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Complex heatmaps in Statistical analysis of Biomarkers and cancer genomics

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ABSTRACT

The National Cancer Institute (NCI) found that cancer patients in the United States bear a huge amount of cancer care costs. In 2019 alone, over $21 billion was spent for patients' cancer care and the costs of cancer treatment will continue to rise in the future as well. Billions of dollars are being spent on clinical trials every year for treating cancer with an average success rate of merely 10%. However, biomarkers offer huge potential to address this challenge of failure rates and greatly increase the likelihood of approval fivefold (Wong et al., 2021). The development of oncology trials with increased efficacy and safety is becoming a promising aspect of the emergence of genomic biomarkers. It is changing the conventional clinical trials landscape in the modern era of cancer genomics. This paradigm shift from conventional treatments to targeted therapeutic approaches has significant implications for all stakeholders within the health care industry. With evolving Biomarkers, statistical analyses of cancer genomics data have been increasingly complex as the data are not reported in a consistent manner across clinical trials. Various heat maps including heat-panels and clustering heatmaps generated by SAS offer an ultimate approach for better understanding the data visualization and patterns analyzing complex and high dimensional biomarkers trial data in the drug development industry. This paper will explain the power of complex heat maps programmed in SAS so users can easily understand the real patterns and associations within multi variate analysis. The examples provided can help a great deal in developing every step of simple or complex heat maps for statistical analyses of biomarkers/genomic alterations.

INTRODUCTION

The United States is witnessing increased cases of lives lost caused by the world's leading group of injury and disease: Cancer. Weir et al. has reported such an increase by approximately 50%. It is well known that these alarming incidence levels will have immense implications on public health safety. Although cancer prevention and treatment strategies have become more efficient, the burden on patients isn't declining. A recent study provided by The National Cancer Institute (NCI) found that cancer patients in the United States bear a huge amount of cancer care costs. In 2019 alone, over $21 billion was unnecessarily spent towards patients' cancer care. Unfortunately, the costs of cancer treatment will continue to rise in the future.

A recent IQVIA study observed that "Oncology trial starts reached historically high levels in 2021, up 56% from 2016 and mostly focused on rare cancer indications." It estimated that Global oncology spending is expected to exceed $300 billion by 2026 (IQVIA, 2022). Despite spending huge amounts on oncology, the success rate in oncology clinical trials is very low as according to Wong et al. (2019), the overall probability of success in oncology clinical trials was only around 3.4% as shown below in the table.

Error! Reference source not found.. **Probability of Success by Clinical Trial Phase and Therapeutic Area**

	PA TO P2	P2 TO P3	P3 TO APPROVAL	OVERALL
ONCOLOGY	57.6	32.7	35.5	3.4
METABOLIC/ENDOCRINOLOGY	76.2	59.7	51.6	19.6
CARDIOVASCULAR	73.3	65.7	62.2	25.5
CENTRAL NERVOUS SYSTEM	73.2	51.9	51.1	15.0
AUTOIMMUNE/INFLAMMATION	69.8	45.7	63.7	15.1
GENITOURINARY	68.7	57.1	66.5	21.6
INFECTIOUS DISEASE	70.1	58.3	75.3	25.2
OPTHALMOLOGY	87.1	60.7	74.9	32.6
VACCINES(INFECTIOUS DISEASE)	76.8	58.2	85.4	33.4
OVERALL	66.4	48.6	59.0	13.8
OVERALL (EXCLUDING ONCOLOGY)	73.0	55.7	63.6	20.9

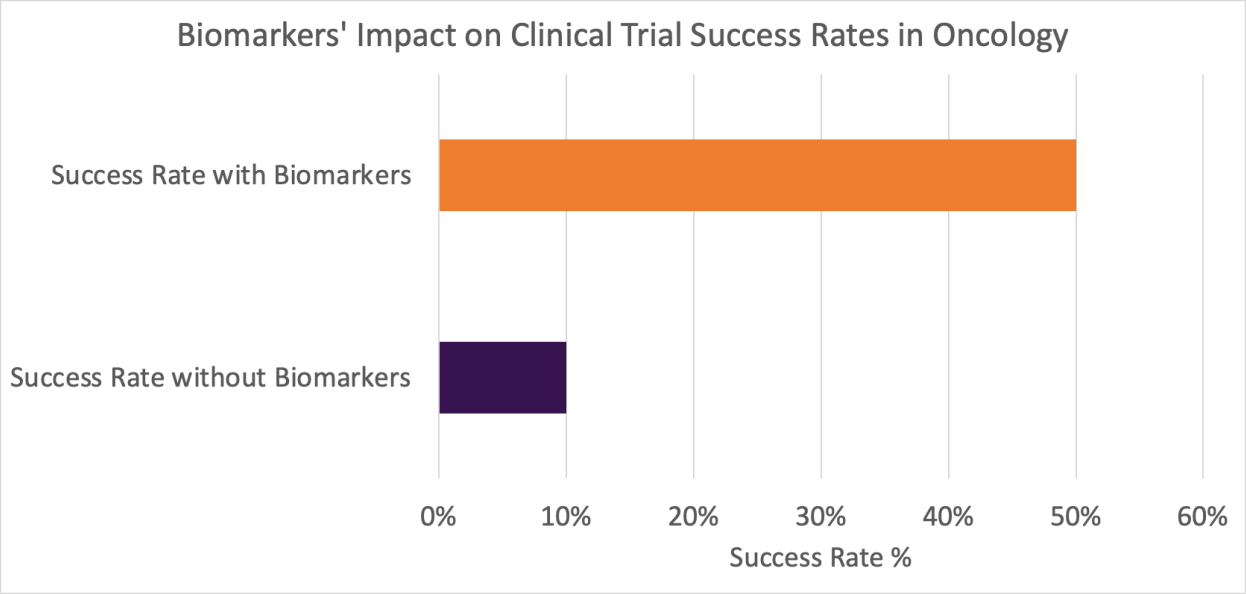
(Source: Chi Heem Wong, Kien Wei Siah, Andrew W Lo, 2019)

To address this challenge, the pharma and clinical industry is exploring new ways to address these failures. In this context, biomarkers and cancer genomics are emerging with great potential to improve the cancer trial success rates.

BIOMARKERS AND GENOMICS

The term “Biomarker” was coined by Depledge in 1994 to mean any medical sign in the form of a behavioral change, which can be measured to indicate a potential disease. The use of biomarkers in diagnosis has dominated the clinical field for many decades as they are useful in predicting and/or monitoring disease. Recently more novel cancer medicines became available and many of them employ precision biomarkers to transform the way patients are treated. The great deal of help they provide in every step of a patient’s care can be the key to future success. Parker et. al., (2021), concluded that biomarkers can increase clinical trial success rates in three different indications in oncology. Use of biomarkers can speed up and improve cancer drug development. The potential uses of biomarkers include estimating risks of the disease, screening for “hard to detect” primary cancers, and

distinguishing benign from malignant findings (or one type of malignancy from another). Although billions of dollars are annually being spent on clinical trials treating cancer, there is an average success rate of merely 10%! However, the medical field is not ready to ignore biomarkers just yet as they offer a chance to address these failure rates and greatly increase the likelihood of approval by fivefold (Discovery, 2021). The emergence of genomic biomarkers has prompted the development of trials, significantly changing the clinical landscape in modern cancer genomics.



(Source: Discovery 2021, https://www.dls.com/blog/biomarker-strategy)

HEAT MAPS

A heat map is a visual illustration of data that renders data values into a comprehensive, color-coded matrix. Readers can quickly gain a profound insight into the intricate relationships between data displayed through the summary heat maps create. Recently gaining traction, these heat maps are being used across various industries to visualize complex data, but can they equally enhance our understanding of biomarkers and cancer genomics? Could we possibly use heat maps to discover new patterns within gene expression, gene mutations, and gene alterations?

Various heat maps including heat-panels and clustering heat maps can now be generated by SAS to offer the ultimate approach to analyzing complex and high dimensional trial data of biomarkers in the drug development industry. This paper aims to explain the power of Complex Heat maps programmed in SAS to interpret real associations in multivariate analysis with many examples described here also help a great deal in developing every step of simple or complex heatmaps for statistical analyses of biomarkers/genomic alterations.

