

OpenGeneMed: a portable, flexible and customizable informatics hub for the coordination of Next-Generation Sequencing studies in support of precision medicine trials.

User Manual

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⚠ This 'User manual' describes the usage of the default configuration and does not reflect changes that your system administrator may have implemented in your version of OpenGeneMed.

Before submitting any inquiry to the authors of this manuscript, please contact your system administrators to make sure your inquiry is not connected to changes they made from the default configuration. ⚠

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1 Document Introduction

This document is a user manual about the OpenGeneMed system.

Some of the text and figures is presented in a recent publication:

Zhao, Yingdong, Eric C. Polley, Ming-Chung Li, Chih-Jian Lih, Alida Palmisano, David J. Sims, Lawrence V. Rubinstein et al. "GeneMed: An Informatics Hub for the Coordination of Next-Generation Sequencing Studies that Support Precision Oncology Clinical Trials." *Cancer informatics* 14, no. Suppl 2 (2015): 45.

This document contains a general presentation of the implemented system, together with step by step instruction about how to use the default configuration of OpenGeneMed. A different document (called 'Technical documentation') contains detailed explanation about how OpenGeneMed is implemented and how to customize the code for specific study needs.

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1.1 Abstract

We developed an informatics system, called OpenGeneMed, to support clinical trial research.

The system is an open and customizable version of the GeneMed system (Zhao et al. (2015)), a web-based interface developed for the National Cancer Institute (NCI) Molecular Profiling based Assignment of Cancer Therapy (MPACT) clinical trial (NCT01827384) conducted in the National Institutes of Health (NIH) Clinical Center.

Similar to the GeneMed system, OpenGeneMed streamlines the work flow of the clinical trial and it can be used by clinicians, lab personnel, statisticians and other researches as a communication hub. The web system automates the annotation of the genomic variants identified by sequencing, classifies the actionable mutations according to customizable rules, and facilitates quality control by the molecular characterization lab in the review of variants.

OpenGeneMed collects baseline information about the patients from the clinic team to determine eligibility for the panel of drugs available. The system generates patient reports containing detected genomic alterations providing summarized information that can be used for treatment assignment by a supervising treatment review team.

OpenGeneMed is distributed as a standalone virtual machine, ready to be deployed and used from a web browser. The code of the informatics system is written in a modular way: this allows easy customization of the existing features and addition new modules to address the needs of specific clinical trials and research teams. Several examples on how to customize the code are provided in the technical manual distributed with the virtual machine.

In summary, OpenGeneMed offers an initial set of features inspired by our experience with GeneMed, a system that has been proven to be an efficient and successful informatics hub for coordinating the reliable application of next-generation sequencing in the MPACT trial. OpenGeneMed facilitates the exchange of real-time information used by the medical and research staff for therapeutic decision-making. A key additional capability of OpenGeneMed is that it is open-source and offers easy customization and expansion.

2 Introduction

Next-generation sequencing (NGS) technologies have been shown to be powerful tools for the clinical diagnosis and treatment of patients with cancer and other diseases, due to the increase of sequencing speed, reduction of cost, and improvement in accuracy over the past decade (Rothberg et al. (2011)). Precision medicine treatments for cancer are gaining momentum due to increase interest in approaches guided by next-generation sequencing (Doroshov (2010); Gargis et al. (2012); Simon and Polley (2013); Simon and Roychowdhury (2013); Tran et al. (2013); Vogelstein et al. (2013)).

The National Cancer Institute (NCI) is now conducting a clinical trial (NCT01827384) titled MPACT (Molecular Profiling based Assignment of Cancer Therapy) to treat late stage cancer patients based on their targeted gene sequencing profile (Kummar et al. (2015)). Patients with progressive solid tumors who have exhausted standard treatments undergo biopsy and have their tumors characterized based on amplicon sequencing of over 380 unique actionable variants in 20 genes.

In MPACT several treatment regimens are used and the sequencing assay is designed to identify mutations likely to de-regulate some specific pathways: for details about the trial we refer to (Kummar et al. (2015)). Mutations are called actionable if they fulfill some pre-specified rules. The rules for actionability were derived from literature documentation, reporting in the Catalogue of Somatic Mutations in Cancer (COSMIC) database (Bamford et al. (2004)) and evidence of functional effects for loss-of-function genes. Patients whose tumors contain at least one actionable mutation are randomized to either the actionable study treatment prospectively identified to work on that mutation/pathway or a control arm consisting of one of the other treatments. The informatics support needed to coordinate the complex set of rules and operations of this clinical trial motivated the creation of the informatics system called GeneMed (Zhao et al. (2015)). Similar principles has been used to develop our open and customizable version of the system called OpenGeneMed.

A key feature of the informatics system is to serve as a communication hub linking the different teams involved in daily management of a clinical trial (sequencing lab, treatment review team, clinic team, statisticians, researchers, etc.). In addition to the bioinformatics pipeline for raw data processing and sequence alignment, the system must have the ability to quickly annotate the sequencing data, predict the functional impact of mutations, and match the detected mutation to the pre-identified genomic changes in tumors found in previous studies (i.e., the actionable mutations of interest). The informatics hub should have the ability to translate and present the mutation findings from a sequencing results into a concise and easy-to-read actionable report for the treatment review team in a timely manner. This information will then be used by the team to assign patients to different arms based on their detected mutations. Clinical trials follow a variety of strategy to assign patients to treatment arms, one of the most commonly used being randomization. While the GeneMed system includes the assignment of the patient to the proper treatment based on randomization tables, OpenGeneMed does not include a module to do this assignment because we wanted the system to be useful for all kind of trials, wheter randomized or not. However the architecture of the system has been designed to allow easy integration of additional modules (some examples presented in this document, with more details available in the technical documentation): in this way the addition of an automated (or semi-automated) treatment assignment module should be an easy task for the IT group to set up the informatics system.

OpenGeneMed contains a module to collect and store patient data, including response data for prior therapies: this data is essential to evaluate eligibility for treatments in the study, assisting the treatment review team and the clinic team in the development of a treatment plan. The system is also equipped to make both sequencing data and clinical response data available to statisticians who are able to evaluate whether there is any improvement in response rate or progression free survival (PFS) favoring assignment of therapy based on genetic sequencing and to determine which actionable mutation-treatment pairs lead to improved patient outcome. OpenGeneMed contains an administrative module that allows the system manager to register users with different roles (e.g., Clinical Team, Lab Team, Treatment Review Team, etc.). Each group will be granted different permissions on data monitoring, uploads and changes. This module, as all others in OpenGeneMed, is customizable and extendable so that each clinical trial setup and workflow can be easily mapped into the system.

3 System design and architecture

OpenGeneMed is designed to be customizable to address the needs of different studies. However a setup inspired by our experience with the GeneMed system is available in the initial instantiation of the system. In this section we describe all the features available “right out the box”, showing that the system already provides very valuable support for the management of a clinical study. In the ‘Technical Documentation’ document we show how to customize existing modules and how to integrate new ones to better match more specific needs.

3.1 Working groups for a basic study

There are six groups of people who participate in a basic trial. The tasks of these groups are as follows:

1. Admin Group: have access to all the different parts of the system. They are responsible for registering new users, assigning them to different groups and updating their information as necessary;
2. Study Coordinator: responsible for editing the eligibility questions, the actionable mutation rules and the gene/drugs of interest for the study;
3. Lab Team: lab members who perform the next-generation sequencing assays and sequence validation. They are responsible for uploading the variant files and for reviewing actionable mutation of interest (aMOI) identified by the OpenGeneMed system. One or more members of this group should act as ‘chief’ with additional responsibilities (more details follow);
4. Clinic Team: treating physicians and nurses who recruit and register patients, gather patient clinical information, treat patients, and delink them after the patient’s disease has progressed or when the patient is taken off the study. One or more members of this group should act as ‘chief’ and with additional responsibilities (more details follow);
5. Treatment Review Team: access the patient clinical information, variant calls and decide on which treatment each patient should receive. This group allow a clear separation (blinding/masking) between the people that have access to the genetic information of the patient and the ones that deliver the actual treatment;
6. Biostatistics Group: researchers who are involved in the design of the study, monitor accrual rates, and analyze the data as required by the study protocol.

Each group can only access data related to the assigned tasks of the group. For example, staff in lab group can access sequence data but can only view partial patient clinical information and cannot not edit it; members in clinic group, instead, can access patient clinic information but not sequence data before the patient is delinked. [Figure 1](#) summarize the main tasks of each team.

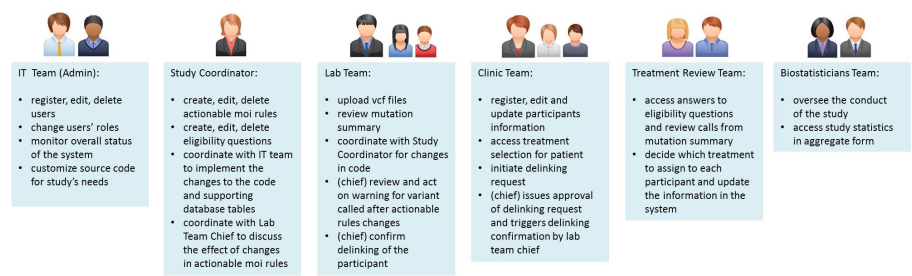


Figure 1: Groups available in the basic study setup of OpenGeneMed. The main tasks of each group are listed. In two groups (Lab and Clinic teams) two subgroups are present: regular members and chief. Note that each role can be assigned to more than one person but each person can only have one role.

3.2 Communication and operation flow of different groups in the basic trial

Managing a clinical study is a complex operation that requires team work, so it is necessary for the different groups to work collaboratively in an enterprise environment to accomplish the tasks required by the study. The basic work flow and communications among different user groups are shown in Figure 2 where all major tasks for each working group are sequentially ordered from top to bottom.

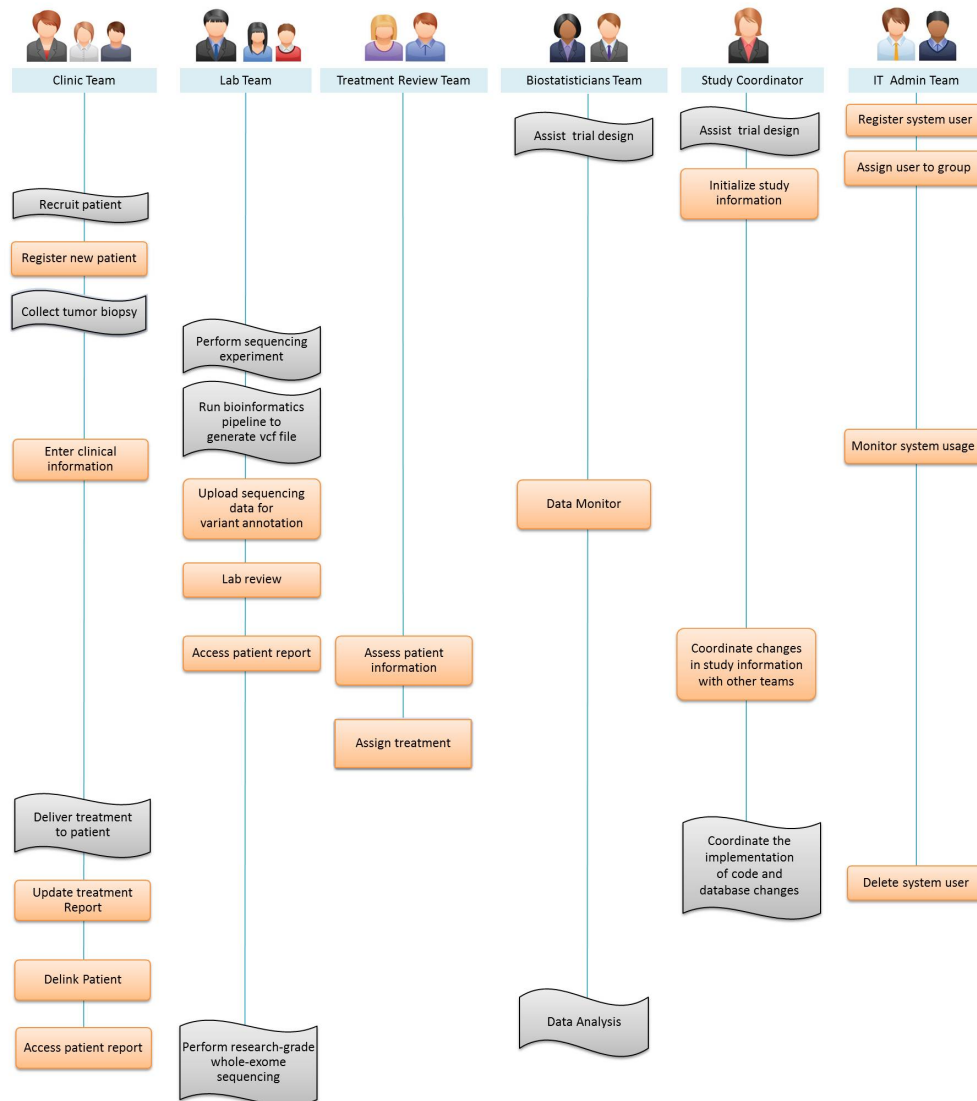


Figure 2: Workflow for the groups available in the basic study setup of OpenGeneMed. The order of tasks is shown vertically from top to bottom. The tasks formatted as orange rectangles are the ones involving user interactions with OpenGeneMed.

Once the Admin Team sets up accounts for the different team members, each of them will be able to access the part of OpenGeneMed devoted to their specific task. Then, when a new patient enters the study, a member of the clinic group accesses OpenGeneMed and registers the patient using a clinical trial assigned patient ID (protocol ID). Some basic demographic information for the patient can be entered into the system. OpenGeneMed performs some standard validation for the input information (e.g., check the uniqueness of the patient ID, make sure that dates are

in reasonable format, etc.): more details on the specific validation can be found in the Technical Documentation of OpenGeneMed.

