Predicting Breast Cancer Mortality in the Presence of Competing Risks Using Smartphone Application Development Software

Yuanyuan Liu[1], Ellen P. McCarthy[1,2] and Long H. Ngo[1,2,*]

[1]*Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston MA 02215, USA*

[2]*Harvard Medical School, Boston MA 02115, USA*

Abstract: The widespread use of smartphone applications (apps) provides a promising new platform for medical research and healthcare decision making. Given the need to help guide clinical discussions about the appropriateness of breast cancer screening in the presence of competing risks among older women, we proposed to incorporate the Fine-Gray prediction model, which offers more intuitive clinical interpretation of risk in the presence of competing risks, into a smartphone-based decision aid application. Clinicians can input the woman's characteristics and medical history, and the app will output prediction estimates of both types of events (i.e. death from breast cancer and competing risk events) given the presence or absence of breast cancer screening. This prototype was built using drag-and-drop visual programming tools provided by the free, cloud-based software "MIT App Inventor for Android." It will be intended for clinicians to use in the context of patients' values to decide whether screening is appropriate for an individual. Our analysis indicated that screening was beneficial to survival, and that older women benefited less from screening due to the increasing incidence of non-breast-cancer competing risk deaths as age increased. The algorithm we implemented for the app provides instant probability estimates that help quantify screening benefits as a function of age, and comorbidity burden.

Keywords: Smartphone applications, App Inventor, competing risks, breast cancer, screening.

1. INTRODUCTION

Breast cancer in older women is an increasingly important public health concern in the United States. Women aged ≥ 65 account for more than 40% of newly diagnosed invasive breast cancers and around 60% of breast cancer deaths [1]. Breast cancer is an important disease associated with high burden, which has a known natural history, clear preclinical stage and reliable screening tests. In addition, early treatment has been shown to be beneficial and reasonably cost-effective [2]. These criteria make breast cancer screening suitable for many women. While early detection of breast cancer with screening mammography has been shown to reduce breast cancer mortality by 20-30% for women aged 50-69, the benefits and harms of screening for breast cancer in women age ≥ 70were less clear because of competing health risks in elderly women [3-7].

To predict the risk of breast cancer mortality and examine the benefits of screening in the presence of compering risks for older women, conventional analytic methods such as the Kaplan-Meier product-limit estimates [8] and Cox proportional hazards regression [9] focus on cause-specific events (e.g., deaths from breast cancer) and do not account for the possibility

that women can have several competing health risks, but can die from only one. In these analyses, deaths from diseases other than breast cancer are often treated as censored observations. In other words, it is assumed that women still have the potential to die from breast cancer even if they have already died from competing risks. Thus, when competing risks are ignored and treated as censored events, the cumulative incidence of death from breast cancer is overestimated [10-14]. The traditional method of using the cause-specific hazards Cox models can be used to indirectly compute the property estimates of cumulative incidence functions (CIFs); however, the derivation is complicated and often is not available from standard survival analysis software. To resolve this issue that has been discussed in statistical literature [11-17], Fine and Gray (FG) [18] proposed the proportional subdistribution hazard regression, which could be used to simultaneously assess the impact of multiple potential causes of death. FG model, in particular, can be used to obtain directly risk prediction CIFs of both the outcome of interest —death from breast cancer and the competing risks events. Nevertheless, clinical researchers have been slow to adopt this method for risk prediction in the presence of competing risks.

Smartphones have revolutionized mobile communication markets by offering advanced computer functions and connectivity. As of January 2014, 58% of American adults have smartphones [19] By the end of 2013, the majority of smartphones ran on Apple's

*Address correspondence to this author at the Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Harvard Medical School, 1309 Beacon Street, Office 203, Brookline, MA 02446, USA; Tel: 617-754-1415; Fax: 617-754-1411; E-mail: lngo@bidmc.harvard.edu

iPhone operating systems (iOS) and Android's operating systems (Android OS), which represents 18% and 78% of this market respectively [20]. The popularity of smartphones drives rapid expansion of mobile applications (apps), which are downloadable programs that run on the smartphone, tablet computers and other mobile devices' OS. As of July 2013, there were around 1 million apps available in the Android Google Play Store and the downloads exceed 50 billion [21]. This widespread use of apps provides a promising new platform for medical research and healthcare decision making. For example, a group of experts [22-25] in geriatrics and palliative care released their first app – ePrognosis Cancer Screening last year (http://eprognosis.ucsf.edu/), which was meant to help with an important primary care issue: cancer screening in older adults. Also, mobile phone applications have been used for alcohol-related health promotion [26].

