

Personalized Prognostic Models for Oncology: A Machine Learning Approach

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Abstract

We have applied a little-known data transformation to subsets of the Surveillance, Epidemiology, and End Results (SEER) publically available data of the National Cancer Institute (NCI) to make it suitable input to standard machine learning classifiers. This transformation properly treats the right-censored data in the SEER data and the resulting Random Forest and Multi-Layer Perceptron models predict full survival curves. Treating the 6, 12, and 60 months points of the resulting survival curves as 3 binary classifiers, the 18 resulting classifiers have AUC values ranging from .765 to .885. Further evidence that the models have generalized well from the training data is provided by the extremely high levels of agreement between the random forest and neural network models predictions on the 6, 12, and 60 month binary classifiers.

Author Summary

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Introduction

Opportunities are emerging in many industries today to develop and deploy services that cater to individual needs and preferences. Music aficionados can create their own radio stations from Pandora¹, bibliophiles can receive book recommendations from goodreads.com², and Google will provide directions between any two points, giving options such as mode of transportation and warnings of delays in realtime.³ These

¹Pandora Internet Radio - Listen to Free Music You'll Love, <http://www.pandora.com/> (accessed 27 Jan 2016)

²Share Book Recommendations With Your Friends, Join Book Clubs, Answer Trivia, <https://www.goodreads.com/> (accessed 27 Jan 2016)

³Google Maps, <https://goo.gl/1D7Jwf> (accessed 27 Jan 2016)

individualized services share many common features. In particular, they leverage large databases to learn and extract information relevant to individuals. A class of techniques that transforms data into actionable information goes by the name of Machine Learning [1]. Machine Learning has recently become a popular method to answer questions and solve problems that are too complex to solve via traditional methods.

The primary objective of this study is to show how machine learning methods can be trained to produce personalized survival prognosis curves. The methods presented below can be applied to any type of survival data. Traditionally, cancer survival curves have been estimated using Kaplan-Meier methods [2]. Kaplan-Meier methodology also uses large datasets to make predictions, but the resulting curves are summaries for a population and not necessarily relevant or particularly accurate for any given individual. This property of Kaplan-Meier methods is exacerbated when dealing with heterogeneous populations. The methods presented in this report generate personalized survival curves relevant to individual patients. This objective is aligned with Predictive, Preventive and Personalized Medicine (PPPM), which aims to leverage increasing amounts of health data to maximize quality of care and to eliminate inefficient use of resources [3]. This capability to provide individualized survival curve prognosis is a direct result of the recent advances in computing power and machine learning algorithms, and similar methodology is becoming commonplace in many industries. These techniques are now infiltrating the healthcare industry.

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) has been collecting data since 1973. Intuitively researchers feel confident that this data will allow researchers to detect information crucial to patients and providers, including the relationships between the collected data (demographics, staging, treatment and disease characteristics) and survival outcomes. Though these relationships evade capture by traditional methods, it is possible to surface them with two machine learning techniques known as *Random Forests* and *Neural Networks*.

The SEER program is the most recognized authoritative source of information on cancer incidence and survival in the United States. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 28 percent of the US population.

One challenge of the SEER data that is shared by many survival datasets is the inclusion of censored data. Observations are labeled censored when the survival information is incomplete. The SEER data contains the number of months each patient survived, as well as the vital status. Traditional methods to deal effectively with this kind of "right-censored data" include Kaplan-Meier curves and Cox Proportional Hazard models [2].

Previous work applying machine learning methods to subsets of the SEER data include creative attempts to deal with the problems presented by right-censored data. Shin et al. [5] use semi-supervised learning techniques to predict 5 year survival, essentially imputing values for SEER records where the survival information is censored at a value less than 5 years. Zolbanin et al. [6] remove all records corresponding to patients who were living but censored within the 60 month study window. This treatment biases the predictions and leads to overly pessimistic predictions.

Previous work applying machine learning methods based on decision trees to survival data in general have a long history, starting with Gordon et al. [7]. A summary of more recent developments concerning *survival trees* is provided by Bou-Hamad et al. [8]. These methods focus on altering the splitting criteria used in decision tree growth to account for the censoring, and use 1958 Kaplan-Meier methods at the resulting nodes for prediction purposes. These methods do not generalize to non-tree-based machine learning algorithms, though Ishwaran et al. have extended the methodology to *random survival forests*, ensembles of *survival trees* [9].

Instead of modifying existing learning algorithms, we focus attention on the input data. This approach allows us to take advantage of powerful and rapidly improving machine learning derived discrete classifiers without modification. The essential idea is to recast the problem as a discrete classification problem (predicting the likelihood that a patient is alive in any given month) instead of a regression problem (predicting survival months). Treating months after diagnosis as just another discrete feature, the SEER data (or any other right-censored data) can be transformed to make predictions for the hazard function (probability of dying in the next month, given that the patient has not yet died). The survival function can then be derived from the hazard function.

Materials and Methods

For this study we use the publically available 1973-2012 SEER incidence data files corresponding to colon, breast and lung cancer contained in the list below. SEER requires that researchers submit a request for the data, which includes an agreement form. Detailed documentation explaining the contents of both the incidence data files used in this study as well as a data dictionary for the 1973-2012 SEER incidence data files are available without the need to register or submit a data request [10]. The raw data files in this study and the subsets defined by the appropriate filters are given in detail in subsection Raw SEER datafiles, in the appendix Supporting Information.

Data preparation and preprocessing

A great deal of data munging is necessary before using these SEER incidence files as input into machine learning algorithms. A preprocessing step common to each of the three cancer types studied involves the SEER STATE-COUNTY RECODE variable. The STATE-COUNTY RECODE field is a state-county combination where the first two characters represent the state FIPS code and the last three digits represent the FIPS county code. The FIPS code is a five-digit Federal Information Processing Standard (FIPS) code which uniquely identifies counties and county equivalents in the United States, certain U.S. possessions, and certain freely associated states. This particular field illustrates an important characteristic of machine learning, that is, the difference between *categorical features* and *numeric features*. All input into a machine learning algorithm must be numeric, but real numbers carry with them the usually extremely useful property known as the well-ordering property. Machine learning algorithms use the well-ordering property of the real numbers to learn. But if one is tasked with encoding a categorical feature into suitable numeric format for machine learning, it is necessary to do so in a way that removes the well-ordering property. Categorical variables are commonly encoded using one-hot encoding, in which the explanatory variable is encoded using one binary feature for each of the variable's possible values [11].

One-hot encoding needs to be applied to all of the nominal categorical variables in the SEER data that we wish to include in our predictive models. In particular, in order to include the geophgraphical information contained in the SEER categorical variable STATE-COUNTY RECODE, it becomes necessary to create a new feature variable for each of the distinct (state,county) pairs in the data. In the United States, there are approximately 3,000 counties. Clearly, transforming the STATE-COUNTY RECODE data representation into distinct (state_county) columns will explode the dataset to become wider than is optimal for machine learning. Adding extra columns to your dataset, making it wider, requires more data rows (making it taller) in order for machine learning algorithms to effectively learn [11]. Because one-hot coding STATE-COUNTY RECODE would cause such drastic shape changes in our data, we wish

to avoid doing so. Fortunately, this variable, though given as a categorical variable, is actually a recode for three ordinal variables. There is an ordering among the (state_county) columns, namely longitude, latitude, and elevation. We can transform the data in STATE-COUNTY RECODE into three new numerical columns: lat, lng, and elevation.

For example, Table (2) shows how five entries of STATE-COUNTY RECODE corresponding to counties within New Mexico can be represented by the elevation, lat, and lng features.

Table 1. Example of the transformation of STATE-COUNTY RECODE to elevation, lat, and lng.

STATE-COUNTY RECODE	address	elevation	lat	lng
35001	Bernalillo+county+NM	5207.579772	35.017785	-106.629130
35003	Catron+county+NM	8089.242628	34.151517	-108.427605
35005	Chaves+county+NM	3559.931671	33.475739	-104.472330
35006	Cibola+county+NM	6443.415570	35.094756	-107.858387
35007	Colfax+county+NM	6147.749089	36.579976	-104.472330

It is a simple exercise to construct the full lookup table from the SEER STATE-COUNTY RECODE variable to the corresponding three values elevation, lat, and lng. We use the publically available datafile from the United States Census Bureau [13] to map the state FIPS and county FIPS codes to query strings like those in the address field in Table (2). It is then possible to programmatically query the Google Maps Geocoding API for the latitude and longitude [14], and the Google Maps Elevation API for the corresponding elevation [15]. An added benefit of this shift from the single categorical variable STATE-COUNTY RECODE to the three continuous numerical variables lat, lng, and elevation is that input into the web applications described later are not restricted to the states and counties covered in the SEER registries; in fact, the input to the models can be any address you would enter into Google Maps and calls to the Google Maps Geocoding API and the Google Maps Elevation API provide the conversion from the address string to the input variables lat, lng, and elevation. The full lookup table analogous to Table (2) is available from a GitHub repository containing supplemental information for this study [16].

This study focused on three different cancer types, namely colorectal cancer, lung cancer, and breast cancer. In the SEER data, there are instances of subjects with multiple rows; whenever a subject, or patient, is diagnosed with a new tumor, an additional record is added. In this study, we restrict attention to the data corresponding to the first record of each subject; i.e., we wish to make models that predict survival prognosis based on the data available right after diagnosis. The full set of conditions defining the subsets of the SEER data used in this study follows below.