After the patient has been registered, the sample can be collected and delivered to the sequencing lab. The lab receives the sample and performs the sequencing assay. The raw data is then processed in the lab using a bioinformatics pipeline for sequence alignment and variant calling. A file containing the variants in VCF (Variant Call Format) version 4.2 format (<https://github.com/samtools/hts-specs>) is generated after sequence alignment and quality control. At this point, the lab member goes into the OpenGeneMed system and uploads the VCF file.

The OpenGeneMed system stores the VCF file, automatically performs annotation of each variant and produces a report of the variant called using the customized rules, previously recorded in the system by the Study Coordinator. A variant is considered actionable if the detected genomic alteration is in the pre-defined aMOI list or if the alteration meets one of the pre-defined actionability rules. Rules can be modified, added or deleted to meet the need of each study, more on this in [Section 4.2 on page 14](#). Information about the VCF submission is recorded (date and submitter identity) and an email is sent to the sequencing lab indicating a new variant file has been processed and is ready for review.

After receiving the email notice, the lab reviewer logs into OpenGeneMed and begins the manual reviewing process following standard operating procedures. The reviewer checks and assigns a review status of either approved or rejected to each variant identified as “aMOI” by OpenGeneMed. Standard procedures suggest that the reviewer rejects aMOI calls if the variant allele frequency is less than 5% for SNVs and less than 15% for short insertions or deletions (indels), or if the variant has been identified as being out of the reportable range (OORR) of the assay. Different approaches can be used in each study, according to the study protocol. If the read depth of the variant is less than 450X, or the variant is within or immediately adjacent to a homo-polymeric region, or the variant creates an insertional tandem repeat, the variant would require further verification in order to be approved.

Once the lab review is completed, the review statuses for all aMOIs for the patient are entered into OpenGeneMed.

The Treatment Review Team members log into OpenGeneMed and look up the patient’s aMOI report, his/her clinical data for treatment specific ineligibilities and prior therapies. The rules governing genomic profiling, definitions of actionable mutations and treatment arms are all pre-defined in the study protocol. The rules also cover how treatments are selected in cases with multiple actionable variants.

After the mutation summary report has been completed, the Treatment Review Team selects the appropriate treatment and records the decision in OpenGeneMed, where the Clinic Team can read the information and deliver the selected treatment to the patient. During the trial, the clinic team will update the treatment report on the clinical information page to document the treatment assignment and the response data.

The clinic team is initially blinded to the sequencing assay report. To share the sequencing results upfront would break the masking needed for randomized studies and endanger the validity of a randomized comparison, since patients might preferentially drop out or be taken off the control arm prior to evaluation of the primary endpoints of disease progression and tumor response. At disease progression, the sequencing results will be shared with the patient and the treating physician. OpenGeneMed is designed to manage both randomized and non-randomized studies and it doesn’t implement any randomization assignment by default.

OpenGeneMed implements the delinking procedure that is essential to de-identify the collected information. In the MPACT trial, research-grade whole-exome sequencing are performed for all patients once they are off study. Since the whole-exome sequencing is not done in a CLIA lab, the sample identification must be delinked from the patient’s clinical ID. We implemented the delinking process in OpenGeneMed following the same steps as in GeneMed.

The delinking process takes three simple steps: a member of the clinic team initiates the delinking request via the OpenGeneMed system, the Clinic Team chief receives the notice from OpenGeneMed and issues approval after determining that the patient is ready to be delinked (i.e., all clinical information have been correctly added to the system); a second notice is sent to the Lab chief who will be the one to complete the delinking process. All research specimens in the lab need to be relabeled with the new ID (generated automatically by the system when the

delinking request is issued) as the research lab does not keep any record that can be linked to the original patient ID. When the lab has completed the delinking of the actual specimens, the lab chief logs back into OpenGeneMed to confirm the delinking. At that point, all records of the clinical ID will be automatically scrubbed from OpenGeneMed and replaced with the new ID in all database tables: at this point there will be no way of going back and connecting the delinked ID with the original patient ID. Delinking anonymizes the entry and allows following up studies with the specimens and data.

During the trial, the biostatisticians can log into OpenGeneMed to get the updated patient response data and sequencing data of all those patients who has been delinked because of a disease progression or because they are off-study. The biostatisticians can also access the system to view aggregate data of active patients to monitor accrual rate and make suggestions to the study coordinator if changes to the protocol or to the recruitment methods are needed.

3.3 Functional modules in OpenGeneMed

The main goal of our system is to build a reliable, effective and easy to use bioinformatics platform that provides a seamless bridge between the different teams involved in running a clinical study and a system that can be used for every day communication in real time.

Inspired by the same design principles used to implement the GeneMed system [Zhao et al. \(2015\)](#) and its use in the MPACT clinical trial, we divided the system into several functional modules, each having its own special features and functionality ([Figure 3 on the next page](#)). Each working group has specific permissions and it is able to access only modules related to its defined tasks. At the same time, the design provides mechanisms for seamless communication among different working groups.

The functional modules in the OpenGeneMed system are defined as follows.:

1. **Login module:** accessible to everyone. Access to OpenGeneMed is controlled by this module. Only registered users can access the system using the recorded username and password. The password can be recovered/reset by following the provided link. Passwords are encrypted in the database and nobody (not even the Admin Group) can read the password. If problems are found during the login, the reset module will send a new temporary password to the email address provided in the request;
2. **Customize study information:** accessible only to the Study Coordinator, this module is used to customize the list of genes and drugs used in the study, define the actionable mutation of interest and customize the eligibility information that need to be collected for each patient;
3. **User management module:** accessible only to the Admin Group. When a new user of the system (lab member, statistician, researcher, nurse, etc.) joins the team, one member of the Admin Group will register the user in OpenGeneMed. The registration requires to enter a valid email address as username and a temporary password. The Admin person will assign the new user to the proper group and this will determine what s/he is allowed to see/do within the system. Changes of personal information (name, surname, password) can be done by each user for themselves, but changes to the assigned group can only be done by an Admin. The 'User management module' allows the Admin Group to delete users once they leave the team;
4. **Patient registration and Clinical information module:** accessible to the Clinic Group for information edit/add/delete and read only to the Treatment Review Team and Biostatistics Group. The layout of the Patient Clinical Information page is divided into different tabs as described in more details in [Section 4.3 on page 18](#).
 - **Patients:** it shows patient demographics (e.g., gender, histologic diagnosis, age at diagnosis). This is the tab used to register a new patient (using the 'Register patient' link). When a new patient enters the study, a clinic team member registers the patient in OpenGeneMed with the clinical protocol patient ID. This identifier must be unique and the system will perform validations to make sure that it doesn't contain prohibited characters and that follows a prespecified pattern (determined by the protocol). While registering a new patient, in addition gender, histologic diagnosis and age at diagnosis a 'Comment' section is available and it could be used to add information relevant to the treatment assignment such

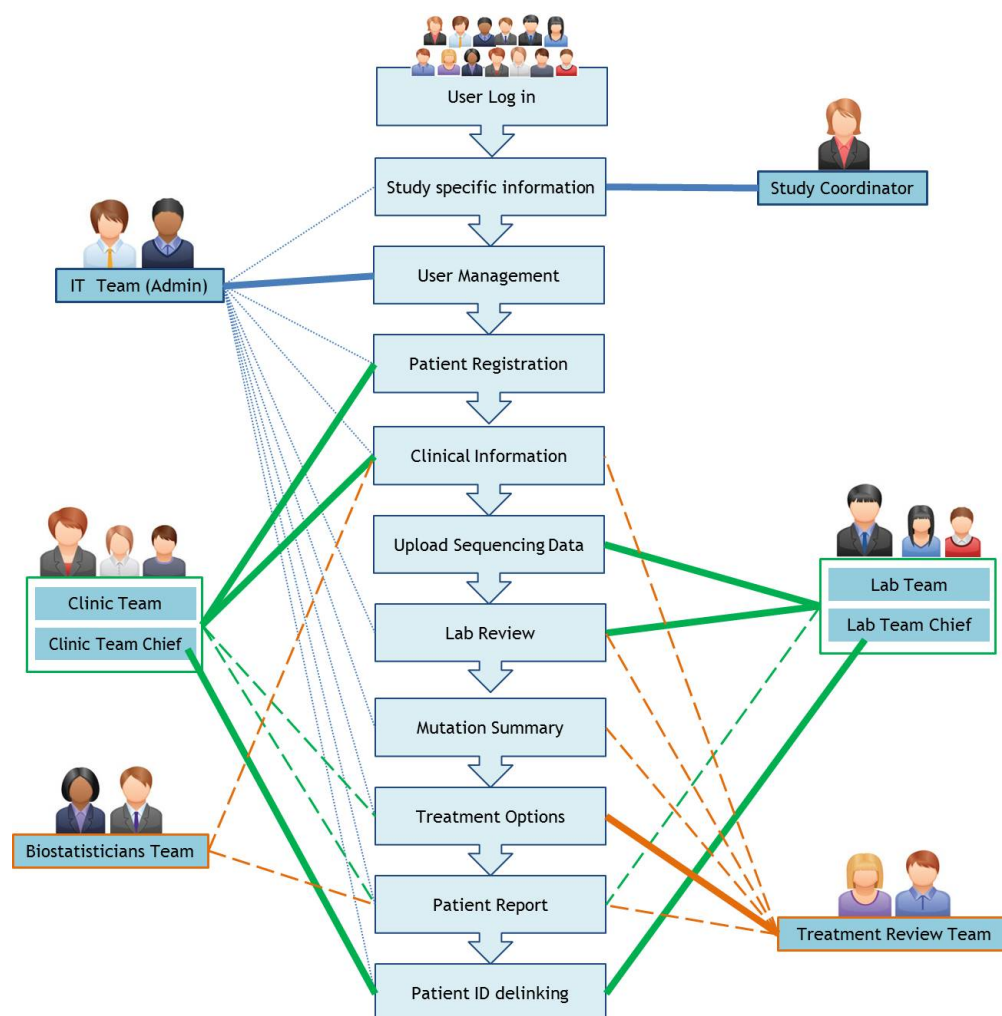


Figure 3: Main modules defined in the default configuration of OpenGeneMed. Solid bold lines connects each team with their main activity, i.e. the module for which they have the main input/edit responsibility. Dashed bold lines shows modules that the team can access in read-only mode: the information in these modules may be essential to perform their main activity, but the editing responsibility belongs to another group. Fine dotted lines indicate modules that are accessible to the team in editing mode but the access is granted only for emergency and unforeseen situations: in the everyday course of the study, those task should be carried out by other groups.

as known allergies, excluded medical conditions, etc. A 'Treatment Eligibility Data' tab may be used to add more structured information about treatment eligibility. The Patients tab offers an overall view of the currently registered patients. Each of them can be edited, delinked or variants information can be accessed using the button in the 'Action' column.

- **Biopsy samples:** this tab offers an overall view of the currently registered biopsy samples for all patients. Each of them can be edited or using the appropriate button in the 'Action' column. This is the tab used to add new samples (using the 'Add sample' link). While registering a new sample, basic information will be asked (patient ID, phase, biopsy site and type, ...).
- **Prior systemic therapies:** in this module, prior therapies information can be recorded (information about the current study should be added in the 'Treatment report' section). A registered Patient ID need to be provided to view the list of existing prior therapies and to add new ones. Once an exiting Patient ID is queried, information about Regimen, Date of Rx, Best response, Duration and Comments for each prior therapies can be added in the database. Exiting records can be edited or deleted using the

appropriate button in the 'Action' column.

- **Treatment Eligibility Data:** in this module, structured information about treatment eligibility questions are recorded. A registered Patient ID need to be provided to view the current state of the records. Once an exiting Patient ID is queried a table containing all the specific treatment eligibility questions, answers and notes will be shown. The questions can be edited/added/deleted in a separate module (the 'Customize' module, above). The Clinic Team will only be able to answer those specific questions for each patient, with the chance to add a note after each answer. Since questions could be changed/added/deleted during the course of the study (even if that is not advisable), the change will be prompted to the user that access a record that contains previously answered questions: if the text of the question has been edited, it will appear in orange with an 'Acknowledge change' button below the answer: the user could revise the question and the answer and decide if changes in the answer need to be done. If a question is deleted, that row will appear in red with an 'Acknowledge change' button below the answer: the user could revise the question and the answer and decide if changes to other answers/notes need to be done before the record is deleted for the patient. If a question is added, it will just appear in the table with an empty record as answer. All these different scenarios are shown in [Figure 22 on page 24](#).
- **Treatment report:** in this module, information about the current study regimen and response are recorded. A registered Patient ID need to be provided to view the list of existing treatment reports and to add new ones. Once an exiting Patient ID is queried, information about Regimen, Date of Rx, Best response, etc. for each treatment report entry can be added in the database. Exiting records can be edited or deleted using the appropriate button in the 'Action' column.

5. **Sequencing data upload module:** used by the sequencing lab to upload the variant file in VCF format (VCF file produced by TorrentSuite version 4.0.2). When uploading the variant file, the system uses the combination of the patient ID and the sample ID (the VCF file name) as the unique identifier. Instructions on how to customize/extend this module to fit different studies' need are presented in the 'Technical documentation' manual and the general workflow is shown in [Figure 4](#).

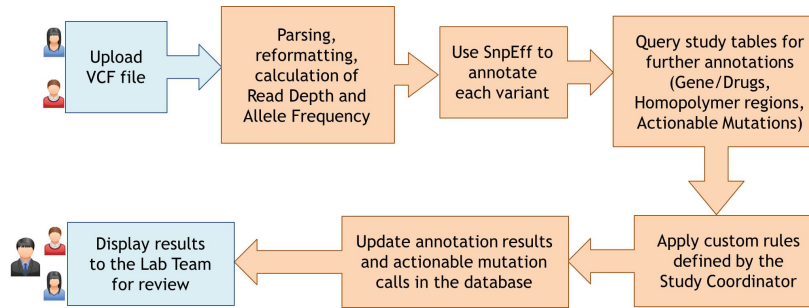


Figure 4: Sequencing data upload, Annotation steps. Upon upload of the vcf file, OpenGeneMed performs a series of steps to provide the final annotated group of variant calls.