Developing heat maps in SAS are very useful and the use of SAS for creating heat maps in clinical SAS is very common but limited. This paper will attempt to address this issue and offer some methods to develop heat maps for analyzing the complex data in biomarkers and cancer genomics. SAS can produce heat maps with PROC SGPLOT and PROC SGPANEL. We can also produce several types of graphs on the same page with Graph Template Language, (GTL), and PROC SGRENDER. GTL and PROC SGRENDER provide the ability to overlay several different types of graphs on a single page. In the subsequent section 9 different types of heatmaps used in different biomarkers/genomics scenarios will be explained along with the subsequent codes used.

Table 1. Estimate New Cases for Selected Cancers by State, 2022

STATE	ALL	BREAST	UTERINEC X	COLREC	UTERCOR	LEUKEMI A	LUNGBRO N	SKIN	NHLYMPH OMA	PROSTATE	BLADDER
Alabama	30210	4280	240	2510	800	780	4280	1480	1000	4650	1140
Alaska	3250	530	0	320	100	90	380	100	120	460	160
Arizona	39970	6110	290	3150	1320	1090	4610	3110	1680	4940	1900
Arkansas	18610	2440	160	1530	570	520	2820	900	690	2510	710
California	189220	31720	1640	15970	7110	5630	17450	10260	8500	26890	7620
Colorado	28480	4730	190	2140	940	870	2550	1850	1140	4030	1220
Connecticut	22810	3550	120	1550	830	680	2760	1050	950	3310	1110
Delaware	7080	1010	0	500	250	230	910	470	280	940	310
Dist. of Columbia	3440	620	0	250	160	90	370	70	120	580	110
Florida	152600	20920	1230	11490	4860	6630	19560	9650	7980	20680	6890
Georgia	58970	9170	490	4970	1730	1860	7700	3640	2140	9150	2100
Hawaii	7730	1430	60	700	370	210	890	530	330	940	300
Idaho	10440	1490	70	750	320	330	1100	940	440	1480	500
Illinois	75350	11340	530	6260	2730	2190	9440	3860	3060	10520	3110
Indiana	39460	5600	290	3290	1340	1160	5920	2250	1520	5020	1720
Iowa	19960	2770	110	1570	690	750	2530	1250	880	2690	870
Kansas	16580	2410	100	1510	540	530	2190	920	680	2550	680
Kentucky	30370	3950	200	2600	930	850	4990	1680	1110	3840	1280
Louisiana	28680	3970	230	2440	730	800	3800	1010	1070	4170	1020
Maine	10060	1420	0	700	370	300	1640	520	420	1180	580
Maryland	34960	5640	240	2540	1400	970	4150	1670	1350	5380	1310
Massachusetts	42190	6710	210	2940	1530	1120	5600	1900	1780	5670	2030
Michigan	62500	8900	370	4680	2270	1850	8720	3180	2670	9240	2880
Minnesota	35130	4950	160	2420	1190	1390	3980	1860	1550	4290	1530
Mississippi	18250	2510	150	1680	490	450	2810	730	580	2970	600
Missouri	37480	5560	250	2970	1290	1160	5690	1690	1480	4830	1550
Montana	7030	1000	0	510	200	240	820	510	300	1100	340
Nebraska	11280	1600	70	960	360	380	1330	630	460	1680	480
Nevada	16390	2570	160	1430	510	510	2030	770	700	2230	800
New Hampshire	9430	1360	0	670	370	260	1270	610	410	1280	550
New Jersey	55730	8410	420	4260	2280	1730	5980	2300	2420	8580	2560
New Mexico	11030	1700	90	890	410	350	940	670	450	1430	400

New York	118830	17800	870	8950	4730	4010	14050	3960	5240	17960	5450
North Carolina	65320	10220	440	4760	2130	2120	8760	3760	2450	9550	2670
North Dakota	4300	590	0	340	120	170	510	230	180	600	200
Ohio	73700	10610	480	5870	2760	1910	10430	4110	2870	9530	3260
Oklahoma	23700	3280	210	1900	660	710	3390	1180	870	2900	870
Oregon	25130	4070	160	1850	860	680	2990	1640	1090	3250	1200
Pennsylvania	85110	12220	500	6610	3270	2600	11170	3540	3740	11740	4130
Rhode Island	7030	1020	0	490	260	240	980	320	300	1030	360
South Carolina	33440	5170	240	2570	1080	1030	4560	1970	1260	5110	1310
South Dakota	5370	750	0	430	160	180	660	320	220	810	230
Tennessee	42200	6040	330	3420	1280	1230	6200	1940	1630	5800	1690
Texas	139320	21040	1500	11780	4140	4750	14790	5020	5590	17850	4470
Utah	13190	1960	80	900	480	420	780	1610	550	2130	480
Vermont	4260	630	0	300	170	130	590	290	190	490	220
Virginia	46670	7600	310	3610	1590	1320	5900	2240	1880	7150	1830
Washington	42620	7020	280	3120	1310	1320	4880	2510	1890	5670	1930
West Virginia	12690	1630	80	1080	490	400	2050	660	520	1550	640
Wisconsin	37320	5380	200	2680	1380	1320	4500	2170	1590	5590	1730

(Source: Cancer statistics 2022)

As shown in the above table, there are 10 major cancer types that include the following: Female Breast, Uterine Cervix, Colon and Rectum, Uterine Corpus, Leukemia, Lung and Bronchus, Melanoma of the skin, Non-Hodgkin Lymphoma, Prostate and Urinary Bladder.

HEAT MAPS RELEVENT TO CANCER GENOMICS

SAS CODE:

```
proc sgplot data=final;

 heatmapparm x=name y=state colorgroup=newcase1 / outline attrid=SortOrder;
xaxis label="Cancer Type" display=all  ;
 yaxis label="State" display=all discreteorder=data;
 keylegend / location=outside position=right  title= "Frequency";
run;
```

