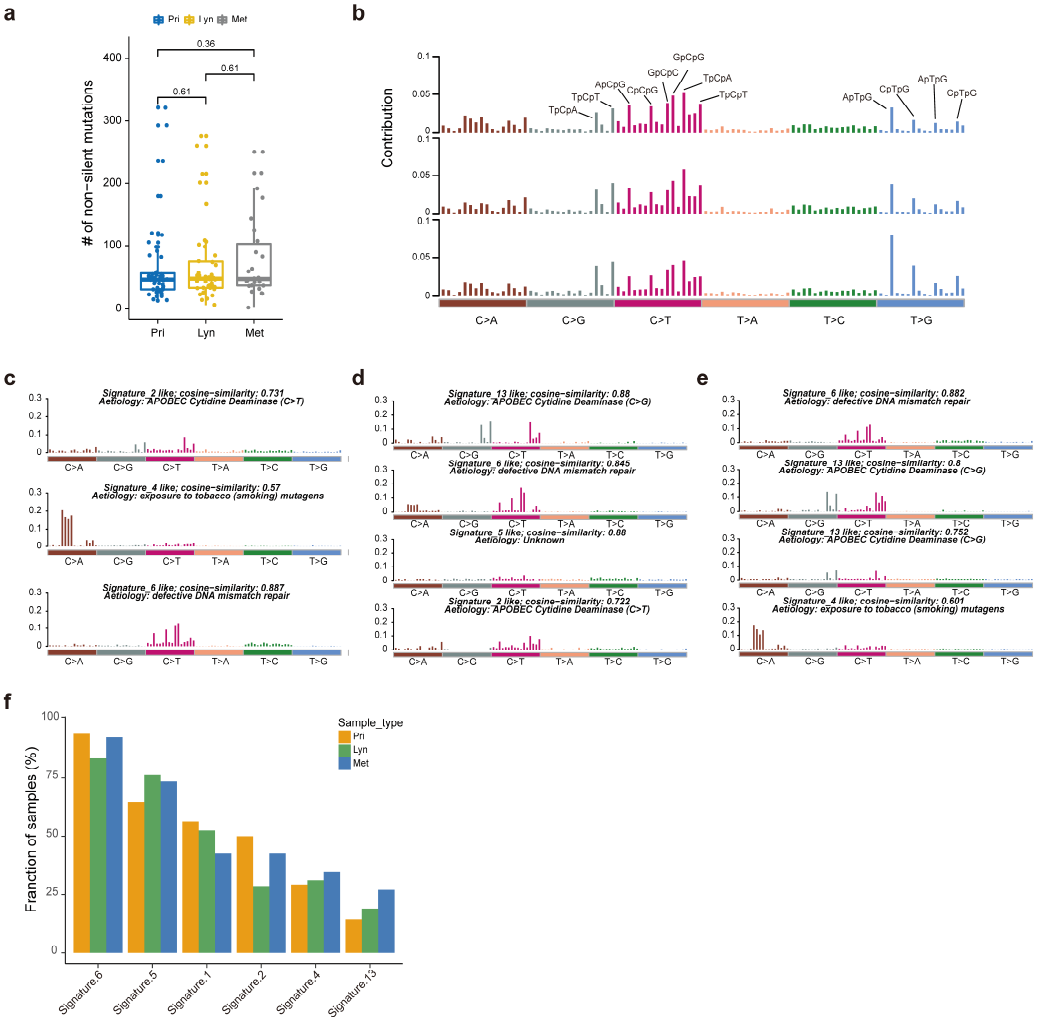
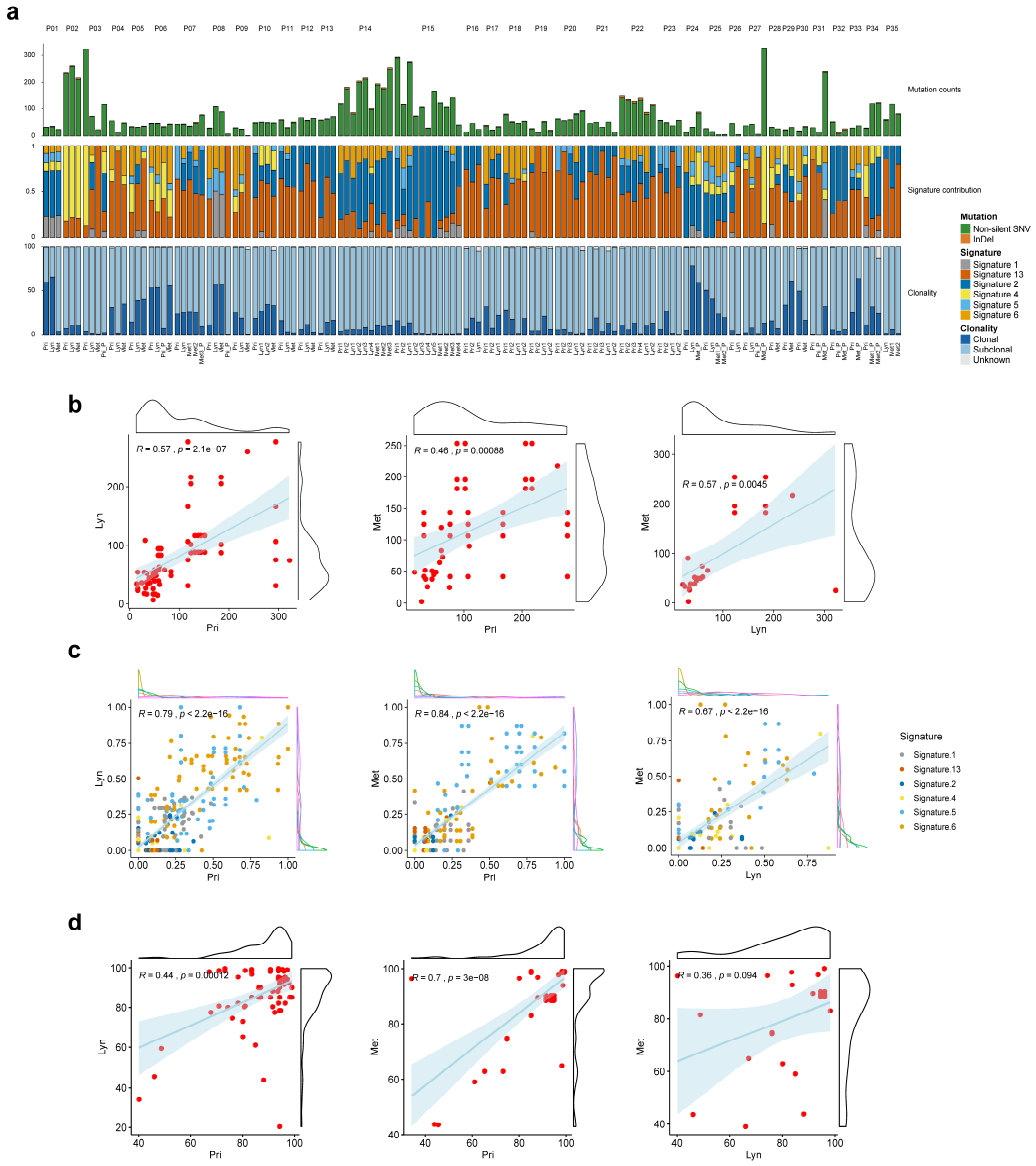
SUPPLEMENTARY FIGURES



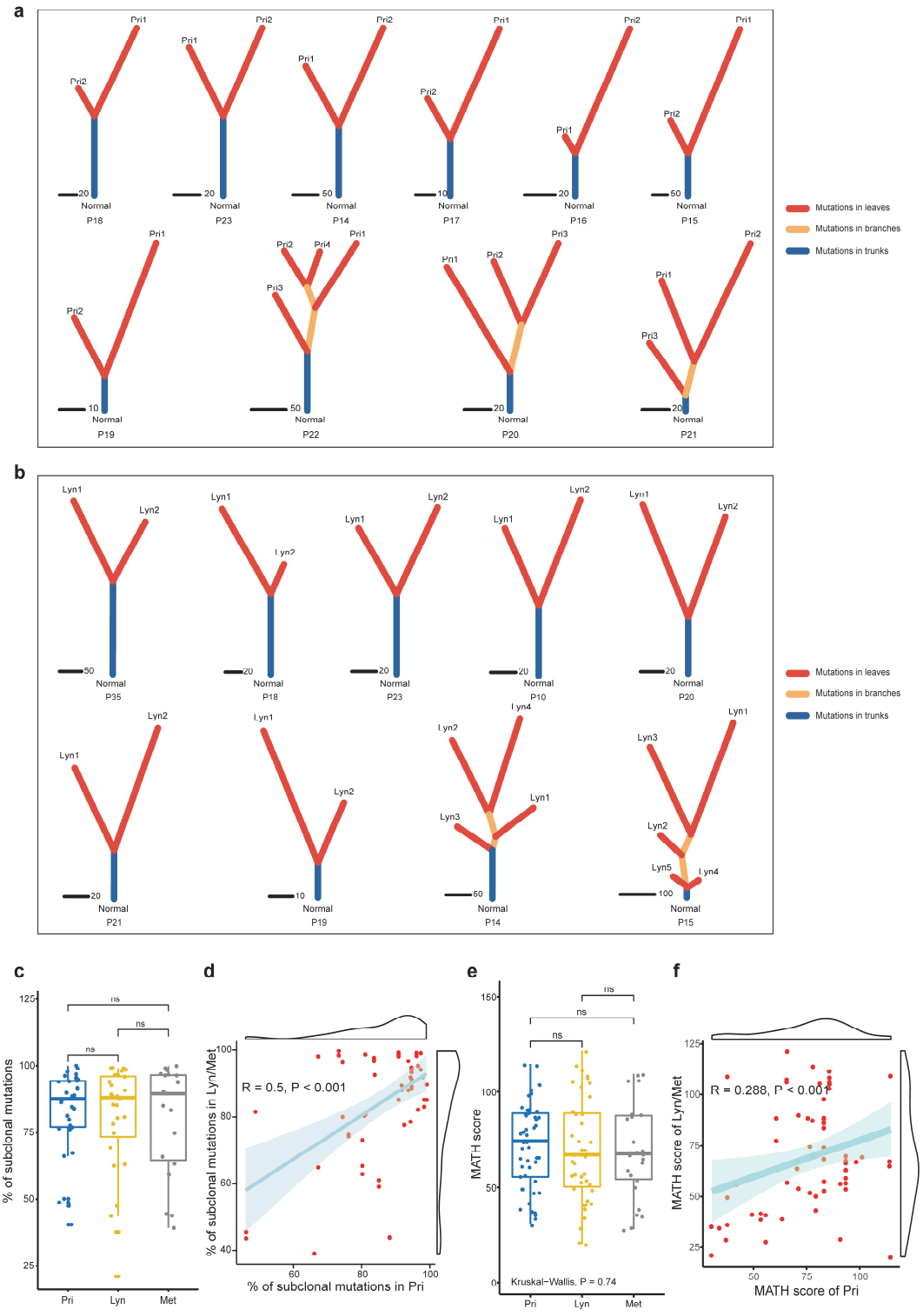
Supplementary Fig. 1, related to Fig. 1. Mutation comparison among primary tumours, and regional lymph node and distant metastases. (a) The numbers of detected nonsilent mutations were similar among Pri (n = 48), Lyn (n = 42) and Met (n = 26). In each box plot, the centre line represents the median, the bounds represent the first and third quartiles and whiskers extend from the hinge to the largest value no further than 1.5 * interquartile range (IQR) from the hinge. A two-sided Wilcoxon signed-rank test was used to calculate P values; "ns": $P \geqslant 0.05$. (b) Similar mutation context (defined by the proportion of A, T, C and G nucleotides within ±2 bp of the variant site) for six mutation categories among Pri (top), Lyn (middle) and Met (bottom). Remarkable mutation contexts are highlighted. (c-e) Signatures decomposed by nonnegative matrix factorization of Pri (c), Lyn (d) and Met (e). Each signature

was compared against known signatures derived from the COSMIC database (https://cancer.sanger.ac.uk/cosmic/signatures), and cosine similarity was calculated to identify the best match. Signatures with a cosine similarity of less than 0.3 were filtered out. (f) Fraction of samples that contributed to the specific signature among Pri, Lyn and Met. Source data are provided as a Source Data file.



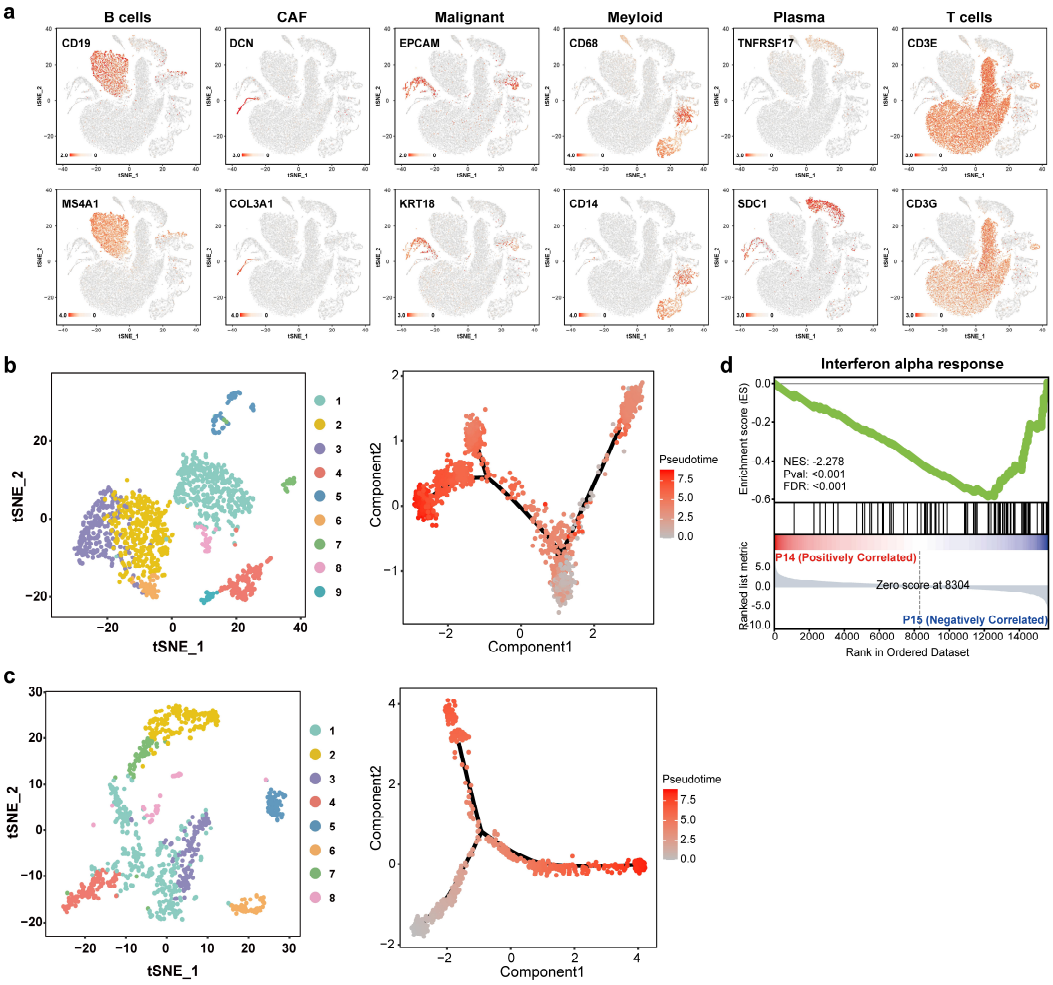
Supplementary Fig. 2, related to Fig. 1. Longitudinal analysis of mutation signatures for each sample. (a) Bar plot showing the number of mutations (top), composition of mutation signatures (meddle) and proportion of clonal mutations (bottom) for each sample. (b) Scatter plot showing the correlation relationship of the number of mutations in primary vs. regional lymph node tumours (left), primary vs. distant metastasis tumours (mediate) and regional lymph node vs. distant metastasis tumour (right). The data are shown along with 95% confidence intervals. Pearson correlation analysis was used to calculate P values (two-sided). (c) Scatter plot showing the correlation of the contribution of different mutation signatures in primary vs. regional lymph node tumours (left), primary vs. distant metastasis tumours (middle) and regional lymph node vs. distant metastasis tumours (right). The data are shown along with 95%

confidence intervals. Pearson correlation analysis was used to calculate P values (two-sided). (d) Scatter plot showing the correlation of the proportion of subclone mutations in primary vs. regional lymph node tumours (left), primary vs. distant metastasis tumours (middle) and regional lymph node vs. distant metastasis tumours (right). The data are shown along with 95% confidence intervals. Pearson correlation analysis was used to calculate P values (two-sided). Pri: primary tumour; Lyn: regional lymph node tumour; Met: distant metastasis tumour. Source data are provided as a Source Data file.



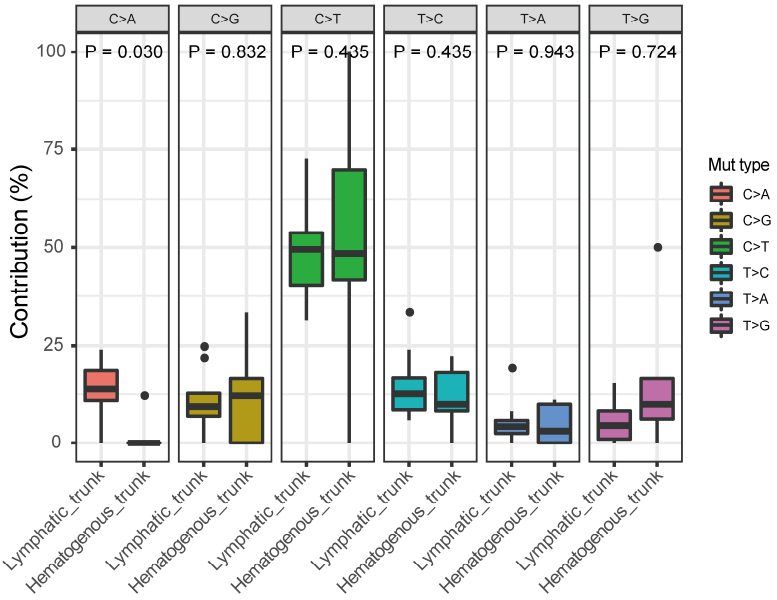
Supplementary Fig. 3, related to Fig. 1. Heterogeneity analysis of primary tumours, regional lymph node metastases and distant metastases. (a) Phylogenetic trees showing intratumour heterogeneity (ITH) based on multiregion samples of primary tumours. The length of the branch reflects the number of mutations and short trunks indicate high level mutation

heterogeneity. Blue, the trunk of the tree indicates mutations shared by all regions; yellow, branches shared by at least two regions; red, the leaves where mutations were detected only in individual regions. (b) Phylogenetic trees showing ITH based on multiregion samples of NPC regional lymph nodes. (c) No significant difference in the percentage of subclonal mutations was detected among Pri (n = 48), Lyn (n = 42) and Met (n = 26). In each box plot, the centre line represents the median, the bounds represent the first and third quartiles and whiskers extend from the hinge to the largest value no further than 1.5 * interquartile range (IQR) from the hinge. A two-sided Wilcoxon signed-rank test was used to calculate P values; "ns" : $P \geqslant 0.05$. (d) Scatter plot showing the correlation of the proportion of subclone mutations between paired Pri and Lyn/Met samples. The data are shown along with 95% confidence intervals. Pearson correlation analysis was used to calculate P values (two-sided). (e) No significant difference in the MATH score was detected among Pri (n = 48), Lyn (n = 42) and Met (n = 26). In each box plot, the centre line represents the median, the bounds represent the first and third quartiles, and whiskers extend from the hinge to the largest value no further than 1.5 * interquartile range (IQR) from the hinge. A two-sided Wilcoxon signed-rank test was used to calculate P values. (f) Scatter plot showing the correlation of the MATH score between paired Pri and Lyn/Met samples. The data are shown along with 95% confidence intervals. Pearson correlation analysis was used to calculate P values (two-sided). Source data are provided as a Source Data file.

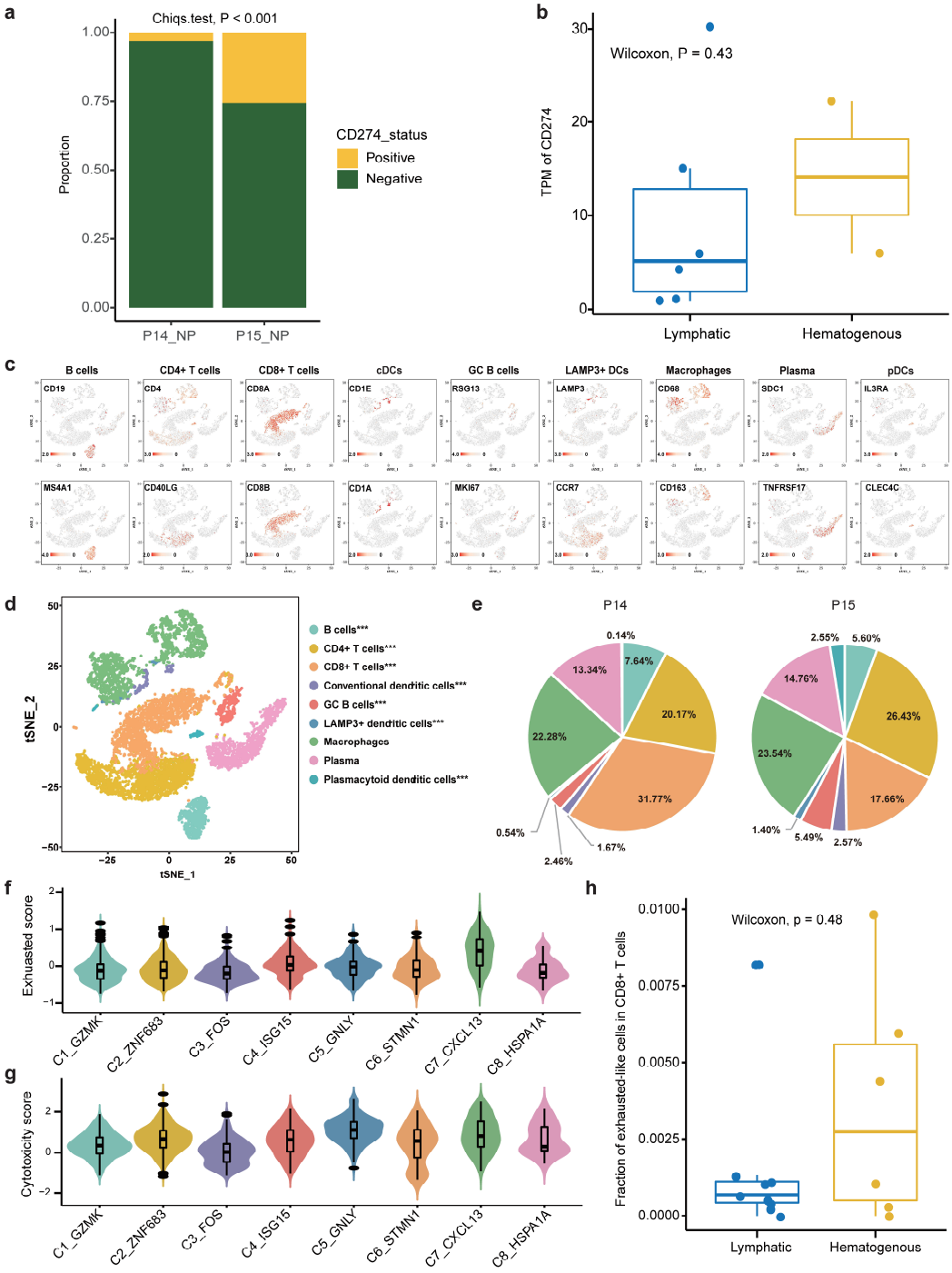


Supplementary Fig. 4, related to Fig. 4. Cell clusters of single cells from the lymphatic and hematogenous routes.

(a) t-SNE projection of single cells from P14 and P15, with cells coloured based on the average expression of sets of marker genes for B cells, cancer-associated fibroblasts, malignant cells, myeloid cells, plasma cells and T cells. (b & c) Pseudotime trajectory analysis of tumour cells from P14 (b) and P15 (c). The left panel shows the subclusters of tumour cells, and the right panel shows the evolutionary trajectory predicted by Monocle2, which is coloured according to the pseudotime score. (d) Hallmark GSEA of P14 primary tumour cells vs. P15 primary tumour cells using scRNA-seq data. An empirical phenotype-based permutation test (two-sided) was used to calculate the P value and false discovery rate (FDR).

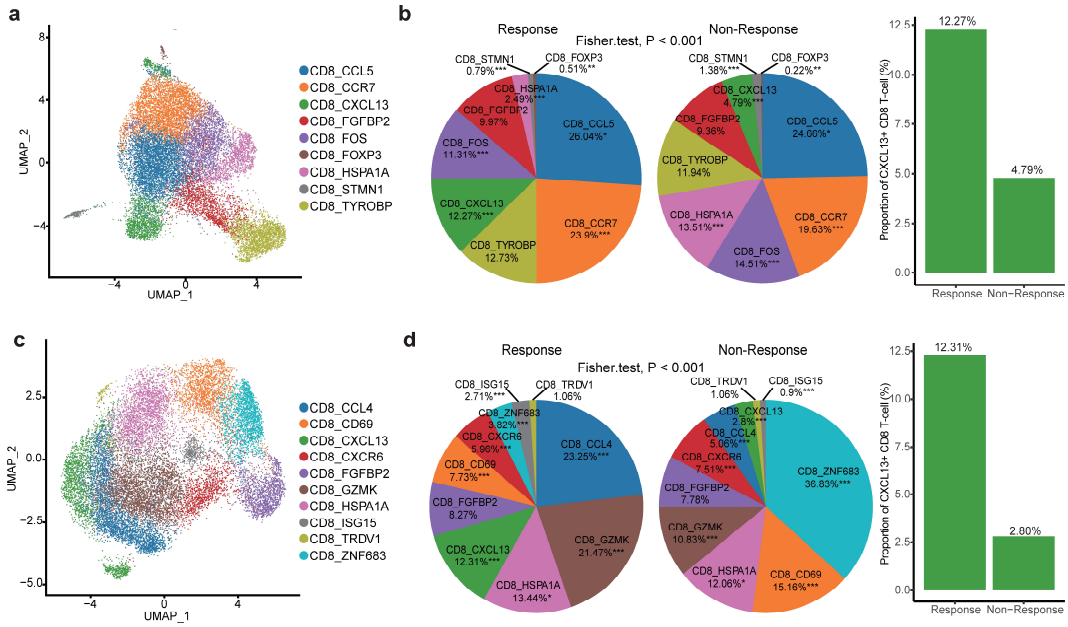


Supplementary Fig. 5, related to Fig. 5. Trunk mutation type comparison of the lymphatic (n = 8) and hematogenous (n = 5) evolutionary models. In each box plot, the centre line represents the median, the bounds represent the first and third quartiles and whiskers extend from the hinge to the largest value no further than 1.5 * interquartile range (IQR) from the hinge. After adjusting for age, gender and tumor stage by using covariance analysis model, two-sided Wilcoxon signed-rank test was used to calculate the adjusted P values. Source data are provided as a Source Data file.

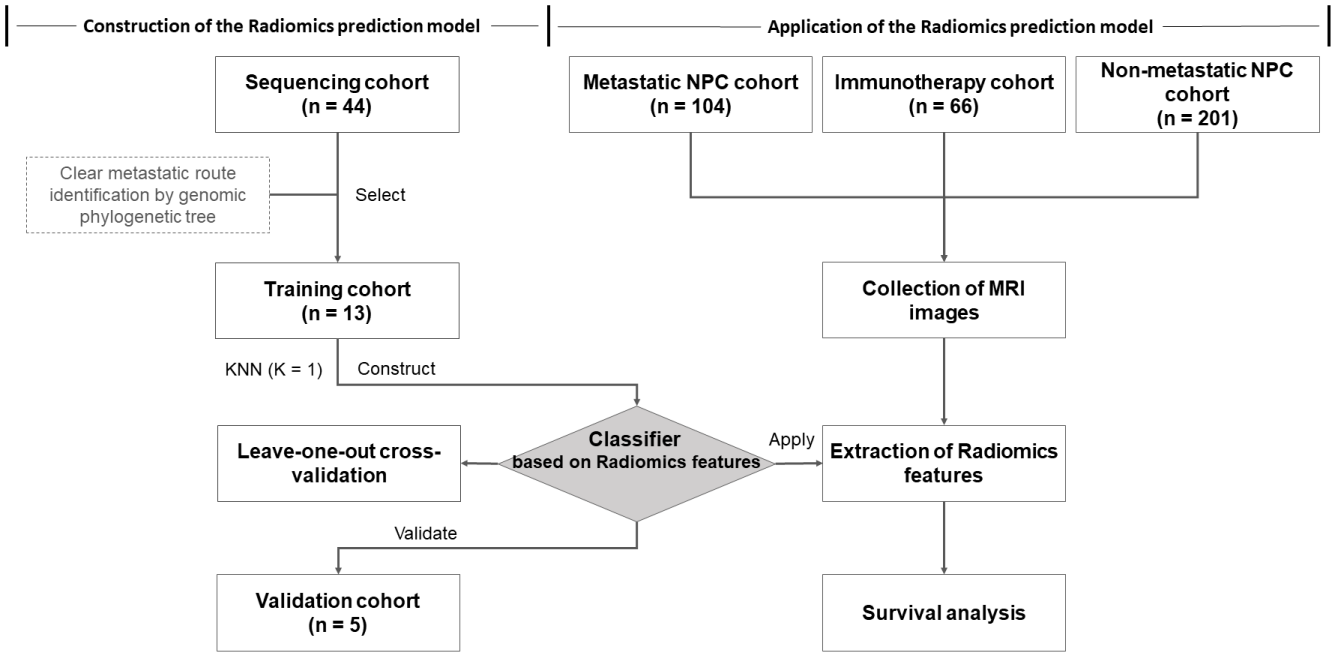


Supplementary Fig. 6, related to Fig. 6. Microenvironment of P14 and P15 revealed by scRNA-seq. (a) Bar plot showing the proportion of PD-L1^{+} tumour cells in the primary tumour of P14 and P15. A two-sided chi-square test was used to calculate the P value. (b) Box plot comparing the expression of *PD-L1* between patients with metastases emerging via the hematogenous route (n = 2) and those with metastases emerging via the lymphatic route (n =

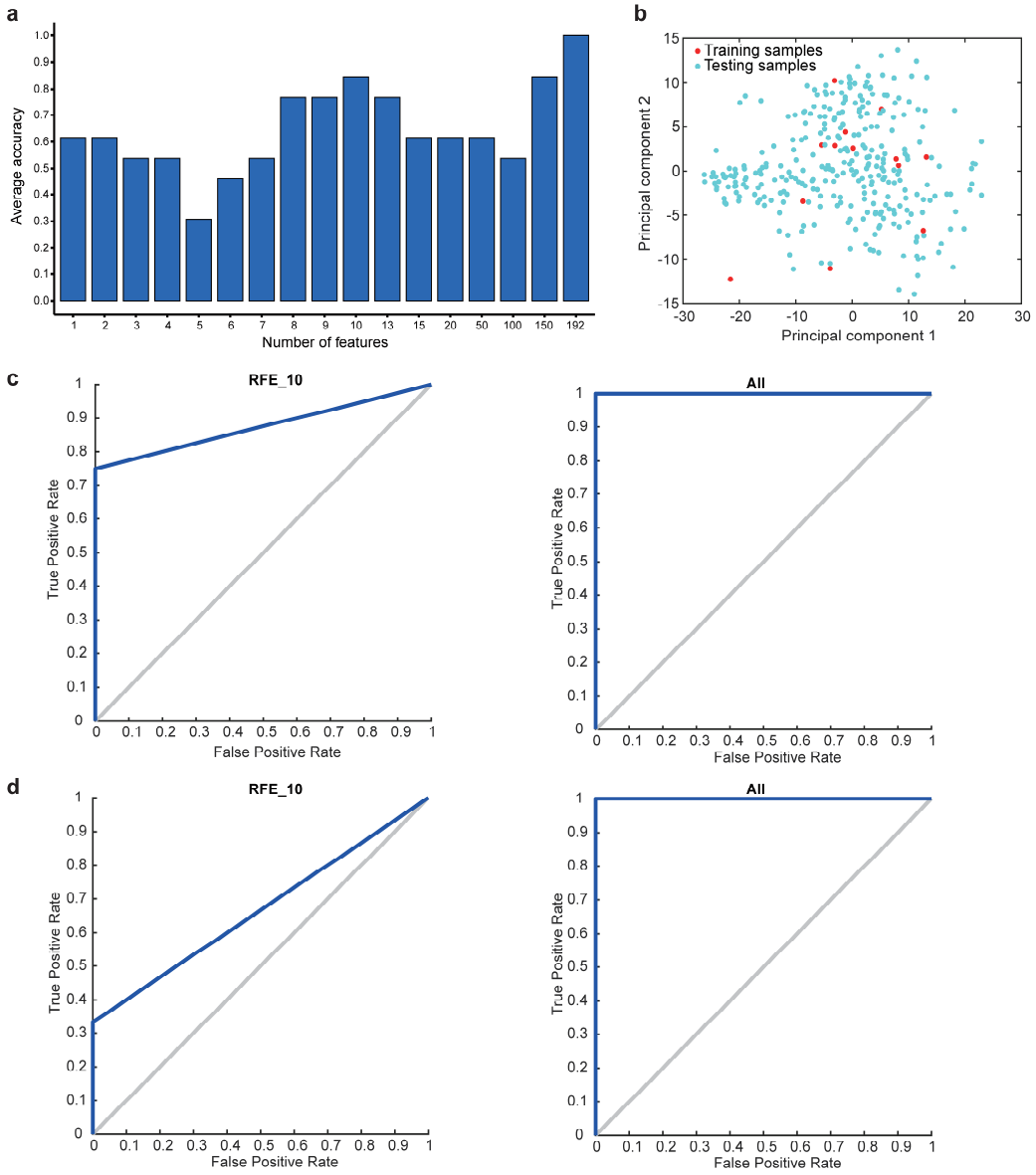
6). In each box plot, the centre line represents the median, the bounds represent the first and third quartiles, and whiskers extend from the hinge to the largest value no further than 1.5 * interquartile range (IQR) from the hinge. A two-sided Wilcoxon signed-rank test was used to calculate P values. (c) t-SNE projection of immune cells from the primary sites of P14 and P15, with cells coloured based on the average expression of sets of marker genes for B cells, $CD4^+$ T cells, $CD8^+$ T cells, classical dendritic cells (cDCs), germinal centre B cells, $LAMP3^+$ DCs, macrophages, plasma cells and plasmatic DCs. (d) t-SNE plot of immune cells from the primary sites of P14 and P15. Clusters are assigned to inferred cell types based on canonical marker expression. The statistical significance of the difference in the proportion of each cell type between P14 and P15 was measured using a two-sided Fisher exact test ("***", $P < 0.001$). (e) Pie charts show the fraction of each immune cell type from primary tumours, which are coloured according to the cell type shown in (b). (f & g) Violin plots comparing the exhaustion score (f) and cytotoxicity score (g) among different $CD8^+$ T-cell subclusters. (h) Box plot showing the ratio of $CXCL13^+TIM3^+CD8^+$ T cells/$CD8^+$ T cells in primary tumour between the lymphatic (n = 8) and hematogenous (n = 5) routes via multiplex IHC staining. In each box plot, the centre line represents the median, the bounds represent the first and third quartiles, and whiskers extend from the hinge to the largest value no further than 1.5 * interquartile range (IQR) from the hinge. A two-sided Wilcoxon signed-rank test was used to calculate P values. Source data are provided as a Source Data file.



