Summary

The dataset for this project was collected from kaggle (https://www.kaggle.com/kevinarvai/clinvar-conflicting) and originates from ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). ClinVar is a public resource containing annotations about human genetic variants. These variants are classified by clinical laboratories on a categorical spectrum ranging from benign, likely benign, uncertain significance, likely pathogenic, and pathogenic. Variants that have conflicting classifications (from laboratory to laboratory) can cause confusion when clinicians or researchers try to interpret whether the variant has an impact on the disease of a given patient.

The objective is to predict whether a ClinVar variant will have conflicting classifications. This is presented here as a binary classification problem, where each record in the dataset is a genetic variant.

Conflicting classifications are when two of any of the following three categories are present for one variant, two submissions of one category are not considered conflicting.

- Likely Benign or Benign
- VUS
- Likely Pathogenic or Pathogenic

Conflicting classification has been assigned to the CLASS column. It is a binary representation of whether or not a variant has conflicting classifications, where **0** represents **consistent classifications** and **1** represents **conflicting classifications**.

In this project, we will employ four different classifier models to find the best candidate algorithm that accurately predicts whether a ClinVar variant will have conflicting classifications.

Exploratory Data Analysis

In [1]:
```
import pandas as pd
import numpy as np
import seaborn as sns
import matplotlib.pyplot as plt
from sklearn.preprocessing import LabelBinarizer, LabelEncoder, OrdinalEn
coder, MinMaxScaler
from sklearn.model_selection import StratifiedShuffleSplit, train_test_sp
lit, GridSearchCV
from sklearn.neighbors import KNeighborsClassifier
from sklearn.metrics import confusion_matrix, accuracy_score, classificat
```

```
ion_report, precision_score, f1_score, roc_auc_score
from sklearn.linear_model import LogisticRegression
from sklearn.tree import DecisionTreeClassifier
from sklearn.ensemble import RandomForestClassifier
from sklearn.metrics import precision_recall_fscore_support as score

# Mute the sklearn and IPython warnings
import warnings
warnings.filterwarnings('ignore', module='sklearn')
warnings.filterwarnings('ignore', module='IPython')
```

In [2]:
```
data = pd.read_csv('./clinvar_conflicting.csv', sep=',')
data.head()
```

Out[2]:

	CHROM	POS	REF	ALT	AF_ESP	AF_EXAC	AF_TGP	CLNDISDB
0	1	1168180	G	C	0.0771	0.10020	0.1066	MedGen:CN169374
1	1	1470752	G	A	0.0000	0.00000	0.0000	MedGen:C1843891,OMI
2	1	1737942	A	G	0.0000	0.00001	0.0000	Human_Phenotype_Ont
3	1	2160305	G	A	0.0000	0.00000	0.0000	MedGen:C1321551,OMI
4	1	2160305	G	T	0.0000	0.00000	0.0000	MedGen:C1321551,OMI

5 rows × 46 columns

In [3]:
```
data.shape
```

Out[3]:
```
(65188, 46)
```

We have a lot more consistent than conflicting classifications.

In [4]:
```
data.CLASS.value_counts()
```

Out[4]:
```
0    48754
1    16434
Name: CLASS, dtype: int64
```

In [5]:
```
pd.DataFrame([[i, len(data[i].unique())] for i in data.columns],
             columns=['Variable', 'Unique Values']).set_index('Variable')
```

Out[5]:

	Unique Values

Variable	
CHROM	38
POS	63115
REF	866
ALT	458
AF_ESP	2842
AF_EXAC	6667
AF_TGP	2087
CLNDISDB	9234
CLNDISDBINCL	94
CLNDN	9260
CLNDNINCL	102
CLNHGVS	65188
CLNSIGINCL	138
CLNVC	7
CLNVI	27655
MC	91
ORIGIN	31
SSR	3
CLASS	2
Allele	374
Consequence	48
IMPACT	4
SYMBOL	2329
Feature_type	3
Feature	2370
BIOTYPE	3

EXON	3265
INTRON	1930
cDNA_position	13971
CDS_position	13664
Protein_position	7340
Amino_acids	1263
Codons	2221
DISTANCE	97
STRAND	3
BAM_EDIT	3
SIFT	5
PolyPhen	5
MOTIF_NAME	3
MOTIF_POS	2
HIGH_INF_POS	2
MOTIF_SCORE_CHANGE	3
LoFtool	1196
CADD_PHRED	9325
CADD_RAW	63804
BLOSUM62	7

Dropping columns that have too many unique values and therefore they do not carry any information.

