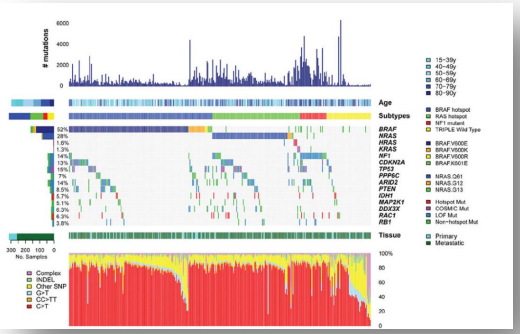
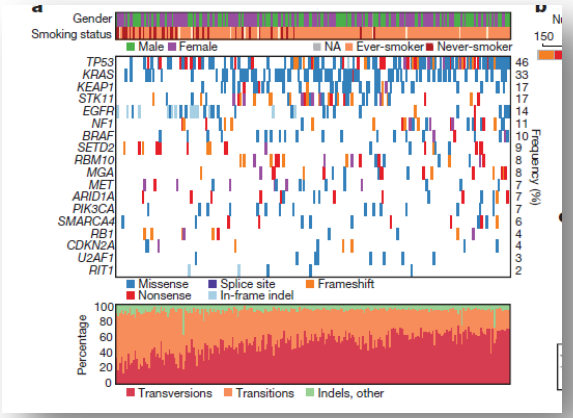
TCGA DATA
where do you come in?

Antien Mooyaart

29-5-2018

Pathology, ErasmusMC





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Genomic Classification of Cutaneous Melanoma

The Cancer Genome Atlas Network[1,*]

[1]Cancer Genome Atlas Program Office, National Cancer Institute at NIH, 31 Center Drive, Bldg. 31, Suite 3A20, Bethesda, MD 20892, USA

ARTICLE

OPEN

doi:10.1038/nature13385

Comprehensive molecular profiling of lung adenocarcinoma

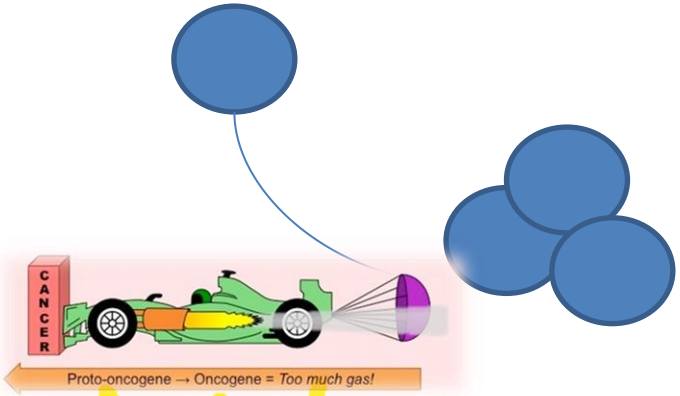
The Cancer Genome Atlas Research Network*

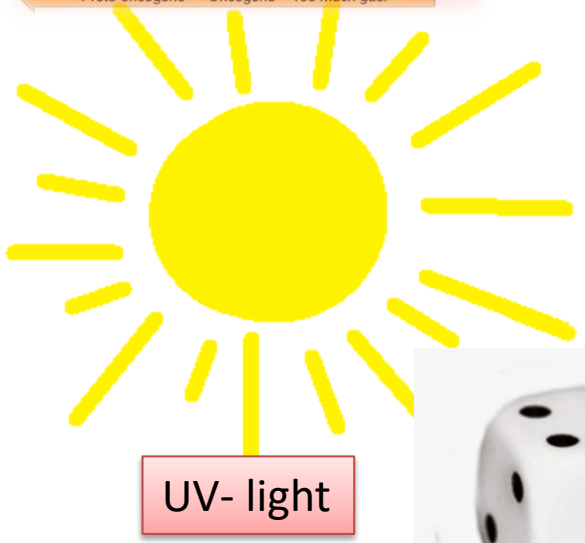
Comprehensive genomic characterization of squamous cell lung cancers

The Cancer Genome Atlas Research Network*

Biology of cancer

Cell (melanocyte)

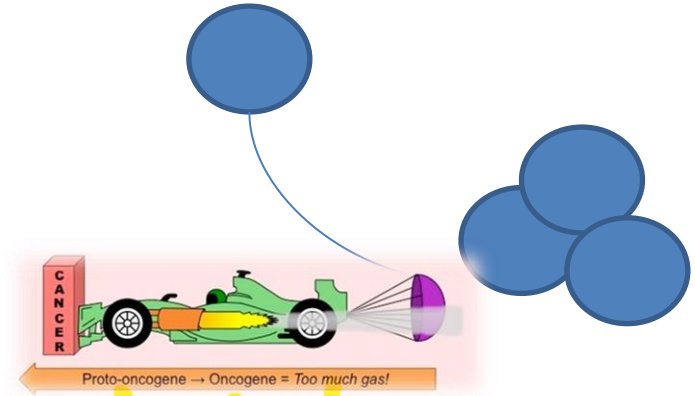


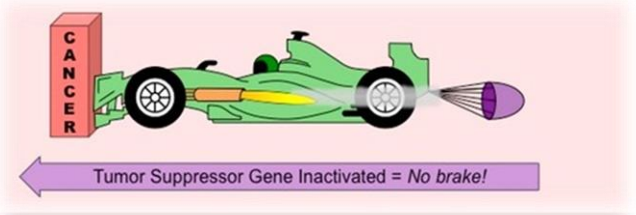


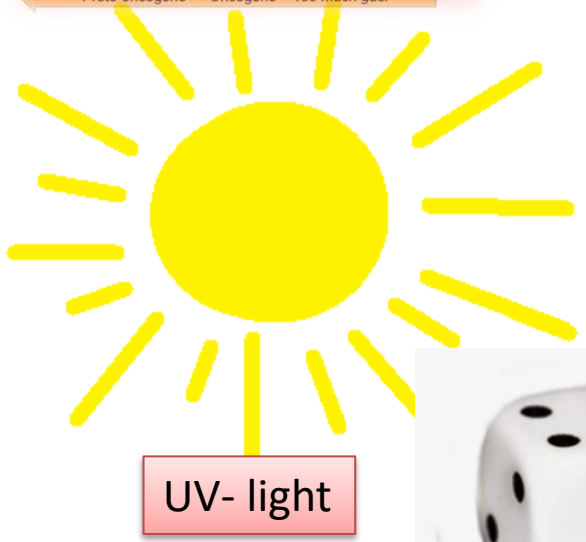
UV- light

Biology of cancer

Cell (melanocyte)

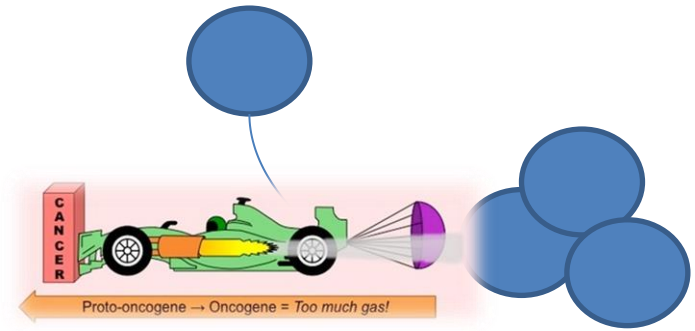


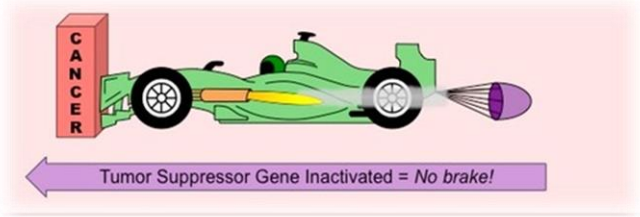


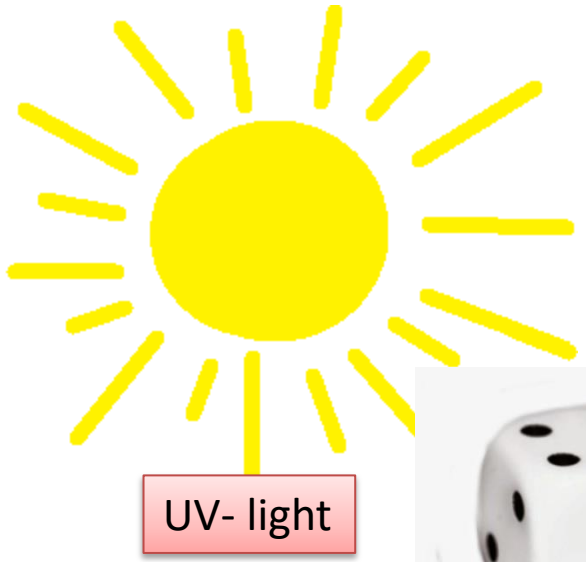


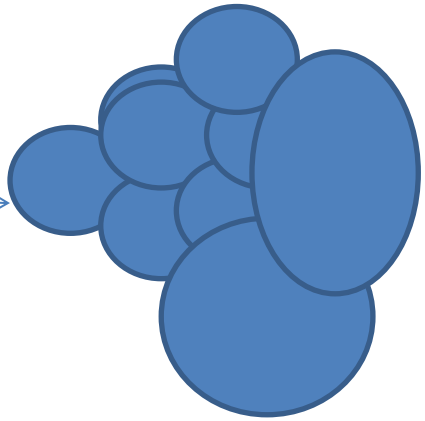
Biology of cancer

Cell (melanocyte)