THE ABOVE SAS CODE WILL GENEARTE THE BELOW FIGURE 1 OUTPUT

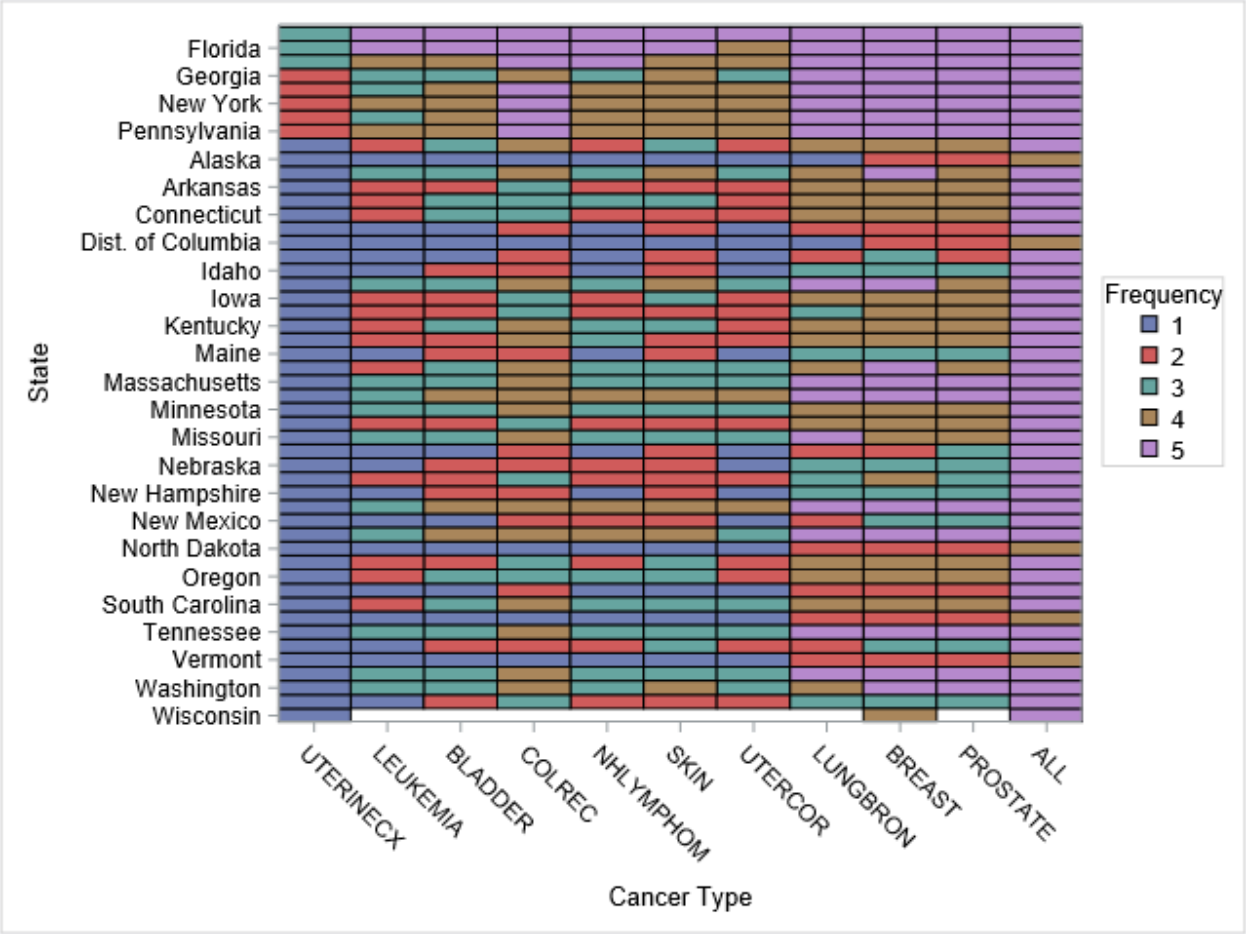


Figure1. Heatmap of New cancer cases in US by State 2022

The distribution of these 10 different cancers in the US will be presented in the Heatmap and the code and figure output will be presented above. Like the heatmap of new cancer case shown above, we can show a simple heatmap for genomic alterations.

The figure 2 below will be developed with gene alterations data plotting patient ids on X-axis and different genes or biomarkers on the Y-axis with filled with colors for 5 different alterations. Proc template with sgrender procedure will was used to develop this heatmap and the SAS code details are provided below so users can easily adopt to their clinical studies when this king of mock shell used for developing heatmaps in the analysis of genomic alterations data.

SAS CODE:

```
proc template;
define statgraph simheat;
begingraph;
  layout lattice/columns=1 rowweights=(.035 .965) rowgutter=1px;
```

```
   layout overlay/xaxisopts=(linearopts=(viewmin=1) label=" " tickvalueattrs=(size=.1pt)
type=discrete display=none offsetmin=1 offsetmax=1);

         blockplot x=subjid block=altna2/class=analyte3_ display=(label fill) blockindex=altnan2
filltype=MULTICOLOR REPEATEDVALUES=TRUE

                  labelattrs=GraphDataText name="cat" dATATRANSPARENCY=0 LABELATTRS=(size=1pt )
INCLUDEMISSINGCLASS=false;

          discretelegend 'cat' /location=outside border=false halign=center valign=bottom
titleattrs=(size=1pt) exclude=(" ") valueattrs=( size=1pt) OUTERPAD=.5px;

   endlayout;

  endlayout;

endgraph;

end;

run;


proc sgrender data=final template=simheat;
run;
```

THE ABOVE SAS CODE WILL GENEARTE THE BELOW FIGURE 2 OUTPUT

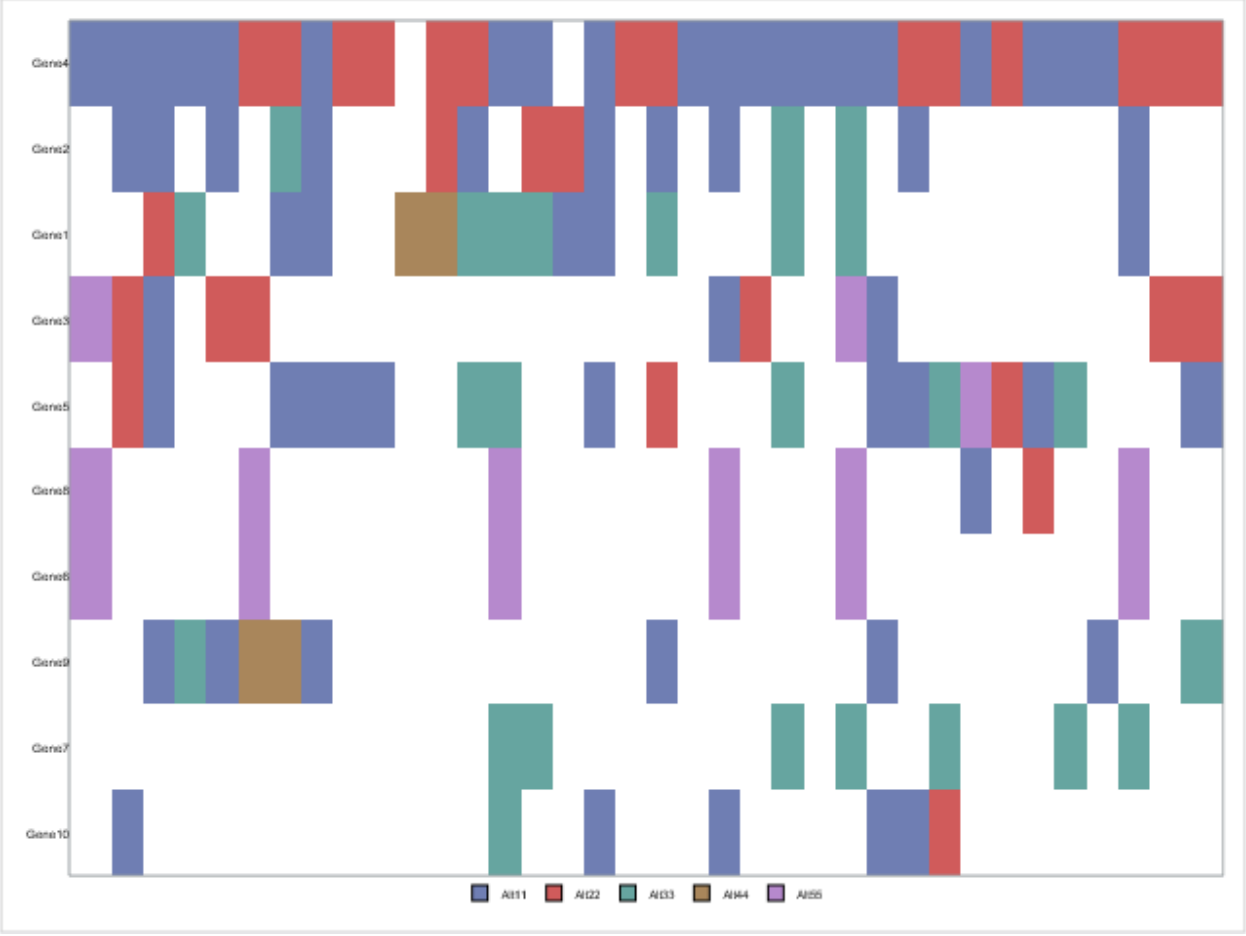


Figure 2. Heatmap of Genomic alterations.

Like the heatmap in the figure 2 above, we can make it more interesting by adding another bar external to the heatmap above for depicting the Best overall response. Therefore the figure 3 below will be developed with gene alterations data like figure 2 and including the Best overall response data and the detailed SAS code provided below. This is very useful in the analysis Biomarkers/genomics studies with heatmap analysis including Best overall response categories such as Complete Response (CR), Partial Response (PR), Stable Disease (SD) etc.