The four COLRECT.txt files were imported into a pandas DataFrame object. This data was then filtered according to the conditions in Table (3). The RESPIR.txt and BREAST.txt files were imported into separate dataframes in similar fashion and filtered according to the conditions in Table (4) and Table (5), respectively. The SEER variable CS TUMOR SIZE records the tumor size in millimeters if known. But if not known, CS TUMOR SIZE is given as '999', to indicate that the tumor size is "Unknown; size not stated; not stated in pateint record." In this study, we discard those records, as indicated in Tables (5, 3, 4).

The following categorical features were one-hot encoded for each of the three datasets:

- SEX,

Table 2. Filters applied to the Colon Cancer data.

Column	Filter
SEQUENCE NUMBER-CENTRAL	≠ "Unspecified"
AGE AT DIAGNOSIS	≠ "Unknown age"
BIRTHDATE-YEAR	≠ "Unknown year of birth"
YEAR OF DIAGNOSIS	≥ 2004
SURVIVAL MONTHS FLAG	= "1"
CS TUMOR SIZE EXT/EVAL	≠ ""
CS TUMOR SIZE	≠ 999
SEER RECORD NUMBER	= 1
PRIMARY SITE	= "LARGE INTESTINE, (EXCL. APPENDIX)"
SEQUENCE NUMBER-CENTRAL	= 0

Table 3. Filters applied to the Lung Cancer data.

Column	Filter
SEQUENCE NUMBER-CENTRAL	≠ "Unspecified"
AGE AT DIAGNOSIS	≠ "Unknown age"
BIRTHDATE-YEAR	≠ "Unknown year of birth"
YEAR OF DIAGNOSIS	≥ 2004
SURVIVAL MONTHS FLAG	= "1"
CS TUMOR SIZE EXT/EVAL	≠ ""
CS TUMOR SIZE	≠ 999
SEER RECORD NUMBER	= 1
PRIMARY SITE	= "LUNG & BRONCHUS"
SEQUENCE NUMBER-CENTRAL	= 0

Table 4. Filters applied to the Breast Cancer data.

Column	Filter
SEQUENCE NUMBER-CENTRAL	≠ "Unspecified"
AGE AT DIAGNOSIS	≠ "Unknown age"
BIRTHDATE-YEAR	≠ "Unknown year of birth"
YEAR OF DIAGNOSIS	≥ 2004
SURVIVAL MONTHS FLAG	= "1"
CS TUMOR SIZE EXT/EVAL	≠ " "
CS TUMOR SIZE	≠ 999
SEER RECORD NUMBER	= 1
SEQUENCE NUMBER-CENTRAL	= 0

- MARITAL STATUS AT DX ,
- RACE/ETHNICITY ,
- SPANISH/HISPANIC ORIGIN ,
- GRADE ,

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- PRIMARY SITE , 152
- LATERALITY , 153
- SEER HISTORIC STAGE A , 154
- HISTOLOGY RECODE--BROAD GROUPINGS , 155
- MONTH OF DIAGNOSIS , 156
- VITAL STATUS RECODE , 157

and the STATE-COUNTY RECODE variable was dropped and replaced with the elevation , lat , and lng variables for all three datasets as illustrated in Table (2). 158 159

Before applying machine learning models trained with these datasets, we review below the salient features of survival analysis and censored data. We then describe in detail a method that takes full advantage of all the data, including the right-censored data, and which involves a simple and intuitive transformation, culminating in the full set of features and target variable listed in the back of this report. 160 161 162 163 164

Transformation of Censored Data for Machine Learning 165

In this section we describe an intuitive way to transform right-censored data appropriately so that it may be used as input to machine learning algorithms that learn the hazard function. The full details of this transformation, and a large inspiration for this study, can be found in this blog post [18]. 166 167 168 169

The key observation is to note that the hazard function can be directly learned via standard machine learning methods. It can be rewritten as 170 171

$$\lambda(\mathbf{X}, t_i) = P(Y = t_i | Y \geq t_i, \mathbf{X}), \quad (1)$$

the probability that, if someone has survived up until month t_i , they will die in that month. where \mathbf{X} represents all of the data for that particular record, and in our case Y represents the true, uncensored number of survival months of the patient. What is actually provided in the SEER data is the related variable SURVIVAL MONTHS T (how long each subject was in the study), and whether they exited by dying or being censored (D), VITAL STATUS RECODE . D is a Boolean variable, so $D = 1$ if $T = Y$, and $D = 0$ if $T < Y$. 172 173 174 175 176 177 178

It follows directly from equation 3 that 179

$$P(Y = t_j | \mathbf{X}) = \lambda(\mathbf{X}, t_j) \prod_{i=1}^{j-1} (1 - \lambda(\mathbf{X}, t_i)) \quad (2)$$

Knowing $P(Y = t_j | \mathbf{X})$ for all t_j gives the full probability distribution of dying at time Y [18]. The survival function is then readily derived from this distribution as 180 181

$$S(\mathbf{X}, t_k) = 1 - CDF(\mathbf{X}, t_k) \quad (3)$$

where $CDF(\mathbf{X}, t_k) = \sum_{i=1}^k P(Y = t_i | \mathbf{X})$ is the cumulative density function corresponding to the probability mass function in equation 4 [12]. 182 183

Treating T as just another covariate is the key to the transformation. Each datapoint in the hidden classification problem is the combination of an \mathbf{X}_i in the original dataset plus some month t_j , and the classification problem is "did point \mathbf{X}_i die in month t_j ." We will call this new variable D_{ij} (**newtarget**). We can transform our original data set into a new one, with one row for each month that each \mathbf{X}_i is in the sample; train a standard classifier on this new dataset with D_{ij} as the target, and derive a survival model from the original dataset. Pseudocode for this transformation is found in section Pseudocode for the Data Transformation. 184 185 186 187 188 189 190 191

Explicit examples will help make this transformation clear. The untransformed datapoint represented Table (6) is transformed to the multiple records shown in Table (8). All uncensored data is transformed in this way. All censored data is similarly transformed. The untransformed datapoint represented Table (7) is transformed to the multiple records shown in Table (9).

Table 5. Example of four columns in an uncensored record in the untransformed dataset.

	cs_tumor_size	year_of_birth	survival_months	vital_status_recode_Death
newindex				
205	60	1951	3	1

Table 6. Example of four columns in a censored record in the untransformed dataset.

	cs_tumor_size	year_of_birth	survival_months	vital_status_recode_Death
newindex				
205	40	1950	3	0

Table 7. Example of four columns in an uncensored record in the transformed dataset.

	cs_tumor_size	year_of_birth	month	newtarget
newindex				
205	60	1951	0	0
205	60	1951	1	0
205	60	1951	2	0
205	60	1951	3	1

One obvious side effect of this transformation is that it explodes the length of the dataset. For this study, the original, untransformed colon cancer DataFrame has shape (113072, 103), and the total transformed colon cancer DataFrame has shape (4165251, 103). Similarly, the original, untransformed lung cancer DataFrame has shape (177089, 115), and the total transformed lung cancer DataFrame has shape (3079931, 115). The biggest explosion in dataset size occurred with the breast cancer data, which is a consequence of the relatively high survival rates in breast cancer. A subject who is censored with a recorded survival months of 48 will contribute an extra 48 rows to the transformed dataset. The original, untransformed breast cancer DataFrame has shape (329949, 67), and the total transformed breast cancer DataFrame has shape (15085711, 67). Training machine learning algorithms on such large datasets, even after splitting into training and testing sets described below, require large RAM. All computations for this study were performed on a Dell XPS 8700 Desktop with 32GB of RAM.

Training and Test Partitions

After performing the data transformation adumbrated above, it is necessary to be mindful of how we partition the data into training and testing data. Each subject that was represented by a single row in the original untransformed dataset now potentially is represented by multiple rows in the transformed dataset, and care must be taken to ensure that all of the rows corresponding to a particular subject are either assigned exclusively to the training set or exclusive to the testing set. An additional

Table 8. Example of four columns in a censored record in the transformed dataset.

	cs_tumor_size	year_of_birth	month	newtarget
newindex				
205	40	1950	0	0
205	40	1950	1	0
205	40	1950	2	0
205	40	1950	3	0

characteristic of this transformed data that requires careful treatment involves balancing. The transformation results in many new records with the target variable `newtarget == 0`. The training and test sets must be chosen such that the ratio of the number of records with `newtarget == 0` to that of the number of records with `newtarget == 1` is the same in the training and test datasets. This ratio turns out to be ≈ 396 for the breast cancer data, ≈ 99 for the colon cancer data, and ≈ 22.75 for the lung cancer data. The shapes of the training and testing datasets for breast cancer used in this study are (14936862, 67) and (148849, 67), respectively. For lung cancer, the corresponding datasets have shapes (2988768, 115) and (91163, 115). Finally, for colon cancer the partition into training and test datasets of the transformed data have the shapes (3958008, 103) and (207243, 103). Multiple rows correspond to the same test patient in these datasets. The colon cancer test dataset represents 5654 distinct subjects; the breast cancer test dataset represents 3300 distinct subjects; and the lung test dataset contains data for 5313 distinct subjects.

The models described below are trained to learn the values of `newtarget`, which is a binary variable: a value of '0' indicating that the subject is still alive at the given month, while a value of '1' indicates that the patient died at that particular value of `months`. The random forests and neural networks described below are binary classifiers with the target `newtarget`. Fortunately, both the random forests and neural networks are capable of not only performing strict class prediction, i.e. predicting whether `newtarget` is '0' or '1', but are also able to predict the *probability* of `newtarget` being '0' or '1', and thus learning the hazard function.