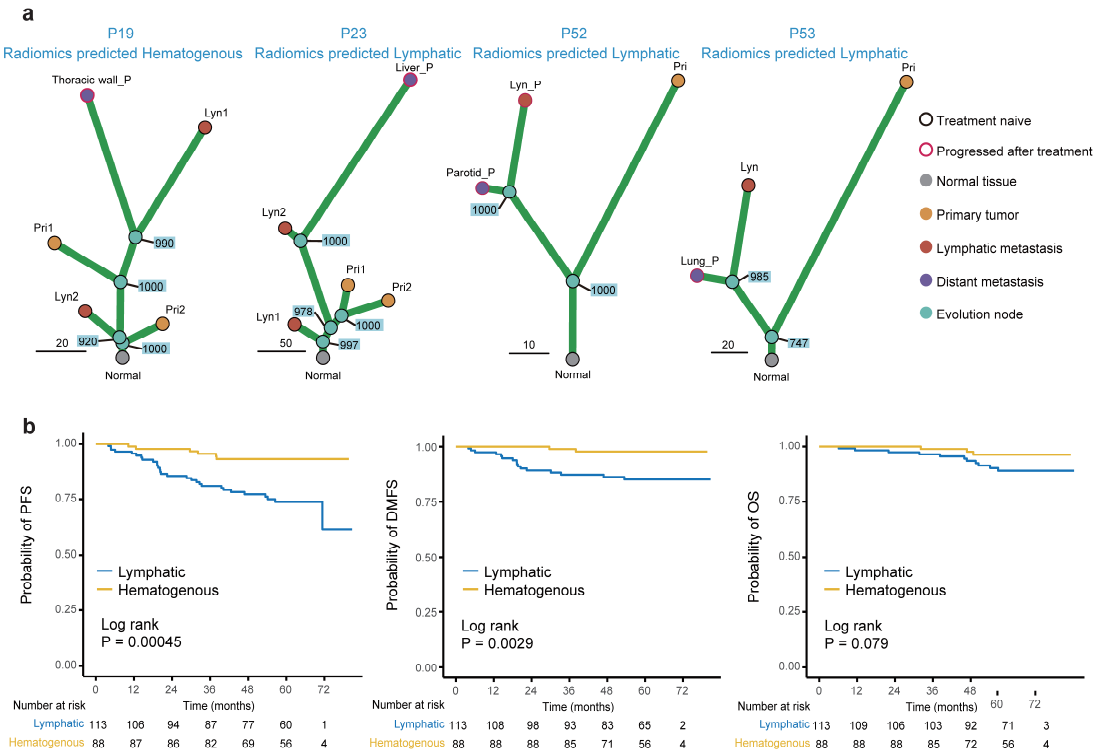
Supplementary Fig. 7, related to Fig 6. CXCL13$^+$ CD8$^+$ T cells were enriched in patients sensitive to immunotherapy. (a) t-SNE plot showing the clusters of CD8$^+$ T cells from BCC patients receiving PD-1 blockade (GSE123813). (b) Pie plot showing that CXCL13$^+$ CD8$^+$ T cells were significantly enriched in BCC patients who responded to PD-1 blockade, and column plot (right) showing the different proportion of CXCL13+ CD8+ T cells between responders and non-responders (*, P < 0.05; **, P < 0.01, ***, P < 0.001). (c) t-SNE plot showing the clusters of CD8$^+$ T cells from ccRCC patients receiving immune checkpoint blockade (PRJNA705464). (d) Pie plot showing that CXCL13$^+$ CD8$^+$ T cells were significantly enriched in ccRCC patients who responded to immune checkpoint blockade, and column plot (right) showing the different proportion of CXCL13+ CD8+ T cell between responders and non-responders (*, P < 0.05; **, P < 0.01, ***, P < 0.001).



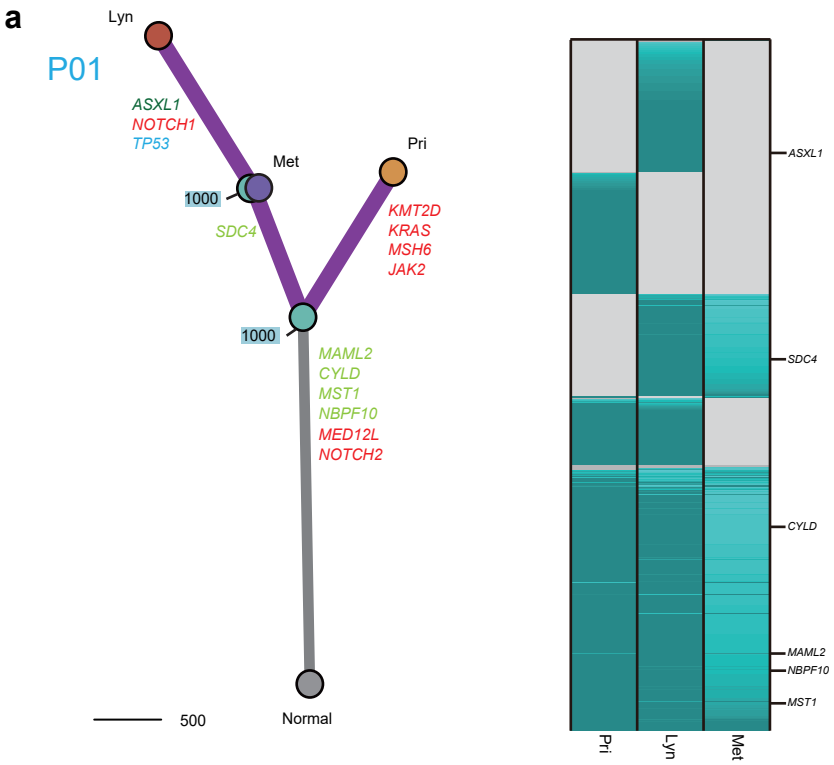
Supplementary Fig. 8, related to Fig. 6. Flow chart of building the prediction model based on radiomics data.



Supplementary Fig. 9, related to Fig. 6. Construction of the radiomics prediction model. (a) Accuracy of different features selection using the recursive feature elimination (REF) algorithm. (b) PCA result from the training and testing samples based on the 192 dimensional features. (c) ROC curve of the training samples using the top ten features selected by the RFE method (left) and whole feature set (right). (d) ROC curve of the classifier on additional validation patients (P49-P53), using the top ten features selected by the RFE method (left), and the whole feature set (right). Source data are provided as a Source Data file.



Supplementary Fig. 10, related to Fig. 6. Validation of the radiomics prediction model. (a) Radiomics prediction model results and phylogenetic trees for patients who developed progression during follow-up (P19 and P23) or patients newly collected (P52, P53) to further validate the radiomics prediction model. (b) Kaplan–Meier curves of PFS (left), DMFS (middle) and OS (right) in the M0-stage NPC cohort (n = 201).



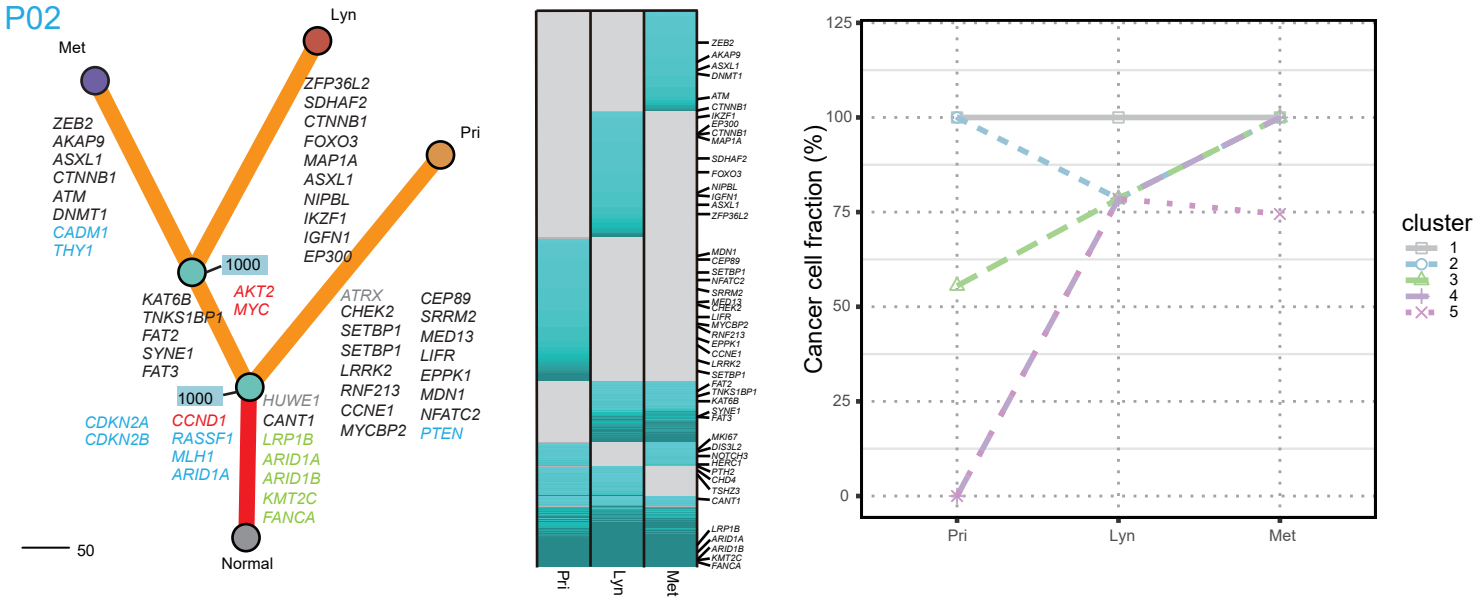
Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node

Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA

Cancer cell fraction
0% 100% Unavailable

TP53	Clonal mutated gene in all samples of this branch
TP53	Clonal mutated gene in some samples of this branch
TP53	Subclonal mutated gene in all samples of this branch
TP53	Clonality infomation unavailable in some samples of this branch
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch

b



- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

- Signature 1 (Age)
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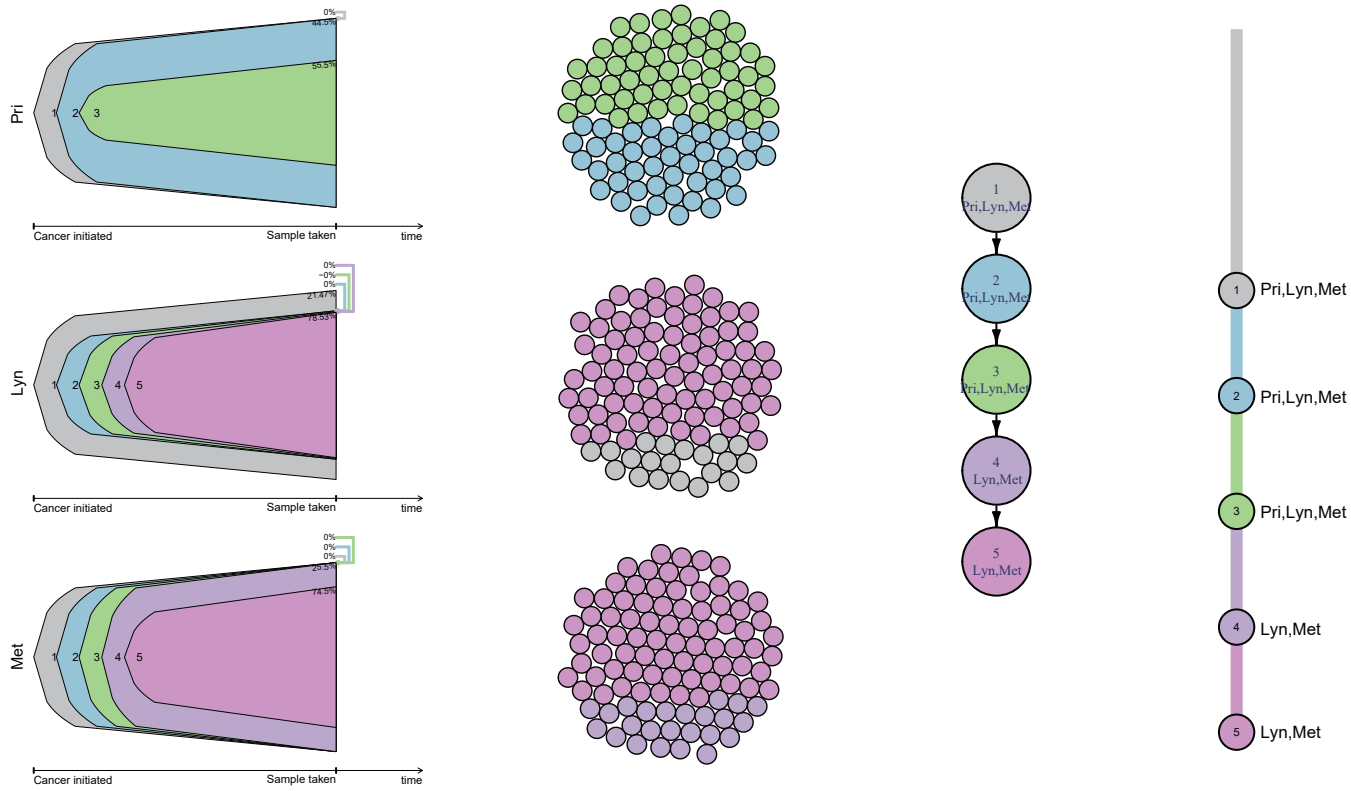
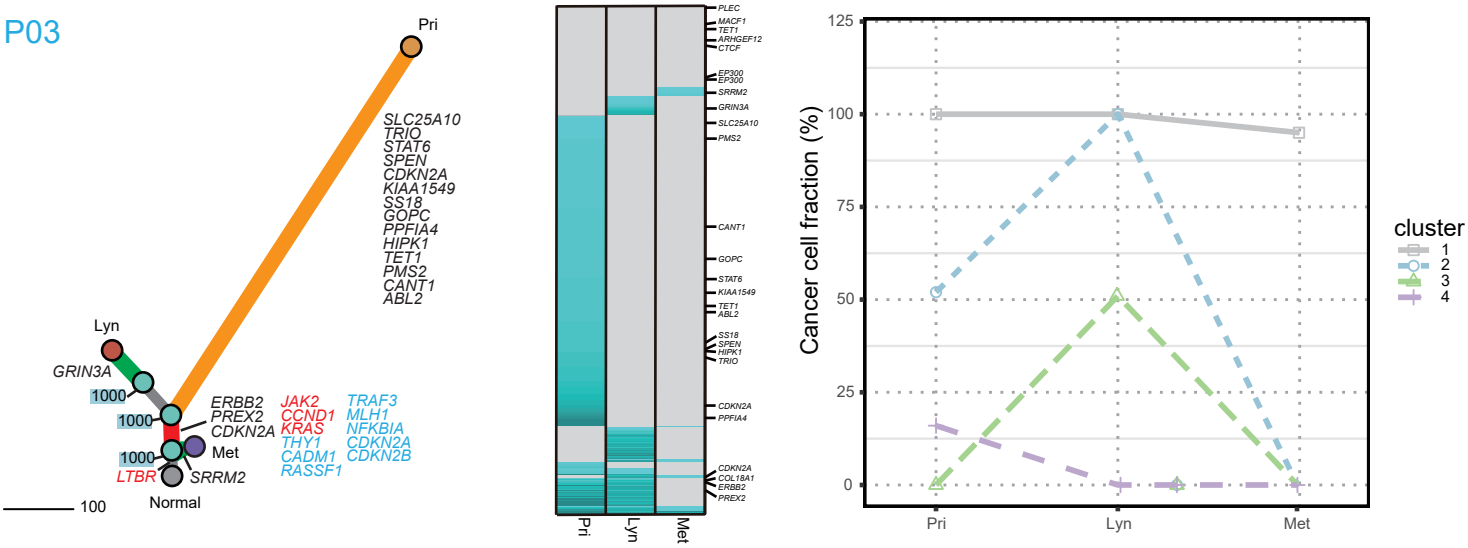


- 1: KMT2C;FANCA;ARID1A;ARID1B;LRP1B
- 2: Amp_TP53;Del_ARID1A;Del_CDKN2A;Del_MLH1;Del_RASSF1 Amp_ATG13;Del_JAK2;Del_CDKN2B;
- 3: NULL
- 4: NULL
- 5: NULL

- Unique location
- Multiple location

c



- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

Cancer cell fraction

0% 100% Unavailable

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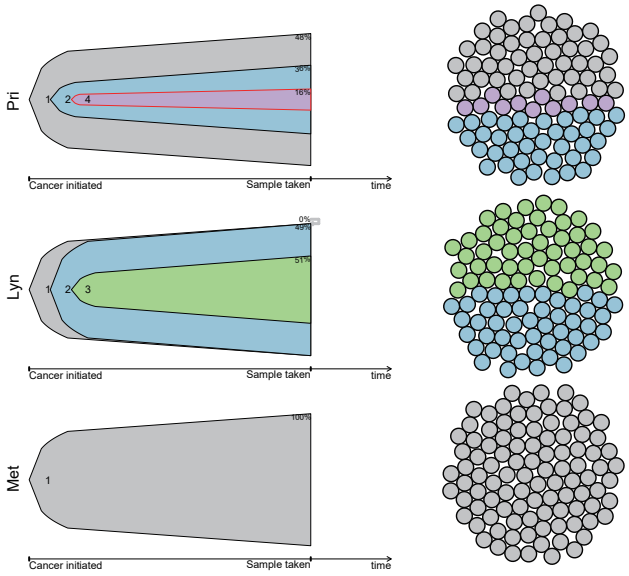
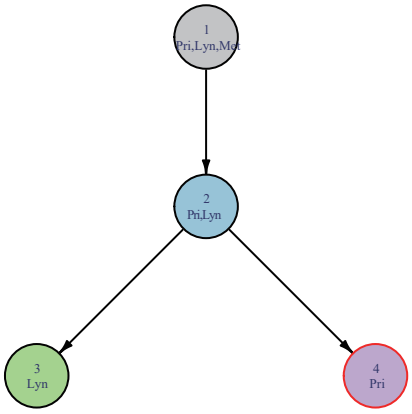
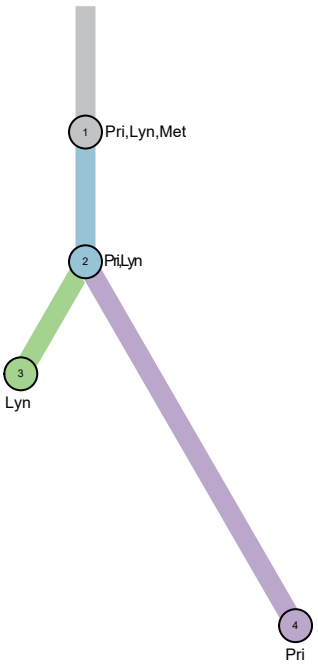
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch





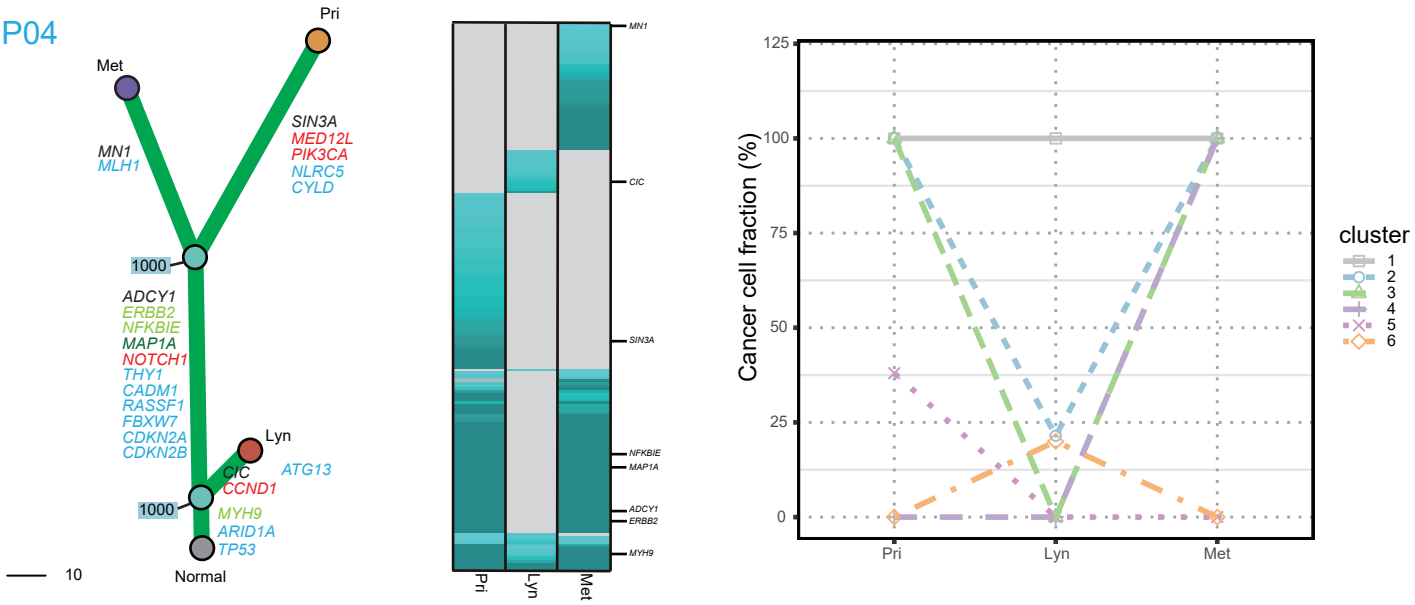


- Unique location
- Multiple location

- 1: NULL
- 2: Amp_CCND1;Amp_JAK2;Del_CADM1;Del_NOTCH1;Del_RASSF1 Del_CDKN2B;
- 3: NULL
- 4: CTCF;HIPK1;KIAA1549;ABL2;EP300 PMS2;STAT6;SLC25A10;GOPC;PPFIA4 PLEC;

Del_CDKN2A;Del_THY1;Del_MLH1;Del_NFKBIA;Amp_KRAS
SRRM2;SPEN;SS18;MACF1;ARHGEF12 CANT1;TRIO;CDKN2A;AHNAK2;TET1

d



Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node

Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA

Cancer cell fraction
0% 100% Unavailable

TP53 Clonal mutated gene in all samples of this branch
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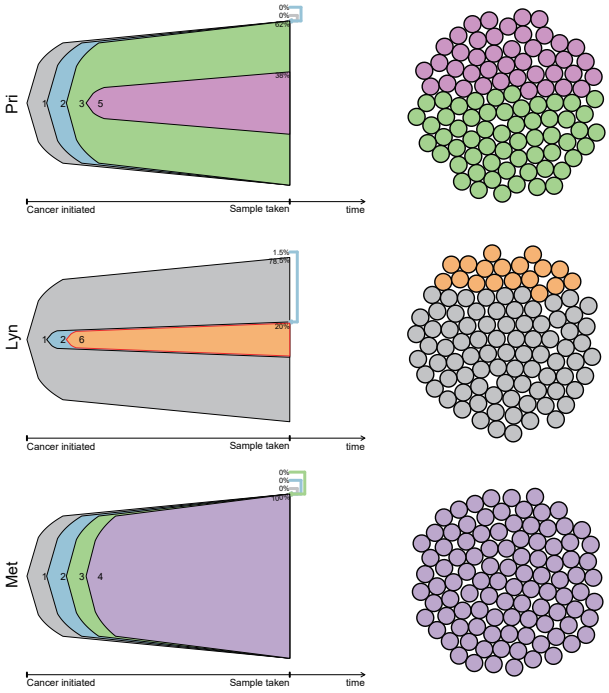
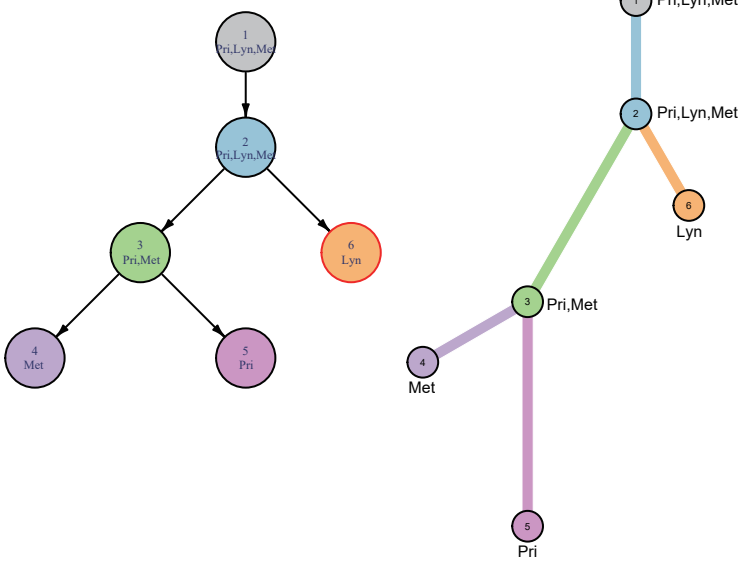
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch





1: Del_ARID1A
2: ERBB2;MYH9;NFKBIE
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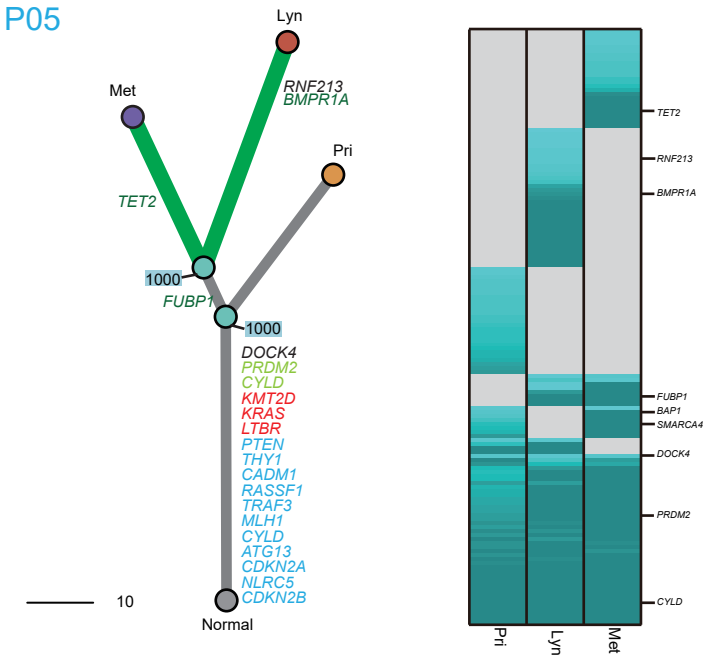
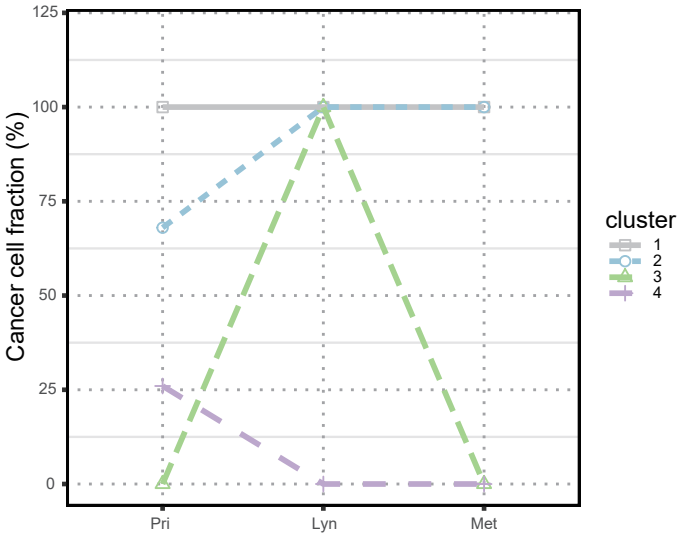
4: Del_MLH1
5: NULL
6: NULL

