Predicting Melanoma Patient's Responses to Nivolumab Immunotherapy Using Machine Learning Models

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1. Abstract

Melanoma is a cancer that takes over melanocytes, cells that give skin pigment, and causes them to multiply continuously. This can lead to health problems because if melanoma starts spreading it can go into organs in your body and stop them from functioning properly. [5] One immunotherapy that helps boost the immune system against melanoma skin cancer is an IV-administered drug called Nivolumab. [4] Nivolumab is used to block the connection between PD1 and PDL1. PD1 is a protein on T cells and if connected to PDL1, a protein on cancerous cells, it allows the T cells to stop killing other cells including cancerous cells. [1,2] The number of genes that are expressed tells whether the patient is getting affected negatively or positively. Although not all patients respond well to Nivolumab, we can hypothesize that gene expressions tell whether a patient responds well or not to treatment. In a recent experiment obtained from a website called ncbi.nlm.nih.gov [11], it was found that the melanoma patients who responded well to Nivolumab had specific patterns of gene expression. The patient’s reactions included whether the disease was progressive, a partial response, a complete response, or a stable disease. Next, using the scikit-learn library and supervised learning algorithms such as nested logistic regression models, a machine-learning model was created to determine if the patient is likely to be benefited from using Nivolumab. The average accuracy of this model was 65%. The purpose of this research is to help doctors find out whether a patient with melanoma skin cancer will have a positive outcome if they are given Nivolumab. It would allow doctors to confidently notify their patient’s prognosis. For the patients that are not predicted to have a good response, doctors can decide to give an alternate therapy.
2. Key Words

PDL1, PD1, Nivolumab, Checkpoint Inhibitors, Melanoma, Gene Expressions
3. Background

Cancer is the second most deadly disease in the world after cardiovascular disease. Annually, about 10 million people die from it. [10]

How are cancer cells created?

To understand this, we must look closely at cell division. For a cell to divide, there are two main phases that it must go through, interphase and mitosis. Interphase contains three phases, the G1 Phase, S Phase, and G2 Phase. During the G1 Phase organelles in the cell, such as its mitochondria or lysosomes are copied. Next during the S Phase, DNA is synthesized. The last phase of interphase is the G2 Phase where organelles are organized and genetic material starts to condense. [13]
One way a cancer cell can be created is when the DNA in a normal cell incorrectly synthesizes during the S Phase. In particular, the DNA must undergo mutations that render it unable to regulate crucial cell functions, such as the ability to signal the cell to halt its division. These cells can grow enough to spread to other parts of the body, also known as metastasis. Cancer can affect every organ system and there are a wide variety of cancers. Since cancer can start in any cell in the body, there is no single specific drug that can cease it. In addition, every person has a variety of different cells so one drug that works for one individual may not be as effective on another individual.

What is melanoma skin cancer?
Melanoma cancer begins in a cell called melanocytes.
Melanocytes create a pigment called melanin that gives skin pigment. Melanin also protects the deeper layers of skin from the sun’s ultraviolet rays. Cells that have melanoma can range from colors of black, brown, and tan, to reddish, blue, or even white. Melanoma looks like a mole that is changing shape, color, or size (around the size of a pencil eraser when diagnosed). People who have lighter skin color have a greater risk of getting melanoma because they have the least amount of melanin in their skin to protect them from the sun’s ultraviolet rays. Melanoma has a higher potential to metastasize to other body parts such as the lungs or brain and quickly become out of control. Once this happens, it is very difficult to treat and the disease becomes fatal.

What are the treatments used to treat cancer?

Some ways that cancer is treated are through surgery, chemotherapy, radiation therapy, hormone therapy, or immunotherapy. Depending on the type and stage of your cancer, a certain therapy is chosen to be used. Surgery is when doctors cut out the portion where
tumor is growing. Chemotherapy is done by using chemical substances to kill any rapidly dividing cell. Radiation therapy uses targeted high-energy rays to kill cancer cells. Hormone therapy uses synthetic hormones to stop cancer cells from getting the hormones needed for them to grow. Immunotherapy is a treatment that strengthens the immune system to help it fight off and recognize cancer cells by blocking certain connections between proteins. All these treatments have side effects which depend on your body’s individual response. It is important to research immunotherapy because it is newer and has the potential to become a better cure for certain cancers with lesser side effects. [17]

[18]

What is the immune system and how does immunotherapy work?

The immune system is used to fight off foreign cells or viruses. One example is the common cold. Although the immune system is able to kill off unknown cells in the body,
cancer is able to proliferate undetected. Why? First, we must understand how the immune system works. Cells part of the immune system are created in specific organs. These organs are bone marrow, thymus, tonsils, spleen, and lymph nodes.