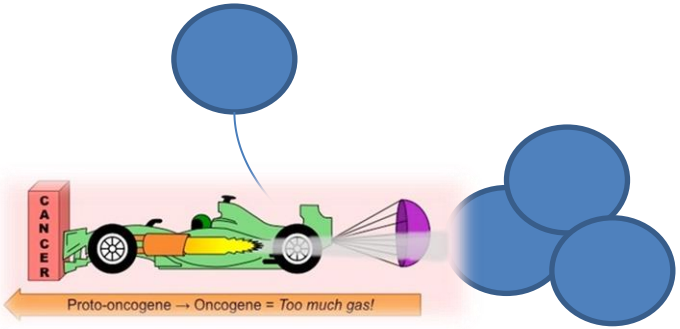


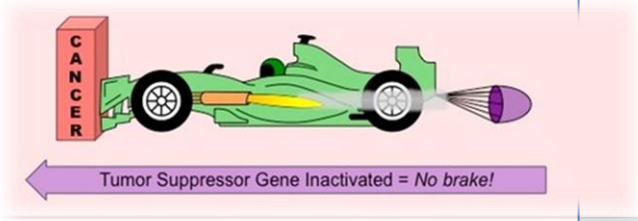




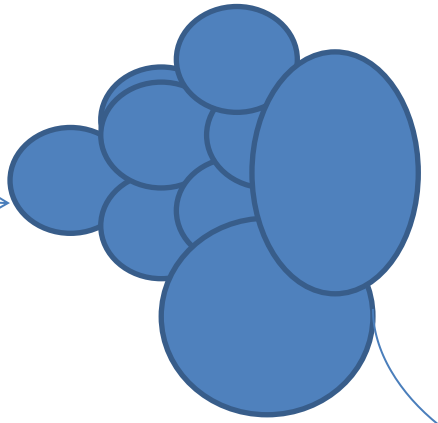
Biology of cancer

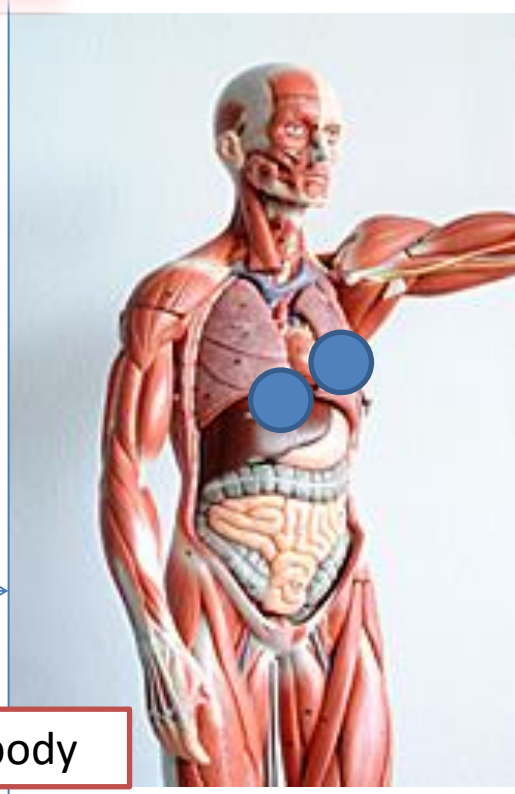
Cell (melanocyte)





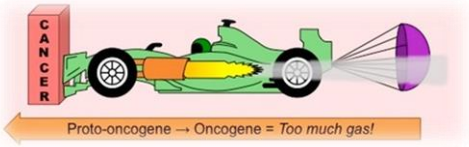
UV- light



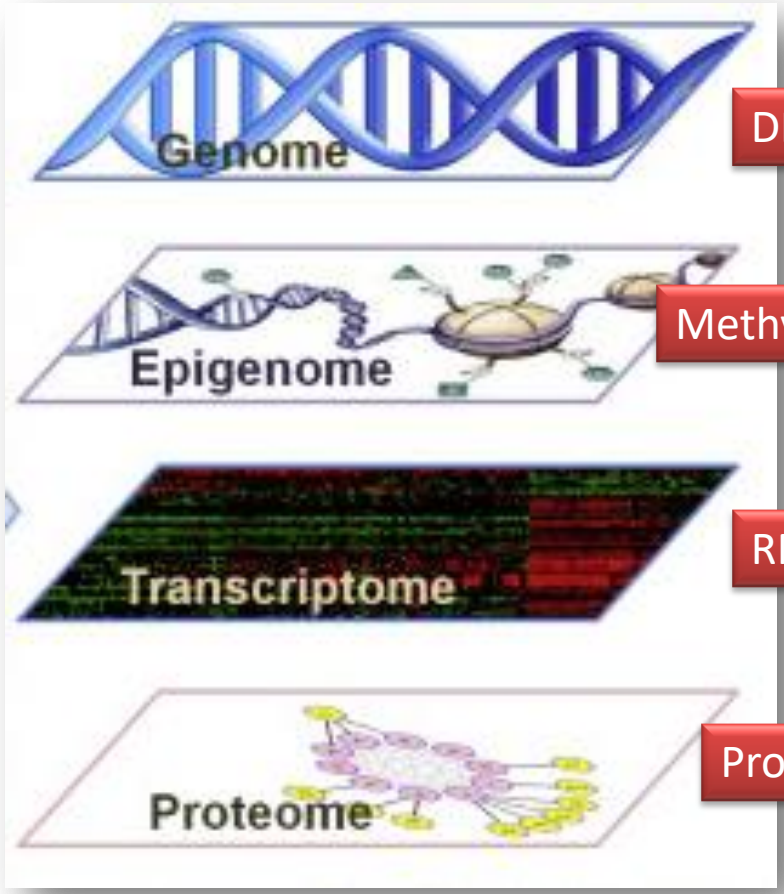


Spread in the body

Biology of cancer



Too much gas!

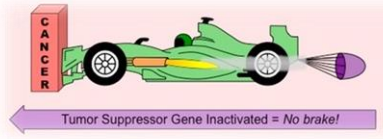


DNA

Methylation

RNA

Protein



No brake!

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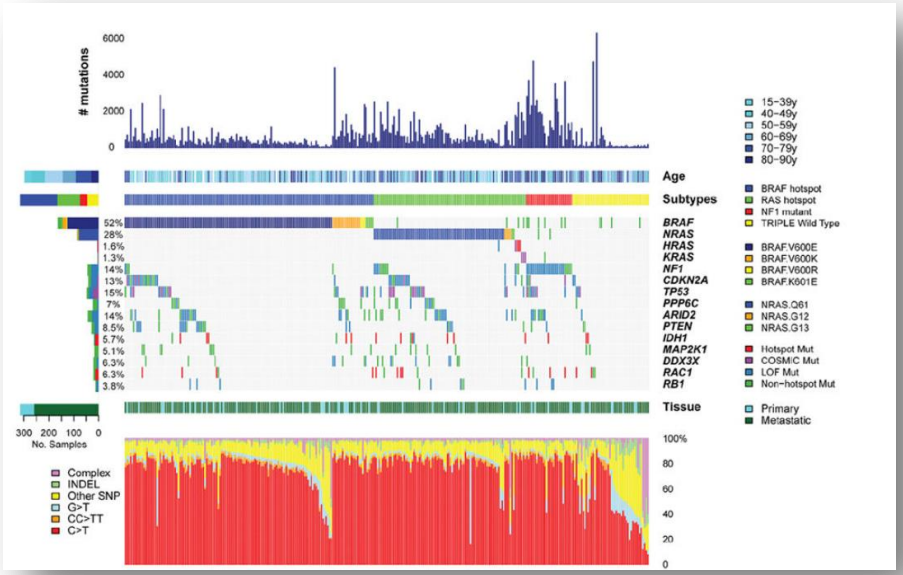