SAS CODE:

```
proc template;

define statgraph simheat2;

begingraph;

  layout lattice/columns=1 rowweights=(.035 .965) rowgutter=1px;

   layout overlay/xaxisopts=(linearopts=(viewmin=1) label=" " tickvalueattrs=(size=1pt)
type=discrete display=none offsetmin=1 offsetmax=1) ;

                  blockplot x=subjid block=bestresp /class=sortf display=(label fill)
blockindex=respn filltype=MULTICOLOR REPEATEDVALUES=TRUE

                  labelattrs=GraphDataText name="sortf" DATATRANSPARENCY=0.5 LABELATTRS=(size=1pt )
INCLUDEMISSINGCLASS=false;

          discretelegend 'sortf' /location=outside border=false halign=center valign=top
titleattrs=(size=1pt) exclude=(" ") valueattrs=( size=1pt) OUTERPAD=.5px;

   endlayout;

   layout overlay/xaxisopts=(linearopts=(viewmin=1) label=" " tickvalueattrs=(size=.1pt)
type=discrete display=none offsetmin=1 offsetmax=1) ;

                  blockplot x=subjid block=altna2/class=analyte3_ display=(label fill)
blockindex=altnan2 filltype=MULTICOLOR REPEATEDVALUES=TRUE

                  labelattrs=GraphDataText name="cat" dATATRANSPARENCY=0 LABELATTRS=(size=1pt )
INCLUDEMISSINGCLASS=false;

          discretelegend 'cat' /location=outside border=false halign=center valign=bottom
titleattrs=(size=1pt) exclude=(" ") valueattrs=( size=1pt) OUTERPAD=.5px;

   endlayout;

  endlayout;

endgraph;

end;

run;


proc sgrender data=final1 template=simheat2;

run;
```

THE ABOVE SAS CODE WILL GENEARTE THE BELOW FIGURE 3 OUTPUT

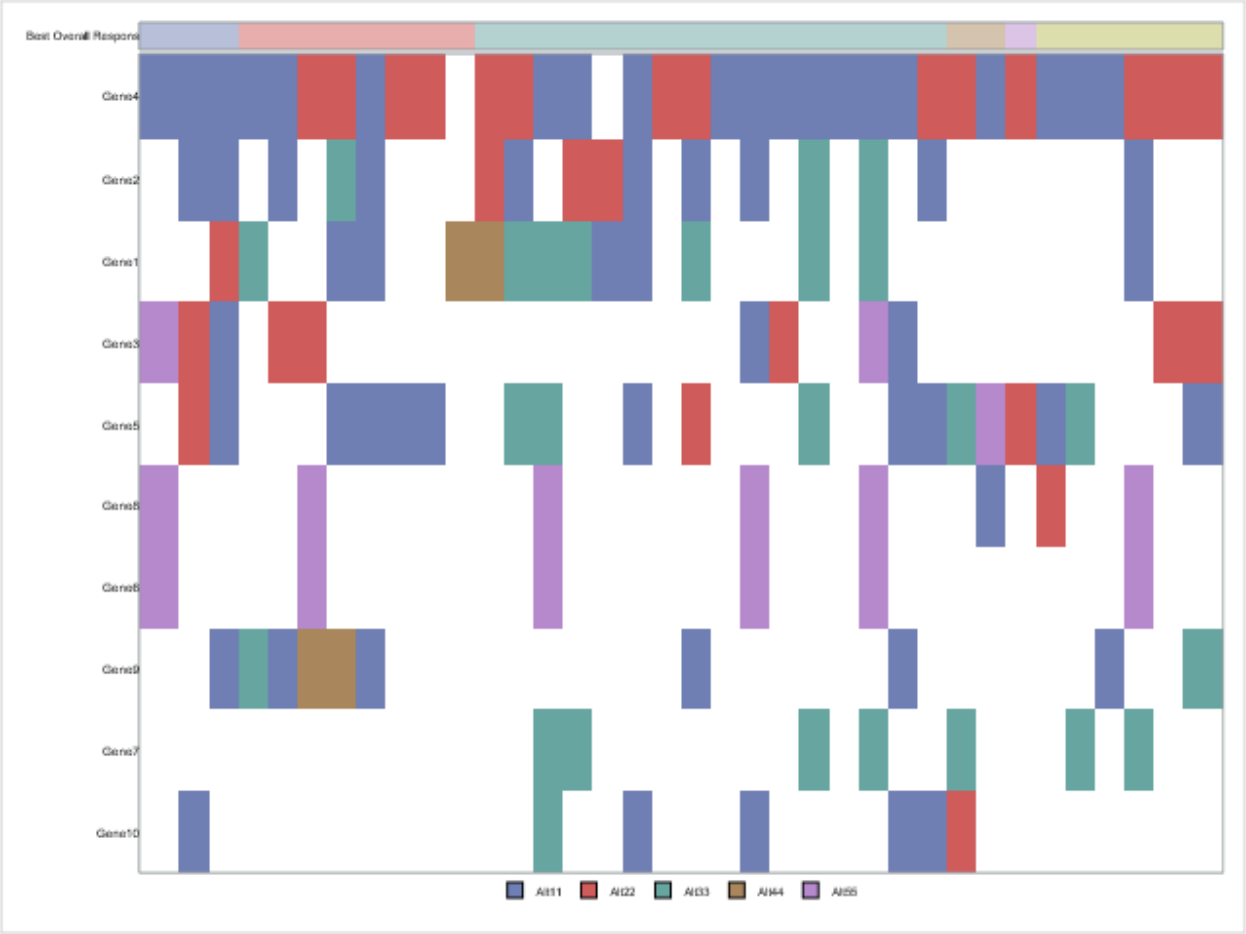


Figure 3. Heatmap of Genomic alterations with Best Overall Response.

The next 3 heatmaps presented below are useful to analyze the gene expression data with different gene pools or signatures available. Figure 4- 6 are set of heatmaps from simple to complex heatmap clusters. Figure 4 is a simple heatmap developed with proc sgplot technique and the details of SAS code provided below.

SAS CODE:

```
proc sgplot data=final1 rattrmap=rattrmap;
  by trt paging trtsrt;
  heatmap x=subjid y=param / colorResponse=aval2 discreteY rattrid=myid colorstat=mean
  outline outlineAttrs=(color=white);
  xaxis discreteorder=data label='Subject' display=(novalues);
  yaxis discreteorder=data label='Signature';
run;
```

