patient diagnosis.

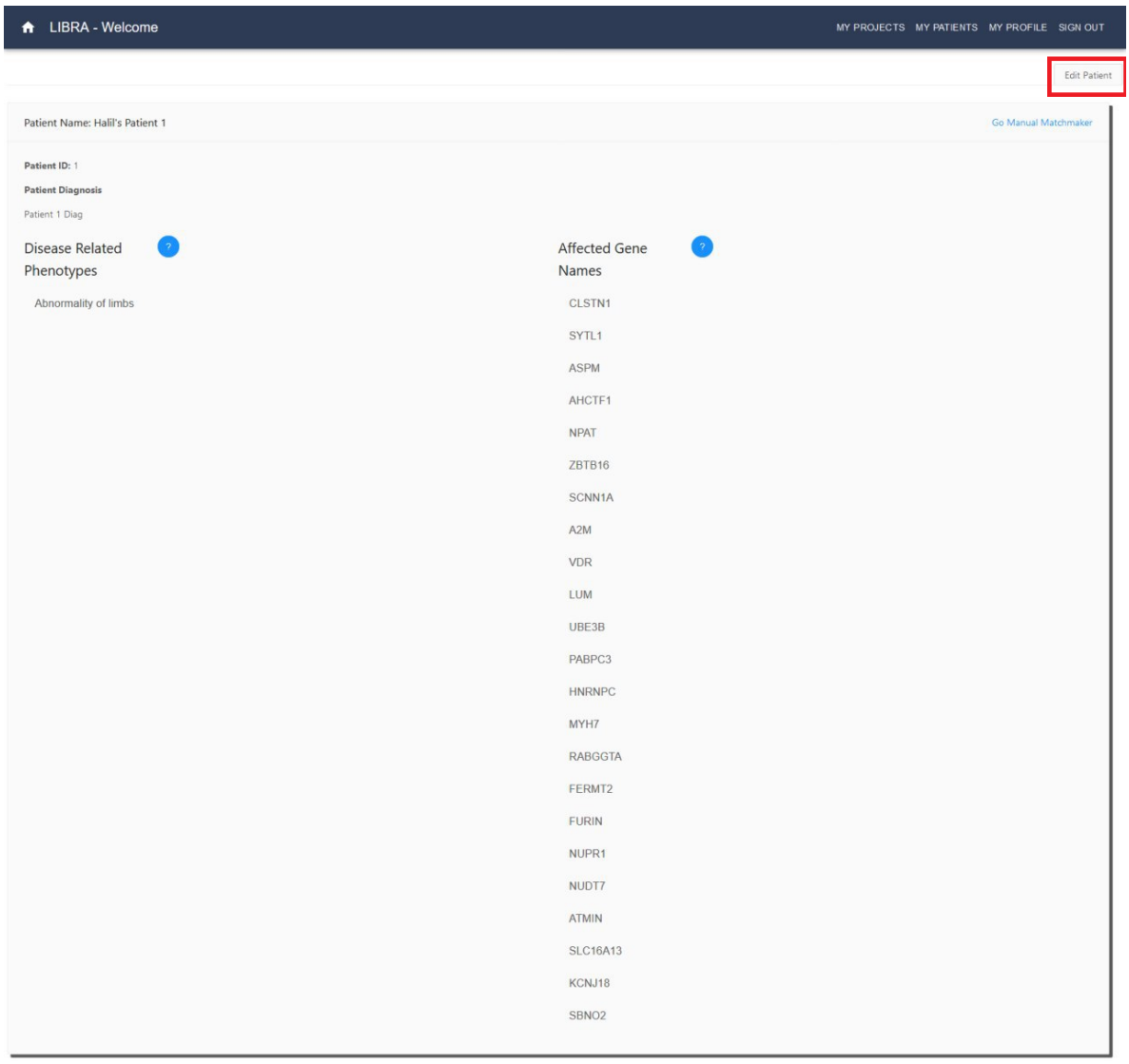


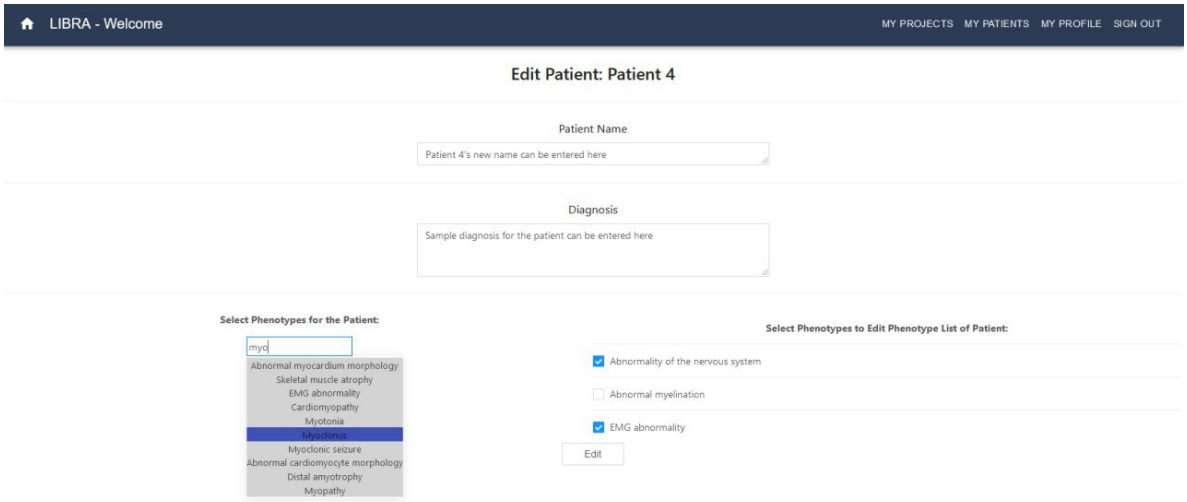
See Details for a Patient

On the overall view for patient, click detail button of correspondent patient. You will see the same information with preview. Also you will see disease related phenotypes and affected gene names. If you click a phenotype, you can see details of phenotype and traverse on phenotypes. If you click gene name, you are redirected to gene information.