Finally, we emphasize the crucial point that the features `survival_months` and `vital_status_recode_Dead` are dropped from both the training and testing data, and are replaced with the features `months` and `newtarget`, as illustrated in Tables (6, 7, 8, 9). The information of which subjects represent censored data (`vital_status_recode_Dead == 0`) and which died is retained and recoverable through the `newindex` variable and is needed for proper evaluation of the performance metrics; when evaluating AUC curves for the 6, 12, and 60 month binary classifiers, we need to limit the test data to those subjects that we know definitively whether or not they survived 6, 12 or 60 months respectively. This requirement will necessitate the elimination of some of the censored data when computing some of the performance metrics. We introduce the two machine learning algorithms used in this study below, chosen because of their high performance in machine learning competitions and their complementary methods, so that their mutual agreement shown below on the test datasets can be taken as indication that they are actually learning useful information.

Random Forests are made up of an ensemble of independent **Decision trees** that are purposefully exposed to only subsets of the data. The general philosophy is presented in the popular science book "The Wisdom of Crowds" [19]. The idea is that a large number of independent non-expert opinions converge on the correct answer when averaged. The success of this philosophy of prediction was startlingly shown by the

success of the political and world event predictions made by the prediction market site Intrade, before its forced closure by the Commodity Futures Trading Commission [20]. The other class of methods used by IOBS to develop predictive models are called neural networks, and are modelled on how the human brain learns high level concepts from lower level ones. As opposed to the crowd-based wisdom of a random forest, a neural network is analogous to a seasoned expert. A Neural network learns from repeated exposure to the training data and improves its predictions with each pass over the data. The general philosophy is similar to that represented by the well-known maxim that it takes 10,000 hours to become an expert in any given field [21].

Prediction Models

With the datasets transformed as described above, we are now able to use them to train and evaluate machine learning classifiers. The classifier models described in this section are learning the hazard function: given all of the data given in the Supporting Information section for each cancer type and includes the field `months` (the months after diagnosis), the models predict the target variable `newtarget`, which is a binary class label equal to 1 if the subject died in that month and 0 otherwise. Fortunately, both random forests and neural networks are capable of not only performing strict class prediction, i.e. predicting whether `newtarget` is 0 or 1, but are also able to predict the *probability* of `newtarget` being 0 or 1, and thus learning the hazard function. The models learn $\lambda(\mathbf{X}, \text{months})$. This prediction task should not be confused with the regression problem of trying to predict precisely in what month a patient will die.

The hazard functions thus learned and predicted are intermediary products; what we are really pursuing are the survival functions for each patient that are derived from the predicted hazard functions. From the resulting hazard functions for each unique patient, we can construct the resulting survival functions as presented in section () and Equation (??) and explicitly given in python code in the notebooks at the github repository containing supplemental material for this study [16]. For each subject i , all input data minus `months` and `newtarget` is represented by \mathbf{X}_i . After the classifier models have trained with target `newtarget` on the (very large) training set, each subject's survival function is computed in the corresponding (much smaller) test set. These functions are computed by using the model to predict $\lambda(\mathbf{X}_i, t_j)$ for j running from 0 to 107 months, and \mathbf{X}_i corresponds to the single row corresponding to subject i in the original untransformed dataset. 107 months was the maximum value of survival months in all three of the cancer datasets, and is a consequence of the data subsets chosen for this study.

Decision Trees and Random Forests *Decision tree* classifiers are attractive models because they can be interpreted easily. Like the name decision tree suggests, we can think of this model as breaking down our data by making decisions based on asking a series of questions. Based on the features in our training set, the decision tree model learns a series of questions to infer the class labels of the samples.

Random forests have gained huge popularity in applications of machine learning during the last decade due to their good classification performance, scalability, and ease of use. Intuitively, a random forest can be considered as an *ensemble of decision trees*. The idea behind ensemble learning is to combine *weak learners* to build a more robust model, a *strong learner*, that has a better generalization error and is less susceptible to overfitting.

The goal behind *ensemble methods* is to combine different classifiers into a meta-classifier that has a better generalization performance than each individual

classifier alone. For example, assuming that we collected predictions from 10 experts, ensemble methods would allow us to strategically combine these predictions by the 10 experts to come up with a prediction that is more accurate and robust than the predictions by each individual expert. The individual decision trees that make an ensemble are called base learners, and as long as the error rate of each base learner is less than .50, the combined random forest will benefit from the affects of combining predictions to achieve a far greater accuracy.

Figure (1) illustrates the power of ensemble methods; the Figure illustrates how the ensemble error rate is much lower than the Base learner error rate, as long as the Base learner error rate is less than 0.5. The Figure illustrates this effect for an ensemble of 500 base learners.

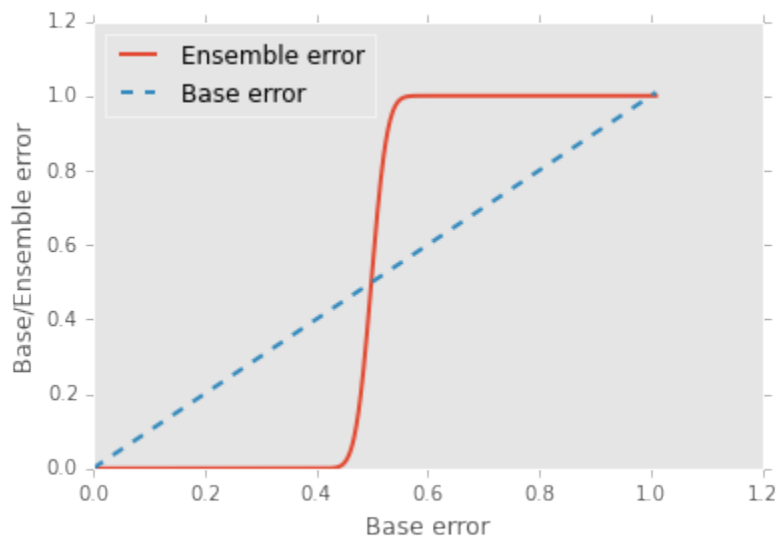


Figure 1. Illustration of ensemble methods showing how a collection of base learners with poor accuracy can combine to produce an accurate ensemble learner.

A big advantage of random forests is that honing in on suitable hyperparameter values (the number of trees in the forest, the depth of each decision tree, the specific measure of information gain used to choose the node splitting, etc) is not very difficult. The ensemble method is robust to noise from the individual decision trees, which helps to prevent overfitting (memorizing the training dataset targets instead of generalizing from learned rules to perform successfully on unseen data). The only parameter that has a clearly noticeable effect on performance is the number of trees to include in the forest; in general, the more trees the better the performance, but there is a price to pay in terms of computational cost. The number of trees for the forests trained in this study was relatively small, 20 trees for breast cancer and 25 for both the lung and colon cancer models.

IOBS has chosen to use the Python scikit-learn implementation of the Random Forest machine learning classifier [22]. Random Forests are frequent winners of the Kaggle machine learning competitions [23]. The model parameters for each cancer type are given in sections (Lung Random Forest Model Hyperparameters, Colon Random Forest Model Hyperparameters, Breast Random Forest Model Hyperparameters).

Multi-Layer Perceptron Neural Networks Neural networks are a biologically-inspired programming paradigm that enable computers to learn from observational data [24]. Deep learning can be understood as a set of algorithms that

were developed to train artificial neural networks with many layers most efficiently. Neural networks are a hot topic not only in academic research, but also in big technology companies such as Facebook, Microsoft, and Google who invest heavily in artificial neural networks and deep learning research. As of today, complex neural networks powered by deep learning algorithms are considered as state-of-the-art when it comes to complex problem solving such as image and voice recognition. In addition, the pharmaceutical industry recently started to use deep learning techniques for drug discovery and toxicity prediction, and research has shown that these novel techniques substantially exceed the performance of traditional methods for virtual screening [?].

IOBS has chosen to use the Multi-Layer Perceptron Neural Network (MLP neural network) implementation Keras developed at MIT. Keras was initially developed as part of the research effort of project ONEIROS (Open-ended Neuro-Electronic Intelligent Robot Operating System) [25]. Keras is a minimalist, highly modular neural networks library, written in Python and capable of running on top of either TensorFlow or Theano. The model architecture for each cancer type are given in sections (Breast Neural Network Model Architecture, Colon Cancer Neural Network Model Architecture, Lung Cancer Neural Network Model Architecture). Training a neural network and choosing an appropriate architecture is as much art as science [24], and the search for a good neural network architecture for the lung cancer case was more demanding than for the breast and colon cases. The presence of both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) in the SEER data may be the source of this need for more iterations and trials of different architectures when training the lung cancer neural network models.

Results

In order to evaluate the performance of the models, we first construct three binary classifiers corresponding to whether or not a subject survived 6, 12, or 60 months after diagnosis. This is done by iterating over all distinct patient indices in the test set, predicting the full survival function, and capturing the values corresponding to 6, 12, and 60 months. If the survival function evaluated at 6 months is greater than or equal to .5 for a given subject, then the 6 months binary classifier predicts that that subject will be alive 6 months after diagnosis. Similarly, if the survival function evaluated at 60 months is less than .5, then the 12 months binary classifier predicts that that subject will be dead 12 months after diagnosis. Figure (2) illustrates the method; in this case the 6-month and 12-month classifiers predict survival, while the 60-month classifier predicts expiry.