The currently implemented strategy is the same used in the GeneMed system ([Zhao et al. \(2015\)](#)) and here quoted as reference.

'The first step is to parse the variant with multiple changes in ALT (alternate non-reference alleles) field and split the field into lines with a single record in the ALT field. For i -th variant among the total of N mutations detected at a given position, we define the Read Depth (RD) and the variant allele frequency (VAF) to be calculated as follows:

$$RD_i = FRO_i + \sum_{j=1}^N FAO_j$$

$$VAF_i = \frac{FAO_i}{FRO_i + \sum_{j=1}^N FAO_j}$$

The next step is to annotate the predicted effect of all variants in the VCF file. This step uses the snpEff variant annotation and effect prediction tool (Cingolani et al. (2012)). The output will annotate all variants as either synonymous or non-synonymous and the predicted amino acid change. In addition, homopolymer regions within the amplicons have been annotated and a variant is marked with the length of the homopolymer region if the reported position is within 1bp of any homopolymer region.'

Finally the variants are compared to a table of actionable mutations of interest (aMOI), customizable to the need of the study as shown in [Section 4.2 on page 14](#).

6. **Lab review module:** used by the sequencing lab to review each aMOI. The lab reviewer can assign four different review statuses to each aMOI: "Review Approved", "Reviewed with Question", "Reviewed Rejected", "Not reviewed yet". A screen shot of the review edit form is shown in [Figure 31 on page 31](#). An email notification can be sent to the treatment review team to alert them that the report is ready for their review.
7. **Patient sequencing report module:** The aMOIs detected by sequencing will be reported in a format shown in [Figure 30 on page 30](#). The patient ID and sample ID are shown on the top left of the table. Each row represents a variant that has been identified as one of the actionable mutations for the study and that has been confirmed by lab review. For each variant, we report several fields as the gene symbol (with links to the COSMIC website), the gene type (which indicates whether this gene has been classified as a Gain or Loss of function), etc. The visibility of the columns can be customized by using the 'Show/hide columns' button, and filtering, sorting and searching is available for easy navigation of the table. In the default setup, each gene is predefined in one of the three pathways studied in the MPACT trial. The drug field lists the drug(s) assigned for the specific pathway in this trial. This information can be customized by the Study Coordinator (see below for details). Impact field is the functional impact of the variant predicted by snpEff. If the variant is in a homopolymer region, the length of the homopolymer region is displayed under 'HP' field. Finally, 'Chromosome', 'REF', 'ALT', 'Start Position', 'Allele Frequency', 'Read Depth', 'Codon Change' and 'Amino Acid Change' for the variant are listed. The canonical transcript IDs are also shown in the report table to provide the isoform information.
8. **Patient delinking module:** Delinking is the essential process needed to de-identify information of patients going off-study to allow the use of that information for further research investigations. Conceptually, it is a very simple process of creating a random identifier that will replace the Patient ID used throughout the different tables, so that the information in the database will not be linked in any way to the actual patient record in the clinic. This module uses three steps described in more details in [Section 4.3.7 on page 26](#) to replace the patient protocol ID with a randomly generated ID once the patient is off-study. The research nurse, the physician, and the lab chief are the parties involved in the delinking process.

4 Detailed How-To user manual

The sections below contains detailed step-by-step instructions on how to use the default configuration of OpenGeneMed. Each kind of user (role) has access only to specific parts of OpenGeneMed. The sections are presented in the order in which the different groups are supposed to access the system in an ideal workflow.

4.1 Users setup (Administrator)

In the basic initial setup, eight accounts are added for demo purposes (usernames and passwords in [Table 2 on page 38](#)).

After login, the admin lands on the Dashboard tab (first on the left), a page with basic statistics about the system. The main action tab of an administrator is the 'Admin' tab, on the far right. The state of the system in the initial setup is shown in [Figure 5](#).

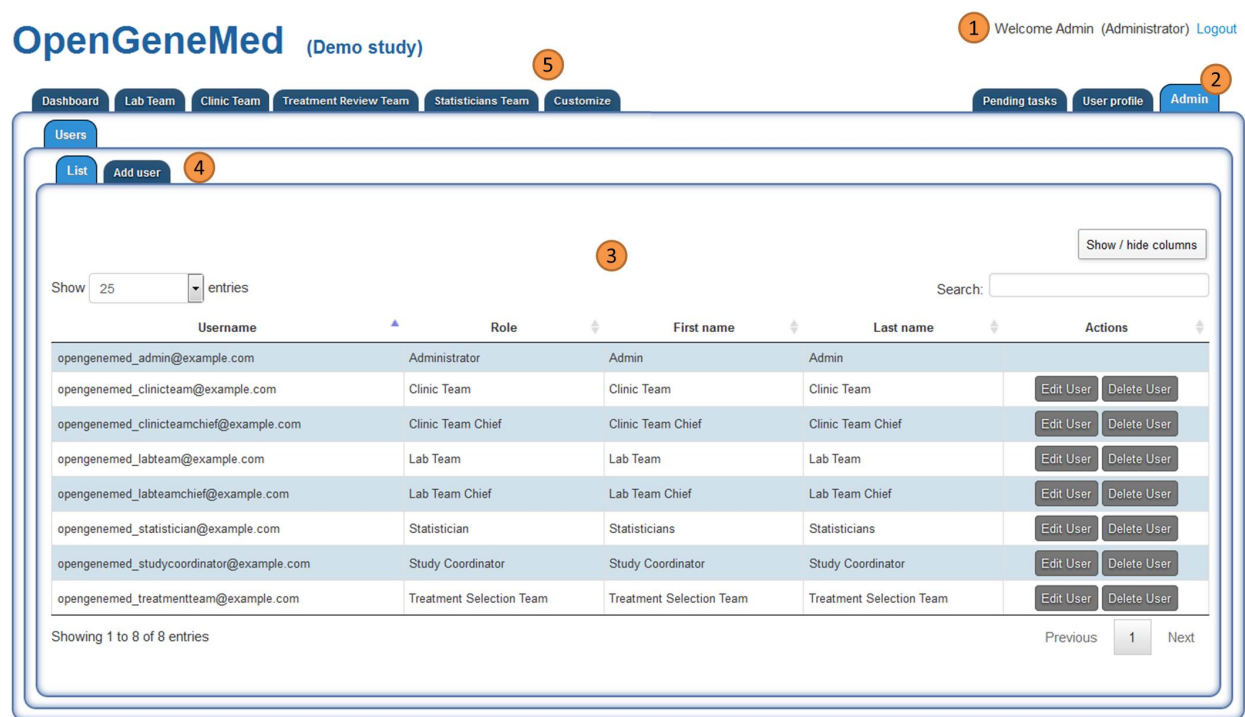


Figure 5: Admin tab. The window is divided as follows: (1) greetings with the name, role and logout link, (2) the active tab is shown with a lighter blue background and a bigger font, (3) the main part of the window displays the list of the cCusturrent users in a tabular format, (4) additional actions in the main topic of 'Users' management are shown as additional subtabs ('Add user' in this case), (5) any additional section that the current user has access to is displayed as a different tab.

Editing and deleting an user is as easy as clicking the Edit or Delete button of the entries that needs to be updated. The table is sortable and filters can be activated just by typing the string that needs to be found. If the length of the table exceeds 25, the table is divided into pages that can be navigated using the numbers in the lower right corner of the table. A 'Show' drop down menu allows to change the amount of entries displayed at any given moment.

How to Edit and Delete users is shown in [Figure 6 on the next page](#).

A

Users

List Add user Delete user

Please confirm the deletion of the following user

Email Address (used as username) opengenedmed_clinicteam@example.com

User Role Clinic Team

First Name Clinic Team

Last Name Clinic Team

Confirm deletion

B

Users

List Add user Edit user

Email Address (used as username) opengenedmed_clinicteamchief@e

User Role Clinic Team Chief

First Name Clinic Team Chief

Last Name Clinic Team Chief

Reset password? No (an email with the new password will be sent to the user)

Submit changes

Figure 6: Admin tab, Edit/Delete user. Deleting a user requires only a single confirmation (A), while editing (B) allows the administrator to change the user role, first and last name or email address (username). A new password cannot be manually entered by the administrator: s/he can only initiate a reset password, which will automatically create a new temporary random password and will send an email to the username address with these new login information.

Adding a new user is done through the 'Add user' tab. The interface to add new users to OpenGeneMed is shown in Figure 7. Once the form has been filled, an email will be sent to the user with the login information. Note that username and password will be sent without any encryption as this should be a temporary password used only to access the system for the first time. Each user should then change it through the 'User profile' tab (see Section 4.6 on page 36).

OpenGeneMed (Demo study)

Welcome Admin (Administrator) Logout

Dashboard Lab Team Clinic Team Treatment Selection Team Statisticians Team Customize Pending tasks User profile Admin

Users

List Add user

Email Address (used as username)

Password

Retype password

User Role

First Name

Last Name

Submit

Administrator
Clinic Team
Clinic Team Chief
Lab Team
Lab Team Chief
Statistician
Study Coordinator
Treatment Selection Team

Figure 7: Admin tab, Add user. The administrator should fill all the information to register a new user. Once the record has been entered, an email will be sent to the user with login information.



WARNING: the administrator role has full access to all different aspects of OpenGeneMed. This is granted with the idea of Administrators being able to quickly assess issues encountered by any user of the system. However editing of samples' data, patient information and treatments should be done exclusively by authorized people. The default configuration of OpenGeneMed can be easily adapted to allow/deny the access to any operation to different user roles: this requires changes in the source code, but it's very straightforward.

4.2 Study setup (Study coordinator)

Once the study protocol has been approved, key information about the study should be entered in OpenGeneMed by the Study Coordinator. The information that needs to be entered is divided into four groups:

1. Actionable rules: a collection of statements declaring which variants should be marked as 'actionable' for the specific study;
2. Gene/Drugs: a table collecting information about the key genes in the study, their pathway, role and the drug that a mutation of this gene may be associated to;
3. Actionable Mutations: a table collecting information about the specific mutations that are considered 'actionable' for the study;
4. Eligibility Questions: collection of yes/no questions assessing eligibility criteria for the study;

The customization of each group is presented in details below.



WARNING: Actionable Rules, Gene/Drugs, Actionable Mutations and Eligibility questions should be properly completed at the beginning of the study, before any patient is recruited. However it is possible that the information in these table need to be changed, as the study progresses, to account for amendment of the study protocol, new information, etc. The impact of editing any entry in these three tables is quite pervasive and it must be done with great care. OpenGeneMed keeps tracks the last modification of these tables, comparing it with the time of any existing variant call report and patient information data. If, for example, a sample has been uploaded at time t1 and the actionable rules or gene/drugs table is changed at a later time t2, the validity of the variant calling may have been compromised (since the change may or may not affect what is determined to be an 'actionable mutation of interest'). OpenGeneMed will prompt the Lab Member reviewing the variant call that a mismatch may be possible and it's up to the Lab Team Chief to decide what action to take: either ignore the warning and proceed with reviewing the current variant report, or rerun the variant call with the updated information. This decision has to be made after the Lab Team Chief get in contact with the Study Coordinator to understand the nature of the change. Note that any future upload of samples will automatically use the new updated information: the problem only arise for samples already uploaded but not reviewed yet. A similar situation happens when eligibility questions are updated after a patient has been registered and his/her answer already recorded: OpenGeneMed will show the inconsistency to the Clinic Team member and his/her action to ignore the warning or to change the existing answer has to be decided in conjunction with the Study Coordinator who issues the changes.

Another step that requires the careful coordination between teams is the delinking of a patient (anonymization of patient ID that allows following up studies with the specimens and data). OpenGeneMed presents warnings to the appropriate recipients (Clinic Team Chief and Lab Team Chief, examples in [Figure 26 on page 27](#)) to make sure all the information is complete and ready to be locked and anonymized. Even if the Study Coordinator is not involved directly in this step, s/he should be aware of this process and s/he should educate all team members to comply to the protocol requirements for delinking.

4.2.1 Actionable rules

In the initial setup of the study, only one custom actionable rule is listed. To add a new rule, the Study Coordinator should access the 'Add entry' tab under the 'Actionable Rules' task. The information entered for each rule is displayed in [Figure 8 on the next page](#).

Rules can be simple and contain one single clause, or could represent more complex logic.

All the clauses within a rule are combined with an 'AND' logic. Exclusion rules are internally 'flipped' and listed as inclusion of their 'flipped' counterpart. The presence of multiple clauses on the same field may lead to incoherent definitions (i.e., conflicting clauses may lead to a definition of an empty set or redundant clauses may be present). OpenGeneMed implements some basic validation to alert the user for possibly incoherent rules. One example of

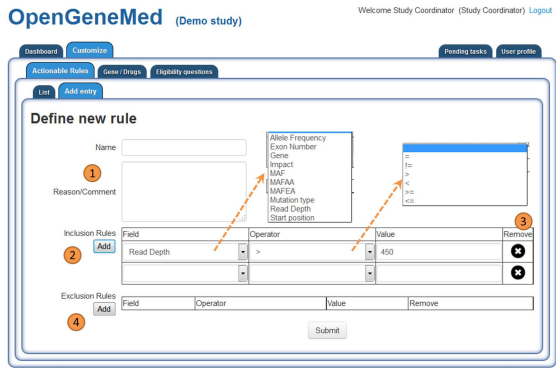


Figure 8: Customize, Actionable Rules, Add entry. Name: a short description of the rule, used for reference. Reason/- Comment: a short text describing the existence of the rule, used for future reference. Inclusion Rules: a list of clauses that determines which conditions have to be met by a variant to be marked as actionable (aMOI='yes'). Rules can refer to values of Allele Frequency, Read Depth, specific Gene names, etc. Each clause is added by using the Add button, then selecting the desired combination of Field, Operator and Value. To delete a clause just click the 'X' button under the Remove column. Exclusion rules can be added in a similar way. Refer to the main text for explanations about validation and interpretation of multiple clauses.

this situation is shown in [Figure 9](#). When the Study Coordinator clicks 'Submit', the validation is executed and a warning is displayed: the user must then decide if to fix the error or to save the rule anyway.