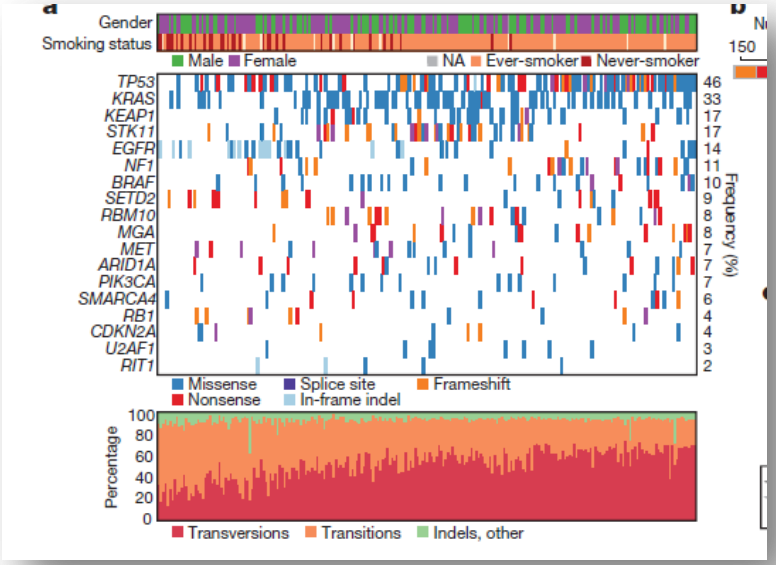

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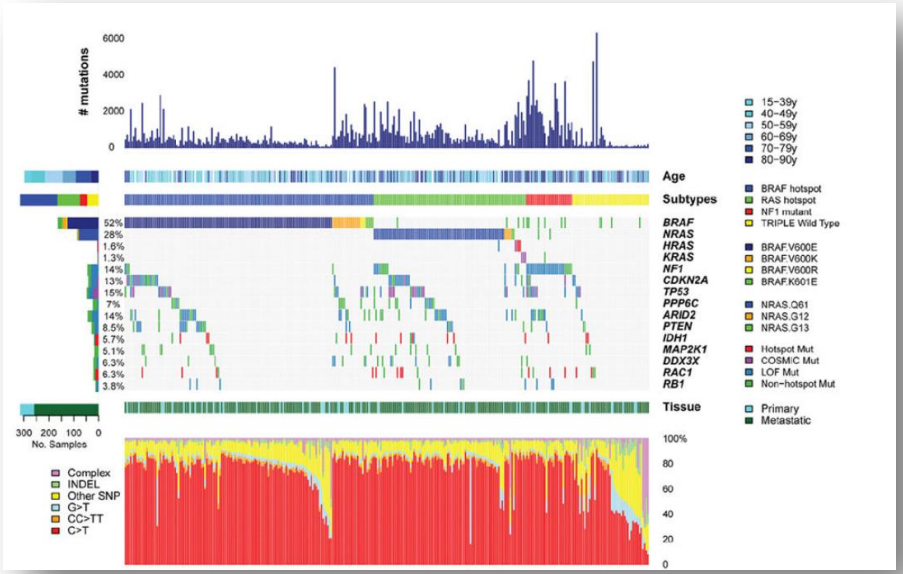
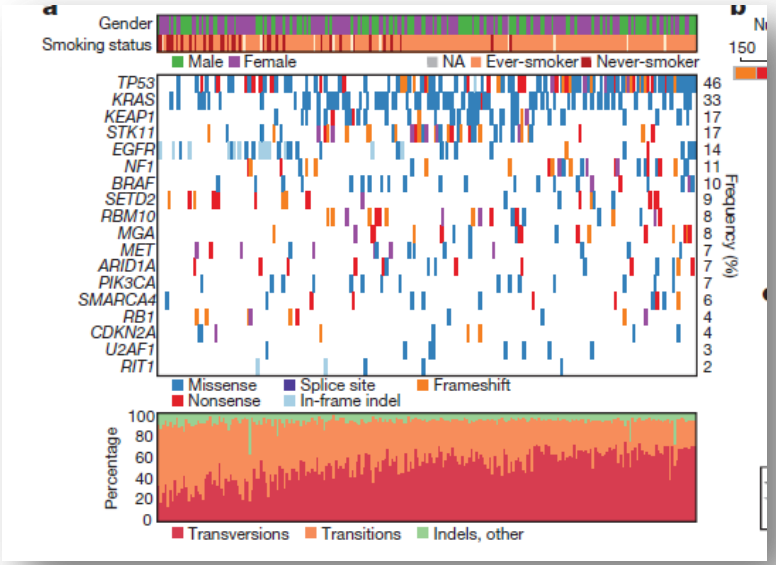
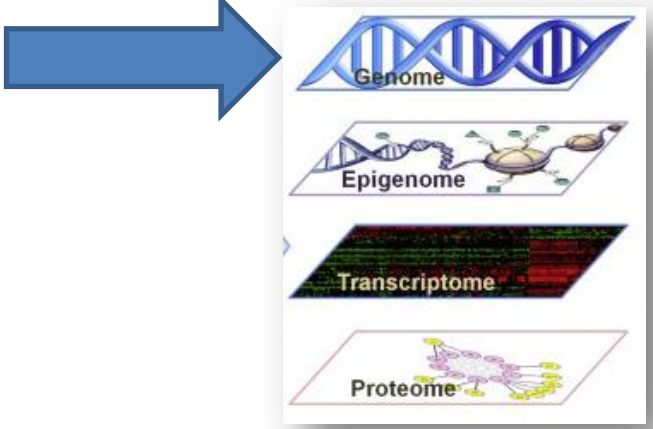
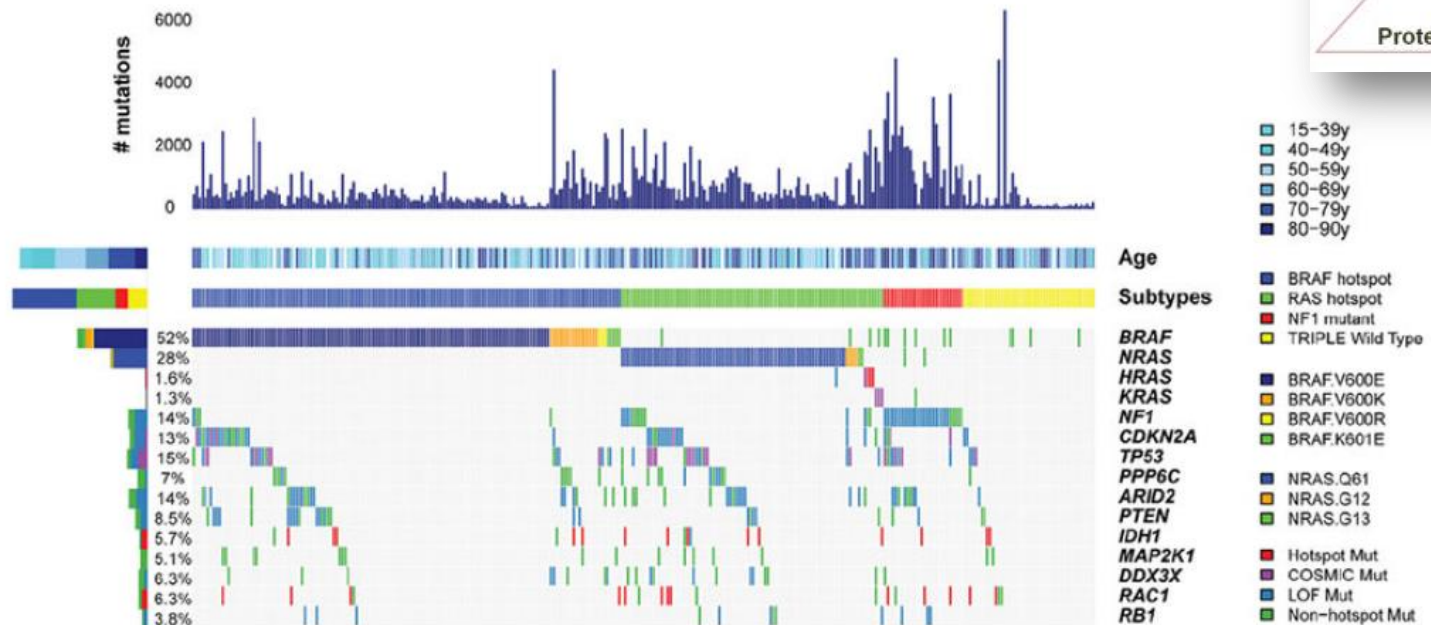
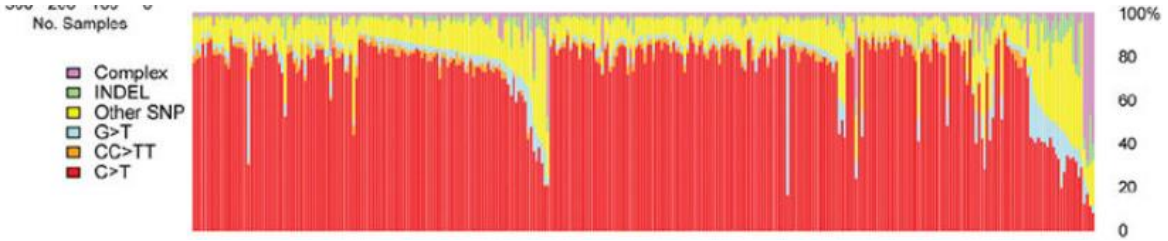


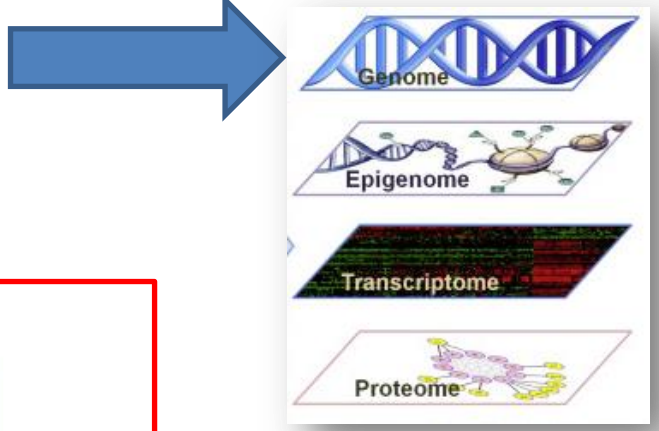


DNA

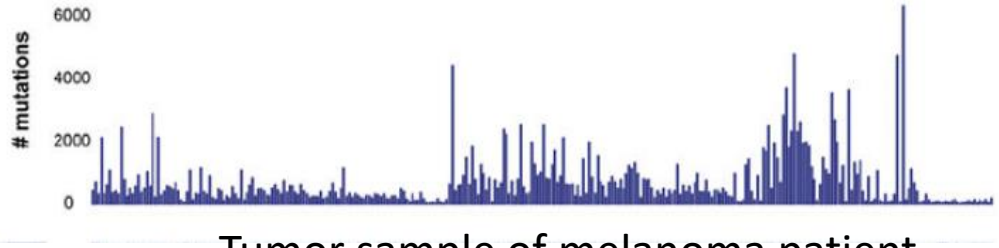

Genome
Epigenome
Transcriptome
Proteome


mutations
6000
4000
2000
0
Age
Subtypes
52%
28%
1.6%
1.3%
14%
13%
15%
7%
14%
8.5%
5.7%
5.1%
6.3%
6.3%
3.8%
BRAF
NRAS
HRAS
KRAS
NF1
CDKN2A
TP53
PPP6C
ARID2
PTEN
IDH1
MAP2K1
DDX3X
RAC1
RB1
15−39y
40−49y
50−59y
60−69y
70−79y
80−90y
BRAF hotspot
RAS hotspot
NF1 mutant
TRIPLE Wild Type
BRAF.V600E
BRAF.V600K
BRAF.V600R
BRAF.K601E
NRAS.Q61
NRAS.G12
NRAS.G13
Hotspot Mut
COSMIC Mut
LOF Mut
Non−hotspot Mut