Because of censoring it is necessary to apply some Boolean filters to the data in order to correctly assess the resulting classifiers. To construct AUC curves for the 6 month classifier, we restrict ourselves to considering subjects in the test data where either of the following mutually exclusive conditions holds:

- `survival_months >= 6 AND vital_status_recode == 0`
- `vital_status_recode == 1`

That is, we restrict ourselves to subsets of the data where we know for certain whether or not the subject survived at least 6 months. Similarly for the 12 and 60 months survival classifiers.

Survival Curve Error Estimates The standard calculation of confidence intervals used in the Kaplan-Meier estimates of survival curves does not apply for these personal predictions. The following bootstrap method was used to calculate the upper and lower

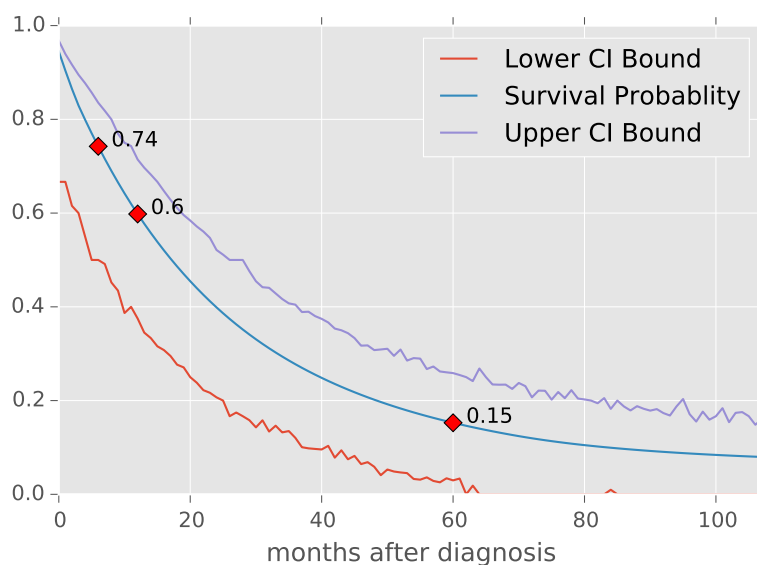


Figure 2. Example of the construction of the binary classifiers for 6, 12, and 60 months survival. A subject's hazard curve $\lambda(\mathbf{X}, t)$ is predicted by the model for times out to 107 months. The survival curve is then readily computed as in Equation (5). For this example, the 6-month and 12-month classifiers predict survival, while the 60-month classifier predicts expiry.

bounds corresponding to 95% confidence intervals. From equation 5, we can obtain the cumulative distribution function (CDF) associated with each individual survival curve. We then sample from this CDF in a way that reflects the underlying data used to produce the model. The training data used to create the model has an underlying distribution of survival months. In the transformed training dataset, each subject contributes as many rows as the number of survival months plus one (patients with zero survival months still represent one row of the training data). A subject that survived 50 months contributes 51 "points" to the training of the model. If all patients lived out to 107 months, the model would contain less uncertainty. This observation leads to the following algorithm for determining the error estimates to the predicted survival curves:

- compute the CDF associated with the survival curve
- use the underlying training data CDF of survival months to choose the number of points to draw from the survival curve CDF, and compute a new survival curve
- Repeat the previous step 10,000 times and collect the curves into a list. Changing the number of curves affects how smooth the upper and lower bounds are, but does not affect the interval size between for each month.
- extract for each month from the list of curves the .975 and .025 percentiles to record the values for the upper and lower curves

The process is somewhat analogous to the following hypothetical situation. Imagine a patient going to an expert, and the expert after collecting data on the patient and keeping records predicts the central, single survival curve. The patient then seeks multiple "second opinions." These second opinions are generated not from independent examinations of the patient, but by outside experts sampling from the data already collected by the expert initially consulted. Then the predictions of 95% of these 10,000 experts all fall within the band determined by the upper and lower curves.

Performance Metrics

The AUC scores for each of the 18 different binary classifiers are listed in Table (10). We emphasize the above-mentioned discussion concerning the correct treatment of the censored test data when evaluating performance metrics. Namely, when computing the AUC for the 12 month survival curve classifiers, we restrict the test data subjects to those that in the untransformed data set that satisfy either of the following mutually exclusive conditions:

- `survival_months >= 12 AND vital_status_recode == 0`
- `vital_status_recode == 1`

We limit evaluation data to subsets of the data where we know for certain whether or not the subject survived at least 12 months. Similar considerations apply to the 12 and 60 months AUC calculations. The lowest AUC in Table 10 is .765, corresponding to the lung neural network model predictions for 6 months survival, while the highest AUC in Table 10 is .885, corresponding to the breast random forest model predictions for 12 months survival.

Table 9. AUC values for the Random Forest and Neural Networks model binary classifiers derived from the full survival curve predictions; see text for details. The number of subjects that were used in the calculation of a given AUC score are given in parenthesis after the score.

Model	6 Months AUC	12 Months AUC	60 Months AUC
Breast RF	.846 (3035)	.885 (2797)	.844 (1392)
Breast NN	.855 (3035)	.867 (2797)	.836 (1392)
Colon RF	.804 (5281)	.806 (5003)	.828 (3232)
Colon NN	.797 (5281)	.804 (5003)	.841 (3232)
Lung RF	.772 (5019)	.796 (4860)	.874 (4143)
Lung NN	.765 (5019)	.796 (4860)	.875 (4143)

Model Agreement

An additional means of validating the predictions of these models is by comparing their predictions to each other for the same set of input data. Table 11 shows the strong agreement between the random forest and neural network classifiers for each cancer type. Python code showing how the values in Table 11 are computed is available in the files `NewPatientBreastCF.html`, `NewPatientColonCF.html`, and `NewPatientLung.html` in the GitHub repository containing supplemental material for this study [16]. Table 11 is computed as follows. For each cancer type (breast, colon, and lung), do the following:

- use the corresponding Random Forest and Neural Network models to compute the survival curves for all of the test subjects
- extract the values of the survival curve evaluated for 6, 12, and 60 months for both models
- if both models predict less than .5 or both models predict greater than or equal to .5, that counts as agreement
- otherwise, the models disagree

The high level of agreement between two models lends confidence to the notion that they have both learned from the training data and are generalizing well. Figures (4, 3, 5) show box plots of the value of the random forest prediction subtracted

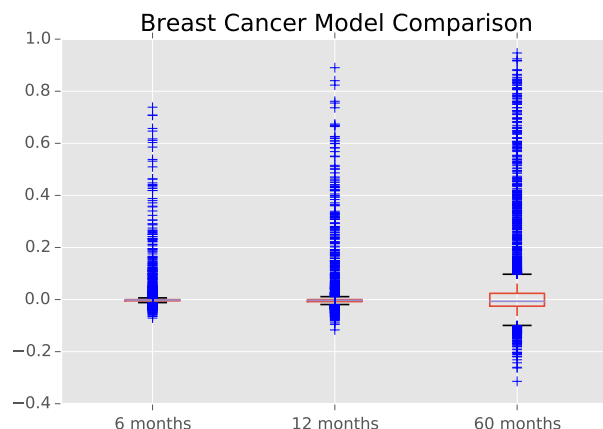


Figure 3. Box plots showing the distributions of the signed difference between the MLP model's prediction for the probability of surviving 6 months and the Random Forest model's prediction of the same quantity for breast cancer. The plot shows the same quantity for the 12 and 60 months classifiers. It is apparent from the figures that the outliers are due to the neural network models predicting higher survival probabilities than the random forest for some few cases. These differences were evaluated for the 3300 test patients in the breast cancer data.

from the neural network prediction. We emphasize that when evaluating the model agreement, we put no restrictions on the distinct subjects in the respective test datasets; we are confronting the models against each other, not some known ground truth as in the AUC performance metric calculations. The number of distinct subjects in all three of the colon cancer survival binary classifiers (6, 12, and 60 month survival) was 5654; for lung cancer the number of subjects entering into the calculation of Table (11) was 5313; and for breast cancer it was 3300.

Table 10. Percentage agreement for the Random Forest and Neural Network classifiers for 6, 12, and 60 month survival predictions on the test data for each cancer type.

Cancer Type	% agreement 6 months	% agreement 12 months	% agreement 60 months
Colon	.981	.971	.915
Breast	.994	.984	.938
Lung	.861	.883	.900

Survival Curve Prediction Apps

The six models described in section Prediction Models, namely the random forest and MLP neural network models for each of the three cancer types considered in this study, have their full hyperparameter and architecture presented in section Supporting Information. Python code for all six model training and evaluation is available at the github repository containing supplemental material for this study [16].

Using the popular Flask microframework for web applications [26], we have made web applications corresponding to the six models. The list of web applications below will allow readers to freely experiment with the models.