In [6]:
```
unique_col = pd.DataFrame([[i, len(data[i].unique())] for i in data.colum
ns],
                          columns=['Variable', 'Unique Values']).set_inde
x('Variable')

to_drop = list(unique_col[unique_col['Unique Values'] > 3000].index)
```

```
data.drop(to_drop, axis=1, inplace=True)
```

In [7]:
```
pd.DataFrame([[i, len(data[i].unique())] for i in data.columns],
             columns=['Variable', 'Unique Values']).set_index('Variable')
```

Out[7]:

	Unique Values
Variable	
CHROM	38
REF	866
ALT	458
AF_ESP	2842
AF_TGP	2087
CLNDISDBINCL	94
CLNDNINCL	102
CLNSIGINCL	138
CLNVC	7
MC	91
ORIGIN	31
SSR	3
CLASS	2
Allele	374
Consequence	48
IMPACT	4
SYMBOL	2329
Feature_type	3
Feature	2370
BIOTYPE	3
INTRON	1930
Amino_acids	1263

Codons	2221
DISTANCE	97
STRAND	3
BAM_EDIT	3
SIFT	5
PolyPhen	5
MOTIF_NAME	3
MOTIF_POS	2
HIGH_INF_POS	2
MOTIF_SCORE_CHANGE	3
LoFtool	1196
BLOSUM62	7

Featureset Exploration

CHROM: Chromosome the variant is located on

REF: Reference Allele

ALT: Alternaete Allele

AF_ESP: Allele frequencies from GO-ESP

AF_EXAC: Allele frequencies from ExAC

AF_TGP: Allele frequencies from the 1000 genomes project

CLNDISDB: Tag-value pairs of disease database name and identifier, e.g. OMIM:NNNNNN

CLNDISDBINCL: For included Variant: Tag-value pairs of disease database name and identifier, e.g. OMIM:NN

CLNDN: ClinVar's preferred disease name for the concept specified by disease identifiers in CLNDISDB

More information on many of the features can be found at these two links:

https://useast.ensembl.org/info/docs/tools/vep/vep_formats.html#output (https://useast.ensembl.org/info/docs/tools/vep/vep_formats.html#output)

https://useast.ensembl.org/info/genome/variation/prediction/predicted_data.html#consequences (https://useast.ensembl.org/info/genome/variation/prediction/predicted_data.html#consequences)

In [8]:
```
num_missing = data.isnull().sum()
percentage_missing = data.isnull().sum().apply(lambda x: x/data.shape[0]*
100)
```

In [9]:
```
missing_data = pd.DataFrame({'Number of Missing':  num_missing,
                             'Percentage of Missing': percentage_missing
})

missing_data['Percentage of Missing'].sort_values(ascending = False)
```

Out[9]:
```
MOTIF_SCORE_CHANGE    99.996932
HIGH_INF_POS          99.996932
MOTIF_POS             99.996932
MOTIF_NAME            99.996932
DISTANCE              99.834325
SSR                   99.800577
CLNDISDBINCL          99.743818
CLNSIGINCL            99.743818
CLNDNINCL             99.743818
INTRON                86.495981
PolyPhen              61.962324
SIFT                  61.900963
BLOSUM62              60.739707
BAM_EDIT              50.958765
Amino_acids           15.346383
Codons                15.346383
LoFtool                6.462846
MC                     1.297785
SYMBOL                 0.024544
BIOTYPE                0.024544
Feature_type           0.021476
Feature                0.021476
STRAND                 0.021476
Consequence            0.000000
Allele                 0.000000
CLASS                  0.000000
IMPACT                 0.000000
```

```
ORIGIN                0.000000
CLNVC                 0.000000
AF_TGP                0.000000
AF_ESP                0.000000
ALT                   0.000000
REF                   0.000000
CHROM                 0.000000
Name: Percentage of Missing, dtype: float64
```

Drop the columns where more than 20% of the data is missing.