No. Samples
Complex
INDEL
Other SNP
G>T
CC>TT
C>T
100%
80
60
40
20
0

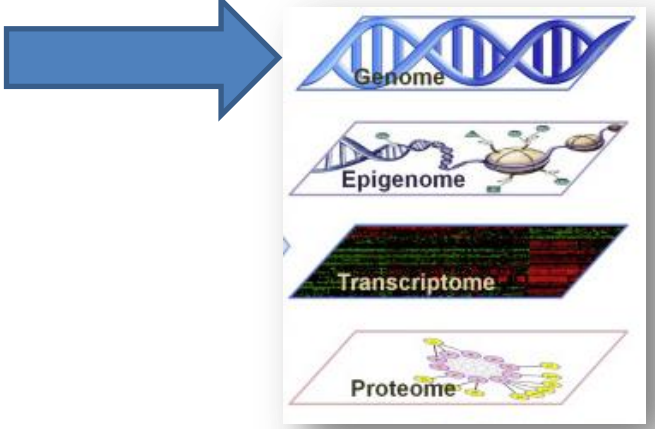


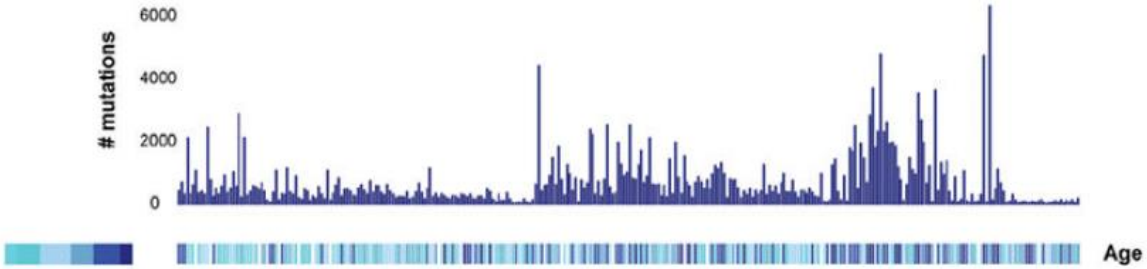
DNA



Tumor sample of melanoma patient

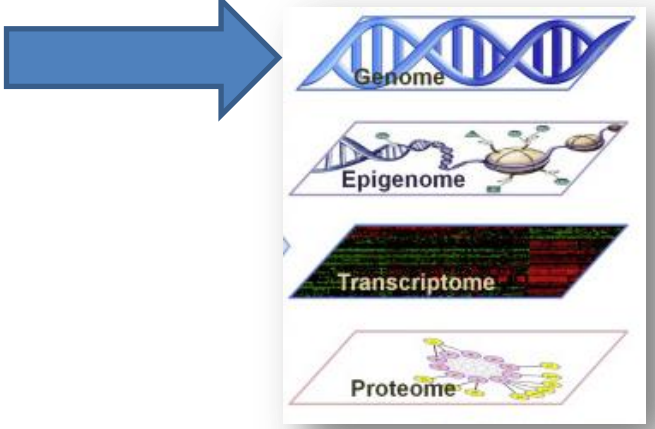
DNA

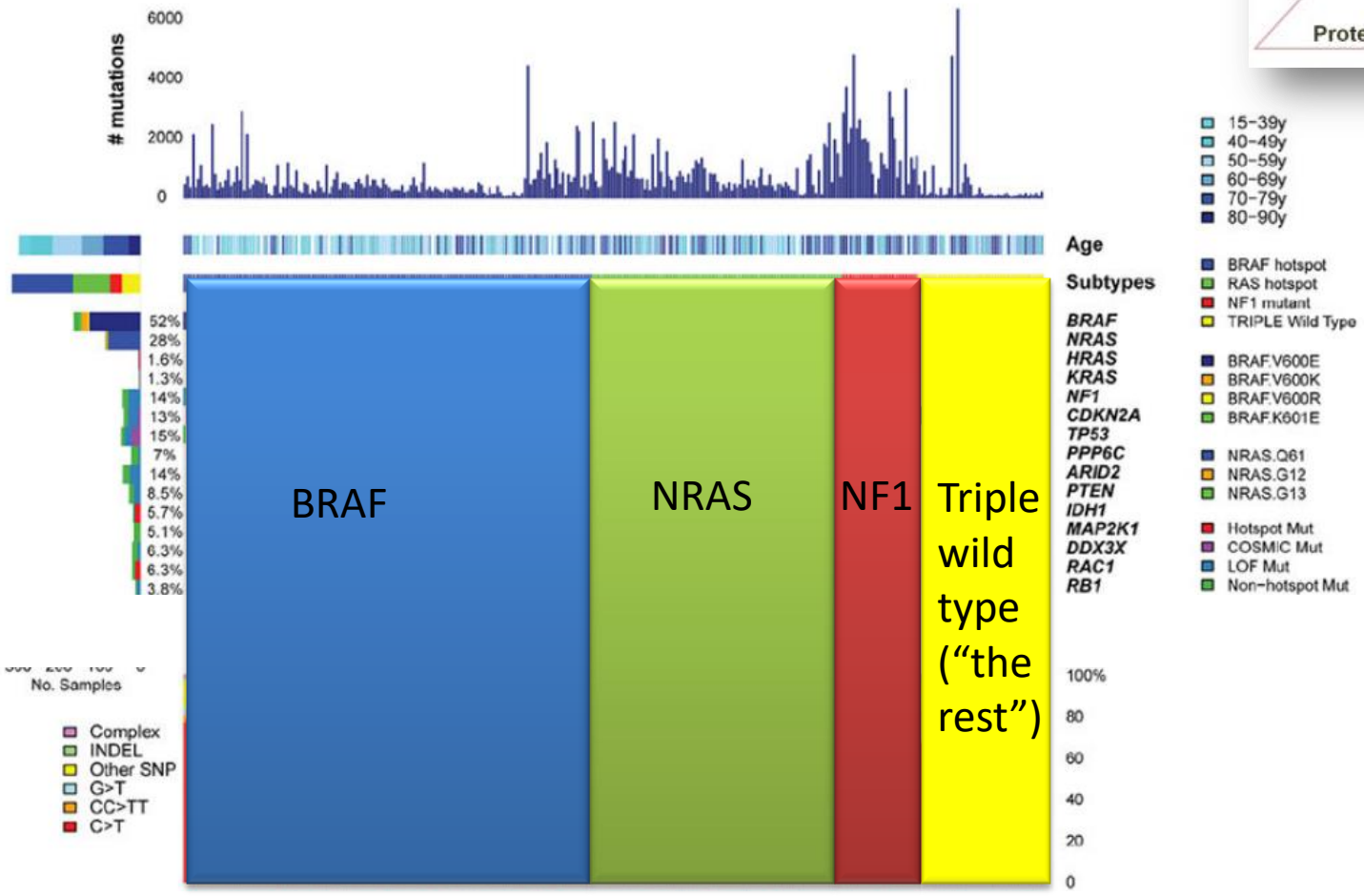

Genome
Epigenome
Transcriptome
Proteome


mutations
6000
4000
2000
0
Age

15–39y
40–49y
50–59y
60–69y
70–79y
80–90y

DNA


Genome
Epigenome
Transcriptome
Proteome


mutations
6000
4000
2000
0
Age
Subtypes
52%
28%
1.6%
1.3%
14%
13%
15%
7%
14%
8.5%
5.7%
5.1%
6.3%
6.3%
3.8%
BRAF
NRAS
NF1
Triple wild type ("the rest")
BRAF
NRAS
HRAS
KRAS
NF1
CDKN2A
TP53
PPP6C
ARID2
PTEN
IDH1
MAP2K1
DDX3X
RAC1
RB1
100%
80
60
40
20
0
No. Samples
Complex
INDEL
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G>T
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BRAF hotspot
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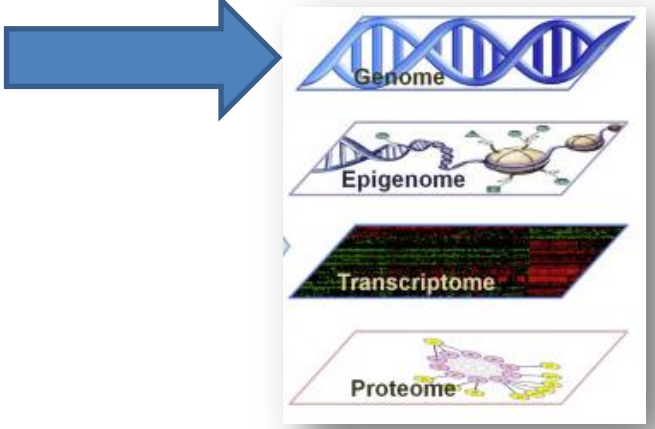
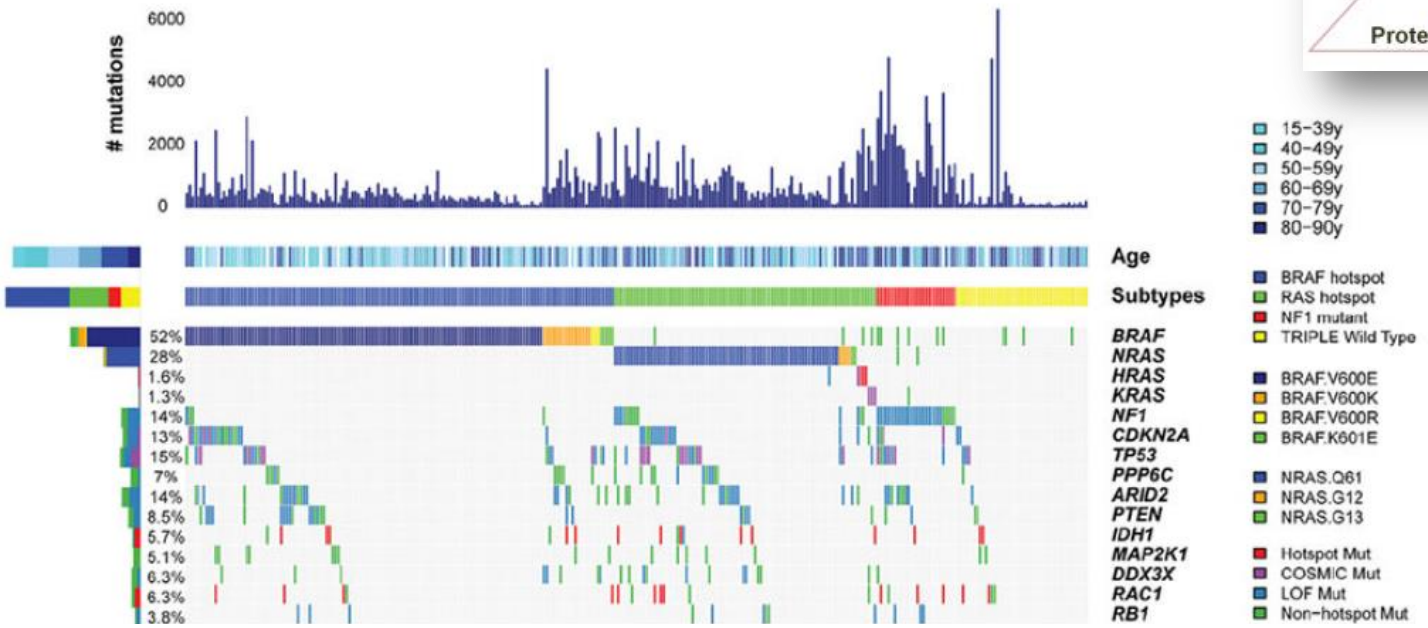
BRAF.V600K
BRAF.V600R
BRAF.K601E
NRAS.Q61
NRAS.G12
NRAS.G13
Hotspot Mut
COSMIC Mut
LOF Mut
Non-hotspot Mut

