BGGN 213

Cancer Genomics & Immunoinformatics

Lecture 18

Barry Grant

UC San Diego

http://thegrantlab.org/bggn213

Today's Menu

Cancer Genomics	Brief review of cancer fundamentals, What is cancer and what causes it?
Mining Cancer Genomic Data	**Hands-on analysis** to identify genomic changes in different cancers and identify new targets for therapy
Towards personalized cancer treatments	Recap on how the immune system normally detects cancer cells and how we can predict mutations that can be recognized by T cells
Cancer Immunoinformatics	**Hands-on analysis** to design personalized cancer vaccines

What is Cancer?

“Cancer is a name given to a collection of related diseases, where some of the body’s cells begin to divide without stopping and spread into surrounding tissue”

Source: https://www.cancer.gov

It is estimated that cancer will strike 40% of people at some point in their lifetime with frequently devastating effects.

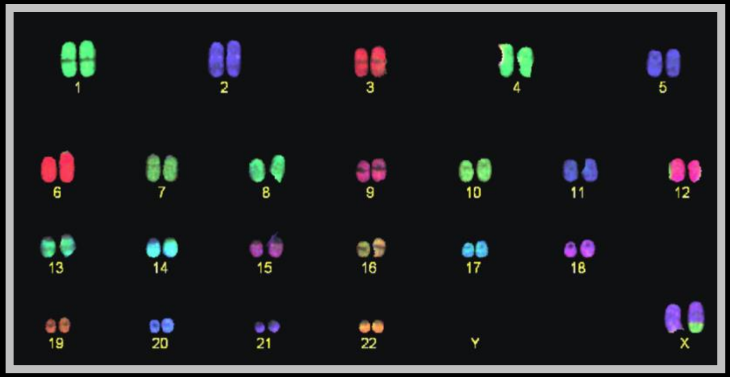
What is Cancer?

“Cancer is a name given to a collection of related diseases, where some of the body’s cells begin to divide without stopping and spread into surrounding tissue”

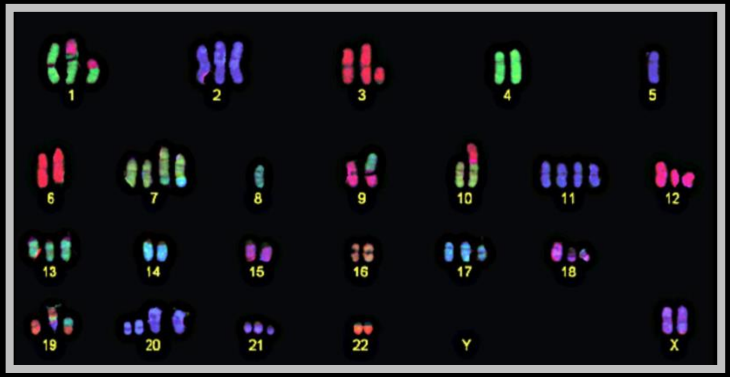
Source: https://www.cancer.gov

Cancer is a disease of the Genome

- Caused by changes to genes that control the way our cells function, especially how they **grow and divide**.
- A major challenge in treating cancer is that every tumor is different: Each person’s cancer has a unique combination of genetic changes (both “driver” & “passenger”).
- As the cancer continues to grow, additional changes will occur.



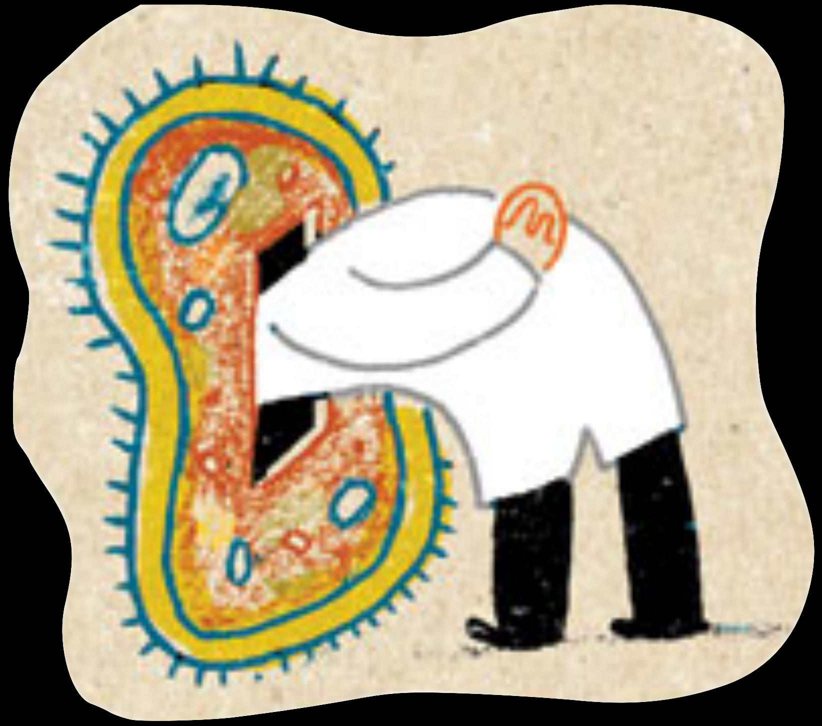
Healthy 46 chromosomes



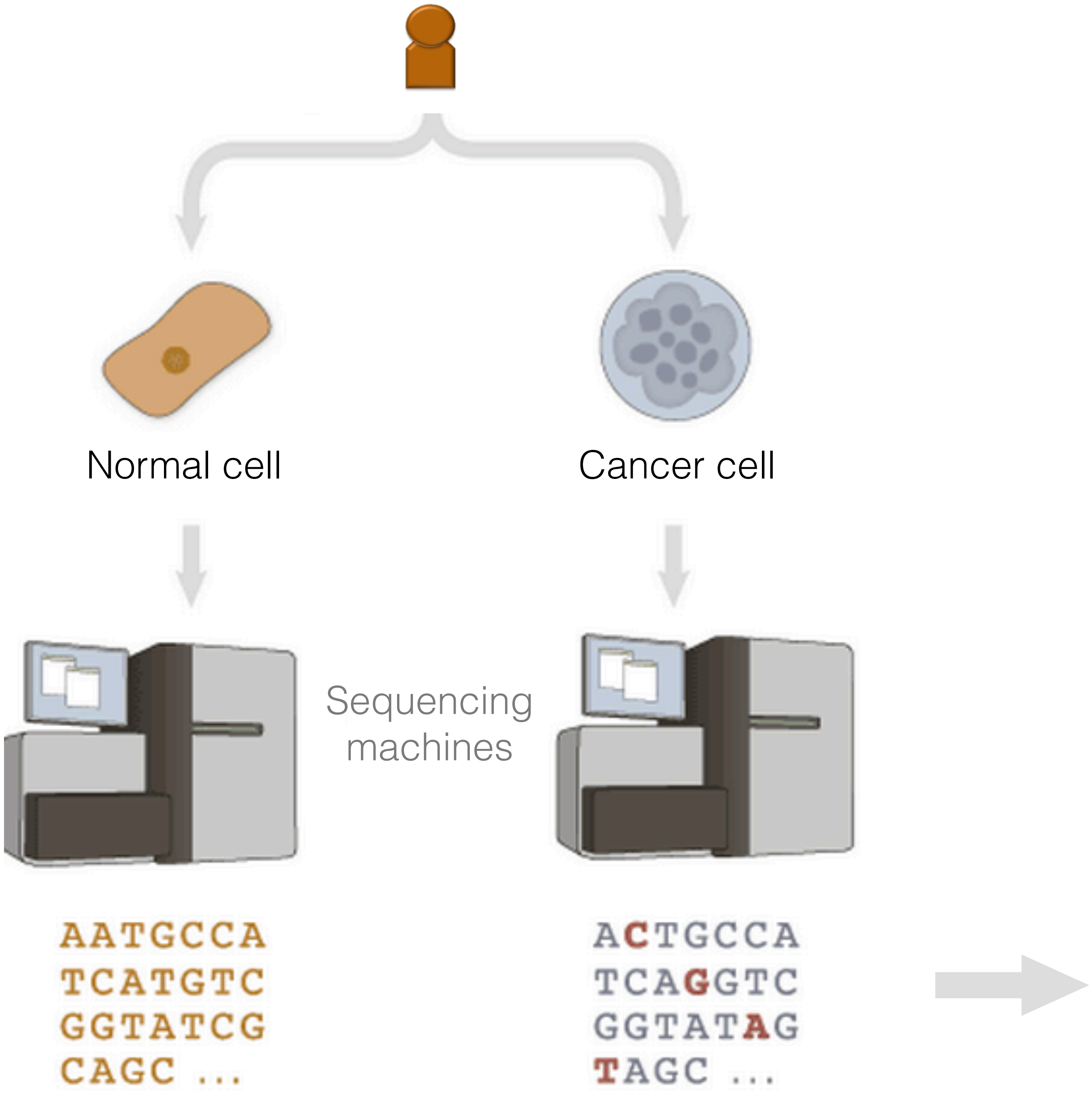
Example cancer 59 chromosomes

Goals of Cancer Genome Research

- Identify changes in the genomes of tumors that drive cancer progression
- Identify new targets for therapy
- Select drugs based on the genomics of the tumor
- Provide early cancer detection and treatment response monitoring
- Utilize cancer specific mutations to derive neoantigen immunotherapy approaches



Finding Cancer Associated Mutations



Normal cell

Cancer cell

Sequencing machines

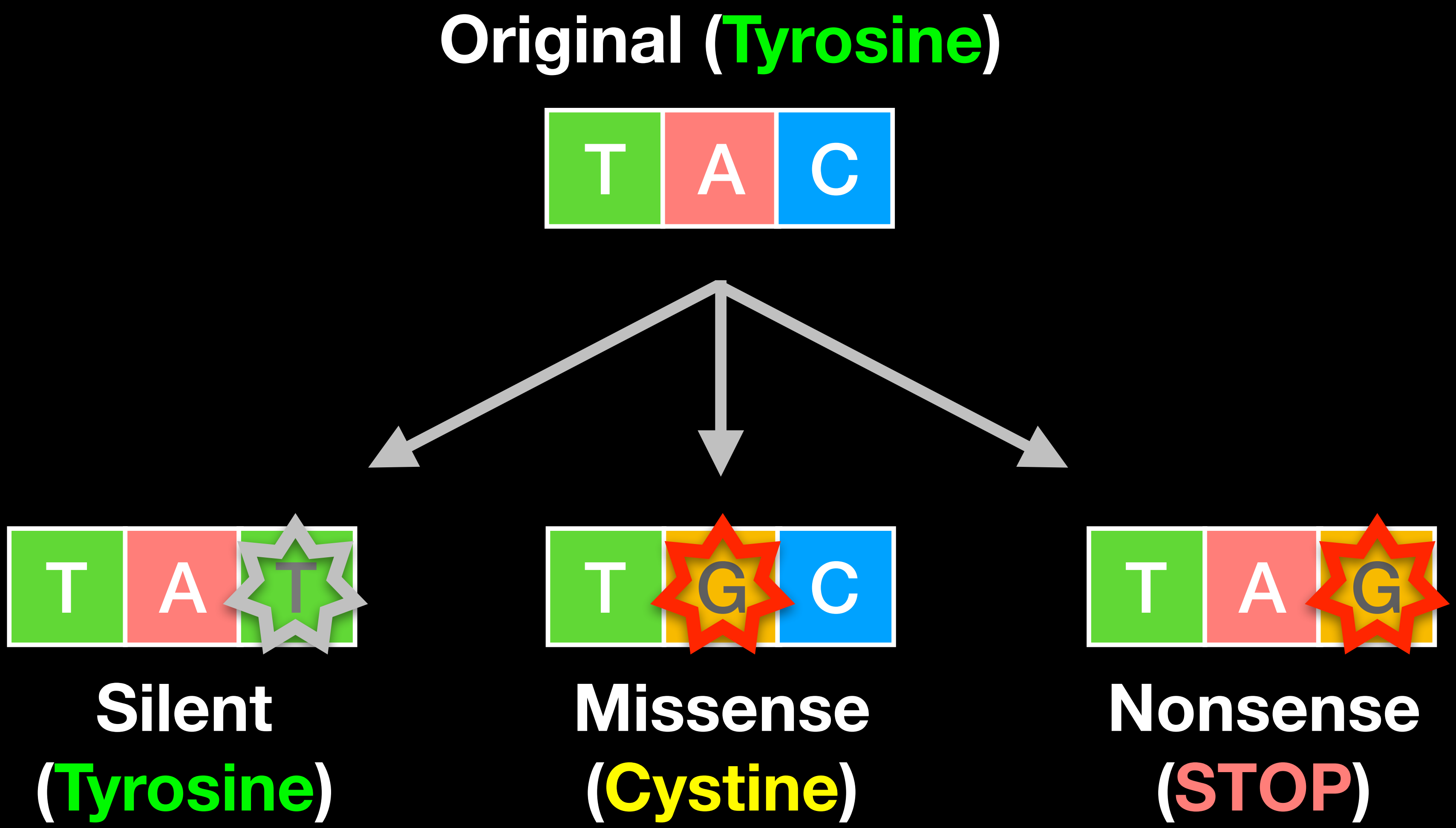
Somatic mutations

Identify all mutations specific to tumor cells

Filter out silent mutations

Mutations detected:

Point mutations



Original (Tyrosine)

T A C

T A T

Silent
(Tyrosine)

T G C

Missense
(Cystine)

T A G

Nonsense
(STOP)

Mutations detected:

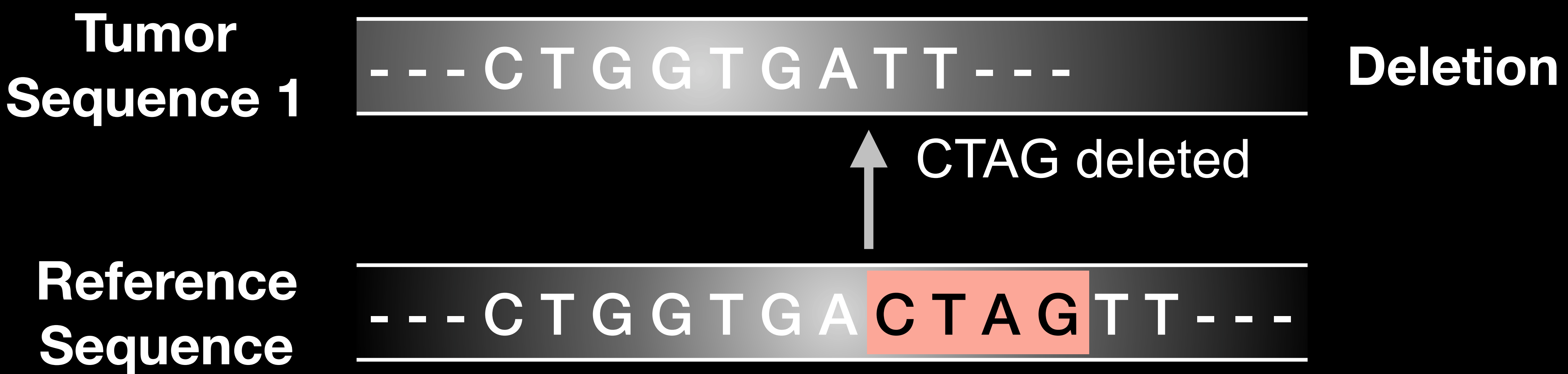
Indels

Reference Sequence

---CTGGTGACTAGTT---

Mutations detected:

Indels



Tumor Sequence 1

---CTGGTGATT---

Deletion

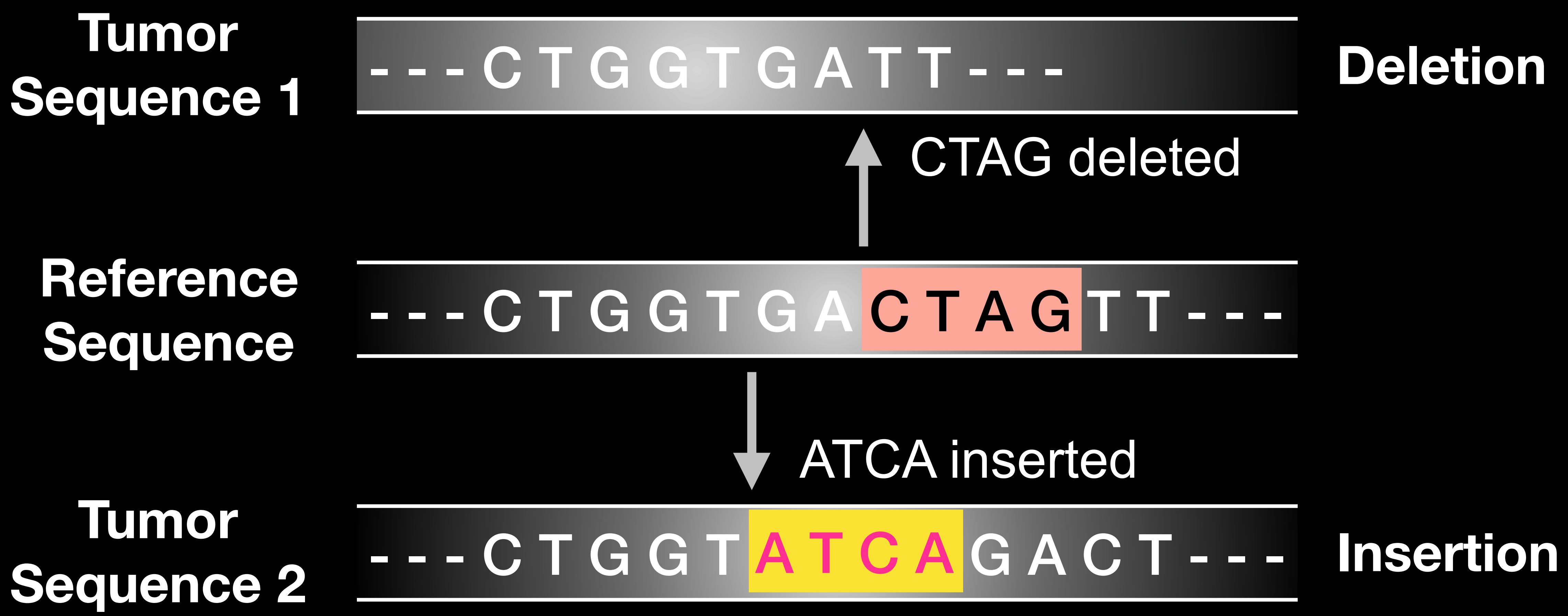
CTAG deleted

Reference Sequence

---CTGGTGACTAGTT---

Mutations detected:

Indels



Tumor Sequence 1 - - - C T G G T G A T T - - - **Deletion**

CTAG deleted

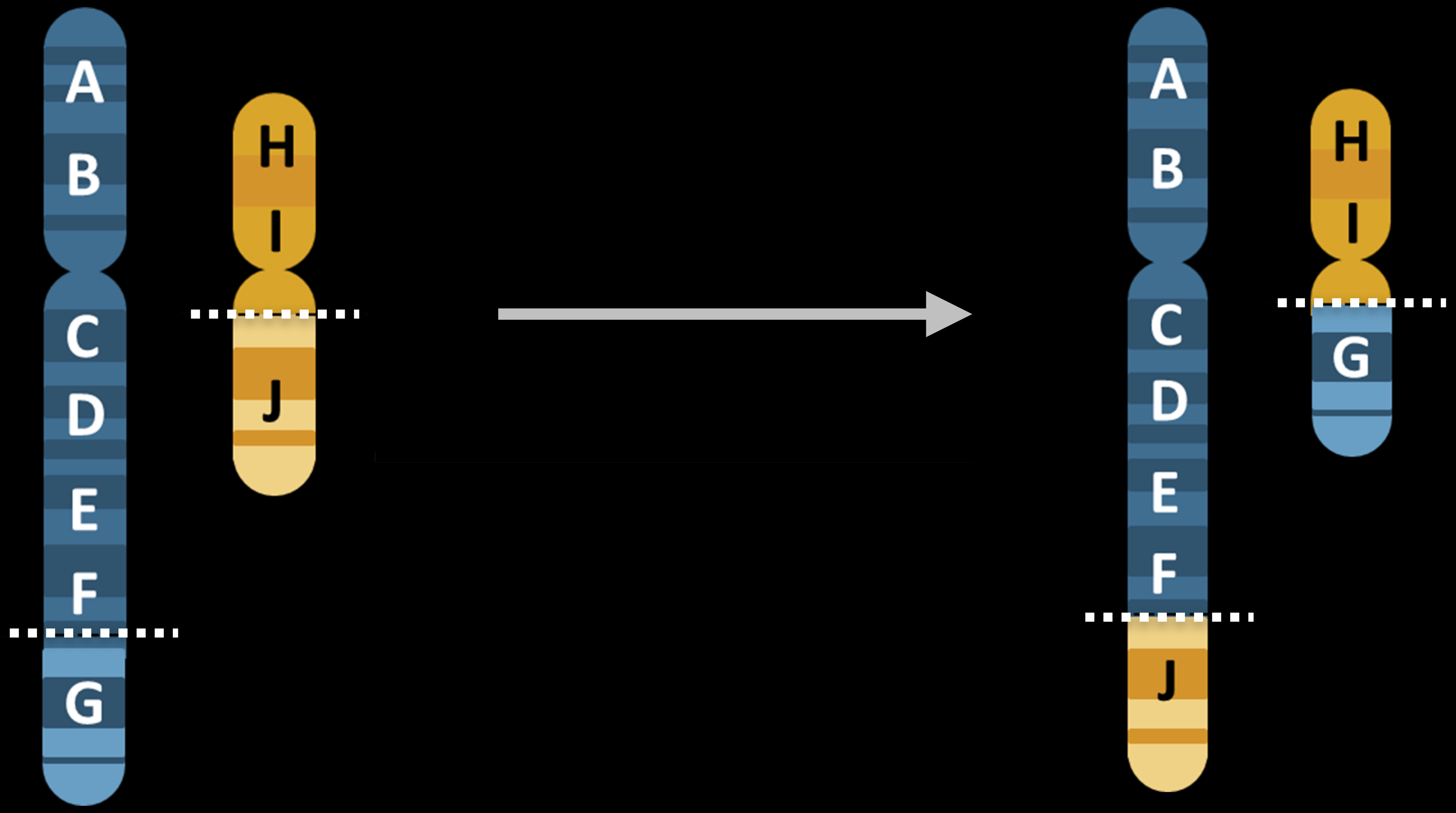
Reference Sequence - - - C T G G T G A C T A G T T - - -

ATCA inserted

Tumor Sequence 2 - - - C T G G T A T C A G A C T - - - **Insertion**

Mutations detected:

Translocations



(e.g. Philadelphia chromosome (Ph, 22-9) and found in over 90% of CML patients)

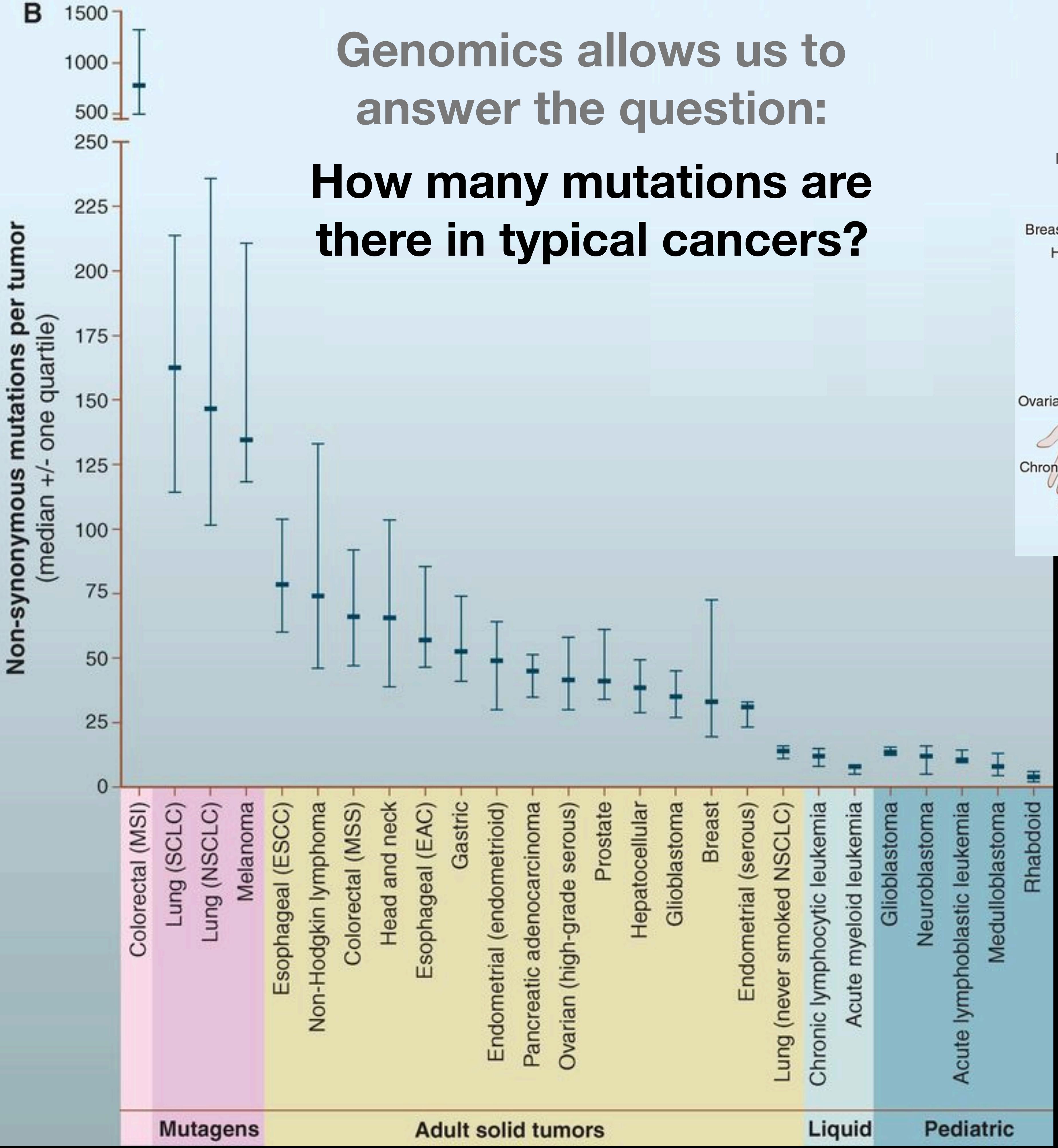
What can go wrong in cancer genomes?

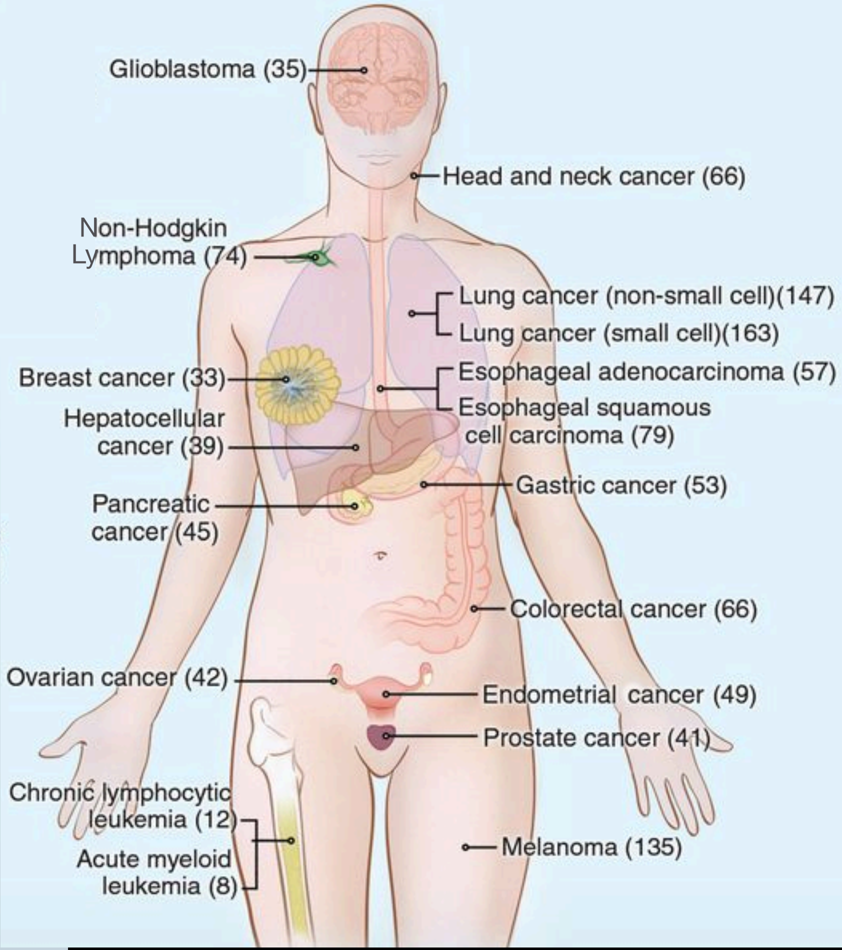
Type of change	**Some common technology to study changes**
DNA mutations	WGS, WXS
DNA structural variations	WGS
Copy number variation (CNV)	CGH array, SNP array, WGS
DNA methylation	Methylation array, RRBS, WGBS
mRNA expression changes	mRNA expression array, RNA-seq
miRNA expression changes	miRNA expression array, miRNA-seq
Protein expression	Protein arrays, mass spectrometry

WGS = whole genome sequencing, WXS = whole exome sequencing
RRBS = reduced representation bisulfite sequencing, WGBS = whole genome bisulfite sequencing

Genomics allows us to answer the question:

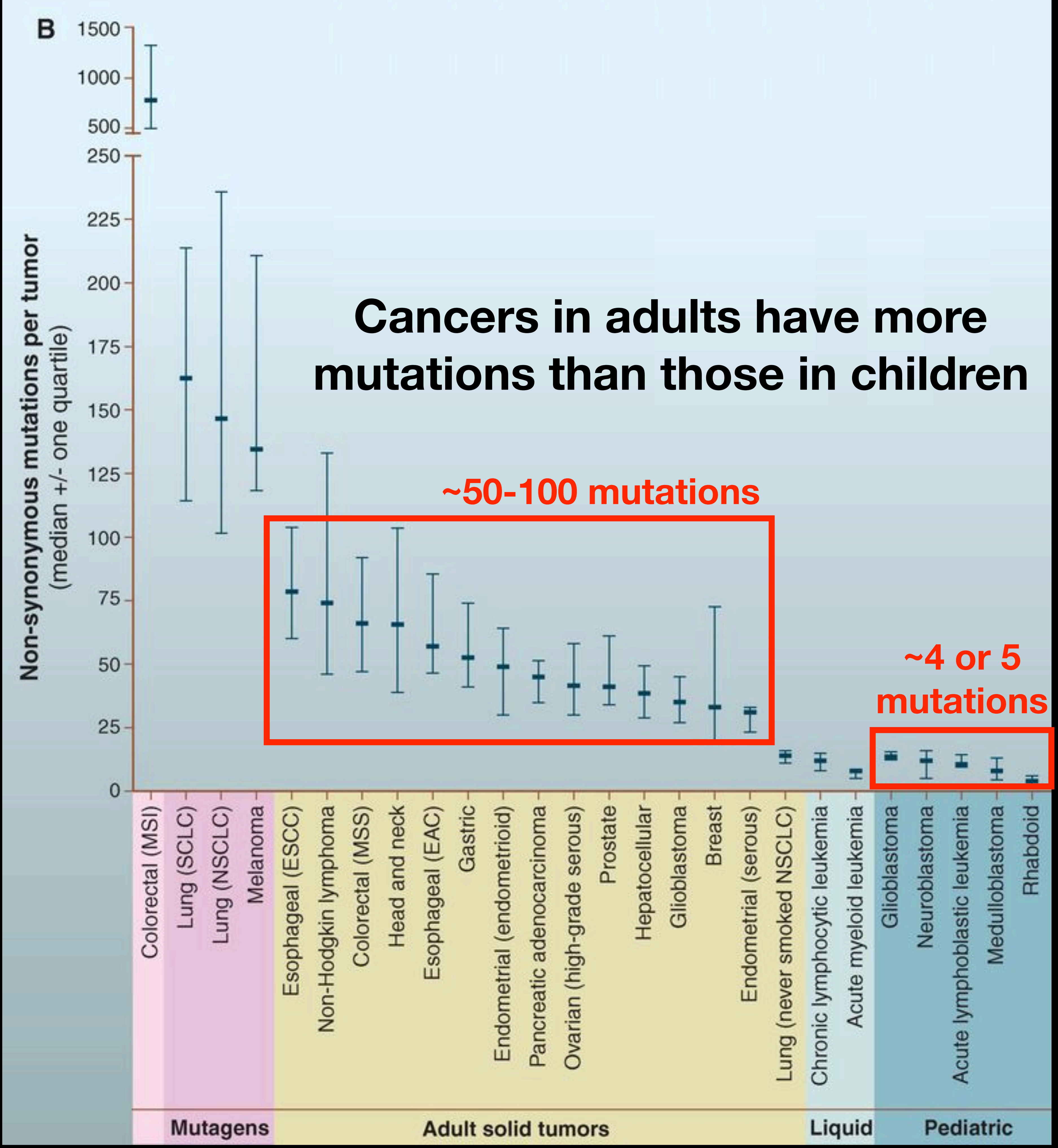
How many mutations are there in typical cancers?





Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

Vogelstein et al. Science (2013)



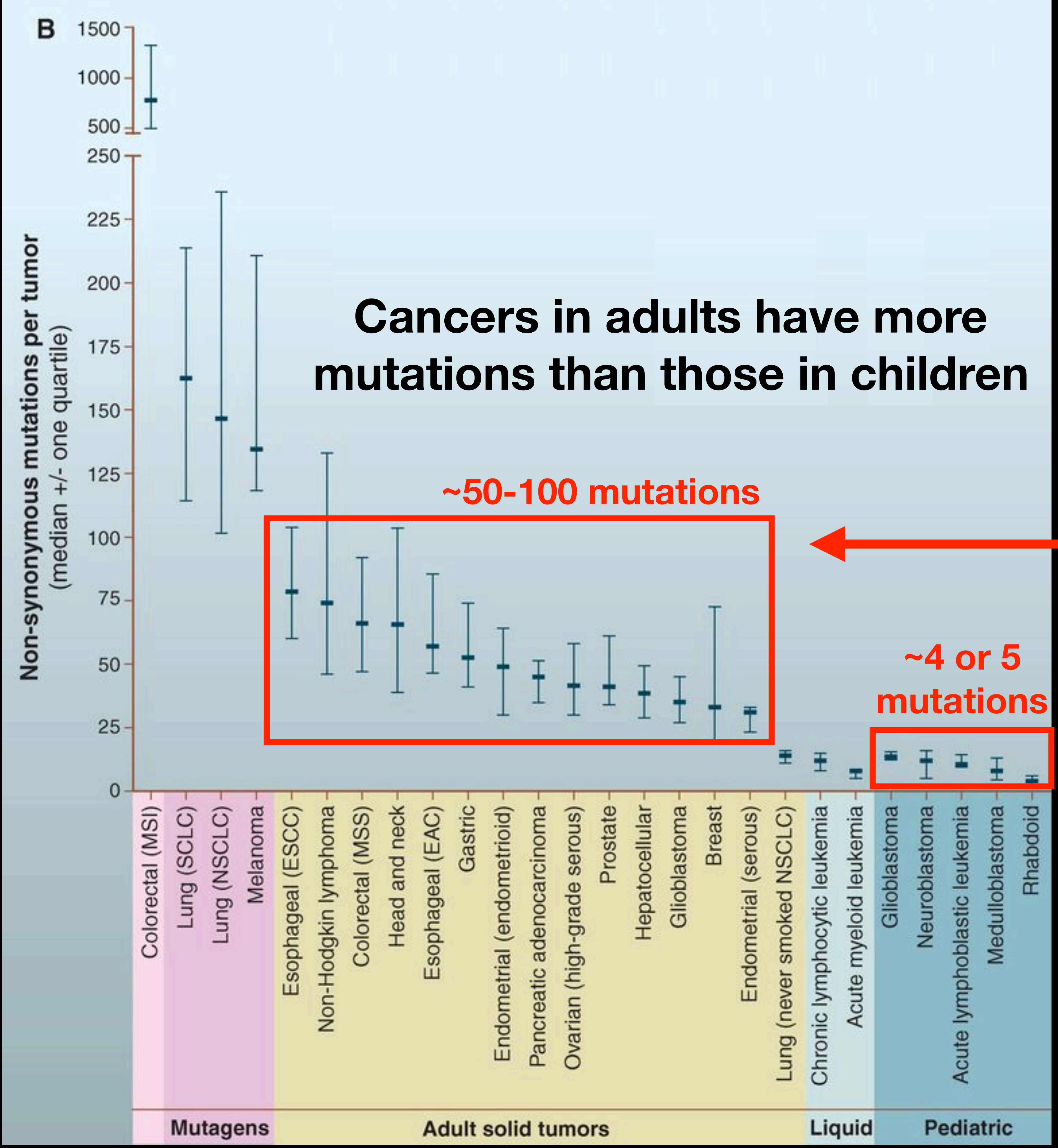
Cancers in adults have more mutations than those in children

~50-100 mutations

~4 or 5 mutations

Vogelstein et al. Science (2013)

Cancers in adults have more mutations than those in children

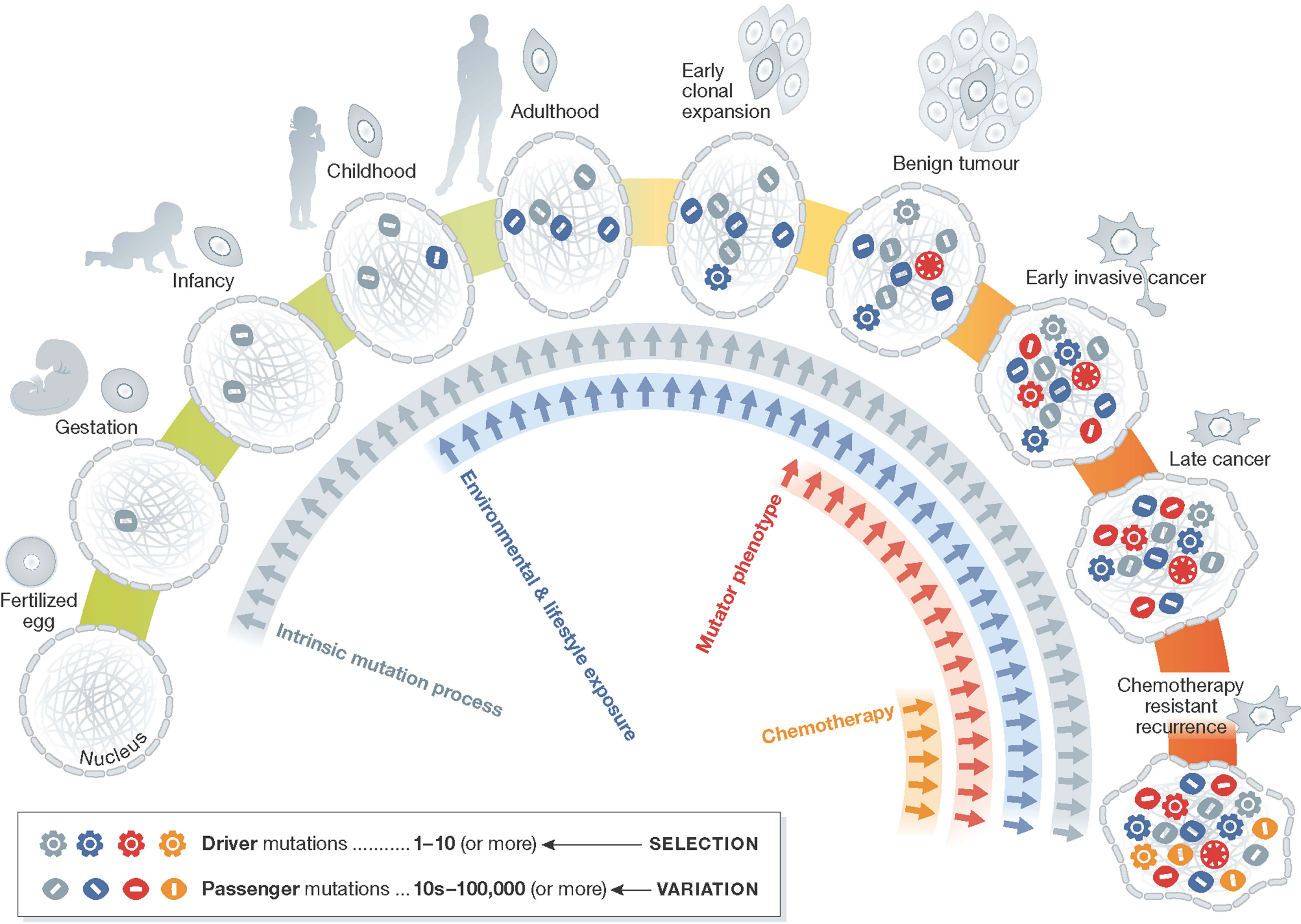


~50-100 mutations

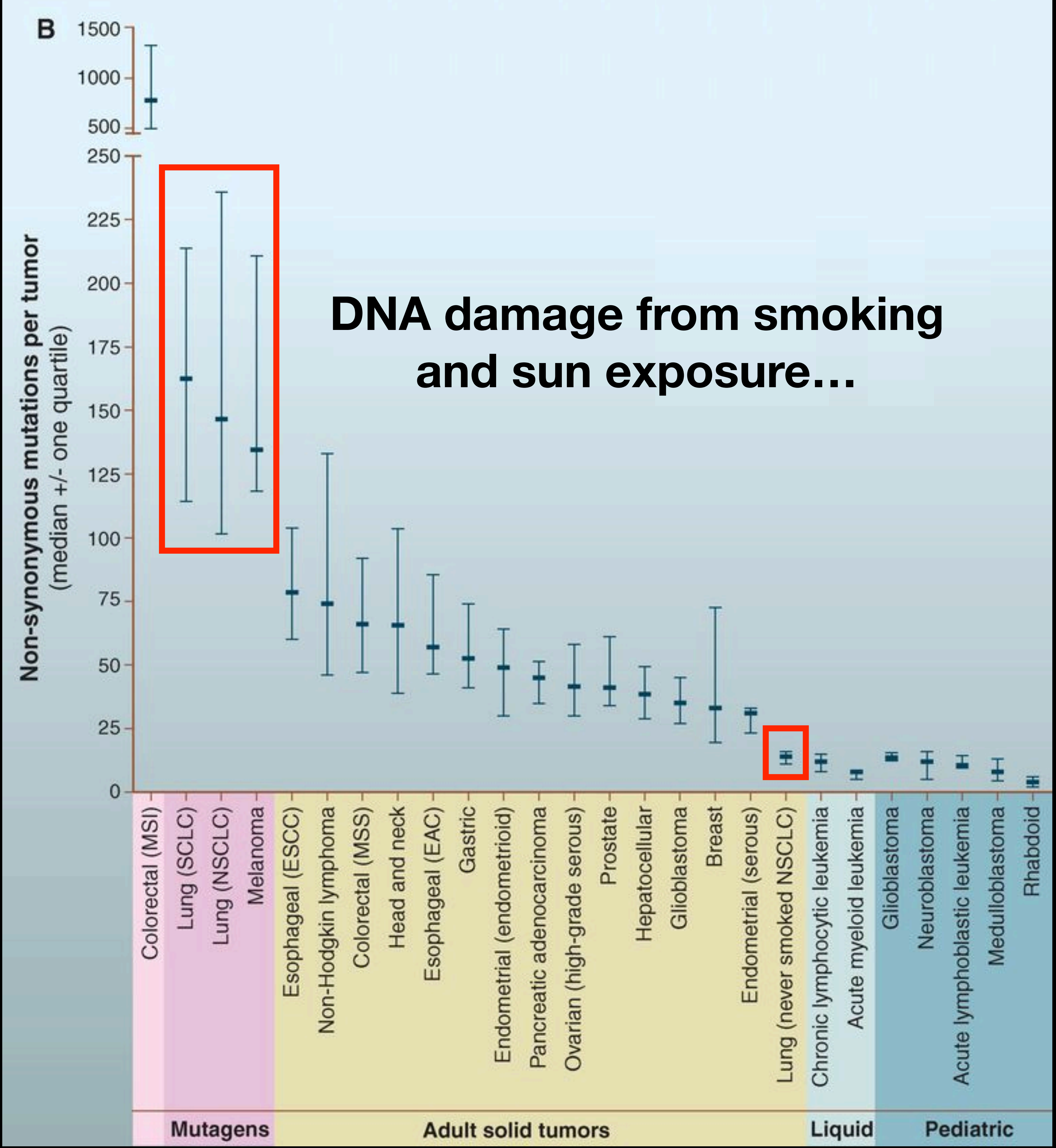
~4 or 5 mutations

Most of these mutations are likely “passenger” mutations

Vogelstein et al. Science (2013)



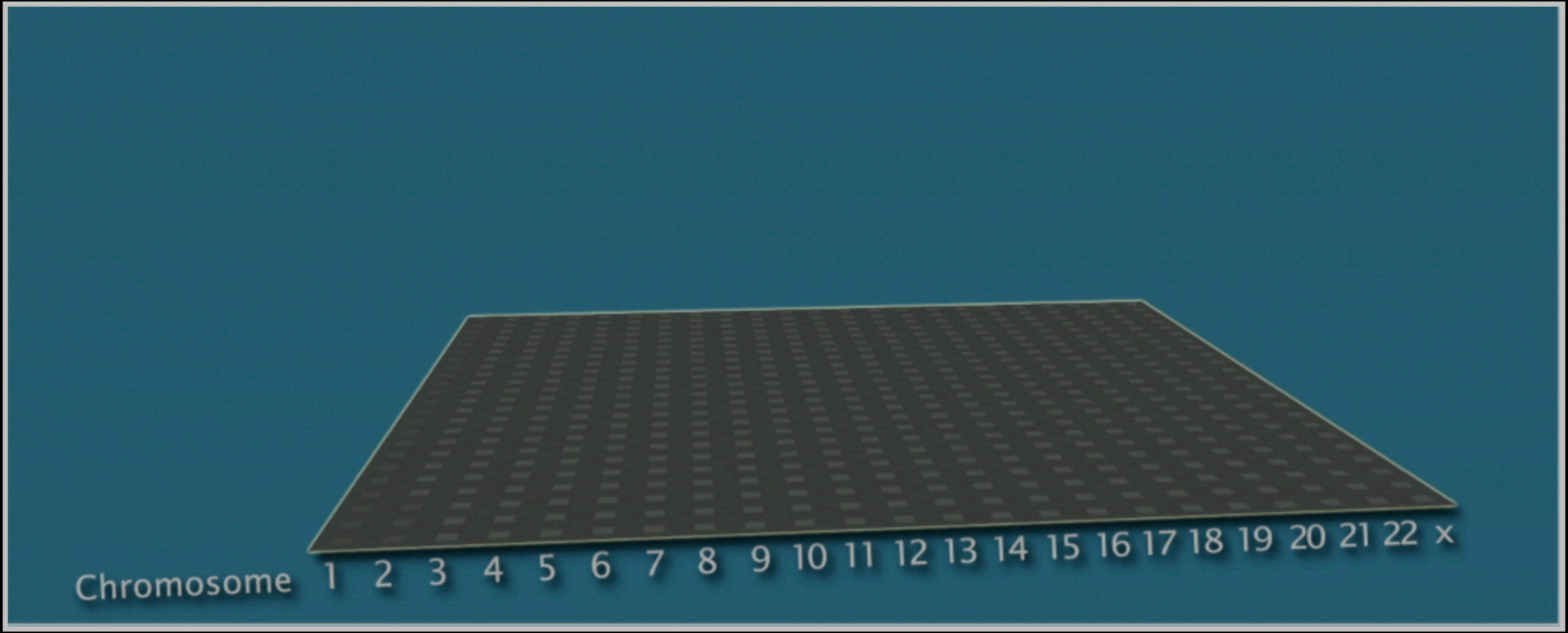
Mike Stratton. EMBO Molecular Medicine (2013)



DNA damage from smoking and sun exposure…

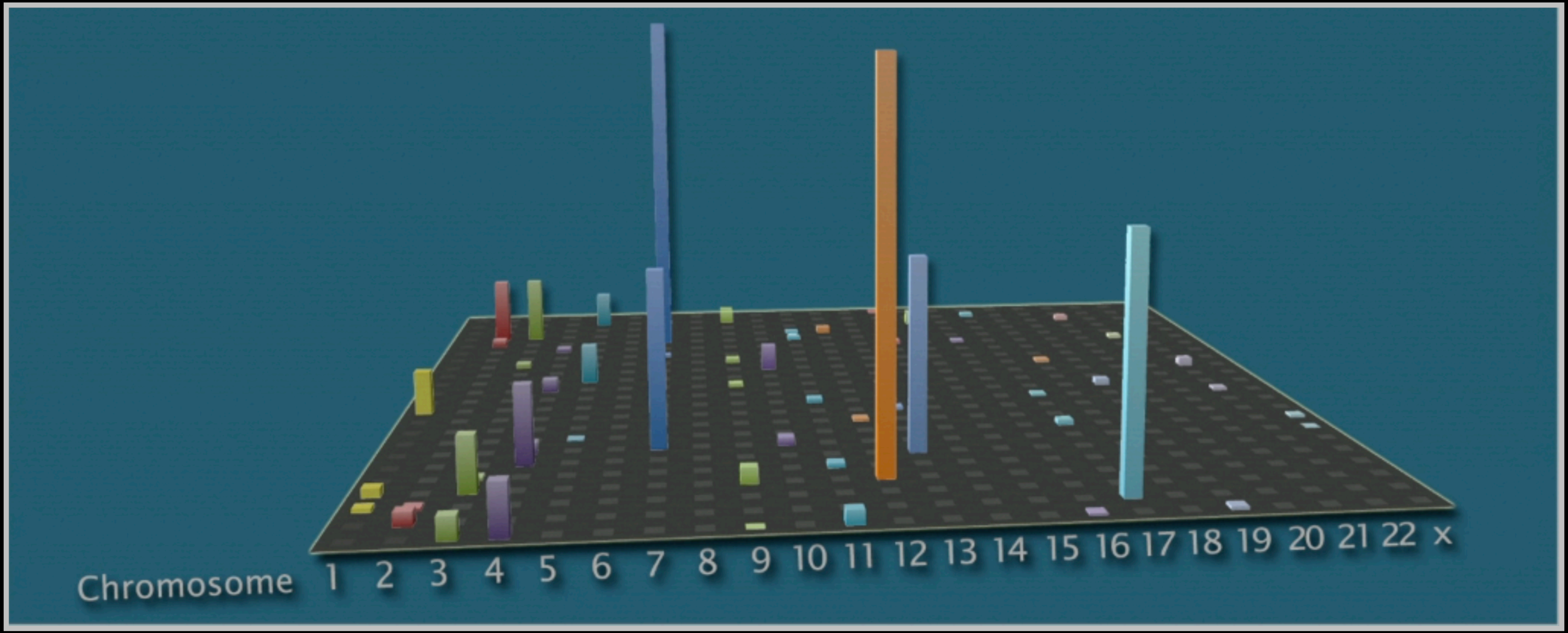
Vogelstein et al.
Science (2013)