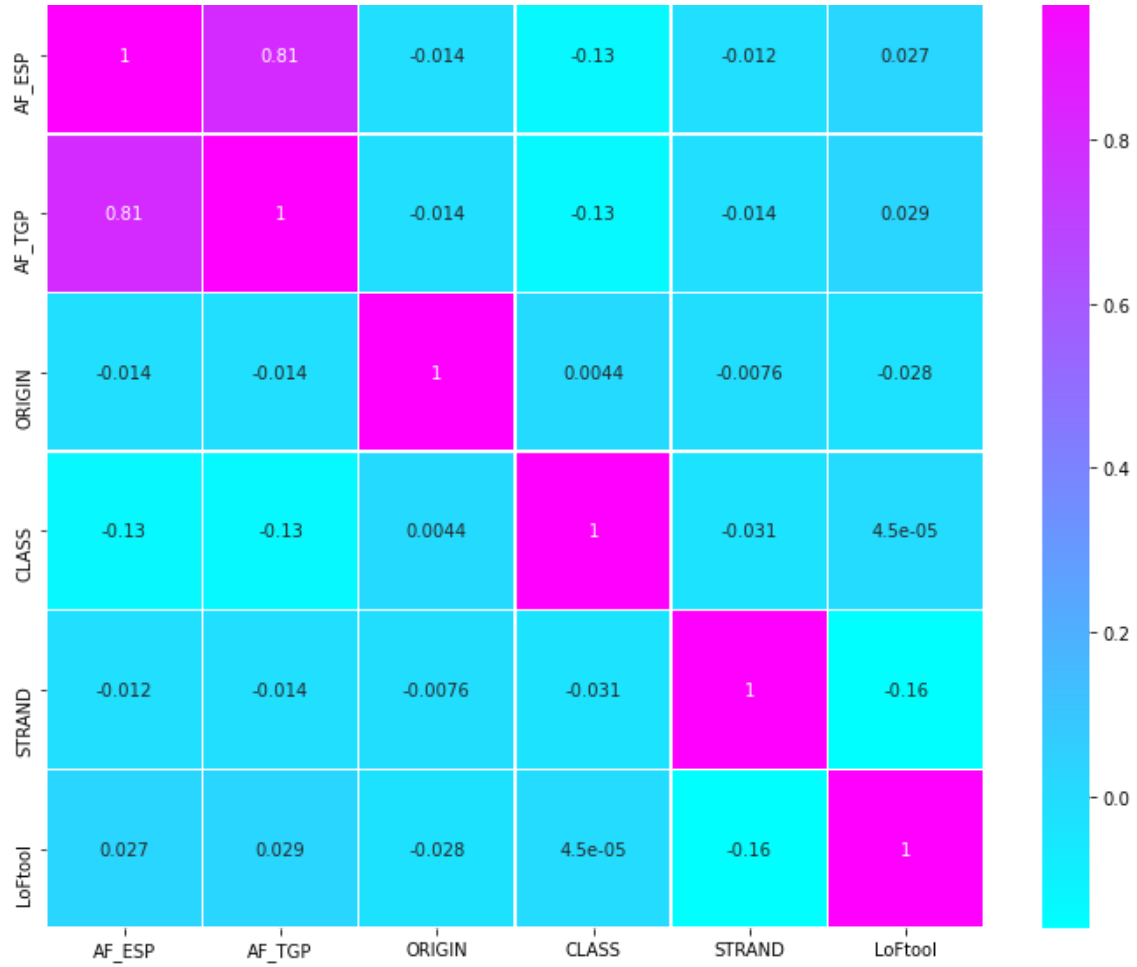
In [10]:
```
drop_list = list(missing_data[missing_data['Percentage of Missing'] >= 20
].index)
data.drop(drop_list,axis = 1, inplace=True)
```

In [11]:
```
data.isnull().sum()
```

Out[11]:
```
CHROM              0
REF                0
ALT                0
AF_ESP             0
AF_TGP             0
CLNVC              0
MC               846
ORIGIN             0
CLASS              0
Allele             0
Consequence        0
IMPACT             0
SYMBOL            16
Feature_type      14
Feature           14
BIOTYPE           16
Amino_acids    10004
Codons         10004
STRAND            14
LoFtool         4213
dtype: int64
```

In [12]:
```
plt.figure(figsize = (12, 10))
sns.heatmap(data.corr(), annot = True, linewidths=.5, cmap = plt.cm.cool)
```

Out[12]: <AxesSubplot:>



The correlation of **AF_ESP** with **AF_TGP** is above 0.8 hence dropping the **AF_TGP** column.