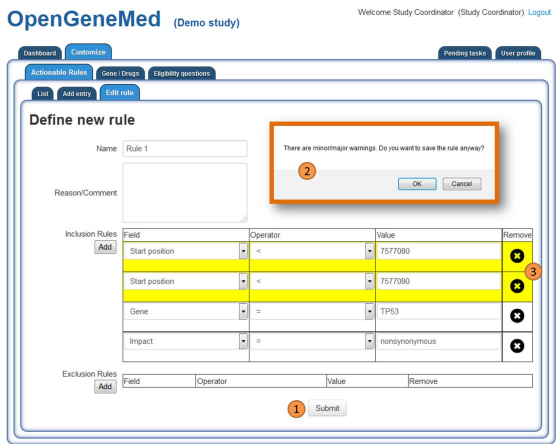


Figure 9: Customize, Actionable Rules, Add entry, Validation. (1) upon submission of the rule a popup (2) is displayed to alert the user about a possible incoherent definition. The current state of the rule declare to include all variants with Start position smaller than 7577080 and, second rule, all variants with Start position smaller than 7577090. This is a combination of rules that contain an extra rule, since being smaller than 7577090 includes all positions smaller than 7577080. Inconsistencies like this one are marked "minor" and colored in yellow. Inconsistency of conflicting rules are marked as 'major' and displayed in red. It's up to the user to decide whether to save the rule anyway or go back and fix the issue.

The collection of rules is combined with an 'OR' logic, meaning that during the variant calling any variant meeting at least one of the different rules will be marked as actionable (aMOI='yes'). This is the reason why any incoherent rule may be, per se, not that critical to the overall variant calling result. However since those incoherencies may be the result of mistype or other human errors, OpenGeneMed marks them as possible issues.

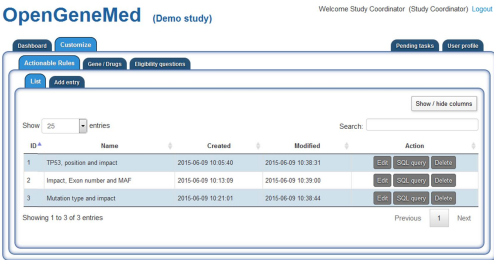


Figure 10: Customize, Actionable Rules, List. Several rules are displayed and ready to be used to call the variants of uploaded vcf files.

4.2.2 Gene/Drugs

In the initial setup of the study, several gene/drugs/pathway are listed and they reflect the state of the MPACT trial for which the GeneMed system (Zhao et al. (2015)) was initially developed. Changing the current list is very easy: to add a new entry, the Study Coordinator should access the 'Add entry' tab under the 'Gene/Drugs' task. The information entered for each entry is displayed in Figure 11.

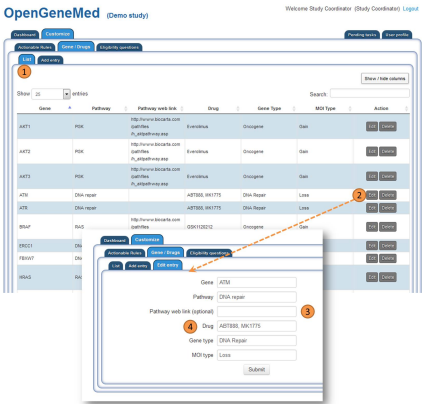


Figure 11: Customize, Gene/Drugs. A table list all the defined genes, with the associated information. Each row can be individually edited/deleted. New entries can be added and the information for each entry is displayed in the lower part of the figure. All fields are mandatory except the pathway web link. However if this link is provided, all the genes that have the same 'Pathway' will have this information filled out automatically. It is important to carefully fill the 'Drug' textfield with a comma separated list of drugs connected to mutation in the gene of interest. The drugs listed in this table are the ones that will be available as 'Treatments' for the 'Treatment Review Team', so make sure that all the information is typed accurately.

4.2.3 Actionable Mutations

In the initial setup of the study, 1220 mutations are listed and they reflect the state of the MPACT trial for which the GeneMed system (Zhao et al. (2015)) was initially developed. Changing the current list is very easy: adding single entries require the Study Coordinator to access the 'Add entry' tab under the 'Actionable Mutations' task. The information entered for each entry is displayed in Figure 12 on the following page. Editing and deleting single entries is as simple as clicking the appropriate action button for the desired entry. Changes to the entire table can be done in bulk using the 'Upload file' tab: the Study Coordinator can upload a CSV file and entirely overwrite the content of the table or just append the new entries to the current table. The CSV header should be gene,chr,start,cosmicid,ref,alt,actionable,reason,cnt and each following lines should contain that information for each mutation. Note that if notes explanation are added (in the 'reason' field for example) commas should NOT be used: use semicolon or other separators instead.

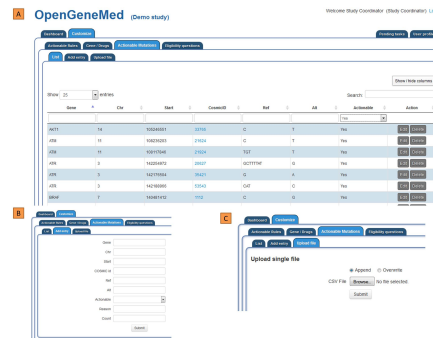


Figure 12: Customize, Actionable Mutation. (A) The table lists all the defined mutations. Each row can be individually edited/deleted. New entries can be added and the information for each entry is displayed in (B). Reason, CosmicID, Alt and Count fields are not mandatory. Reason and CosmicID however are used in the annotation process and reports so it's recommended to fill out this information. (C) Bulk changes to the table can be made uploading a CSV file. Format information is described in the text

4.2.4 Eligibility Questions

In the initial setup of the study, no eligibility questions are listed. To add a new question, the Study Coordinator should access the 'Add entry' tab under the 'Eligibility Questions' task. The information entered for each question is displayed in [Figure 13](#).

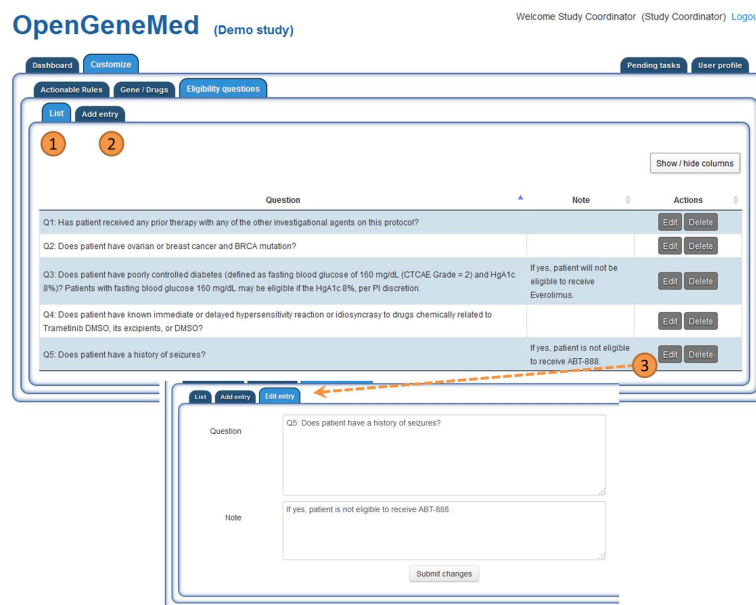


Figure 13: Customize, Eligibility Questions. List of few eligibility questions. New rows can be added clicking the 'Add entry' tab. Existing entries can be edited and deleted, using the appropriate button. Eligibility questions can be stored together with additional notes or comments. These will be displayed to the Clinic Team member when filling the patient information. Questions should have a Yes/No/NA answer. Clinicians are allowed to add notes to the answer, but the basic content of the question should be based on a Yes/No answer.

4.3 Patient registration and editing (Clinic Team)



WARNING: the instructions in this sections are presented using the 'Clinic Team Chief' role. People assigned to this role have additional responsibilities and capabilities compared to the 'Clinic Team' member. Operations allowed only to the 'chief' role have been clearly marked as such.

The main responsibilities of the Clinic Team are:

1. register new patients
2. record information about biopsy samples collected within the study
3. record prior therapies for each patient
4. answer treatment eligibility questions for each patient
5. interact with the Treatment Review Team to receive information about a treatment assignment
6. deliver treatments to the patients and record information about it
7. initiate delinking request (to de-identify information of patients going off-study and allow the use of that information for further research investigations)
8. (chief role) finalize the delinking request

Each task, usually corresponding to a specific tab in the web interface, is described in details in the sections that follow.

4.3.1 Patient registration

Registering a patient into the study requires some basic information to be entered. The most important element is the Patient ID (referred also as PID), which is the identifier used across the entire system to refer to information of that specific patient.

In its default setup, OpenGeneMed imposes only minimal constraints to the format of this ID (i.e., should only contain letters, numbers and _). However since this is a critical information that cannot be modified later on, it is reasonable to add more constraints in the code to warn clinicians of possible typing errors or to make sure that it conforms to a specific pattern (for example, the first four digits refer to a protocol number, the next three digits refer to a clinical center and the last four digits are the incremental patient number). Customizing the code to these needs is easy and examples of this are provided in the 'Technical Documentation' document.

Several fields across the different tasks have validation rules to warn clinicians about missing mandatory data or malformed information. The system has been modelled to the design of the GeneMed system and its everyday use. Adding/removing restriction on any of the field is straightforward and examples are provided in the 'Technical documentation' manual.

Once the patient information has been submitted, the record will be added in the list of patient, as displayed in [Figure 15 on the following page](#). Each patient record can be then accessed, edited and delinked using the appropriate button on the right of each entry.



Note that the table in [Figure 15 on the next page](#) (as any other table in OpenGeneMed) has built-in features that allow to hide/show columns, view the records over different pages, sort the entries and search for specific content.

OpenGeneMed (Demo study) Welcome Clinic Team Chief (Clinic Team Chief) [Logout](#)

Dashboard **Clinic Team** Pending tasks User profile

Patients Biopsy samples Prior systemic therapies Treatment Eligibility Data Ongoing Treatments Pending Treatments

List **Register patient**

1 Patient ID 12349990001 2

Gender This field cannot be empty 3

Histologic Dx Pancreatic cancer

Histologic Dx Subtype Adenocarcinoma

Date of Diagnosis 2015-04-14 4

Age at Diagnosis 64

Comments

Submit

0 April 2015 0

Su	Mo	Tu	We	Th	Fr	Sa
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

Figure 14: Clinic Team, Patients, Register patient. Information needed to register a patient. Some fields (like Patient ID and Gender) are mandatory and cannot be left empty. A message is displayed if mandatory information is missing or malformed. Drop downs or popup are implemented to help the clinician filling structured information. Several fields can contain arbitrary text.

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Dashboard **Clinic Team** Pending tasks User profile

Patients Biopsy samples Prior systemic therapies Treatment Eligibility Data Ongoing Treatments Pending Treatments

List **Register patient**

Show 25 entries Show / hide columns

ID	Samples	Gender	Diagnosis	Dx Date	Submit Date	Action
12349990001	0	M	Pancreatic cancer	2015-04-14	2015-05-12 16:31:05	Edit patient Delete
12349990002	0	F	Ovarian cancer	2015-03-29	2015-05-12 16:42:01	Edit patient Delete
12349990003	0	M	Colon Cancer	2015-05-05	2015-05-12 16:42:37	Edit patient Delete
12349990004	0	F	Ovarian cancer	2015-04-09	2015-05-12 16:43:28	Edit patient Delete
12349990005	0	M	NSCLC	2015-04-14	2015-05-12 16:44:12	Edit patient Delete
12349990006	0	F	Breast Cancer	2015-03-10	2015-05-12 16:44:54	Edit patient Delete
12349990007	0	F	Breast Cancer	2015-03-09	2015-05-12 16:45:32	Edit patient Delete
12349990008	0	M	NSCLC	2015-05-07	2015-05-12 16:46:24	Edit patient Delete
12349990009	0	M	Colon Cancer	2015-03-03	2015-05-12 16:47:03	Edit patient Delete
12349990010	0	F	Ovarian cancer	2015-03-18	2015-05-12 16:47:37	Edit patient Delete

Showing 1 to 10 of 10 entries Previous 1 Next

Figure 15: Clinic Team, Patients, List. View of the current list of registered patients. Each record can be then accessed, edited and delinked using the appropriate button on the right of each entry. The table has built-in features that allow to hide/show columns, view the records over different pages, sort the entries and search for specific content.

[List](#)
[Register patient](#)
[Edit patient](#)

Patient Clinical Information

Patient ID: 12349990002
 Gender: Female
 Histologic Dx: Ovarian cancer
 Histologic Dx Subtype: carcinosarcoma
 Date of Diagnosis: 2015-03-29
 Age at Diagnosis: 58
 Comments:

Molecular Characterized Biopsies

Patient ID	Site	Phase	Biopsy Date	Drug	Action
12349990002	Neck	Initial	2015-05-08		<input type="button" value="Edit"/> <input type="button" value="Delete"/>

Prior Systemic Therapies

Regimen	Time Rx started (month/year)	Best response	Duration	Action
FOLFOLX, Bevacizumab	2014-07-14	PR	3	<input type="button" value="Edit"/> <input type="button" value="Delete"/>
Pemetrexed	2014-12-03	Disease Progression	2	<input type="button" value="Edit"/> <input type="button" value="Delete"/>

Treatments

Regimen	Date Rx started	Best response	No. of cycles	Action
No data available in table				

Treatment eligibility data

Figure 16: Clinic Team, Patients, Patient record. A patient record, collecting information from different tables.

4.3.2 Biopsy samples

Biopsy samples are presented in a collective view, to allow an overall evaluation of the sample collection of the team (Figure 18). Adding each sample requires similar steps as the ones described to add patient clinical information. Details on which information is required is displayed in Figure 17.