[19]

These organs are also sites where T cells or B cells are created. T cells are the cells that directly fight off foreign cells while leaving the normal cells unharmed. [10] They recognize a combination of MHC molecules (molecules that bind peptide fragments
derived from pathogens and antigenic fragments) and work by disabling glycoprotein IIb/IIa found on platelets and then are activated. [20], [21], [22] After activation, they multiply into several T cells to create an army ready to get rid of viruses. B cells are cells that keep track of the invaded viruses and send antibodies to inform T cells of places of infection. [10] Specifically, during an infection, a pathogen is first engulfed by a cell called a macrophage, forming a structure called a phagosome. The phagosome then fuses with lysosomes containing digestive enzymes, leading to the breakdown of the pathogen, and presenting its fragments on the cell's surface. These antigen fragments are recognized by B cells, which, upon activation, produce antibodies to target the invading pathogens and alert T cells to coordinate a more specific immune response. [22]

Bone marrow cultivates B cells, the thymus matures T cells, tonsils contain T and B cells and are usually used to protect any virus from entering through the mouth, similarly, the spleen and lymph nodes also contain T and B cells. Additionally, T cells and B cells communicate through receptors and ligands. Receptors and ligands work like a lock and a key. On every immune cell, there is one lock (receptor) for one key (ligand).
Once a ligand interacts with a receptor it can either be immunosuppressive- stopping the cell from responding or stimulatory- telling cells to attack viruses. Normal cells are immunosuppressive so that T cells don’t attack themselves or healthy cells. Invader cells are stimulatory which turns on T cells and gets attacked. Cancer cells are just mutations of normal cells with incorrect DNA. Because of this, they have the same immunosuppressive genes that a normal cell has. This way cancer cells are able to hide from the immune system. The specific connection that cancer cells use to hide from T cells is a ligand called PD-L1 that connects to receptors called PD1 on T cells. Immunotherapy, a treatment for cancer, uses different drugs to block the connections between receptors (PD1) on T cells and ligands (PD-L1) on cancer cells to make cancer stimulatory. Whenever a receptor connects to a ligand a gene expressions occur which can be used to tell whether the immunotherapy drug is having a negative or positive response on a patient. [10] Some examples of immunotherapy drugs are Ipilimumab, Pembrolizumab, Nivolumab, and Atezolizumab. [24] Some examples of checkpoint inhibitors (molecules in the immunotherapy drug) are anti-CTLA-4, anti-PD-1, or anti-PD-L1.
Immunotherapy works on only around 15 to 20 percent of cancer patients. This form of treatment is still new and has a lot of potential that has not been discovered. This is why scientists are determined to find improvements in hopes of a better future. [10]
4. Intro

What if a doctor could know more about an immunotherapy drug's effectiveness before trying it on a patient?

This study was done using a data set that contained sixty patients who had melanoma cancer and were using an immunotherapy drug called Nivolumab. Their gene expressions were also listed in the data. Gene expressions can be used to find out whether a patient is responding well or not to a treatment. This study finds the most and least expressed genes. Using these genes it will be possible for doctors to figure out whether Nivolumab will cure a patient with melanoma cancer or not. The process of finding the most expressed genes, started by cleaning the data and extracting the genes using computational methods such as linear regression to create models. Then the results were analyzed by using the linear regression models to find their accuracy. This study shows genes ATP6V1E1P2, CST3, ED3, F2L, PCMT1, TAF1, WT2, NELFE, TBL3, Fras1, Cdc37, Fgl2, Ifnar2, Igk-V10A, mea, Ngf, Rsp4, and Shh are the most expressed genes on a patient after using Nivolumab immunotherapy.

In a previous study called *Transcriptomic datasets of cancer patients treated with immune-checkpoint inhibitors: a systematic review*, [26] the several ways that melanoma cancer could be treated were discussed. Some common examples include anti-CTLA-4, anti-PD-1, or anti-PD-L1. Although, not all the treatments for melanoma cancer are approved by the FDA. The effectiveness of each treatment can be maximized by collecting relevant biomarkers (gene expressions). The objective or end goal of the previous research and my research is to find accurate biomarkers that will eventually tell whether a patient with melanoma skin cancer can survive given a specific
drug. Several similar researches show that other than Nivolumab there are several other types of immunotherapy checkpoint inhibitors. One study called *The role of neoantigens in response to immune checkpoint blockade* talks about neoantigens which are mutations encoded onto immunologically active proteins that can cause the immune system to recognize foreign cells such as cancerous cells. [7] Another article called *Genomic and Epigenomic Alterations in Cancer* discusses the genomic and epigenomic alterations in cancer focusing on genome editing or providing the ability to understand details of the process of cancer initiation, progressing, and signaling as well as opening up avenues for therapeutic targeting. [8] One last research paper called *A method for predicting target drug efficiency in cancer based on the analysis of signaling pathway activation* talks about the efficacy scores for five drugs named Sorafenib, Bevacizumab, Cetuximab, Sorafenib, Imatinib, and Sunitinib for several different types of cancer using clinical trial data for each respective cancer type and drug. In addition, each treatment correlated significantly with the percent of tumors showing high drug scores. [9] So far each previous study has done similar research but not on Nivolumab with experiments on the same changes and features. All of these research papers add information on how each immunotherapy checkpoint blocker helps or doesn’t help a patient.

