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Anegene

Digital Discovery Workbook

Nov 8th, 2018

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Value Proposition

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Regulatory Assessment

FDA Regulatory Assessment - Anegene

1. Who is the user?
Any Perioperative Health Care Provider (for example: Anesthesiologist, Intensivist, Surgeon, or Internist/Nurse Practitioner/Physician's Assistant)

2. What is the purpose of the app? (Provide a 1 paragraph description)
An increasing percentage of patients have genetic information available at the time they present for surgery, however, physicians and other health care providers (stakeholders) are distrustful and not trained to contextualize this information.

Anegene is a comprehensive, easy-to-use platform that enables these providers to (i) identify patient attributes that may affect their care and (ii) stratifies the risk of perioperative complications to delivery personalized medicine and improve the care provided.

3. What are the inputs to the app? Be specific.
Patient Demographic:
- *Age*
- *Sex*
- *Gender*
- *Race*
- *Height*
- *Weight*
- *BMI*

Patient Past Medical History:
- *Sleep Apnea*
- *Tobacco Use*

- *Motion sickness*
- *Anxiety*
- *DVT/PE*
- *Autoimmune Disease*
- *Coronary Artery Disease*
- *COPD*
- *Hypertension*
- *Congestive Heart Failure*
- *Renal Disease*
- *Diabetes*
- *Medications (ACE-inhibitor, Beta-blocker, Oral Contraceptive)*

Laboratory values:

- *Hemoglobin*
- *INR*
- *Platelets*
- *Cholesterol*
- *HgbA1C*

Patient Genetic: in whatever form available, designed to accommodate:

- *Michigan Genomics Initiative (GWAS)*
- *Direct-to-Consumer Genetic Testing (23andMe, AncestryDNA, FamilyTreeDNA, etc)*
- *Exome sequencing*
- *Whole Genome Sequencing*

4. What are the outputs of the app? Be specific.

Comorbidity Identification: *will "flag" patients that may be at greater than population-baseline risk for the following conditions impacting anesthetic management*:

- Hypertrophic Obstructive Cardiomyopathy (HOCM)
- Long QT Syndrome
- Multiple Sclerosis
- Pseudocholinesterase Deficiency
- Malignant Hyperthermia
- Postoperative Nausea/Vomiting
- Stroke/Cerebrovascular Disease
- Pulmonary Hypertension
- Asthma
- Porphyria
- Pernicious Anemia
- Factor V Leiden

Pharmacologic Variation: *Identify patients with genetic variants that would influence dosage, resistance, or potential toxicity to commonly used anesthetic drugs, including (but not limited to):*

- Propofol
- Rocuronium
- Heparin
- Codeine

Risk Stratification: Predict adverse medical outcomes following surgery, including (but not limited to):

- Adverse Cardiac event (myocardial infarction)

- Prolonged hospitalization
- Sepsis
- Renal Failure
- Postoperative Pulmonary Complication

5. If the app provides recommendation for patient treatment, briefly describe the scientific basis for the algorithm used to generate the treatment recommendations.

Identification:

- We have developed a generalized probabilistic framework to predict whether a patient will have a phenotype. Our model will incorporate (i) patient medical history (from the electronic medical record), (ii) available genetic data (including whole genome, exome, and GWAS formats) with (iii) patient demographic information to predict the risk of key anesthetic phenotypes.
- Initial phenotypes will be static (independent of the perioperative course, such as malignant hyperthermia, pseudocholinesterase deficiency, or familial long QT syndrome. This will be expanded to dynamic outcomes (such as postoperative nausea/vomiting and stroke) through the incorporation of machine-learning techniques.
- Our validation metric we will quantify the *sensitivity* and *specificity* of our algorithm to detect each of the defined comorbidity (or phenotype). The diagnostic *gold standard* for each phenotype will be composite of (i) ICD-9/10 billing codes, (ii) diagnoses listed in the Operative *History and Physical*, and (iii) natural language processing review of the full electronic medical record with post-query physician audit. We expect our algorithm to have high concordance with gold standard definitions for comorbidities with Mendelian inheritance patterns and relatively high penetrance, such as malignant hyperthermia, pseudocholinesterase deficiency, and Factor V Leiden. We expect much lower concordance with more complex inheritance patterns and interplay between environmental and genetic factors, such as asthma and multiple sclerosis. We have deliberately selected a combination of comorbidities to characterize the potential value of genetic prediction in varied disease pathology.

Risk Prediction:

- We will combine genetic data with patient demographics and past medical history including laboratory results to predict the probability of developing a postoperative complications, including *perioperative myocardial infarction*(initial validation). Initial variables to be included in our model will be selected using multivariable logistic regression and GWAS analysis of MGI Data.
- Relative weight to each predictive node will be assigned using MGI Database, the Electronic Medical Record, and University of Michigan Anesthetic records as a training dataset
- Our predictive algorithm will be validated against commonly used risk assessment metrics.

6. What is the hardware platform?

Web-based server, for marketing directly to Anesthesiologist and other perioperative health care providers (surgeons, intensivists, internal medicine). The platform will be capable of uploading and processing the spectrum of genetic data: (i) Genome Wide Association Studies (GWAS), (ii) Exome Sequencing, and (iii) Whole Genome Sequencing and interfacing with personal and institutional sources of genetic data.

7. How will the software be provided? (e.g, downloaded from App store, pre-installed on hardware platform).

Initial algorithm will be linked from my Lab research website (and freely distributed). Subsequent iterations will (potentially) be automated and integrated into EMR.

Initial Regulatory Review

Donna-Bea Tillman, Ph.D, Biologics Consulting
October 23, 2018

The proposed software appears to fall into the general category of clinical decision support. FDA's December 8, 2017, "Clinical and Patient Decision Support Software: Draft Guidance for Industry and Food and Drug Administration Staff" (CDS Guidance) defines CDS as software functions that meet the following three criteria:

(1) not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system; and
(2) intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines); and
(3) intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition.

The 21st Century Cures Act and FDA's draft CDS guidance further state that CDS software that meets the following criterion will not be regulated by FDA as a medical device:
intended for the purpose of enabling such health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient.

FDA's CDS guidance expands upon this last criterion as follows:

In order for the software function to be excluded from the definition of device, the intended user should be able to reach the same recommendation on his or her own without relying primarily on the software function. The sources supporting the recommendation or underlying the rationale for the recommendation should be identified and easily accessible to the intended user, understandable by the intended user (e.g., data points whose meaning is well understood by the intended user), and publicly available (e.g., clinical practice guidelines, published literature). A practitioner would be unable to independently evaluate the basis of a recommendation if the recommendation were based on non-public information or information whose meaning could not be expected to be independently understood by the intended health care professional user.

If the App were simply to display the patient information, it would not be regulated as a medical device. If the App were to present a risk score using a widely accepted and completely transparent method such as MEWS or APACHE, FDA would not regulate it as a medical device.

However, the App includes what appears to be a new risk model "to predict whether a patient will have a phenotype. Our model will incorporate (i) patient medical history (from the electronic medical record), (ii) available genetic data (including whole genome, exome, and GWAS formats) with (iii) patient demographic

information to predict the risk of key anesthetic phenotypes". Furthermore, it appears that the model (at least in future versions) will incorporate a machine-learning based algorithm. Given the apparently complexity of the proposed model, I do not believe that the intended user could reach the same recommendation on his or her own without relying primarily on the software function. Therefore, I believe that the proposed App will be regulated by FDA as a medical device.

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Use Case Definition

Use case definition contains requirements for the Anegene application.

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Use Case Definition

Project: Anegene – Use Case
Date: October 5, 2018
Owners: Sarah Jomaa, April Kwon

Goal:

As a physician, I want to improve my patient outcomes through a unified digital platform that identifies patient attributes that may affect their care and stratifies the risk of key perioperative complications.