Unique location
Multiple location

e





- Primary tumor
- Progressed tumor
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- Distant metastasis
- Evolution node

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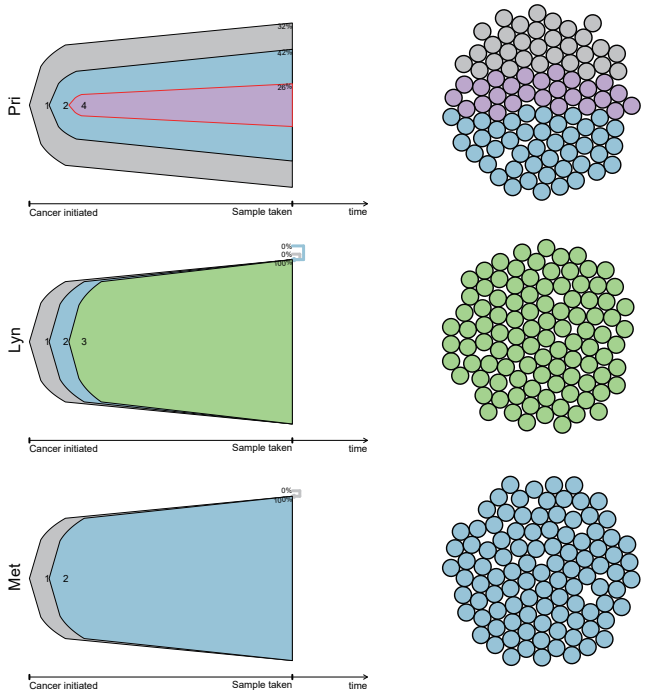
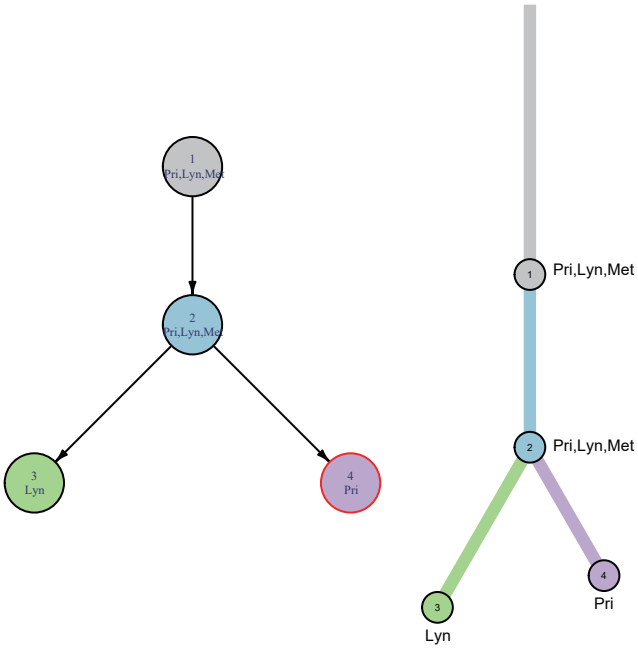
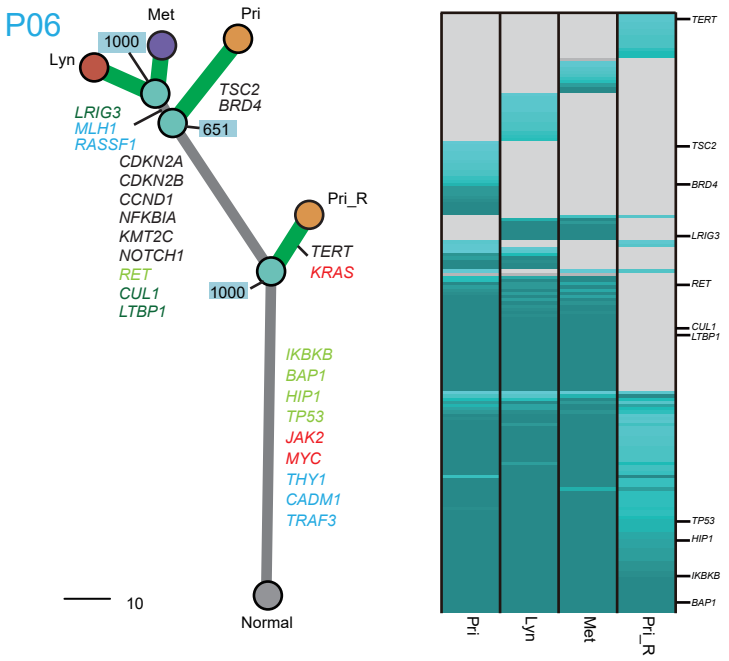


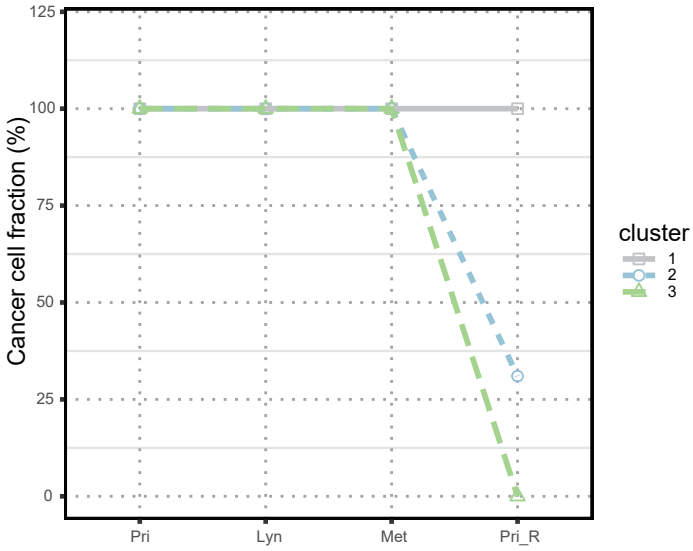


- 1: Del_CDKN2A;Del_NLRC5;Amp_LTBR;Amp_KRAS;Del_CADM1 Del_CYLD;Del_CDKN2B;Del_PTEN;CYLD;Amp_KMT2D Del_THY1;Del_MLH1;Del_RASSF1;Del_TRAF3;Del_JAK2 Del_ATG13;
- 2: PRDM2
- 3: Del_NOTCH1
- 4: NULL

- Unique location
- Multiple location

f





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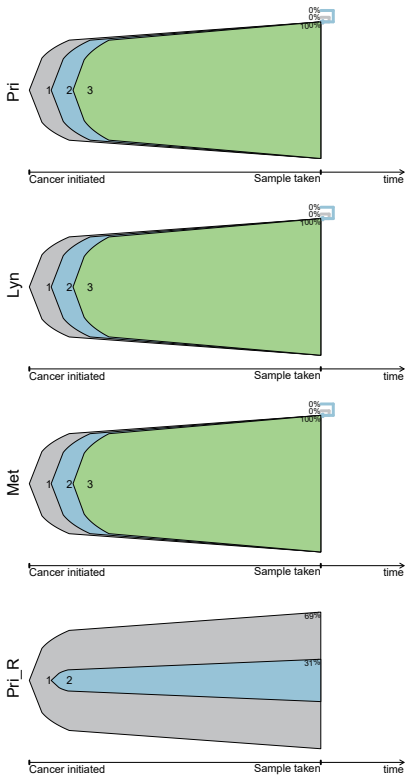
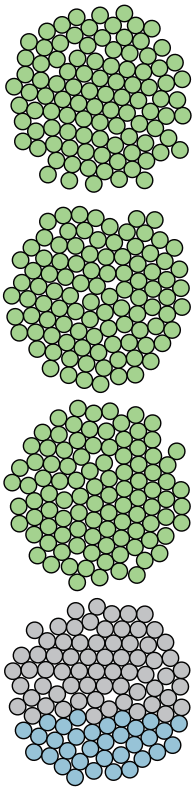
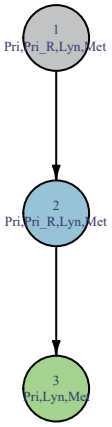
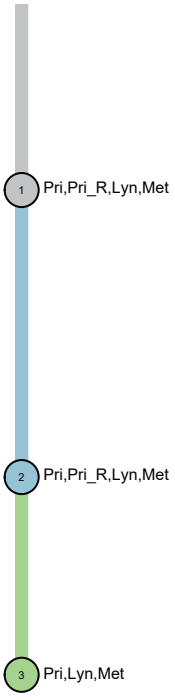
TP53	Deleted gene in all samples of this branch





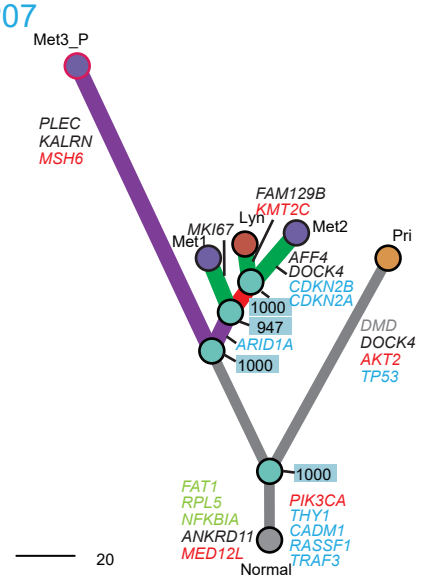


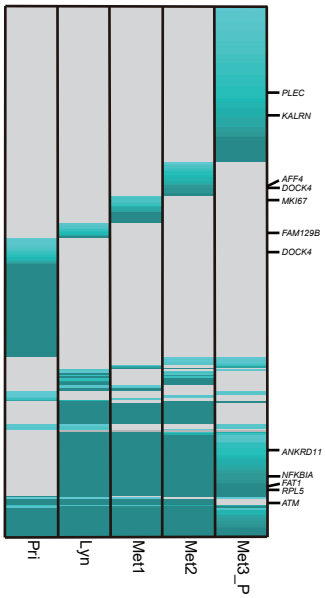


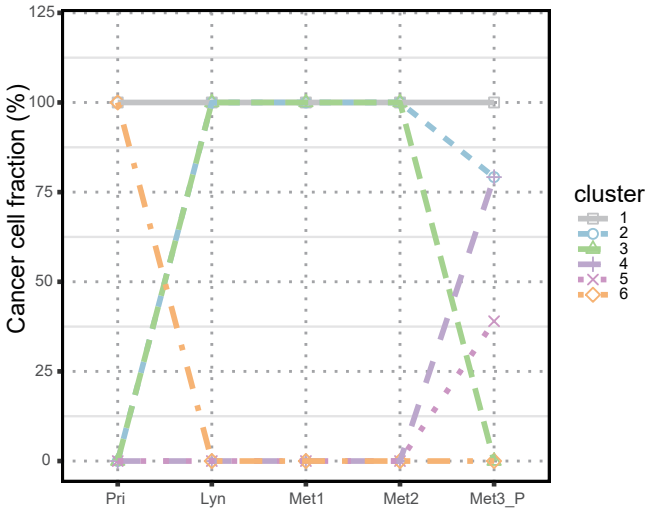
1: IKBKB;Del_AKT2;Amp_MYC;Del_TRAF3;BAP1
2: LTBP1
3: Del_NFKBIA;Amp_CCND1;Del_NOTCH1;CUL1;Del_KMT2C Amp_CDKN2A;Amp_CDKN2B;

Unique location
Multiple location

g P07







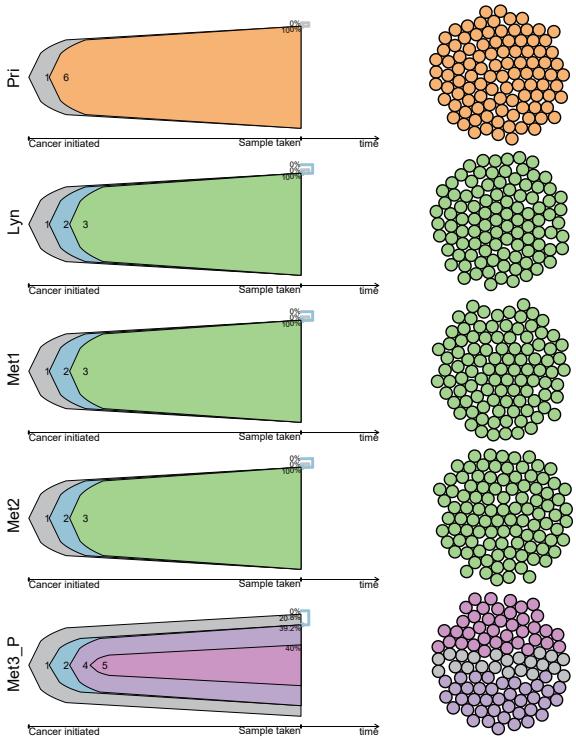
- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

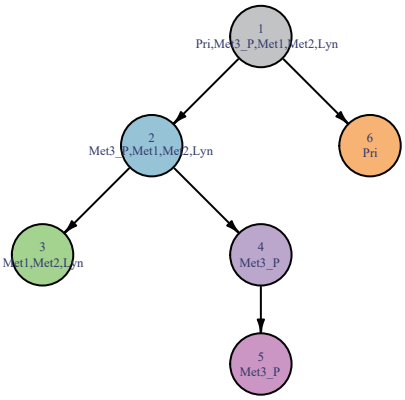
- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

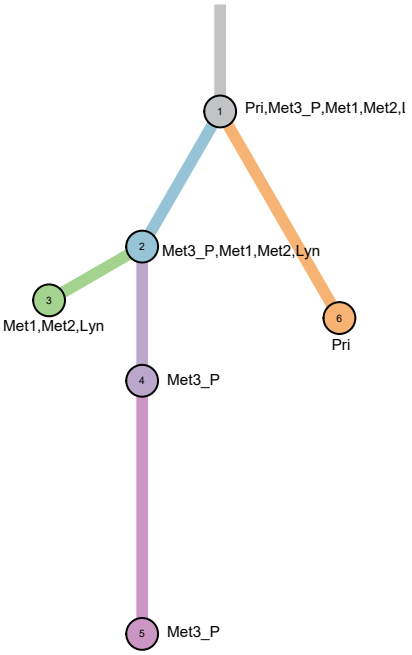
Cancer cell fraction

0% 100% Unavailable

TP53	Clonal mutated gene in all samples of this branch
TP53	Clonal mutated gene in some samples of this branch
TP53	Subclonal mutated gene in all samples of this branch
TP53	Clonality infomation unavailable in some samples of this branch
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch



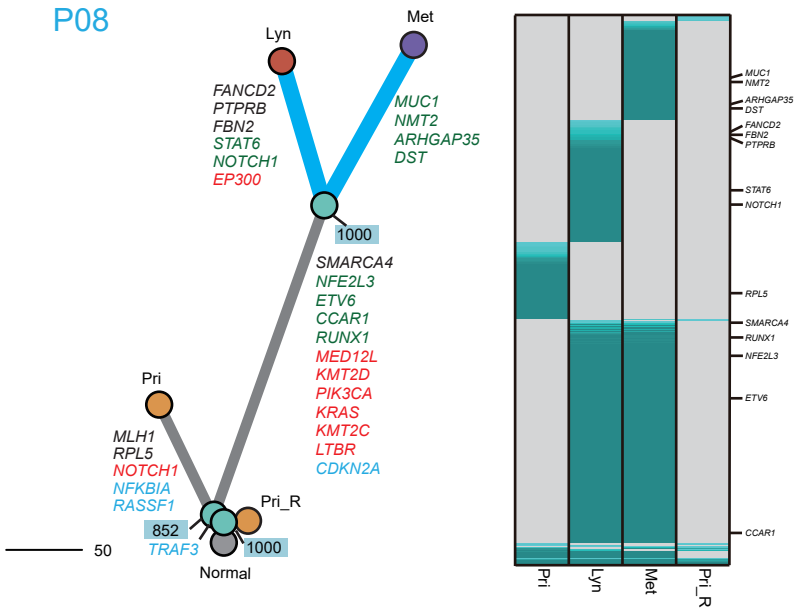


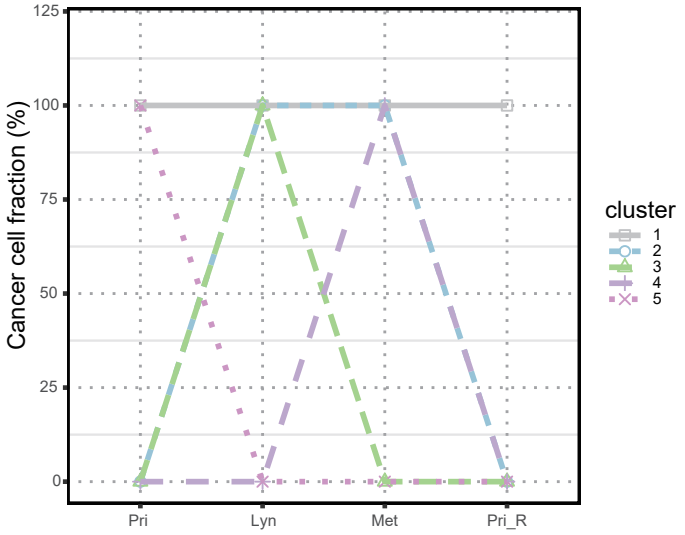


- 1: Del_THY1;Del_CADM1;Amp_MED12L;Del_RASSF1;Del_TRAF3 Amp_PIK3CA;
- 2: NFKBIA;ANKRD11
- 3: Del_ARID1A
- 4: Del_AKT2;Del_NOTCH1;Amp_CDKN2A;Amp_CDKN2B;Amp_MSH6
- 5: KALRN;PLEC
- 6: Amp_AKT2;Del_JAK2;Del_TP53

- Unique location
- Multiple location

h



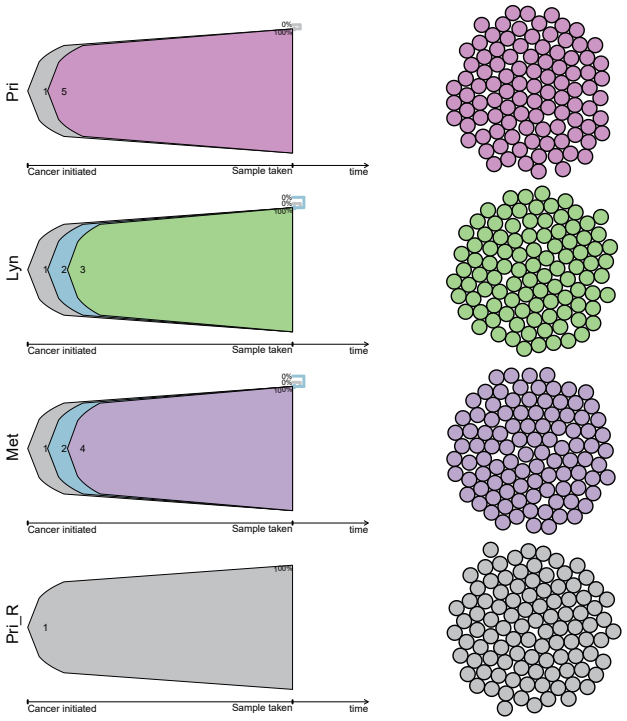


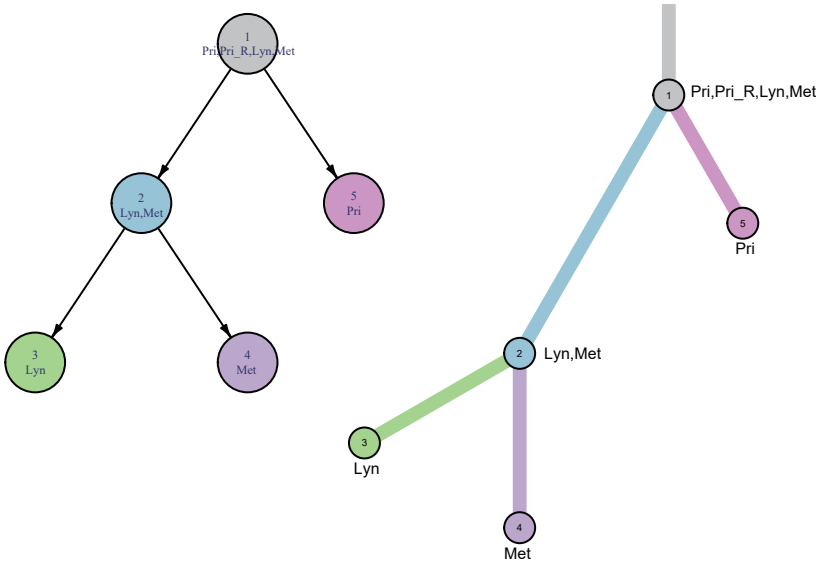
Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node

Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA

Cancer cell fraction
0% 100% Unavailable

TP53 Clonal mutated gene in all samples of this branch
TP53 Clonal mutated gene in some samples of this branch
TP53 Subclonal mutated gene in all samples of this branch
TP53 Clonality infomation unavailable in some samples of this branch
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch





1: NULL

2: Del_CDKN2A;Amp_KMT2D;Amp_KMT2C;Amp_LTBR;Amp_KRAS Amp_MED12L;NFE2L3;Amp_PTEN;Amp_PIK3CA;CCAR1 ETV6;RUNX1;

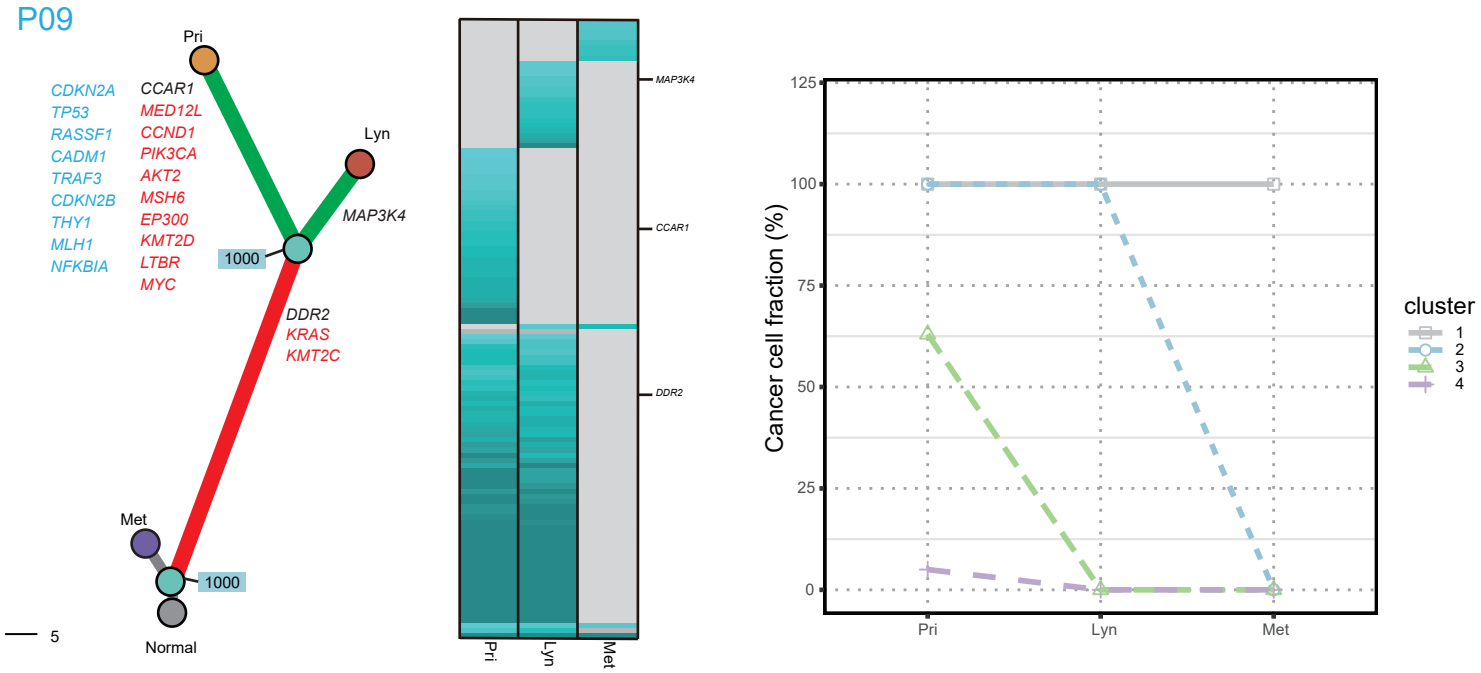
3: NOTCH1;Amp_EP300;STAT6;Del_JAK2

4: MUC1;DST;NMT2;ARHGAP35

5: RPL5;Amp_NOTCH1;Del_MLH1;Del_NFKBIA;Del_RASSF1

Unique location
Multiple location

i

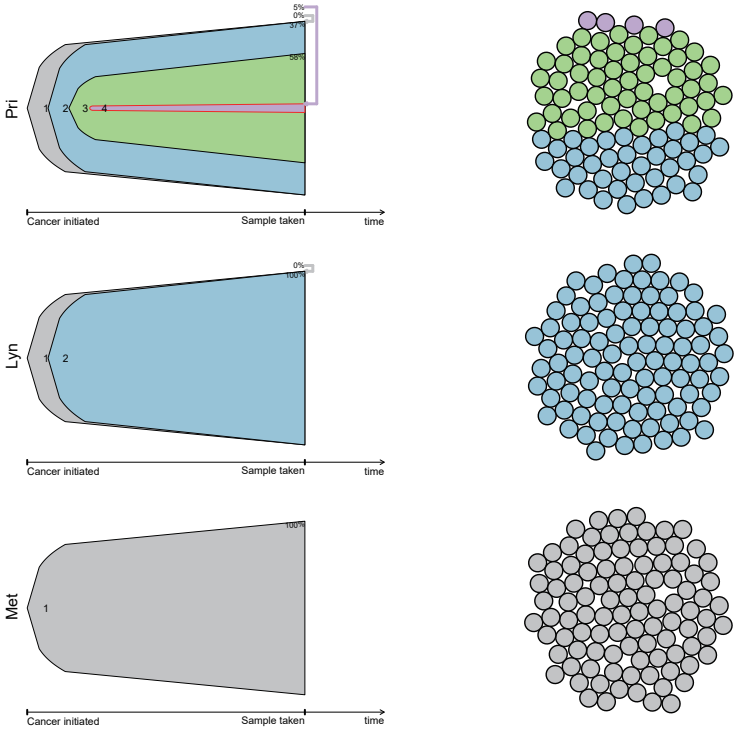


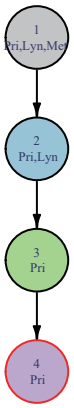
Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node

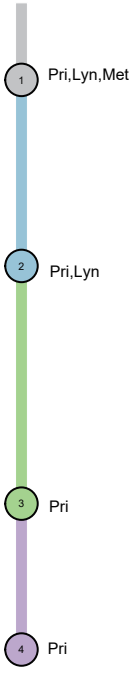
Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA

Cancer cell fraction
0% 100% Unavailable

TP53 Clonal mutated gene in all samples of this branch
TP53 Clonal mutated gene in some samples of this branch
TP53 Subclonal mutated gene in all samples of this branch
TP53 Clonality infomation unavailable in some samples of this branch
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch



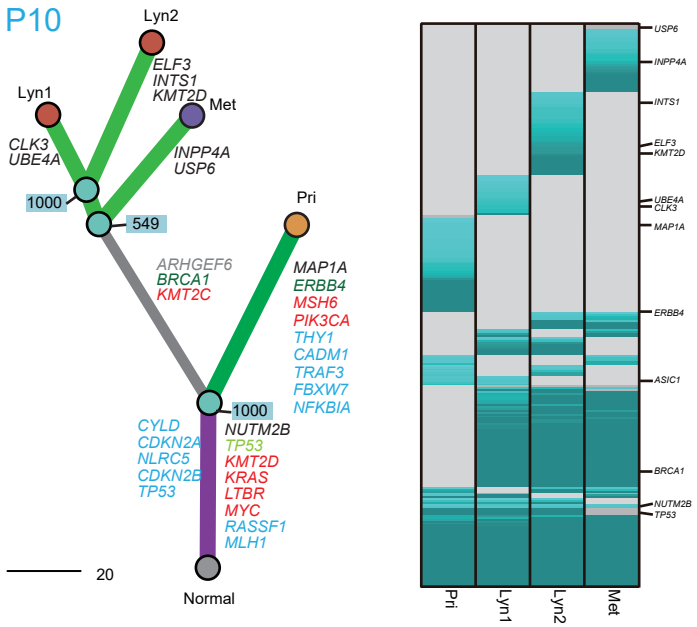


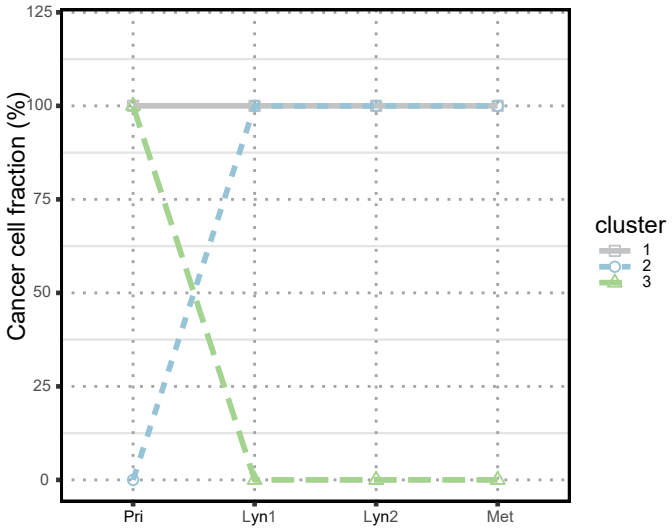


1: NULL
2: NULL
3: Del_CDKN2A;Amp_LTBR;Amp_EP300;Amp_CCND1;Del_CADM1
Amp_AKT2;Amp_ATG13;Del_CDKN2B;Amp_KMT2D;Del_THY1
Del_MLH1;Del_NFKBIA;Amp_MED12L;Amp_MYC;Del_RASSF1
Del_TRAF3;Del_TP53;Amp_PIK3CA;Amp_MSH6;
4: NULL

Unique location
Multiple location

j



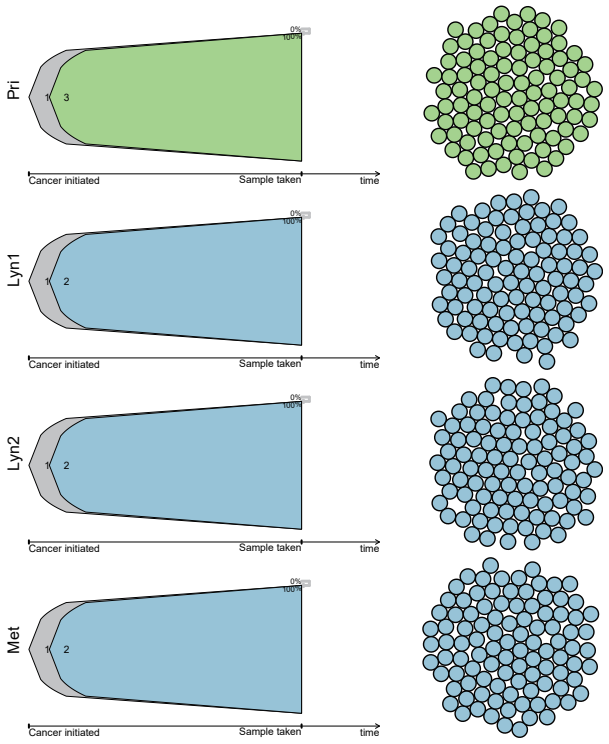


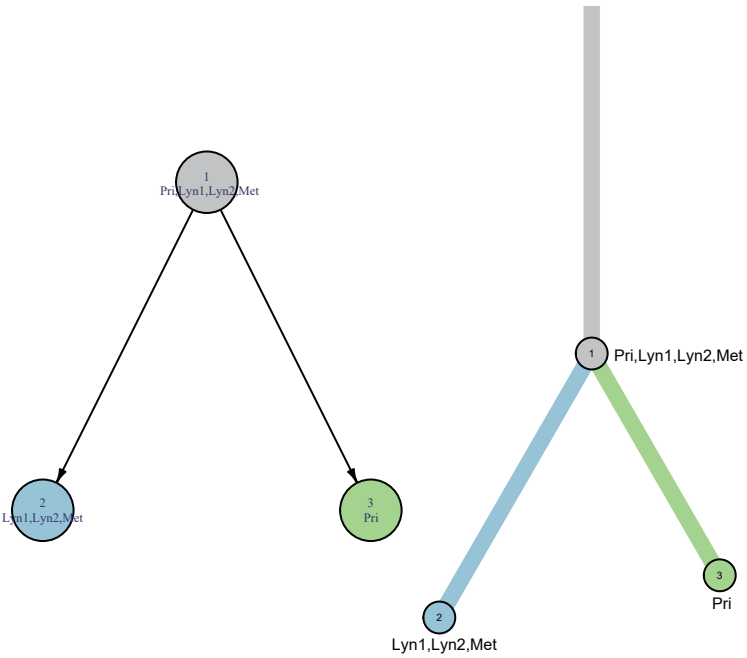
Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node

Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA

Cancer cell fraction
0% 100% Unavailable

TP53 Clonal mutated gene in all samples of this branch
TP53 Clonal mutated gene in some samples of this branch
TP53 Subclonal mutated gene in all samples of this branch
TP53 Clonality infomation unavailable in some samples of this branch
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch



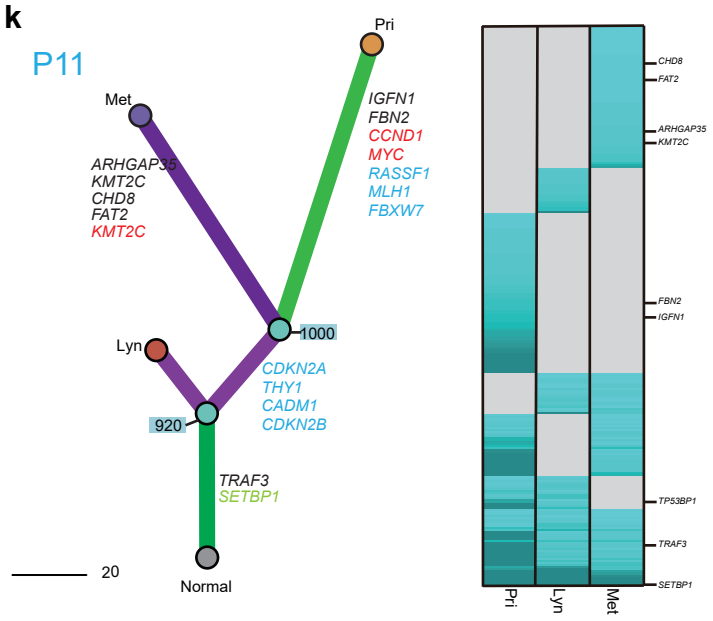


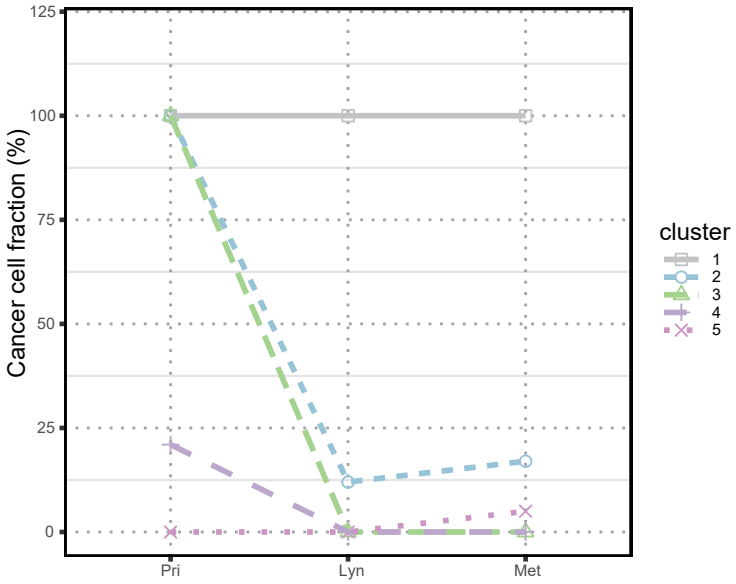
1: Del_CDKN2A;Amp_KMT2D;Del_NLRC5;Amp_LTBR;Del_MLH1 Amp_KRAS;Del_RASSF1;Del_CYLD;Del_JAK2;Del_TP53 Del_CDKN2B;

2: Amp_KMT2C;BRCA1

3: Del_THY1;Del_FBXW7;Del_NFKBIA;ERBB4;Del_CADM1 Del_NOTCH1;Amp_MYC;Del_TRAF3;Amp_PIK3CA;Amp_MSH6

Unique location
Multiple location





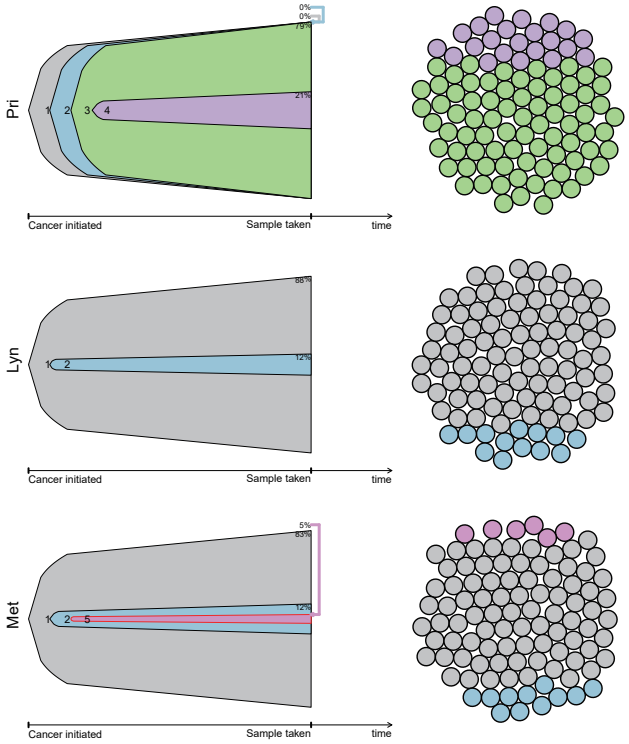
- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

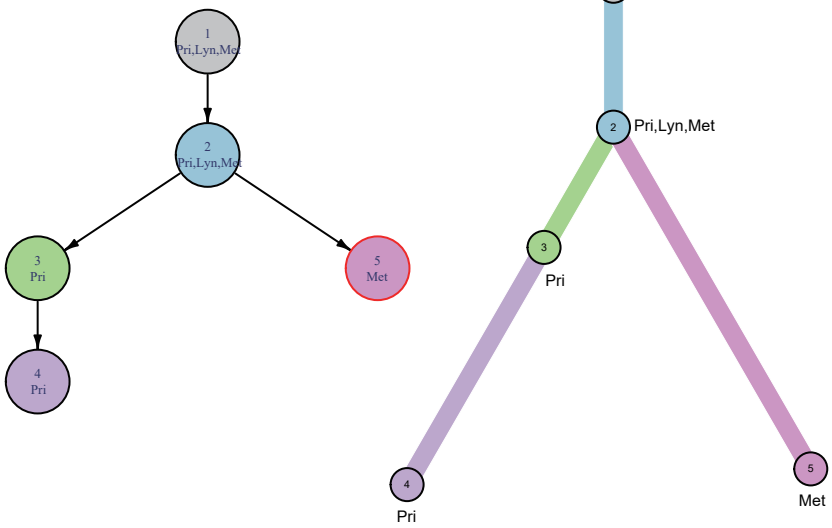
- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

Cancer cell fraction

0% 100% Unavailable

TP53	Clonal mutated gene in all samples of this branch
TP53	Clonal mutated gene in some samples of this branch
TP53	Subclonal mutated gene in all samples of this branch
TP53	Clonality infomation unavailable in some samples of this branch
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch

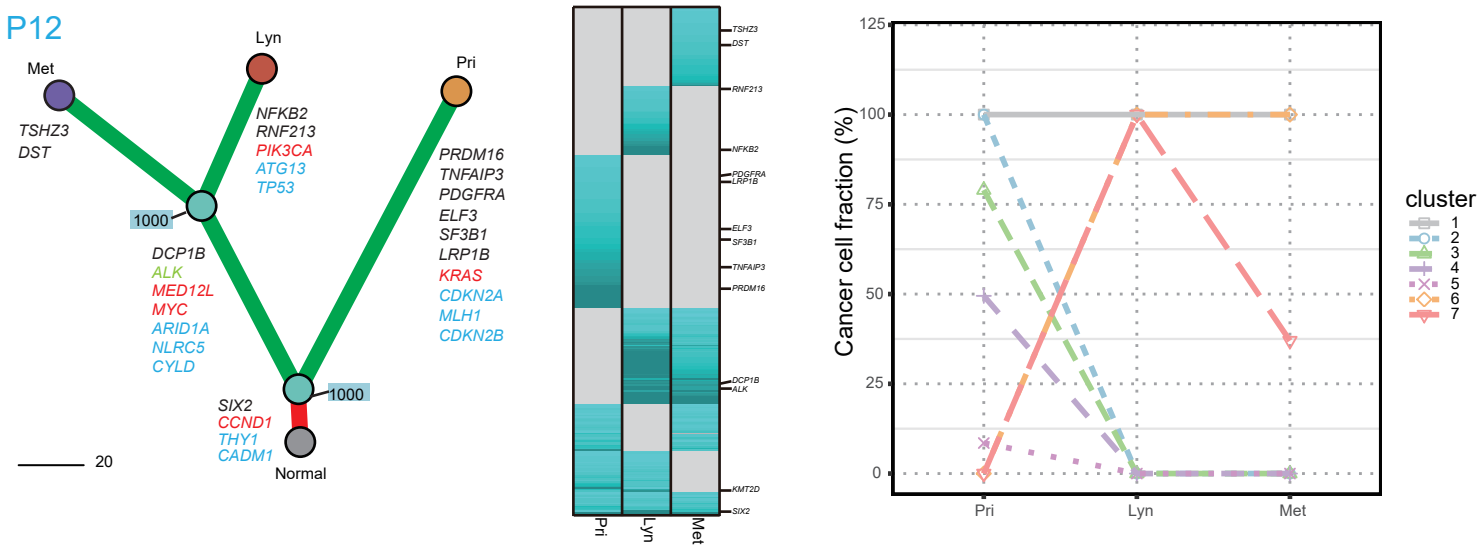




- 1: SETBP1
- 2: TRAF3
- 3: NULL
- 4: FBN2;Del_FBXW7;Del_MLH1;Amp_CCND1;Del_NOTCH1 Amp_MYC;Del_RASSF1;Amp_ARID1A;Amp_ATG13;IGFN1
- 5: CHD8;KMT2C;FAT2;ARHGAP35

- Unique location
- Multiple location

I



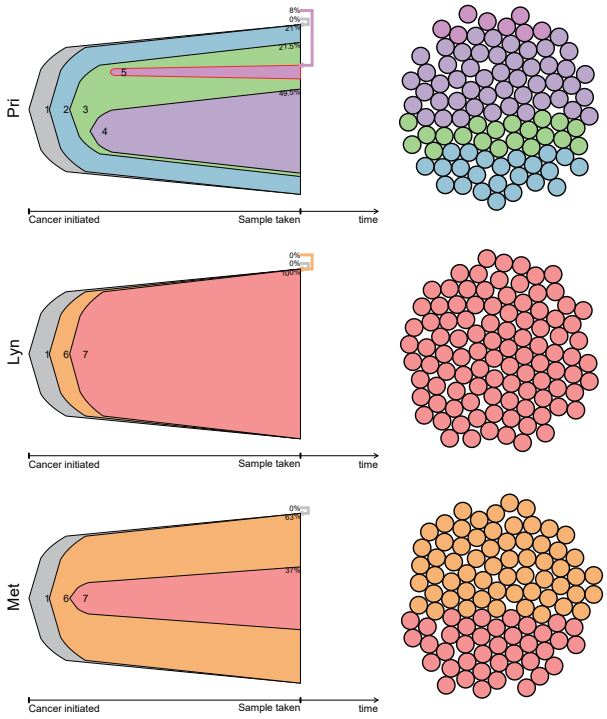
- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

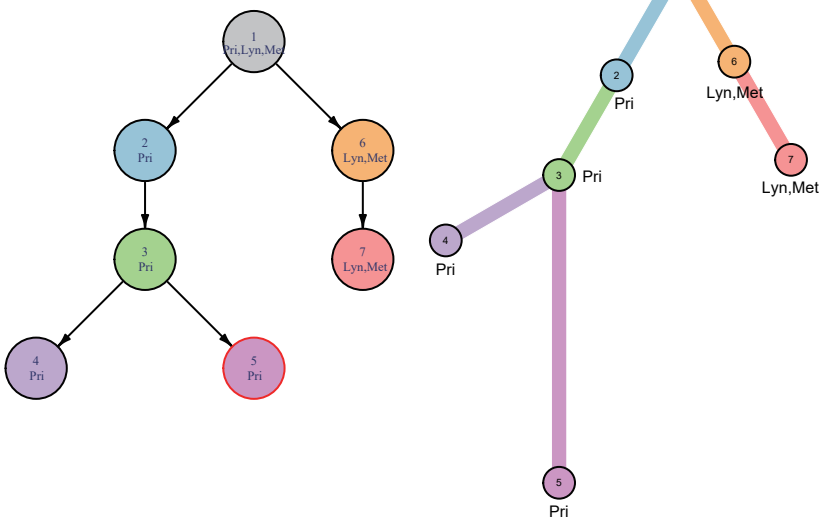
- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

Cancer cell fraction

0% 100% Unavailable

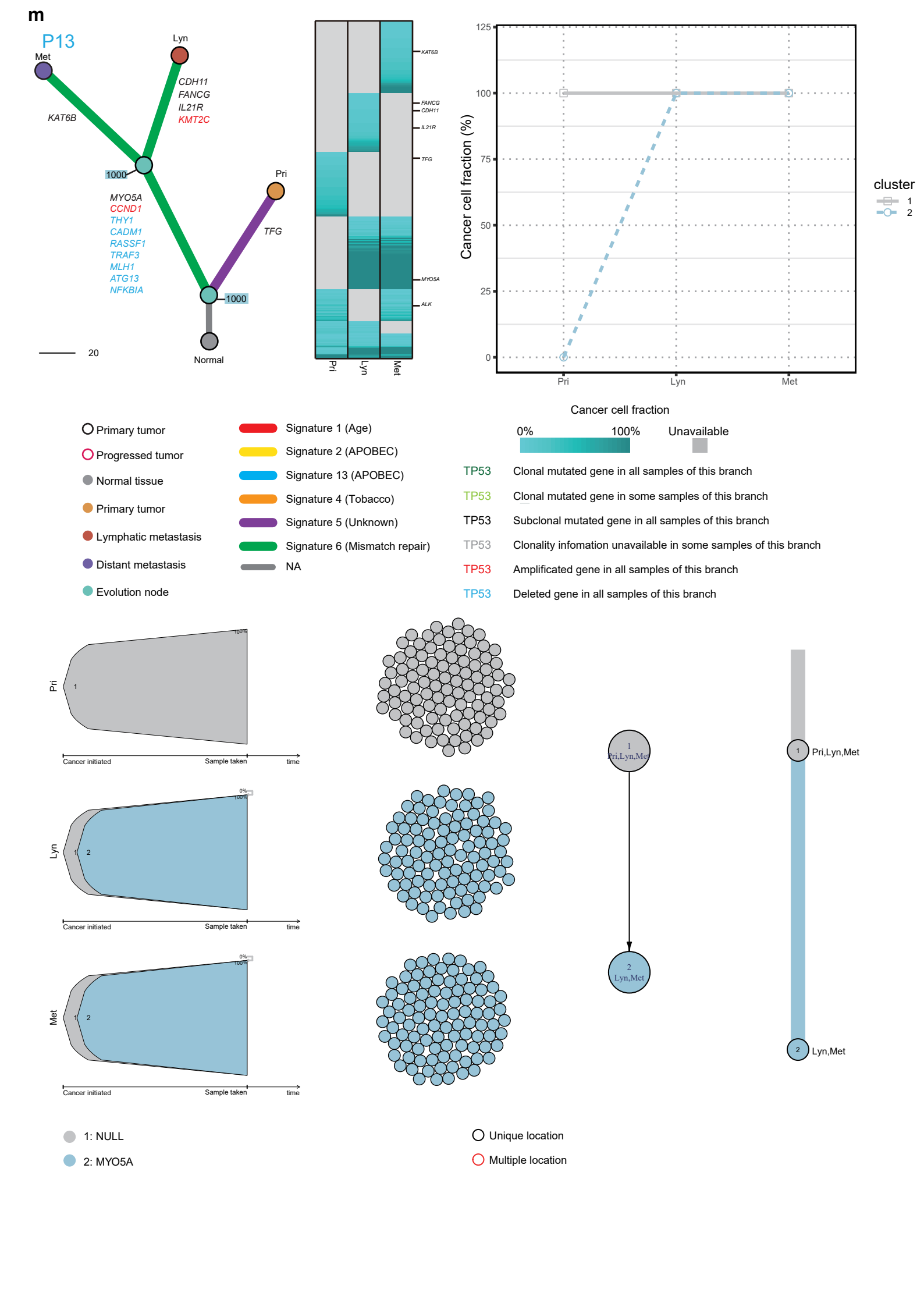
TP53	Clonal mutated gene in all samples of this branch
TP53	Clonal mutated gene in some samples of this branch
TP53	Subclonal mutated gene in all samples of this branch
TP53	Clonality infomation unavailable in some samples of this branch
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch



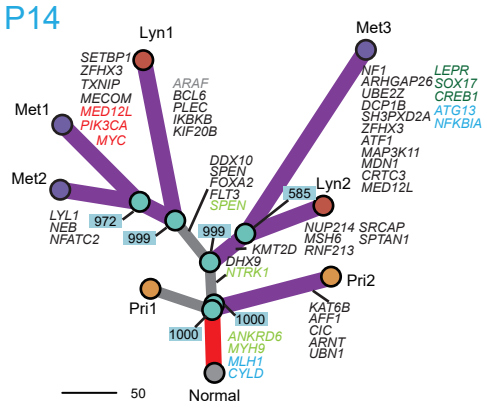


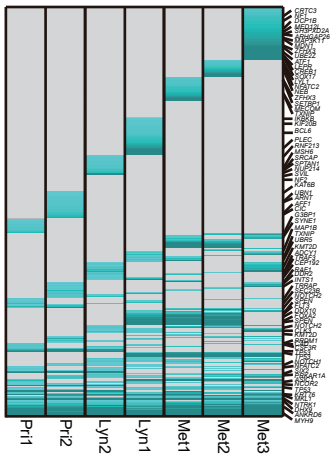
- 1: Del_THY1;Del_CADM1
- 2: Del_CDKN2A;Del_MLH1;Amp_KRAS;PRDM16;Del_CDKN2B
- 3: TNFAIP3
- 4: ELF3;SF3B1
- 5: PDGFRA;RNF213;TSHZ3;DST;AHNAK2 LRP1B;
- 6: Del_ARID1A;Del_NLRC5;Amp_MED12L;Amp_MYC;Del_CYLD
- 7: NULL

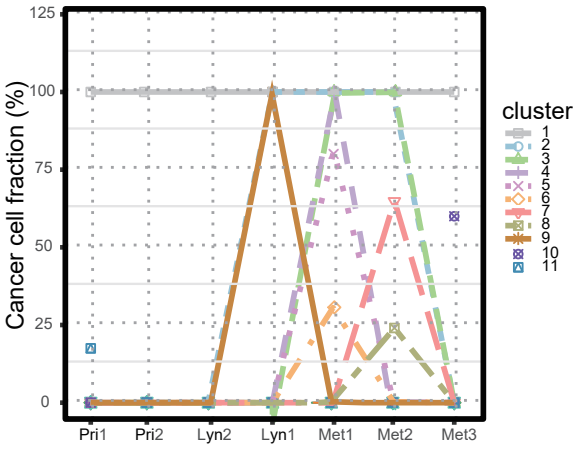
- Unique location
- Multiple location


m
P13
Met
Lyn
Pri
Normal
KAT6B
CDH11
FANCG
IL21R
KMT2C
1000
MYO5A
CCND1
THY1
CADM1
RASSF1
TRAF3
MLH1
ATG13
NFKBIA
TFG
1000
20
KAT6B
FANCG
CDH11
IL21R
TFG
MYO5A
ALK
Pri
Lyn
Met
Cancer cell fraction (%)
125
100
75
50
25
0
Pri
Lyn
Met
cluster
1
2
Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node
Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA
Cancer cell fraction
0%
100%
Unavailable
TP53 Clonal mutated gene in all samples of this branch
TP53 Clonal mutated gene in some samples of this branch
TP53 Subclonal mutated gene in all samples of this branch
TP53 Clonality infomation unavailable in some samples of this branch
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch
Pri
Lyn
Met
Cancer initiated
Sample taken
time
1
2
1: NULL
2: MYO5A
1
Pri,Lyn,Met
2
Lyn,Met
Pri,Lyn,Met
Lyn,Met
Unique location
Multiple location

n







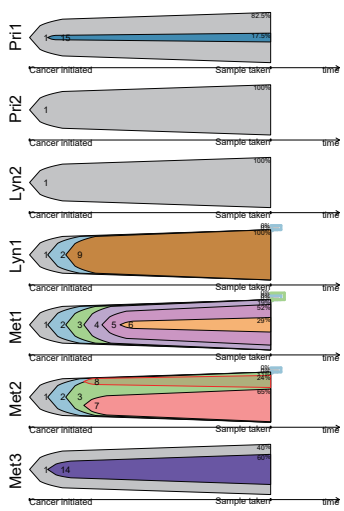
- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

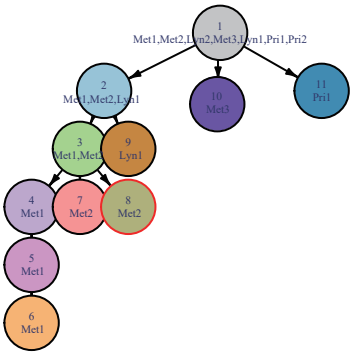
- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

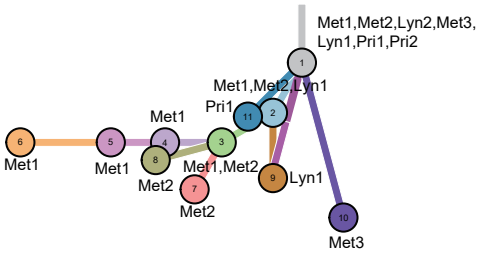
Cancer cell fraction

0% 100% Unavailable

TP53	Clonal mutated gene in all samples of this branch
TP53	Clonal mutated gene in some samples of this branch
TP53	Subclonal mutated gene in all samples of this branch
TP53	Clonality infomation unavailable in some samples of this branch
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch

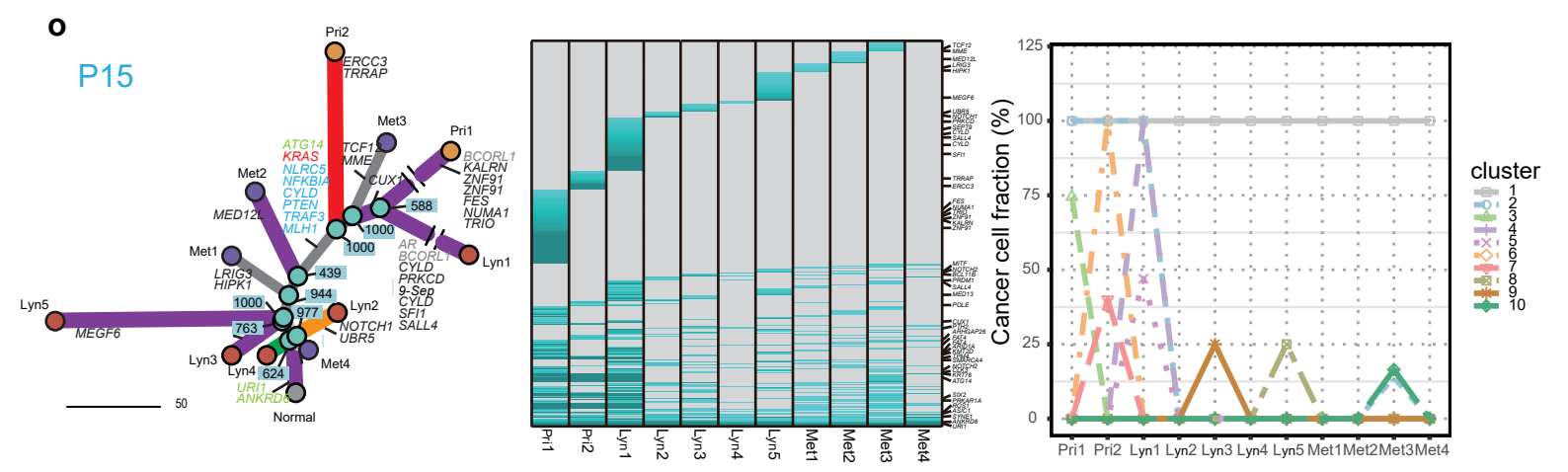






- 1: NULL
- 2: SPEN
- 3: NULL
- 4: Amp_MED12L;Amp_MYC;Del_EP300;Amp_PIK3CA
- 5: NULL
- 6: SETBP1;MECOM
- 7: NULL
- 8: LYL1
- 9: NULL
- 10: ATF1;ZFHX3;CRTC3;CAD;UBE2Z ARHGAP26;MED12L;Del_NFKBIA;CREB1;SH3PXD2A SOX17;Del_CCND1;NF1;Del_ATG13;MAP3K11 MDN1;
- 11: NULL

- Unique location
- Multiple location

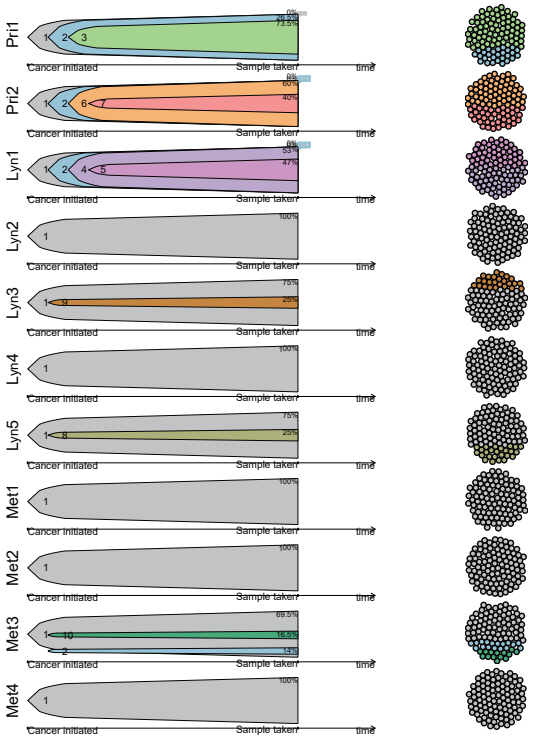


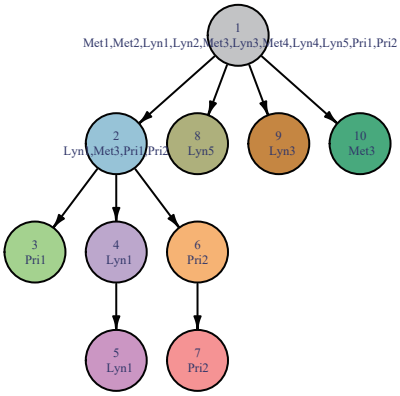
Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node

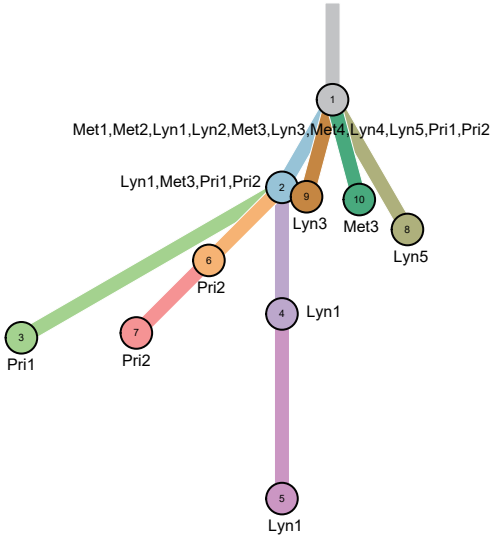
Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA

Cancer cell fraction
0% 100% Unavailable

TP53 Clonal mutated gene in all samples of this branch
TP53 Clonal mutated gene in some samples of this branch
TP53 Subclonal mutated gene in all samples of this branch
TP53 Clonality infomation unavailable in some samples of this branch
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch



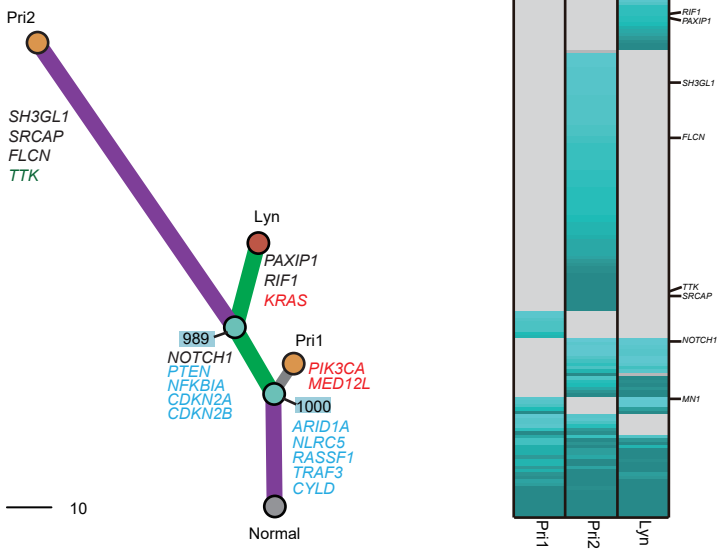


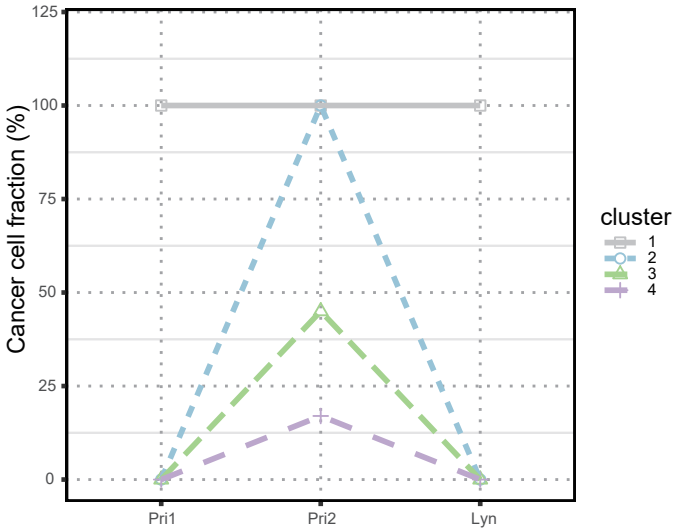


1: NULL
2: Del_PTEN;Del_NLRC5;Del_MLH1;Del_NFKBIA;Amp_KRAS TPM4;Del_CYLD;Del_KMT2C;ATG14;
3: ZNF91;TRIO;NUMA1;FES;Del_NOTCH1 AHNAK2;FAT4;KALRN;
4: NULL
5: CYLD;SEPT9;SALL4;PRKCD
6: ERCC3
7: TRRAP
8: NOTCH2
9: NULL
10: NULL