1. breast cancer

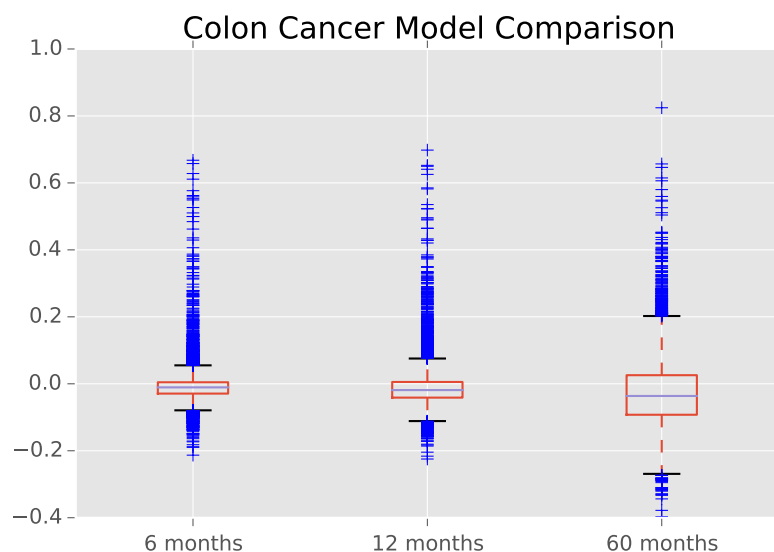


Figure 4. Box plots showing the distributions of the signed difference between the MLP model's prediction for the probability of surviving 6 months and the Random Forest model's prediction of the same quantity for colon cancer. The plot shows the same quantity for the 12 and 60 months classifiers. It is apparent from the figures that the outliers are due to the neural network models predicting higher survival probabilities than the random forest for some few cases. These differences were evaluated for the 5654 test patients in the colon cancer data.

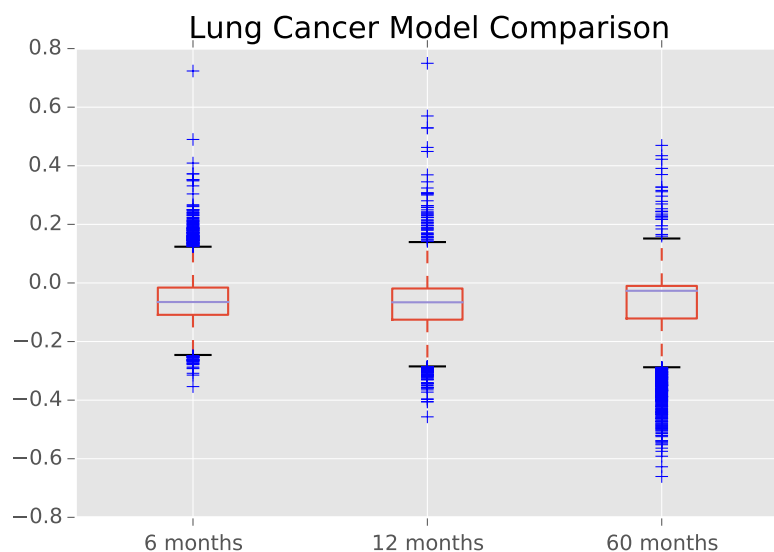


Figure 5. Box plots showing the distributions of the signed difference between the MLP model's prediction for the probability of surviving 6 months and the Random Forest model's prediction of the same quantity for lung cancer. The plot shows the same quantity for the 12 and 60 months classifiers. These differences were evaluated for the 5313 test patients in the lung cancer data. The Interquartile Ranges for lung cancer are visibly larger than those for breast cancer and colon cancer shown in fig 3 and fig 4.

- (a) random forest: 460
<https://github.com/doolingdavid/breast-cancer-rf-errors.git> 461
- (b) neural network: 462
<https://github.com/doolingdavid/breast-cancer-nn-errors.git> 463
2. lung cancer 464
- (a) random forest: 465
<https://github.com/doolingdavid/lung-cancer-rf-errors.git> 466
- (b) neural network: 467
<https://github.com/doolingdavid/lung-cancer-nn-errors.git> 468
3. colon cancer 469
- (a) random forest: 470
<https://github.com/doolingdavid/colon-cancer-rf-errors.git> 471
- (b) neural network: 472
<https://github.com/doolingdavid/colon-cancer-nn-errors.git> 473

After downloading the .zip file associate with one of the above web applications, and assuming python is installed on your system, you can launch the application by running 474

```
>python hello.py 475
```

and pointing the browser to the local server: <http://127.0.0.1:5000> . 476

These machine learning models are used to predict survival curves for a given set of 477
input data. The resulting survival curves predict the probability that a patient with the 478
given input data will survive at least up to month x . 479
480

For example, using the Colon Cancer neural network app, and inputting the values listed in Table (12) results in the survival curve depicted in Figure (6); the predicted probabilities of living at least 6, 12, and 60 months are .89, .83, and .50, respectively.

Table 11. Example input data to the Colon Cancer neural network app
<https://github.com/doolingdavid/colon-cancer-nn-errors.git>.

Variable	Value
What is the tumor size (mm)	300
What is the patient's address?	boston massachusetts
Grade	moderately differentiated
Histology	adenomas and adenocarcinomas
Laterality	not a paired site
Marital Status at Dx	Single, never married
Month of Diagnosis	Jan
How many primaries	1
Race_ethnicity	White
seer_historic_stage_a	Regional
Gender	Male
spanish_hispanic_origin	Non-spanish/Non-hispanic
Year of Birth	1940
Year of Diagnosis	2010

Changing the data in Table 12 so that the address field is changed from Boston, Massachusetts to Denver, Colorado but keeping all other variables are unchanged results in the predicted probabilities of living at least 6, 12, and 60 months: .945, .902, .665. Behind the scenes, the apps use the input to the address field to make a call to the Google Maps API to convert the address into a latitude, longitude and elevation. These probabilities are noticeably higher and reflect the documented effects of both longitude and elevation on cancer treatment and prognosis in the United States [27].

A similar example of how changing the inputs to the models affects the predicted survival curves in interesting ways can be seen with the random forest model for lung cancer. Changing the data in Table 13 by toggling between the male/female, and married/single four possible permutations results in the following prediction probabilities for 6, 12, and 60 month survival:

- male/married: .53, .27, .01
- male/single: .35, .18, .009
- female/married: .55, .31, .01
- female/single: .50, .27, .01

Inputting the same combinations of data into the lung cancer neural network app <https://github.com/doolingdavid/lung-cancer-nn-errors.git> yields the following probabilities:

- male/married: .42, .24, .04
- male/single: .40, .22, .03
- female/married: .44, .26, .04
- female/single: .42, .24, .04

It is interesting to note that both the random forest and neural network lung cancer models predict greater 6 month survival rates for married people, with a slightly greater benefit for males than females. The effect is greater in the random forest model, but is also visible in the neural network model.

Colon Cancer Survival Curve Prediction

Prediction:

1. Probability of Surviving 6 months is **0.897**
2. Probability of Surviving 12 months is **0.831**
3. Probability of Surviving 60 months is **0.504**

Predicted Survival Curve from Model

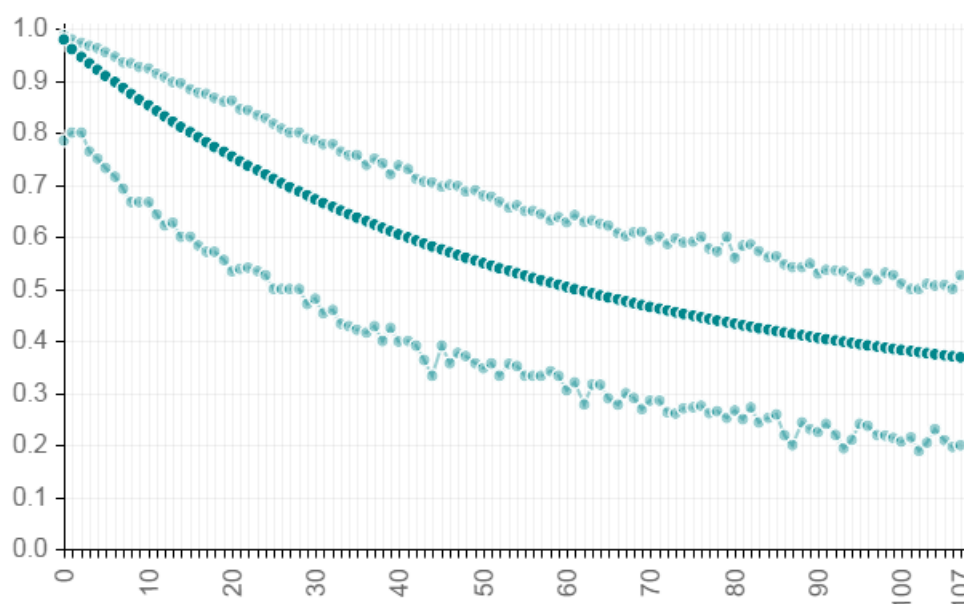


Figure 6. Colon Cancer Survival Curve predicted from the data in Table (12) using the neural network web app
<https://github.com/doolingdavid/colon-cancer-nn-errors.git>.

Discussion

The purpose of this study has been twofold; to develop a general methodology of data transformation to survival data with censored observations so that machine learning algorithms can be applied and to help further the cause of PPPM medicine by developing models of personalized survival curve prognosis. To help further refine the methodology, we would like to apply it to different survival datasets [28], not necessarily within the healthcare domain. In particular, the methods presented in this paper do not take into account time varying features. For example, the `cs.tumor_size` variable that has been a part of this study is kept fixed at the value measured at diagnosis for all records corresponding to a given subject. Clearly, the actual tumor size varies along with time and a sophisticated model can be developed to take this into account, given available datasets. Unfortunately, the SEER datasets considered in this study do not provide this kind of granularity over time.

The SEER database has been linked with claims data in the SEER-Medicare Linked Database [29]. This linkage allows for the identification of additional clinical data for

Table 12. Example input data to the Lung Cancer random forest app
<https://github.com/doolingdavid/lung-cancer-rf-errors.git>.