DNA


Genome
Epigenome
Transcriptome
Proteome


mutations
6000
4000
2000
0
Age
Subtypes
52% BRAF
28% NRAS
1.6% HRAS
1.3% KRAS
14% NF1
13% CDKN2A
15% TP53
7% PPP6C
14% ARID2
8.5% PTEN
5.7% IDH1
5.1% MAP2K1
6.3% DDX3X
6.3% RAC1
3.8% RB1
15−39y
40−49y
50−59y
60−69y
70−79y
80−90y
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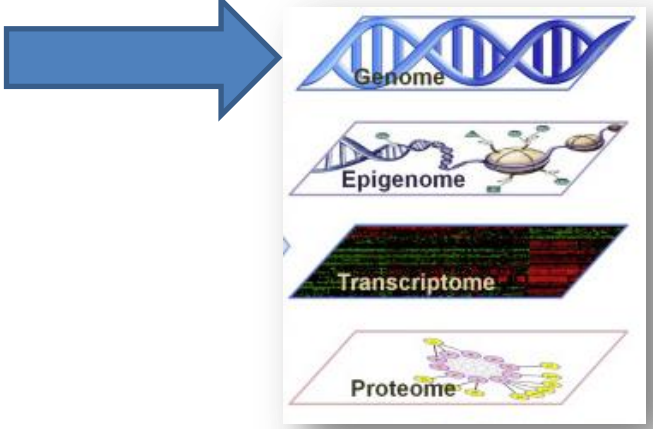
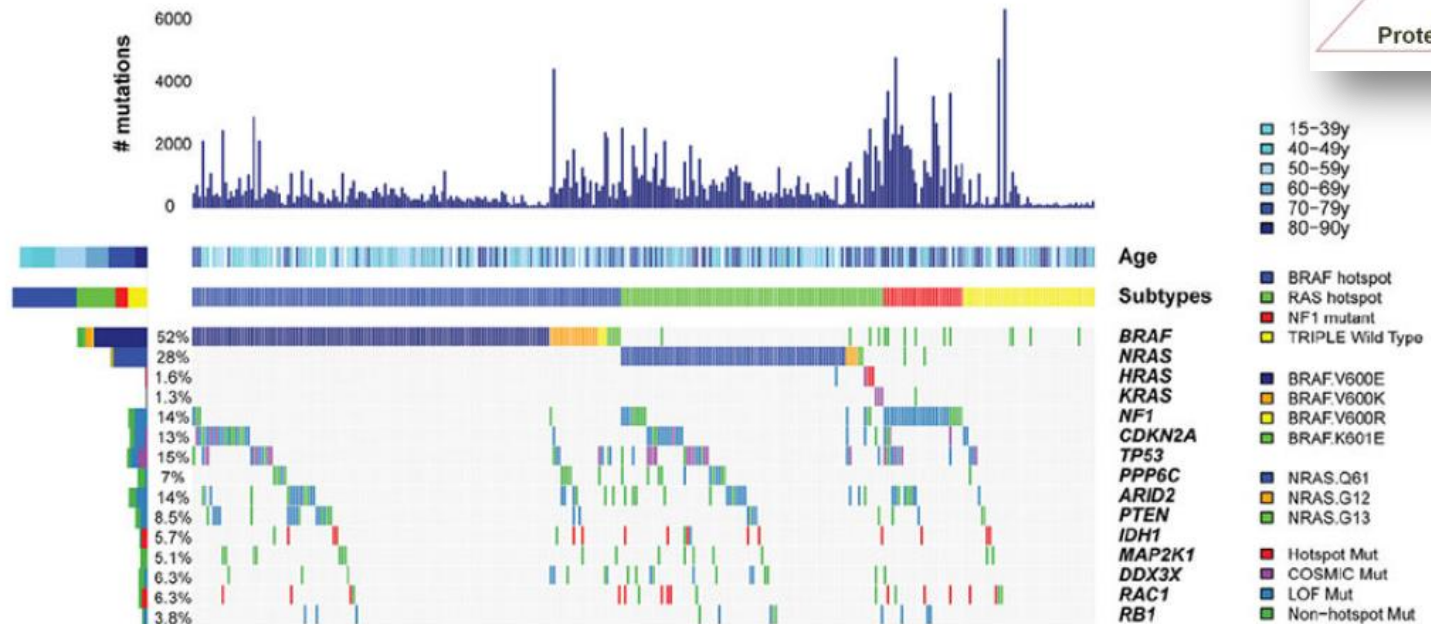
BRAF.V600R
BRAF.K601E
NRAS.Q61
NRAS.G12
NRAS.G13
Hotspot Mut
COSMIC Mut
LOF Mut
Non−hotspot Mut

DNA


Genome
Epigenome
Transcriptome
Proteome


mutations
6000
4000
2000
0
Age
Subtypes
15-39y
40-49y
50-59y
60-69y
70-79y
80-90y
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RAS hotspot
NF1 mutant
TRIPLE Wild Type
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7% PPP6C
14% ARID2
8.5% PTEN
5.7% IDH1
5.1% MAP2K1
6.3% DDX3X
6.3% RAC1
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BRAF.V600K
BRAF.V600R
BRAF.K601E
NRAS.Q61
NRAS.G12
NRAS.G13
Hotspot Mut
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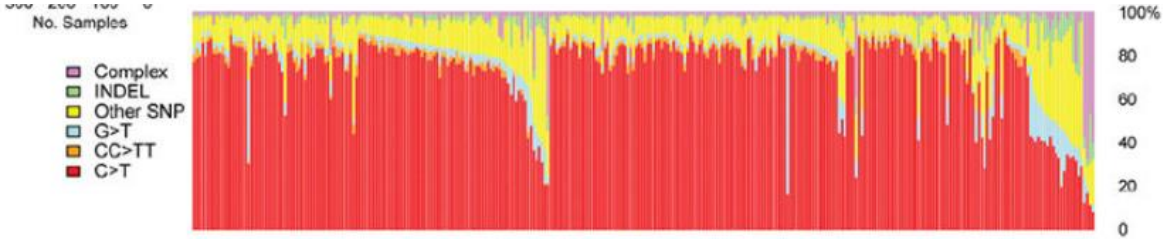
LOF Mut
Non-hotspot Mut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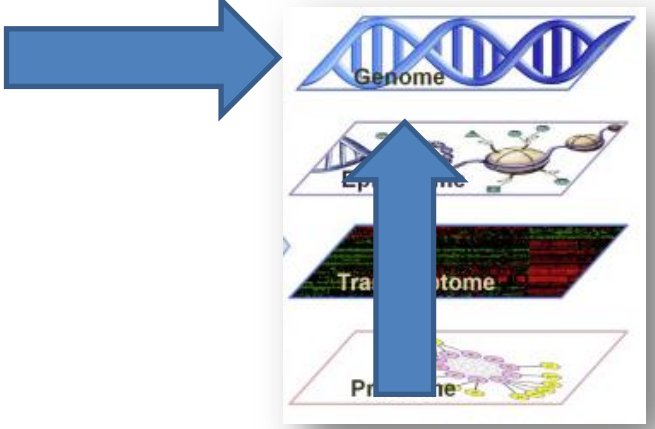
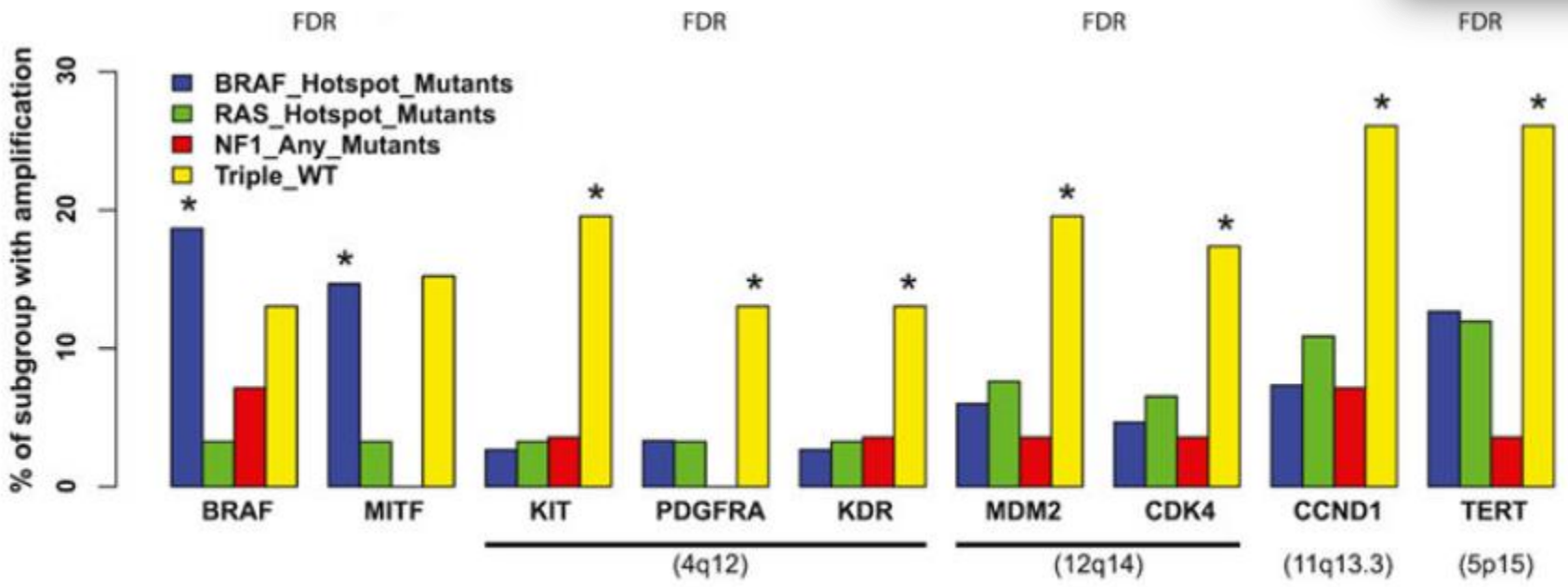
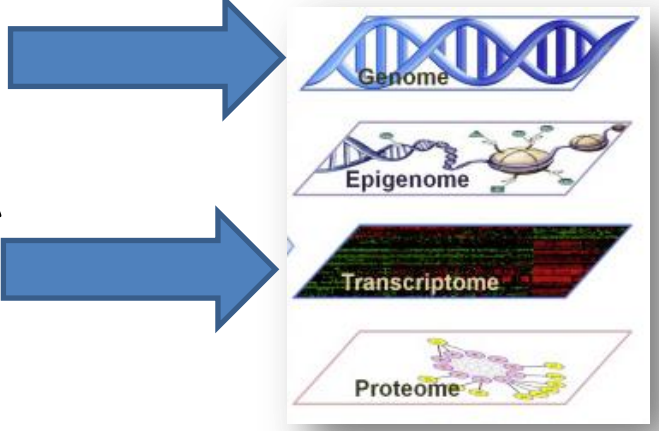
INDEL
Other SNP
G>T
CC>TT
C>T
100%
80
60
40
20
0