Provider Use Cases:

1. As a physician, I want to onboard to the application without a steep learning curve so I do not have to spend too much time learning a new software during my busy schedule.
2. As a physician, I want my existing medical organization portal accounts to be linked to the service and import existing patient data so I don't have to manually fill in everything myself.
3. As a physician, I want a patient dashboard that allows me to see the overview of patients with an organized and informative list that I can check the patients in my charge at a glance.
4. As a physician, I want to be able to organize the patient dashboard based on the analyzed levels of patients' perioperative risks and to check any related urgencies that I should take an action so I can better prioritize my tasks.
5. As a physician, I want to generate an intuitive, accountable analysis of the patient's perioperative complication risk based on the patient's genetic factors.
6. As a physician, I want to generate an analysis on any possible comorbidity/pharmacologic responses based on the drugs that are planned in a surgical process so I can be aware of the risks and take action or plan for eventualities based on the analysis.
7. As a physician, I want myself or my patients to be able to input their demographic or medical history data easily so I can incorporate the patient's data in the analysis.
8. As a physician, I want to see the analysis result in real-time as I change factors as well as comparative results so the analysis can beneficially influence my risk stratification decision making.
9. As a physician, I want to ensure the data and calculations are accurate to the best they can be and operate within safe medical standards.
10. As a physician, I want to have some parameters for the user interface that prioritizes the perioperative complication risk factors so I can organize the information in the best way for my decision making.
11. As a physician, I want the data analysis visualization to have several view options such as organ view, list view, filtered group view, so I can use them to communicate with different groups; peer physicians, patients.

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User Comps

User Comps are provided to allow an inventor the opportunity to review the navigation of the website's flow.

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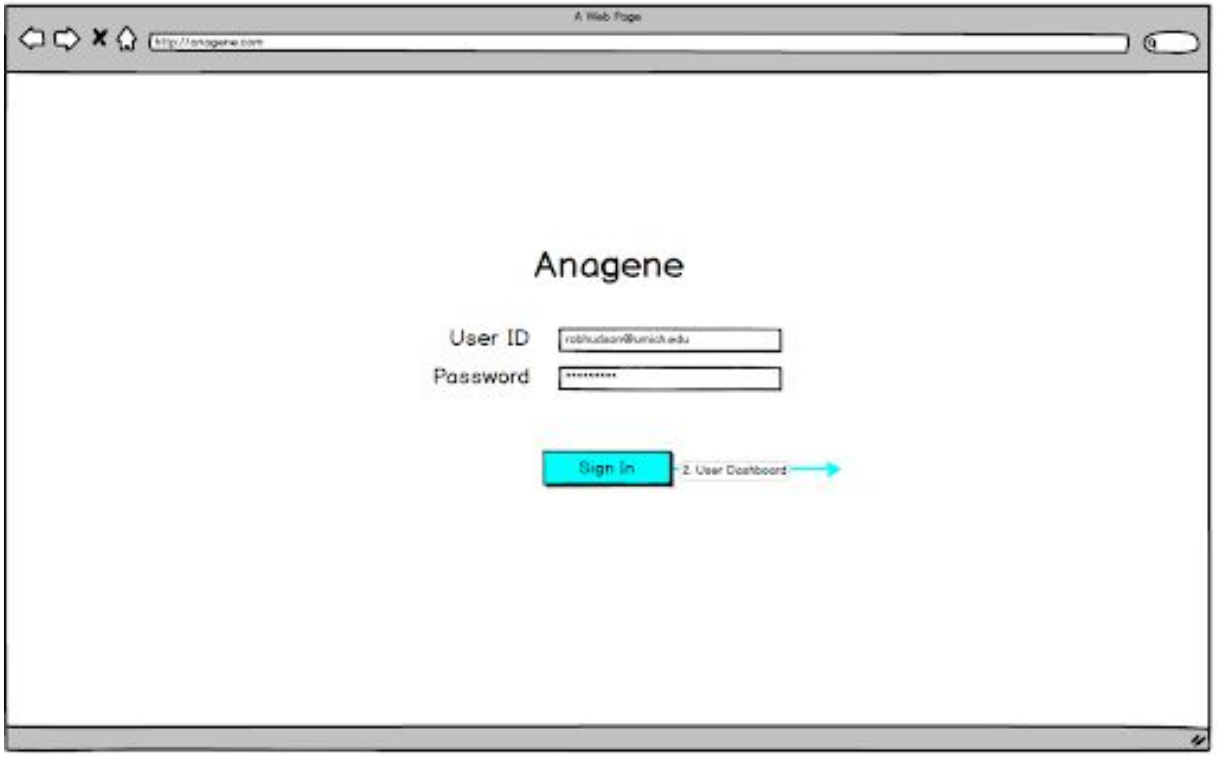
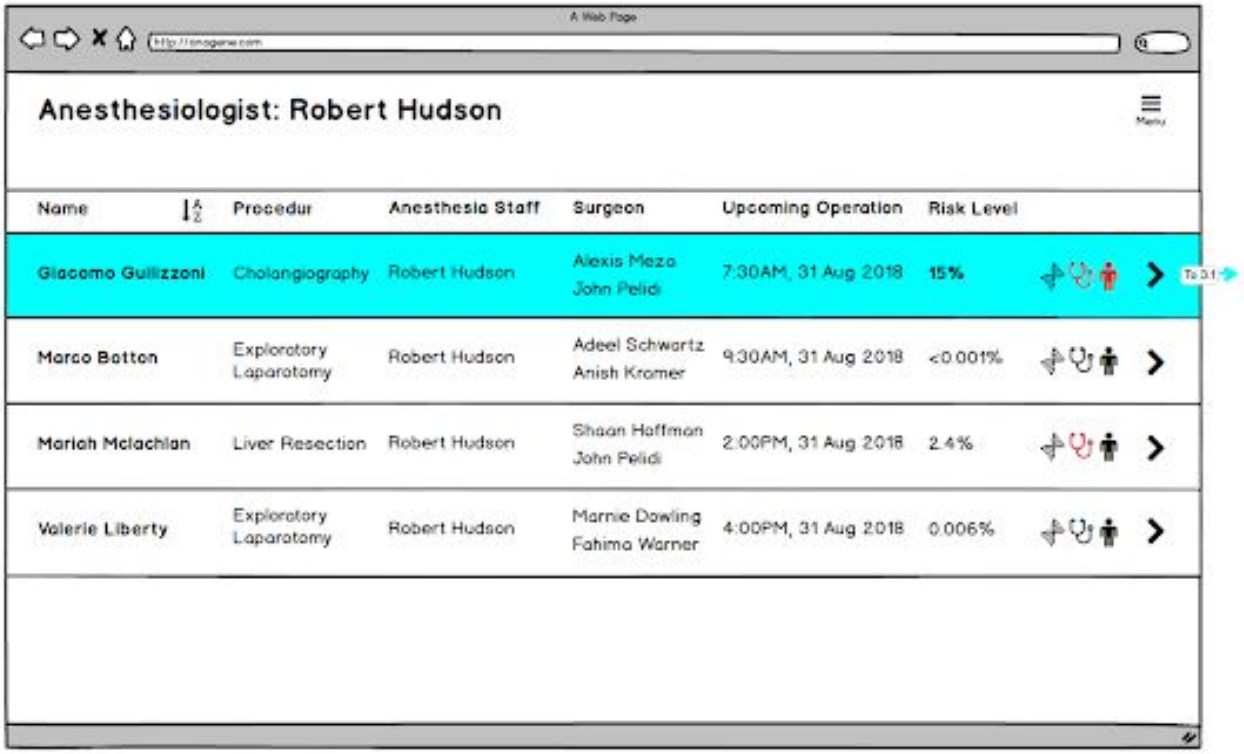
Low-Fi Prototype Version 1