Figure 17: Clinic Team, Patients, Biopsy samples, Add. Information needed to record a new biopsy sample. Some fields (like Patient ID and Phase) are mandatory and cannot be left empty. A message is displayed if mandatory information is missing or malformed. Drop downs or popup are implemented to help the clinician filling structured information: for example, the drugs listed in the 'On Drug' field are the ones added by the Study Coordinator as drugs of the study. Several fields can contain arbitrary text.

Note that it is possible add Biopsy samples for a specific patient directly from the patient record (clicking the 'Edit' button of Figure 15 on page 19 opens the complete record of the patient with all his/hers biopsy samples, prior therapies, eligibility questions and treatments. Each table can be edited either from there or using the dedicated generic tab ('Biopsy samples', 'Prior systemic therapies', etc.).

Patient ID	Site	Phase	Biopsy Date	Drug	Action
12349990001	Lung	Initial	2015-05-07		Edit Delete
12349990002	Neck	Initial	2015-05-08		Edit Delete
12349990003	Bone	Initial	2015-04-09		Edit Delete
12349990003	Liver	At Progression	2015-05-20	GSK1120212	Edit Delete

Figure 18: Clinic Team, Patients, Biopsy samples, List. View of the current list of recorded biopsy samples. Each record can be then accessed, edited and deleted using the appropriate button on the right of each entry. The table has built-in features that allow to hide/show columns, view the records over different pages, sort the entries and search for specific content.

4.3.3 Prior Systemic Therapies

Prior therapies are accessed as a per-patient base, so the first information needed to add/edit/delete these records is the Patient ID. After that has been selected, adding records for prior systemic therapies requires similar steps as described in previous sections. Details on which information is required is displayed in [Figure 20](#).

Note that it is possible add prior therapies records for a specific patient directly from the patient record (clicking the 'Edit' button of [Figure 15 on page 19](#) opens the complete record of the patient with all his/hers biopsy samples, prior therapies, eligibility questions and treatments. Each table can be edited either from there or using the dedicated generic tab ('Biopsy samples', 'Prior systemic therapies', etc.).

OpenGeneMed (Demo study) Welcome Clinic Team Chief (Clinic Team Chief) Logout

Dashboard Clinic Team Pending tasks User profile

Patients Biopsy samples Prior systemic therapies Treatment Eligibility Data Ongoing Treatments Pending Treatments

List Add entry

Patient ID: 12349990002

Show 25 entries Search:

Regimen	Time Rx started (month/year)	Best response	Duration (months)	Action
FOLFIRI, Bevacizumab	2014-07-14	PR	3	Edit Delete
Pemetrexed	2014-12-03	Disease Progression	2	Edit Delete

Showing 1 to 2 of 2 entries Previous 1 Next

Figure 19: Clinic Team, Patients, Prior Systemic Therapies, List. View of the current list of recorded Prior Systemic Therapies. Each record can be then accessed, edited and deleted using the appropriate button on the right of each entry. The table has built-in features that allow to hide/show columns, view the records over different pages, sort the entries and search for specific content.

OpenGeneMed (Demo study) Welcome Clinic Team Chief (Clinic Team Chief) Logout

Dashboard Clinic Team Pending tasks User profile

Patients Biopsy samples Prior systemic therapies Treatment Eligibility Data Ongoing Treatments Pending Treatments

List Add entry

Patient ID 12349990002

Regimen Pemetrexed

Date of Rx 2014-12-03

Best Response Disease Progression

Duration (months) 2

Comments

Submit

CR
PR
NA
Disease Progression
Stable Disease
Non-evaluable

Figure 20: Clinic Team, Patients, Prior Systemic Therapies, Add. Information needed to record prior systemic therapies. Some fields (like Patient ID and Regimen) are mandatory and cannot be left empty. A message is displayed if mandatory information is missing or malformed. Drop downs or popup are implemented to help the clinician filling structured information: for example, the 'Best Response' field offers a choice between Complete Response (CR), Partial Response (PR), Not Accessed (NA), Disease Progression, Stable Disease, Non-evaluable. Several fields can contain arbitrary text.

4.3.4 Treatment Eligibility

Treatment Eligibility are accessed as a per-patient base, so the first information needed to add/edit/delete these records is the Patient ID. After that has been selected, a table containing the study eligibility questions is presented to the clinician (Figure 21). The text of each question and associate note is customized by the Study Coordinator at the beginning of the study (See Section 4.2.4). Note that it is possible answer treatment eligibility questions for a specific patient directly from the patient's record (clicking the 'Edit' button of Figure 15 on page 19 opens the complete record of the patient with all his/hers biopsy samples, prior therapies, eligibility questions and treatments. Each table can be edited either from there or using the dedicated generic tab ('Biopsy samples', 'Prior systemic therapies', etc.).

The figure shows two screenshots of the OpenGeneMed interface for a patient with ID 12349990003. Screenshot A shows the initial state with question marks in the 'Answer' column. Screenshot B shows the completed state with specific answers (No, N/A, No, No, Yes) and corresponding notes in the 'Note' column.

OpenGeneMed (Demo study) Welcome Clinic Team Chief (Clinic Team Chief) Logout

Dashboard Clinic Team Pending tasks User profile

Patients Biopsy samples Prior systemic therapies Treatment Eligibility Data Ongoing Treatments Pending Treatments

A Patient ID: 12349990003

Edit answers Show / hide columns

Question	Answer	Note
Q1: Has patient received any prior therapy with any of the other investigational agents on this protocol?	?	
Q2: Does patient have ovarian or breast cancer and BRCA mutation?	?	
Q3: Does patient have poorly controlled diabetes (defined as fasting blood glucose of 160 mg/dL (CTCAE Grade = 2) and HgA1c 8%)? Patients with fasting blood glucose 160 mg/dL may be eligible if the HgA1c 8%, per PI discretion.	?	If yes, patient will not be eligible to receive Everolimus.
Q4: Does patient have known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to Trametinib DMSO, its excipients, or DMSO?	?	
Q5: Does patient have a history of seizures?	?	If yes, patient is not eligible to receive ABT-888.

B Patient ID: 12349990003

Edit answers Show / hide columns

Question	Answer	Note
Q1: Has patient received any prior therapy with any of the other investigational agents on this protocol?	No	
Q2: Does patient have ovarian or breast cancer and BRCA mutation?	N/A	
Q3: Does patient have poorly controlled diabetes (defined as fasting blood glucose of 160 mg/dL (CTCAE Grade = 2) and HgA1c 8%)? Patients with fasting blood glucose 160 mg/dL may be eligible if the HgA1c 8%, per PI discretion.	No	If yes, patient will not be eligible to receive Everolimus.
Q4: Does patient have known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to Trametinib DMSO, its excipients, or DMSO?	No	
Q5: Does patient have a history of seizures?	Yes	If yes, patient is not eligible to receive ABT-888.

Figure 21: Clinic Team, Patients, Treatment Eligibility Data, List. View of the initial (A) and completed (B) treatment eligibility for a patient. To edit the answer, the 'Edit answers' button need to be used. The table has built-in features that allow to hide/show columns and sort the entries. For explanation about the possible answers and messages in case of incoherent information, see text.

If no answer has been provided for a question, the entry will contain a question mark (?). If the question has been answered, the clinician will see one of the three possible answers (Yes, No, N/A for not answered/refused to answer). Note that there is a difference between N/A and ? as the former acknowledges the fact that the patient didn't provide an answer, while the latter simply marks the fact that the information has not been entered in the system.

As mentioned before, the list of eligibility questions presented to the Clinic Team is managed by the Study Coordinator, who should initialize these information at the beginning of the study, before any patient is recruited. However in real situation, study protocols changes over time, and the content of eligibility questions may need to be corrected, changed, new questions may need to be added, or not relevant questions may need to be deleted. These actions can easily be done by the Study Coordinator, but the impact on records already entered in the system may vary. OpenGeneMed provides visual clues to the Clinic Team Member in situations where changes in the question format are done after an answer has already been recorded. An example of all the possible scenarios is depicted in Figure 22 on the next page.

A Patient ID: 12349990002

Edit answers		Show / hide columns	
Question	Answer	Note	
Q1: Has patient received any prior therapy with any of the other investigational agents on this protocol?	?		
Q2: Does patient have ovarian or breast cancer and BRCA mutation?	?		
Q3: Does patient have poorly controlled diabetes (defined as fasting blood glucose of 160 mg/dL (CTCAE Grade = 2) and HgA1c 8%)? Patients with fasting blood glucose 160 mg/dL may be eligible if the HgA1c 8%, per PI discretion.	?	If yes, patient will not be eligible to receive Everolimus.	
Q5: Does patient have a history of seizures? THIS TEXT HAS BEEN ADDED FOR DEMO PURPOSES	?	If yes, patient is not eligible to receive ABT-888.	
Q6: QUESTION ADDED FOR DEMO PURPOSES	?		

B Patient ID: 12349990003

Edit answers		Show / hide columns	
Question	Answer	Note	
Q1: Has patient received any prior therapy with any of the other investigational agents on this protocol?	No		
Q2: Does patient have ovarian or breast cancer and BRCA mutation?	N/A		
Q3: Does patient have poorly controlled diabetes (defined as fasting blood glucose of 160 mg/dL (CTCAE Grade = 2) and HgA1c 8%)? Patients with fasting blood glucose 160 mg/dL may be eligible if the HgA1c 8%, per PI discretion.	No	If yes, patient will not be eligible to receive Everolimus.	
i) Q4: Does patient have known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to Trametinb DMSO, its excipients, or DMSO?	No Acknowledge change		
ii) Q5: Does patient have a history of seizures? THIS TEXT HAS BEEN ADDED FOR DEMO PURPOSES	Yes Acknowledge change	If yes, patient is not eligible to receive ABT-888.	
iii) Q6: QUESTION ADDED FOR DEMO PURPOSES	?		

Figure 22: Clinic Team, Patients, Treatment Eligibility, Effect of question editing. The Study Coordinator changed the eligibility questions after the study has started recruiting patients. (A) The eligibility answers were not recorded for this patient, so the change in the eligibility questions (text editing, deleted question, added question) is transparent to the clinician: the updated questions are displayed and the clinician can add the patient's answer as explained before. (B) The answers for this patient were recorded with the previous version of the questions, so it's now the responsibility of the clinician to decide if the answer to the changed questions need to be changed. In particular: i) question Q4 (marked in red) was deleted from the list. This change has been marked because there may be cases in which the information from the patient may be important, so the clinician can acknowledge the change (so deleting the question from this table as well) but s/he may decide to record this information as a 'Comment' in the patient record. ii) question Q5 has been changed (some text has been added): since the system cannot understand if the change is only stylistic/typo or if it substantially changes the meaning of the question, the entry is marked as orange and is the clinician responsibility to decide if to leave the previous answer or to change it to a different one. iii) question Q6 was added in the list, so the previous group of answers do not contain an answer to this entry: it is shown as a missing record (?).

4.3.5 Ongoing treatments

Ongoing treatments refer to the treatments administered within the study. They are accessed as a per-patient base, so the first information needed to add/edit/delete these records is the Patient ID. After that has been selected, adding records for treatments requires similar steps as described in previous sections. Details on which information is required are displayed in Figure 24.

Note that it is possible add ongoing treatment records for a specific patient directly from the patient record (clicking the 'Edit' button of Figure 15 on page 19 opens the complete record of the patient with all his/hers biopsy samples, prior therapies, eligibility questions and treatments. Each table can be edited either from there or using the dedicated generic tab ('Biopsy samples', 'Prior systemic therapies', etc.).

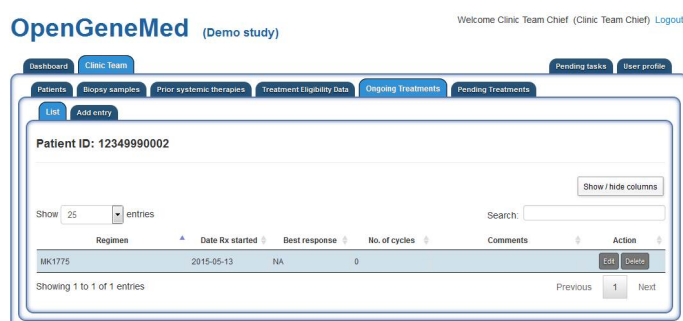


Figure 23: Clinic Team, Patients, Ongoing treatments, List. View of the current list of recorded Ongoing treatments. Each record can be accessed, edited and deleted using the appropriate button on the right of each entry. The table has built-in features that allow to hide/show columns, view the records over different pages, sort the entries and search for specific content.

Figure 24: Clinic Team, Patients, Ongoing treatments, Add. Information needed to record an ongoing treatment. Some fields (like Patient ID and Regimen) are mandatory and cannot be left empty. A message is displayed if mandatory information is missing or malformed. Drop downs or popup are implemented to help the clinician filling structured information: for example, the drugs listed in the 'Regimen' field are the ones added by the Study Coordinator as drugs of the study. Several fields can contain arbitrary text.

4.3.6 Pending treatments

After biopsy samples are collected and analyzed by the lab, the information of the sample is uploaded in OpenGeneMed (in the form of VCF files), properly annotated and the variant calls are reviewed by the lab. Once this step is completed, the Treatment Review Team assess all the information (mutation profile, clinical information, etc) and comes to a decision about the treatment that the patient should undergo within the study. When the Treatment Review Team uploads this decision in OpenGeneMed the Clinic Team will be able to see which treatment deliver to each patient and this information is displayed in the 'Pending treatment' tab (Figure 25). Members of the Clinic Team receive a notification each time new information is available and they should access this task to acknowledge it. Note that recording the actual treatment delivery to the patient needs to be done manually through the 'Ongoing treatment' task described in the previous section.