Genomic approaches can identify the genes most commonly mutated in cancer



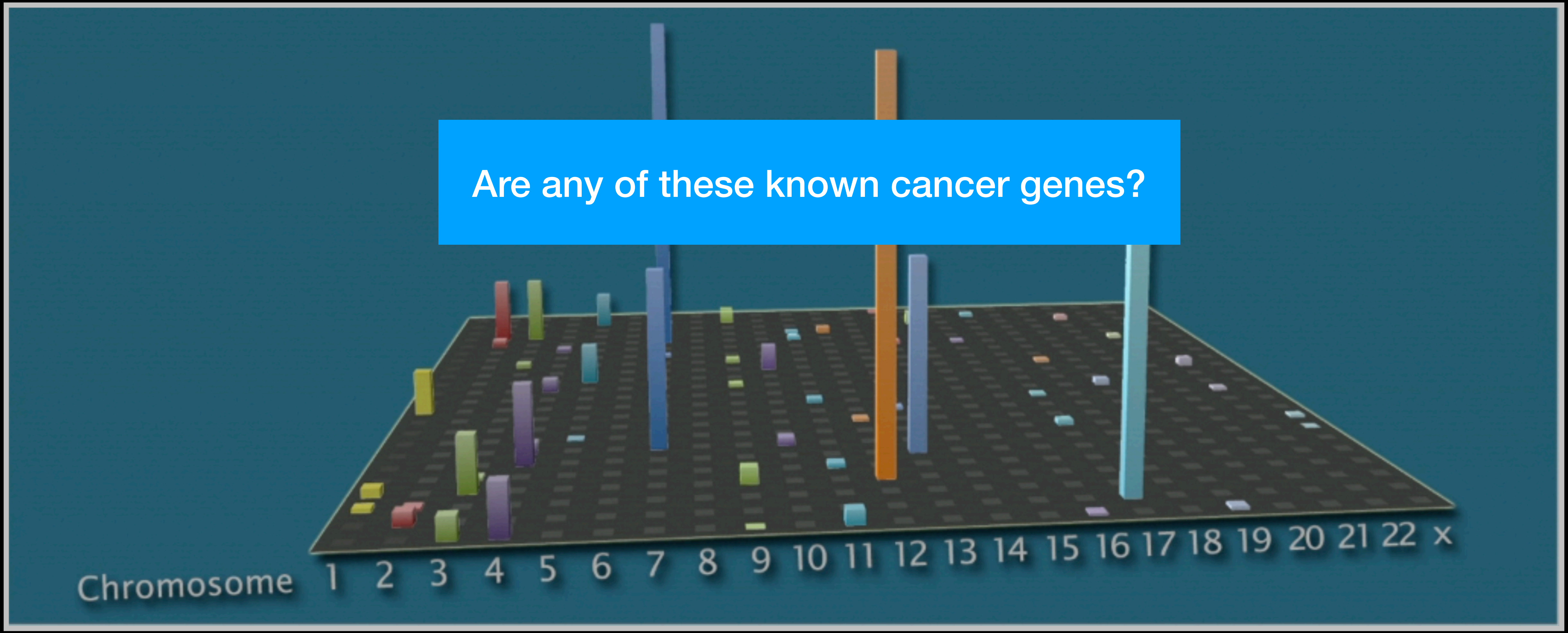
Arrange all genes in a matrix, ordered by chromosomes

Identifying genes most commonly mutated in cancer



Add all data together to see which genes are most often mutated

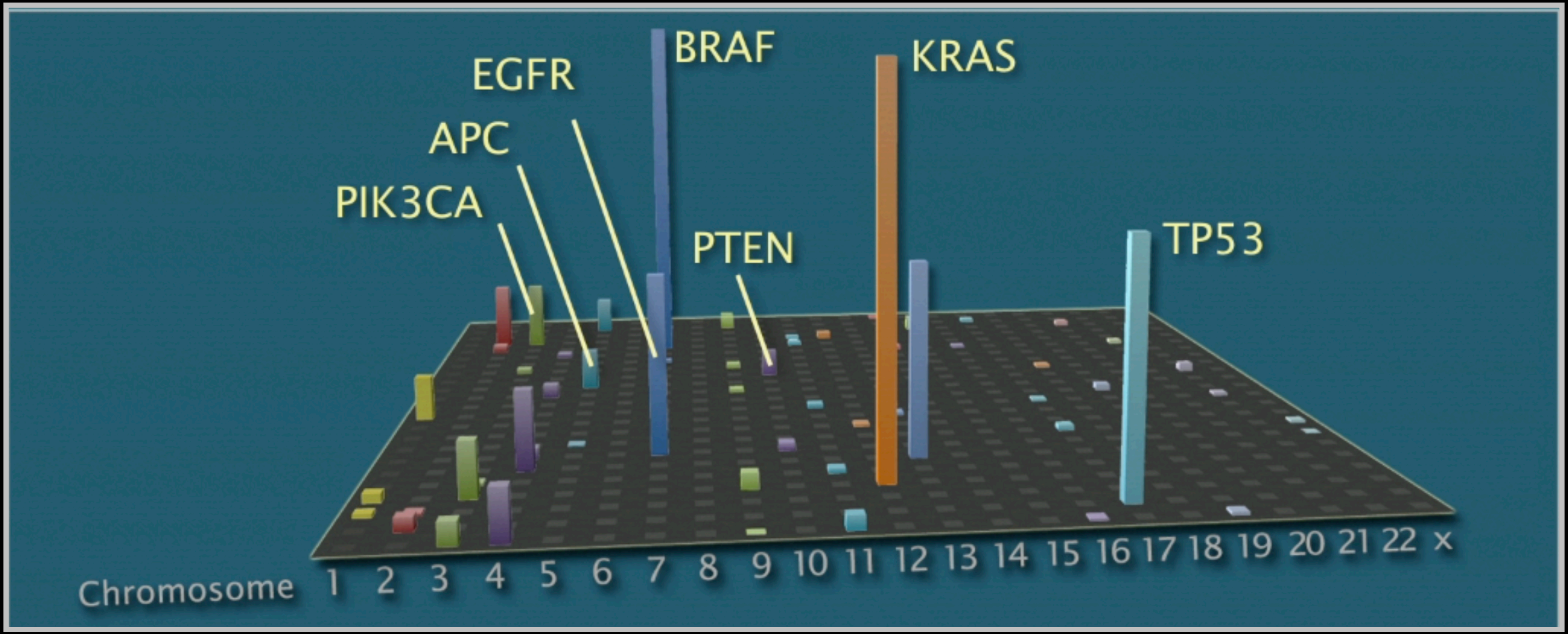
Identifying genes most commonly mutated in cancer



Are any of these known cancer genes?

Add all data together to see which genes are most often mutated

Identifying genes most commonly mutated in cancer



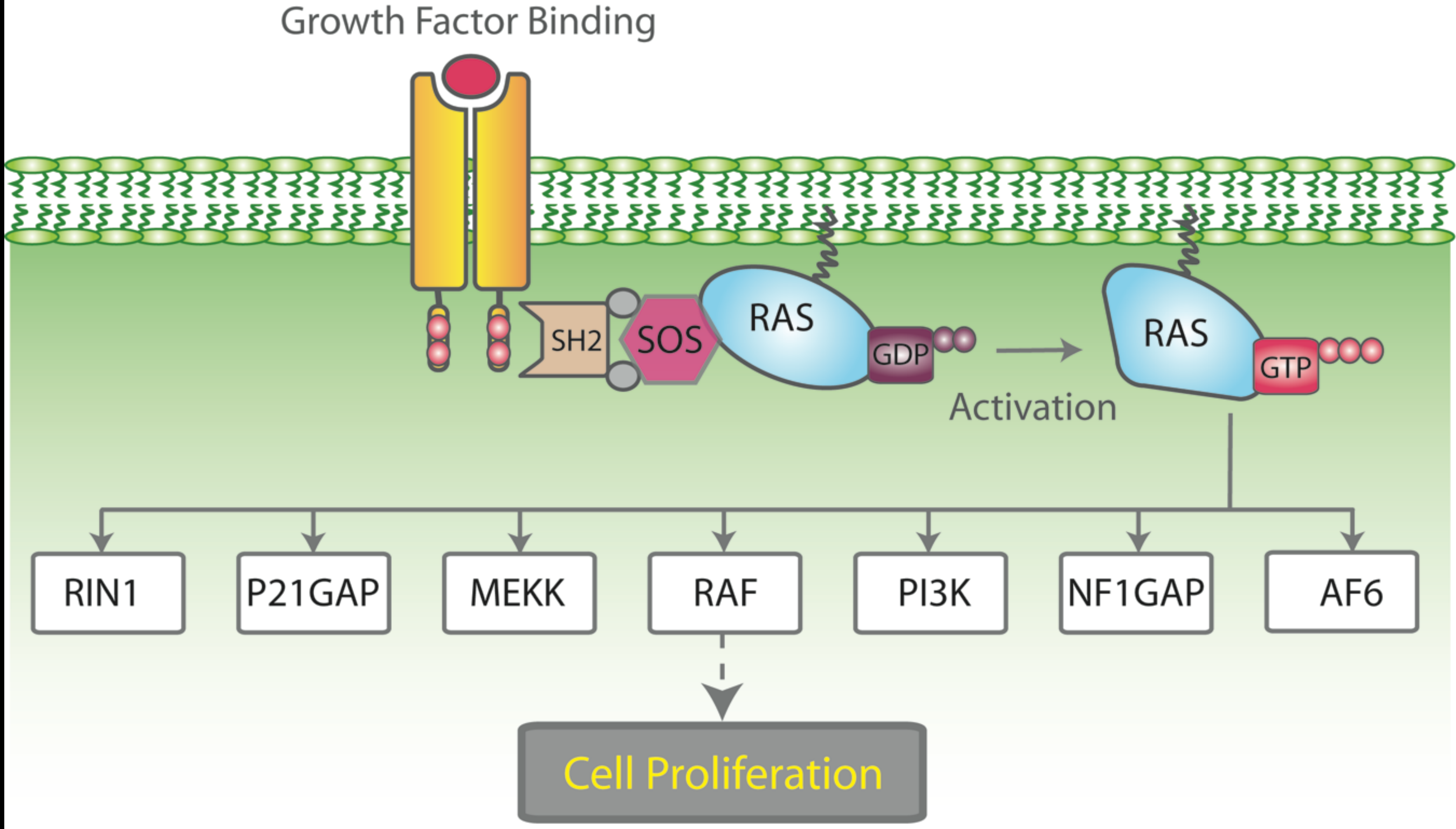
Many are famous porto-oncogenes, many others are new cancer genes!

Three Main Types of Cancer Genes:

- Oncogenes, such as **Ras**, normally function to accelerate cell division and growth. They can be mutated to act like stuck gas pedals.
- Tumor suppressor genes, such as **p53** normal act like breaks. Mutations can cause these breaks to fail.
- DNA repair genes, such as **BRCA1** & **2**, normally function to fix minor damage to DNA when it replicates. When these genes are mutated, DNA damage can accumulate and lead to cancer.

Cell growth and survival genes

Many participate in signaling pathways that promote cell proliferation (E.G. EGFR, Ras, BRAF, MEK etc.)



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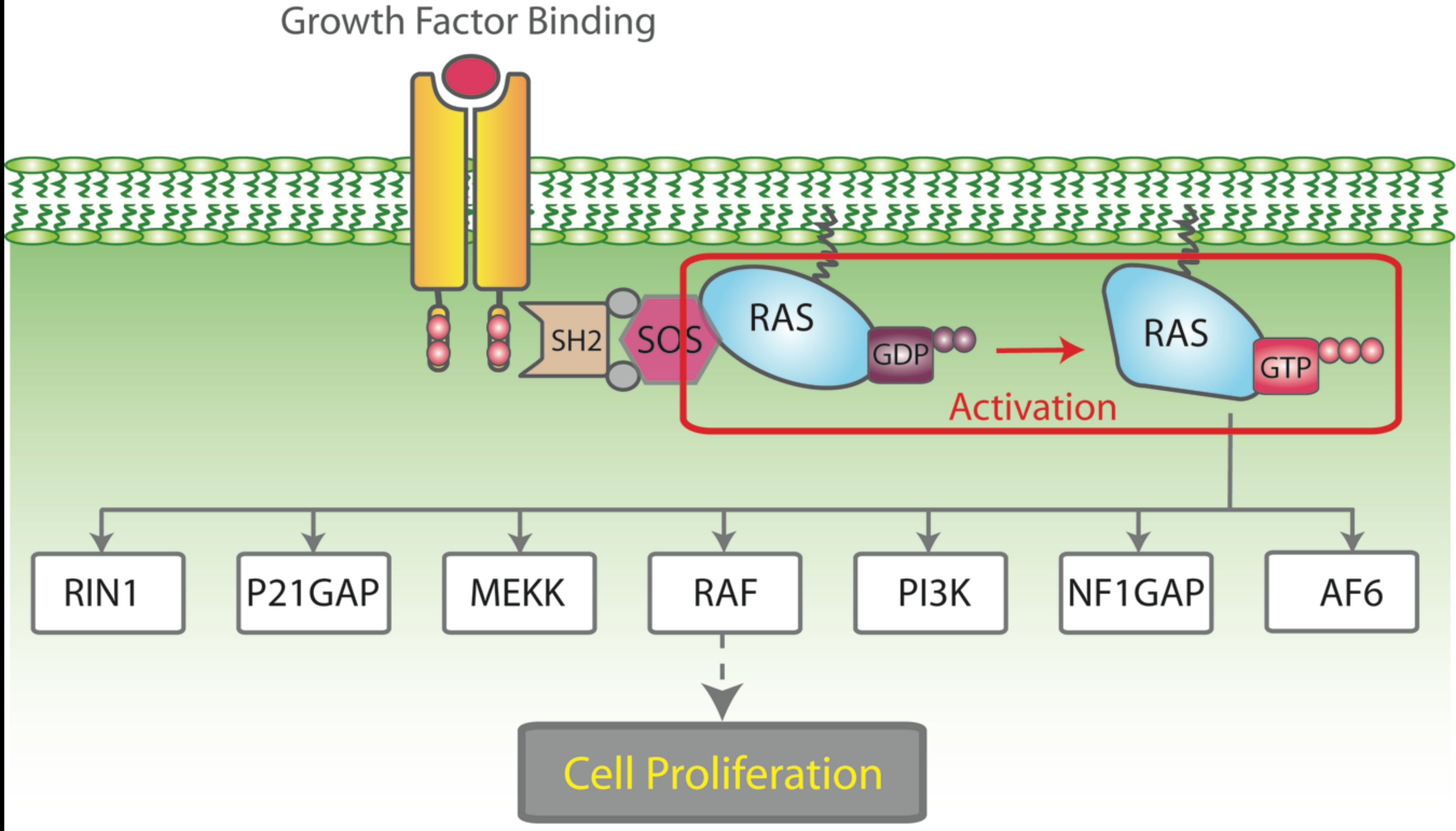