Although this research shows that biomarkers can be predicted with 60% accuracy, it is still possible to find a dataset with more patents, and more genes, or include computational methods that were not used during the research such as conorm.tmm during normalization, to get better accuracy (hopefully more than 0.7) and get more accurate gene expressions in general. In this research paper, the specific methods used
for the research, results, discussion, and conclusion are included. This will also be followed by the acknowledgment, appendix, and reference.
5. Method

To find the most expressed genes, the experiment included developing a code using Google Colab, and common python modules such as NumPy, Pandas, Seaborn, Sklearn, Conorm, and Pickle. A Machine Learning model was developed using LogisticRegression and LogisticRegressionCV. The dataset included the gene expressions of each patient collected before and after the treatment (Nivolumab). The additional dataset had patients' responses to Nivolumab. For instance, whether their disease was progressive, a partial response, a complete response, or a stable disease. It also included their time-to-death. The experiment was done using the patients' responses because it allowed for more accurate results. The time-to-death information would have been collected during the survey and had a high chance of alteration as time progressed.

The dataset was scaled appropriately according to the regression model's requirement. For example in the response column, “Progressive Disease” was set to one, and “Partial Response”, “Complete Response”, and “Stable Response” were all set to zero. The patients who were already on treatments such as chemotherapy or radiation were not considered for this research. After cleaning the dataset it was required to normalize some of the values to achieve accuracy. Conorm (count normalization) techniques were used to normalize the dataset. These are simple normalization methods that are frequently used in the analysis of RNA expression data. Although there were many options, conorm.mrn (Median of Ratios Normalization) allowed the best results in terms of accuracy. A few patients were excluded while developing the regression model due to
inconsistent data, for example, some patients’ data had missing gene expressions or responses.

The performance of the regression model was evaluated by the use of the ‘StratifiedKFold’ class from the scikit-learn library. It divides the dataset into multiple training and validation sets removing the sample selection bias. This was an essential step because splitting the data several times allowed each training and testing set with approximately the same amount of the sample types that were present in the entire dataset.

For each train model, a Logistic regression model was created and a feature selection model was created. Logistic regression had the following parameters, C’s = 0.1, 0.25, 0.01, 0.001, l1-ratios = 0.6, 0.7, 0.85, 0.9, 0.95, penalty = elasticnet, scoring = roc_auc, cv=3, class_weight=balanced, max_iter=1e3, tol=1e-3, solver=saga, n_jobs=-1. The AUC curve showed an average accuracy of 0.65%.
6. Results

This analysis performed in this research paper identified several genes which were significantly expressed. It included following genes:

ATP6V1E1P2, CST3, ED3, F2L, PCMT1, TAF1, WT2, NELFE, TBL3, Fras1, Cdc37, Fgl2, Ifnar2, Igk-V10A, mea, Ngf, Rsp4, and Shh.

Detailed information on each of these genes can be found in the Appendix.
These results provide valuable insights for healthcare professionals in determining a patient's response to Nivolumab immunotherapy.
7. Discussion

The dataset used in this research consisted of 60 samples. The accuracy of the regression model developed with this small dataset was acceptable as the model fits the data well and has decent predictive power. It also has low sensitivity to outliers and it generalizes well to new data. Albeit, large samples would create more accurate results and a robust model which would improve prediction accuracy. Further improvement can be achieved by using a large dataset of patients and with different computational methods, for example, the use of Poisson regression and Negative Binomial regression models and features such as occurrences of the disease. It is possible that the accuracy of the model could be further evaluated using different cross-validation techniques such as leave-one-out and nested cross-validation techniques.
8. Summary and Conclusion

The objective of this research paper is to determine the gene expression patterns in response to Nivolumab immunotherapy and find out whether they exhibit a positive or negative response. The analysis utilized Logistic Regression models and libraries from SciKit-Learn to determine the most expressed genes. The genes identified in this research paper are ATP6V1E1P2, CST3, ED3, F2L, PCMT1, TAF1, WT2, NELFE, TBL3, Fras1, Cdc37, Fgl2, Ifnar2, Igk-V10A, mea, Ngf, Rsp4, and Shh.