THE ABOVE SAS CODE WILL GENEARTE THE BELOW FIGURE 4 OUTPUT

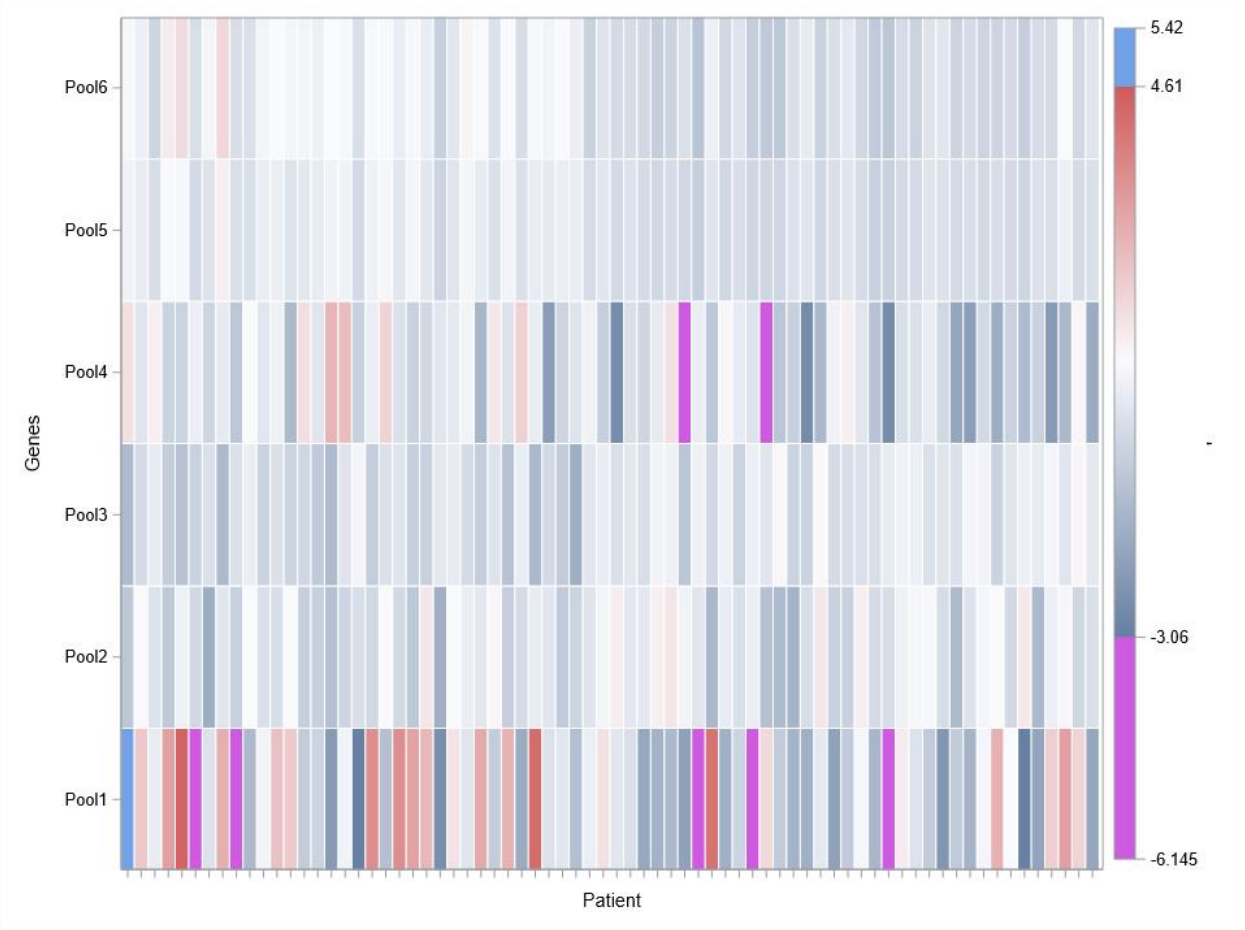


Figure 4 Heatmap of gene expression gene pools.

Figure 5 below will be like figure 4 and adding a bar chart above the heatmap. The bar chart could be anything but here bar chart added is with Survival that could be either Progression free survival or disease-free survival depending on the type of data availability and what analysis is needed as specified in the mock shells of figures. The details of SAS code are provided below for following easily by the users when a similar one need to be developed without any extra code and the below code will just be enough to produce the heatmap just by changing the variable names as available in their protocol or clinical study.

SAS CODE:

```
proc template;
define statgraph sgplot;
begingraph / collation=binary discreteAxisOffsetPad=false;
layout lattice;
layout overlay / xaxisopts=(display=(ticks line));
barchart x=subjid y=survs;
endlayout;
layout overlay /  xaxisopts= (Label="Subject" labelFitPolicy=Split display=(ticks label line)
type=discrete discreteopts=( TickValueFitPolicy=SplitRotate sortOrder=data ) )
         yaxisopts=( Label="Genes" );
   HeatMap X=SUBJID Y=PARAM /  discretey=true   colorstat=mean ColorResponse=aval2 NAME="HEATMAP"
```

```
fillattrs=(transparency=0.4);
   ContinuousLegend "HEATMAP" / title="'";
endlayout;
endlayout;
endgraph;
end;
run;

proc sort data=final1;
 by trt paging trtord survs;
 run;
proc sgrender data=final1 template=sgplot;
run;
```

THE ABOVE SAS CODE WILL GENEARTE THE BELOW FIGURE 5 OUTPUT

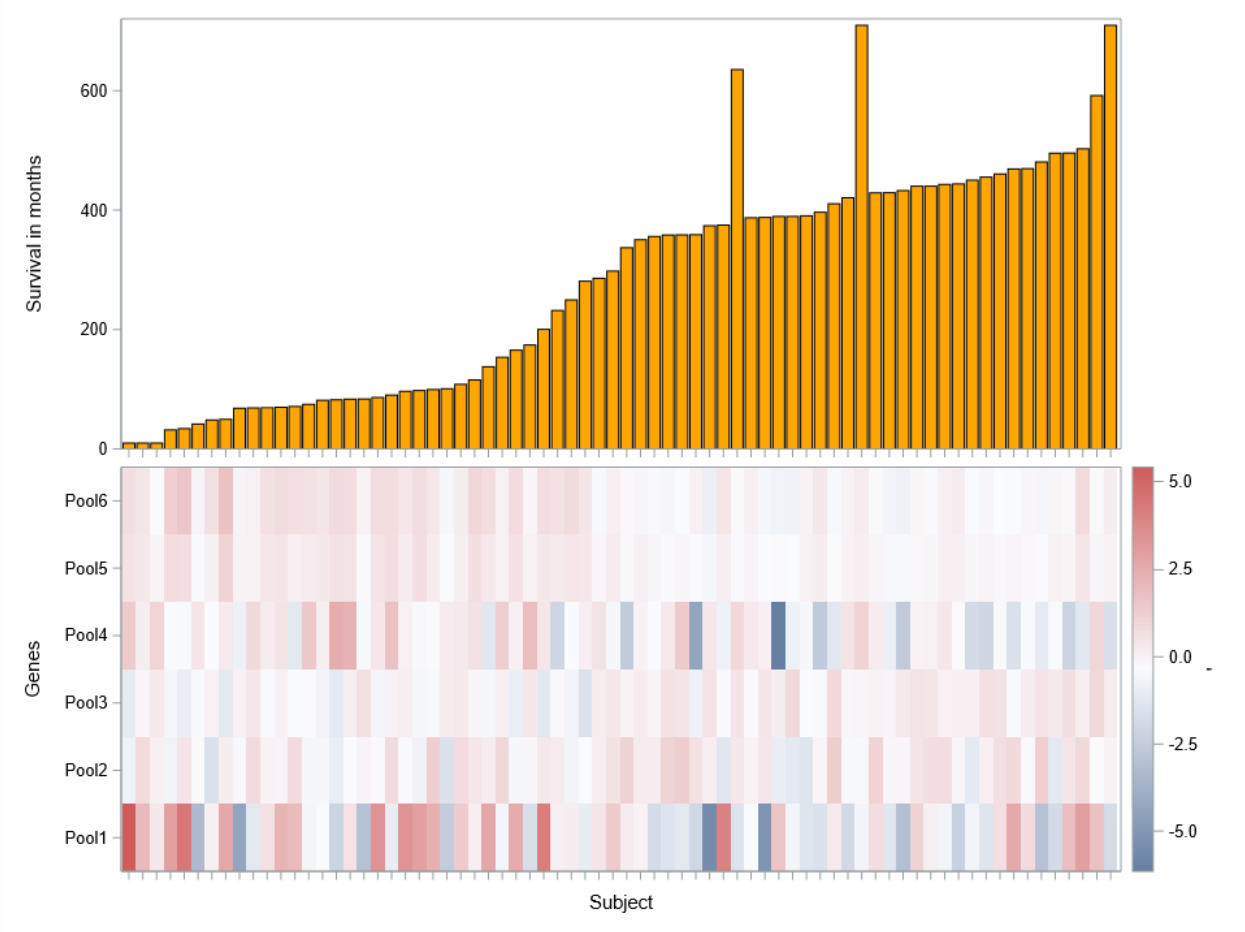


Figure 5 Heatmap of gene expression gene pools with bar chart.

Figure 6 will be little more complex in the series and in this heatmap there will be two more bar charts will be added and all the 3 graphs will be on the same page. Like the figure 5 above there will be one more class (could be treatment group or different population set etc.) will be added and the details of SAS code will be provided below so users can easily replicate this complex heatmap without many coding efforts.