In [13]:
```
data.drop(['AF_TGP'],axis = 1, inplace=True)
```

In [14]:
```
# check the types
df = pd.DataFrame(data.isnull().sum().astype(int), columns=['Null'])
null_list = list(df[df['Null'] != 0].index)
data[null_list].dtypes
```

Out[14]:
```
MC              object
SYMBOL          object
Feature_type    object
Feature         object
BIOTYPE         object
Amino_acids     object
```

```
Codons           object
STRAND          float64
LoFtool         float64
dtype: object
```

In [15]:
```
data[null_list].sample(5)
```

Out[15]:

	MC	SYMBOL	Feature_type	Feature	BI
16552	SO:0001819|synonymous_variant	WNK1	Transcript	XM_005253733.1	pro
22550	SO:0001583|missense_variant	ESRRB	Transcript	XM_005267403.1	pro
46034	SO:0001819|synonymous_variant	JPH2	Transcript	NM_020433.4	pro
42307	SO:0001583|missense_variant	TTN	Transcript	NM_001267550.1	pro
60830	SO:0001583|missense_variant	PLEC	Transcript	XM_005250976.1	pro

Feature Transformation

- Replace nan in **MC**, **SYMBOL**, **Feature_type**, **Feature**, **BIOTYPE**, **Amino_acids**, **Codons**, **STRAND** with the most frequent value
- Replace nan in **LoFtool** with the mean

In [16]:
```
for x in ["MC", "SYMBOL", "Feature_type", "Feature",
          "BIOTYPE", "STRAND", "Amino_acids", "Codons" ]:
    data[x].fillna(data[x].mode()[0], inplace=True)

data['LoFtool'].fillna(data['LoFtool'].mean(), inplace=True)

data.isnull().sum()
```

Out[16]:
```
CHROM          0
REF            0
ALT            0
AF_ESP         0
CLNVC          0
MC             0
ORIGIN         0
CLASS          0
Allele         0
Consequence    0
IMPACT         0
```

```
SYMBOL          0
Feature_type    0
Feature         0
BIOTYPE         0
Amino_acids     0
Codons          0
STRAND          0
LoFtool         0
dtype: int64
```

Now identify which variables are binary, categorical and ordinal by looking at the number of unique values each variable takes, then create list variables for categorical, numeric, binary, and ordinal variables.

In [17]:
```
dg = pd.DataFrame([[str(i),data[i].dtypes == 'object'] for i in data.colu
mns],
                  columns=['Variable','Object Type']).set_index('Variabl
e')
object_columns_names = list(dg[dg['Object Type'] == True].index)
```

In [18]:
```
#display the number of unique values for columns type object
df = data[object_columns_names]
df_uniques = pd.DataFrame([[i, len(df[i].unique())] for i in df.columns],
                          columns=['Variable', 'Unique Values']).set_inde
x('Variable')
```

In [19]:
```
df_uniques
```

Out[19]:

	Unique Values
Variable	
CHROM	38
REF	866
ALT	458
CLNVC	7
MC	90
Allele	374
Consequence	48
IMPACT	4

SYMBOL	2328
Feature_type	2
Feature	2369
BIOTYPE	2
Amino_acids	1262
Codons	2220

In [20]:
```
binary_variables = list(df_uniques[df_uniques['Unique Values'] == 2].inde
x)
binary_variables
```

Out[20]:
```
['Feature_type', 'BIOTYPE']
```

In [21]:
```
categorical_variables = list(df_uniques[(df_uniques['Unique Values'] > 2
)].index)
categorical_variables
```

Out[21]:
```
['CHROM',
 'REF',
 'ALT',
 'CLNVC',
 'MC',
 'Allele',
 'Consequence',
 'IMPACT',
 'SYMBOL',
 'Feature',
 'Amino_acids',
 'Codons']
```

In [22]:
```
for col in categorical_variables:
    data[col] = data[col].apply(lambda x: str(x))

data[categorical_variables].dtypes
```

Out[22]:
```
CHROM          object
REF            object
ALT            object
CLNVC          object
MC             object
Allele         object
```

```
Allele          object
Consequence     object
IMPACT          object
SYMBOL          object
Feature         object
Amino_acids     object
Codons          object
dtype: object
```

In [23]:
```
numeric_variables = list(set(data.columns) - set(categorical_variables) -
set(binary_variables))
data[numeric_variables].dtypes
```

Out[23]:
```
CLASS        int64
LoFtool    float64
STRAND     float64
ORIGIN       int64
AF_ESP     float64
dtype: object
```

In [24]:
```
lb, le = LabelBinarizer(), LabelEncoder()

#encoding ordinary variables
for col in categorical_variables:
    data[col] = le.fit_transform(data[col])

# binary encoding binary variables
for col in binary_variables:
    data[col] = lb.fit_transform(data[col])
```