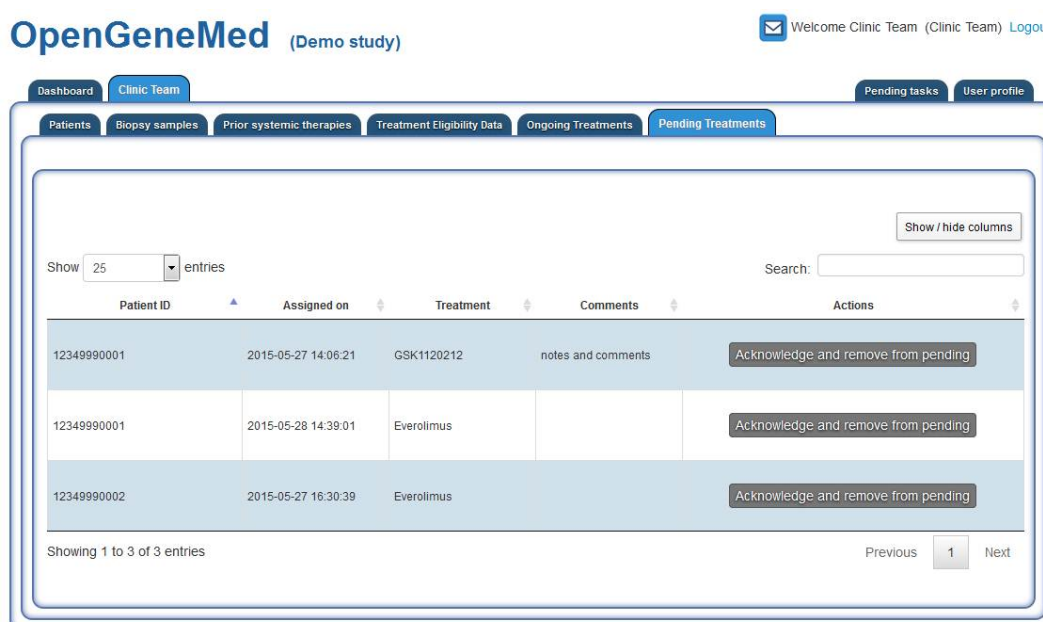


Figure 25: Clinic Team, Patients, Pending treatments. The list of all patient for which the Treatment Review Team reviewed the information and assigned the treatment is displayed. The Clinic Team member should make note of which treatment need to be delivered (with any important note) and click 'Acknowledge and remove from pending' to record the completion of the task.

4.3.7 Delinking

Delinking is the essential process needed to de-identify information of patients going off-study to allow the use of that information for further research investigations. Conceptually, it is a very simple process of creating a random identifier that will replace the Patient ID used throughout the different tables, so that the information in the database will not be linked in any way to the actual patient record in the clinic.

Even if the technical steps are very straightforward, since many groups are involved, and they all use the Patient ID (pid) to label samples and other information internally, a three-steps process is implemented in OpenGeneMed to make sure everyone is aware of the change and everyone updates the records as required.

Once a patient has been delinked, all his/her information will still be accessible though OpenGeneMed but in read-only mode and no information can be deleted or added to delinked records. This is the reason why the responsibility of confirming delink steps is given to Chiefs (for the Lab and Clinic Teams), as they must make sure that all information is updated and complete before the delink can be finalized.

The three steps of delinking are:

1. initial request: done by any member of the Clinic Team (Figure 26 (A));
2. confirmation by the Lab: done by the Lab Team Chief and described in Section 4.4.4 on page 33;
3. final step: done by the Clinic Team Chief (Figure 26 (B)).

Each step triggers an email to the next actor, as well as an internal notification that will be shown in the 'Pending tasks' tab of the designated user (see Section 4.6 on page 36 for more explanations on how to use this tab).

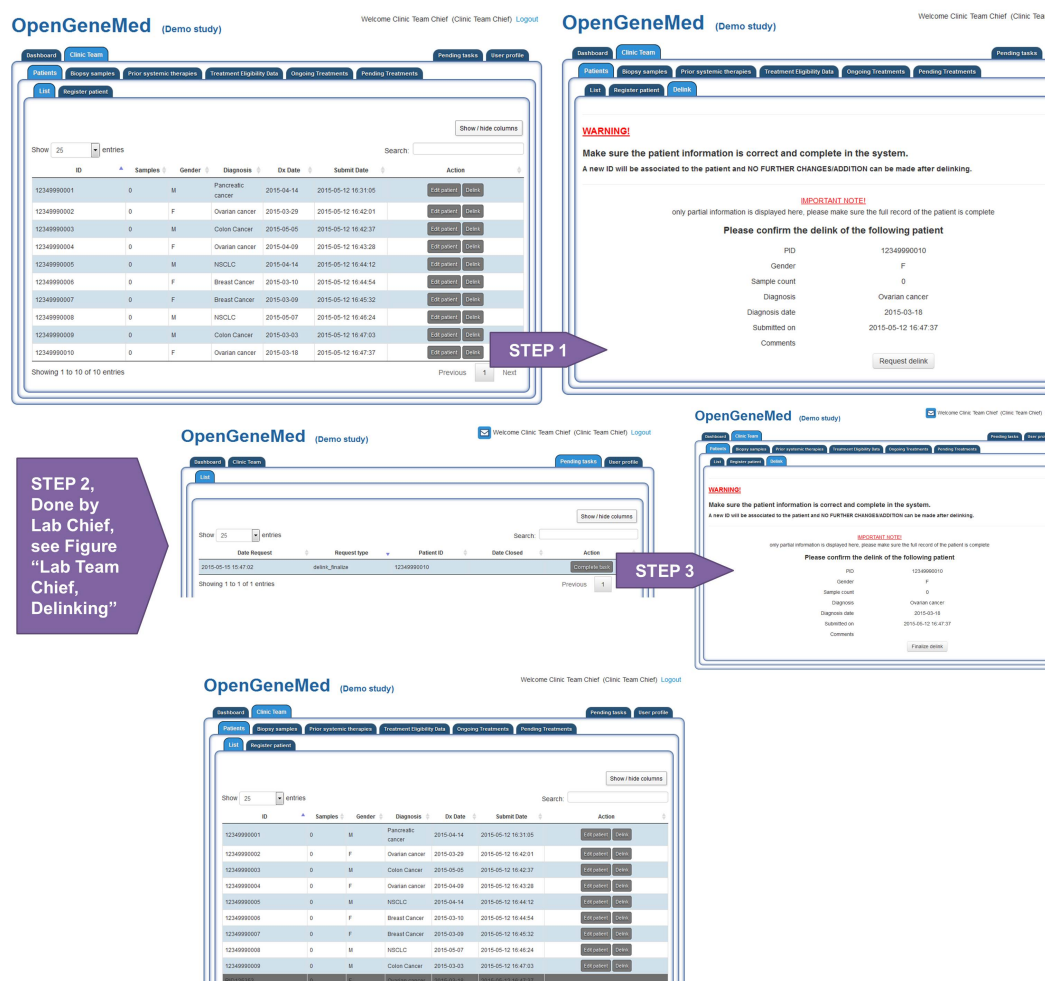


Figure 26: Clinic Team, Delinking. The three steps of delinking. Step 1: the delink of a specific patient is initialized clicking the 'Delink' button in the list of patient view. Anyone in the Clinic Team can initialize the request. Clicking the 'Request delink' button will initiate the process, sending an email and an internal notification to the Lab Team Chief. Step 2: the Lab Team Chief will receive the request and perform his/her task (here omitted, shown in Section 4.4.4 on page 33). Once completed and email and internal notification will be sent to the Clinic Team Chief. Step 3: the Clinic Team Chief can see the delink_finalise task in the list pending tasks. Clickin the 'Complete task' button will automatically redirect the user to the final page for delinking. It's the Clinic Team Chief responsibility to make sure all the records of the patient are complete and accurate (Note that the page only show a partial record for the patient, all the detail information can be accessed through the different tabs explained in previous sections). Once the verification is complete, clicking the 'Finalize delink' button will trigger the replacement of the random generated id in all the tables where the old pid was stored. The record will now be accessible in read-only mode and marked as grey in the different tables.

4.4 Sample upload and variant calling (Lab Team)

WARNING: the instructions in this sections are presented using the 'Lab Team Chief' role. People assigned to this role have additional responsibilities and capabilities compared to the 'Lab Team' member. Operations allowed only to the 'chief' role have been clearly marked as such.

The main responsibilities of the Lab Team are:

1. uploading VCF files from patient samples
2. access variant calling information and review them
3. monitor general variants trends and interact with the Study Coordinator
4. (chief role) execute one of the steps in the delink process (to de-identify information of patients going off-study and allow the use of that information for further research investigations)

Each task, usually corresponding to a specific tab in the web interface, is described in details in the sections that follow.

4.4.1 Sample upload

The 'Upload' tab displays the form used by the sequencing lab to upload the variant file in VCF format. OpenGeneMed analyses VCF files produced by TorrentSuite version 4.0.2. When uploading the variant file, the system uses the combination of the Patient ID and the Sample ID (the VCF file name) as the unique identifier. [Figure 4 on page 10](#) shows the workflow in the data upload and annotation module. Instructions on how to customize/extend this module to fit different studies needs and file format are presented in the 'Technical documentation' manual.

Uploading a file requires to list the Patient ID, Sample Date and select the VCF file from a File explorer window. Once the information is entered, submitting the form will trigger the import of the raw data and the call of the annotation procedure will start ([Figure 27](#)).

The screenshot shows the OpenGeneMed web interface for a 'Demo study'. The user is logged in as 'Lab Team Chief'. The 'Lab Team' tab is active, and the 'Upload' sub-tab is selected. The 'Upload single file' form is displayed with the following fields:

- Patient ID: 12349990001
- Sample Date: 2015-05-04
- VCF File: MCC-177_ceph.vcf (selected via a 'Browse...' button)
- A 'Submit' button is located below the VCF File field.

A large spinning wheel icon is centered below the form, indicating that the upload and annotation process is in progress.

Figure 27: Lab Team, Upload VCF file. Uploading a file requires to list the Patient ID, Sample Date and select the VCF file from a File explorer window. Once the information is entered, submitting the form will trigger the annotation procedure to start. The process may take between few seconds to few minutes (depending on the size and content of the uploaded file). A spinning icon is displayed while the annotation process is ongoing. Once completed, a message will appear and a link to the variant report is provided. All the uploaded sample can also be accessed from the 'Sample' tab as shown in [Figure 28 on the following page](#)

4.4.2 Access and review variant calling information

All the uploaded samples are listed in a summarized view in the 'Samples' tab as shown in [Figure 28](#).

OpenGeneMed (Demo study) Welcome Lab Team Chief (Lab Team Chief) Logout

Dashboard Lab Team Upload Samples Patients Pending tasks User profile

List

Show / hide columns

Show 25 entries Search:

Sample ID	Patient ID	Submit Date	Review Status	Sample Date	Action
PCC-191_ceph	12349990006	05/19/2015 11:37	Incomplete	2015-03-09	View Patient View Variant
MCC-204_ceph	12349990005	05/19/2015 11:31	Incomplete	2015-04-27	View Patient View Variant
MCC-199_ceph	12349990004	05/19/2015 11:30	Incomplete	2015-04-13	View Patient View Variant
MCC-192_ceph	12349990003	05/19/2015 11:27	Incomplete	2015-04-08	View Patient View Variant
MCC-188_ceph	12349990002	05/19/2015 11:26	Incomplete	2015-05-01	View Patient View Variant
MCC-177_ceph	12349990001	05/19/2015 11:19	Incomplete	2015-05-04	View Patient View Variant

Showing 1 to 6 of 6 entries Previous 1 Next

Figure 28: Lab Team, Samples. Summary of the uploaded samples. The table has built-in features that allow to hide/show columns, view the records over different pages, sort the entries and search for specific content. From each sample information about the Variant and Patient details are accessible using the button in the Action column.

Member of the Lab Team can access the basic clinical information of each patient either by clicking the 'View Patient' button in the Samples table or using the 'Patients' tab. Note that this information cannot be edited by the Lab Team and it represents the data entered by the Clinic Team up to that moment. The Lab Team could use this information as reference when reviewing the variant calls.

OpenGeneMed (Demo study) Welcome Lab Team Chief (Lab Team Chief) Logout

Dashboard Lab Team Upload Samples Patients Pending tasks User profile

List View patient

Patient Clinical Information

Patient ID	12349990006
Gender	F
Histologic Dx	Breast Cancer
Histologic Dx Subtype	HER2 type
Date of Diagnosis	2015-03-10
Age at Diagnosis	47
Comments	

Figure 29: Lab Team, Patient information. Basic clinical data of a patient is displayed to the Lab Team group only for general information. No editing is allowed and additional information about prior therapies, eligibility criteria are omitted.

The variants for each uploaded sample can be viewed by clicking the 'View Variant' button for the desired entry in the table of samples. An example of the variant call table is shown in [Figure 30 on the following page](#). Embedded hyperlinks for each variant enables detailed lookup in COSMIC and dbSNP databases, dynamic queries in the dbSNP database, and manual review of variants.

The members of the Lab Team are expected to review the variants and approve them if they meet criteria decided by the Lab Team. Variant calls can be rejected if the team suspect some technical issue with the sequencing and some further verification is necessary, or if the variant belongs to a list that the protocol explicitly asks to be ignored, etc.