SAS CODE:

```
proc template;
define statgraph heatbar;
begingraph / collation=binary discreteAxisOffsetPad=false;
layout lattice / rows=3 rowweights=(.20 .20 .60);
layout overlay / xaxisopts=(display=(ticks line))
yaxisopts=(label="Survival (months)");
barchart x=subjid y=eval(survs*(IFN(flag='Y',1,.))) / fillattrs=(color=orange);
endlayout;
layout overlay / xaxisopts=(display=(ticks line));
barchart x=subjid y=survs /
group=desexc groupdisplay=cluster name="b";
discretelegend "b" / across=1 halign=right title="Class" border=false ;
endlayout;
layout overlay /  xaxisopts= (Label="Patient" labelFitPolicy=Split display=(ticks label line)
type=discrete discreteopts=( TickValueFitPolicy=SplitRotate sortOrder=data ) )
        yaxisopts=( Label="Genes" );
  HeatMap X=subjid Y=PARAM /  discretey=true   colorstat=mean ColorResponse=aval2 NAME="HEATMAP";
  ContinuousLegend "HEATMAP" / title="'";
endlayout;
endlayout;
endgraph;
end;
run;

proc sgrender data=final1 template=heatbar;
by trt trtord;
run;
```

THE ABOVE SAS CODE WILL GENEARTE THE BELOW FIGURE 6 OUTPUT

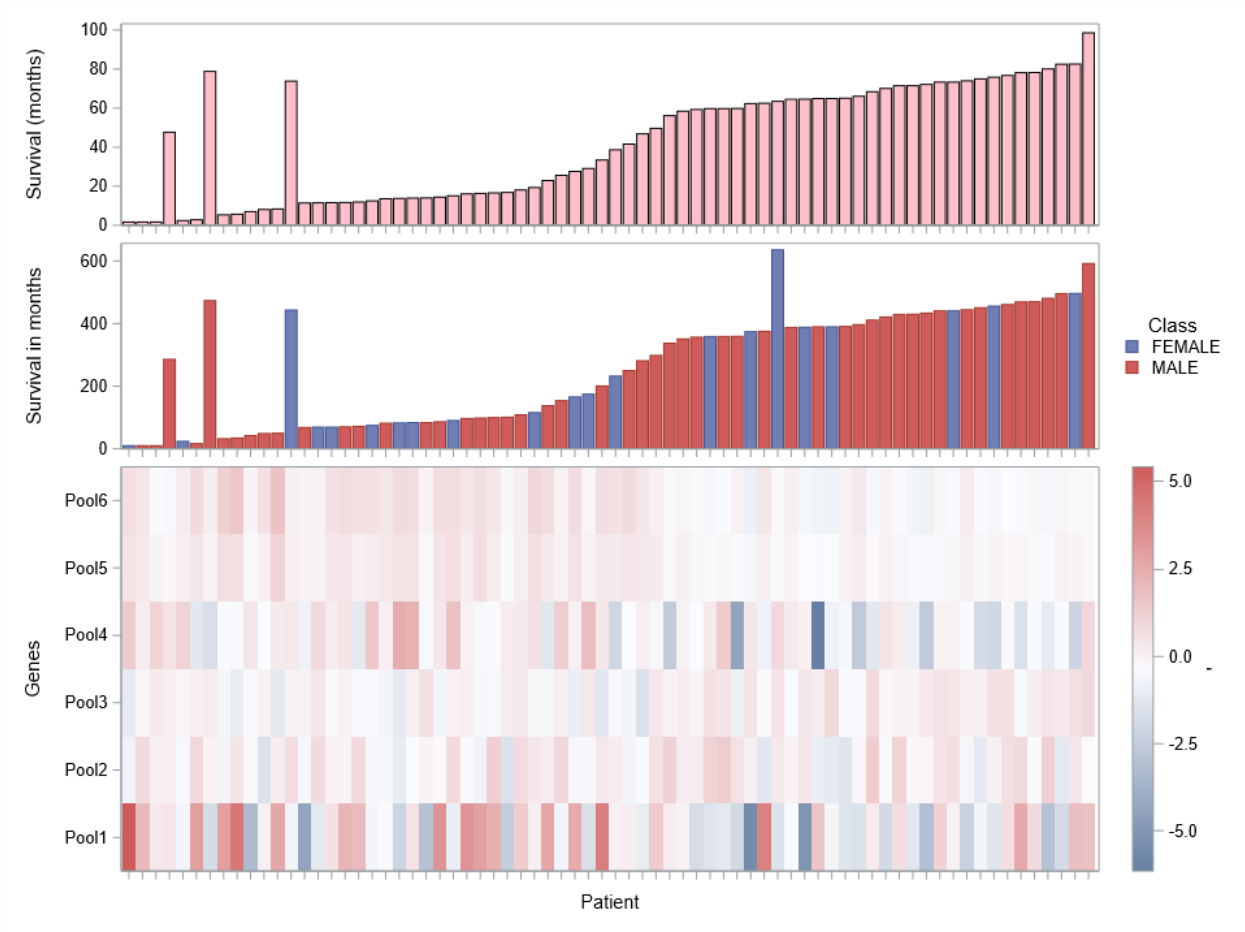


Figure 6 Complex Heatmap of gene expression with bar charts.

With little adjustment and sorting, we can produce even more complex heatmap with 2 treatments survival (PFS or OS or DFS) side by side as shown below:

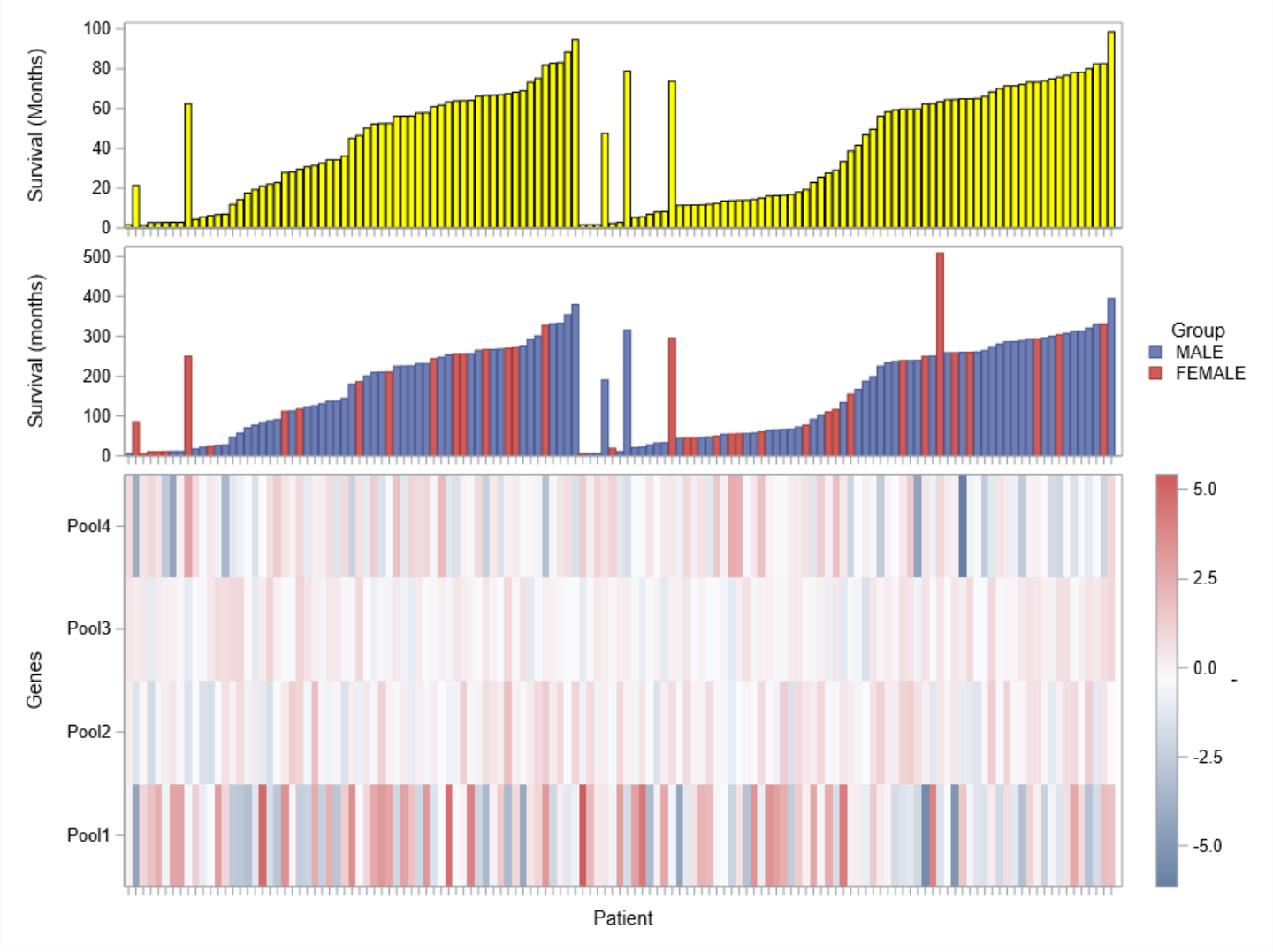


Figure 6a. Complex Heatmap of gene expression gene pools with bar chars with treatments side by side

The following 3 heatmaps are heat panels that includes simple to complex heat panel graphs that are useful in the analysis of genomic alterations. Figure 7 will be a simple one in the series followed by complex heat panel graphs.