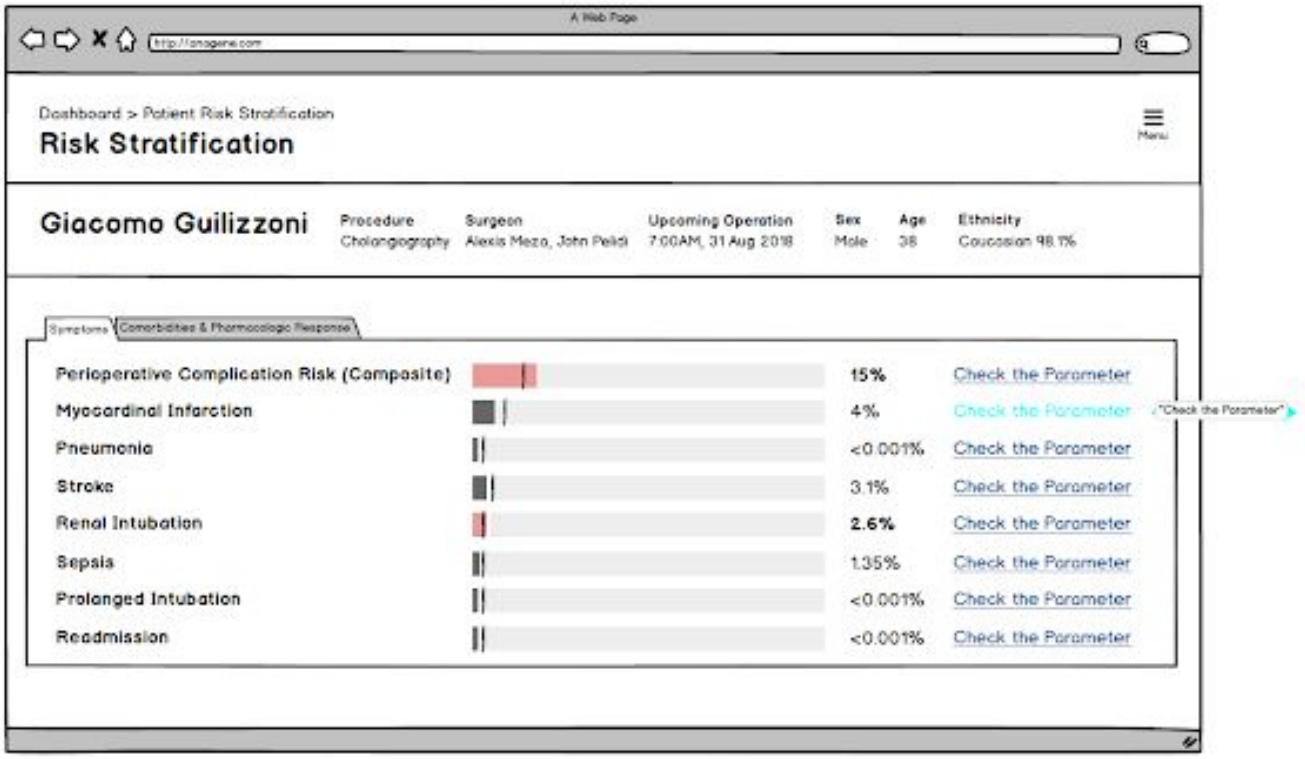
1. User Login Page



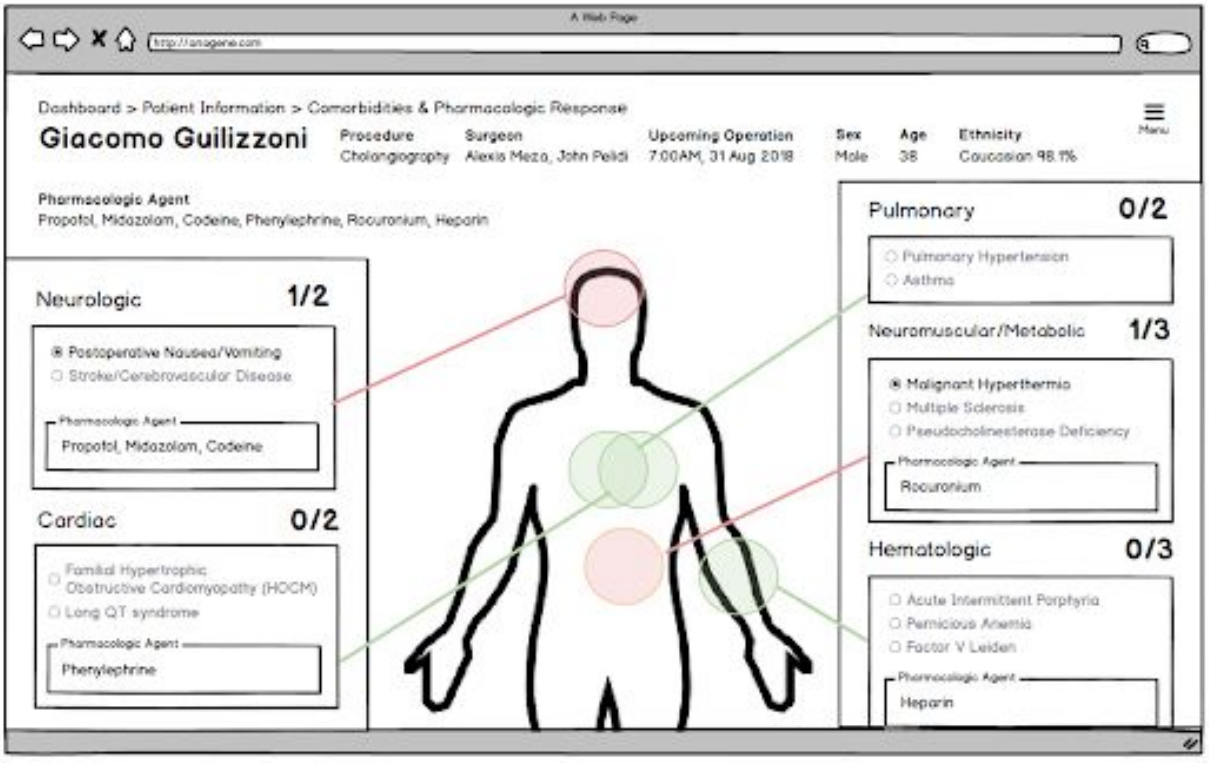
2. User Dashboard



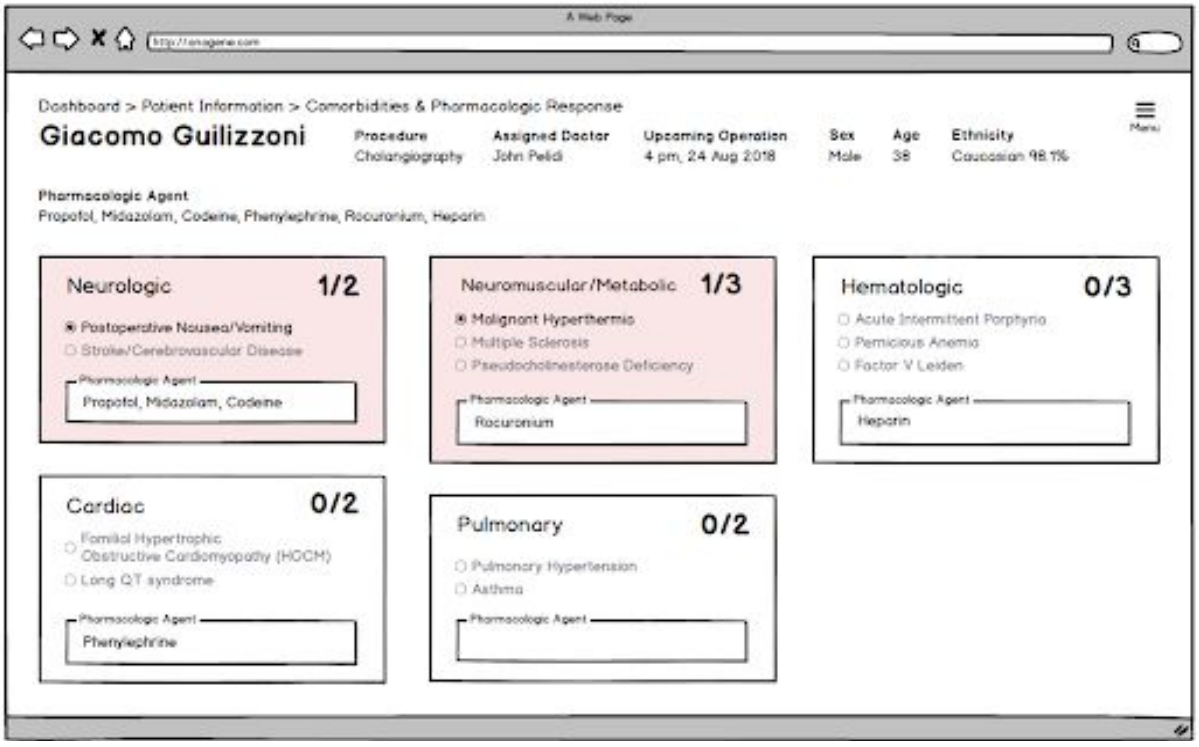
3-1. Individual Patient Dashboard - Graph View