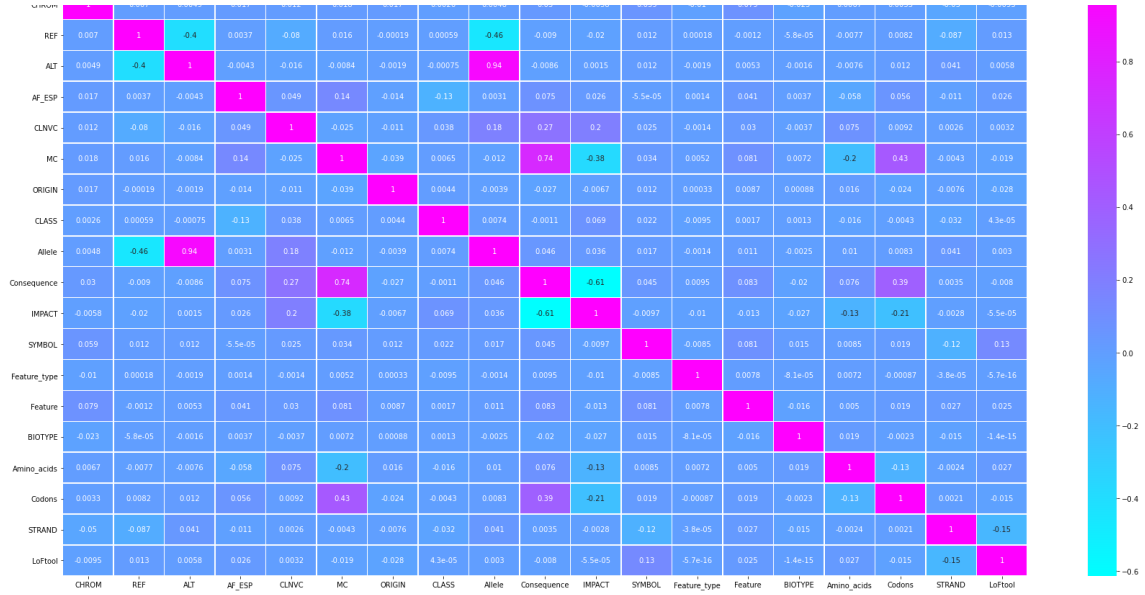
In [25]:
```
data.sample(3)
```

Out[25]:

	CHROM	REF	ALT	AF_ESP	CLNVC	MC	ORIGIN	CLASS	Allele	Consequer
29581	8	644	213	0.0	6	10	1	0	168	24
57695	19	644	106	0.0	6	81	1	0	88	31
21641	5	437	0	0.0	6	89	1	1	1	46

In [26]:
```
plt.figure(figsize = (30, 15))
sns.heatmap(data.corr(), annot = True, linewidths=.5, cmap = plt.cm.cool)
```

Out[26]:
```
<AxesSubplot:>
```



The correlation of **ALT** with **Allele** and **MC** with **Consequence** are both above 0.8 hence dropping the **ALT** and **MC** columns.

In [27]:
```
data.drop(["ALT", "MC"],axis = 1, inplace=True)
categorical_variables.remove('ALT')
categorical_variables.remove("MC")
```

Apply Feature Scaling

In [28]:
```
mm = MinMaxScaler()
for column in [categorical_variables + numeric_variables]:
    data[column] = mm.fit_transform(data[column])
```

In [29]:
```
# Save a copy of the processed data for later use
outputfile = 'clinvar_conflicting_processed.csv'
data.to_csv(outputfile, index=False)
```

Split the data

Split the data into train and test data sets using **StratifiedShuffleSplit** to maintain the same ratio of predictor classes.

In [30]:
```
data = pd.read_csv('./clinvar_conflicting_processed.csv', sep=',')
```

In [31]:
```
feature_cols = list(data.columns)
feature_cols.remove('CLASS')
```

In [32]:
```
# Get the split indexes
strat_shuf_split = StratifiedShuffleSplit(n_splits=1,
                                          test_size=0.3,
                                          random_state=42)

train_idx, test_idx = next(strat_shuf_split.split(data[feature_cols], dat
a.CLASS))

# Create the dataframes
X_train = data.loc[train_idx, feature_cols]
y_train = data.loc[train_idx, 'CLASS']

X_test  = data.loc[test_idx, feature_cols]
y_test  = data.loc[test_idx, 'CLASS']
len(X_test), len(X_train)
```