SAS CODE:

```
proc sort data=newfin1 out=final;
by ord;
run;
proc sgplot data=final;
 heatmapparm x=subjid y=analyte colorgroup=altna / outline attrid=SortOrder;
 xaxis label="Patient" DISPLAY=(NOTICKS NOVALUES) ;
 yaxis label="Gene" display=all discreteorder=data;
 keylegend / location=outside position=right  title= "Alterations:";
```

```
run;
```

THE ABOVE SAS CODE WILL GENEARTE THE BELOW FIGURE 7 OUTPUT

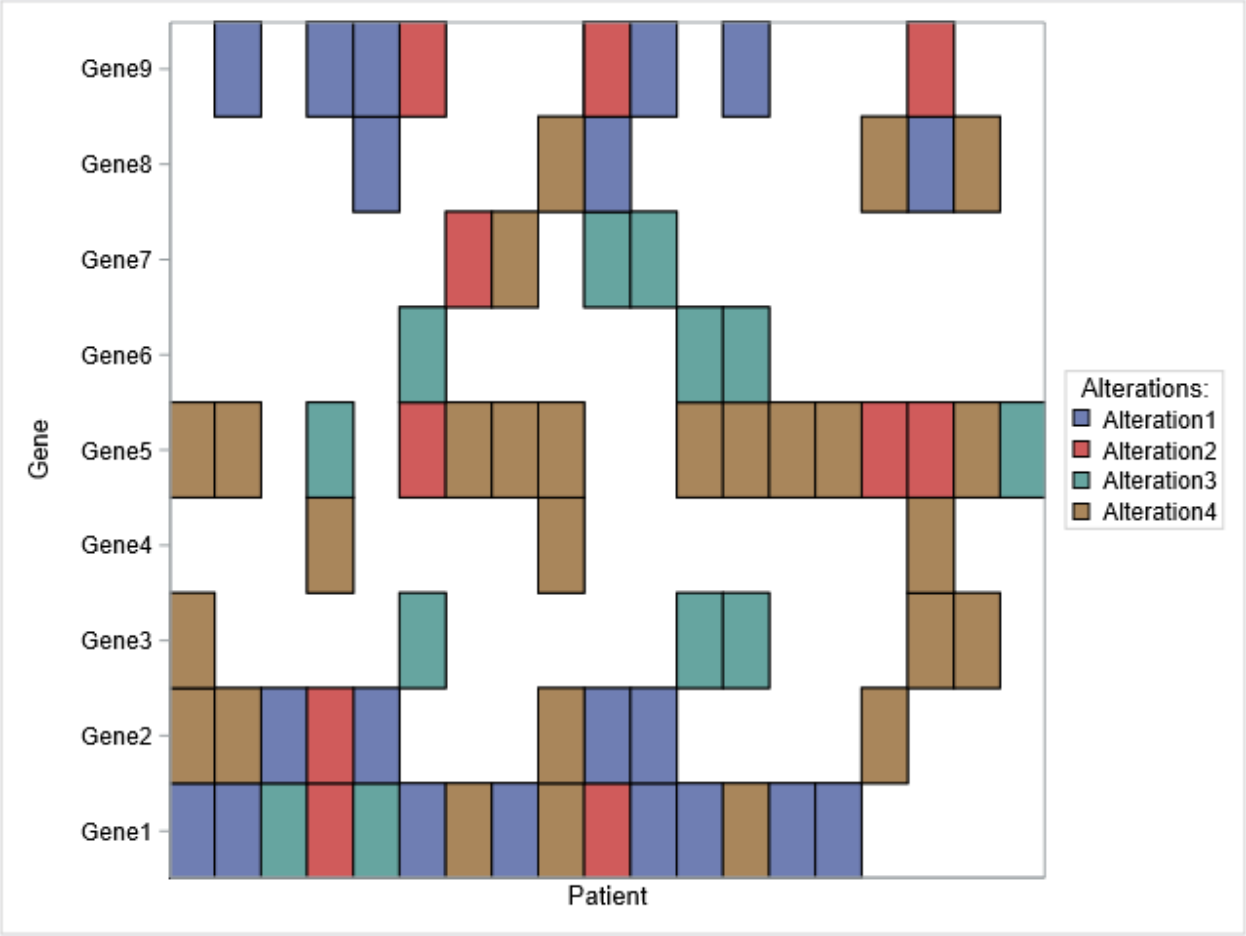


Figure 7: Simple Heatmap of genomic mutations

Figure 8 is typical heat panel graph useful with presenting a 3 panel heatmap. 3 panels can be used for 3 different groups or treatments or mutation status etc. GTL proc template is used to develop this heatmap using the heatmapparm statement and the details of SAS code will be provided below.

SAS CODE:

```
proc template;
define statgraph heat;
 begingraph  ;
        layout datapanel classvars=(cat) / columns=3 COLUMNDATARANGE=union headerborder=false
columnaxisopts=(display=(line ))
              rowaxisopts=(display=(line ticks tickvalues));
layout prototype;
            heatmapparm x=subjid y=analyte colorgroup=altna / name='heat';

          endlayout;
```

```
      endlayout;

endgraph;
end;
run;
run;  proc sgrender data=newfin2 template=heat;
run;
```