OpenGeneMed (Demo study)

Welcome Lab Team Chief (Lab Team Chief) Logout

Dashboard Lab Team

Upload Samples Patients

List View variants

Patient ID: 12349990006

Available samples: (1)

PCC-161_ceph

Sample annotated on: 05/19/2015 11:37

Notify Treatment selection team of completed review

Show / hide columns

Search:

25 entries

Review	aMOL	Gene	Pathway	Type	Drug	HP	Impact	COSMIC ID	Count	Chr	Position	REF (hg19)	ALT (tumor)	Allele Freq	Read Depth	Codon Change	AA Change
Yes	PARP1	DNA repair	Loss	MK1775	3	FRAME_SHIFT	21691	1	1	226551691	TC	T	0.00	1218	-	-913	
Yes	MSH2	DNA repair	Loss	ABT888, MK1775		FRAME_SHIFT			2	47630526	T	TG	0.05	541	-G	-667	
Yes	MSH2	DNA repair	Loss	ABT888, MK1775		STOP_GAINED	26121	1	2	47639565	G	T	0.00	549	Gga/Tga	G220*	
Yes	MSH2	DNA repair	Loss	ABT888, MK1775	7	FRAME_SHIFT	26124	1	2	47639587	GA	G	0.00	538	-	-227	
Yes	MSH2	DNA repair	Loss	ABT888, MK1775		FRAME_SHIFT	26126	1	2	47641547	AC	A	0.00	841	-	-311	
Yes	ATR	DNA repair	Loss	ABT888, MK1775	5	STOP_GAINED	35421	3	3	142176504	G	A	0.00	934	Cga/Tga	R2533*	
Yes	ATR	DNA repair	Loss	ABT888, MK1775		FRAME_SHIFT	53543	1	3	142188966	CAT	C	0.00	1223	-	-2093	
Yes	ATR	DNA repair	Loss	ABT888, MK1775		FRAME_SHIFT	20627	1	3	142254972	GCTTTTAT	G	0.00	996	-	-1264	

Showing 1 to 25 of 385 entries

Save as

Previous 1 2 3 4 5 ... 16 Next

Figure 30: Lab Team, Variants table. Variant call report for the selected sample.

- (1) the Patient ID and the currently selected sample are shown at the top of the page. If more than one sample is available for a patient, the user can access the information of the other samples using the drop-down menu;
- (2) The table containing variant calls is a big and dynamic table with built-in features that allow to hide/show columns, view the records over different pages, sort the entries and search for specific content;
- (3) Some columns are hidden by default, and the complete list of columns, each selectable using the specific checkbox, is available in the top right corner of the table;
- (4) A generic textual search filter is positioned on the top right corner of the table. This filter hides all the rows of the table not containing the text typed in the search field. The filter operates on the content of the entire table, not on specific columns;
- (5) Sorting and Filters are provided for each separate column. Clicking on the column header would sort the entries in increasing/decreasing order with respect to the content of that column. Several columns have special filters: some columns display drop-down menus, some numerical filters to help showing only rows meeting criteria like 'Allele Frequency greater than 0.74', while other filter are just generic text filters. To reset any filter, simply delete the content of the filter or select the empty option in the drop-downs;
- (6) Each variant call should be reviewed by the Lab Team: clicking the icon in the 'Review' column opens an additional page (Figure 31 on the following page) where the user can review details of the call and decide how to review the entry. The icons represent the different status of the review (not reviewed, accepted, rejected, etc.);
- (7) Since the table may contain a large number of entries, the table divides the content into pages (accessible from page numbers in the lower right corner of the table). The total number of entries is shown in the lower left corner of the table and the number of entries per page is determined by a drop-down menu on the top left corner of the table;
- (8) The entire table can be saved into a CSV (comma separated value) format for access on a local machine and further off-line reviews;
- (9) Once the review of the sample is complete, the Lab Team member should click the button at the top of the page to notify the Treatment Review Team that their action is required for this patient. Note that it is not required to assign a reviewed status to each single entry in the variant call table: however it is the responsibility of the Lab Team to make an accurate and complete assessment of the sample;
- (10) The date and time of the current annotation result is displayed. If only the date is shown (as in the case above) this data is for informational purposes only. However if an additional button is shown to 'Rerun variant call', this is an indication that the rules for the variant annotation calls has been changed by the Study Coordinator after this sample was uploaded and annotated. This may create a major inconsistency since the rules that determines what is defined as variant impact the results shown in the table. It is the Lab Team Chief responsibility to decide how to manage the situation (i.e., if to rerun the variant call with the new rules, or if to ignore the warning and review the current state of the sample variant calls).

OpenGeneMed (Demo study)

Welcome Lab Team Chief (Lab Team Chief) [Logout](#)

Variant Review Record

Is this variant called an actionable mutation? Yes

Is this variant in our AMOI list? Yes

Reason to be called an actionable mutation: Loss of function: FRAM_SHT

Review Status: Not Reviewed Yet

Comments:

[Submit changes](#)

Annotation information for this Variant

Patient ID	1234567890	Amino Acid Change	-913	Chromosome	1
Sample ID	PCC-161_c9ph	Codon Change		Position	226551691
Gene	PARP1	Impact	FRAM_SHT	Homo Polymer	3
Allele Frequency (ALT)	0.00	Pathway	DNA repair		
Coverage (Read Depth)	1218	Str Predict		Minor Allele Freq in Population	
REF	TC	Str Score		European American	0.00
ALT	T	COSMIC id	21691	African American	0.00
CNT	1	dbSNP id		Total (combined)	0.00

Figure 31: Lab Team, Variant review. All the information for a single variant call is displayed in this page. The Lab Team member should decide how to review the variant. Comments can be added. Upon submitting the information, the review status of that entry in the table will be characterized by a different icon corresponding to the choice previously entered. Editing any entry can be achieved by clicking again on the corresponding icon in the variant call table.

4.4.3 Visualize summarized study information

As the study progresses and patients are registered and treated, aggregated trends can be accessed by the Lab Team as well as the Biostatisticians Team to access trends and possibly discussing changes/addition to the protocol to account for observed results.

The information in the different 'Trial Stats' tabs it's presented with similar graphics so here we present only the 'In study variants' tab.

This tab collects information about the variants of interest in the current study (Figure 32). A pie chart (color coded for the pathways included in the study) shows the current variants found in samples uploaded in the system. The pie chart is dynamic and slices' visibility can be toggled on/off. Right below the pie chart, a table containing the same information is displayed for easy of query. A dynamic bar chart with the same information is also displayed on the page. If additional information is needed for a specific set of genes' variants, the user can select the desired genes and click the 'Show variants for selected genes' button: this will reload the page with an additional table at the end containing the specific information for the requested gene variants.

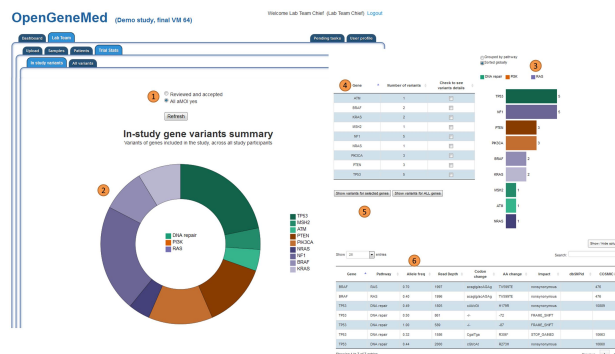


Figure 32: Lab Team, In study variants. Aggregate information about the variants of interest in the current study. (1) the user can select to visualize only the approved variants, or all the ones that have been called. (2) the pie chart (color coded for the pathways included in the study) shows the current variants found in samples uploaded in the system. The pie chart is dynamic and slices' visibility can be toggled on/off. (3) Dynamic bar chart with the same information and (4) a table containing the same information for easy of query; (5) visualize additional information about selected variants by clicking the appropriate button, (6) additional table containing the specific information for the requested variants.

Information about all the variant called can be retrieved easily from the Trial Stats/All Variant tab. This feature allows the Lab Team to query all variants with a defined allele frequency and read depth and see the distribution of those across the uploaded samples. For research purposes it's important to be able to query the data beyond the specific rules defined for the study, as this could also help in identifying interesting targets that could trigger changes in the protocol or inclusion of new drugs in the study.

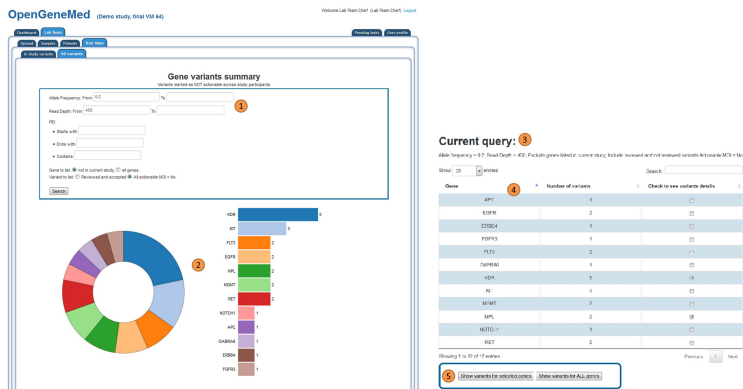


Figure 33: Lab Team, All identified variants. Aggregate information about all the variants in the uploaded samples. (1) The user can define the parameter for the query as Allele frequency ranges, Read depth ranges and specific string patterns for the patient ID (helpful to limit the search to few samples of interest). (2) the pie chart and the bar chart show the current variants found in samples. (3) The textual representation of the submitted query, printed for reference. (4) A table containing the same information for easy of query and sorting; (5) If further information is needed for specific variants, the user can select the variants from the table and, by clicking the appropriate button, an additional table will appear. This table contains the detailed information for the selected variants.

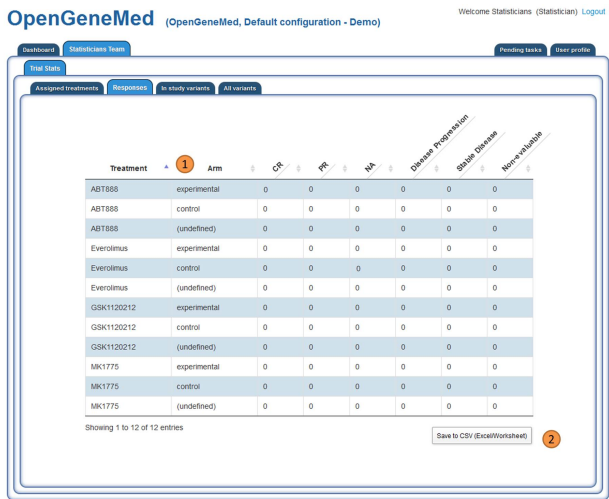


Figure 34: Biostatisticians Team, Responses. Count of patients assigned to each treatment, displayed according to the response and arm assignment (if available) (1) in the dynamic table each column can be sorted by clicking the header (note that in the demo version, no treatment response is stored, so the table contains only zeros); (2) the table can be exported in a comma separated value file that can be processed by Excel or any other external platform for further analysis.

4.4.4 Delinking

As explained in [Section 4.3.7 on page 26](#), delinking is the essential process needed to de-identify information of patients going off-study to allow the use of that information for further research investigations. Conceptually, it is a very simple process of creating a random identifier that will replace the Patient ID used throughout the different tables, so that the information in the database will not be linked in any way to the actual patient record in the clinic.

Even if the technical steps are very straightforward, since many groups are involved, and they all use the Patient ID (pid) to label samples and other information internally, a three-steps process is implemented in OpenGeneMed to make sure everyone is aware of the change and everyone updates the records as required.

Once a patient has been delinked, all his/her information will still be accessible through OpenGeneMed but in read-only mode and no information can be deleted or added to delinked records. This is the reason why the responsibility of confirming delink steps is given to Chiefs (for the Lab and Clinic Teams), as they must make sure that all information is updated and complete before the delink can be finalized.

The three steps of delinking are:

1. initial request: done by any member of the Clinic Team ([Figure 26 on page 27 \(A\)](#)) and described in [Section 4.3.7 on page 26](#);
2. confirmation by the Lab: done by the Lab Team Chief;
3. final step: done by the Clinic Team Chief ([Figure 26 on page 27 \(B\)](#)) and described in [Section 4.3.7 on page 26](#).

Each step triggers an email to the next actor, as well as an internal notification that will be shown in the 'Pending tasks' tab of the designated user (see [Section 4.6 on page 36](#) for more explanations on how to use this tab).

Once the initial request is submitted, the Lab Team Chief will access the record, and perform the task as shown in [Figure 35](#).

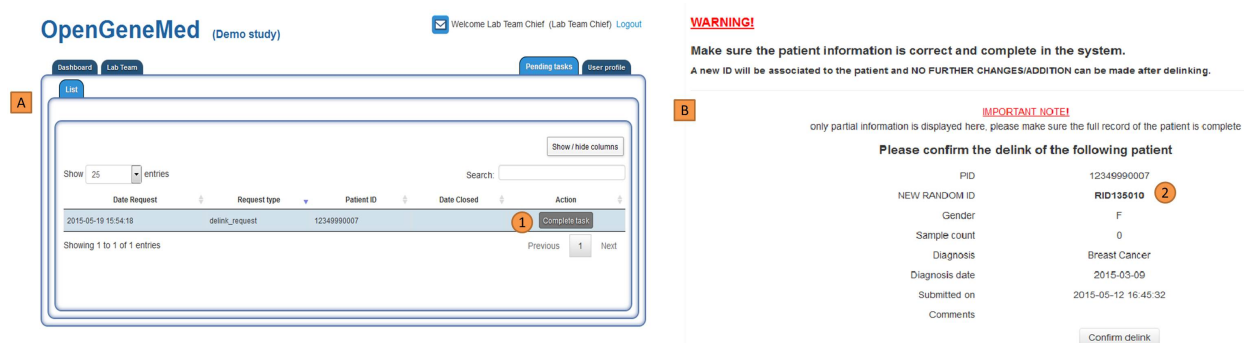


Figure 35: Lab Team Chief, Delinking. (A) The Lab Team Chief receives the request to delink from the Clinic Team (steps shown [Section 4.3.7 on page 26](#)). Clicking the 'Complete task' button will automatically redirect the user to the page with the information to confirm the delinking. (B) It's the Lab Team Chief responsibility to take note of the new Random ID generated by OpenGeneMed and to make sure that the previous PID is replaced with the new Random ID on all the samples and in all the records stored in the lab. Once the verification is complete, clicking the 'Confirm delink' button will trigger an email to be sent to the Clinic Team Chief for the final delink of the patient from the system.

4.5 Treatment assignment (Treatment Review Team)

Once the Lab Team completes the review of the annotated variants, they will use the button shown in [Figure 30 on page 30](#) (9) to notify the Treatment Review Team that the patient information is ready to be accessed and the treatment assignment decision need to be taken. [Figure 36](#) shows how the notification and the task of reviewing the patient information is carried out by the Treatment Review Team.