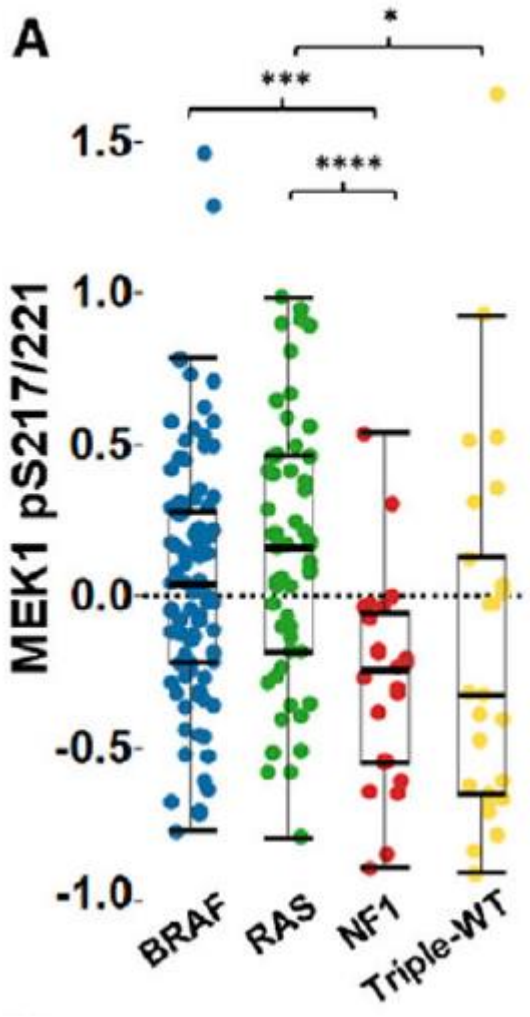
DNA


Genome

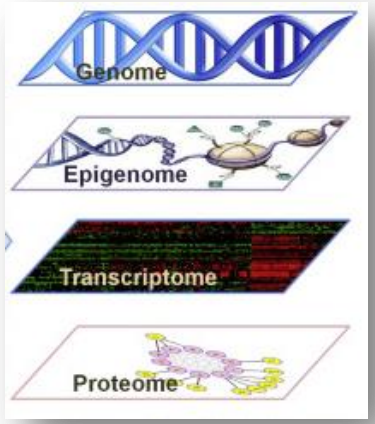

FDR
FDR
FDR
FDR
% of subgroup with amplification
0
10
20
30
BRAF_Hotspot_Mutants
RAS_Hotspot_Mutants
NF1_Any_Mutants
Triple_WT
*
BRAF
MITF
KIT
PDGFRA
KDR
MDM2
CDK4
CCND1
TERT
(4q12)
(12q14)
(11q13.3)
(5p15)