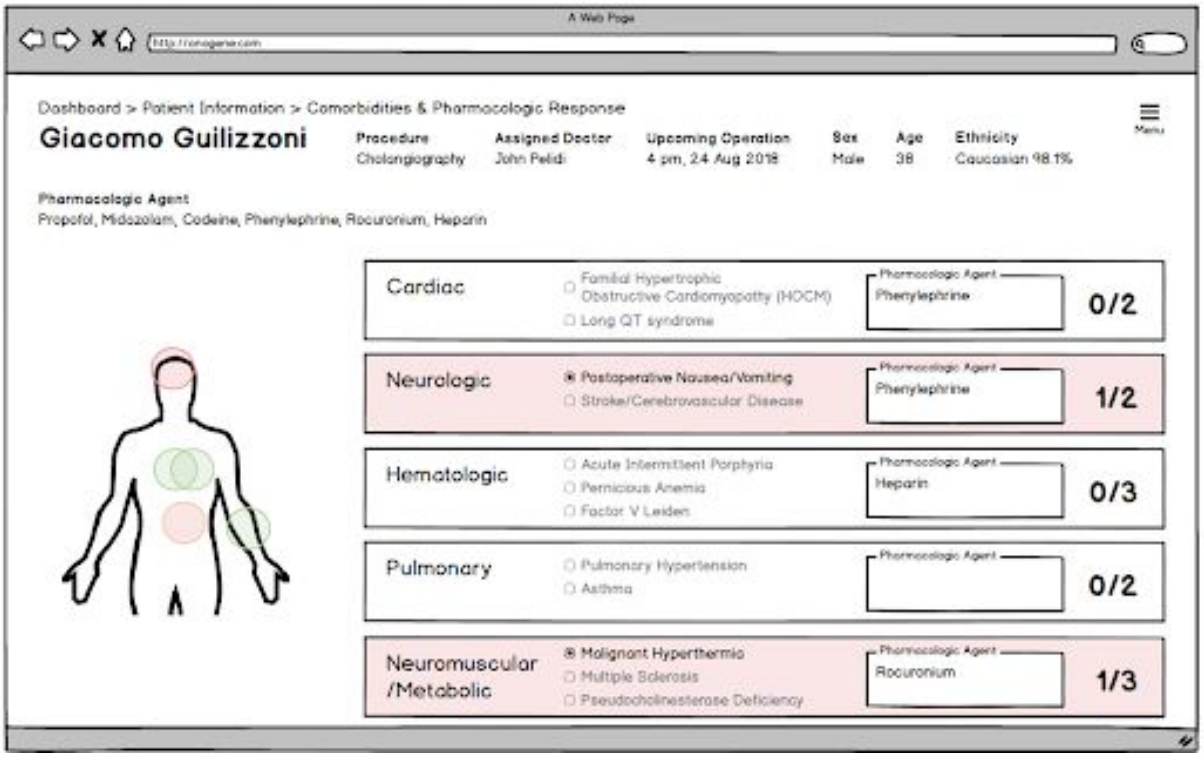
3-2. Individual Patient Dashboard - Organ Visualization View



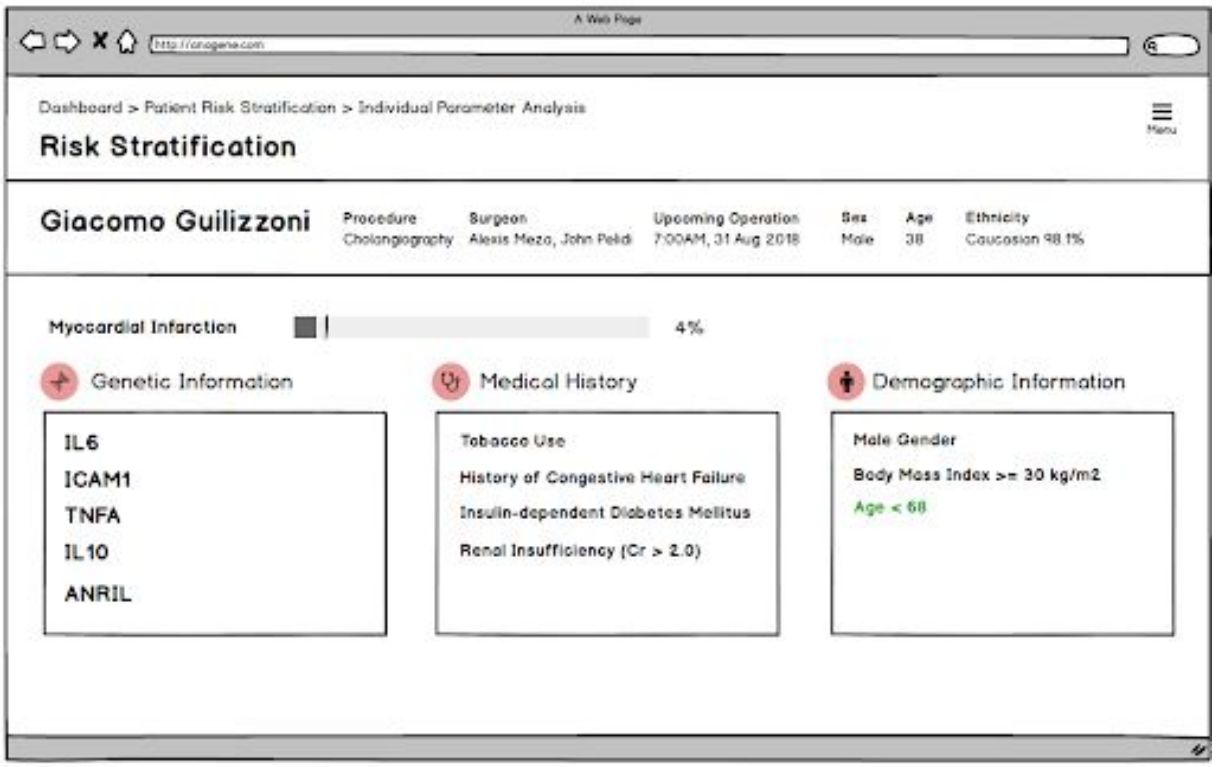
3-3. Individual Patient Dashboard - Module View