Given the need to help guide clinical discussions about the appropriateness of breast cancer screening in the presence of competing risks among older women, we proposed to incorporate the Fine-Gray prediction model into a smartphone-based decision aid application so that clinicians can input the woman's characteristics (e.g. age, hospitalization history, chronic conditions), and the app will output prediction estimates of both types of events (event of interest, and competing risk events) given the presence or absence of breast cancer screening. In our study of the effect of breast cancer screening in the elderly patients, we were interested in the prediction of mortality from breast cancer and that of competing risks within a particular interval of time, for example within 5 years of being at risk for breast cancer. We hope this app will serve as a tool to provide clinicians with information as a supplement to clinical judgment that will be helpful in shared-decision making around the harms and benefits of breast cancer screening.

2. METHODS

2.1. Participants

This app prototype was a product of the "Breast Cancer Screening in Older Women: Comorbidity and Competing Risks" project, which was funded by American Cancer Association RSGT-10-080 (PI: McCarthy). This project was proposed to evaluate breast cancer mortality in older women as a function of age (especially age 75-79, 80-84, and 85+) and illness burden after accounting for competing mortality risks. Our inception cohort includes 93,504 women from a US

national registry, who were aged ≥ 67 and at risk for breast cancer in 1993. They were followed from 1994 through 2005. Cancer information was merged with healthcare utilization and costs data for analysis purposes. We included women aged ≥ 67 so that each woman would have been enrolled in the registry for at least 2 years, and therefore would have at least 2 years of health care utilization data to adequately assess chronic health conditions and illness burden. Over forty percent of the women died from competing risk events, whereas less than 6% died from breast cancer during the entire follow-up. One of the aims of this project was to develop a web-based clinical tool that will help clinicians gauge the impact of screening mammography as a function of patient's age and competing mortality risks by presenting relevant risk estimates – 5-year breast cancer and competing risk mortality – with and without screening. A 10% random sample (n=9398) from the inception cohort was used for the development of this prototype.

2.2. Prediction Algorithm – Fine-Gray Method

To develop the parsimonious competing risk model, which would yield the best predictive probability of death due to breast cancer for groups of older women especially in the context of age and illness burden, we first split the original sample randomly - 2/3 for model development and 1/3 for internal validation; unadjusted analysis was conducted for the Charlson Comorbidity Index (CCI) [27] and specific Elixhauser conditions [28-31] with prevalence ≥1% and variables with p-values <0.2 was retained; Then we compared Akaike Information Criterions (AICs) [32] from all-subset selection and added back additional comorbidity variables into the model based on clinical judgment. The final model includes age, prior mammography use, hospitalization history and 13 comorbidity conditions, which are input variables (covariates) for the app.

The conventional analytical method of relating the time-to-the event of interest to covariates is to model the hazard semi-parametrically by using the Cox regression model with competing risk events being treated as censored observations. This could be biased especially if the prevalence of competing risk events is high in the sample. Therefore, we used the proportional subdistribution hazard regression proposed by Fine and Gray [18], which assumes that the effects of covariates on the subdistribution hazard [i.e. the hazard of the cumulative incidence function (CIF)] are stable over time: $\gamma(t, X) = \gamma_0(t)e^{X\beta}$, with X denoting a row vector of covariates, $\gamma_0(t)$ the unspecified baseline hazard function. Patients who experience a competing risk event are left 'forever' in the risk set with decreasing

weight to account for declining observability [33, 34]. This method accounts for past competing risk events in the model's partial likelihood function, and assigns weights to the competing risk events based on the time between the event and the currently evaluated breast cancer event. The partial likelihood will then be used to estimate the Fine-Gray model coefficients and the baseline cumulative subdistribution hazard. $\hat{\Lambda}_0(t)$ denotes the baseline cumulative subdistribution hazard at the time point of interest, relating to an individual with a zero covariate vector [34]. It is a single value from a vector of cumulative subdistribution hazards at different time points, whose size equals to the number of time points of interest. $\hat{\beta}$ is a vector for the Fine-Gray model coefficients. The internally validated values of $\hat{\beta}$ and $\hat{\Lambda}_0(t)$ were stored in the app for prediction purpose. We fit two separate Fine-Gray proportional subdistribution hazard regression models for the two outcomes -- death due to breast cancer, and death due to competing risks and used the cumulative incidence function (CIF) to obtain the cumulative probability of the outcomes at a specific time, which in this case is 5-year. Given a patient's demographic and comorbidity conditions (X), the mortality from breast cancer or competing risks $F(\widehat{t, X})$ was predicted using the baseline cumulative