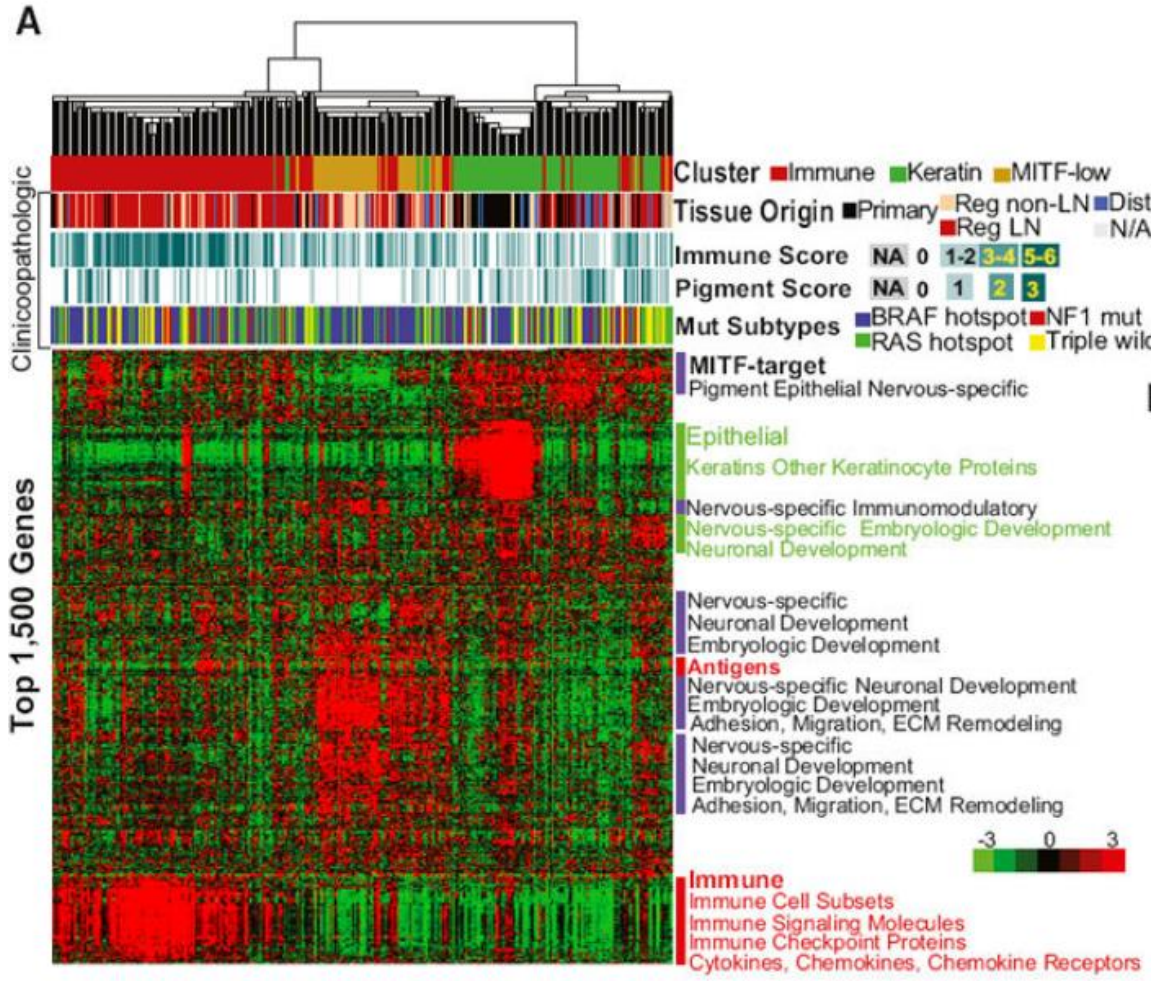
DNA vs. RNA

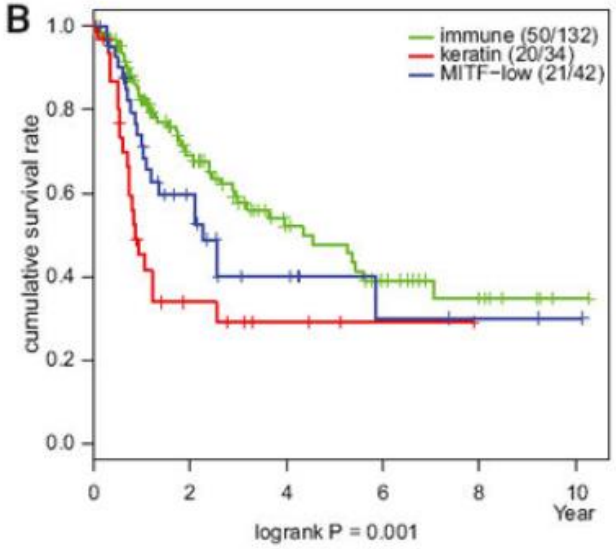

Genome
Epigenome
Transcriptome
Proteome


A
*
***
****
1.5
1.0
0.5
0.0
-0.5
-1.0
MEK1 pS217/221
BRAF
RAS
NF1
Triple-WT

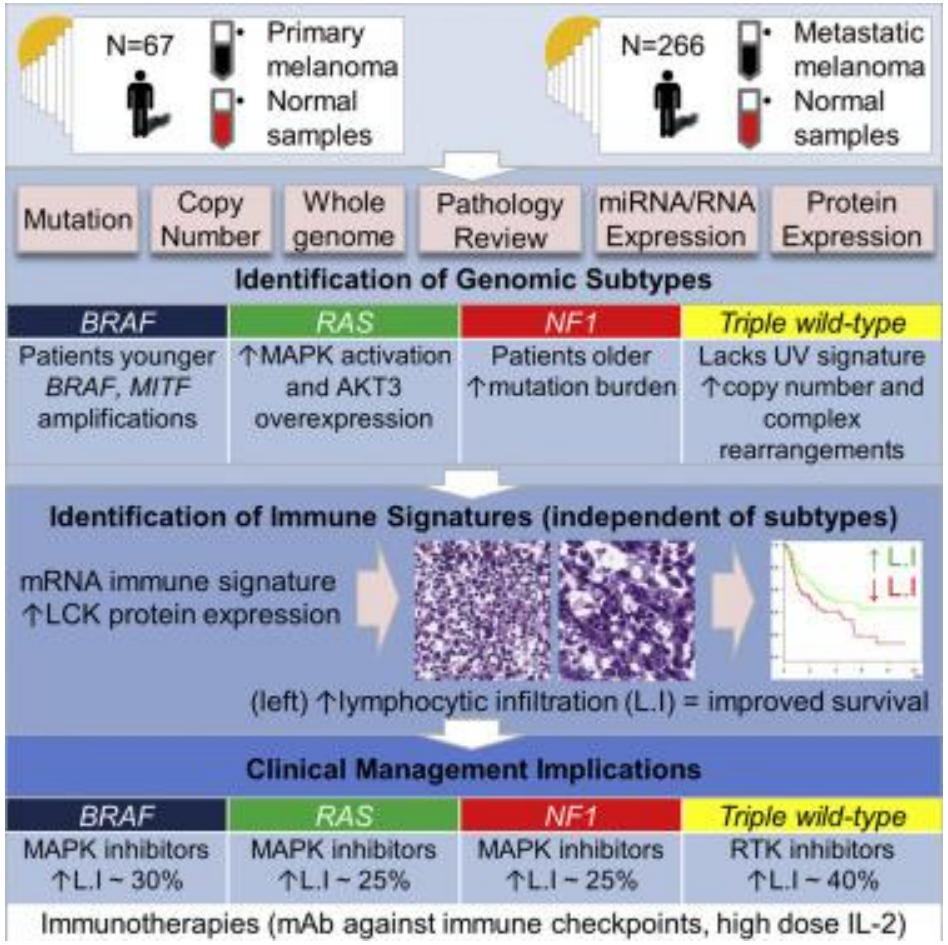
RNA


Genome
Epigenome
Transcriptome
Proteome

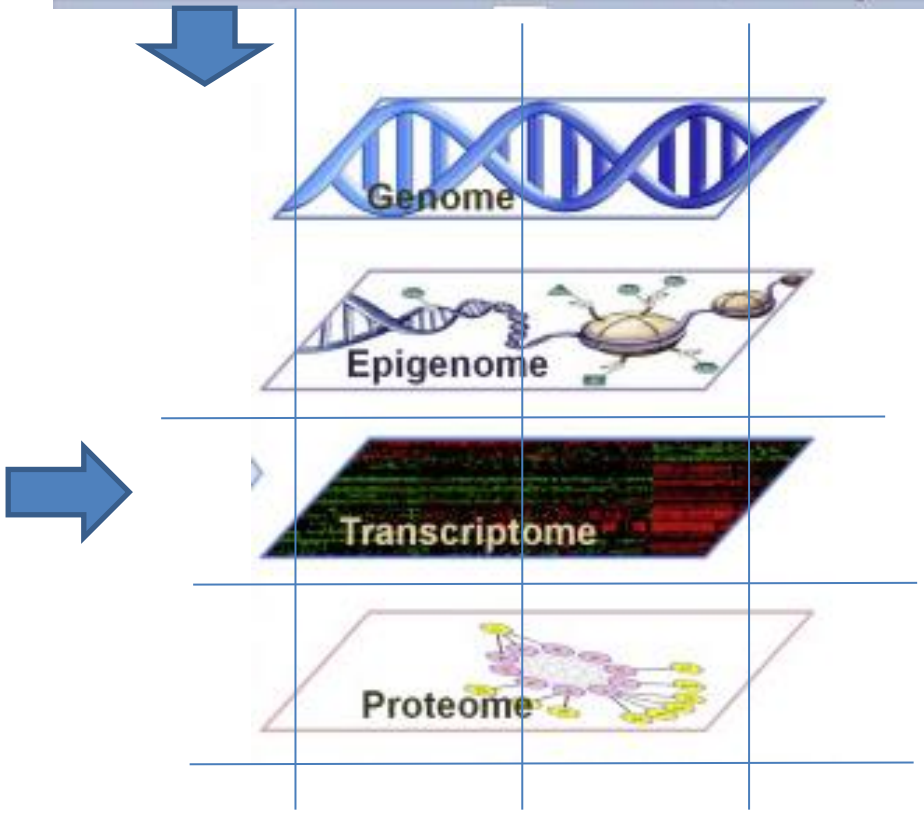

A
Clinicopathologic
Top 1,500 Genes
Cluster Immune Keratin MITF-low
Tissue Origin Primary Reg non-LN Dist Mets
Reg LN N/A
Immune Score NA 0 1-2 3-4 5-6
Pigment Score NA 0 1 2 3
Mut Subtypes BRAF hotspot NF1 mut
RAS hotspot Triple wild type
MITF-target
Pigment Epithelial Nervous-specific
Epithelial
Keratins Other Keratinocyte Proteins
Nervous-specific Immunomodulatory
Nervous-specific Embryologic Development
Neuronal Development
Nervous-specific
Neuronal Development
Embryologic Development
Antigens
Nervous-specific Neuronal Development
Embryologic Development
Adhesion, Migration, ECM Remodeling
Nervous-specific
Neuronal Development
Embryologic Development
Adhesion, Migration, ECM Remodeling
-3 0 3
Immune
Immune Cell Subsets
Immune Signaling Molecules
Immune Checkpoint Proteins
Cytokines, Chemokines, Chemokine Receptors


B
cumulative survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Year
immune (50/132)
keratin (20/34)
MITF-low (21/42)
logrank P = 0.001

Conclusion


N=67
Primary melanoma
Normal samples
N=266
Metastatic melanoma
Normal samples
Mutation
Copy Number
Whole genome
Pathology Review
miRNA/RNA Expression
Protein Expression
Identification of Genomic Subtypes
BRAF
Patients younger
BRAF, MITF amplifications
RAS
↑MAPK activation and AKT3 overexpression
NF1
Patients older
↑mutation burden
Triple wild-type
Lacks UV signature
↑copy number and complex rearrangements
Identification of Immune Signatures (independent of subtypes)
mRNA immune signature
↑LCK protein expression
↑L.I
↓L.I
(left) ↑lymphocytic infiltration (L.I) = improved survival
Clinical Management Implications
BRAF
MAPK inhibitors
↑L.I ~ 30%
RAS
MAPK inhibitors
↑L.I ~ 25%
NF1
MAPK inhibitors
↑L.I ~ 25%
Triple wild-type
RTK inhibitors
↑L.I ~ 40%
Immunotherapies (mAb against immune checkpoints, high dose IL-2)

Identification of Genomic Subtypes			
BRAF	*RAS*	*NF1*	*Triple wild-type*
Patients younger *BRAF, MITF* amplifications	↑MAPK activation and AKT3 overexpression	Patients older ↑mutation burden	Lacks UV signature ↑copy number and complex rearrangements



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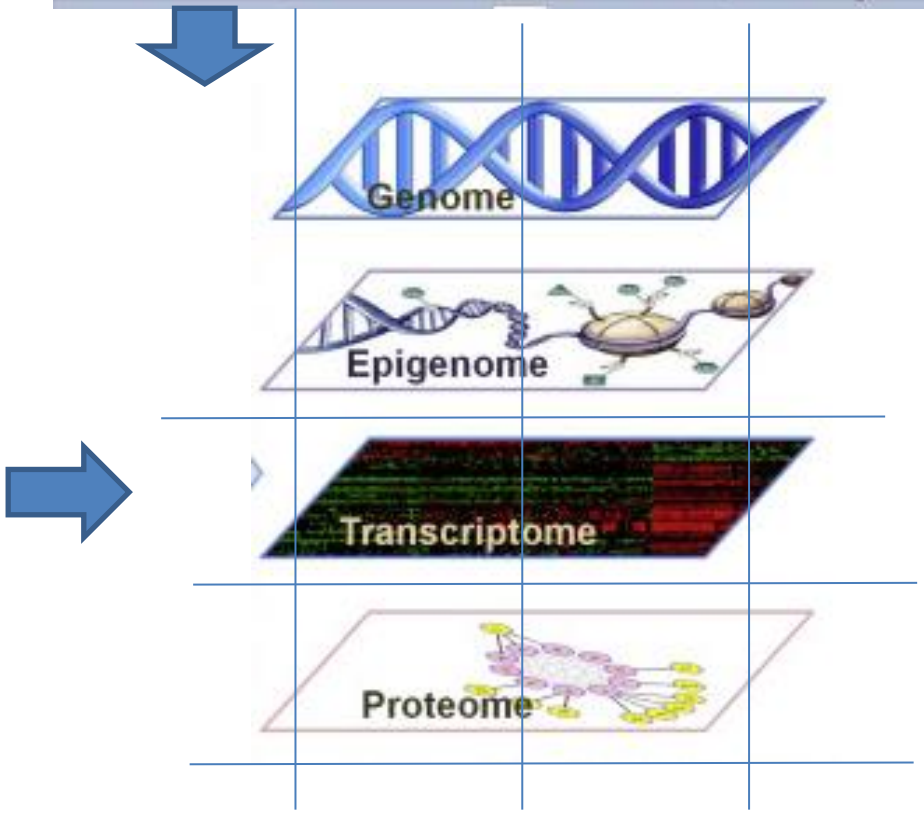
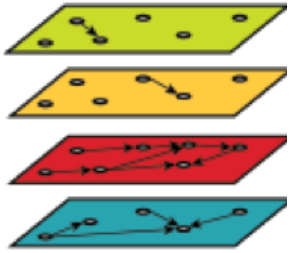
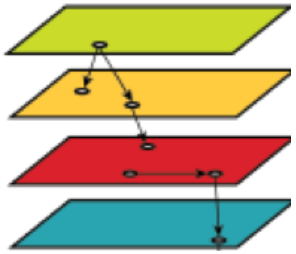


Single omics

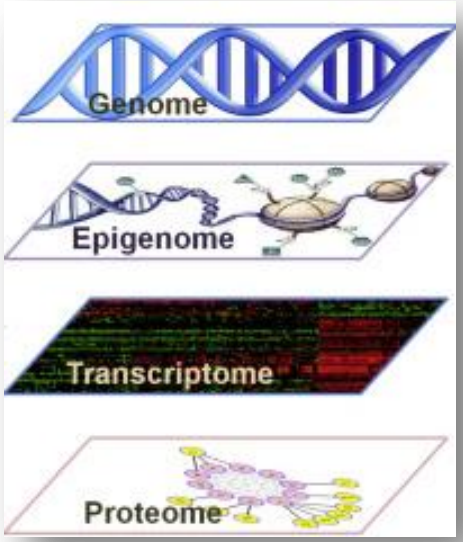


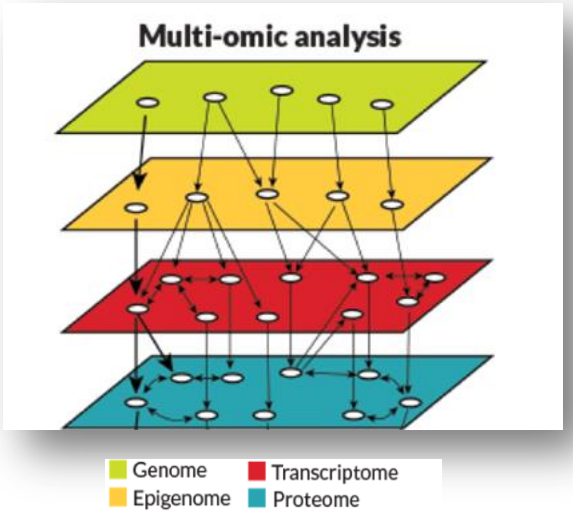
Focus on one or two molecules



Genome
Epigenome
Transcriptome
Proteome

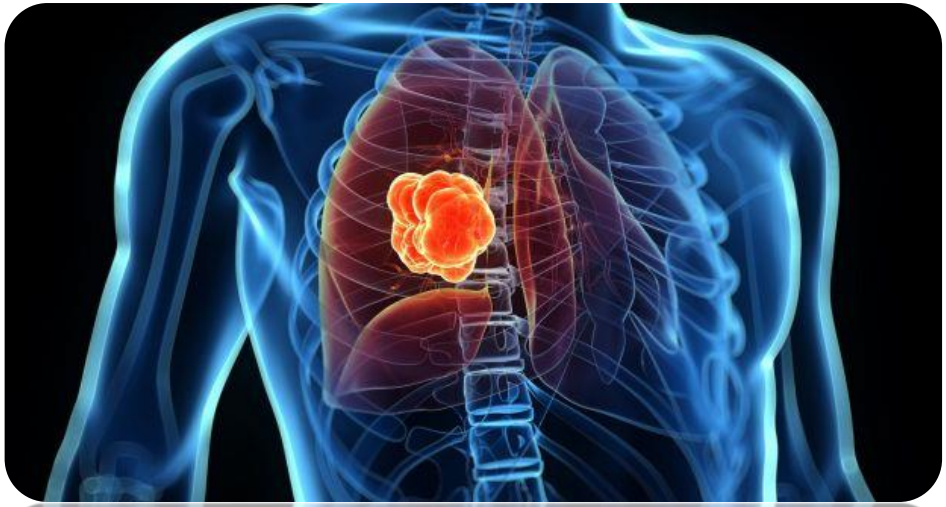
Where do you come in?