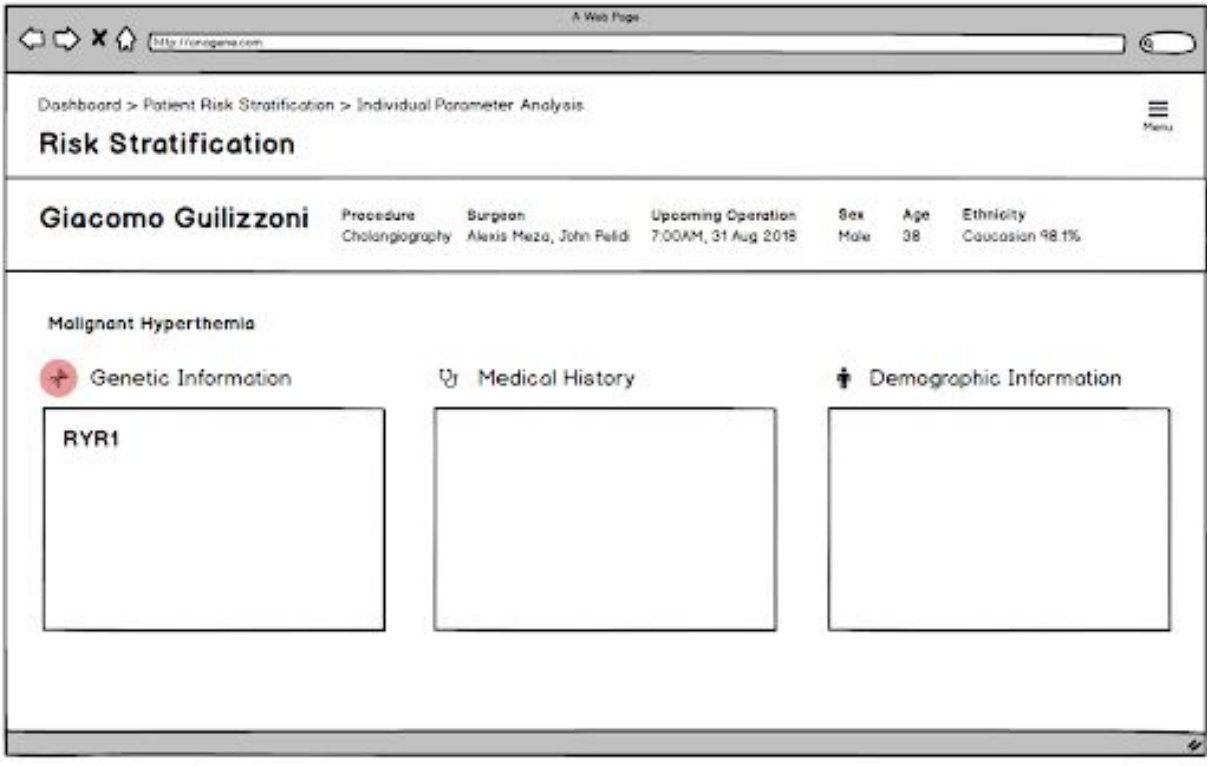
3-4. Individual Patient Dashboard - List View



4-1. Individual Parameter Dashboard - Case of Myocardial Infarction



4-2. Individual Parameter Dashboard - Case of Malignant Hyperthermia



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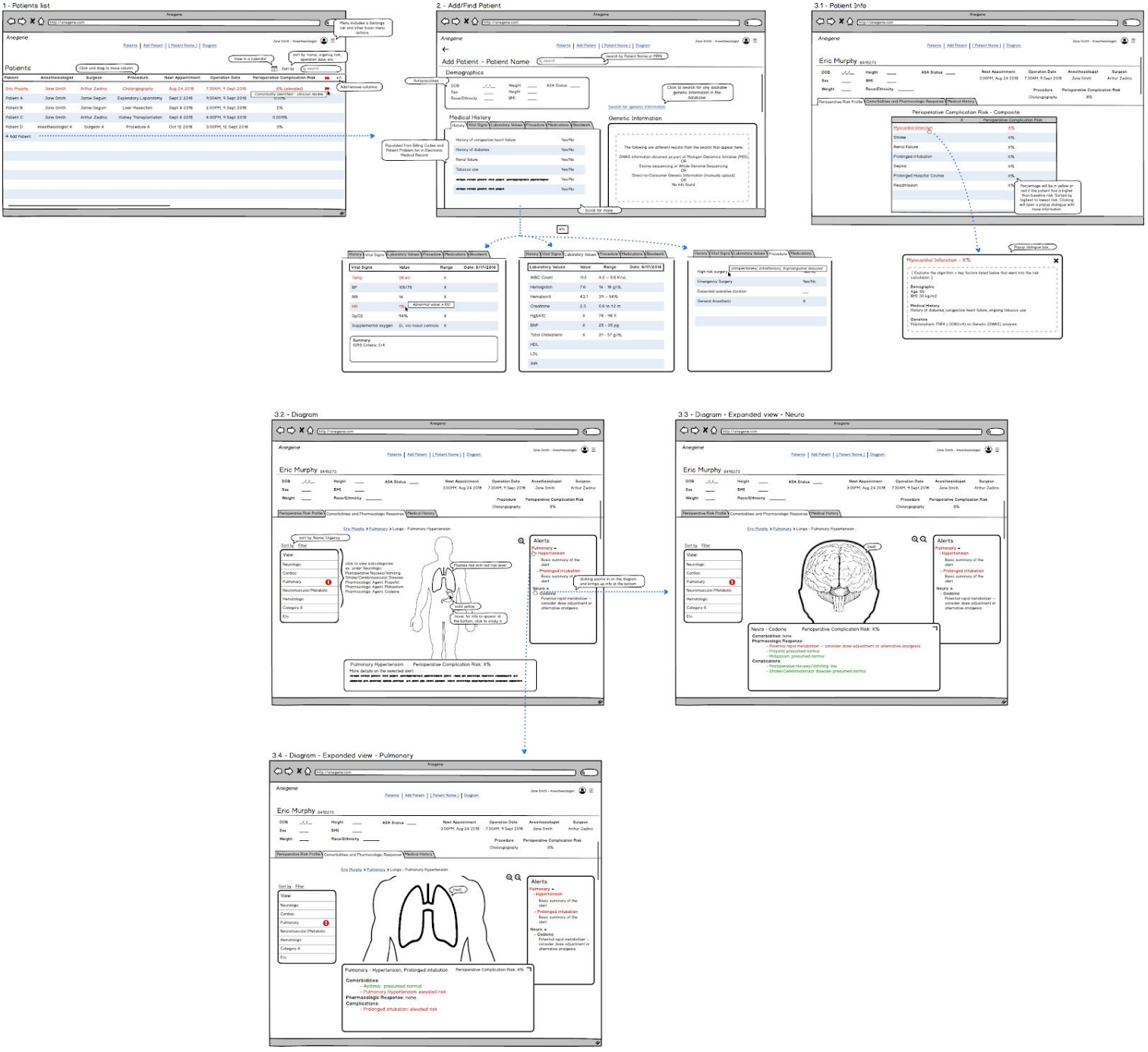
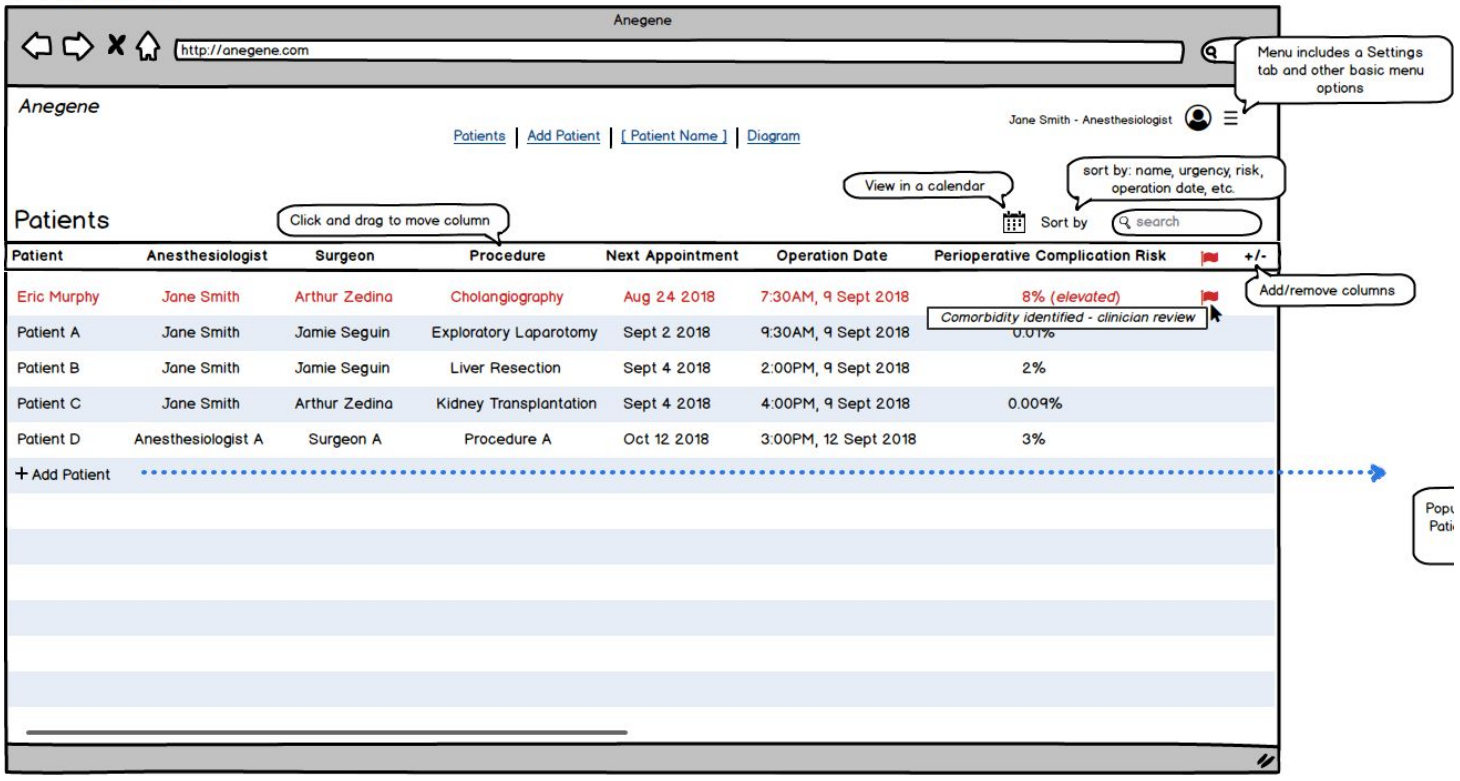
Low-Fi Prototype Version 2