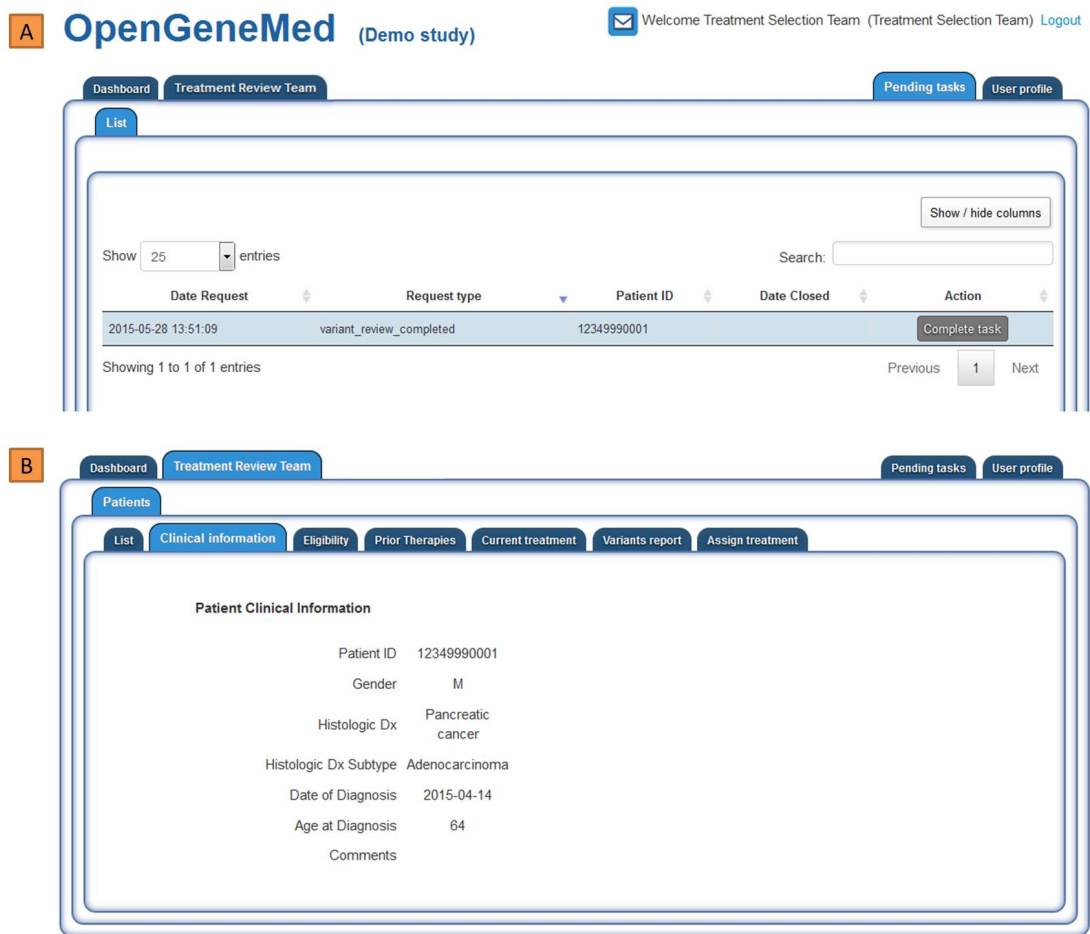


Figure 36: Treatment assignment task. (A) Notification from the Lab Team that the variant review is complete for the patient and his/her record can be accessed. (B) all information about the patient should be reviewed by the Treatment Review Team before selecting which treatment to assign. Of particular importance, the 'Eligibility' and the 'Variant report' tab, explained in the text

Information in each tab should be carefully reviewed to assess the patient status. Two of the most critical piece of information to make a sensible treatment assignment are 'Variant report' and 'Eligibility'. The former contains a list of the variant calls approved by the Lab Team ([Figure 37 on the next page](#) (A)), while the latter (as well as all other tabs) shows the data entered by the Clinic Team after registering the patient in the study. Since the variant reviewed notification may come before the Clinic Team has the chance to complete the Eligibility criteria answers, a warning message is displayed if this information is missing ([Figure 37 on the following page](#) (B)). A notification can be sent to the Clinic Team about this missing information and a second notification to the Treatment Review Team will be sent once the Clinic Team completes its task. At this point all the information for the patient is complete ([Figure 37 on the next page](#) (C)) and the Treatment Review Team can access the 'Assign Treatment' tab and select the appropriate treatment as shown in [Figure 38 on the following page](#).

A

Patient ID: 12349990001

Only variants that have been reviewed by the lab team and have a positive review are shown. If a sample has not been processed yet or it does not have positively reviewed variants, the table below will be empty.

Sample annotated on: 05/19/2015 11:19

Show / Hide columns

Show 25 entries

Review	alt	Gene	Pathway	Type	Drug	Impact	COSMIC ID	Count	Chr	Position	REF (hg19)	ALT (tumor)	Allele Freq	Read Depth	Codon Change	AA Change
Yes	PRAP1	DNA repair	Loss	MK1775	FRAME_SHIFT	21691	1	1	23551691	TC	T	0.00	1992	-	-	-913
Yes	MSH2	DNA repair	Loss	ABT888	STOP_GAINED	20121	1	2	47636950	G	T	0.00	754	Gga>Tga	G220P	

Showing 1 to 2 of 2 entries

Save as

B

Patient ID: 12349990001

Eligibility questions

Eligibility answers for the patients are incomplete!

Notify clinic team of missing information

C

Patient Clinical Information

Patient ID: 12349990001

Gender: M

Histologic Dx: Pancreatic cancer

Histologic Dx Subtype: Adenocarcinoma

Date of Diagnosis: 2015-04-14

Age at Diagnosis: 64

Comments

Patient ID: 12349990001

Treatments

Regimen: Date Rx started: Best response: No. of cycles: No data available in table

Patient ID: 12349990001

Prior Systemic Therapies

Regimen: Date Rx started: Best response: Duration: No data available in table

Patient ID: 12349990001

Eligibility questions

Question	Answer	Note
Q1: Has patient received any prior therapy with any of the other investigational agents on this protocol?	No	
Q2: Does patient have mutation in breast cancer and BRCA mutation?	No	
Q3: Does patient have poorly controlled diabetes (defined as fasting blood glucose of 160 mg/dL, (CTCAE Grade = 2) and HgA1c > 8%)? Patients with fasting blood glucose 160 mg/dL, may be eligible if the HgA1c < 8%, per PI discretion.	No	If yes, patient will not be eligible to receive Everolimus
Q4: Does patient have known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to Trametinib (GSK), its excipients, or DMARD?	No	
Q5: Does patient have a history of seizures?	No	If yes, patient is not eligible to receive ABT-888

Figure 37: Treatment assignment task. (A) Variant report. (B) Missing information in the Eligibility tab requires a notification to be sent to the Clinic Team. (C) Patient information is collected in different tabs and needs to be reviewed to assess the treatment assignment task.

OpenGeneMed (Demo study) Welcome Treatment Selection Team (Treatment Selection Team) [Logout](#)

Dashboard **Treatment Review Team** Pending tasks User profile

Patients

List **Clinical information** **Eligibility** **Prior Therapies** **Current treatment** **Variants report** **Assign treatment**

Patient ID: 12349990001

Available treatments:

Arm (optional):

Comments:

Figure 38: Treatment assignment task. The Treatment Review Team can select which treatment to assign between the list of available drugs in the study. Comments can be added to communicate special instruction to the Clinic Team. The optional information about experimental/control arm can also be submitted. Once the 'Submit' button is clicked, a notification is sent to the Clinic Team and they will be able to access this information and deliver the proper care to the patient.

4.6 Pending tasks and User Profile (common across roles)

Each member of a OpenGeneMed study has a different role and responsibilities, but many interactions are tightly interconnected. Taking action within a reasonable timeframe is essential for a smooth management of the study. In order to support this issue, OpenGeneMed allows to send notifications to the 'next team' in the pipeline in critical steps of the process. Notifications are sent via email (using the registered username address) but they are also directly accessible through the 'Pending task' tab of OpenGeneMed (Figure 39). Each notification is meant only for specific groups, so the figure shows just few examples of the notifications available. The complete list of tasks/teams is described in Table 1).

Date Request	Request type	Patient ID	Date Closed	Action
2015-05-27 14:06:21	treatment_assignment_completed	12349990001		Complete task
2015-05-27 16:30:39	treatment_assignment_completed	12349990002		Complete task
2015-05-27 16:30:11	eligibility_incomplete	12349990006		Complete task

Figure 39: Pending task. Notifications are sent via email (using the registered username address) and directly accessible through the 'Pending task' tab. The Figure shows few notification visible to the Clinic Team. The complete list of tasks/teams is described in Table 1).

Task label	Displayed to		Description
uploaded_vcf	Lab Team	and Lab Chief	when a memeber of the Lab Team uploads a new VCF file, this notification alerts all the people in the group that a new file has been added and it is ready to be reviewed.
variant_review_completed	Treatment Team	Review Team	once the Lab Team reviews the patient variants, this notification alerts the Treatment Review Team that the new information is ready to be reviewed for treatment assignment.
eligibility_incomplete	Clinic Team		as the Treatment Review Team proceeds to review the patient variants, the treatment Review cannot be done if eligibility questions are not answered for the patient. This notification alert the team of missing information
eligibility_completed	Treatment Team	Review Team	if the Treatment Review Team issued a 'eligibility_incomplete' notification, this notification will alert the Treatment Review Team of the completion of the task by the Clinic Team.
treatment_assignment_completed	Clinic Team		once the Treatment Review team reviews the patient variants and clinical information, the treatment is selected and this notification alert the Clinic Team of the new information
randomid_issue	Admin		during the delinking process, if issues arise in generating the unique random id, this notification alerts the Admin team of the issue.
delink_request	Lab Team Chief		a member of the Clinic Team initialized the delinking process. This notification alerts the Lab Team Chief that a new random id is available to be viewed and used for relabelling samples in the lab.
delink_finalize	Clinic Team Chief		once the Lab Chief completed the delinking process on their end, this notification alerts the Clinic Team Chief that everything is ready for the final step of the delinking process

Table 1: Notifications generated within the OpenGeneMed system to coordinate the actions of different teams.

Each user of OpenGeneMed can access and update his/her own information using the 'User Profile' tab (upper right corner). As shown in [Figure 40](#), each user can change email address, password, first and last name. No changes are allowed to the User role, since this information is managed by the Admin team.

The screenshot shows the 'User profile' tab selected in the top navigation bar. Below it, the 'Personal information' sub-tab is active. The form contains the following fields and labels:

- Email Address (used as username):** A text input field containing 'opengenemed_clinicteam@examp'.
- User Role:** A dropdown menu showing 'Clinic Team'.
- First Name:** A text input field containing 'Clinic Team'.
- Last Name:** A text input field containing 'Clinic Team'.
- New Password:** A text input field.
- (if you want to change it, otherwise leave empty):** A label for the new password field.
- Retype new password:** A text input field.
- Submit changes:** A button at the bottom right of the form.

Figure 40: User Profile. Users can change their own email address, password, first and last name. No changes are allowed to the User role, since this information is managed by the Admin team.

5 Implementation of the OpenGeneMed system

The OpenGeneMed system has been designed and developed by the Biometric Research Branch in the Division of Cancer Treatment and Diagnosis of the National Cancer Institute.

The OpenGeneMed system is operating on Virtual Machine running a CentOS 64 bit Linux (CenOS 6.7, kernel 2.6.32) and it uses MySQL (version 5.1.73) as back-end database. Technical documentation about how to setup and initialize the system is provided in the 'Technical documentation' file.

The application is built on a client-server architecture, which provides multiuser access to the application. The application can be launched in any modern web browser and presents an intuitive graphic user interface.

The front end (client side) interface is scripted using HTML, CSS, and JavaScript. The back end (server side) are scripted using Perl (details on modules used are provided below). Java (version 1.8.0_51) is installed as pre-requirement to run the annotation software snpEff (version 3.4, released Jan 16, 2014, downloaded from <http://sourceforge.net/projects/snpeff/files/>).

There are 21 MySQL tables in the default setup of the OpenGeneMed system. More technical details about the context and structure of the database, about how to setup the system, access the client and customize the code are available in the 'Technical Documentation' file.

5.1 Accessing the client

Once the VM is running, type the IP address of the VM in any web browser to use the OpenGeneMed system. If you don't see a login screen there may be something wrong with the VM setup: contact the IT personnel responsible of this setup for any help on these issues (the server may be running behind a firewall, or the VM has not be configured correctly).

If the VM is setup correctly, the login screen should be visible and the IT personnel that setup the VM should have provided you details on which username and password to use to access OpenGeneMed. In the basic initial setup, eight accounts are added for demo purposes (usernames and passwords in [Table 2](#)). However the first recommendation while setting up the VM is to change/delete these accounts, so they may not work. Please contact your IT team with questions about this.

Role	Username	Password
Admin	opengenemed_admin@example.com	aaaAAA111
Clinic Team	opengenemed_clinicteam@example.com	bbbBBB222
Lab Team	opengenemed_labteam@example.com	cccCCC333
Lab Team Chief	opengenemed_labteamchief@example.com	dddDDD444
Clinic Team Chief	opengenemed_clinicteamchief@example.com	eeeEEE555
Study Coordinator	opengenemed_studycoordinator@example.com	fffFFF666
Statistician	opengenemed_statistician@example.com	gggGGG777
Treatment Review Team	opengenemed_treatmentteam@example.com	hhhHHH888

Table 2: Eight accounts added in the OpenGeneMed system for demo purposes. The first recommendation while setting up the VM is to change/delete these accounts, so they may not work on your specific system: please contact the IT team that set up your system with questions about this issue.

Details about how to use the different features of the system are presented in [Section 4 on page 12](#).

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