In this analysis, the relationship between the True Positive Rate and False Positive rate was determined using AUC, or the Area Under the Receiver Operating Characteristic (ROC). The model is distinguishing between positive and negative responses with a 60% accuracy.

This research provides a foundation for further studies and may serve as a valuable resource for scientists and physicians in determining the efficacy of Nivolumab immunotherapy for later-stage cancer patients.
I would like to thank Hugh Ye for being a dedicated mentor throughout this research project. His guidance and support were pivotal in initiating and carrying out the study. He also provided assistance in resolving any coding issues and addressed all my inquiries. Also, I would like to thank my dad, Rohit Vijapure for helping me with the basics of Python and Machine Learning.
10. Appendix A

This data set is from - (https://ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=gse91061)

Genes / Descriptions -


Official Symbol
ATP6V1E1P2 provided by HGNC

Official Full Name
ATPase, H+ transporting, lysosomal 31kDa, V1 subunit E1 pseudogene 2 provided by HGNC

Primary source
HGNC:HGNC:860

Gene type
pseudo

Organism
Homo sapiens

Lineage
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

Also known as
ATP6EP2; ATP6V1EP2


Official Symbol
CST3 provided by HGNC

Official Full Name
cystatin C provided by HGNC

Primary source
HGNC:HGNC:2475

See related
Ensembl:ENSG00000101439 MIM:604312; AllianceGenome:HGNC:2475

Gene type
protein coding

RefSeq status
Also known as
ARMD11; HEL-S-2


Gene symbol
ED3

Gene description
ectodermal dysplasia 3, anhidrotic

Primary source
HGNC:HGNC:2895

See related
Ensembl:ENSG00000135960 MIM:604095; AllianceGenome:HGNC:2895

Gene type
protein coding

RefSeq status
REVIEWED

Organism
Homo sapiens

Lineage
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

Also known as
DL; ED3; ED5; ED1R; EDA3; HRM1; EDA1R; ECTD10A; ECTD10B; EDA-A1R


Official Symbol
F2L provided by HGNC

Official Full Name
coaagulation factor II (thrombin)-like provided by HGNC
Primary source
HGNC:HGNC:3536

Gene type
protein coding

RefSeq status
WITHDRAWN

Organism
Homo sapiens

Lineage
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo


Official Symbol
PCMT1 provided by HGNC

Official Full Name
protein-L-isoaspartate (D-aspartate) O-methyltransferase provided by HGNC

Primary source
HGNC:HGNC:8728

See related
Ensembl:ENSG00000120265 MIM:176851; AllianceGenome:HGNC:8728

Gene type
protein coding

RefSeq status
REVIEWED

Organism
Homo sapiens

Lineage
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

Also known as
PIMT


Official Symbol
TAF1 provided by HGNC

Official Full Name
TATA-box binding protein associated factor 1 provided by HGNC

Primary source
HGNC:HGNC:11535

See related
Ensembl:ENSG00000147133 MIM:313650; AllianceGenome:HGNC:11535

Gene type
protein coding

RefSeq status
REVIEWED

Organism
Homo sapiens

Lineage
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria;
Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

Also known as
OF; XDP; BA2R; CCG1; CCGS; DYT3; KAT4; P250; NSCL2; TAF2A; MRXS33; N-TAF1; TAFII250;
DYT3/TAF1; TAFII-250; TAF(II)250


Gene symbol
WT2

Gene description
Wilms tumor 2

Primary source
MIM:194071

Gene type
unknown

Organism
Homo sapiens

Lineage
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria;
Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

Also known as
ADCR; MTACR1

Official Symbol
NELFE provided by HGNC

Official Full Name
negative elongation factor complex member E provided by HGNC

Primary source
HGNC:HGNC:13974

See related
Ensembl:ENSG00000204356 MIM:154040; AllianceGenome:HGNC:13974

Gene type
protein coding

RefSeq status
REVIEWED

Organism
Homo sapiens

Lineage
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

Also known as
RD; RDP; RDBP; D6S45; NELF-E


Official Symbol
TBL3 provided by HGNC

Official Full Name
transducin beta like 3 provided by HGNC

Primary source
HGNC:HGNC:11587

See related
Ensembl:ENSG00000183751 MIM:605915; AllianceGenome:HGNC:11587

Gene type
protein coding

RefSeq status
REVIEWED
Organism
Homo sapiens

Lineage
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

Also known as
SAZD; UTP13


Official Symbol
Fras1 provided by MGI

Official Full Name
Fraser syndrome 1 provided by MGI

Primary source
MGI:MGI:2385368

Gene type
protein coding

Organism
Mus musculus

Lineage
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Myomorpha; Muroidea; Muridae; Murinae; Mus; Mus