subdistribution hazard $\hat{\Lambda}_0(t)$ and the Fine-Gray model coefficients $\hat{\beta}$:

$$F(\widehat{t, X}) = 1 - \exp\{-[\exp(X\hat{\beta})\hat{\Lambda}_0(t)]\}$$

The proportional subdistribution hazard model can be estimated using any standard software packages for Cox regression that allows for counting process representation of times and weighting [34]. SAS 9.3 was used for the analysis.

2.3. Development Tool – App Inventor

This app was developed using a free, cloud-based software called App Inventor 2 for Android (AI2), which provides drag-and-drop visual programming tool for designing and building fully functional mobile apps for Android [35]. The App Inventor project was led by Hal Abelson, Professor of Computer Science and Engineering at Massachusetts Institute of Technology (MIT), who worked at Google as a visiting professor in 2008 [35, 36]. The idea of App Inventor was originally brought up by him as a way to make use of the motivating force of cell phones to help introduce students to programming concepts in computer science
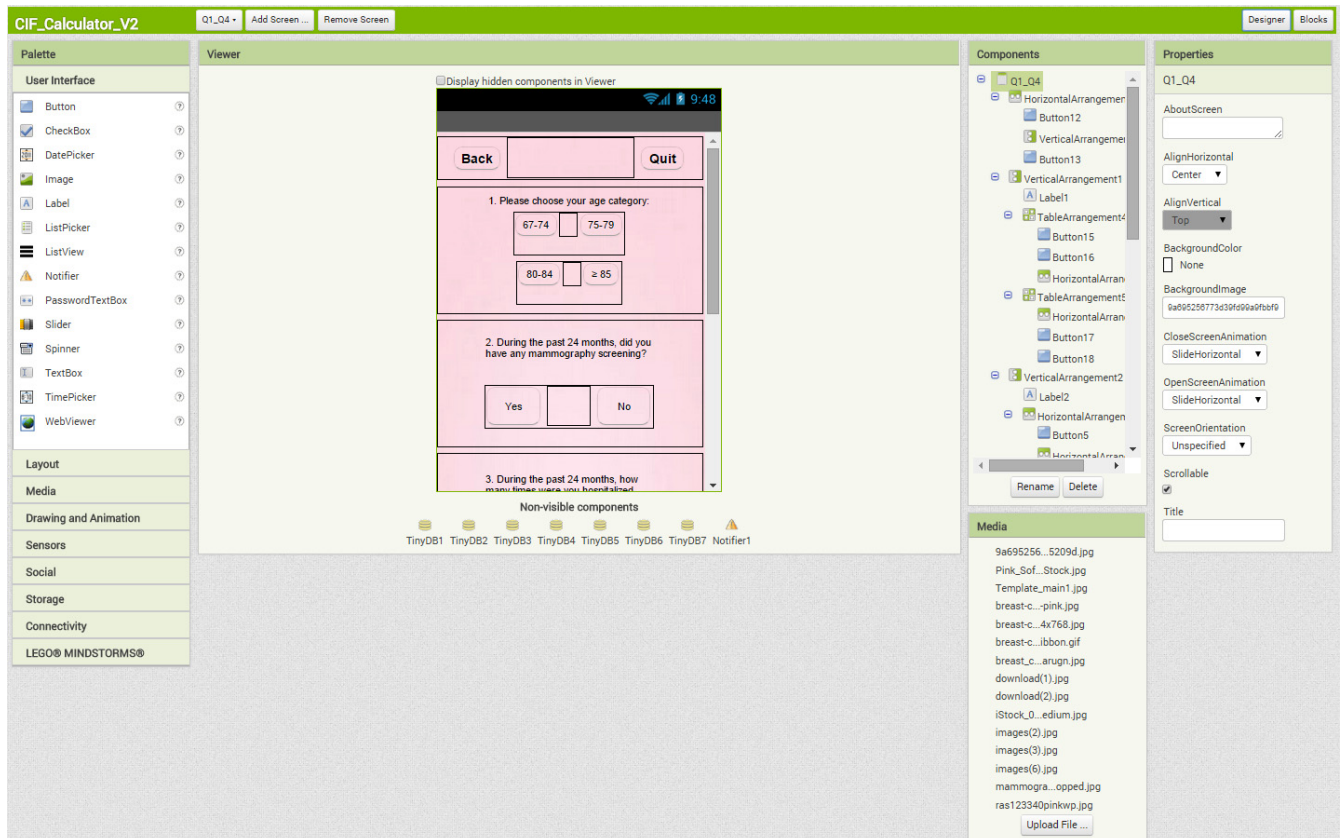

Figure 1: The designer window of AI2.