Editing a Patient

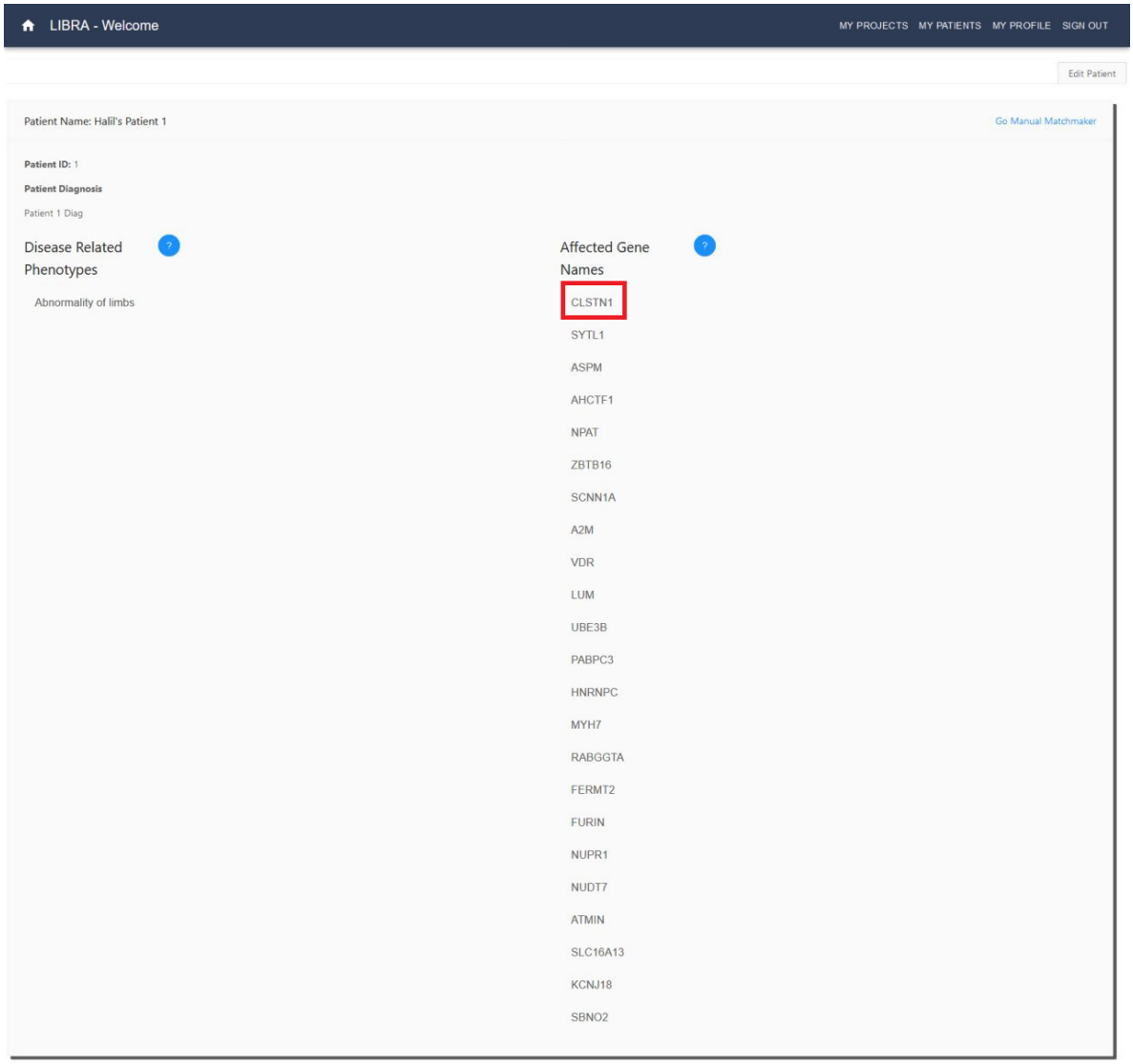
On the detailed Patient page, click "Edit Patient" button. You can give a new name to the patient. You can change diagnosis via text box. You can add new phenotype via search bar. Also you can remove phenotypes by unchecking the checkbox of corresponded phenotype.