Full View

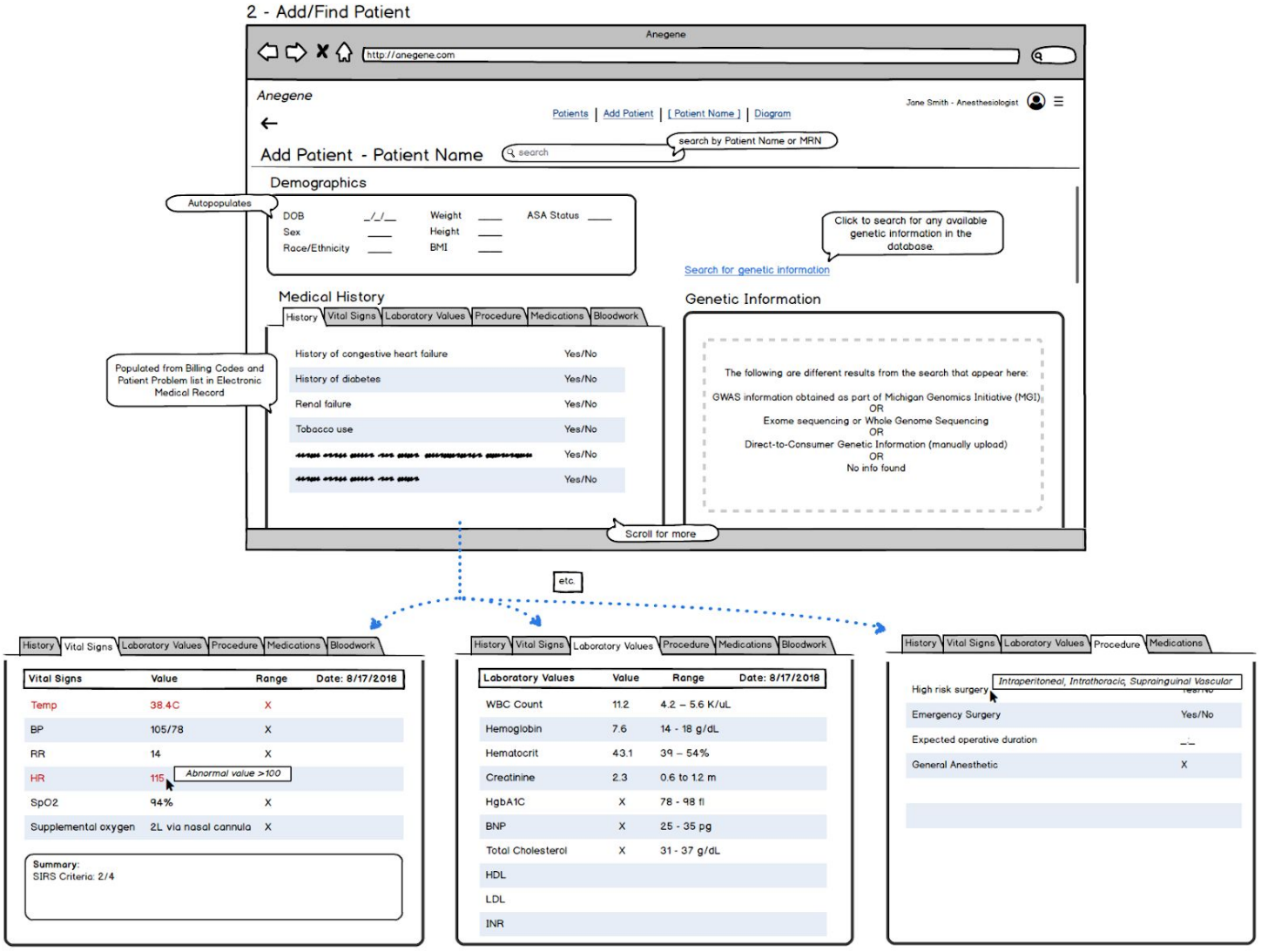


1. Patients List

1 - Patients list

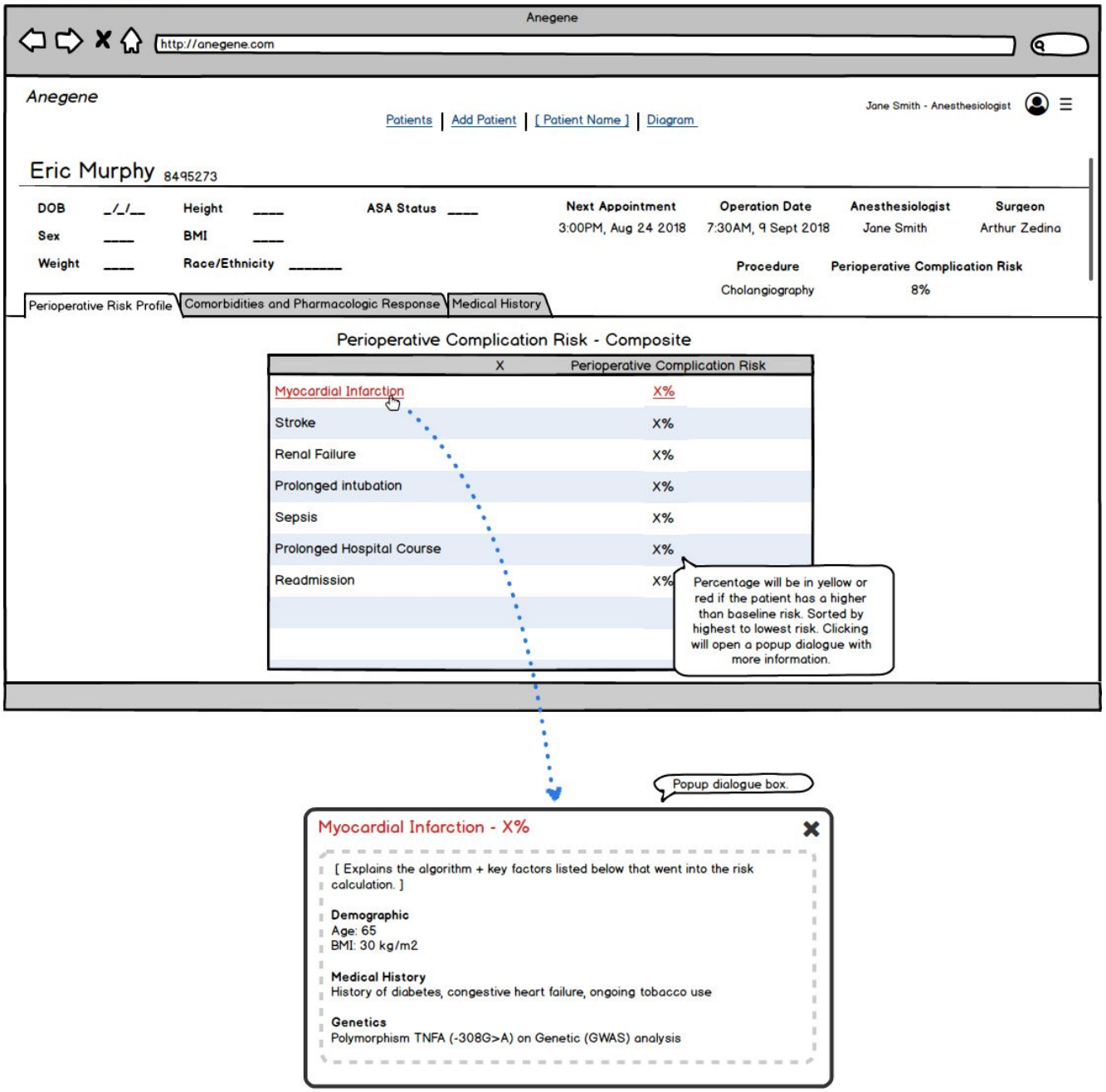


2. Add/Find Patient



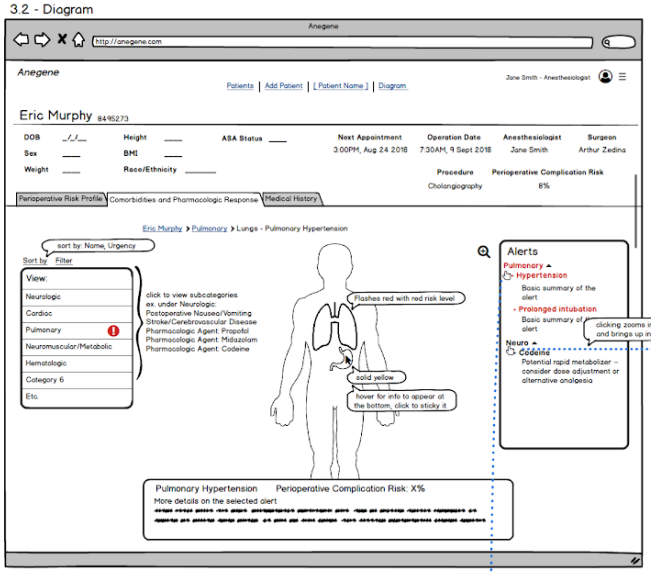
3. Patient Info

3.1 - Patient Info