[36]. The first trial version of this software, called the Google App Inventor, was released in July 2010 by Google. However, in August 2011, Google shut down the service to streamline its operations [37] and handed App Inventor to MIT [38], who has been maintaining and updating it since then. MIT launched its own beta version of App Inventor in early 2012 (which is also called App Inventor Classic now) and released a new version named AI2 on December 3rd, 2013 (http://ai2.appinventor.mit.edu). As the "Do-It-Yourself App Creation Software" (called by the *New York Times*), App Inventor has gained great popularity over years.

AI2 is a visual, drag-and-drop tool for building mobile apps on the Android platforms. It is available to users with Google accounts. The user can design the interface (the visual appearance) of an app using a

web-based graphical user interface (GUI) builder called "designer" and specify the app's behavior by piecing together virtual, color-coded instruction "blocks" instead of having to write traditional computer code. For instance, to create an interface asking the patient's for health-related information (Figure **1**), the user could first drag four label blocks and then change the text on them to the four related questions; the user also needs to drag a few button blocks, place them under the question labels and label the buttons as different answer choices; the layout of the screen can be organized with horizontal, vertical or table arrangement blocks; then, to determine what the button will do when it is touched, the user would switch from a designer window to a block editor window and snap blocks that define different functions — like assigning a new value to a pre-defined variable, or going to the next screen — into the button blocks (Figure **2**). This blocks language
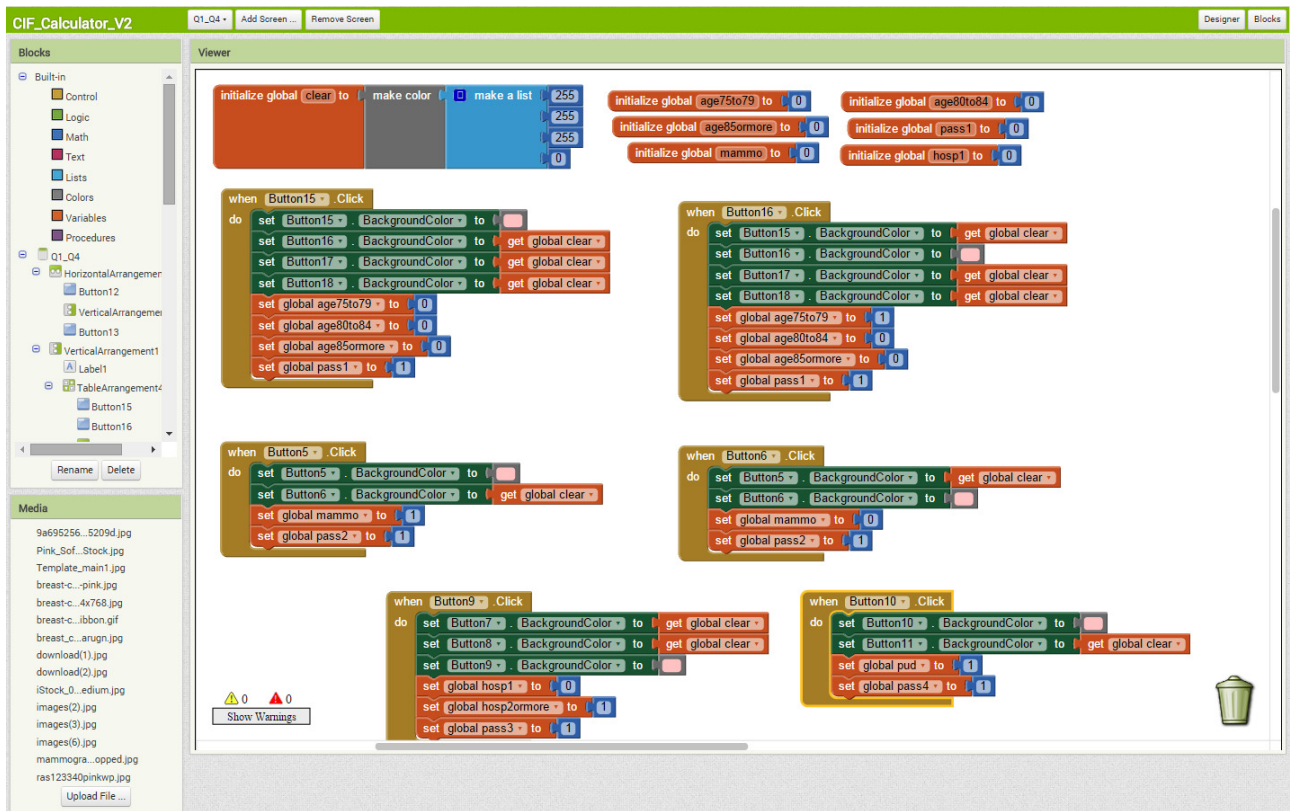