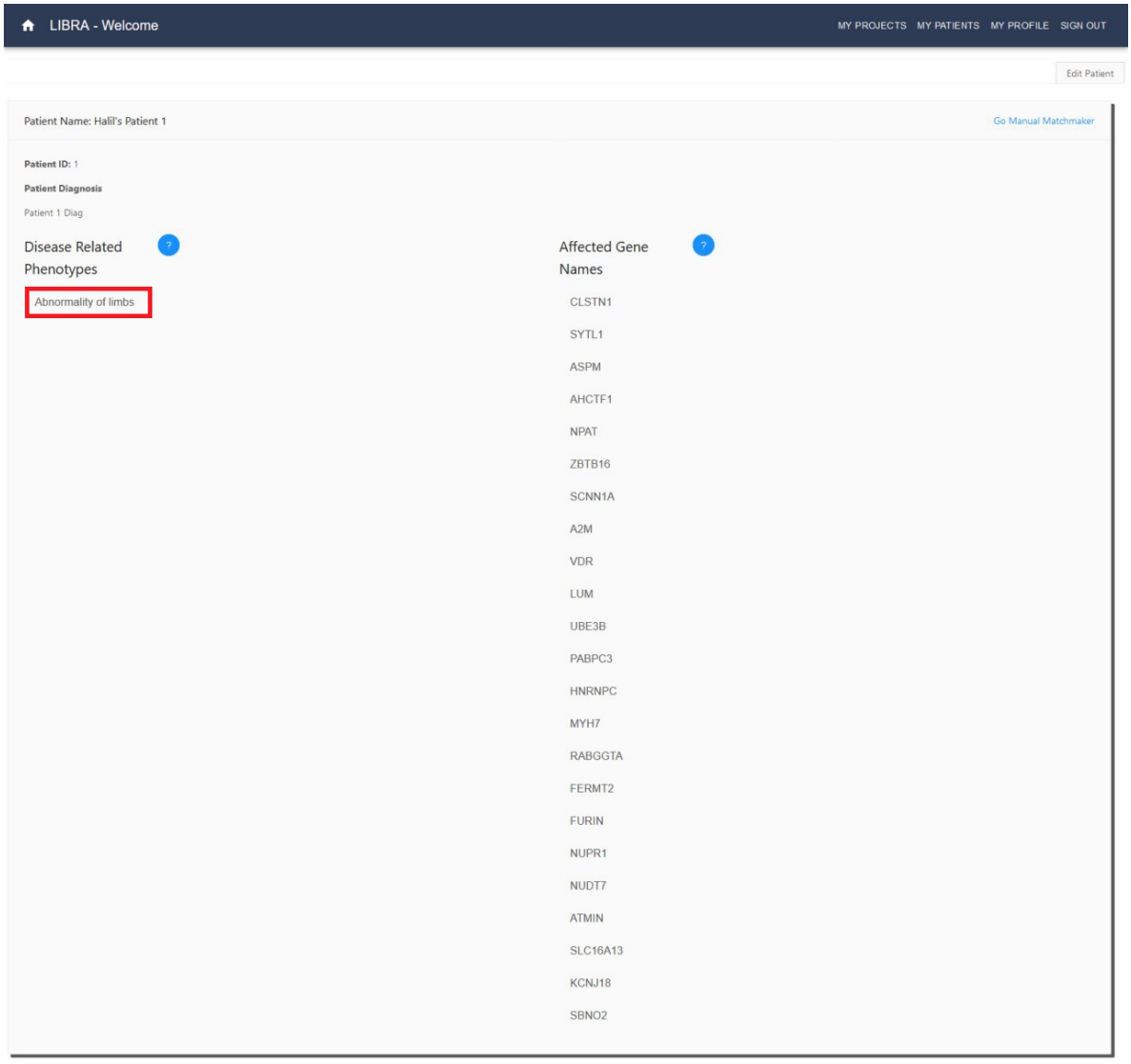
Get Highly Affected Genes For a Patient

After uploading the vcf file, click patient logo. Select name of the patient. Automatically highly affected genes will be added to the patient.