Out[32]:
```
(19557, 45631)
```

Train models

- Standard logistic regression, K-nearest neighbors algorithm, Decision Tree,mRandom Forest
- Plot the results using heatmaps
- Compare scores: precision, recall, accuracy, F1 score, auc

Logistic Regression

In [33]:
```
# create dataframe for metrics
metrics = pd.DataFrame()

# Standard logistic regression
lr = LogisticRegression(solver='liblinear').fit(X_train, y_train)
y_pred_lr = lr.predict(X_test)

precision_lr, recall_lr = (round(float(x),2) for x in list(score(y_test,
                                                                 y_pre
```

```
d_lr,
                                                                    avera
ge='weighted'))[:-2])
# adding lr stats to metrics DataFrame
lr_stats = pd.Series({'precision':precision_lr,
                      'recall':recall_lr,
                      'accuracy':round(accuracy_score(y_test, y_pred_lr),
2),
                      'f1score':round(f1_score(y_test, y_pred_lr), 2),
                      'auc': round(roc_auc_score(y_test, y_pred_lr),2)},
                     name='Logistic Regression')
# Report outcomes
pd.DataFrame(classification_report(y_test, y_pred_lr, output_dict=True)).
iloc[:3,:2]
```

Out[33]:

	0.0	1.0
precision	0.747773	0.130435
recall	0.998633	0.000609
f1-score	0.855186	0.001211

K-nearest Neighbors

In [34]:

```
# Estimate KNN model and report outcomes
knn = KNeighborsClassifier(n_neighbors=3, weights='distance')
knn = knn.fit(X_train, y_train)
y_pred_knn = knn.predict(X_test)

precision_knn, recall_knn = (round(float(x),2) for x in list(score(y_test
,
                                                                    y_p
red_knn,
                                                                    ave
rage='weighted'))[:-2])
# adding KNN stats to metrics DataFrame
knn_stats = pd.Series({'precision':precision_knn,
                      'recall':recall_knn,
                      'accuracy':round(accuracy_score(y_test, y_pred_knn
), 2),
                      'f1score':round(f1_score(y_test, y_pred_knn), 2),
                      'auc': round(roc_auc_score(y_test, y_pred_knn),2)},
name='KNN')
```

```
# Report outcomes
pd.DataFrame(classification_report(y_test, y_pred_knn, output_dict=True))
.iloc[:3,:2]
```

Out[34]:

	0.0	1.0
precision	0.773786	0.349403
recall	0.817324	0.291075
f1-score	0.794960	0.317583

Decision Tree

In [35]:
```
dt = DecisionTreeClassifier(random_state=42)
dt = dt.fit(X_train, y_train)
dt.tree_.node_count, dt.tree_.max_depth
```

Out[35]: (21179, 44)

In [36]:
```
y_train_pred = dt.predict(X_train)
y_pred_dt = dt.predict(X_test)

precision_dt, recall_dt = (round(float(x),2) for x in list(score(y_test,
                                                                 y_pred_dt
,
                                                                 average=
'weighted'))[:-2])
# adding dt stats to metrics DataFrame
dt_stats = pd.Series({'precision':precision_dt,
                      'recall':recall_dt,
                      'accuracy':round(accuracy_score(y_test, y_pred_dt),
2),
                      'f1score':round(f1_score(y_test, y_pred_dt), 2),
                      'auc': round(roc_auc_score(y_test, y_pred_dt),2)},
name='Decision Tree')
# Report outcomes
pd.DataFrame(classification_report(y_test, y_pred_dt, output_dict=True)).
iloc[:3,:2]
```

Out[36]:

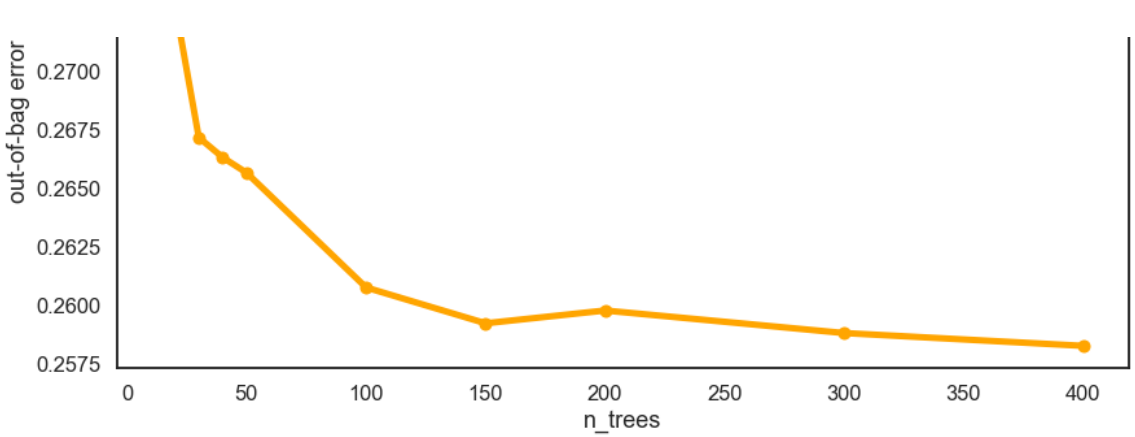
	0.0	1.0
precision	0.788235	0.381372

recall	0.803377	0.359635
f1-score	0.795734	0.370185

Random forest

In [37]:
```
# Initialize the random forest estimator
RF = RandomForestClassifier(oob_score=True,
                            random_state=42,
                            warm_start=True,
                            n_jobs=-1)

# initialise list for out of bag error
oob_list = list()

# Iterate through all of the possibilities for number of trees
for n_trees in [15, 20, 30, 40, 50, 100, 150, 200, 300, 400]:

    # Use this to set the number of trees
    RF.set_params(n_estimators=n_trees)

    # Fit the model
    RF.fit(X_train, y_train)

    # Get the out of bag error and store it
    oob_error = 1 - RF.oob_score_
    oob_list.append(pd.Series({'n_trees': n_trees, 'oob': oob_error}))

rf_oob_df = pd.concat(oob_list, axis=1).T.set_index('n_trees')
```

In [38]:
```
sns.set_context('talk')
sns.set_style('white')

ax = rf_oob_df.plot(legend=False, marker='o', color="orange", figsize=(14
, 7), linewidth=5)
ax.set(ylabel='out-of-bag error');
```



The error looks like it has stabilized around 100-150 trees.

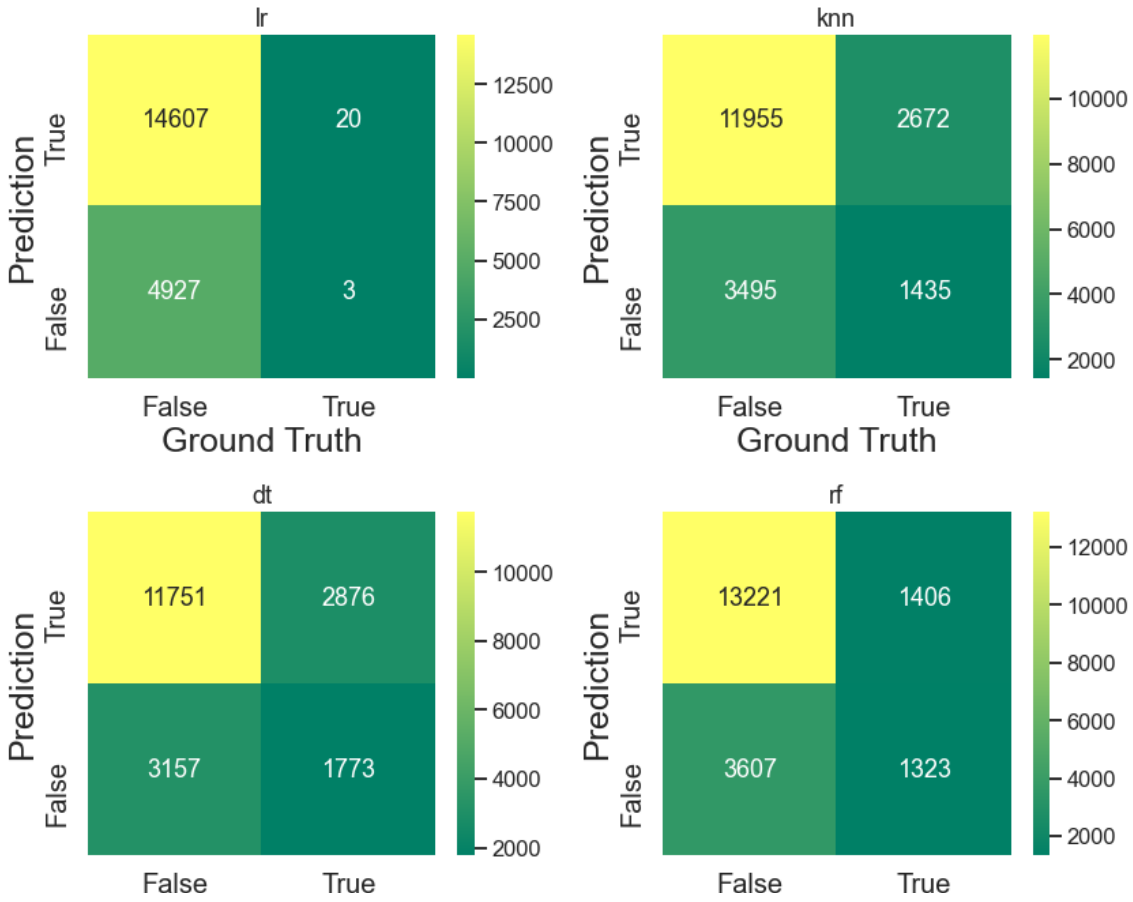
In [39]:
```
rf = RF.set_params(n_estimators=100)

y_pred_rf = rf.predict(X_test)
precision_rf, recall_rf = (round(float(x),2) for x in list(score(y_test,
                                                                 y_pre
d_rf,
                                                                 avera
ge='weighted'))[:-2])
rf_stats = pd.Series({'precision':precision_rf,
                      'recall':recall_rf,
                      'accuracy':round(accuracy_score(y_test, y_pred_rf),
2),
                      'f1score':round(f1_score(y_test, y_pred_rf), 2),
                      'auc': round(roc_auc_score(y_test, y_pred_rf),2)},
name='Random Forest')
# Report outcomes
pd.DataFrame(classification_report(y_test, y_pred_rf, output_dict=True)).
iloc[:3,:2]
```