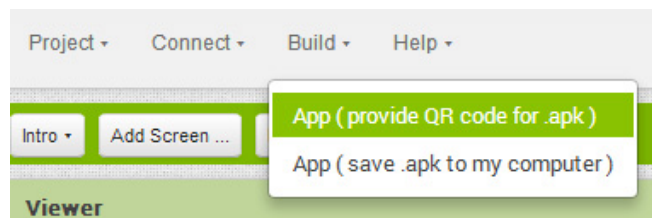**Figure 2:** The Block Editor Window of AI2.

Figure 3: Compile the app in an executable form (.apk or QR code) that can be installed on a device.
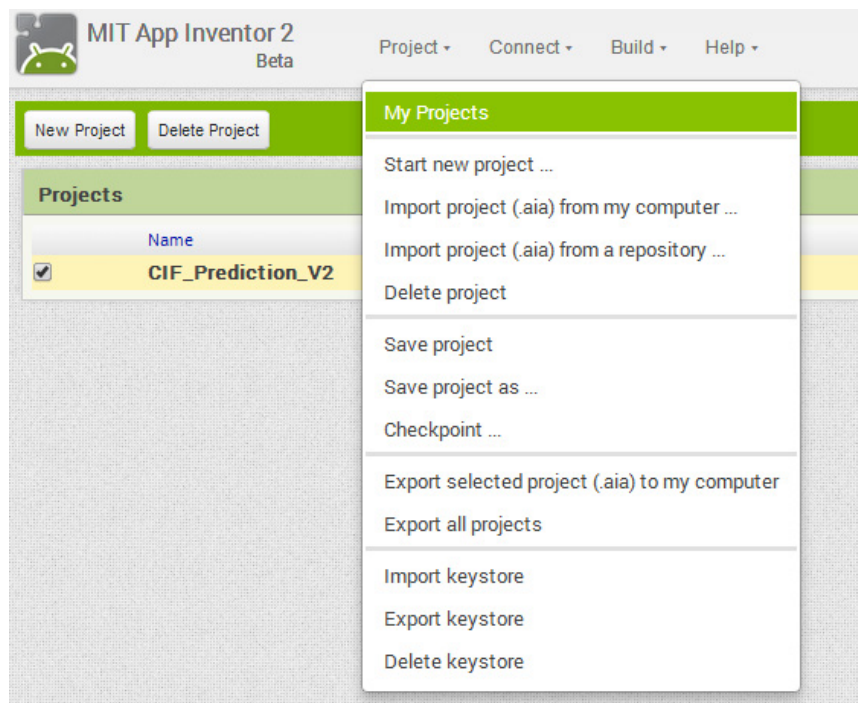
Figure 4: Export the app project in source code form (.aia).

provides all the fundamental programming building blocks like loops and conditionals [36]. In addition, it also prevents programmers from making many mistakes in the first place by only allowing some blocks to plug into each other. While developing the app, the user can do 'live testing" on a real Android device through wireless or USB connection. If the user does not have access to an Android device, he/she can use the on-screen Android emulator to see the app on an emulated screen. After the user has built an app, it can be shared in an executable form (.apk or QR code) that can be installed on a device (Figure **3**), or in source code form (.aia) that can be loaded into App Inventor and remixed (Figure **4**) [39]. The user can also distribute the app on the Google Play Store for public use.

3. RESULTS

3.1. Key Features of the App

This app has a user-friendly GUI that enables easy access and utilization by clinicians. The prediction is made for a time period of 5 years, but the app can also be modified to incorporate prediction for other time frames. It was developed for the Android operating system. The implementation reported in this paper runs on Samsung Galaxy S4. Though the calculation was based on the modeling results from SAS 9.3 and the development process for this app requires cloud

technology and internet access, this app can be used as a stand-alone calculator to predict mortalities without communicating with SAS and internet connection. This ensures greater flexibility and decreases the complexity to use the app. We note that the algorithm we have used in the app was based on a population of women with age of at least 67 years.