Unique location
Multiple location

p P16





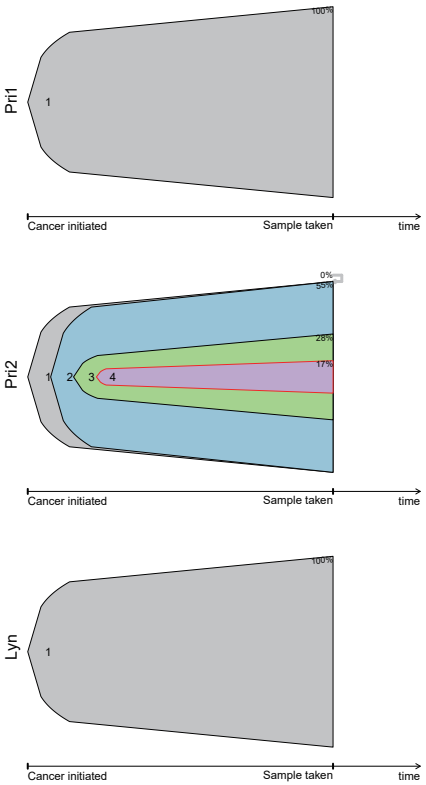
- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

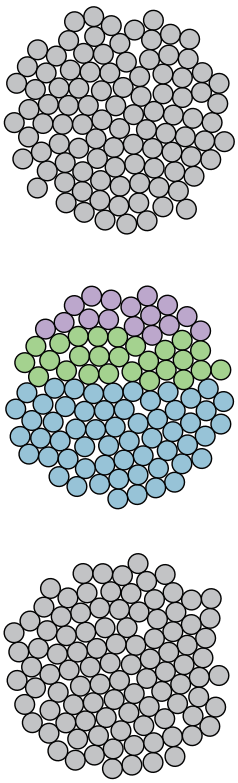
- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

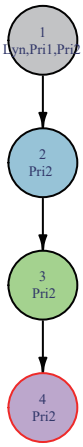
Cancer cell fraction

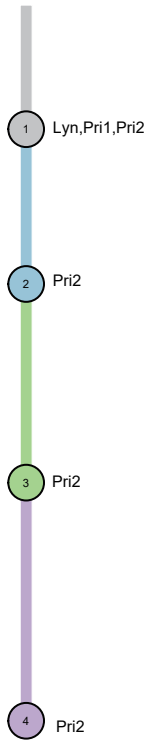
0% 100% Unavailable

TP53	Clonal mutated gene in all samples of this branch
TP53	Clonal mutated gene in some samples of this branch
TP53	Subclonal mutated gene in all samples of this branch
TP53	Clonality infomation unavailable in some samples of this branch
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch



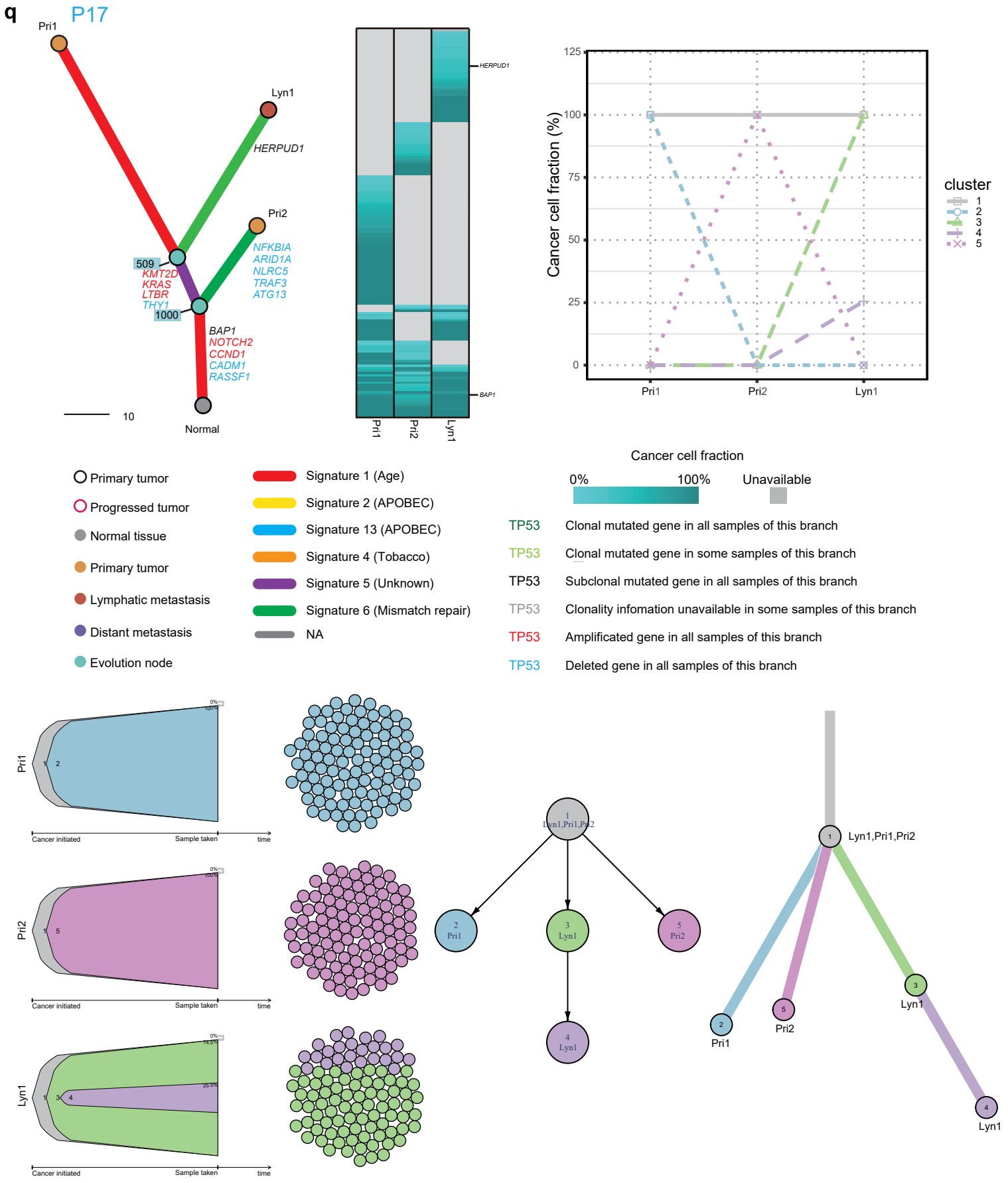




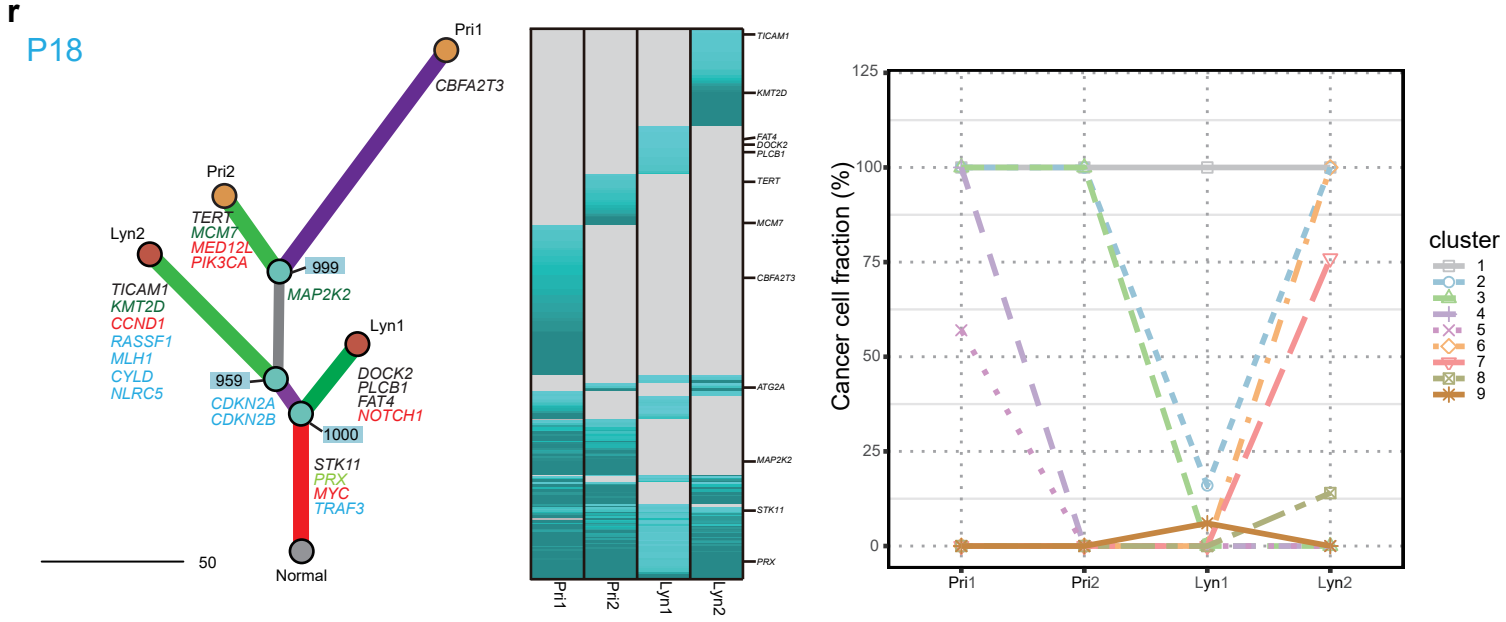


- 1: Del_ARID1A;Del_NLRC5;Del_RASSF1;Del_TRAF3
- 2: Del_CDKN2A;SRCAP;TTK;Del_JAK2;Del_CDKN2B
- 3: FLCN
- 4: SH3GL1;RUNX1

- Unique location
- Multiple location


q
P17
Pri1
Lyn1
HERPUD1
Pri2
509
KMT2D
KRAS
LTBR
THY1
1000
NFKBIA
ARID1A
NLRC5
TRAF3
ATG13
BAP1
NOTCH2
CCND1
CADM1
RASSF1
10
Normal
HERPUD1
BAP1
Pri1
Pri2
Lyn1
Cancer cell fraction (%)
125
100
75
50
25
0
cluster
1
2
3
4
5
Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node
Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA
Cancer cell fraction
0%
100%
Unavailable
TP53 Clonal mutated gene in all samples of this branch
TP53 Clonal mutated gene in some samples of this branch
TP53 Subclonal mutated gene in all samples of this branch
TP53 Clonality infomation unavailable in some samples of this branch
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch
Cancer initiated
Sample taken
time
1: Amp_NOTCH2;Amp_CCND1;Del_CADM1;Del_RASSF1
2: NULL
3: NULL
4: NULL
5: Amp_FBXW7;Del_ARID1A;Del_NLRC5;Del_LTBR;Del_NFKBIA Del_AKT2;Del_KMT2D;Del_NOTCH1;Del_TRAF3;Amp_CDKN2A Amp_CDKN2B;Del_ATG13;
Unique location
Multiple location

r

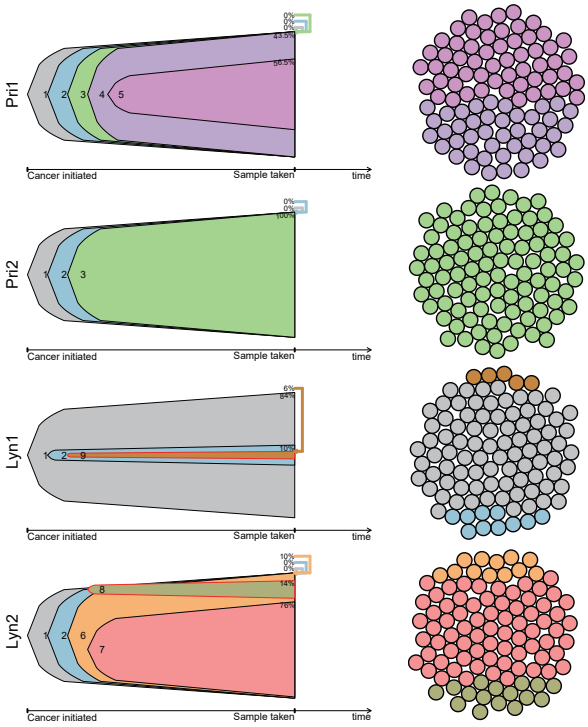


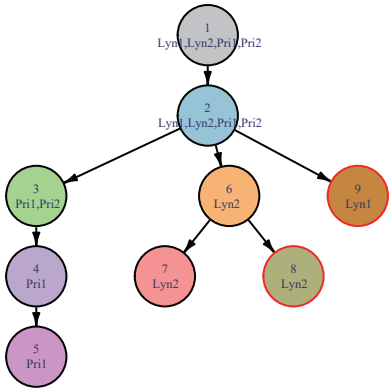
Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node

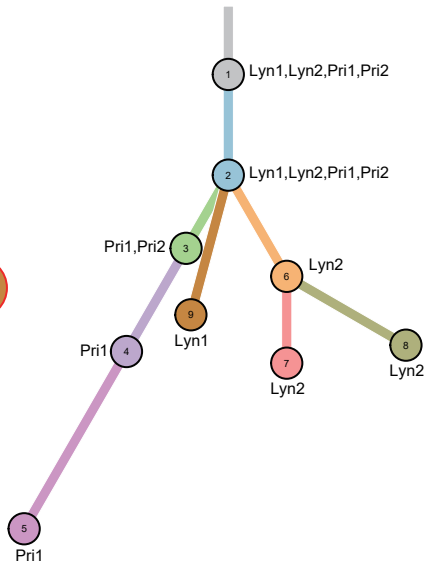
Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA

Cancer cell fraction
0% 100% Unavailable

TP53 Clonal mutated gene in all samples of this branch
TP53 Clonal mutated gene in some samples of this branch
TP53 Subclonal mutated gene in all samples of this branch
TP53 Clonality infomation unavailable in some samples of this branch
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch

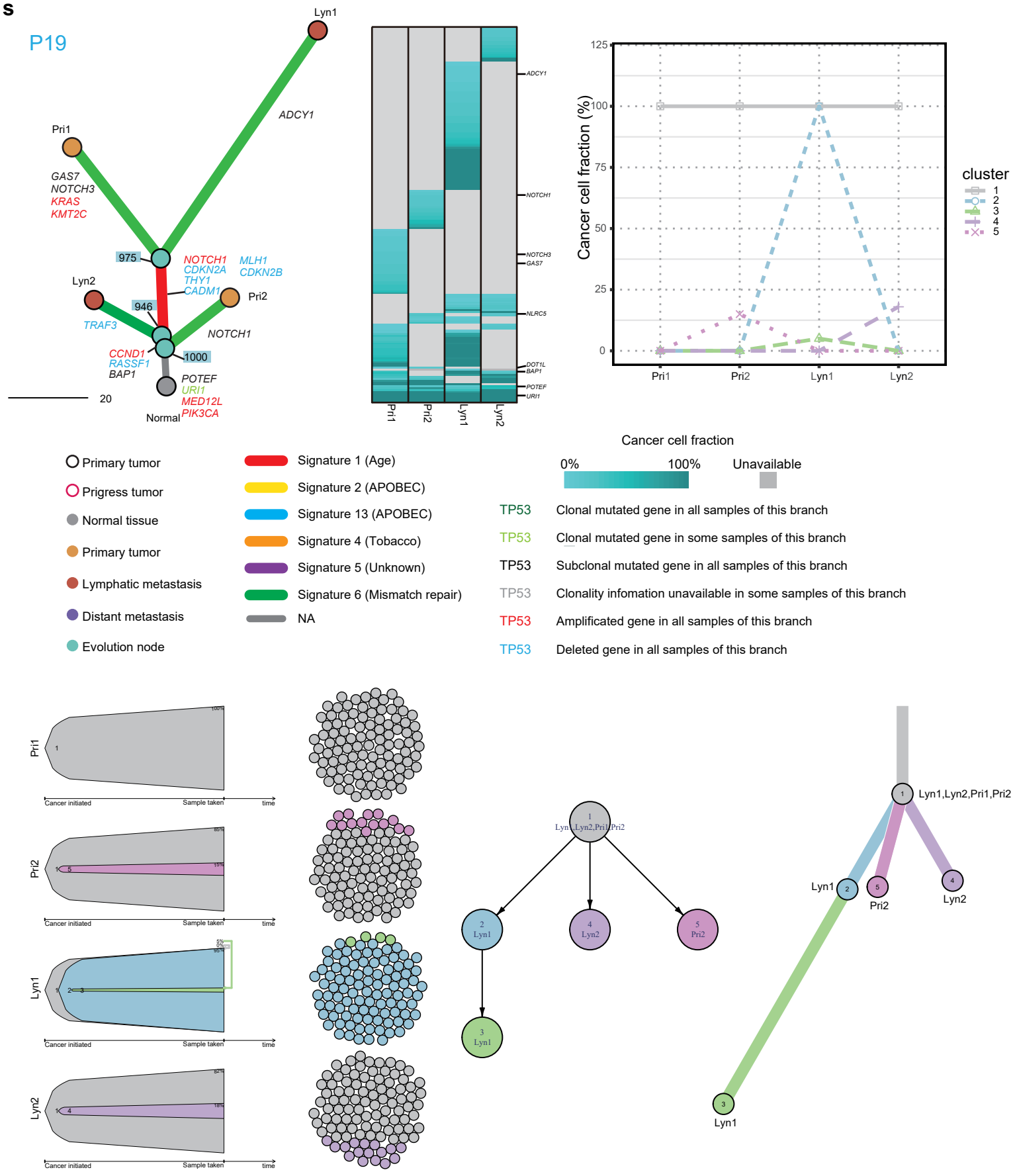




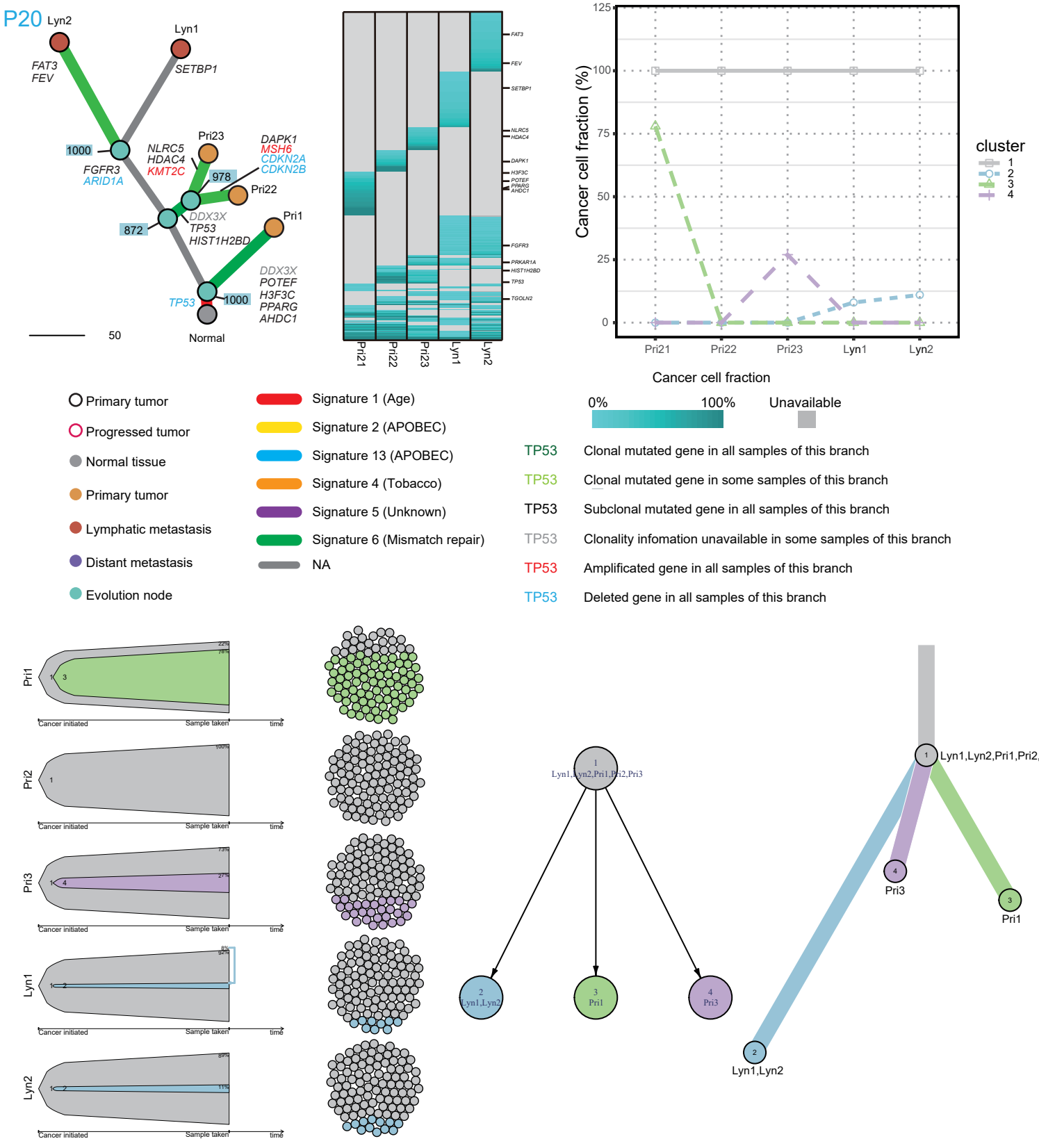


1: NULL
2: PRX
3: MAP2K2
4: Del_JAK2
5: CBFA2T3
6: KMT2D
7: Amp_TP53;Del_NLRC5;Amp_THY1;Del_LTBR;Del_MLH1 Amp_CCND1;Del_RASSF1;Del_CYLD;Del_KMT2C;Amp_CADM1
8: AHNAK;TICAM1
9: Amp_NOTCH1;AHNAK2;FAT4;DOCK2

Unique location
Multiple location


s
P19
Lyn1
ADCY1
Pri1
GAS7
NOTCH3
KRAS
KMT2C
975
NOTCH1
CDKN2A
THY1
CADM1
MLH1
CDKN2B
Lyn2
946
Pri2
TRAF3
NOTCH1
CCND1
RASSF1
BAP1
1000
POTEF
URI1
MED12L
PIK3CA
Normal
20
ADCY1
NOTCH1
NOTCH3
GAS7
NLRC5
DOT1L
BAP1
POTEF
URI1
Pri1
Pri2
Lyn1
Lyn2
Cancer cell fraction (%)
125
100
75
50
25
0
cluster
1
2
3
4
5
Primary tumor
Prigress tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node
Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA
Cancer cell fraction
0%
100%
Unavailable
TP53 Clonal mutated gene in all samples of this branch
TP53 Clonal mutated gene in some samples of this branch
TP53 Subclonal mutated gene in all samples of this branch
TP53 Clonality infomation unavailable in some samples of this branch
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch
Cancer initiated
Sample taken
time
Lyn1,Lyn2,Pri1,Pri2
1: URI1;Amp_MED12L;Amp_PIK3CA
2: NULL
3: NOTCH3;AHNAK;ADCY1;GAS7
4: NULL
5: NOTCH1;DOT1L
Unique location
Multiple location

t



- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

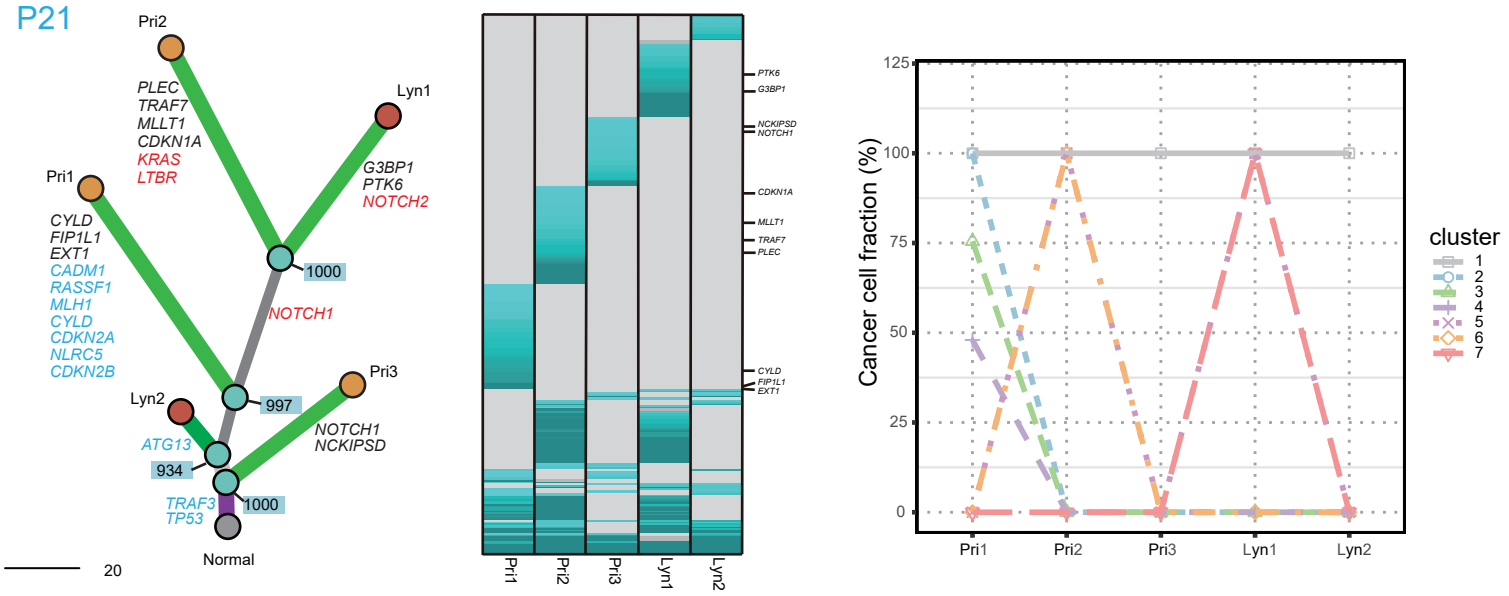
- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

TP53	Clonal mutated gene in all samples of this branch
TP53	Clonal mutated gene in some samples of this branch
TP53	Subclonal mutated gene in all samples of this branch
TP53	Clonality infomation unavailable in some samples of this branch
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch

- 1: Del_TP53
- 2: SETBP1;FEV;FAT3
- 3: PPARG;AHDC1
- 4: NLRC5

- Unique location
- Multiple location

u



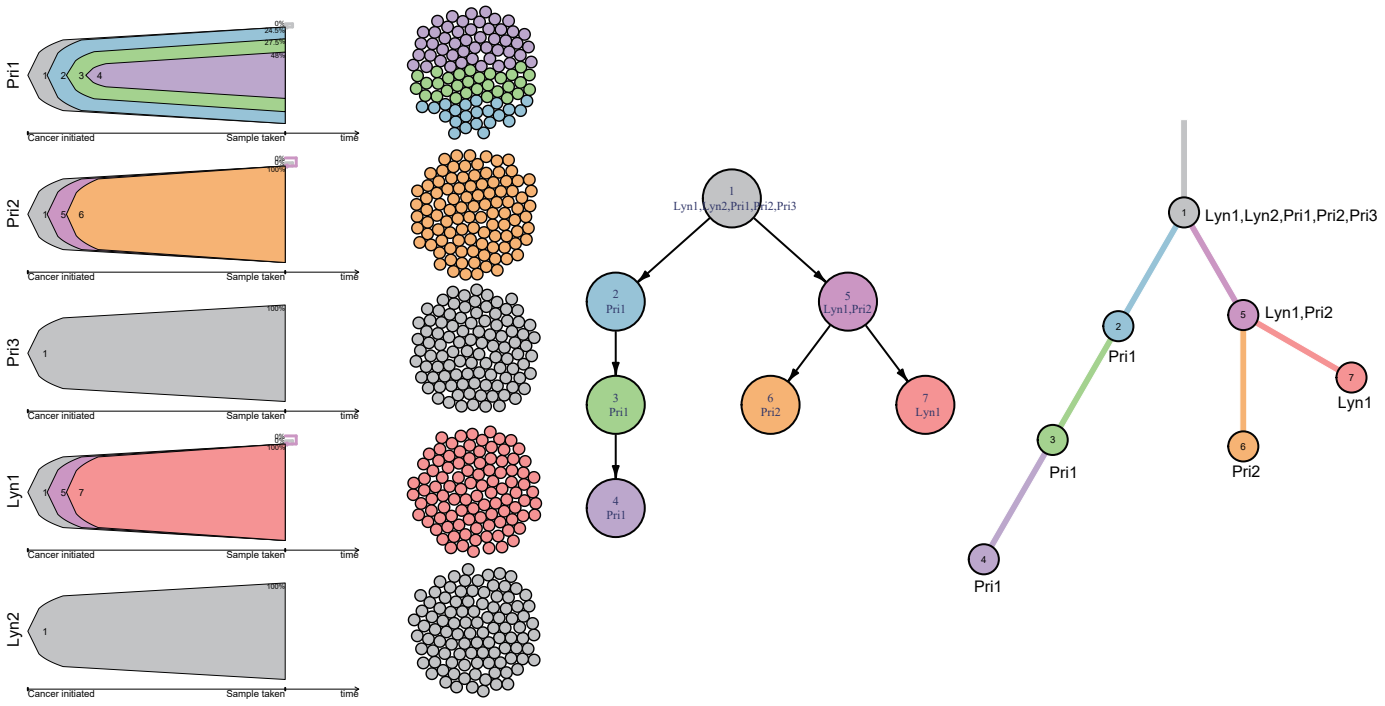
- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

Cancer cell fraction

0% 100% Unavailable

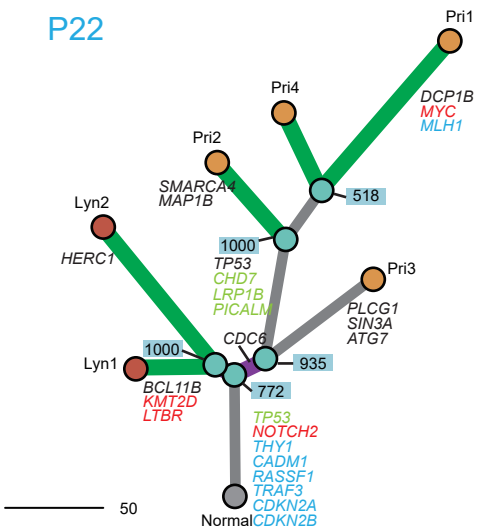
TP53	Clonal mutated gene in all samples of this branch
TP53	Clonal mutated gene in some samples of this branch
TP53	Subclonal mutated gene in all samples of this branch
TP53	Clonality infomation unavailable in some samples of this branch
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch

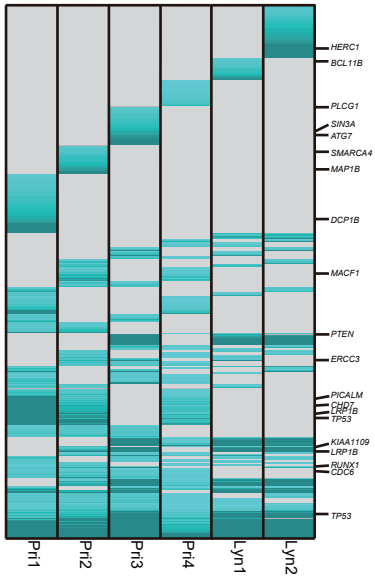


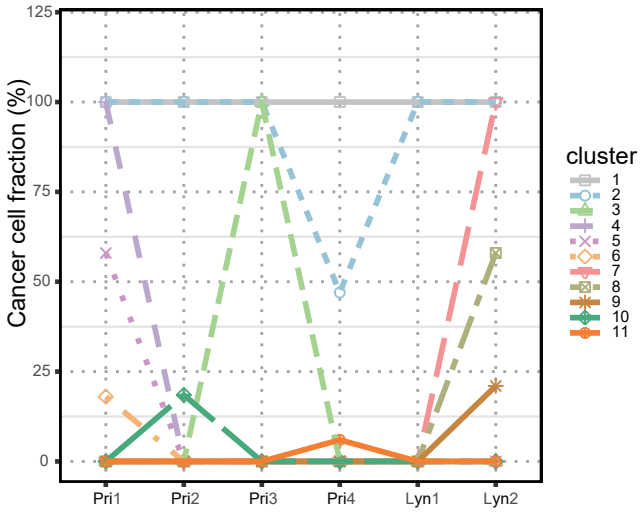
- 1: Del_TRAF3;Del_TP53
- 2: EXT1;Del_CDKN2A;Del_NLRC5;Del_MLH1;FIP1L1 Del_CADM1;Del_RASSF1;Del_CYLD;Amp_ATG13;Del_CDKN2B
- 3: CYLD
- 4: NULL
- 5: Amp_NOTCH1
- 6: Amp_FBXW7;Amp_LTBR;Amp_KRAS
- 7: Amp_NOTCH2;Amp_CADM1

- Unique location
- Multiple location

v







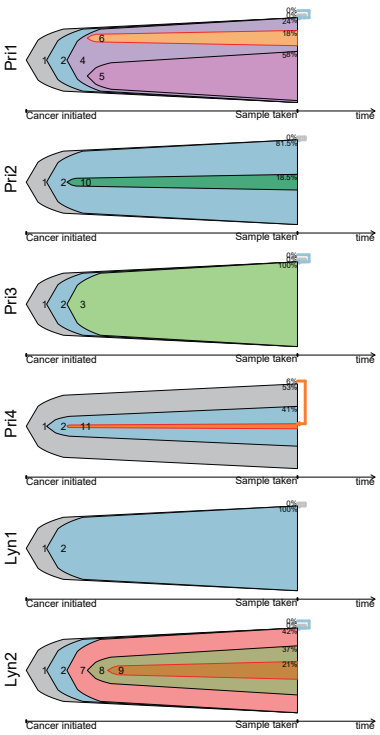
- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

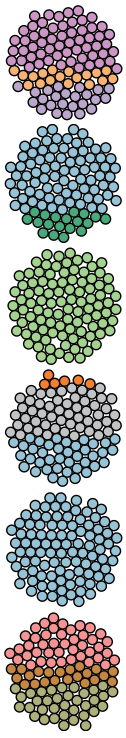
- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

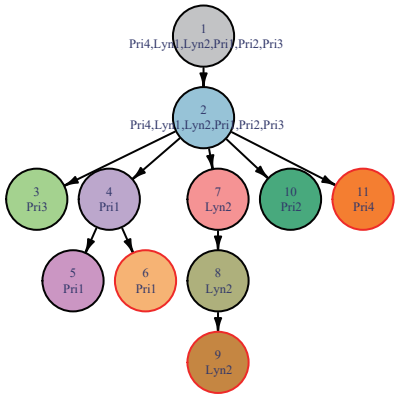
Cancer cell fraction

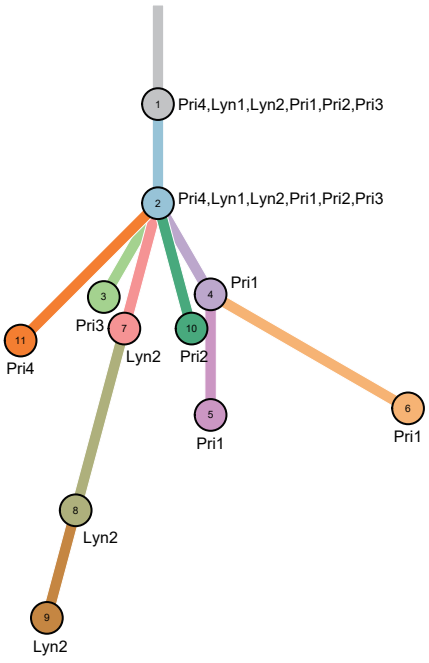
0% 100% Unavailable

TP53	Clonal mutated gene in all samples of this branch
TP53	Clonal mutated gene in some samples of this branch
TP53	Subclonal mutated gene in all samples of this branch
TP53	Clonality infomation unavailable in some samples of this branch
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch



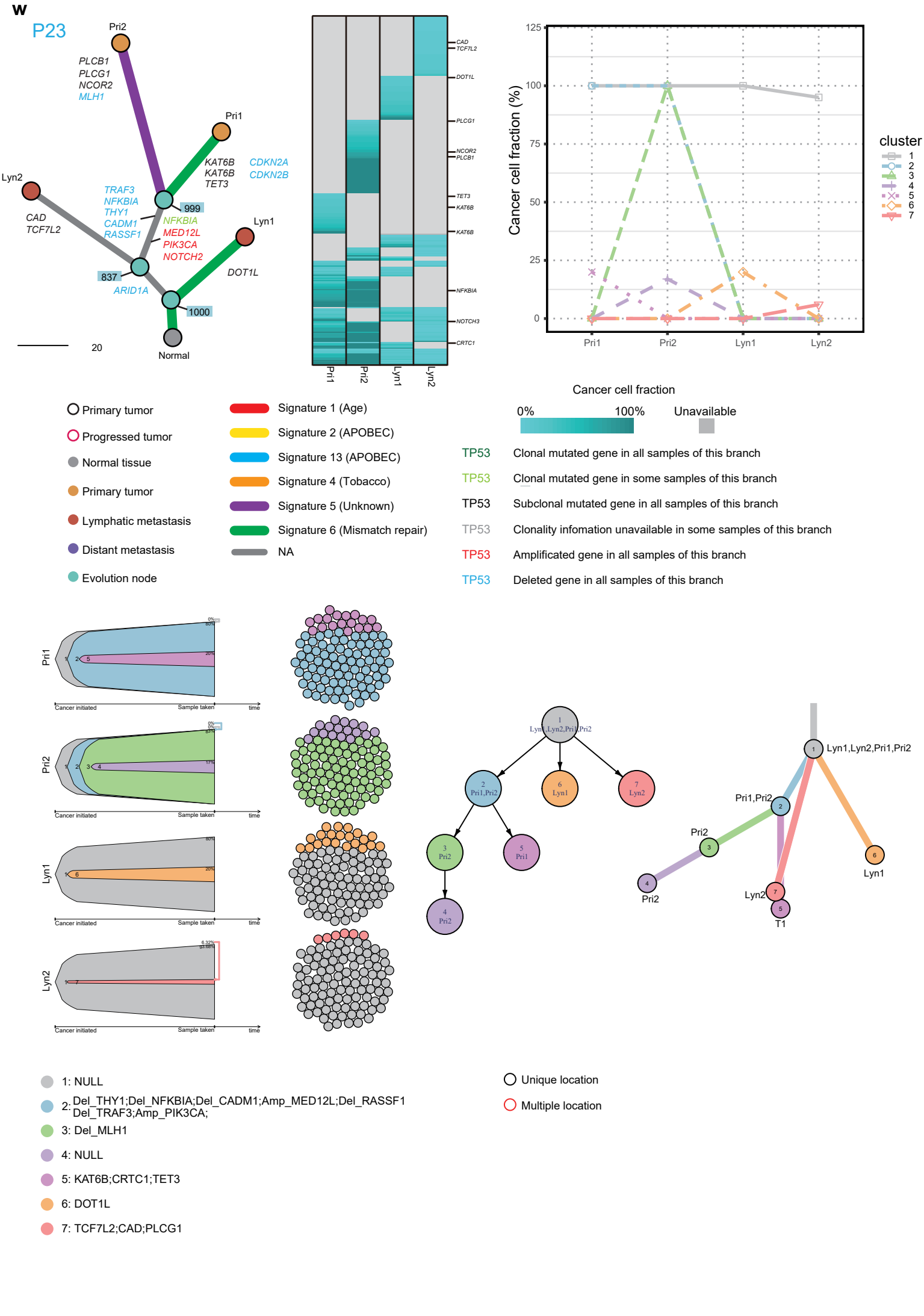




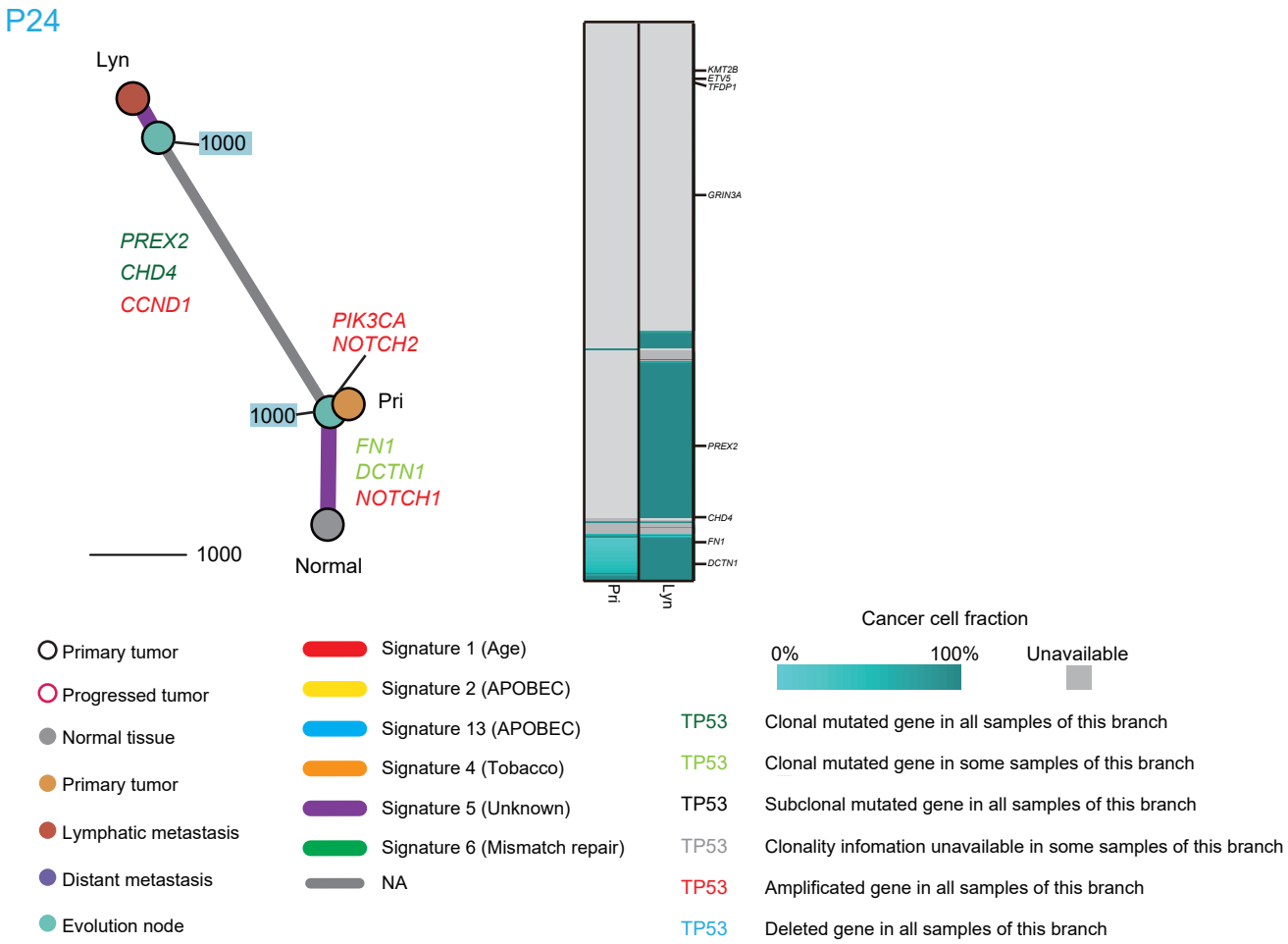


- 1: NULL
- 2: Del_CDKN2A;Del_THY1;Del_CADM1;Del_RASSF1;Del_TRAF3 Del_JAK2;Del_CDKN2B;
- 3: NULL
- 4: Del_MLH1;Amp_MYC
- 5: DCP1B
- 6: NULL
- 7: HERC1
- 8: NULL
- 9: NULL
- 10: SMARCA4
- 11: AHNAK2;PLCG1

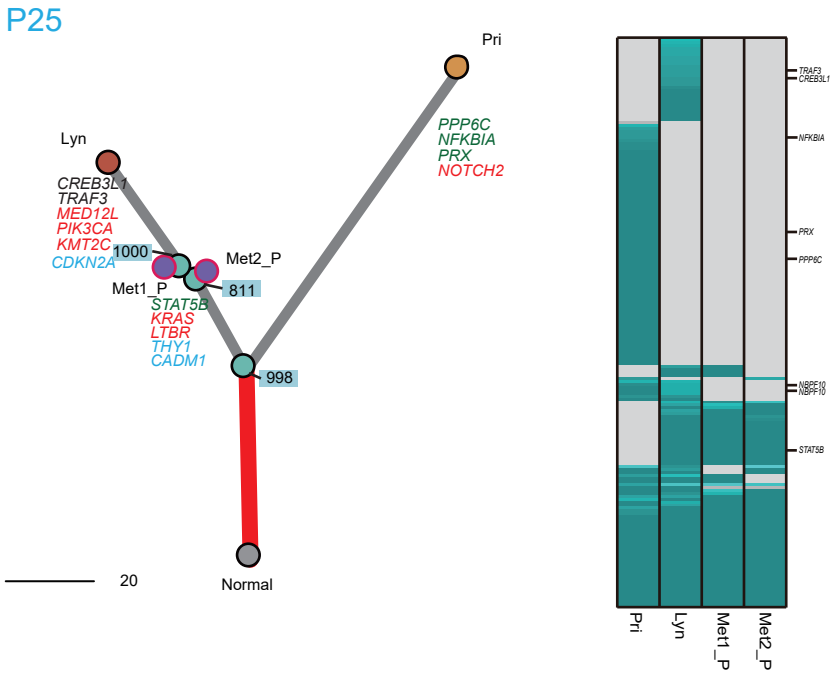
- Unique location
- Multiple location


w
P23
Pri2
PLCB1
PLCG1
NCOR2
MLH1
Pri1
KAT6B
KAT6B
TET3
CDKN2A
CDKN2B
Lyn2
TRAF3
NFKBIA
THY1
CADM1
RASSF1
999
NFKBIA
MED12L
PIK3CA
NOTCH2
Lyn1
CAD
TCF7L2
837
ARID1A
DOT1L
1000
20
Normal
CAD
TCF7L2
DOT1L
PLCG1
NCOR2
PLCB1
TET3
KAT6B
KAT6B
NFKBIA
NOTCH3
CRTC1
Pri1
Pri2
Lyn1
Lyn2
Cancer cell fraction (%)
125
100
75
50
25
0
Pri1
Pri2
Lyn1
Lyn2
cluster
1
2
3
4
5
6
7
Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node
Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA
Cancer cell fraction
0%
100%
Unavailable
TP53
Clonal mutated gene in all samples of this branch
TP53
Clonal mutated gene in some samples of this branch
TP53
Subclonal mutated gene in all samples of this branch
TP53
Clonality infomation unavailable in some samples of this branch
TP53
Amplificated gene in all samples of this branch
TP53
Deleted gene in all samples of this branch
Pri1
Pri2
Lyn1
Lyn2
Cancer initiated
Sample taken
time
1
Lyn1,Lyn2,Pri1,Pri2
2
Pri1,Pri2
6
Lyn1
7
Lyn2
3
Pri2
5
Pri1
4
Pri2
Lyn1,Lyn2,Pri1,Pri2
Pri1,Pri2
Pri2
Lyn1
Lyn2
Pri2
T1
1: NULL
2: Del_THY1;Del_NFKBIA;Del_CADM1;Amp_MED12L;Del_RASSF1 Del_TRAF3;Amp_PIK3CA;
3: Del_MLH1
4: NULL
5: KAT6B;CRTC1;TET3
6: DOT1L
7: TCF7L2;CAD;PLCG1
Unique location
Multiple location

x


P24
Lyn
1000
PREX2
CHD4
CCND1
PIK3CA
NOTCH2
Pri
1000
FN1
DCTN1
NOTCH1
1000
Normal
KMT2B
ETV6
TFDP1
GRIN3A
PREX2
CHD4
FN1
DCTN1
Pri
Lyn
Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node
Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA
Cancer cell fraction
0%
100%
Unavailable
TP53 Clonal mutated gene in all samples of this branch
TP53 Clonal mutated gene in some samples of this branch
TP53 Subclonal mutated gene in all samples of this branch
TP53 Clonality infomation unavailable in some samples of this branch
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch

y



- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

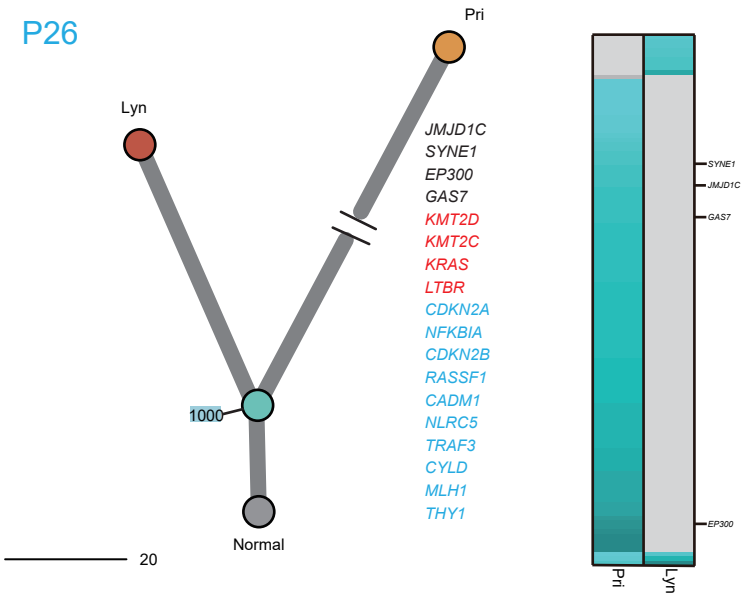
- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

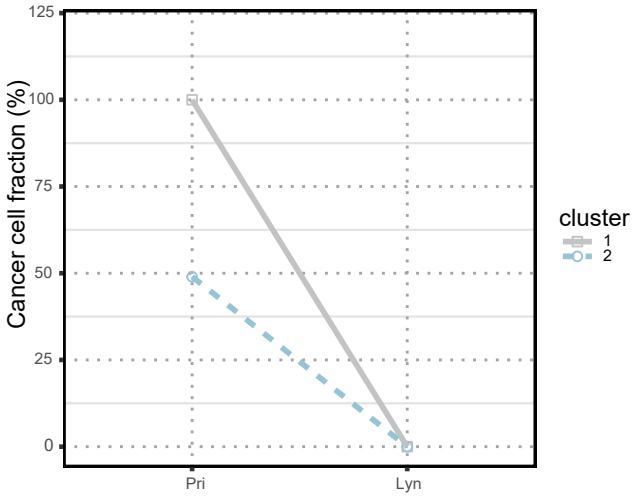
Cancer cell fraction

0% 100% Unavailable

TP53	Clonal mutated gene in all samples of this branch
TP53	Clonal mutated gene in some samples of this branch
TP53	Subclonal mutated gene in all samples of this branch
TP53	Clonality infomation unavailable in some samples of this branch
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch

z





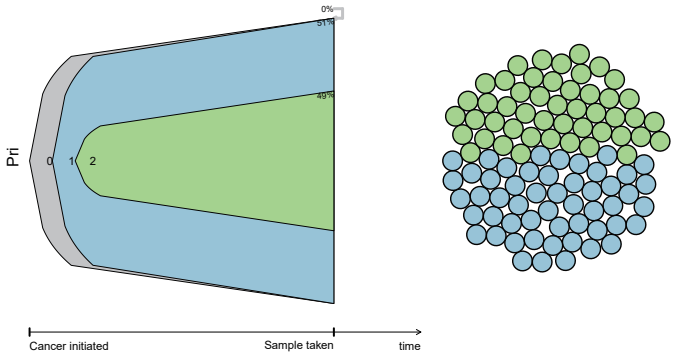
- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

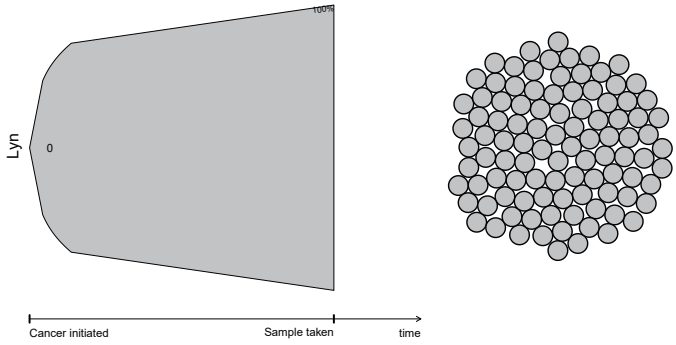
- Signature 1 (APOBEC)
- Signature 2 (Mismatch rep)
- Signature 13 (Smoking)
- Signature 4
- Signature 5
- Signature 6
- NA

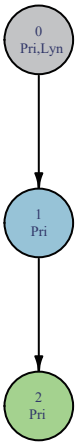
Cancer cell fraction

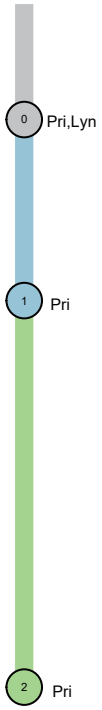
0% 100% Unavailable

TP53	Clonal mutated gene in all samples of this branch
TP53	Clonal mutated gene in some samples of this branch
TP53	Subclonal mutated gene in all samples of this branch
TP53	Clonality infomation unavailable in some samples of this branch
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch





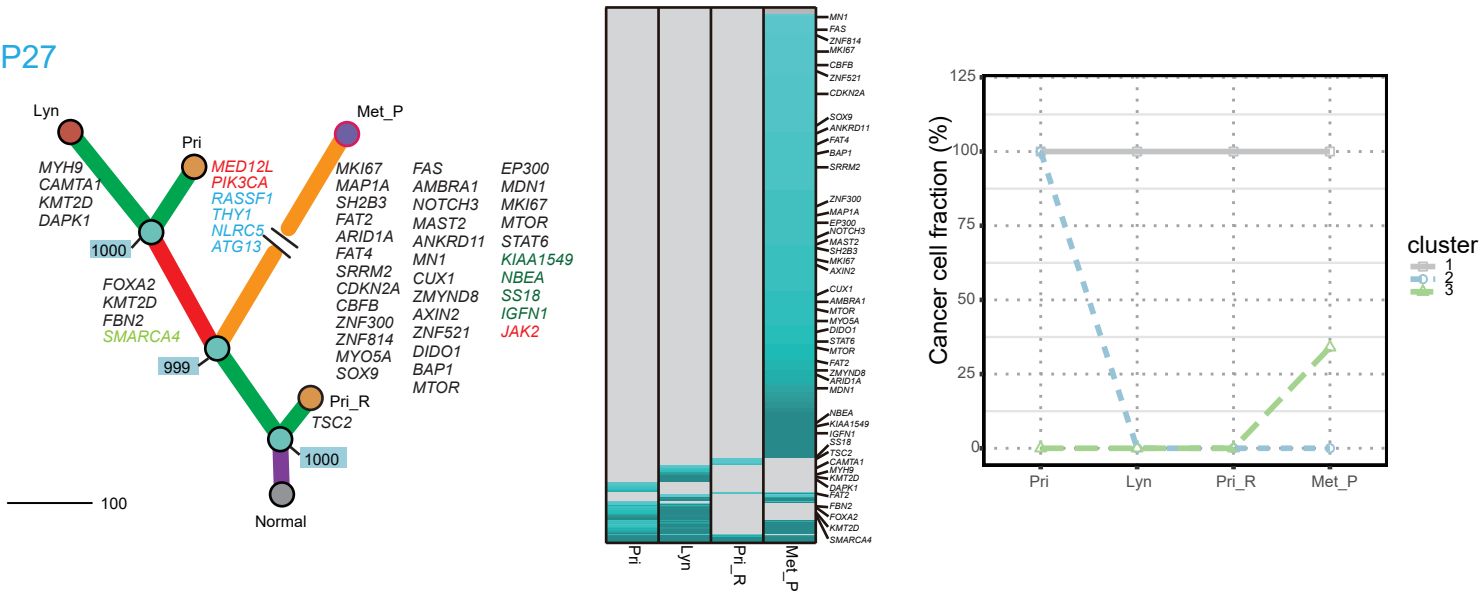




- 0: NULL
- 1: Del_CDKN2A;Del_NLRC5;Amp_LTBR;Amp_KRAS;Del_CADM1 Del_NOTCH1;Del_CYLD;Del_CDKN2B;Amp_KMT2D;Del_THY1 Amp_KMT2C;Del_MLH1;Del_NFKBIA;Del_RASSF1;Del_TRAF3 Del_JAK2;
- 2: JMJD1C;GAS7;SYNE1

- Unique location
- Multiple location

aa



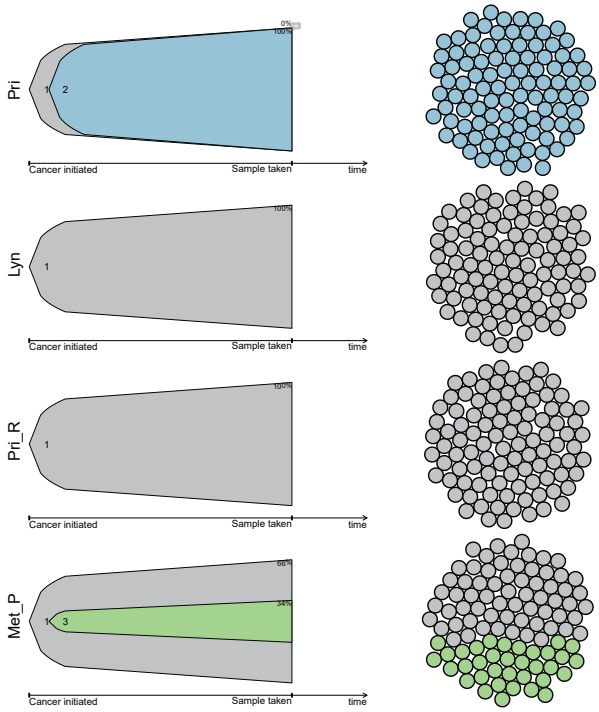
- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

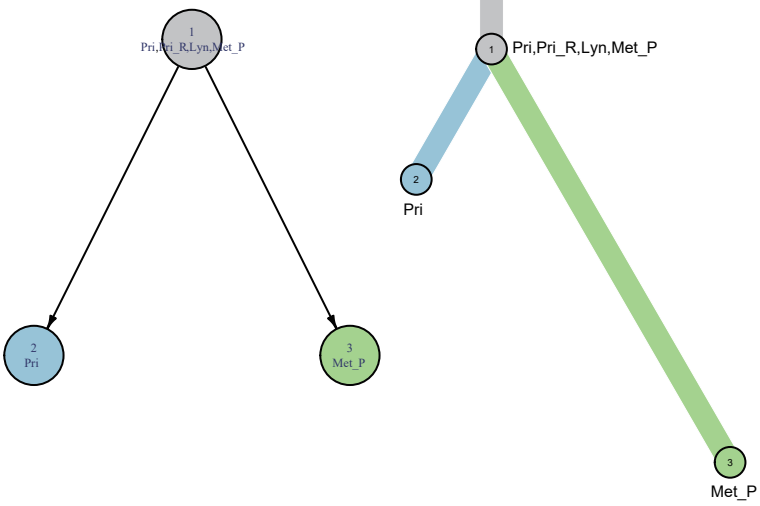
- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

Cancer cell fraction

0% 100% Unavailable

TP53	Clonal mutated gene in all samples of this branch
TP53	Clonal mutated gene in some samples of this branch
TP53	Subclonal mutated gene in all samples of this branch
TP53	Clonality infomation unavailable in some samples of this branch
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch





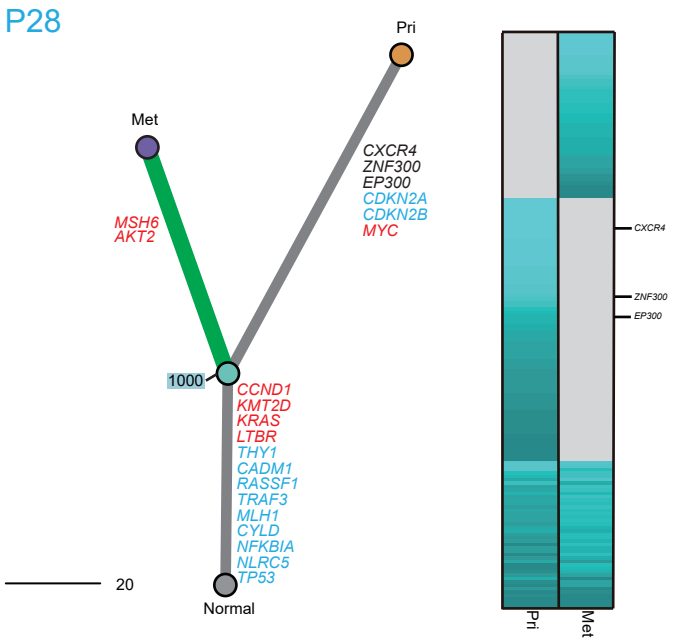
1:NULL

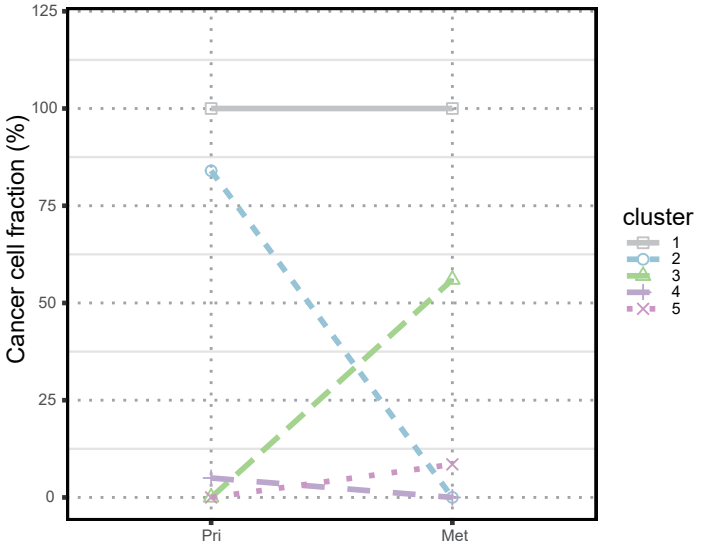
2:Amp_FBXW7;Del_THY1;Del_CCND1;Del_KMT2D;Amp_MED12L
Del_RASSF1;Amp_CDKN2A;Amp_CDKN2B;Amp_PIK3CA;Del_ATG13
Del_NLRC5;Del_LTBR;Del_NOTCH1;Del_KMT2C;Amp_CADM1

3:NOTCH3;DIDO1;CBFB;ANKRD11;MAST2
ZMYND8;AMBRA1;MKI67;GNAI1;KIAA1549
CUX1;Amp_JAK2;EP300;STAT6;SOX9
SH2B3;ZNF521;ZNF300;MDN1;SRRM2
SS18;CDKN2A;AHNAK2;MYO5A;AXIN2
ARID1A;IGFN1;MTOR;MN1;NBEA
ZNF814;MAP1A;FAS;FAT2;FAT4
BAP1;