THE ABOVE SAS CODE WILL GENEARTE THE BELOW FIGURE 8 OUTPUT

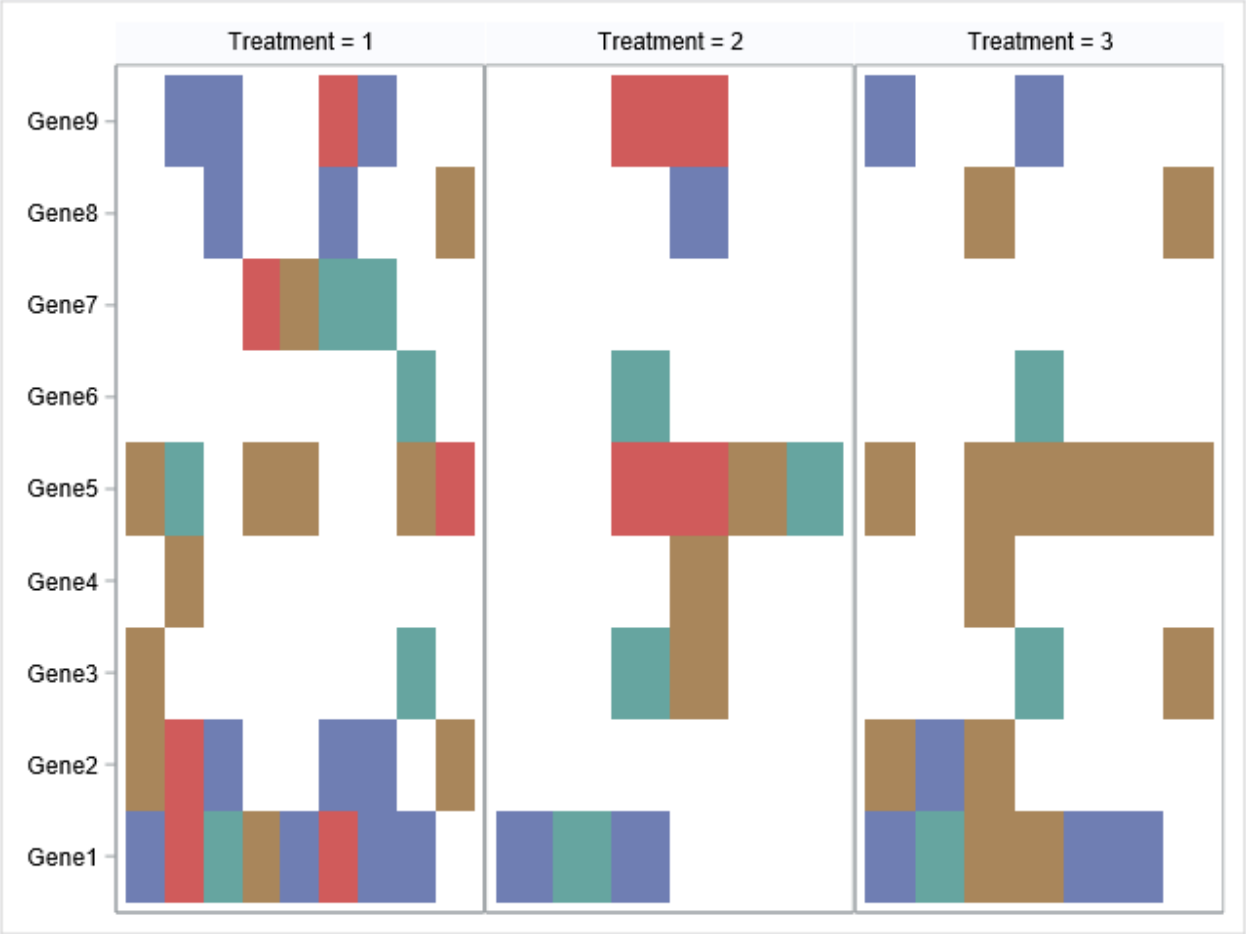


Figure 8: Heatmap panel of genomic alterations.

Lastly the third and complex heat panel graph in the series is presented in figure 9. This heatmap is having an additional classification (here local and central class) included in each panel. This additional classification will be developed using option of inner margin and sideband. The details of SAS code are presented below for easy replication.

SAS CODE:

```
proc template;
define statgraph heat;
 begingraph  ;
```

```
        layout datapanel classvars=(cat) / columns=3 COLUMNDATARANGE=union headerborder=false
columnaxisopts=(display=(line ))
              rowaxisopts=(display=(line ticks tickvalues));
layout prototype;
            heatmapparm x=subjid y=analyte colorgroup=altna / name='heat';
            innermargin / separator=true
              separatorattrs=(color=darkred thickness=2px);
              blockplot x=subjid block=bestresp /class=respvar display=(fill values)
                  blockindex=bestresp filltype=alternate
                  valueattrs=(size=10pt);
              endinnermargin;
          endlayout;
            sidebar /align=bottom;
              discretelegend 'heat';
              endsidebar;
       endlayout;
endgraph;
end;
run;
run;  proc sgrender data=newfin3 template=heat;
format bestresp respname. ord altname.;
run;
```

THE ABOVE SAS CODE WILL GENEARTE THE BELOW FIGURE 9 OUTPUT

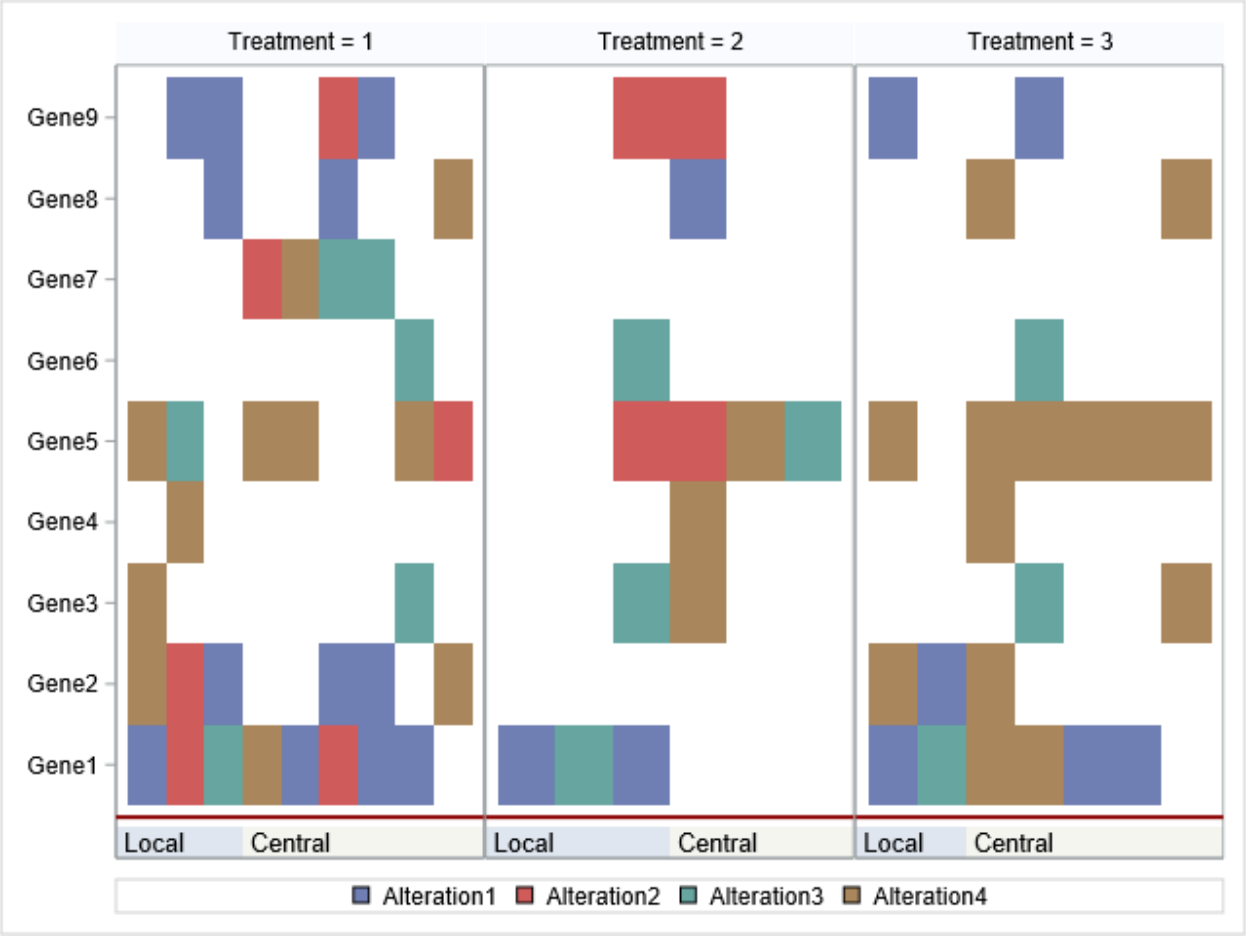


Figure 9: Complex Heatmap panel genomic alterations

CONCLUSION

With increase new cancer case in the US, patients bear a huge amount of cancer care costs. Biomarkers

are used in clinical studies to improve approval rates. The emergence of Biomarkers/genomics statistical analyses of cancer genomics data have been increasingly complex. Various heatmaps including heat-panels and clustering heatmaps generated by SAS offer an ultimate approach for better understanding the data visualization and patterns analyzing complex and high dimensional biomarkers trial data in the drug development industry. This paper attempted to provide some Complex Heatmaps programmed in SAS to easily replicate the SAS programs using the SAS code in this paper depending on the type of heatmaps users need for their statistical analyses of biomarkers and genomic alterations.

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RECOMMENDED READING

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