3.2. Data Processing and Prediction

Users of this app will be asked sixteen questions regarding their age, mammography screening history, hospitalization history and chronic conditions during the past 24 months (Figure **5**). The questions are displayed on four separate screens. For modeling purposes, age and hospitalization information corresponds to 3 (75-79 years old, 80-84 years old, and ≥85 years old) and 2 (one prior hospitalization and 2 or more prior hospitalizations) dummy variables respectively, whereas each of the other 14 questions is linked with one binary variable in the Fine-Gray model. All the variables are pre-defined with an initial value of 0 when their corresponding screens initialize. When the patient taps the answer to the question on each screen, the values of these variables are modified based on the patients' answers to the corresponding questions. For example, if a patient answers 'Yes' to the question 'During the past 24 months, did you have any mammography screening?', the value of the variable denoting screening history will be changed from 0 to 1;

however, if the patient answers 'No', the value of this variable will remain 0. The user will have the opportunity to review and modify her answers before she gets the final predicted probabilities (Figure **5**). Once the patient's profile is confirmed, for each outcome, the linear predictor $X\hat{\beta}$ will be calculated by first multiplying the value of the variables with the parameter estimates from the model for the corresponding outcome and then adding them up. The linear predictor will then be plugged into the formula with the pre-stored baseline cumulative subdistribution hazard $\hat{\Lambda}_0(t)$ and the Fine-Gray model coefficients $\hat{\beta}$. The 5-year predicted CIFs will then be calculated and output to the screen (Figure. **6**). Using our data, the 5-year predicted CIFs range from 0.0041% to 1.11% for breast cancer death and 1.53% - 98.17% for death from competing risks, depending on the patients' comorbidity profiles.

We used R function for competing risks 'CMPRSK' and Stata 'STCRREG' to validate the results we obtained from the app algorithm. We obtained identical results for both the point estimates and confidence intervals for the subdistribution hazards ratios. The runtime for R was the fastest, then SAS, then Stata. All tests were done on the same Windows-based computer.

We performed goodness-of-fit statistics for the prediction model using discrimination (c-statistic) and calibration (E/O ratio). For breast cancer death, the c-statistic was 0.57. For competing risks death, it was 0.63. To evaluate calibration, we divided into deciles the predicted probabilities and E/O ratio estimates were computed for each decile. For breast cancer death, the E/O ratios ranged from 0.92 to 1.13. For competing risk deaths, it was 0.97 to 1.11. The Hosmer and Lemeshow test indicated no significant difference between the observed and predicted frequency.