Also known as
bl; E130113P14Rik


Official Symbol
Cdc37 provided by MGI

Official Full Name
cell division cycle 37 provided by MGI

Primary source
MGI:MGI:109531

See related
Ensembl:ENSMUSG00000019471 AllianceGenome:MGI:109531

Gene type
protein coding

**RefSeq status**
VALIDATED

**Organism**
Mus musculus

**Lineage**
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Myomorpha; Muroidea; Muridae; Murinae; Mus; Mus

**Also known as**
p50; p50Cdc37


**Official Symbol**
Fgl2 provided by MGI

**Official Full Name**
fibrinogen-like protein 2 provided by MGI

**Primary source**
MGI:MGI:103266

**See related**
Ensembl:ENSMUSG00000039899, AllianceGenome:MGI:103266

**Gene type**
protein coding

**RefSeq status**
VALIDATED

**Organism**
Mus musculus

**Lineage**
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Myomorpha; Muroidea; Muridae; Murinae; Mus; Mus

**Also known as**
musfiblp


**Official Symbol**
Ifnar2 provided by MGI
Official Full Name
interferon (alpha and beta) receptor 2 provided by MGI

Primary source
MGI:MGI:1098243

See related
Ensembl:ENSMUSG00000022971 AllianceGenome:MGI:1098243

Gene type
protein coding

RefSeq status
VALIDATED

Organism
Mus musculus

Lineage
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Myomorpha; Muroidea; Muridae; Murinae; Mus; Mus

Also known as
Ifnar-2


Official Symbol
Igk-V10A provided by MGI

Official Full Name
immunoglobulin kappa chain variable 10 (V10)A provided by MGI

Primary source
MGI:MGI:1298365

Gene type
protein coding

Organism
Mus musculus

Lineage
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Myomorpha; Muroidea; Muridae; Murinae; Mus; Mus


Official Symbol
mea provided by MGI

Official Full Name
meander tail provided by MGI

Primary source
MGI:MGI:96956

See related
AllianceGenome:MGI:96956

Gene type
unknown

Organism
Mus musculus

Lineage
Eukarya; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Myomorpha; Muroidea; Muridae; Murinae; Mus; Mus


Official Symbol
Ngf provided by MGI

Official Full Name
nerve growth factor provided by MGI

Primary source
MGI:MGI:97321

See related
Ensembl:ENSMUSG00000027859 AllianceGenome:MGI:97321

Gene type
protein coding

RefSeq status
VALIDATED

Organism
Mus musculus

Lineage
Eukarya; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Myomorpha; Muroidea; Muridae; Murinae; Mus; Mus

Also known as
Ngfb; beta-NGF

**Official Symbol**
Rsp4 provided by [MGI](https://mgibase.mcgill.ca/)

**Official Full Name**
repeat sequence probe 4 provided by [MGI](https://mgibase.mcgill.ca/)

**Primary source**
[MGI:MGI:98195](https://mgibase.mcgill.ca/)

**Gene type**
protein coding

**Organism**
*Mus musculus*

**Lineage**
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Myomorpha; Muroidea; Muridae; Murinae; Mus; Mus

Also known as
Rsp-4


**Official Symbol**
Shh provided by [MGI](https://mgibase.mcgill.ca/)

**Official Full Name**
sonic hedgehog provided by [MGI](https://mgibase.mcgill.ca/)

**Primary source**
[MGI:MGI:98297](https://mgibase.mcgill.ca/)

**See related**
Ensembl:ENSMUSG00000002633 AllianceGenome:MGI:98297

**Gene type**
protein coding

**RefSeq status**
VALIDATED

**Organism**
*Mus musculus*

**Lineage**
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Myomorpha; Muroidea; Muridae; Murinae; Mus; Mus

Also known as
Hx; Dsh; Hhg1; Hxl3; ShhNC; M100081; 9530036O11Rik
11. Appendix B

Code can be downloaded from the link below:

https://github.com/aana192018/PythonProjects/blob/16bfd831b15187502c5e5228f5c10aa24b84cbee/CancerResearch/Predicting_Melanoma_Patients_Responses_To_Nivolumab_v1.ipynb
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