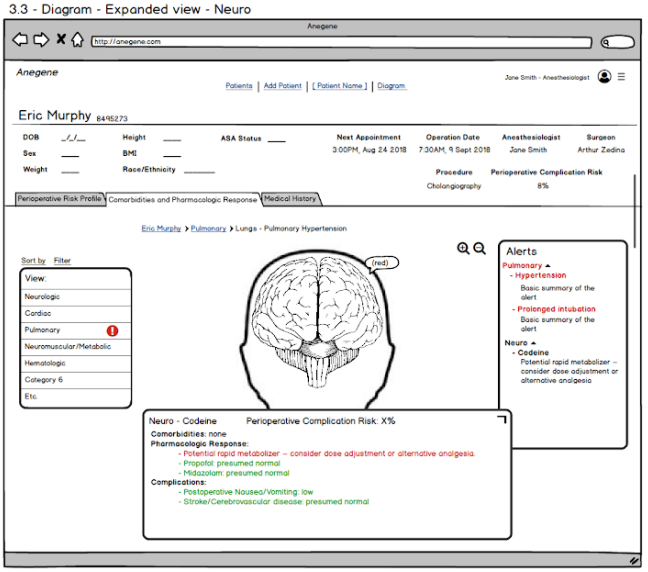


4. Full Diagram

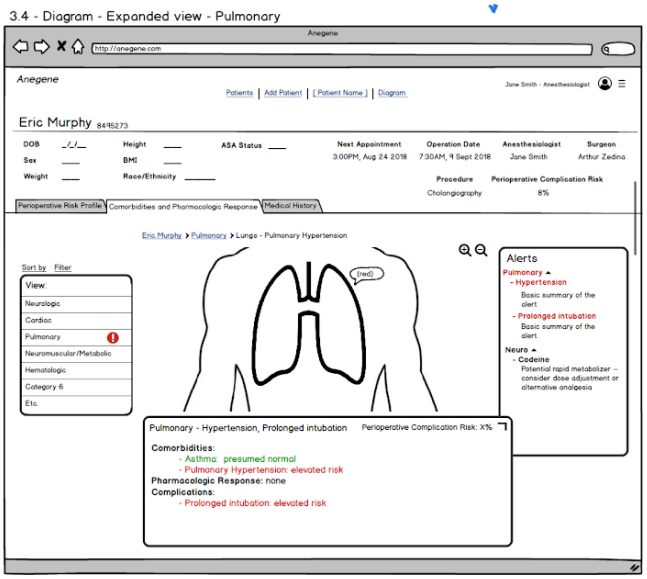
3.2 - Diagram



3.3 - Diagram - Expanded view - Neuro

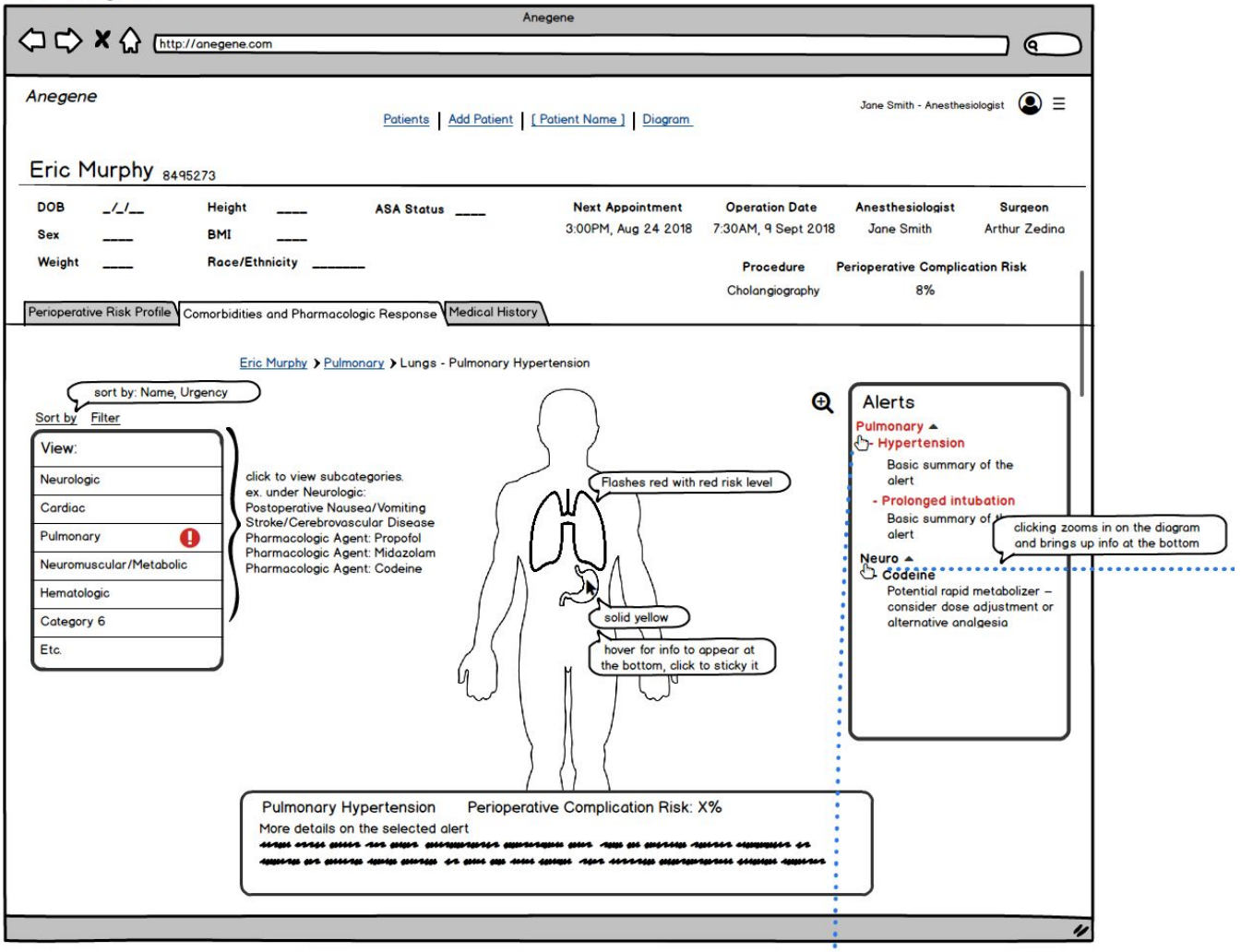


3.4 - Diagram - Expanded view - Pulmonary