Regulators of Cell Cycle and Cell Death

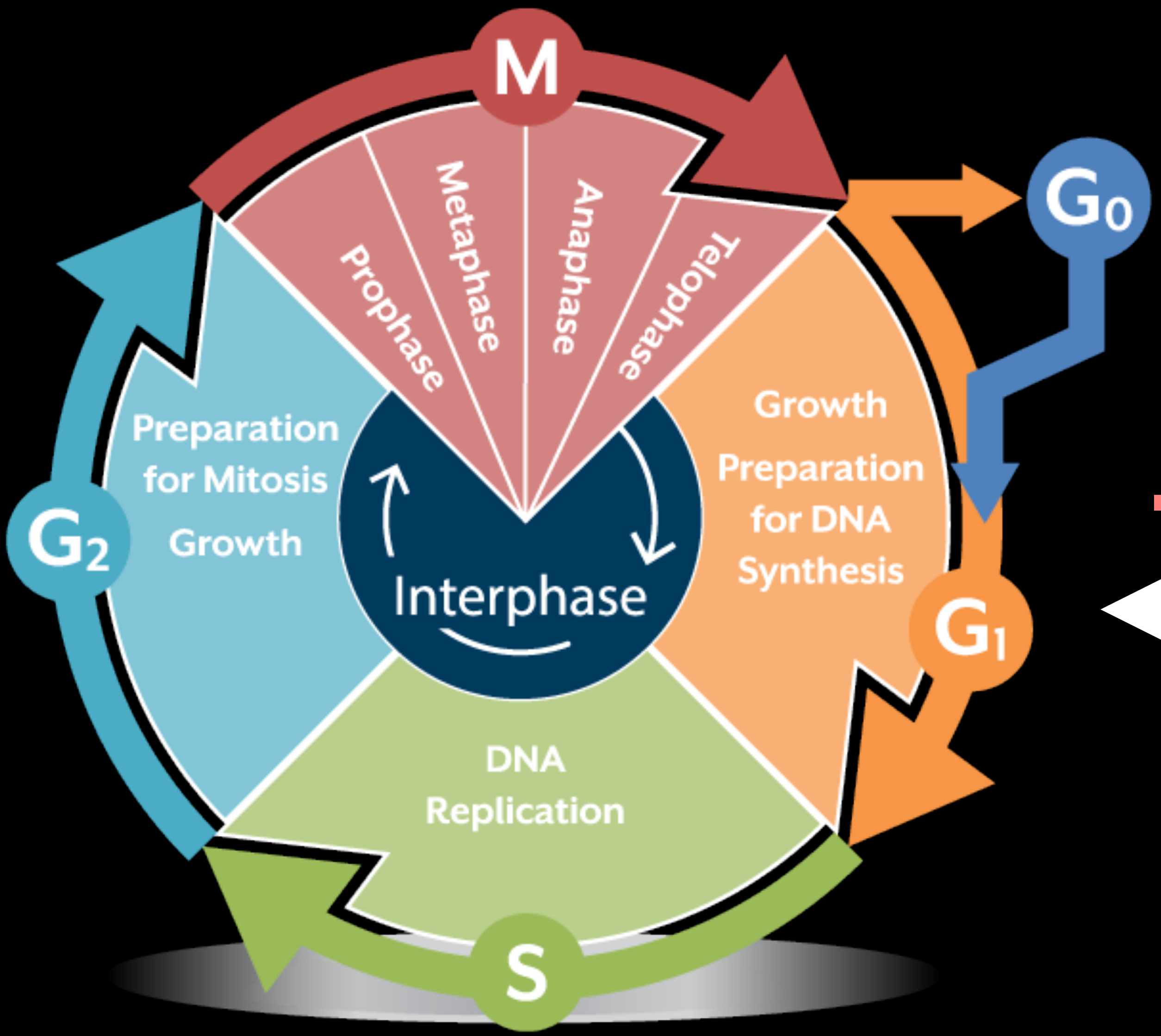
Some stimulate the cell cycle

Cyclin D1

CDK4

+

Oncogenes



Some inhibit the cell cycle

-

P53

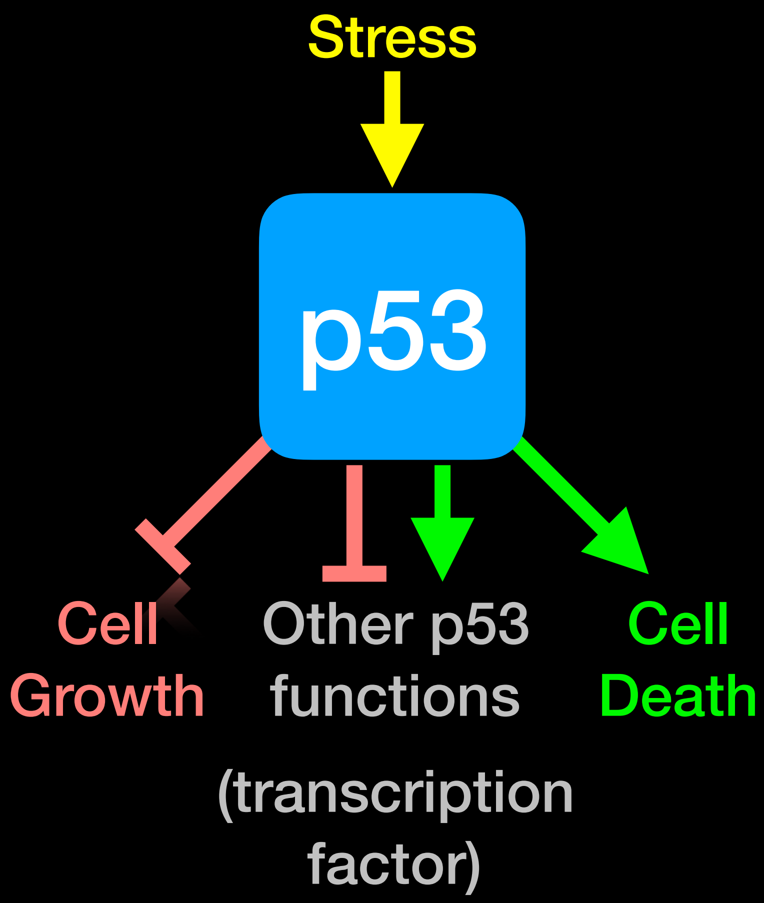
RB

Suppressor genes

p53 Regulates Cell Division

Probably the most famous cancer gene that is mutated in about half of all tumors. Often called the '*guardian of the genome*'

- p53 normally shuts down cell division when a cell is stressed (e.g. by DNA damage)
- When DNA is damaged, p53 activates genes that stop cell growth or trigger the cell to die.
- Thus, p53 guards against changes to cells that might lead to tumor formation.
- It appears necessary to inactivate p53 to develop many forms of cancer.


Stress

p53

Cell Growth

Other p53 functions

Cell Death

(transcription factor)

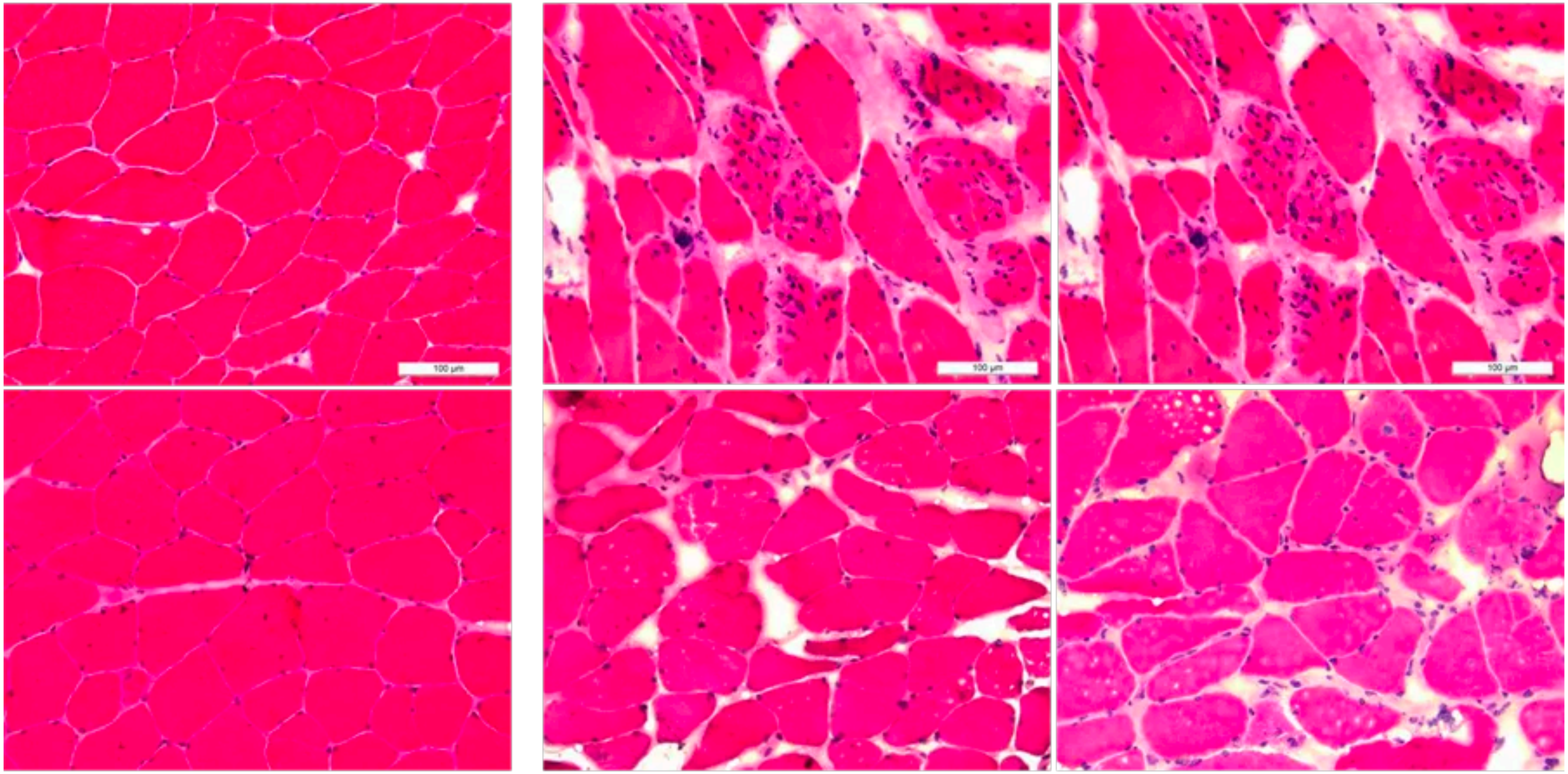
Do it Yourself!

Hands-on time!

https://bioboot.github.io/bggn213_W20/lectures/#18

Part 1 Only Please

Control **Pancreatic Cancer**



Representative H&E micrographs of rectus abdominis biopsies are displayed for two patients without cancer (*left*) and four patients with pancreatic cancer (*right*)

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Towards personalized cancer treatments	Recap on how the immune system normally detects cancer cells and how we can predict mutations that can be recognized by T cells
Cancer Immunoinformatics	**Hands-on analysis** to design personalized cancer vaccines

Next Up:

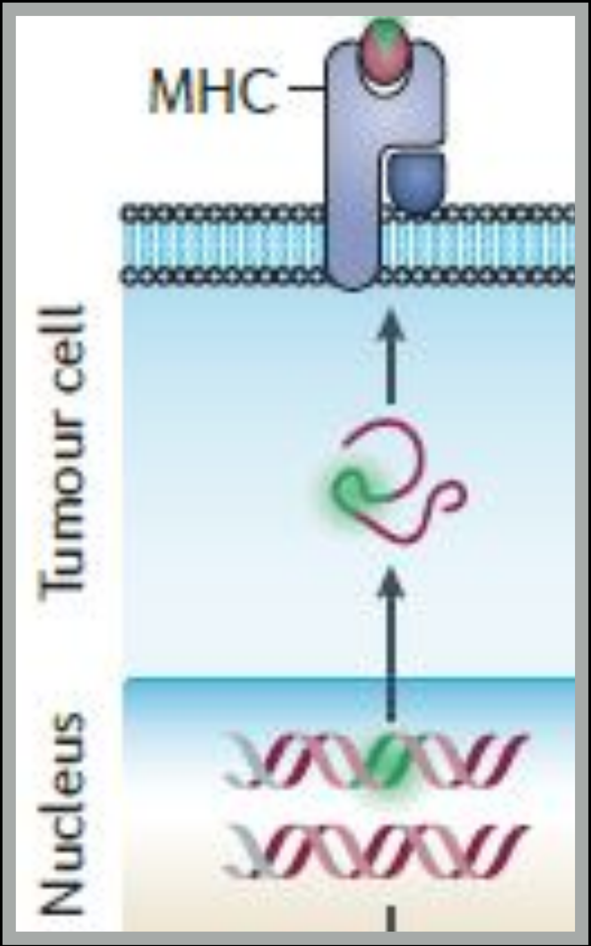
Next Up:

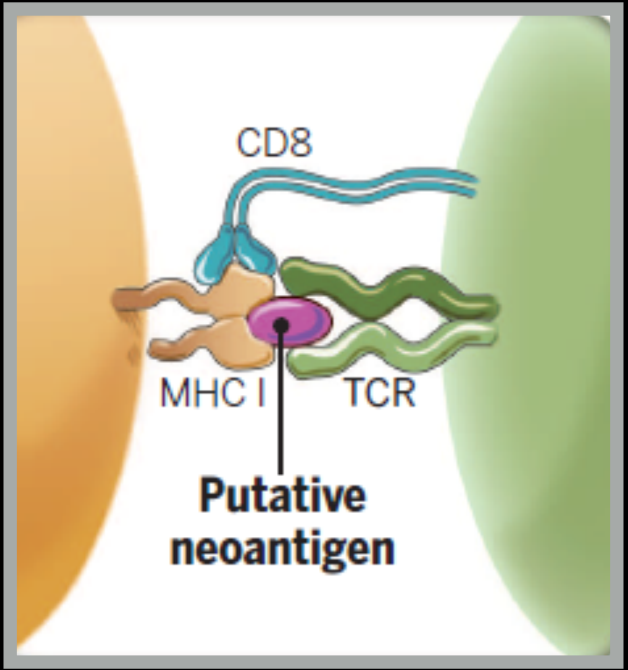
Cancer Immunotherapy

Dr. Bjoern Peters **(La Jolla Institute)**

10:00

- Cancers genomes accumulate mutations
- Mutations in coding regions are translated in mutated protein sequences
- Mutated peptides can be presented as epitopes on **MHC** to **T cells**





- **Neoepitopes** are presumably recognized by tumor-infiltrating lymphocytes (TILs)

- **Neoepitopes** are highly tumor-specific!

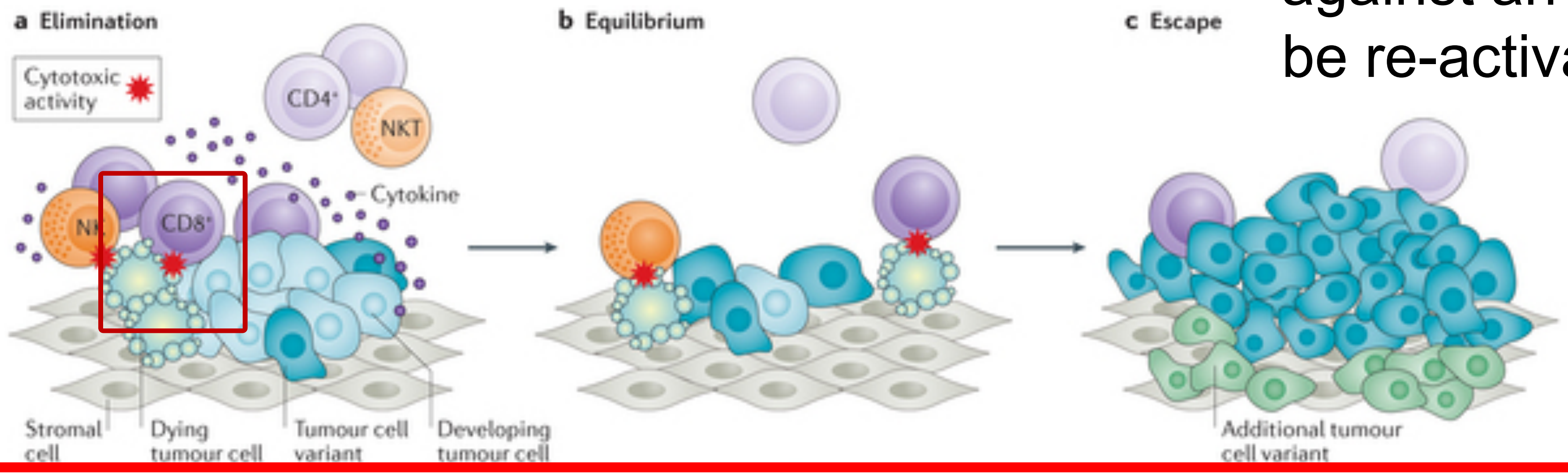
Coulie et al, Nat Rev Cancer. 2014 Feb;14(2):135-46
Schumacher & Schreiber, Science. 2015 Apr 3;348(6230):69-74

Slide from: **Bjoern Peters** (LIAI)

Cancer immune surveillance and escape

- Mutations in cells occur frequently
- The immune system has the capacity to detect and eliminate such mutated cells, and will do so on a regular basis
- Only when mutated cells find ways to hide from- or suppress an attack by the immune system, they can grow and spread unhindered leading to clinically apparent tumors

Can the immune response against an ‘escaped’ cancer be re-activated?



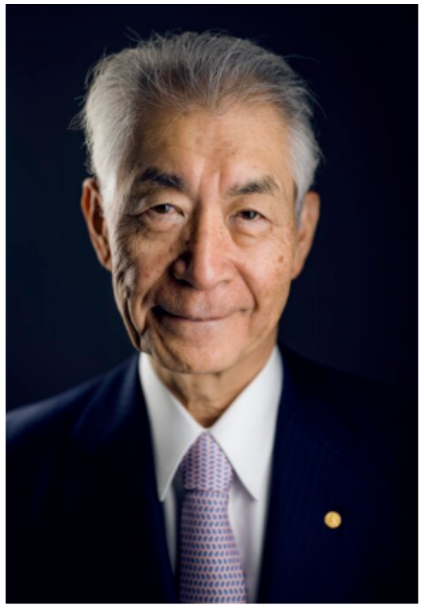
Van der Burg et al, Nature Reviews Cancer 16, 219–233 (2016)

Nobel Prize 2018 in Medicine

- Identification of the molecules PD-1 and CTLA-4 that function as 'T cell brakes' (immune checkpoints)
- Blockade of PD-1 and CTLA-4 results in activation of T cells which has "*fundamentally changed the outcome for certain groups of patients with advanced cancer*"
- *"Similar to other cancer therapies, adverse side effects are seen, which can be serious and even life threatening. They are caused by an overactive immune response leading to autoimmune reactions […]"*

© Nobel Media AB. Photo: A. Mahmoud

James P. Allison



© Nobel Media AB. Photo: A. Mahmoud

Tasuku Honjo

"for their discovery of cancer therapy by inhibition of negative immune regulation"

https://www.nobelprize.org/uploads/2018/10/press-medicine2018.pdf

Slide from: **Bjoern Peters** (LIAI)

- **Vaccination**: Introduce or boost an immune response against a specific target (antigen)

- Cancer cells contain non-self antigens that *could* be recognized by T cells, but the presence of cancer means this mechanism has failed, typically by the tumor suppressing immune responses

- **Checkpoint blockade treatments**: Block immune suppressive mechanisms to boost T cell immune responses against cancer cells.

- **Problem**: Checkpoint blockade is unspecific, and will also boost unwanted autoimmune responses

- **Personalized Cancer Immunotherapy**: Boost anti-tumor response with vaccine containing peptides corresponding to cancer mutations that can be recognized by T cells.