4. DISCUSSION

Given the computational intensity to fit a Fine-Gray model, the app can make efficient prediction without refitting the model. The current version can provide
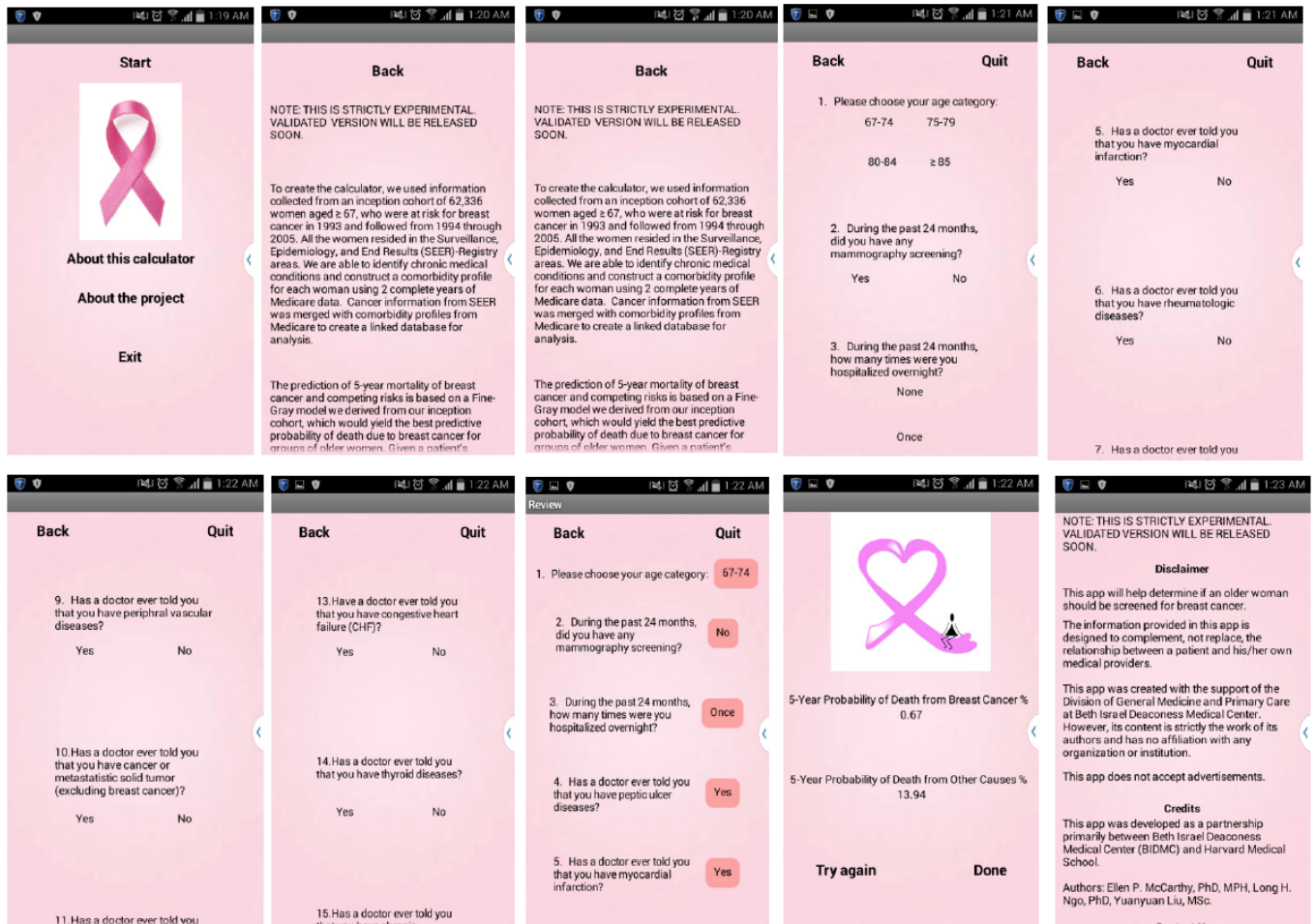

Figure 5: Screenshots of the app.

Input patient characteristics and medical history within the past 24 months:

- Age
- Mammography screening
- Hospitalization
- Peptic Ulcer Diseases
- Myocardial Infarction
- Rheumatologic diseases
- Diabetes
- Diabetes with sequela
- Periphral vascular diseases
- Cancer or metastatistic solid tumor (excluding breast cancer)
- Heart valve disorders
- cerebrovascular diseases
- Congestive heart failure
- Thyroid diseases
- Chronic obstructive pulmonary diseases (COPD)
- Cardiac dysrhythmias

Calculation conducted in the app:

$$\widehat{F(t, X)} = 1 - \exp\{-[\exp(X\widehat{\beta})\widehat{\Lambda}_0(t)]\}$$

Pre-stored Fine-Gray model coefficients $\widehat{\beta}$ and the baseline cumulative subdistribution hazard for breast cancer (or competing risks) $\widehat{\Lambda}_0(t)$ at 5 years