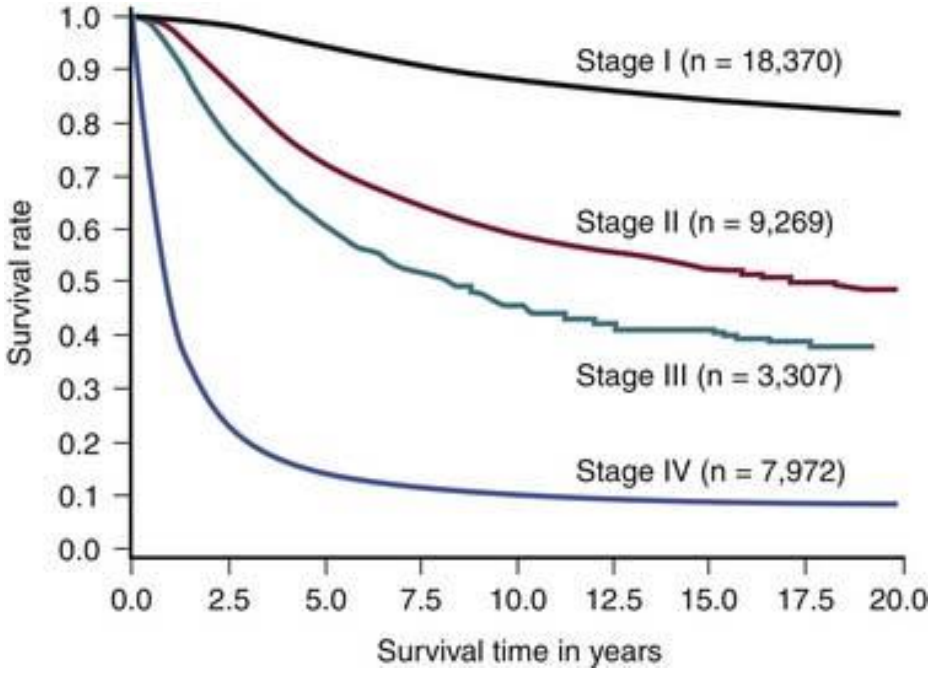
Why relevant?

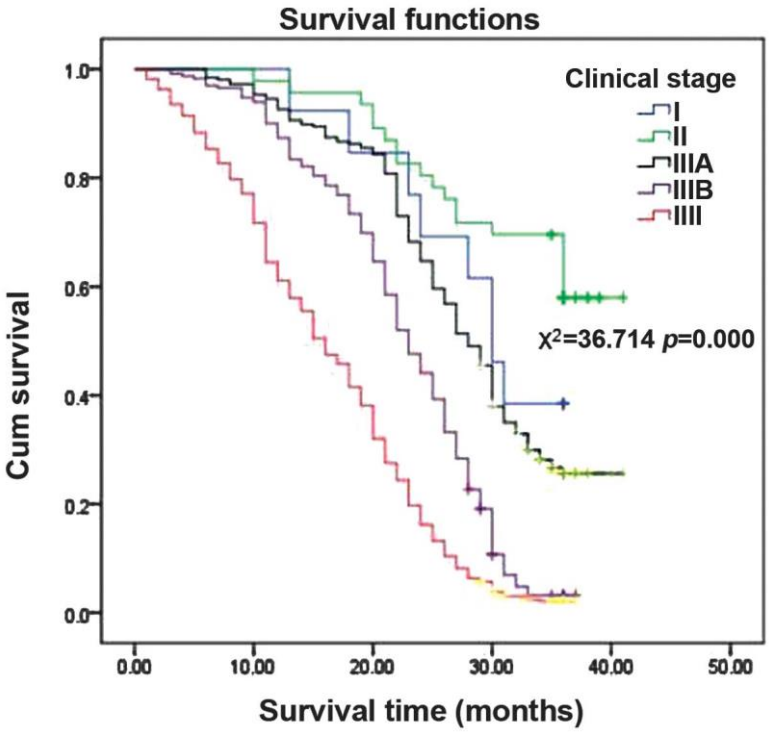
Melanoma

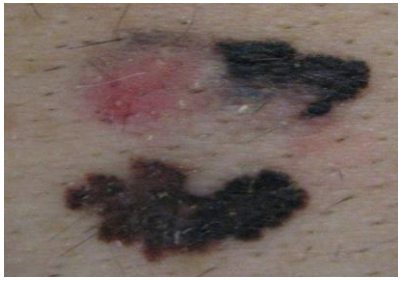


Lung cancer

Poor prognosis







Treatment

- Chemotherapy
  - All dividing cells
- Targeted therapy (specific for the tumor)
- Immunotherapy

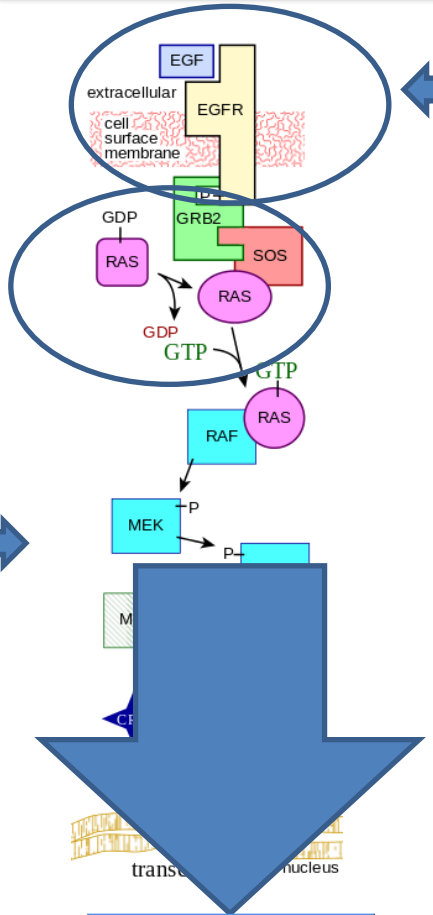
Targeted therapy

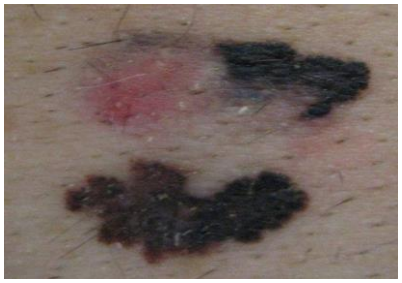
MAP Kinase pathway

EGFR inhibitor

BRAF inhibitor

MEK inhibitor





Targeted therapy

MAP Kinase pathway

EGFR inhibitor

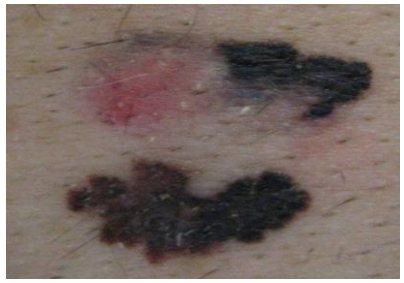
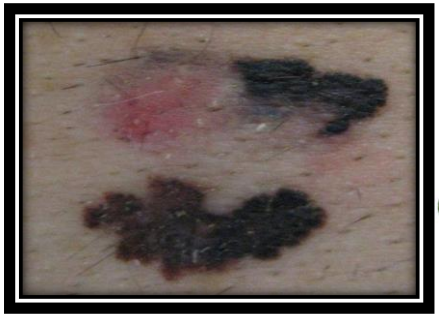
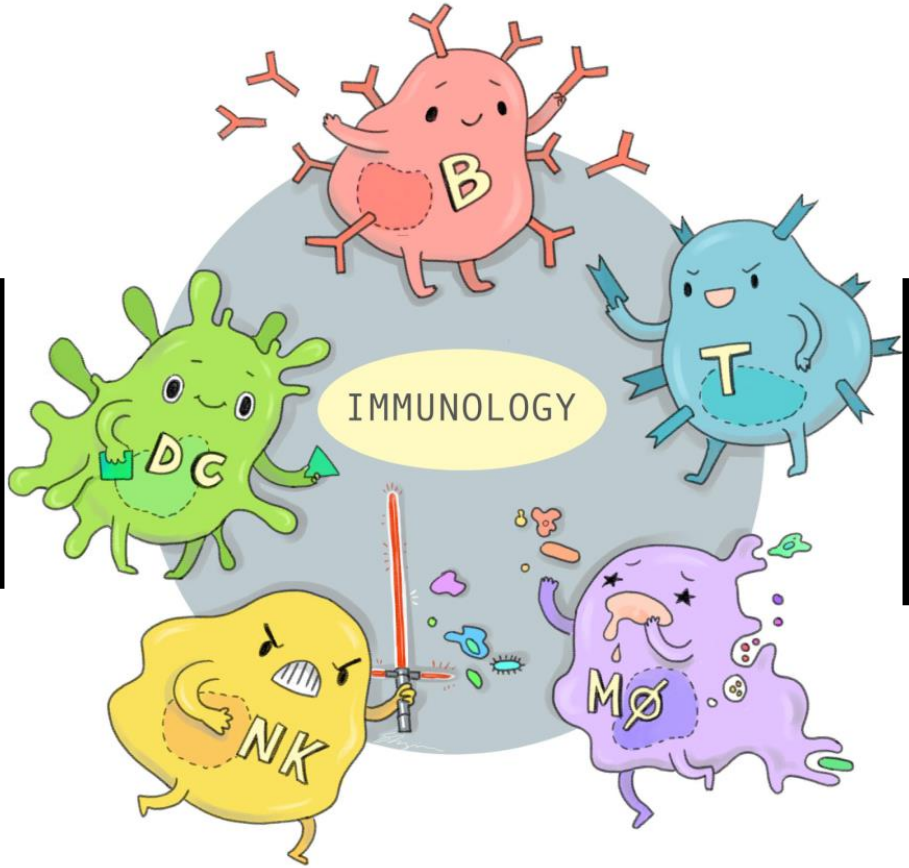
BRAF inhibitor

MEK inhibitor

MOSTLY NOT DURABLE (3-6 month)

More drug targets?

Cell division



Immunotherapy