Q. How can such a vaccine be designed?

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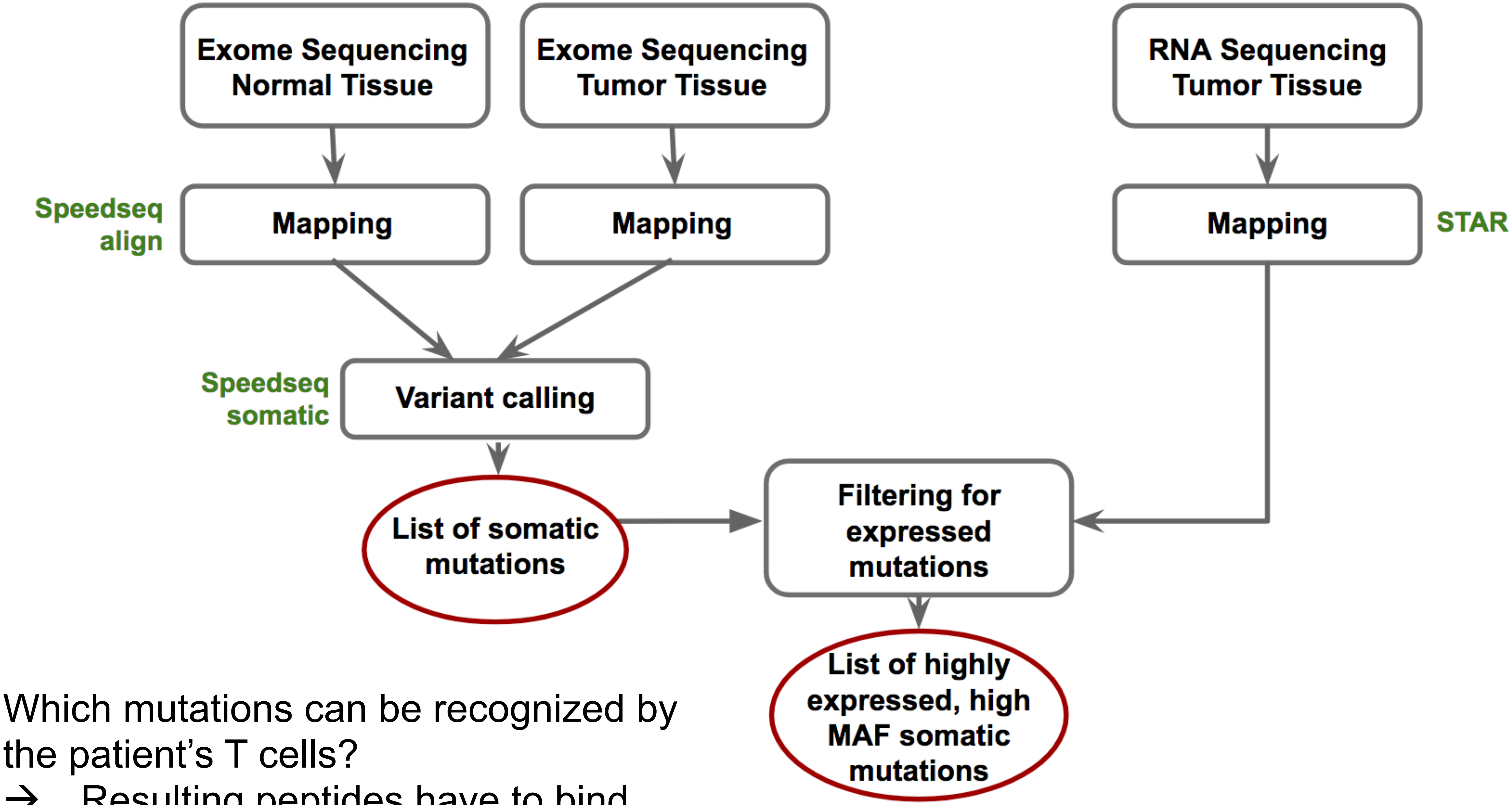
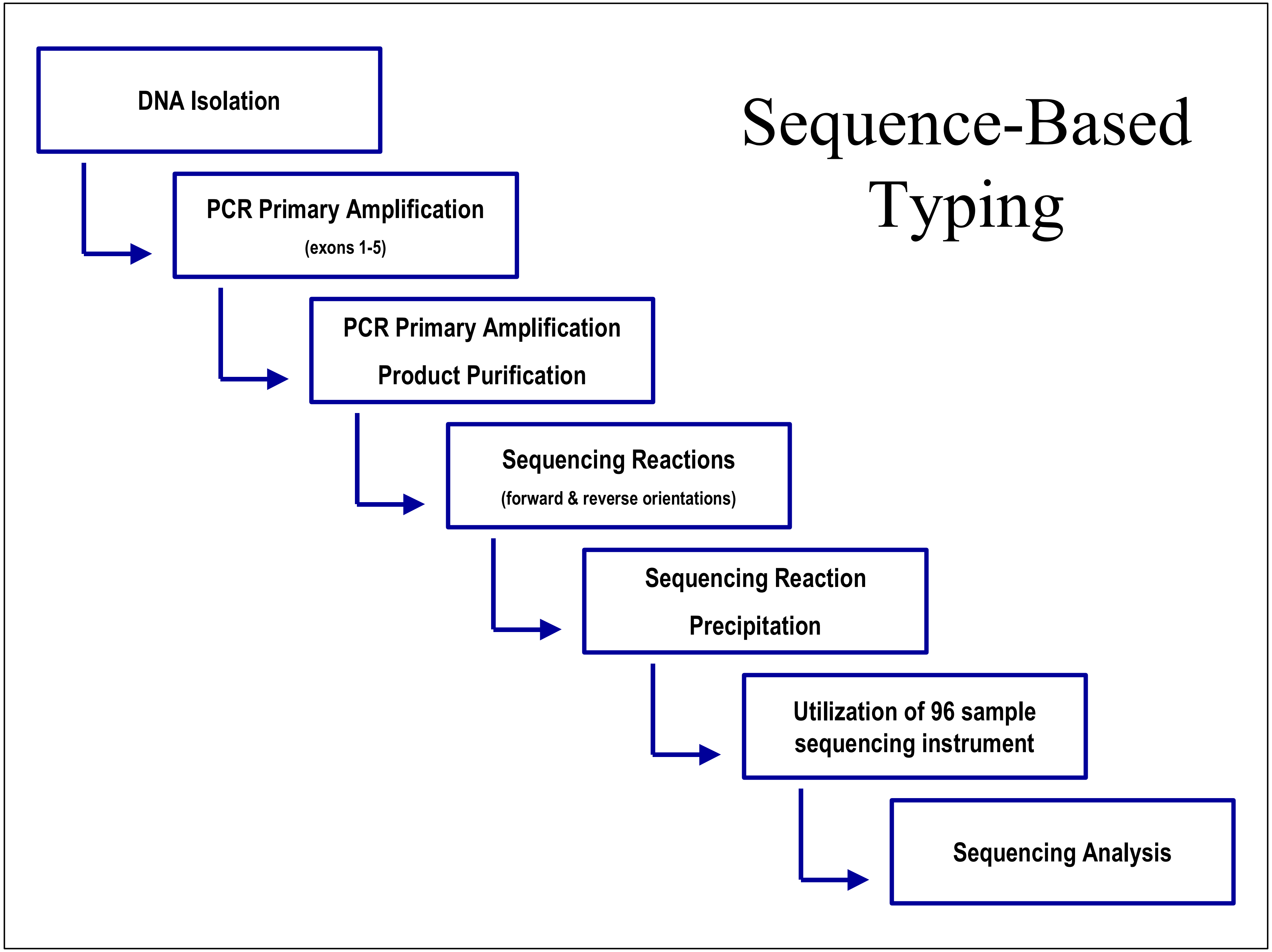
DNA and RNA sequencing identifies tumor specific somatic mutations



Which mutations can be recognized by the patient’s T cells?
→ Resulting peptides have to bind HLA molecules of the patient

Slide from: **Bjoern Peters** (LIAI)

HLA Typing: Targeted sequencing of HLA locus



Sequence-Based Typing

DNA Isolation

PCR Primary Amplification
(exons 1-5)

PCR Primary Amplification
Product Purification

Sequencing Reactions
(forward & reverse orientations)

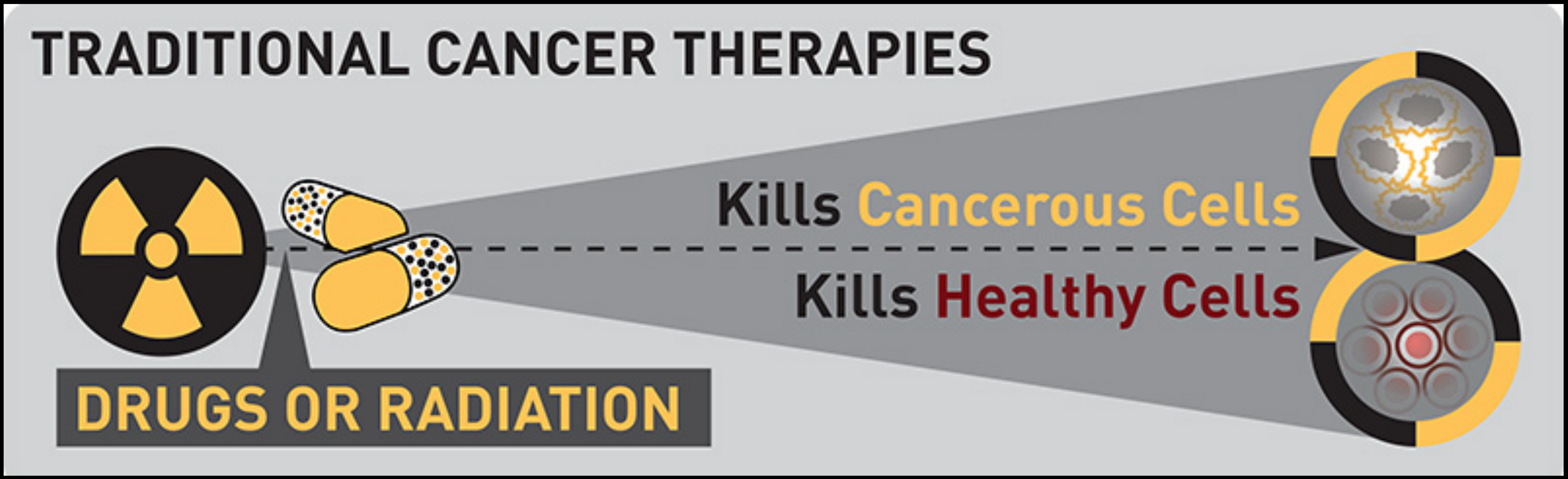
Sequencing Reaction
Precipitation

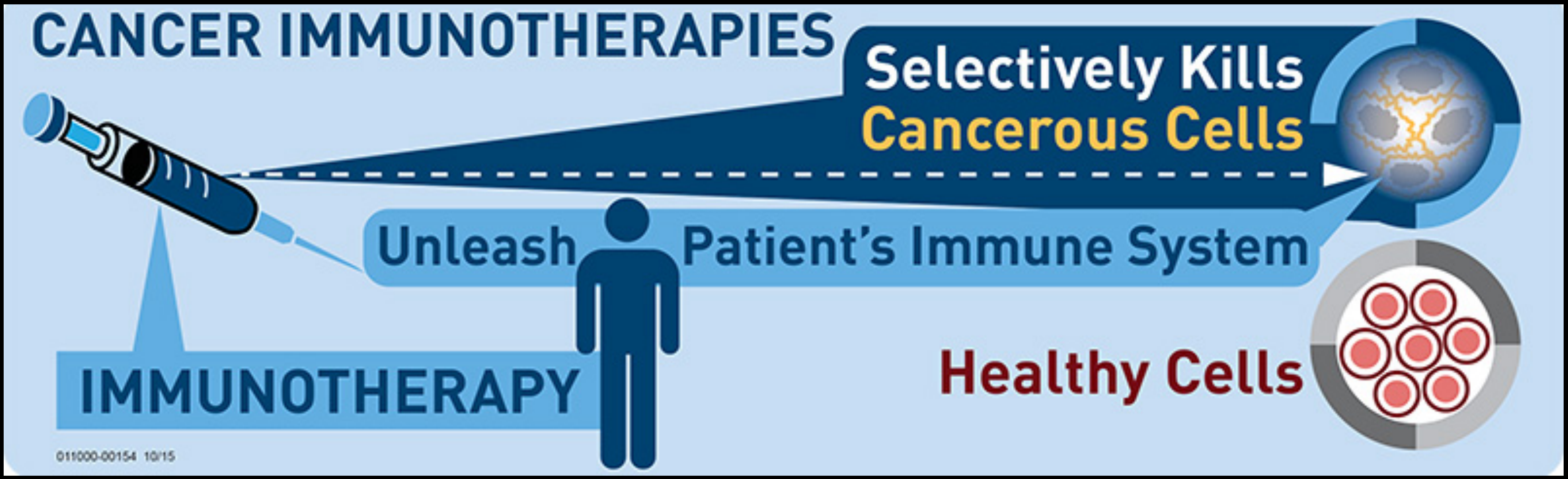
Utilization of 96 sample
sequencing instrument

Sequencing Analysis

•http://www.ashi-hla.org/publicationfiles/ASHI_Quarterly/25_2_2001/highthrusbt3.htm

Slide from: **Bjoern Peters** (LIAI)


TRADITIONAL CANCER THERAPIES
Kills Cancerous Cells
Kills Healthy Cells
DRUGS OR RADIATION


CANCER IMMUNOTHERAPIES
Selectively Kills
Cancerous Cells
Unleash Patient's Immune System
Healthy Cells
IMMUNOTHERAPY
011000-00154 10/15

Do it Yourself!

Hands-on time!

Part 2: Designing a personalized cancer vaccine

Workflow:

- **Step 1:** Identify sequence regions that contain all **9-mer** peptides that are **only** found in the tumor

- **Step 2:** Run HLA binding prediction to identify 9-mer peptides in the sequence regions unique to the tumor to select peptides that can be **presented to T cells** in this patient

- **Step 3:** Determine if the identified peptides are specific for the tumor (i.e. are they found anywhere else?)

- **Final question:** Which peptide would you choose?

Workflow:

- **Step 1:** Identify sequence regions that contain all **9-mer** peptides that are **only** found in the tumor
    - What are the tumor specific amino-acids?
    - What peptides include these amino acids?

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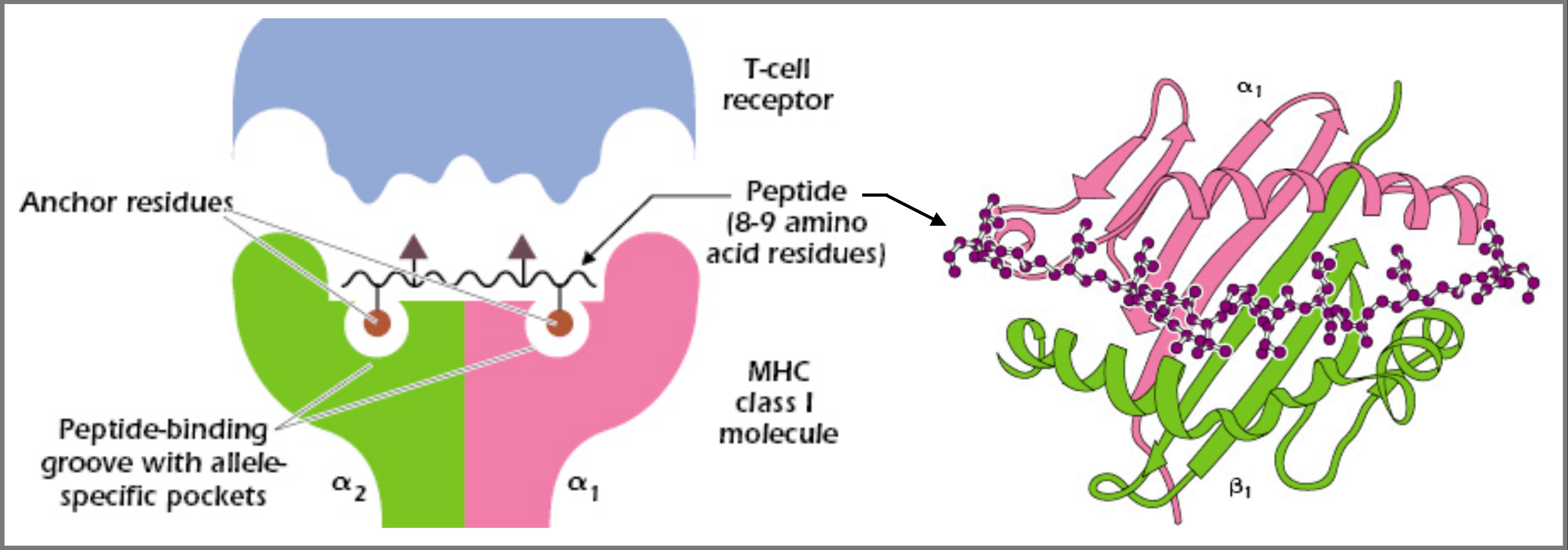
  - **Which peptide would you choose?**

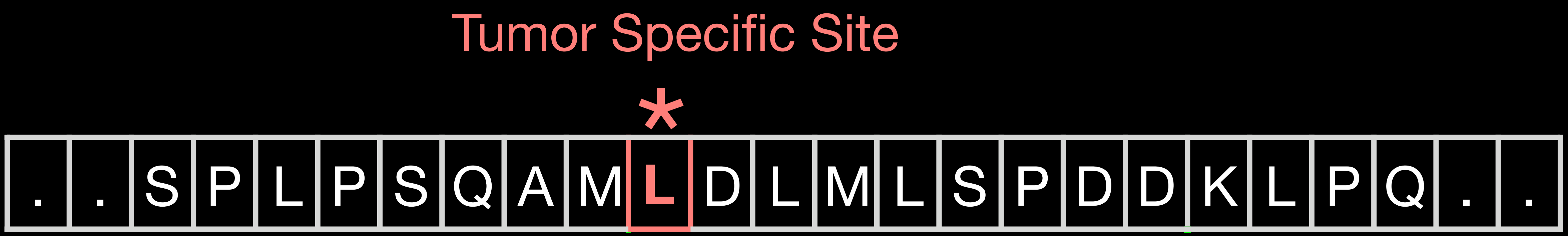
Depictions of the peptide bound MHC and T-cell receptor



Note:

- Anchor residues in the peptide bind to the allele-specific pockets of the MHC molecule.
- Certain MHC molecules (alleles) preferentially bind peptides with specific anchor residues in the 8- or 9-amino-acid peptide sequence.
- We want our tumor specific residues to be within 8 to 9-mer sequences bound by a patient HLA alleles!