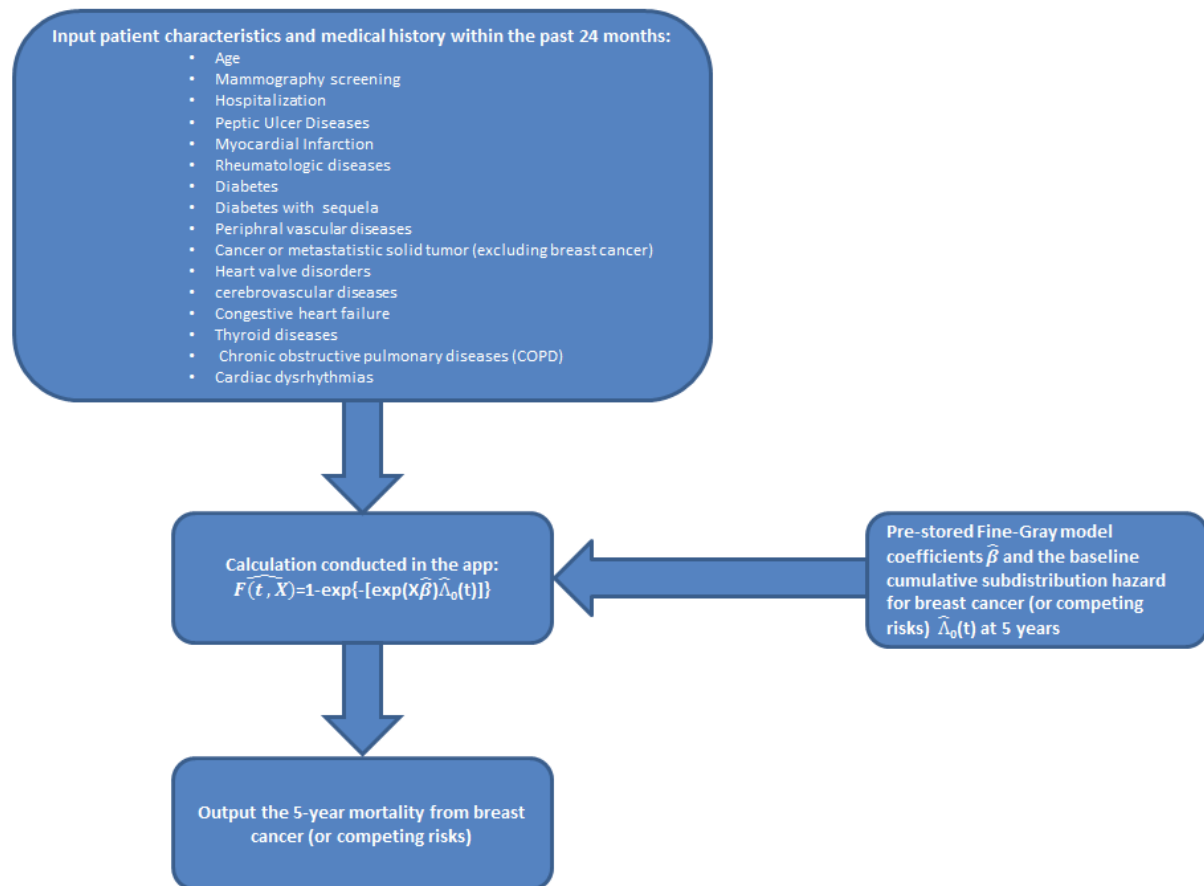**Output the 5-year mortality from breast cancer (or competing risks)**

Figure 6: Work flow of the app.

prediction at 5 years, but it is possible to add other time points by simply pre-storing the Fine-Gray estimate of baseline cumulative subdistribution hazard $\widehat{\Lambda}_0(t)$ at the time point of interest. The built-in calculation process does not require any internet or cell phone data connection or statistical software. This app also has a user-friendly GUI. However, we have to acknowledge a few limitations of this app. Due to the mathematical complexity of Fine-Gray models, a closed form of the confidence interval for a predicted CIF has not been developed, which makes the app unable to provide any estimates for confidence intervals since it is not linked to any statistical packages. In addition, this app was developed using AI2, so its performance largely depends on the capacity of AI2. For example, the programming-free drag- and –drop visual blocks were provided in AI2 instead of real programming languages, which enables easy utilization, but limit the functionality of AI2 to build certain complex features for an app such as saving or retrieving patients' files from the file system of the device. Also, AI2's design makes it expensive in terms of computing resources to have an app with multiple screens, so it does not recommend more than 10 screens in any single app, otherwise its stability on some Android devices will be affected. Currently the external validation has not been conducted on the Fine-Gray models which this prototype was based upon due to lack of data, so we have to treat this app as an experimental version and interpret the prediction results with caution.

This prototype will be modified and uploaded to Google Play as the first version of our Android application that is open to public testing. The later versions of this app will also be available on the IPhone Operating System (IOS). We will upgrade it based on the feedback of users. We would also modify this app so that it has the capability to incorporate updates periodically as new relevant data become available. In the meantime, we will work on incorporating database components into the app, which could store the data into a custom database for future analysis and assessment purposes. This app will be intended for clinicians to use in the context of patients' values to decide whether screening is appropriate for an individual. Overall, our analysis indicated that

screening was beneficial to survival, and that older women benefited less from screening due to the increasing incidence of non-breast-cancer competing risk deaths as age increased. The algorithm we implemented for the app provides instant probability estimates that help quantify screening benefits as a function of age, and co-morbidity burden.

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