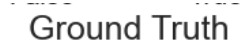
Out[39]:

	0.0	1.0
precision	0.785655	0.484793
recall	0.903876	0.268357
f1-score	0.840629	0.345476

In [40]:
```
fig, axList = plt.subplots(nrows=2, ncols=2)
axList = axList.flatten()
```

```
fig.set_size_inches(12, 10)


models = coeff_labels = ['lr', 'knn', 'dt', 'rf']
cm = [confusion_matrix(y_test, y_pred_lr),
      confusion_matrix(y_test, y_pred_knn),
      confusion_matrix(y_test, y_pred_dt),
      confusion_matrix(y_test, y_pred_rf)]
labels = ['False', 'True']

for ax,model, idx in zip(axList, models, range(0,4)):
    sns.heatmap(cm[idx], ax=ax, annot=True, fmt='d', cmap='summer');
    ax.set(title=model);
    ax.set_xticklabels(labels, fontsize=20);
    ax.set_yticklabels(labels[::-1], fontsize=20);
    ax.set_ylabel('Prediction', fontsize=25);
    ax.set_xlabel('Ground Truth', fontsize=25)

plt.tight_layout()
```





In [41]:
```
pd.DataFrame(classification_report(y_test, y_pred_lr, output_dict=True)).
iloc[:3,:2]
```

Out[41]:

	0.0	1.0
precision	0.747773	0.130435
recall	0.998633	0.000609
f1-score	0.855186	0.001211

In [42]:
```
pd.DataFrame(classification_report(y_test, y_pred_knn, output_dict=True))
.iloc[:3,:2]
```

Out[42]:

	0.0	1.0
precision	0.773786	0.349403
recall	0.817324	0.291075
f1-score	0.794960	0.317583

In [43]:
```
pd.DataFrame(classification_report(y_test, y_pred_dt, output_dict=True)).
iloc[:3,:2]
```

Out[43]:

	0.0	1.0
precision	0.788235	0.381372
recall	0.803377	0.359635
f1-score	0.795734	0.370185

In [44]:
```
pd.DataFrame(classification_report(y_test, y_pred_rf, output_dict=True)).
iloc[:3,:2]
```

Out[44]:

	0.0	1.0
precision	0.785655	0.484793
recall	0.903876	0.268357

f1-score	0.840629	0.345476

Results

The classsification report of each classifier shows that I am able to predict consistent classification, with an F1 score of 0.855186 for **Logistic Regression** model. Similar result can be achieved using any of the model above. I predicted conflicting classification with F2 score 0.370185 with **Decision Tree** algorithm