- Unique location
- Multiple location

ab





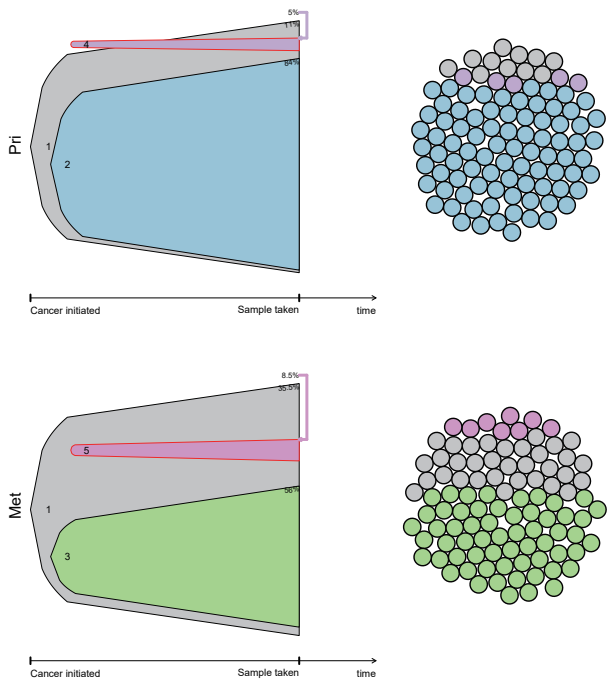
- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

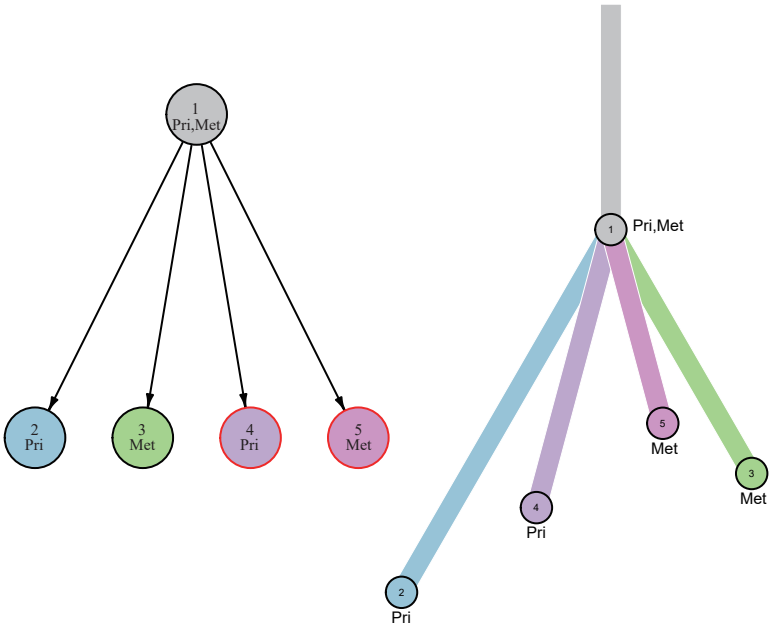
- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

Cancer cell fraction

0% 100% Unavailable

- TP53 Clonal mutated gene in all samples of this branch
- TP53 Clonal mutated gene in some samples of this branch
- TP53 Subclonal mutated gene in all samples of this branch
- TP53 Clonality infomation unavailable in some samples of this branch
- TP53 Amplificated gene in all samples of this branch
- TP53 Deleted gene in all samples of this branch

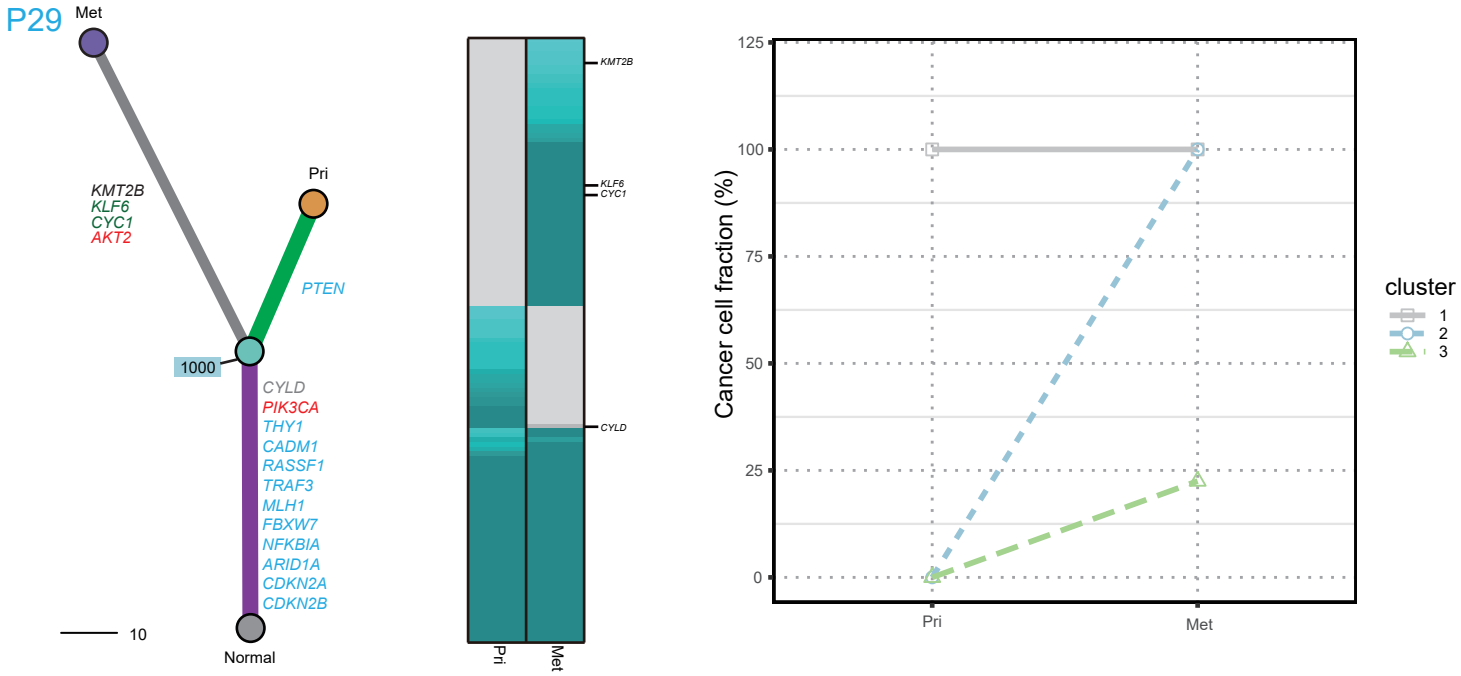


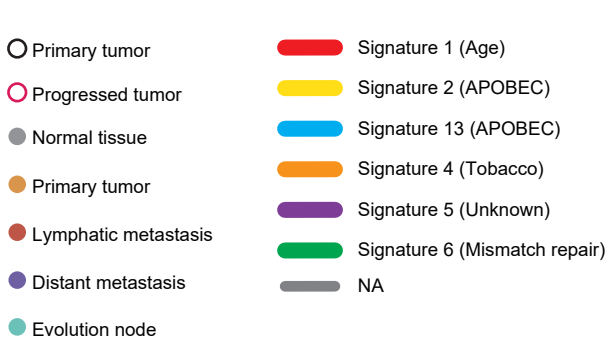


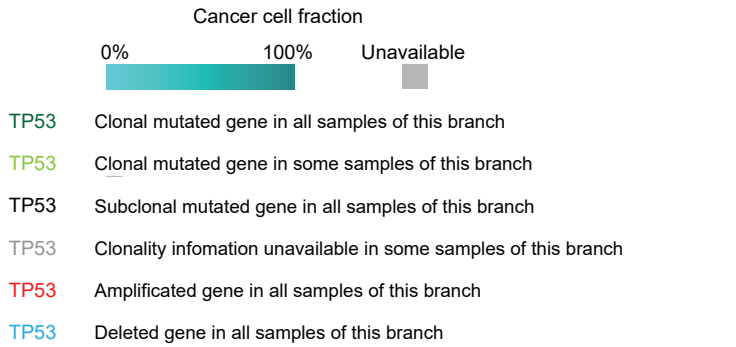
- 1: Del_NLRC5;Amp_LTBR;Amp_KRAS;Amp_CCND1;Del_CADM1 Del_CYLD;Amp_KMT2D;Del_THY1;Del_MLH1;Del_NFKBIA Del_RASSF1;Del_TRAF3;Del_TP53;
- 2: Del_CDKN2A;Del_NOTCH1;Amp_MYC;EP300;Del_JAK2 Del_CDKN2B;
- 3:NULL
- 4:CXCR4
- 5:NULL

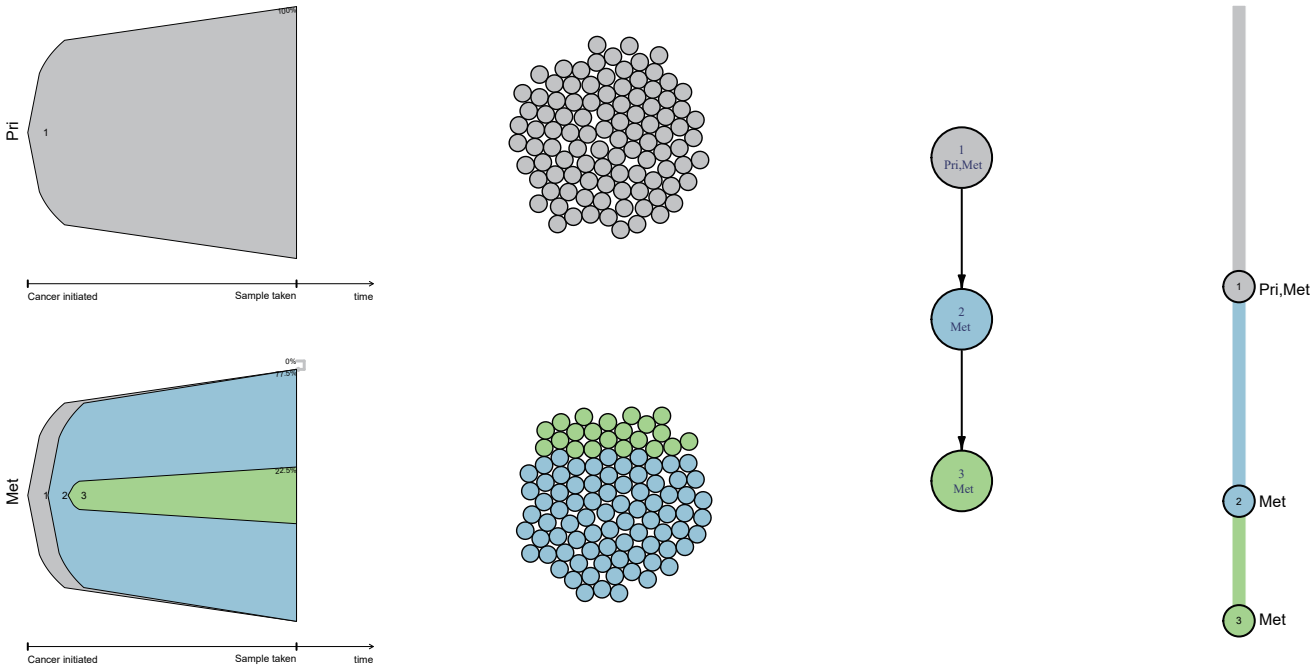
- Unique location
- Multiple location

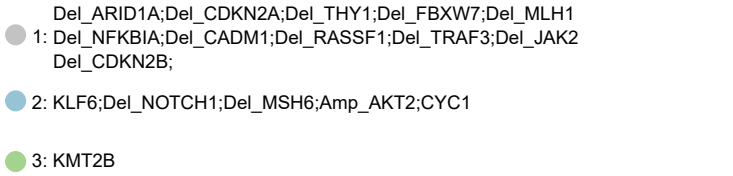
ac

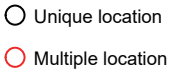

P29
Met
Pri
KMT2B
KLF6
CYC1
AKT2
PTEN
1000
CYLD
PIK3CA
THY1
CADM1
RASSF1
TRAF3
MLH1
FBXW7
NFKBIA
ARID1A
CDKN2A
CDKN2B
10
Normal
KMT2B
KLF6
CYC1
CYLD
Pri
Met
Cancer cell fraction (%)
125
100
75
50
25
0
Pri
Met
cluster
1
2
3


Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node
Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA

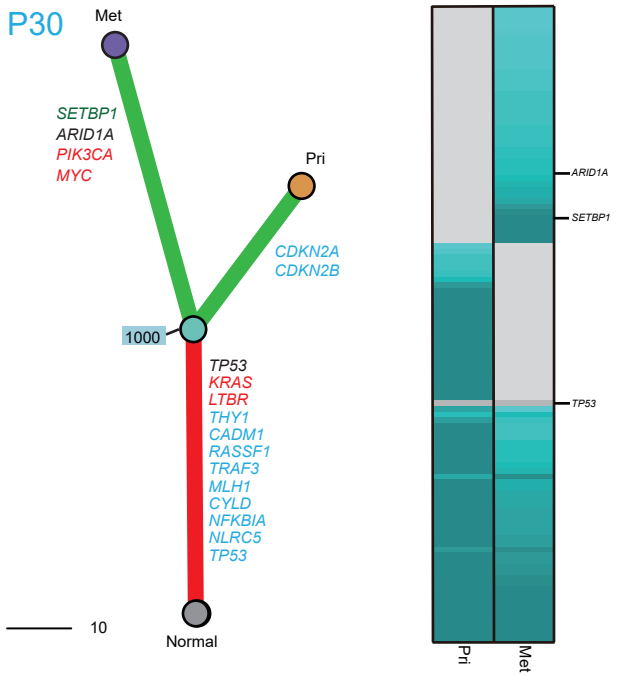

Cancer cell fraction
0%
100%
Unavailable
TP53 Clonal mutated gene in all samples of this branch
TP53 Clonal mutated gene in some samples of this branch
TP53 Subclonal mutated gene in all samples of this branch
TP53 Clonality infomation unavailable in some samples of this branch
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch

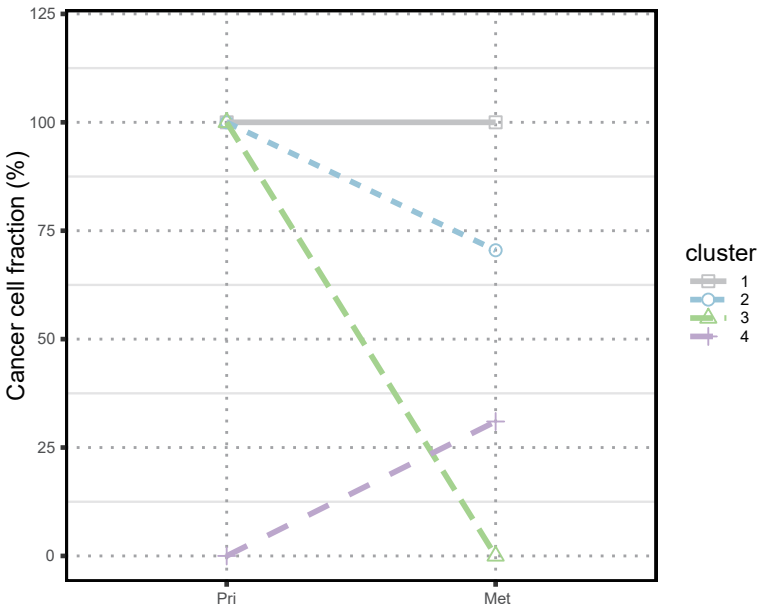

Pri
1
Cancer initiated
Sample taken
time
Met
1
2
3
22.5%
Cancer initiated
Sample taken
time
1
Pri,Met
2
Met
3
Met
1
Pri,Met
2
Met
3
Met


Del_ARID1A;Del_CDKN2A;Del_THY1;Del_FBXW7;Del_MLH1
1: Del_NFKBIA;Del_CADM1;Del_RASSF1;Del_TRAF3;Del_JAK2
Del_CDKN2B;
2: KLF6;Del_NOTCH1;Del_MSH6;Amp_AKT2;CYC1
3: KMT2B


Unique location
Multiple location

ad





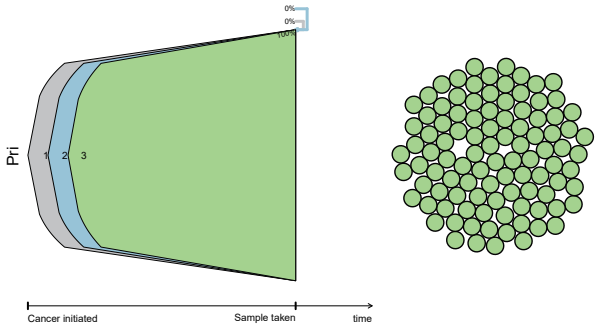
- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

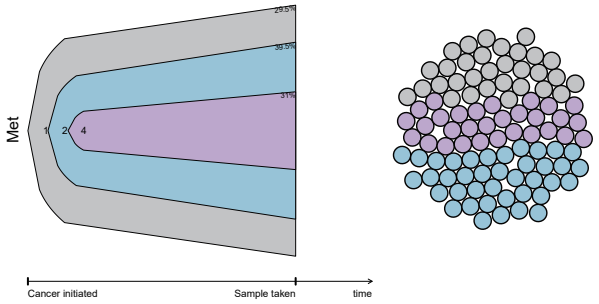
- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

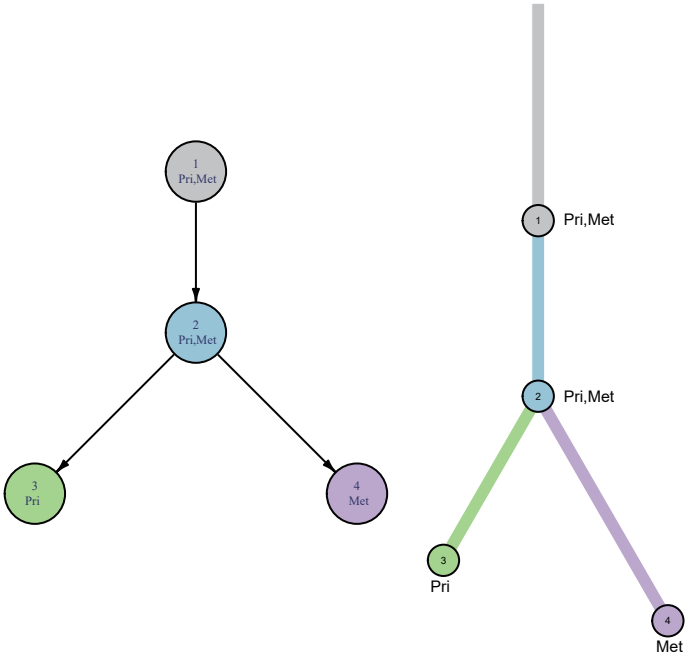
Cancer cell fraction

0% 100% Unavailable

TP53	Clonal mutated gene in all samples of this branch
TP53	Clonal mutated gene in some samples of this branch
TP53	Subclonal mutated gene in all samples of this branch
TP53	Clonality infomation unavailable in some samples of this branch
TP53	Amplificated gene in all samples of this branch
TP53	Deleted gene in all samples of this branch

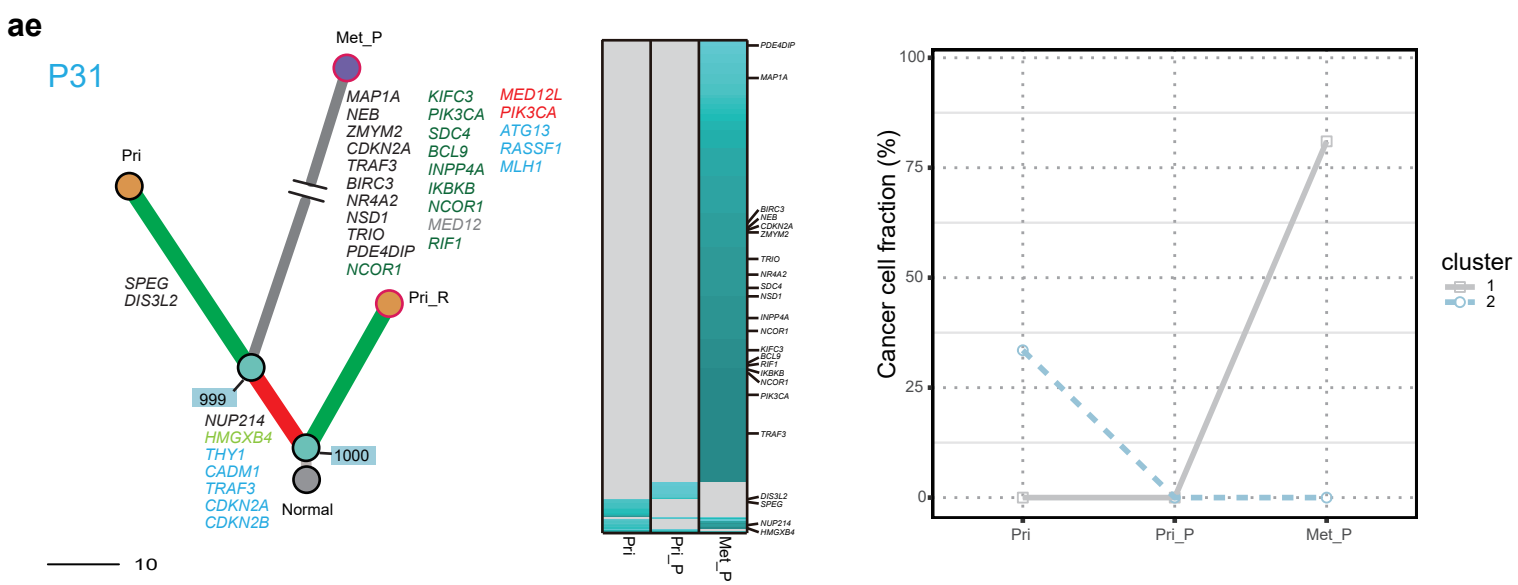


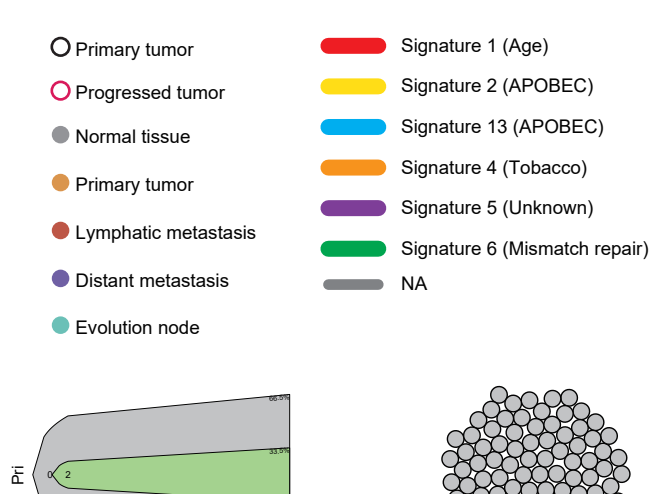


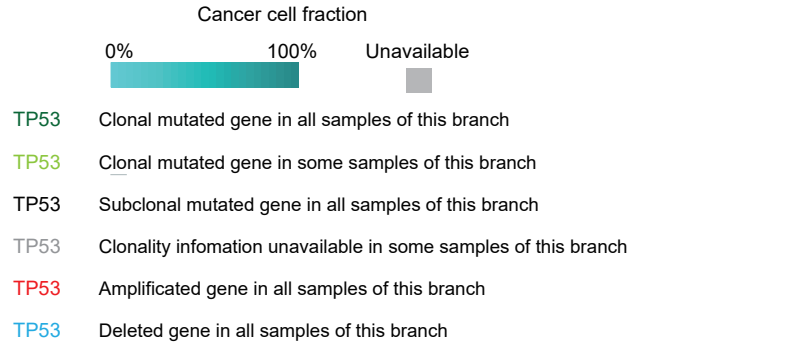


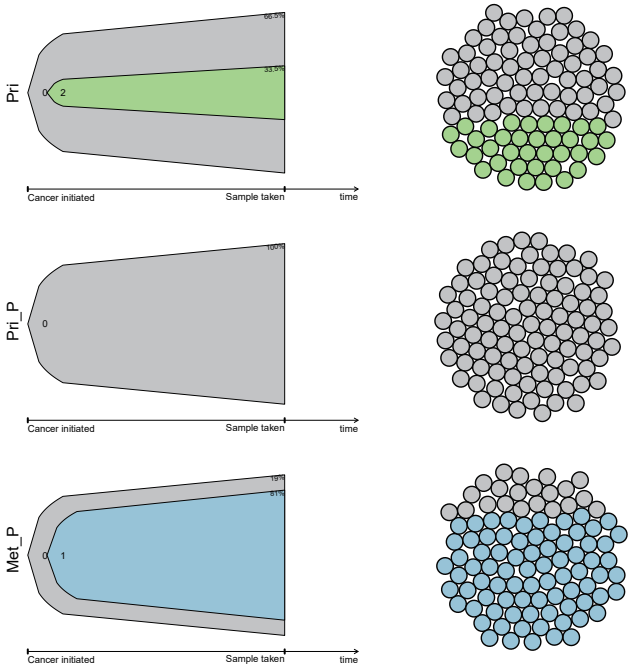
- 1: Del_NLRC5;Del_THY1;Del_MLH1;Del_NFKBIA;Del_CADM1 Del_RASSF1;Del_CYLD;Del_TRAF3;Del_TP53;
- 2: NULL
- 3: Del_MED12L;Del_JAK2
- 4: ARID1A

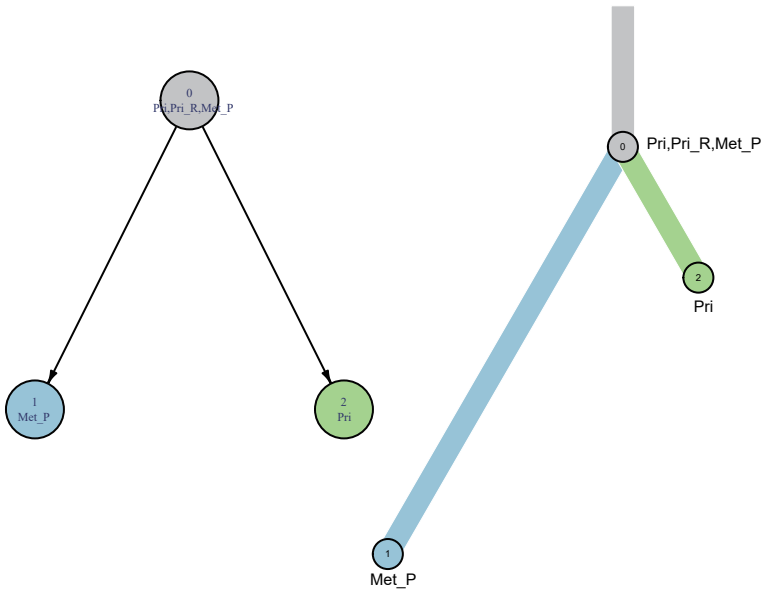
- Unique location
- Multiple location

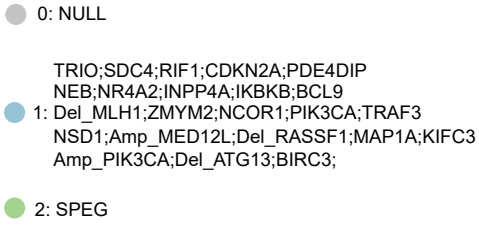

ae
P31
Met_P
Pri
Pri_R
SPEG
DIS3L2
MAP1A
NEB
ZMYM2
CDKN2A
TRAF3
BIRC3
NR4A2
NSD1
TRIO
PDE4DIP
NCOR1
KIFC3
PIK3CA
SDC4
BCL9
INPP4A
IKBKB
NCOR1
MED12
RIF1
MED12L
PIK3CA
ATG13
RASSF1
MLH1
999
NUP214
HMGXB4
THY1
CADM1
TRAF3
CDKN2A
CDKN2B
1000
Normal
10
Pri
Pri_P
Met_P
Cancer cell fraction (%)
100
75
50
25
0
cluster
1
2

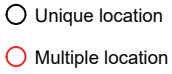

Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node
Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA

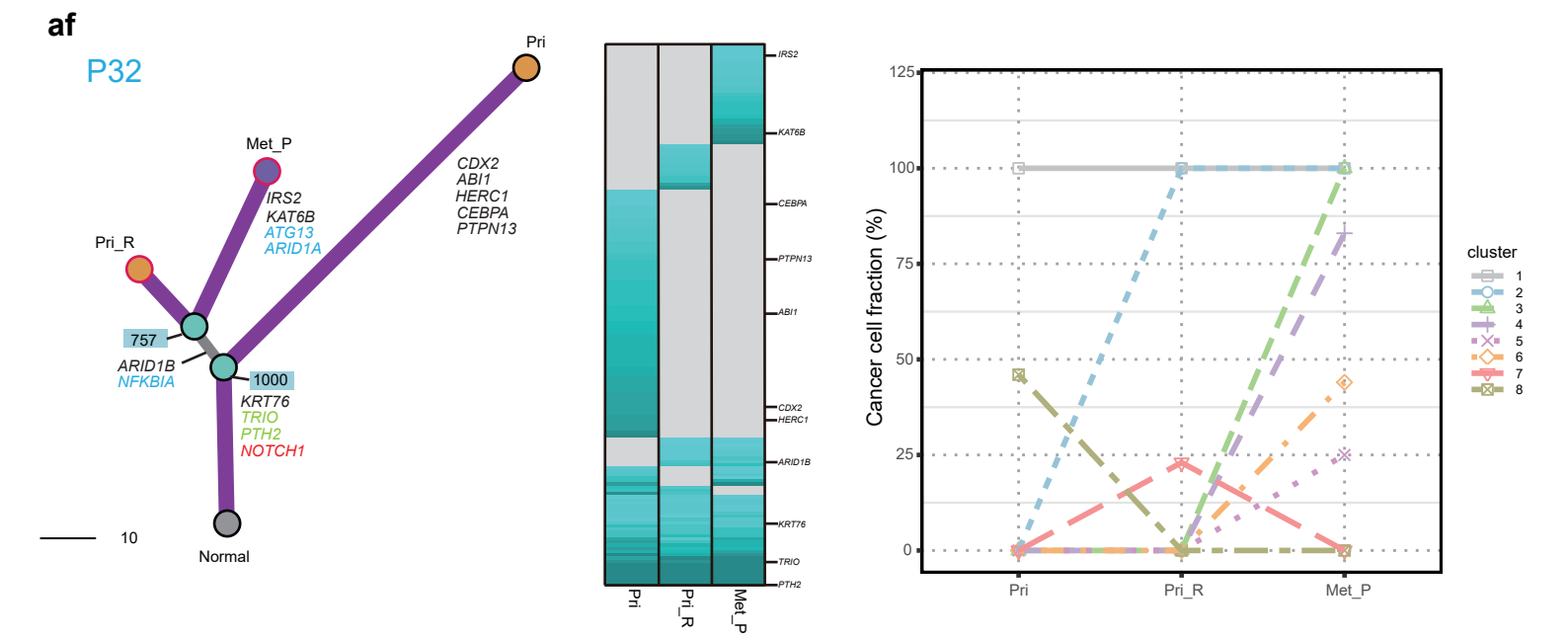

Cancer cell fraction
0%
100%
Unavailable
TP53 Clonal mutated gene in all samples of this branch
TP53 Clonal mutated gene in some samples of this branch
TP53 Subclonal mutated gene in all samples of this branch
TP53 Clonality infomation unavailable in some samples of this branch
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch


Pri
Pri_P
Met_P
Cancer initiated
Sample taken
time


0
Pri,Pri_R,Met_P
1
Met_P
2
Pri


0: NULL
1: Del_MLH1;ZMYM2;NCOR1;PIK3CA;TRAF3
NSD1;Amp_MED12L;Del_RASSF1;MAP1A;KIFC3
Amp_PIK3CA;Del_ATG13;BIRC3;
TRIO;SDC4;RIF1;CDKN2A;PDE4DIP
NEB;NR4A2;INPP4A;IKBKB;BCL9
2: SPEG


Unique location
Multiple location

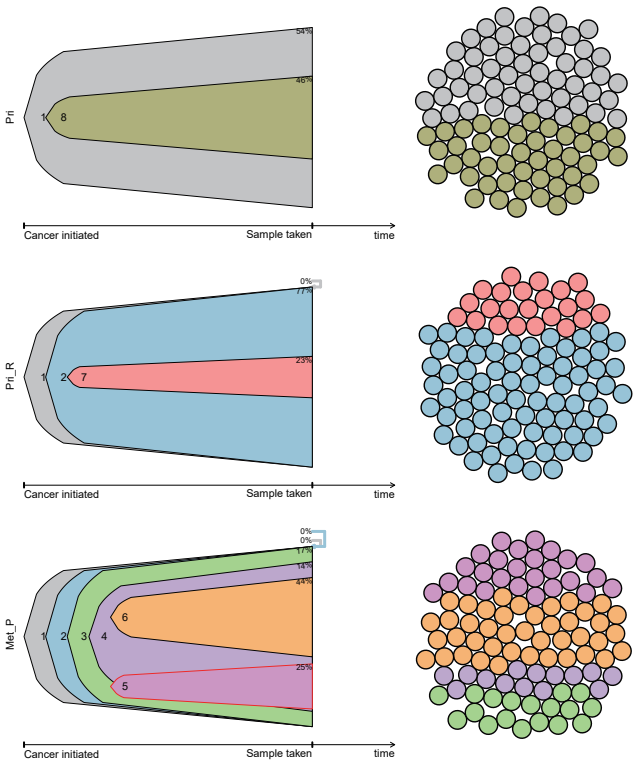


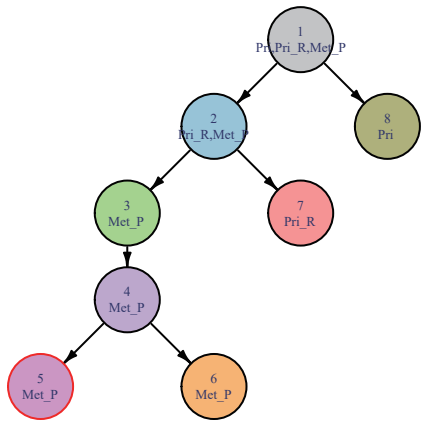
Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node

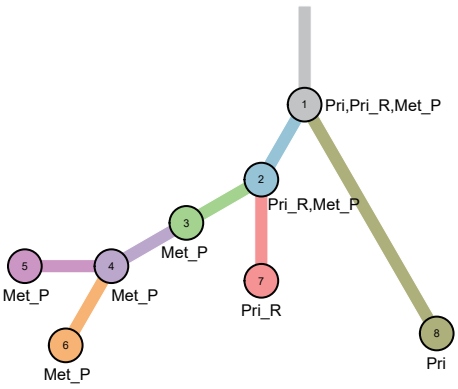
Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA

Cancer cell fraction
0% 100% Unavailable

TP53 Clonal mutated gene in all samples of this branch
TP53 Clonal mutated gene in some samples of this branch
TP53 Subclonal mutated gene in all samples of this branch
TP53 Clonality infomation unavailable in some samples of this branch
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch







1: Amp_NOTCH1;PTH2
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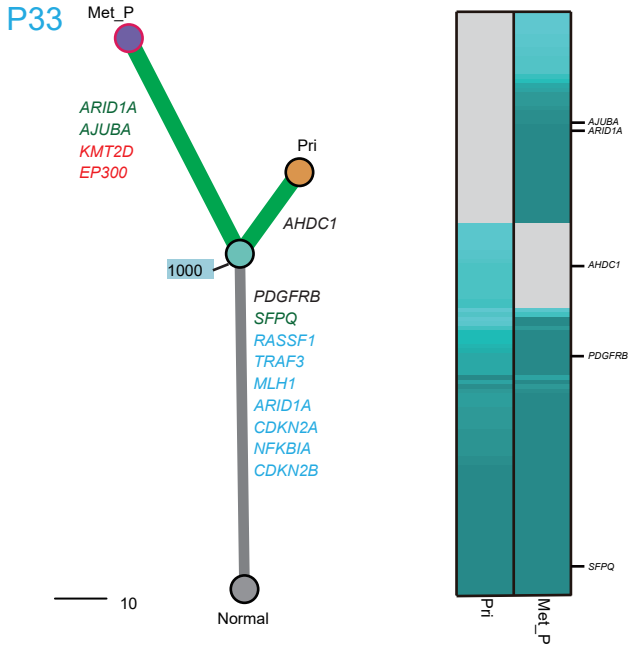
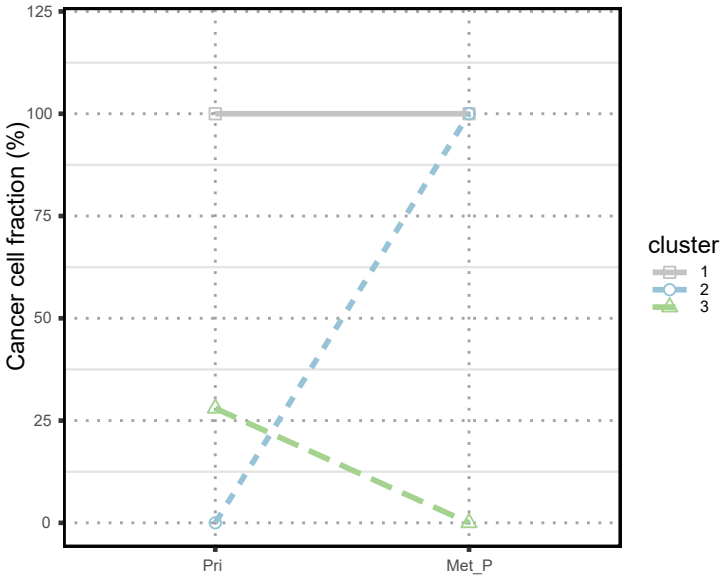
3: Del_ARID1A;Del_EP300;Del_ATG13
4: KAT6B
5: NULL
6: NULL
7: NULL
8: CEBPA;CDX2;HERC1;ABI1;PTPN13

Unique location
Multiple location

ag



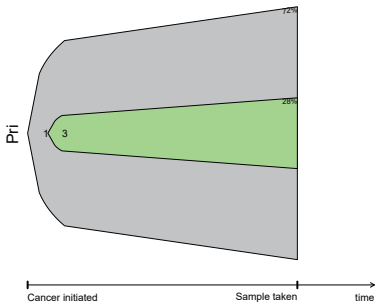


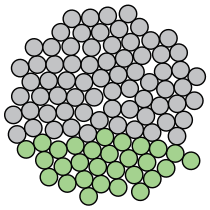
Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node

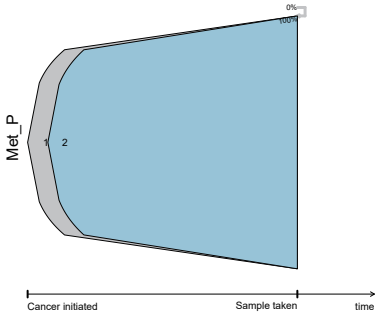
Signature 1 (Age)
Signature 2 (APOBEC)
Signature 13 (APOBEC)
Signature 4 (Tobacco)
Signature 5 (Unknown)
Signature 6 (Mismatch repair)
NA

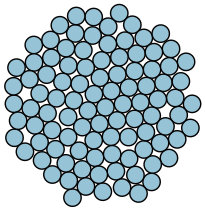
Cancer cell fraction
0% 100% Unavailable

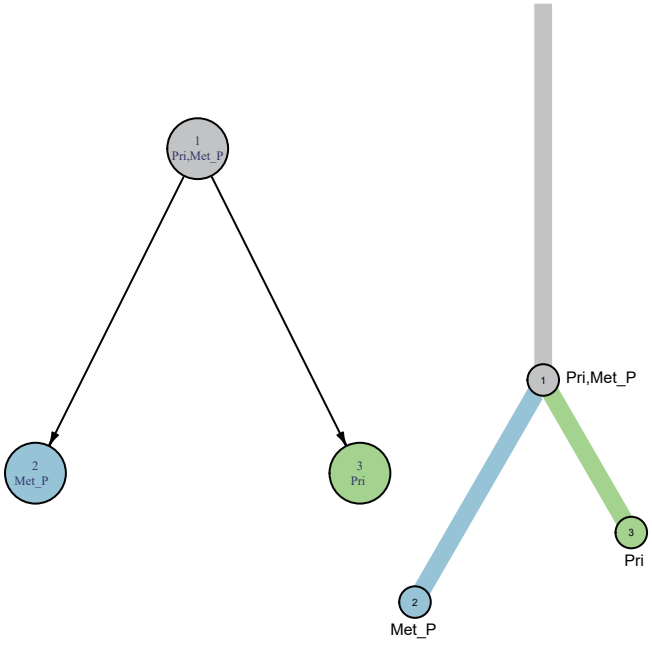
TP53 Clonal mutated gene in all samples of this branch
TP53 Clonal mutated gene in some samples of this branch
TP53 Subclonal mutated gene in all samples of this branch
TP53 Clonality infomation unavailable in some samples of this branch
TP53 Amplificated gene in all samples of this branch
TP53 Deleted gene in all samples of this branch











1: SFPQ
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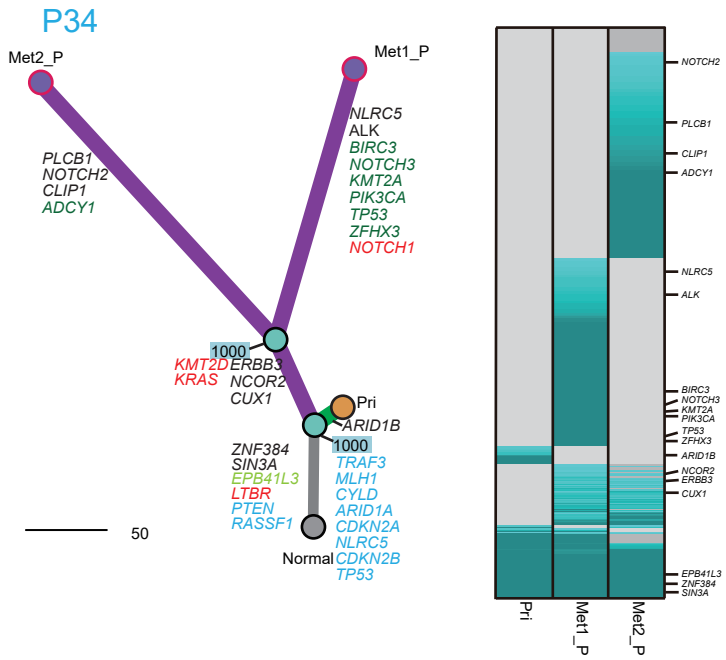
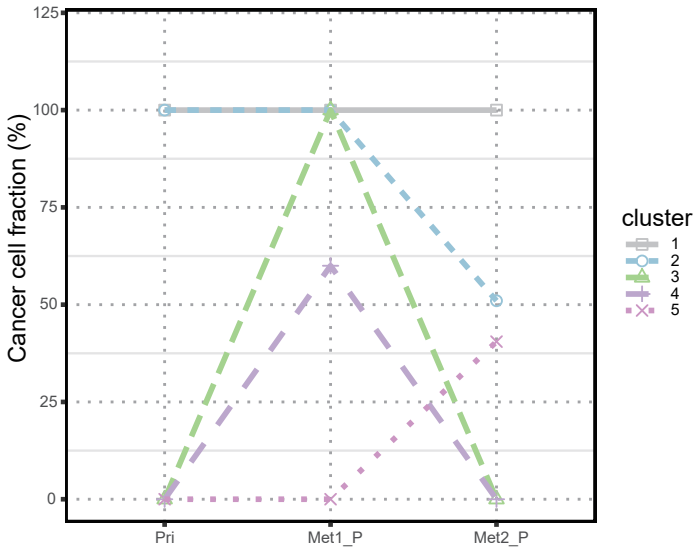
3: AHDC1

Unique location
Multiple location

ah





- Primary tumor
- Progressed tumor
- Normal tissue
- Primary tumor
- Lymphatic metastasis
- Distant metastasis
- Evolution node

- Signature 1 (Age)
- Signature 2 (APOBEC)
- Signature 13 (APOBEC)
- Signature 4 (Tobacco)
- Signature 5 (Unknown)
- Signature 6 (Mismatch repair)
- NA

Cancer cell fraction

0% 100% Unavailable

TP53	Clonal mutated gene in all samples of this branch
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TP53	Clonality infomation unavailable in some samples of this branch
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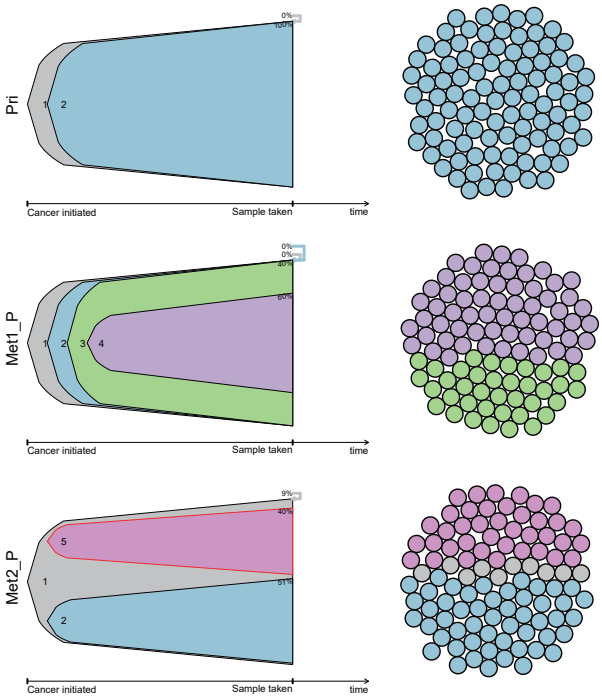
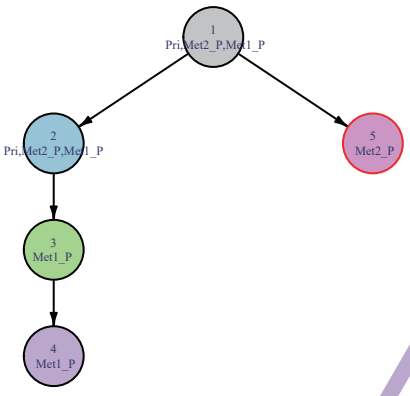
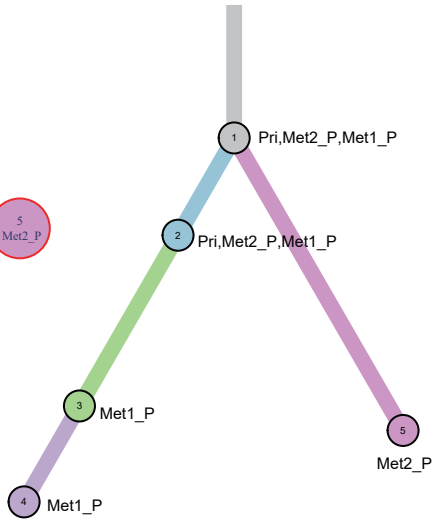


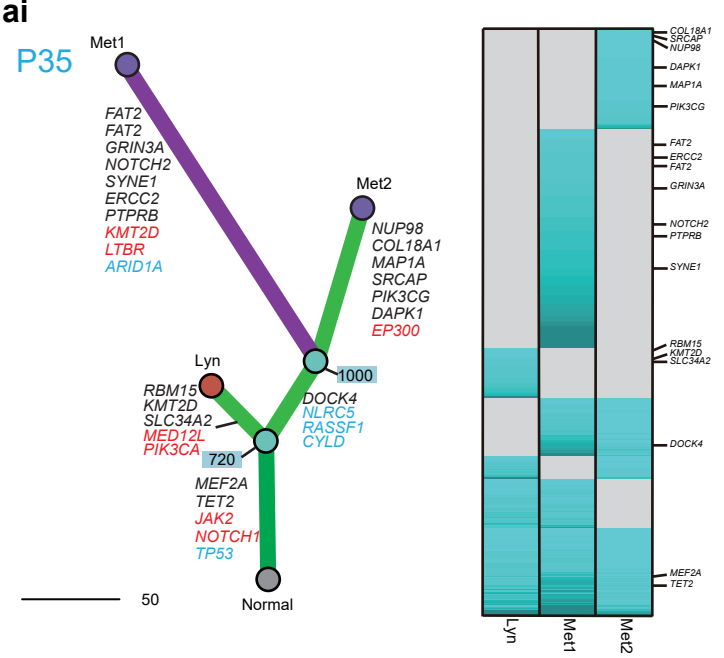


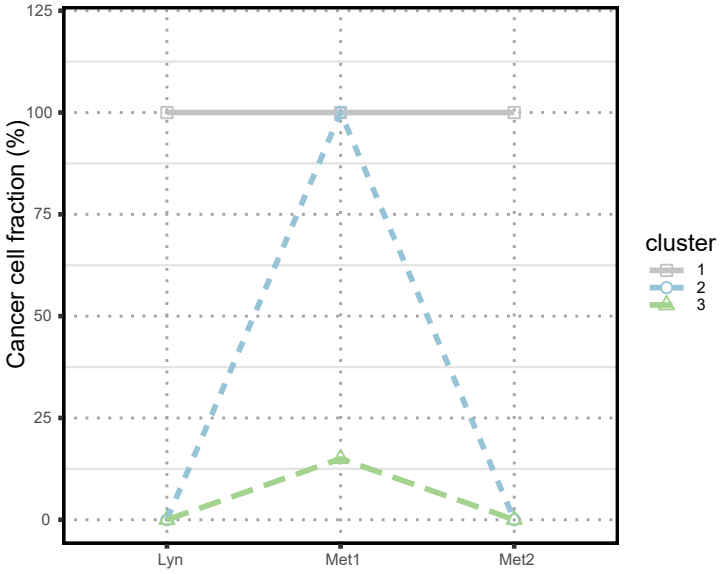


- 1: ZNF384;SIN3A;EPB41L3
- 2: Del_PTEN;Del_ARID1A;Del_CDKN2A;Del_NLRC5;Del_RASSF1 Del_CYLD;Del_TP53;Del_CDKN2B;
- 3: ZFHX3;Amp_NOTCH1;KMT2A;PIK3CA;TP53 BIRC3;
- 4: NULL
- 5: NOTCH2;ALK;CLIP1;Del_NOTCH1;AHNAK2 NLRC5;FN1;ADCY1;PLCB1;ACTB ACTG1;

- Unique location
- Multiple location

ai





Primary tumor
Progressed tumor
Normal tissue
Primary tumor
Lymphatic metastasis
Distant metastasis
Evolution node

Signature 1 (Age)
Signature 2 (APOBEC)
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Signature 4 (Tobacco)
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Signature 6 (Mismatch repair)
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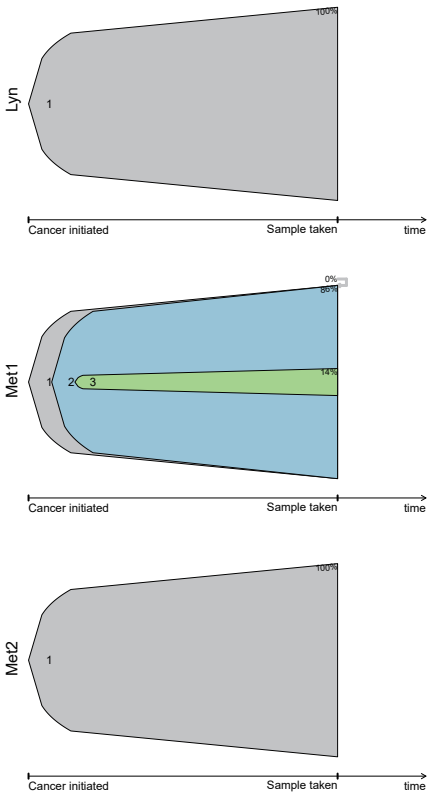

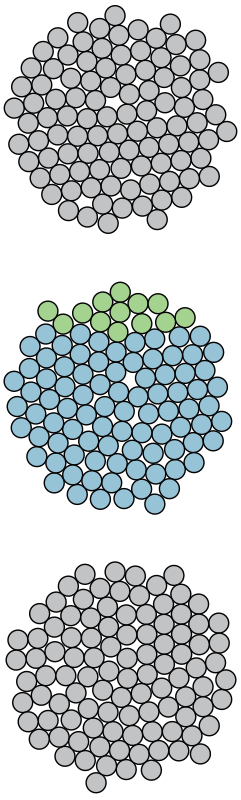

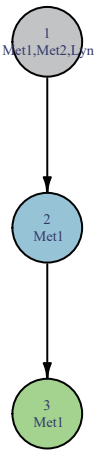

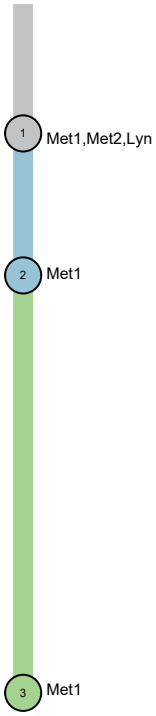

1: Amp_NOTCH1;Amp_JAK2;Amp_CDKN2A;Del_TP53;Amp_CDKN2B

2: Del_ARID1A;Amp_KMT2D;Amp_LTBR

3: NOTCH2;KMT2D;COL18A1;SLC34A2;RBM15 SRCAP;DAPK1;AHNAK2;PIK3CG;SYNE1 PTPRB;GRIN3A;MAP1A;ERCC2;FAT2 NUP98;

Unique location
Multiple location

Supplementary Fig. 11. Evolution analysis of each patient.

Evolution analysis for 35 patients. A phylogenetic tree was constructed for each patient (top left figure for each patient). For each branch, key variants are highlighted in the tree, including clonal mutated driver genes in all samples (dark green), clonal mutated driver genes in some samples (light green), subclonal mutated driver genes in all samples (black), and mutated driver genes with unclear clonality (grey) as well as key amplified or deleted driver genes (red and blue). Bootstrap values are marked on each divergence node, and dominant signatures (contribution > 0.5) of each branch are mapped in different colours (except the branches that contain less than 10 mutations or had no dominant signature detected). The top middle figures for each patient show the fraction of tumour cells with shared and private mutations for each tumour sample, and key mutations are also marked. The top right figures show the CCF flow of each mutation cluster (subclones) according to each sample. The bottom left figures show the subclone-based evolution architecture of each sample and their sampling transect, which reflect the fractions of each subclone at the time of sampling. The bottom right two figures show the evolution architecture of subclones in node-based and branch-based trees. The black boundary subclones in the node-based tree indicate that these subclones are located in a unique place of the architecture, whereas the red subclones indicate that the subclones are so small that they could be placed in multiple locations without penalty (see Method). Driver variants are also listed for each subclone.

SUPPLEMENTARY TABLES

Supplementary Table 1. Clinical data of the sequenced NPC cohort.

Type	Group	Frequency	Percent
Age			
	Median (yrs)		42
Sex			
	Female	4	9.09%
	Male	40	90.91%
Smoking			
	No	27	61.36%
	Yes	17	38.64%
T stage			
	1	2	4.55%
	2	4	9.09%
	3	17	38.64%
	4	21	47.73%
N stage			
	1	7	15.91%
	2	14	31.82%
	3	23	52.27%
M stage			
	0	9	20.45%
	1	35	79.55%
Disease stage			
	II	1	2.27%
	III	2	4.55%
	IVa	5	13.63%
	IVb	35	79.55%
Progression status			
	no	10	22.73%
	yes	34	77.27%
PFS			
	Median (months)		12

Supplementary Table 2. Single cell RNA sequencing information.

Patient	Sample	UMI (mean)	Genes (mean)	UMI (std)	Genes (std)	Cells
P14	Pri	4763.9	1203.1	5931.7	847.1	4921
	LLN	2983.2	938.9	3615.9	615.7	1954
	RLN	3217	962.7	2561.3	466.1	3074
	Liver	7335.2	1473.2	11502.2	1218.9	3156
	Bone	4203.6	1019.9	6380	837.8	478
	ILN	2694.8	811.1	2533.2	494.3	6102
P15	Pri	4428.3	1131.8	5811	895.3	4868
	LLN	3665.2	966.3	2934.5	468.3	6809
	RLN	3877.3	1081.1	3246.5	484.8	7172
	LALN	3559.5	981.4	2579.2	485.3	7886
	RALN	4952.8	1195.1	5989.2	807.7	7493

Supplementary Table 3. Key image characteristics of the training and validation datasets.

Type	Lymphatic median(range)	Hematogenous median(range)	P value*
Training dataset (n = 13)			
Axial maximum diameter of tumor (mm)	19.4 (14.9-46.4)	48.9 (28-53.2)	0.006216
Coronal maximum diameter (mm)	22.75 (16.1-47)	53.7 (38-64.8)	0.003108
Sagittal maximum diameter (mm)	18.7 (10.7-64.7)	48.7 (35.2-74.1)	0.010878
Number of lower cervical lymph nodes	14.5 (5-22)	5 (0-12)	0.0225166
Number of organ metastasis	2 (0-9)	6 (0-52)	0.2370052
Number of bone metastasis	18 (0-27)	0 (0-7)	0.0594305
Metastatic NPC cohort (n = 104)			
Axial maximum diameter of tumor(mm)	34.35 (14.1-59.0)	39.55 (29.9-66.1)	0.03881
Coronal maximum diameter (mm)	32.15 (13.5-67.5)	38.15 (25.7-69.4)	0.012888
Sagittal maximum diameter (mm)	27.7 (4.12-63.9)	35.3 (20.1-62.1)	0.039573
Number of lower cervical lymph nodes	3 (0-33)	2.5 (0-6)	0.09207
Number of organ metastasis	1 (1-4)	1 (0-3)	0.950072
Number of bone metastasis	3 (0-5)	1.5 (0-5)	0.513893
M0 stage NPC cohort (n = 201)			
Axial maximum diameter of tumor(mm)	18 (5-48)	28 (8-71)	1.657E-09
Coronal maximum diameter (mm)	19 (5-48)	28 (7-61)	2.158E-09
Sagittal maximum diameter (mm)	19 (5-70)	25.5 (8-59)	4.267E-11
Number of lower cervical lymph nodes	0 (0-6)	0 (0-7)	0.0374658
Immunotherapy cohort (n = 66)			
Axial maximum diameter of tumor(mm)	31 (9.5-40)	37.15 (19.9-58.5)	0.0123199
Coronal maximum diameter (mm)	34.9 (15.9-46.2)	36.2 (13.1-60.3)	0.3505177
Sagittal maximum diameter (mm)	28.5 (13.1-44.4)	35.3 (13.7-60.9)	0.0390839
Number of lower cervical lymph nodes	2 (0-8)	0 (0-10)	0.051894

*P value was calculated using Wilcoxon signed-rank test (two-sided).

Supplementary Table 4. Clinical characteristics of the de novo metastatic NPC cohort used for the validation of the radiomics prediction model (N = 104 individuals).

Type	Group	Frequency	Percent
Metastatic route			
	Lymphatic route	78	75.0%
	Hematogenous route	26	25.0%
Local-regional radiotherapy			
	Yes	50	48.1%
	No	54	51.9%
Age, years			
	Media (IQR)		37.0-52.0
Gender			
	Male	87	83.7%
	Female	17	16.3%
Smoking			
	Yes	32	30.8%
	No	72	69.2%
KPS score			
	Median (IQR)		90-90
Pathology (WHO)			
	I/II	5	4.8%
	III	99	95.2%
T stage			
	1-2	12	11.5%
	3-4	92	88.5%
N stage			
	0-1	22	21.2%
	2-3	82	78.8%
Bone metastases			
	No	27	26.0%
	Yes	77	74.0%
Liver metastases			
	No	73	70.2%
	Yes	31	29.8%
Lung metastases			
	No	74	71.10%
	Yes	30	28.90%
Number of metastatic lesions			
	1-2	31	30.00%
	≥3	73	70.00%

Supplementary Table 5. Comparison of clinicopathologic features of the training and de novo metastatic NPC cohorts.

Category and variable	training cohort (n = 13)	validation cohort (n=104)	P value*
Age	46.0 (38.5-51.0)	47.0 (36.5-53.0)	0.423[a]
Sex			0.455
Female	1(7.7%)	15(14.4%)	
Male	12(92.3%)	89(85.6%)	
Number of metastatic sites			0.327
Single	5(38.5%)	28(26.9%)	
Multiple	8(61.5%)	76(73.1%)	
Liver involvement			0.053
No	6(46.2%)	72(69.2%)	
Yes	7(53.8%)	32(30.8%)	
Treatment			0.257
CT+RT	4(30.8%)	46(44.2%)	
CT	9(69.2%)	58(55.8%)	
Group			0.388
Lymphatic	78(75.0%)	8(61.5%)	
Hematogenous	26(25.0%)	5(38.5%)	

*P value was calculated using Chi-square test (two-sided). [a] P value was calculated using two-sided t test. CT: Chemotherapy; RT: Radiotherapy.

Supplementary Table 6. Clinical characteristics of the M0-stage nasopharyngeal carcinoma cohort used for the validation of the radiomics prediction model (N=201 individuals).

Type	Group	Frequency	Percent
Metastatic route			
	Lymphatic route	113	56.22%
	Hematogenous route	88	43.78%
Age			
	Median (IQR)	45	38-53
KPS			
	Median (IQR)	90	90-90
Gender			
	Male	144	71.64%
	Female	57	28.36%
Pathology (WHO)			
	I/II	8	3.98%
	III	193	96.02%
T stage			
	1-2	92	45.77%
	3-4	109	54.23%
N stage			
	0-1	147	73.13%
	2-3	54	26.87%
Chemotherapy			
	No	18	8.96%
	Yes	183	91.04%

Supplementary Table 7. Clinical characteristics of the immunotherapy NPC cohort (N = 66 individuals).

Type	Lymphatic route (n=52)	Hematogenous route (n=14)	P value*
Stage			0.766
Primary metastases	1	0	
Recurrence with distant metastases	43	11	
Local regional-recurrence	8	3	
Age, years			0.899[a]
Median (IQR)	47 (35.0-56.0)	44 (37.0-53.0)	
Gender			0.73
Male	40	10	
Female	12	4	
Smoking			0.971
Yes	22	6	
No	30	8	
KPS score			1[a]
Median (IQR)	90 (90-90)	90 (90-90)	
Pathology (WHO)			1
I/II	2	0	
III	50	14	

*P values were calculated by Chi-square test. [a] P value was calculated using two-sided t test.

Supplementary Table 8. Multivariate analysis assessing the risk factors for PFS in the de novo metastatic NPC cohort.

Category and variable	PFS HR (95% CI)	PFS P value*
Age		
	0.978 (0.955-1.003)	0.082
Sex		
Female	Ref	
Male	0.894(0.467-1.714)	0.737
Number of metastatic sites		
Single	Ref	
Multiple	1.103(0.64-1.898)	0.725
Liver involvement		
No	Ref	
Yes	0.986(0.569-1.709)	0.96
Treatment		
CT	Ref	
CT+RT	2.65(1.612-4.356)	<0.001
Group		
Lymphatic	Ref	
Hematogenous	0.397(0.191-0.825)	0.013

*P values were calculated using a Cox proportional hazards model. CT: Chemotherapy; RT: Radiotherapy.