Variable	Value
What is the tumor size (mm)	500
What is the patient's address?	newark new jersey
Grade	well differentiated
Histology	acinar cell neoplasms
Laterality	bilateral involvement, lateral origin unknown; stated to be single primary
Marital Status at Dx	Married including common law
Month of Diagnosis	Jan
How many primaries	1
Race_ethnicity	White
seer_historic_stage_a	Distant
Gender	Female
spanish_hispanic_origin	Non-spanish/Non-hispanic
Year of Birth	1970
Year of Diagnosis	2011

each record in the SEER database and allows for an enrichment of the models presented in this study, and is an avenue for further investigation.

An additional avenue of research concerns the broad concept of causality. As demonstrated in section Survival Curve Prediction Apps, there appears to be a correlation between marital status and survival prognosis. Does this mean that if a single person in Boston, Massachusetts is diagnosed with cancer, that they should immediately get married and move to Denver? Of course not. But personal discussions with providers has confirmed for one of the authors (D.D.) that married males tend to be much more diligent in following instructions than their single counterparts. What appears to be in effect is that some of the SEER data is providing an identifiable signature of underlying causes not directly represented by the data. Latent variables not directly seen in the data are still providing echos of patterns in the data and the sheer volume allows us to see glimpses of these patterns. Marital status is in some instances a surrogate for the presence of a strong social structure and support group surrounding a patient, which presence presumably leads to more desirable survival prognosis. The daunting and exciting task of teasing out actual causality relationships within machine learning contexts has been pioneered by Judea Pearl of the University of California, Los Angeles ⁴ and seems particularly relevant and applicable to censored survival data. Combining the methodology presented in this study for the marriage of machine learning and censored survival data with that of the pioneering work of Judea Pearl on causality will be a fruitful avenue for future research.

Supporting Information

Raw SEER datafiles

- incidence\yr1973_2012.seer9\COLRECT.txt
- incidence\yr1973_2012.seer9\BREAST.txt
- incidence\yr1973_2012.seer9\RESPIR.txt

⁴Judea Pearl homepage at the University of California, Los Angeles, http://bayes.cs.ucla.edu/jp_home.html, accessed 11 Jan 2016.

- incidence\yr1992_2012.sj_la_rg_ak\COLRECT.txt 552
- incidence\yr1992_2012.sj_la_rg_ak\BREAST.txt 553
- incidence\yr1992_2012.sj_la_rg_ak\RESPIR.txt 554
- incidence\yr2000_2012.ca_ky_lo_nj_ga\COLRECT.txt 555
- incidence\yr2000_2012.ca_ky_lo_nj_ga\BREAST.txt 556
- incidence\yr2000_2012.ca_ky_lo_nj_ga\RESPIR.txt 557
- incidence\yr2005.lo_2nd_half\COLRECT.txt 558
- incidence\yr2005.lo_2nd_half\BREAST.txt 559
- incidence\yr2005.lo_2nd_half\RESPIR.txt 560

Colon Cancer Feature Selection 561

The feature set used as input into both the Random Forest and Neural Network models, after the transformation described in section Transformation of Censored Data for Machine Learning is given below and also available in full detail in the file NewPatientColonML.html . 562
563
564
565

- cs_tumor_size 566
- elevation 567
- grade_cell type not determined 568
- grade_moderately differentiated 569
- grade_poorly differentiated 570
- grade_undifferentiated; anaplastic 571
- grade_well differentiated 572
- histology_recode_broad_groupings_acinar cell neoplasms 573
- histology_recode_broad_groupings_adenomas and adenocarcinomas 574
- histology_recode_broad_groupings_blood vessel tumors 575
- histology_recode_broad_groupings_complex epithelial neoplasms 576
- histology_recode_broad_groupings_complex mixed and stromal neoplasms 577
- histology_recode_broad_groupings_cystic, mucinous and serous neoplasms 578
- histology_recode_broad_groupings_ductal and lobular neoplasms 579
- histology_recode_broad_groupings_epithelial neoplasms, NOS 580
- histology_recode_broad_groupings_fibromatous neoplasms 581
- histology_recode_broad_groupings_germ cell neoplasms 582
- histology_recode_broad_groupings_lipomatous neoplasms 583
- histology_recode_broad_groupings_miscellaneous bone tumors 584
- histology_recode_broad_groupings_myomatous neoplasms 585
- histology_recode_broad_groupings_neuroepitheliomatous neoplasms 586
- histology_recode_broad_groupings_nevi and melanomas 587
- histology_recode_broad_groupings_paragangliomas and glomus tumors 588
- histology_recode_broad_groupings_soft tissue tumors and sarcomas, NOS 589
- histology_recode_broad_groupings_squamous cell neoplasms 590
- histology_recode_broad_groupings_synovial-like neoplasms 591
- histology_recode_broad_groupings_transistional cell papillomas and carcinomas 592
- histology_recode_broad_groupings_unspecified neoplasms 593
- lat 594
- laterality_Left: origin of primary 595
- laterality_Not a paired site 596
- laterality_Only one side involved, right or left origin unspecified 597
- laterality_Paired site, but no information concerning laterality; midline tumor 598
- laterality_Right: origin of primary 599
- lng 600
- marital_status_at_dx_Divorced 601

• marital_status_at_dx_Married (including common law)	602
• marital_status_at_dx_Separated	603
• marital_status_at_dx_Single (never married)	604
• marital_status_at_dx_Unknown	605
• marital_status_at_dx_Unmarried or domestic partner	606
• marital_status_at_dx_Widowed	607
• month_of_diagnosis_Apr	608
• month_of_diagnosis_Aug	609
• month_of_diagnosis_Dec	610
• month_of_diagnosis_Feb	611
• month_of_diagnosis_Jan	612
• month_of_diagnosis_Jul	613
• month_of_diagnosis_Jun	614
• month_of_diagnosis_Mar	615
• month_of_diagnosis_May	616
• month_of_diagnosis_Nov	617
• month_of_diagnosis_Oct	618
• month_of_diagnosis_Sep	619
• number_of primaries	620
• race_ethnicity_Amerian Indian, Aleutian, Alaskan Native or Eskimo	621
• race_ethnicity_Asian Indian	622
• race_ethnicity_Asian Indian or Pakistani	623
• race_ethnicity_Black	624
• race_ethnicity_Chinese	625
• race_ethnicity_Fiji Islander	626
• race_ethnicity_Filipino	627
• race_ethnicity_Guamanian	628
• race_ethnicity_Hawaiian	629
• race_ethnicity_Hmong	630
• race_ethnicity_Japanese	631
• race_ethnicity_Kampuchean	632
• race_ethnicity_Korean	633
• race_ethnicity_Laotian	634
• race_ethnicity_Melanesian	635
• race_ethnicity_Micronesian	636
• race_ethnicity_New Guinean	637
• race_ethnicity_Other	638
• race_ethnicity_Other Asian	639
• race_ethnicity_Pacific Islander	640
• race_ethnicity_Pakistani	641
• race_ethnicity_Polynesian	642
• race_ethnicity_Samoan	643
• race_ethnicity_Thai	644
• race_ethnicity_Tongan	645
• race_ethnicity_Unknown	646
• race_ethnicity_Vietnamese	647
• race_ethnicity_White	648
• seer_historic_stage_a_Distant	649
• seer_historic_stage_a_In situ	650
• seer_historic_stage_a_Localized	651
• seer_historic_stage_a_Regional	652
• seer_historic_stage_a_Unstaged	653

- sex_Female 654
- spanish_hispanic_origin_Cuban 655
- spanish_hispanic_origin_Dominican Republic 656
- spanish_hispanic_origin_Mexican 657
- spanish_hispanic_origin_Non-Spanish/Non-hispanic 658
- spanish_hispanic_origin_Other specified Spanish/Hispanic origin (excludes Dominican Repuclic) 659
- spanish_hispanic_origin_Puerto Rican 660
- spanish_hispanic_origin_South or Central American (except Brazil) 661
- spanish_hispanic_origin_Spanish surname only 662
- spanish_hispanic_origin_Spanish, NOS; Hispanic, NOS; Latino, NOS 663
- spanish_hispanic_origin_Uknown whether Spanish/Hispanic or not 664
- year_of_birth 665
- year_of_diagnosis 666
- month 667

and `newtarget` is the target variable, indicating whether or not the subject died in month given by the value of the `month` variable. 669

Lung Cancer Feature Selection 671

The feature set used as input into both the Random Forest and Neural Network models, after the transformation described in section Transformation of Censored Data for Machine Learning is given below and also available in full detail in the file `NewPatientLungML.html` . 672

- cs_tumor_size 676
- elevation 677
- grade_cell type not determined 678
- grade_moderately differentiated 679
- grade_poorly differentiated 680
- grade_undifferentiated; anaplastic 681
- grade_well differentiated 682
- histology_recode_broad_groupings_acinar cell neoplasms 683
- histology_recode_broad_groupings_adenomas and adenocarcinomas 684
- histology_recode_broad_groupings_blood vessel tumors 685
- histology_recode_broad_groupings_complex epithelial neoplasms 686
- histology_recode_broad_groupings_complex mixed and stromal neoplasms 687
- histology_recode_broad_groupings_cystic, mucinous and serous neoplasms 688
- histology_recode_broad_groupings_ductal and lobular neoplasms 689
- histology_recode_broad_groupings_epithelial neoplasms, NOS 690
- histology_recode_broad_groupings_fibroepithelial neoplasms 691
- histology_recode_broad_groupings_fibromatous neoplasms 692
- histology_recode_broad_groupings_germ cell neoplasms 693
- histology_recode_broad_groupings_gliomas 694
- histology_recode_broad_groupings_granular cell tumors & alveolar soft part sarcomas 695
- histology_recode_broad_groupings_lipomatous neplasms 696
- histology_recode_broad_groupings_miscellaneous bone tumors 697
- histology_recode_broad_groupings_miscellaneous tumors 698
- histology_recode_broad_groupings_mucoepidermoid neoplasms 699
- histology_recode_broad_groupings_myomatous neoplasms 700
- histology_recode_broad_groupings_myxomatous neoplasms 701