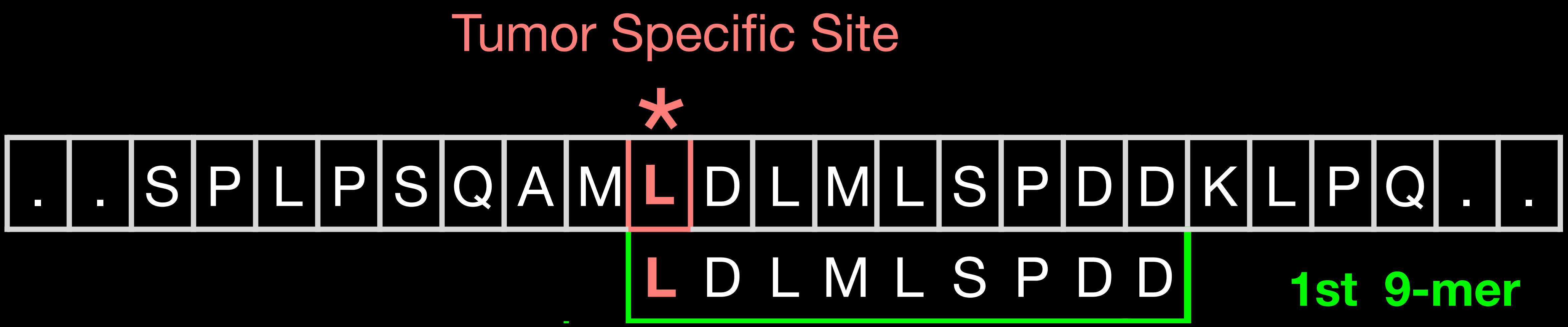
Reference: https://oncohemakey.com/how-t-cells-recognize-antigen-the-role-of-the-major-histocompatibility-complex/



Tumor Specific Site

*

.	.	S	P	L	P	S	Q	A	M	**L**	D	L	M	L	S	P	D	D	K	L	P	Q	.	.



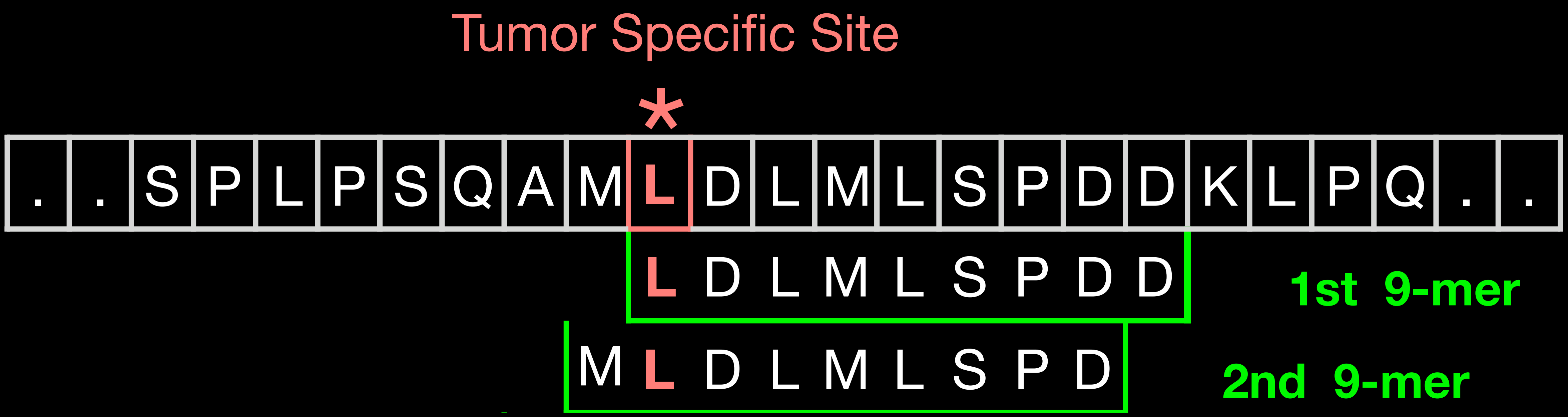
Tumor Specific Site

*

.	.	S	P	L	P	S	Q	A	M	**L**	D	L	M	L	S	P	D	D	K	L	P	Q	.	.

L D L M L S P D D

1st 9-mer



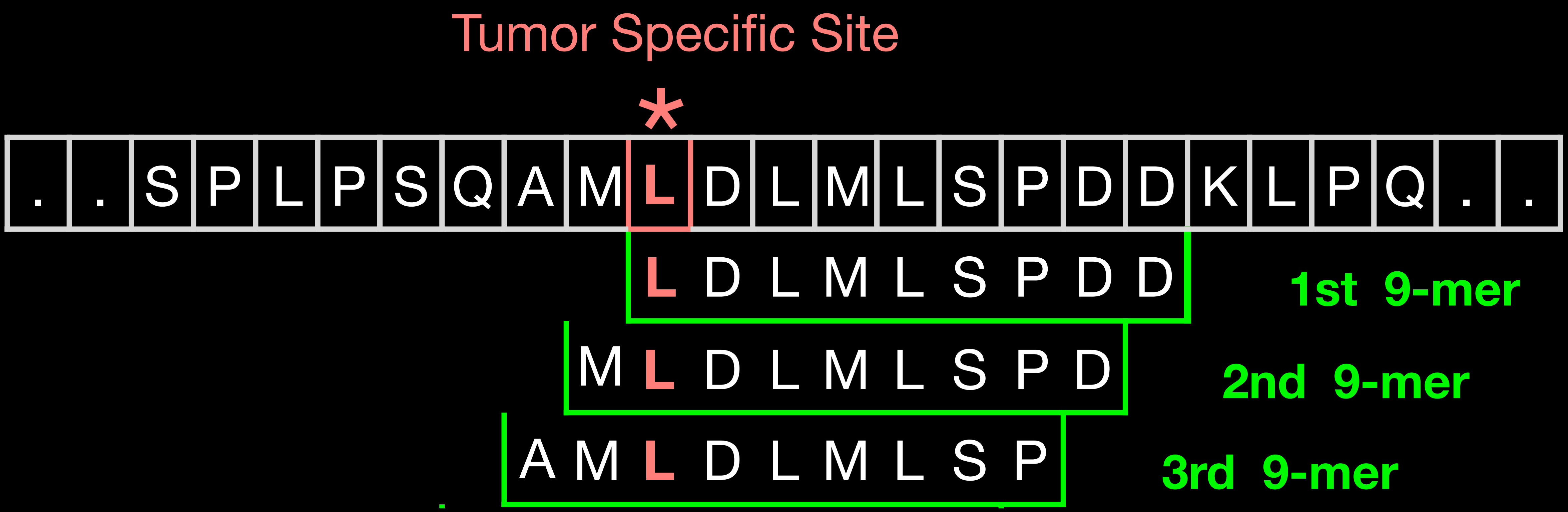
Tumor Specific Site

*

.	.	S	P	L	P	S	Q	A	M	L	D	L	M	L	S	P	D	D	K	L	P	Q	.	.

L D L M L S P D D **1st 9-mer**

M L D L M L S P D **2nd 9-mer**



Tumor Specific Site

*

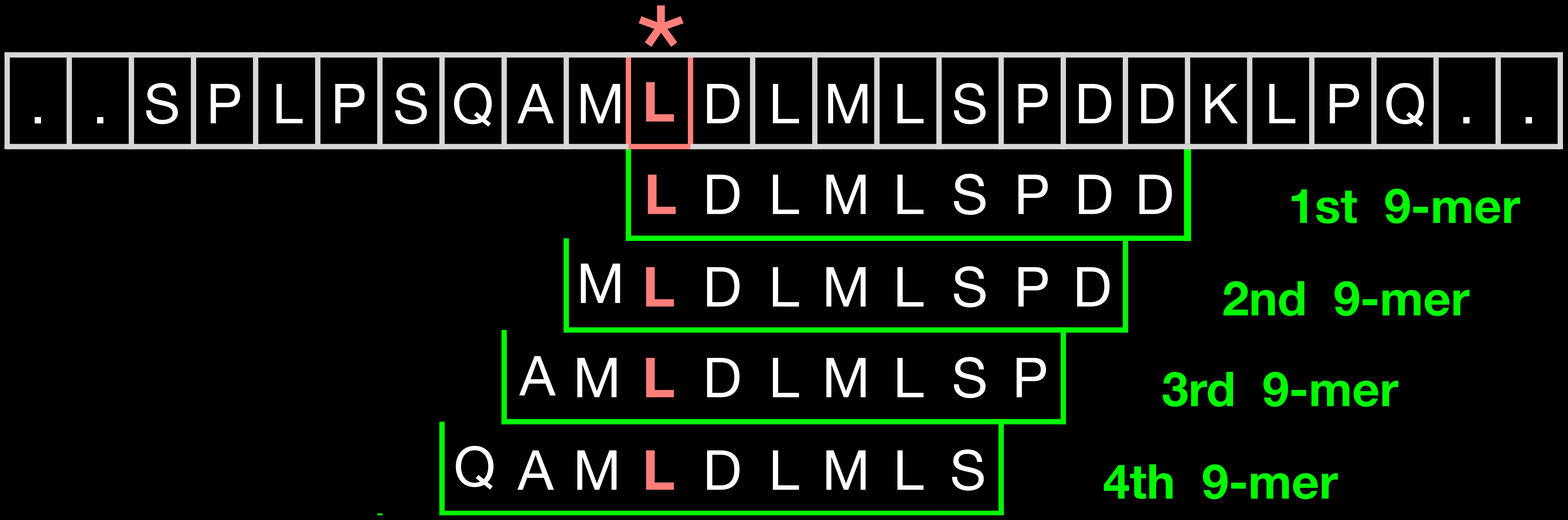
. . S P L P S Q A M **L** D L M L S P D D K L P Q . .

L D L M L S P D D — **1st 9-mer**

M **L** D L M L S P D — **2nd 9-mer**

A M **L** D L M L S P — **3rd 9-mer**

Tumor Specific Site



*

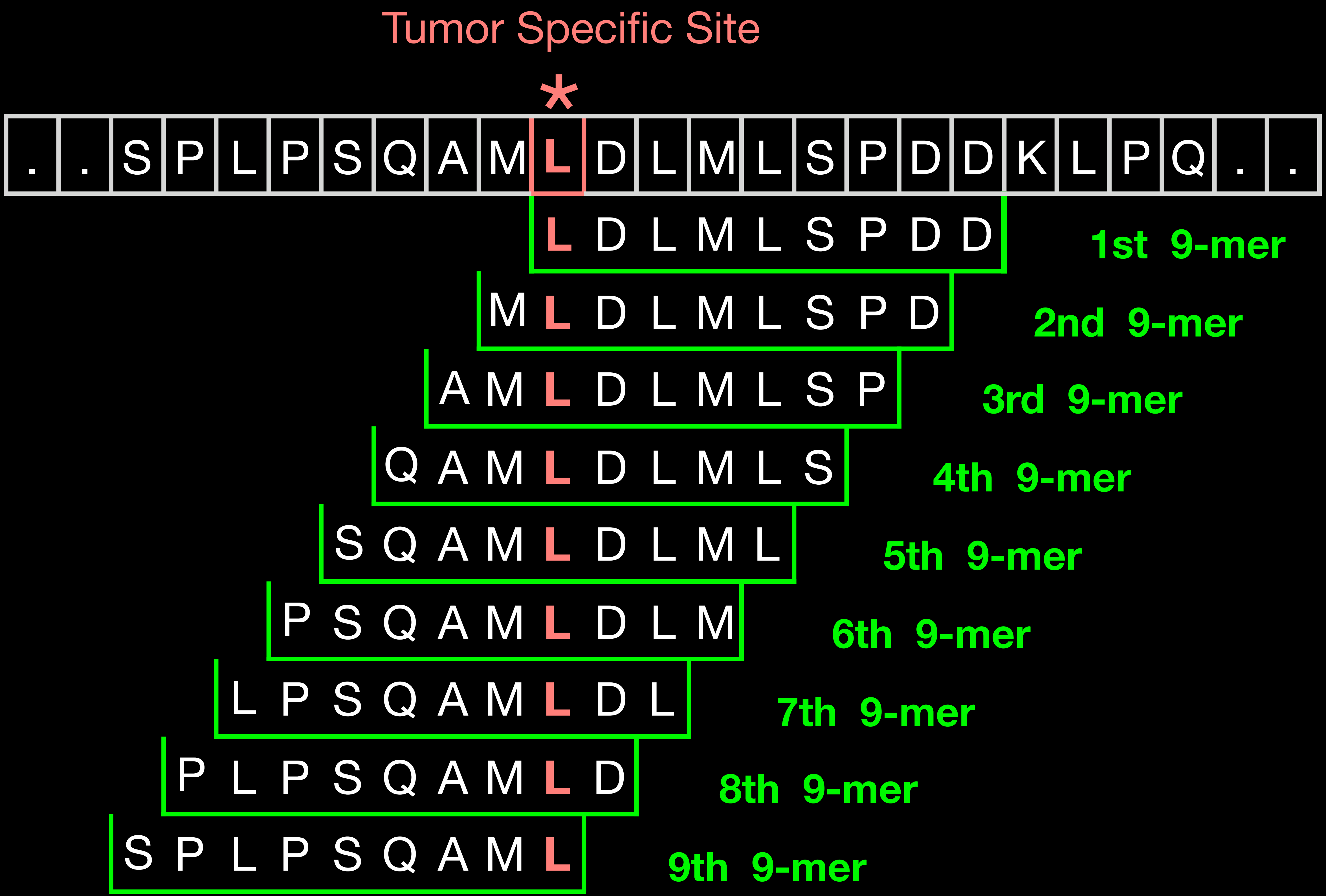
. . S P L P S Q A M L D L M L S P D D K L P Q . .

L D L M L S P D D 1st 9-mer

M L D L M L S P D 2nd 9-mer

A M L D L M L S P 3rd 9-mer

Q A M L D L M L S 4th 9-mer



Tumor Specific Site

*

. . S P L P S Q A M **L** D L M L S P D D K L P Q . .