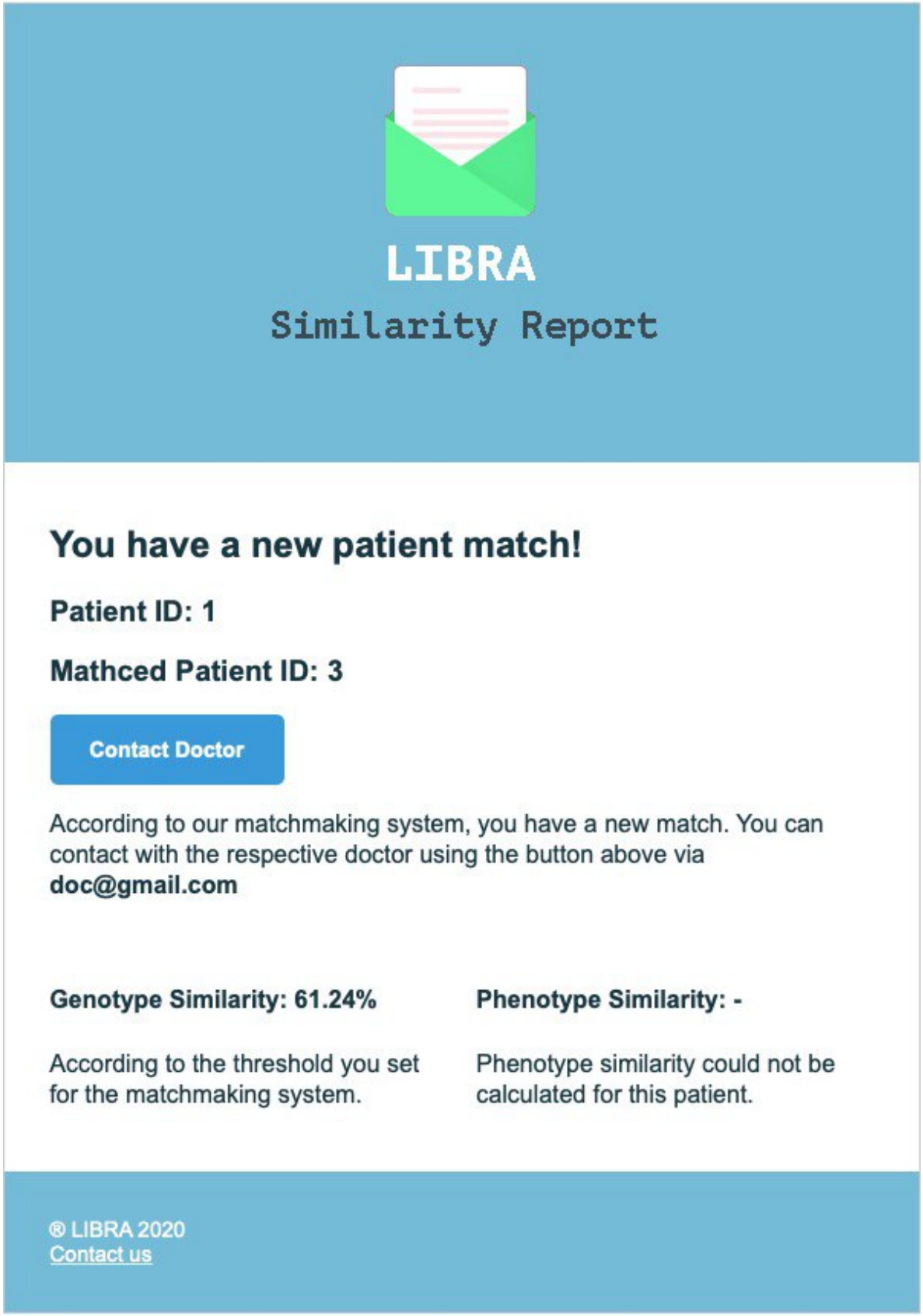
HPO traverser

When you click phenotype name on the detailed patient page, you will be directed to the HPO traverser. On the traverser, you will see name of the phenotype, definition of the phenotype and relative phenotypes. You can traverse parents and children by clicking name of that phenotype.



Automated Similarity Notification System

According to the threshold, if there is a similar patient to your patient, you will automatically get an e-mail which informs you about contact info of doctor who has the similar patient. Also e-mail indicates both the HPO similarity and GO similarity.



Manual Similarity System

On the detailed Patient page, click "Go Manual Matchmaker" link. There are three different systems to use. Firstly, you can choose some phenotypes and search patients with those phenotypes and click "Run Manual Matchmaker" button. It returns proper patients for the query. Secondly, you can list patients which are most similar to the patient according to phenotype by

clicking "Run HPO Matchmaker". Finally, you can list patients which are most similar to the patient according to affected genes by clicking "Run GO Matchmaker".

Similarity Threshold Configuration

Click "My Profile" button on the navigator. After that, enter value between 0 and 1 for both "Phenotype Similarity Threshold" and "Genotype Similarity Threshold". Click "Save Changes". New configuration affects Automated Similarity Notification System.