• histology_recode_broad_groupings_nerve sheath tumors	703
• histology_recode_broad_groupings_neuroepitheliomatous neoplasms	704
• histology_recode_broad_groupings_nevi and melanomas	705
• histology_recode_broad_groupings_osseous and chondromatous neoplasms	706
• histology_recode_broad_groupings_paragangliomas and glumus tumors	707
• histology_recode_broad_groupings_soft tissue tumors and sarcomas, NOS	708
• histology_recode_broad_groupings_squamous cell neoplasms	709
• histology_recode_broad_groupings_synovial-like neoplasms	710
• histology_recode_broad_groupings_thymic epithelial neoplasms	711
• histology_recode_broad_groupings_transistional cell papillomas and carcinomas	712
• histology_recode_broad_groupings_trophoblastic neoplasms	713
• histology_recode_broad_groupings_unspecified neoplasms	714
• lat	715
• laterality_Bilateral involvement, lateral origin unknown; stated to be single primary	716
• laterality_Left: origin of primary	717
• laterality_Not a paired site	718
• laterality_Only one side involved, right or left origin unspecified	719
• laterality_Paired site, but no information concerning laterality; midline tumor	720
• laterality_Right: origin of primary	721
• lng	722
• lng	723
• marital_status_at_dx_Divorced	724
• marital_status_at_dx_Married (including common law)	725
• marital_status_at_dx_Separated	726
• marital_status_at_dx_Single (never married)	727
• marital_status_at_dx_Unknown	728
• marital_status_at_dx_Unmarried or domestic partner	729
• marital_status_at_dx_Widowed	730
• month_of_diagnosis_Apr	731
• month_of_diagnosis_Aug	732
• month_of_diagnosis_Dec	733
• month_of_diagnosis_Feb	734
• month_of_diagnosis_Jan	735
• month_of_diagnosis_Jul	736
• month_of_diagnosis_Jun	737
• month_of_diagnosis_Mar	738
• month_of_diagnosis_May	739
• month_of_diagnosis_Nov	740
• month_of_diagnosis_Oct	741
• month_of_diagnosis_Sep	742
• number_of primaries	743
• race_ethnicity_Amerian Indian, Aleutian, Alaskan Native or Eskimo	744
• race_ethnicity_Asian Indian	745
• race_ethnicity_Asian Indian or Pakistani	746
• race_ethnicity_Black	747
• race_ethnicity_Chamorran	748
• race_ethnicity_Chinese	749
• race_ethnicity_Fiji Islander	750
• race_ethnicity_Filipino	751
• race_ethnicity_Guamanian	752
• race_ethnicity_Hawaiian	753
• race_ethnicity_Hmong	754

• race_ethnicity_Japanese	755
• race_ethnicity_Kampuchean	756
• race_ethnicity_Korean	757
• race_ethnicity_Laotian	758
• race_ethnicity_Melanesian	759
• race_ethnicity_Micronesian	760
• race_ethnicity_New Guinean	761
• race_ethnicity_Other	762
• race_ethnicity_Other Asian	763
• race_ethnicity_Pacific Islander	764
• race_ethnicity_Pakistani	765
• race_ethnicity_Polynesian	766
• race_ethnicity_Samoan	767
• race_ethnicity_Thai	768
• race_ethnicity_Tongan	769
• race_ethnicity_Unknown	770
• race_ethnicity_Vietnamese	771
• race_ethnicity_White	772
• seer_historic_stage_a_Distant	773
• seer_historic_stage_a_In situ	774
• seer_historic_stage_a_Localized	775
• seer_historic_stage_a_Regional	776
• seer_historic_stage_a_Unstaged	777
• sex_Female	778
• spanish_hispanic_origin_Cuban	779
• spanish_hispanic_origin_Dominican Republic	780
• spanish_hispanic_origin_Mexican	781
• spanish_hispanic_origin_Non-Spanish/Non-hispanic	782
• spanish_hispanic_origin.Other specified Spanish/Hispanic origin (excludes Dominican Repuclic)	783
• spanish_hispanic_origin.Puerto Rican	784
• spanish_hispanic_origin.South or Central American (except Brazil)	785
• spanish_hispanic_origin.Spanish surname only	786
• spanish_hispanic_origin.Spanish, NOS; Hispanic, NOS; Latino, NOS	787
• spanish_hispanic_origin.Uknown whether Spanish/Hispanic or not	788
• year_of_birth	789
• year_of_diagnosis	790
• month	791

and `newtarget` is the target variable, indicating whether or not the subject died in month given by the value of the `month` variable.

Breast Cancer Feature Selection

The feature set used as input into both the Random Forest and Neural Network models, after the transformation described in section Transformation of Censored Data for Machine Learning is given below and also available in full detail in the file `NewPatientBreastML.html` .

• cs_tumor_size	800
• elevation	801
• grade_moderately differentiated	802
• grade_poorly differentiated	803

• grade_ndifferentiated; anaplastic	804
• grade_well differentiated	805
• histology_recode_broad_groupings_adenomas and adenocarcinomas	806
• histology_recode_broad_groupings_adnexal and skin appendage neoplasms	807
• histology_recode_broad_groupings_basal cell neoplasms	808
• histology_recode_broad_groupings_complex epithelial neoplasms	809
• histology_recode_broad_groupings_cystic, mucinous and serous neoplasms	810
• histology_recode_broad_groupings_ductal and lobular neoplasms	811
• histology_recode_broad_groupings_epithelial neoplasms, NOS	812
• histology_recode_broad_groupings_nerve sheath tumors	813
• histology_recode_broad_groupings_unspecified neoplasms	814
• lat	815
• laterality_Bilateral involvement, lateral origin unknown; stated to be single primary	816
• laterality_Paired site, but no information concerning laterality; midline tumor	817
• laterality_Right: origin of primary	818
• lng	819
• marital_stats_at_dx_Divorced	820
• marital_stats_at_dx_Married (inclnding common law)	821
• marital_stats_at_dx_Separated	822
• marital_stats_at_dx_Single (never married)	823
• marital_stats_at_dx_Unknown	824
• marital_stats_at_dx_Unmarried or domestic partner	825
• marital_stats_at_dx_Widowed	826
• month_of_diagnosis_Apr	827
• month_of_diagnosis_Aug	828
• month_of_diagnosis_Dec	829
• month_of_diagnosis_Feb	830
• month_of_diagnosis_Jan	831
• month_of_diagnosis_Jul	832
• month_of_diagnosis_Jun	833
• month_of_diagnosis_Mar	834
• month_of_diagnosis_May	835
• month_of_diagnosis_Nov	836
• month_of_diagnosis_Oct	837
• month_of_diagnosis_Sep	838
• race_ethnicity_Amerian Indian, Aletian, Alaskan Native or Eskimo	839
• race_ethnicity_Asian Indian	840
• race_ethnicity_Black	841
• race_ethnicity_Chinese	842
• race_ethnicity_Japanese	843
• race_ethnicity_Melanesian	844
• race_ethnicity_Other	845
• race_ethnicity_Other Asian	846
• race_ethnicity_Pacific Islander	847
• race_ethnicity_Thai	848
• race_ethnicity_Unknown	849
• race_ethnicity_Vietnamese	850
• race_ethnicity_White	851
• seer_historic_stage_a_Distant	852
• seer_historic_stage_a_In sit	853
• seer_historic_stage_a_Localized	854
	855

- `seer_historic_stage_a.Unstaged`
- `sex.Female`
- `spanish_hispanic_origin.Cuban`
- `spanish_hispanic_origin.Mexican`
- `spanish_hispanic_origin.Non-Spanish/Non-hispanic`
- `spanish_hispanic_origin.Other specified Spanish/Hispanic origin (excludes Dominican Republic)`
- `spanish_hispanic_origin.Spanish surname only`
- `spanish_hispanic_origin.Spanish, NOS; Hispanic, NOS; Latino, NOS`
- `year_of_birth`
- `year_of_diagnosis`
- `month`

and `newtarget` is the target variable, indicating whether or not the subject died in month given by the value of the `month` variable.