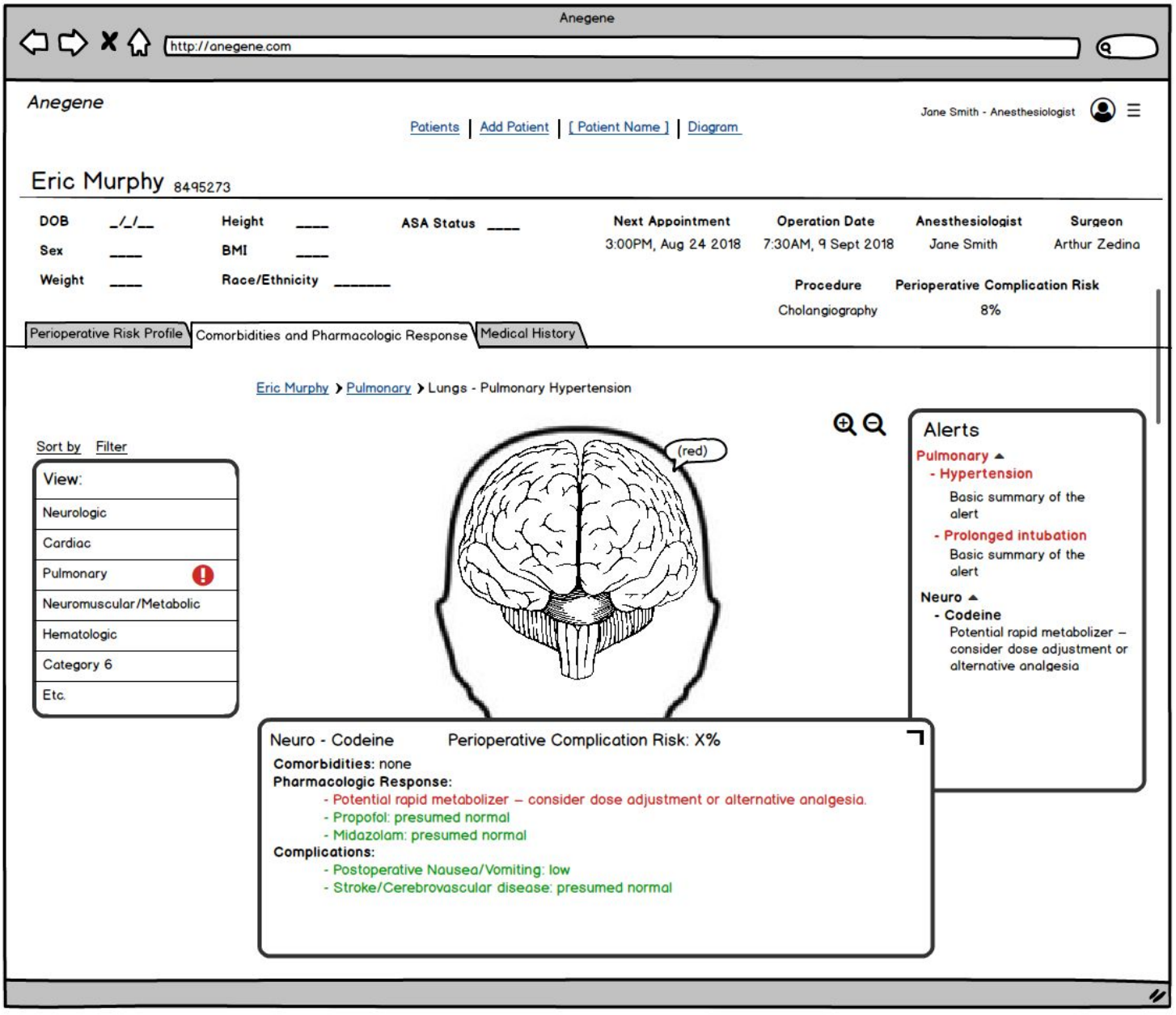
4.1. Diagram - Main

3.2 - Diagram



4.2. Diagram - Expanded View - Neuro

3.3 - Diagram - Expanded view - Neuro



4.3. Diagram - Expanded View - Pulmonary

3.4 - Diagram - Expanded view - Pulmonary