Pseudocode for the Data Transformation

```
def train(X, T, D)
    // X, T, D are the original dataset
    X' = []
    D' = []

    // the transformation
    for each index i in X:
        for t=1 to T[i]:
            new_D = (0 if t < T[i], else D[i])
            append new_D to D'
            new_X = (X[i], t)
            append new_X to X'

    return a decision tree trained on (X', D')
```

```
def pmf(h, X)
    // X is a single datapoint
    // returns an array A where A[i] = P(Y = i | X)
    A = []
    p_so_far = 1 // this is p(T >= t | X)
    for t = 1 to (the last month where h has any data):
        // h knows p(T = t | T >= t, X), we call this p_cur
        p_cur = h's prediction for (X, t)
        append (p_so_far * p_cur) to A
        p_so_far *= (1 - p_cur)
```

Breast Random Forest Model Hyperparameters

```
f = RandomForestClassifier(n_estimators=20,min_samples_split=3,
                           max_depth = 15,
                           max_features = .8,
                           n_jobs=5,verbose=2,random_state=33)
```

Colon Random Forest Model Hyperparameters

```
rf = RandomForestClassifier(n_estimators=25,min_samples_split=3,
                           max_depth = 10,
                           max_features = .5,
                           n_jobs=5,verbose=2,random_state=3)
```

Lung Random Forest Model Hyperparameters

```
rf = RandomForestClassifier(n_estimators=25,min_samples_split=3,
                           max_depth = 11,
                           max_features = .8,
                           n_jobs=5,verbose=2,random_state=3)
```

Breast Neural Network Model Architecture

The architecture of the Keras multilayer perceptron neural network model trained on the breast cancer data is given explicitly below:

```
modelbreast = Sequential()
modelbreast.add(Dense(114, input_shape=(66,) ,init='normal'))
modelbreast.add(Activation('relu'))
modelbreast.add(Dropout(0.05))
modelbreast.add(Dense(50, init='normal'))
modelbreast.add(Activation('relu'))
modelbreast.add(Dropout(0.05))

modelbreast.add(Dense(36, init='normal'))
modelbreast.add(Activation('relu'))
modelbreast.add(Dropout(0.05))

modelbreast.add(Dense(2, init='normal'))
modelbreast.add(Activation('softmax'))

rms = RMSprop(lr=0.001)

modelbreast.compile(loss='binary_crossentropy',
                    optimizer=rms, class_mode="binary")
```

and trained with a batch size of 1500 for 200 epochs.

Colon Cancer Neural Network Model Architecture

The architecture of the Keras multilayer perceptron neural network model trained on the colon cancer data is given explicitly below:

```
modelcolon = Sequential()
modelcolon.add(Dense(114, input_shape=(102,) ,init='normal'))
modelcolon.add(Activation('relu'))
modelcolon.add(Dropout(0.05))
modelcolon.add(Dense(50, init='normal'))
```

```

modelcolon.add(Activation('relu'))
modelcolon.add(Dropout(0.05))

modelcolon.add(Dense(35, init='normal'))
modelcolon.add(Activation('relu'))
modelcolon.add(Dropout(0.05))

modelcolon.add(Dense(2, init='normal'))
modelcolon.add(Activation('softmax'))

rms = RMSprop(lr=0.001)

modelcolon.compile(loss='binary_crossentropy',
                    optimizer=rms, class_mode="binary")

```

and trained with a batch size of 1500 for 200 epochs.

Lung Cancer Neural Network Model Architecture

The architecture of the Keras multilayer perceptron neural network model trained on the lung cancer data is given explicitly below:

```

modellung = Sequential()
modellung.add(Dense(114, input_shape=(114,) ,init='normal'))
modellung.add(Activation('relu'))
modellung.add(Dropout(0.1))
modellung.add(Dense(80, init='normal'))
modellung.add(Activation('relu'))
modellung.add(Dropout(0.1))
modellung.add(Dense(40, init='normal'))
modellung.add(Activation('relu'))
modellung.add(Dropout(0.1))

modellung.add(Dense(2, init='normal'))
modellung.add(Activation('softmax'))

rms = RMSprop(lr=0.001)

modellung.compile(loss='binary_crossentropy',
                  optimizer=rms, class_mode="binary")

```

and trained with a batch size of 2000 for 50 epochs.

S1 Video

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S1 Text 993

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S1 Fig 997

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S2 Fig 1001

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S1 Table 1005

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Acknowledgments 1009

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References

1. Sebastian Raschka. Python Machine Learning Essentials. Packt Publishing; 2015.
2. Cam Davidson-Pilon. Quickstart – lifelines 0.8.0.1 documentation; 2016 (accessed 14 Jan 2016).
<http://lifelines.readthedocs.org/en/latest/Quickstart.html>.
3. Van Poucke S, Zhang Z, Schmitz M, Vukicevic M, Laenen MV, Celi LA, et al. Scalable predictive analysis in critically ill patients using a visual open data analysis platform. PLoS ONE. 2016;11(1). Cited By 0. Available from:
<http://www.scopus.com/inward/record.url?eid=2-s2.0-84953931466&partnerID=40&md5=7a0cad7137c03146e4b75f3295f84cc6>.
4. National Cancer Institute, the Surveillance, Epidemiology, and End Results Program. About the SEER Program - SEER; 2016 (accessed 14 Jan 2016).
<http://seer.cancer.gov/about>.
5. Shin, Hyunjung and Nam, Yonghyun; ISCB Asia. A coupling approach of a predictor and a descriptor for breast cancer prognosis [Article; Proceedings Paper]. BMC MEDICAL GENOMICS. 2014 MAY 8;7(1). 3rd Annual Translational Bioinformatics Conference (TBC) / ISCB-Asia, Seoul, SOUTH KOREA, OCT 02-04, 2013.

6. Zolbanin, Hamed Majidi and Delen, Dursun and Zadeh, Amir Hassan. Predicting overall survivability in comorbidity of cancers: A data mining approach [Article]. *DECISION SUPPORT SYSTEMS*. 2015 JUN;74:150–161.
7. Gordon L, Olshen RA. Tree-structured survival analysis. *Cancer Treatment Reports*. 1985;69(10):1065–1068. Cited By 97. Available from: <http://www.scopus.com/inward/record.url?eid=2-s2.0-0021875130&partnerID=40&md5=9e112ed840960f801b6260b23bf6811d>.
8. Bou-Hamad I, Larocque D, Ben-Ameur H. A review of survival trees. *Statistics Surveys*. 2011;5:44–71. Cited By 15. Available from: <http://www.scopus.com/inward/record.url?eid=2-s2.0-84857308440&partnerID=40&md5=f8af82017ade68e335fd258c6857bf49>.
9. Ishwaran H, Kogalur UB. Consistency of random survival forests. *Statistics and Probability Letters*. 2010;80(13-14):1056–1064. Cited By 26. Available from: <http://www.scopus.com/inward/record.url?eid=2-s2.0-77953020220&partnerID=40&md5=1e4478c51150f0159fdc6c1cb631968b>.
10. National Cancer Institute, the Surveillance, Epidemiology, and End Results Program. Documentation for ASCII Text Data Files - SEER Datasets; 2016 (accessed 15 Jan 2016). <http://seer.cancer.gov/data/documentation.html>.
11. Michael Bowles. *Machine Learning in Python: Essential Techniques for Predictive Analysis*. Wiley; 2015.
12. Allen Downey. *Think Stats*. O'Reilly Media; 2014.
13. United States Census Bureau. 2010 FIPS Code Files for Counties - Geography - U.S. Census Bureau; 2016 (accessed 18 Jan 2016). <https://www.census.gov/geo/reference/codes/cou.html>.
14. Google Developers. The Google Maps Geocoding API — Google Maps Geocoding API — Google Developers; 2016 (accessed 18 Jan 2016). <https://developers.google.com/maps/documentation/geocoding/intro>.
15. Google Developers. The Google Maps Elevation API — Google Maps Elevation API — Google Developers; 2016 (accessed 18 Jan 2016). <https://developers.google.com/maps/documentation/elevation/intro?hl=en>.
16. IOBS. Supplemental Material — PAPERDATA; 2016 (accessed 18 Jan 2016). <https://github.com/doolingdavid/PAPERDATA.git>.
17. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association*. 1958;53(282):457–481. Cited By 34216. Available from: <http://www.scopus.com/inward/record.url?eid=2-s2.0-33845382806&partnerID=40&md5=1b3d05fab93fcd0e37f176c799b3cfff6>.
18. Ben Kuhn. Decision trees for survival analysis; 2016 (accessed 14 Jan 2016). <http://www.benkuhn.net/survival-trees>.
19. James Surowiecki. *The Wisdom of Crowds*. Doubleday; 2004.
20. John Cassidy. What killed Intrade?; 13 Mar 2013 (accessed 25 Jan 2016). <http://www.newyorker.com/news/john-cassidy/what-killed-intrade>.
21. Malcolm Gladwell. *Outliers*. Back Bay Books; 2011.

22. scikit-learn developers. 3.2.4.3.1. sklearn.ensemble.RandomForestClassifier; 2014 (accessed 25 Jan 2016). <http://scikit-learn.org/stable/modules/generated/sklearn.ensemble.RandomForestClassifier.html>.
23. Kaggle Inc . Random Forests — Kaggle; 2015 (accessed 25 Jan 2016). <https://www.kaggle.com/wiki/RandomForests>.
24. Michael Nielsen. Neural Networks and Deep Learning; Jan 2016 (accessed 25 Jan 2016). <http://neuralnetworksanddeeplearning.com/>.
25. F Chollet. Keras Documentation; 2015 (accessed 25 Jan 2016). <http://keras.io/>.
26. Armin Roncaher. Welcome — Flask (A Python Microframework; 2014 (accessed 29 Jan 2016). <http://flask.pocoo.org>.
27. Kai Porter, KOB Eyewitness News 4. Study links higher elevation with lower lung cancer risk; 26 Jan 2016 (accessed 27 Jan 2016). <http://www.kob.com/article/stories/s4029233.shtml#.VqlUafkrJhF>.
28. Statistical Software Information, University of Massachusetts Amherst. Software - Statistical Consulting Center - UMass Amherst; 2004 (accessed 29 Jan 2016). <https://www.umass.edu/statdata/statdata/stat-survival.html>.
29. National Cancer Institute, Division of Cancer Control and Population Sciences. SEER-Medicare Linked Database; 2015 (accessed 10 Feb 2016). <http://healthcaredelivery.cancer.gov/seermedicare/>.