L D L M L S P D D 1st 9-mer

M **L** D L M L S P D 2nd 9-mer

A M **L** D L M L S P 3rd 9-mer

Q A M **L** D L M L S 4th 9-mer

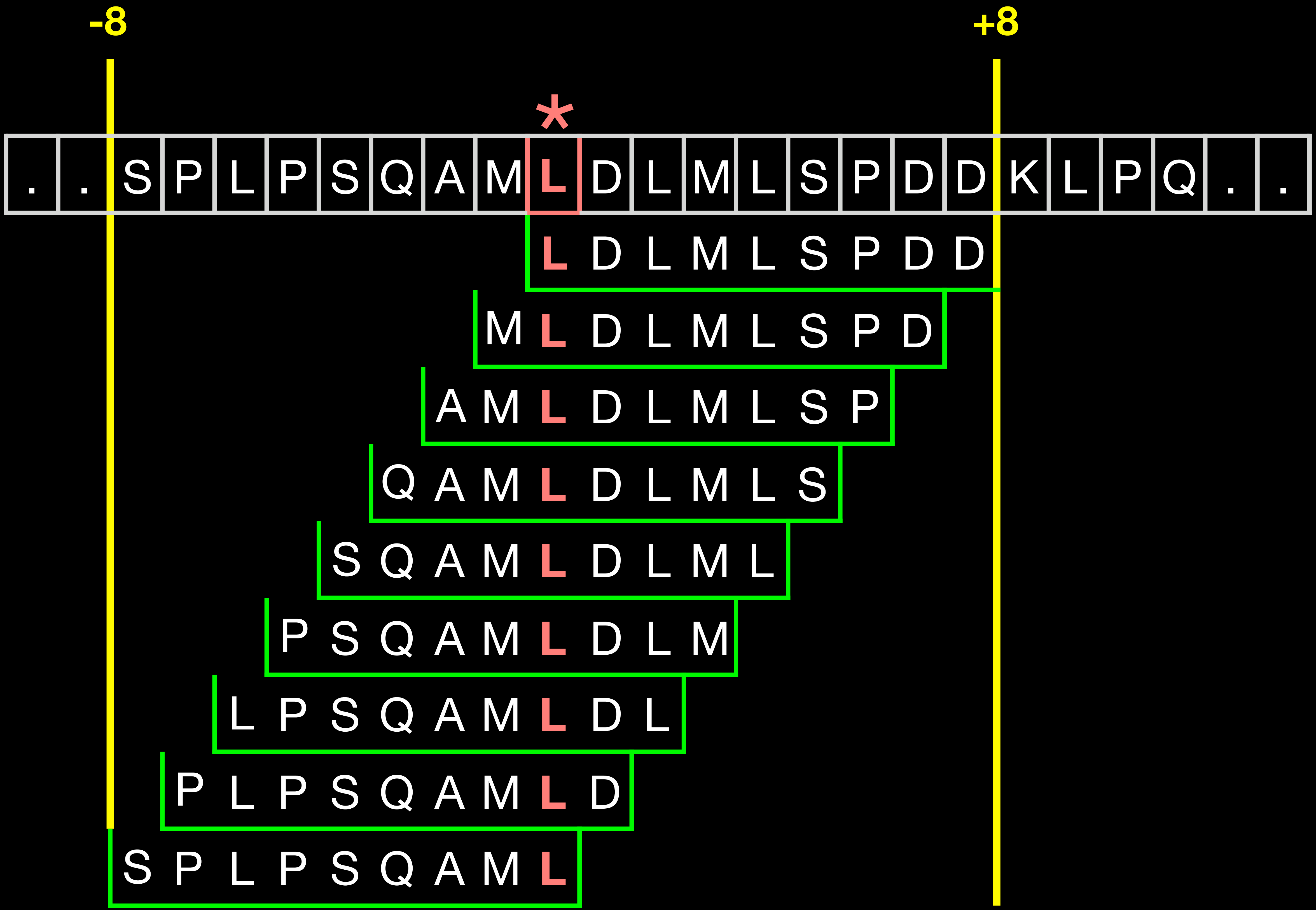
S Q A M **L** D L M L 5th 9-mer

P S Q A M **L** D L M 6th 9-mer

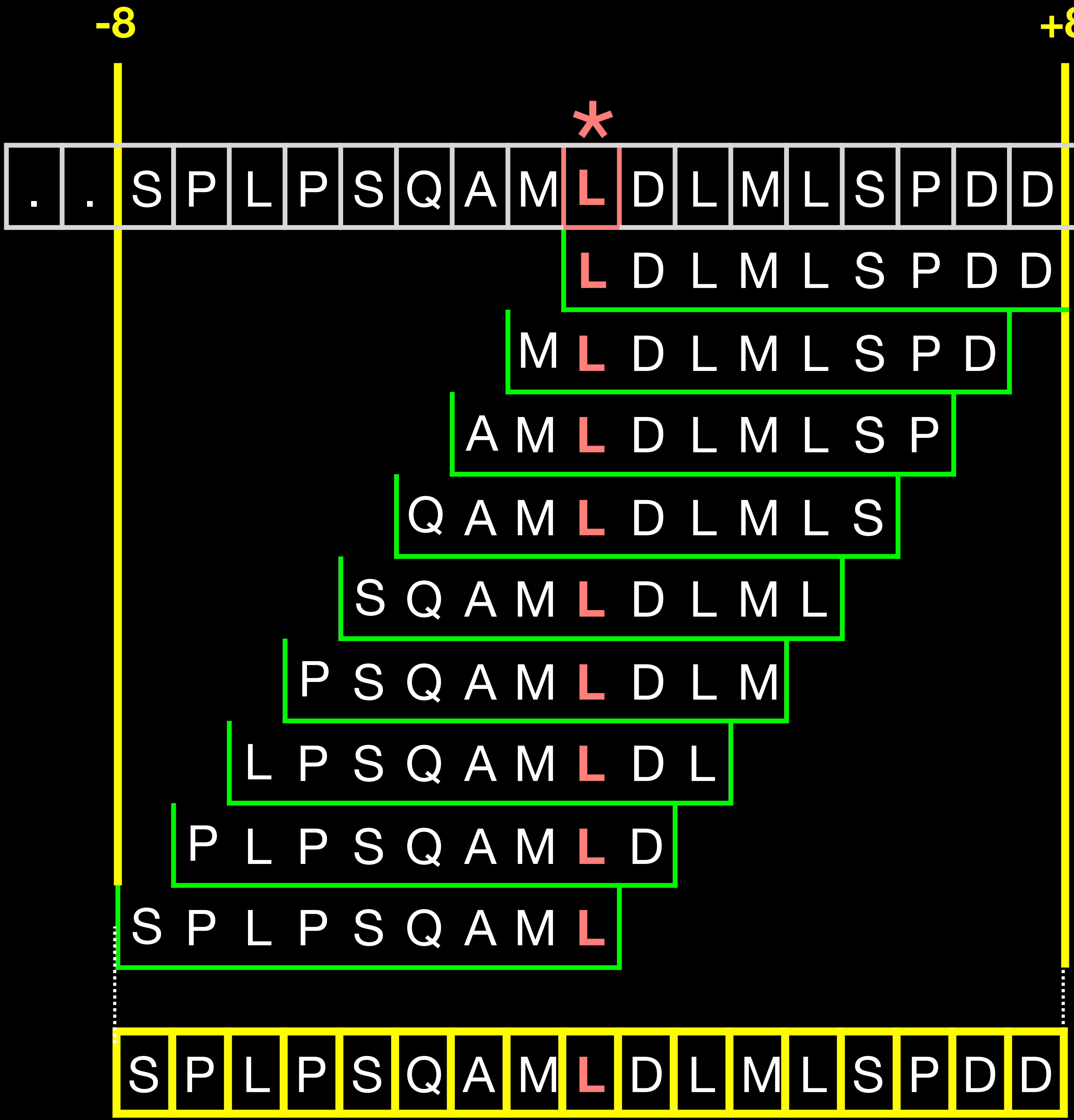
L P S Q A M **L** D L 7th 9-mer

P L P S Q A M **L** D 8th 9-mer

S P L P S Q A M **L** 9th 9-mer



```
    -8                              +8
                    *
. . S P L P S Q A M L D L M L S P D D K L P Q . .
                    L D L M L S P D D
                  M L D L M L S P D
                A M L D L M L S P
              Q A M L D L M L S
            S Q A M L D L M L
          P S Q A M L D L M
        L P S Q A M L D L
      P L P S Q A M L D
    S P L P S Q A M L
```



-8 +8

*

. . S P L P S Q A M L D L M L S P D D K L P Q . .

L D L M L S P D D

M L D L M L S P D

A M L D L M L S P

Q A M L D L M L S

S Q A M L D L M L

P S Q A M L D L M

L P S Q A M L D L

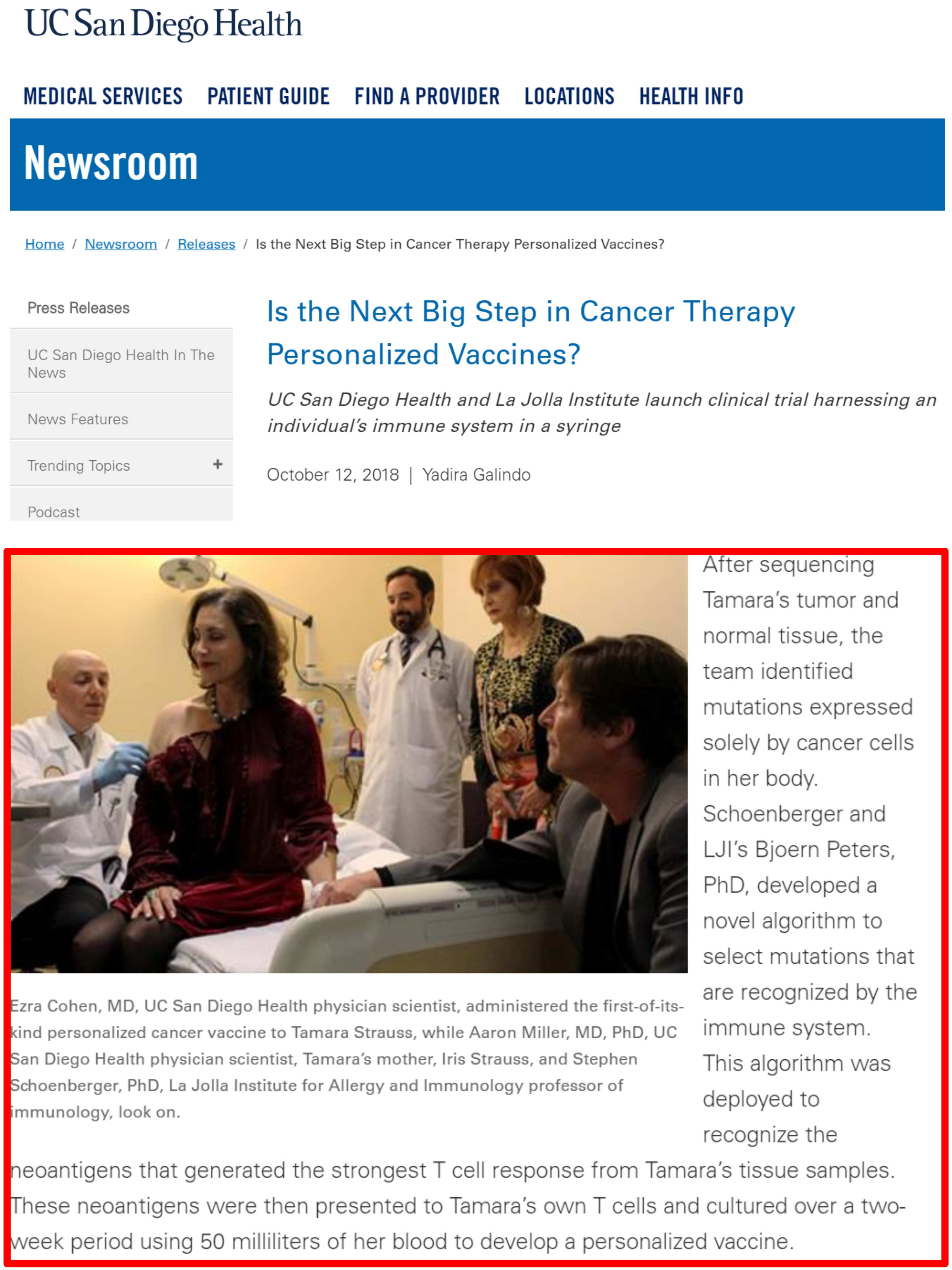
P L P S Q A M L D

S P L P S Q A M L

S P L P S Q A M L D L M L S P D D

Cancer specific sub-sequence!

Several trials for personalized cancer vaccines are currently ongoing



Is the Next Big Step in Cancer Therapy Personalized Vaccines?

UC San Diego Health and La Jolla Institute launch clinical trial harnessing an individual's immune system in a syringe

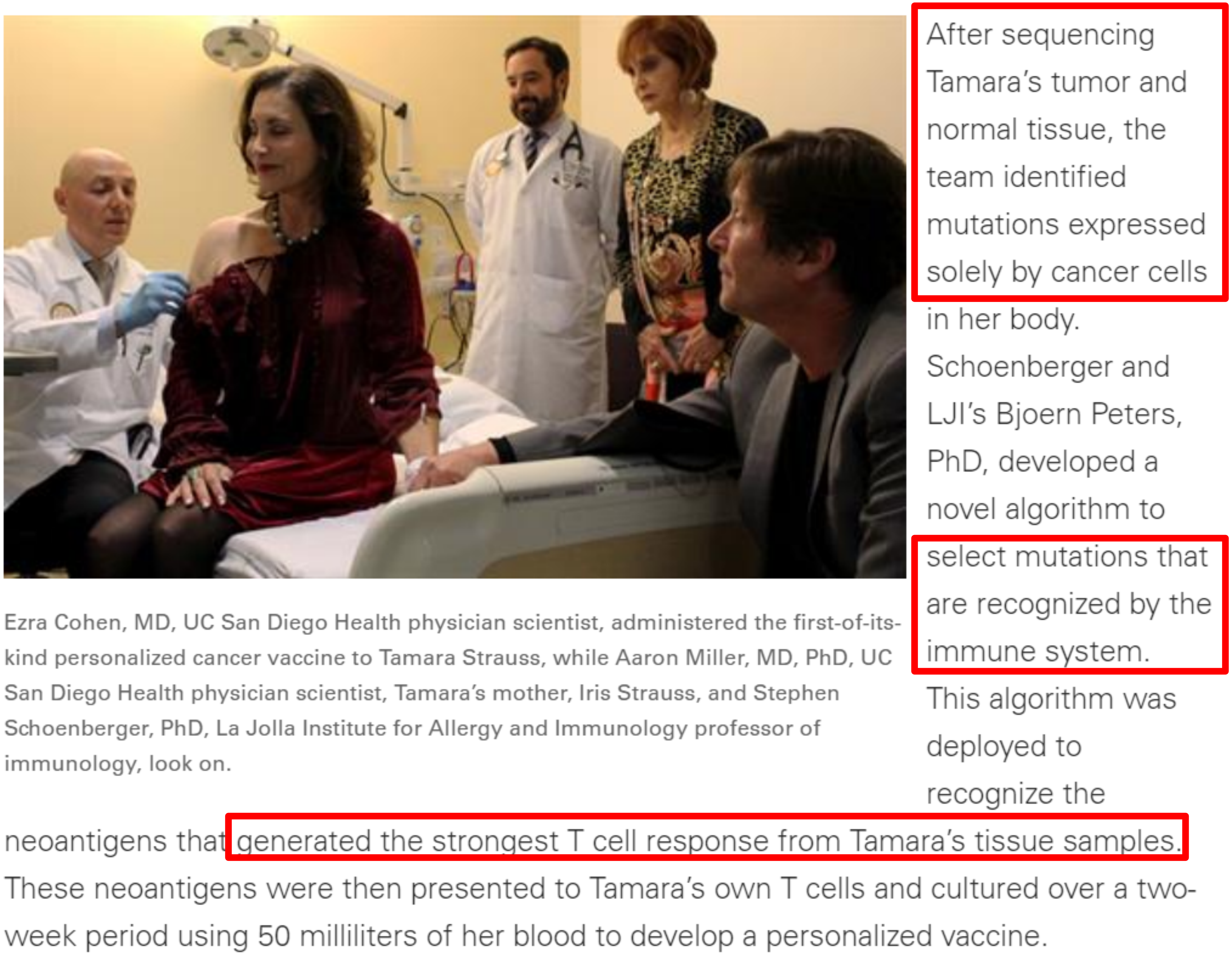
October 12, 2018 | Yadira Galindo

Ezra Cohen, MD, UC San Diego Health physician scientist, administered the first-of-its-kind personalized cancer vaccine to Tamara Strauss, while Aaron Miller, MD, PhD, UC San Diego Health physician scientist, Tamara's mother, Iris Strauss, and Stephen Schoenberger, PhD, La Jolla Institute for Allergy and Immunology professor of immunology, look on.

After sequencing Tamara's tumor and normal tissue, the team identified mutations expressed solely by cancer cells in her body. Schoenberger and LJI's Bjoern Peters, PhD, developed a novel algorithm to select mutations that are recognized by the immune system. This algorithm was deployed to recognize the neoantigens that generated the strongest T cell response from Tamara's tissue samples. These neoantigens were then presented to Tamara's own T cells and cultured over a two-week period using 50 milliliters of her blood to develop a personalized vaccine.

Slide from: **Bjoern Peters** (LIAI)

Personalized Cancer Immunotherapy



Ezra Cohen, MD, UC San Diego Health physician scientist, administered the first-of-its-kind personalized cancer vaccine to Tamara Strauss, while Aaron Miller, MD, PhD, UC San Diego Health physician scientist, Tamara's mother, Iris Strauss, and Stephen Schoenberger, PhD, La Jolla Institute for Allergy and Immunology professor of immunology, look on.

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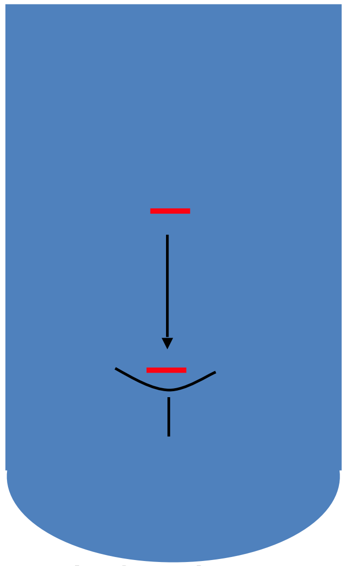
Slide from: **Bjoern Peters** (LIAI)

Measuring and predicting MHC:peptide binding

Experimental Basis: MHC Binding Assay

List of peptides with allele specific binding affinity



Sequence	IC_{50}
QIVTMFEAL	3.6
LKGPDIYKG	308
NFCNLTSAF	50,000
AQSQCRTFR	38,000
CTYAGPFGM	143
CFGNTAVAK	50,000
. . .	

$\log(IC_{50})$ ~ Binding free Energy

low IC_{50} → high affinity

Impossible to measure all peptides

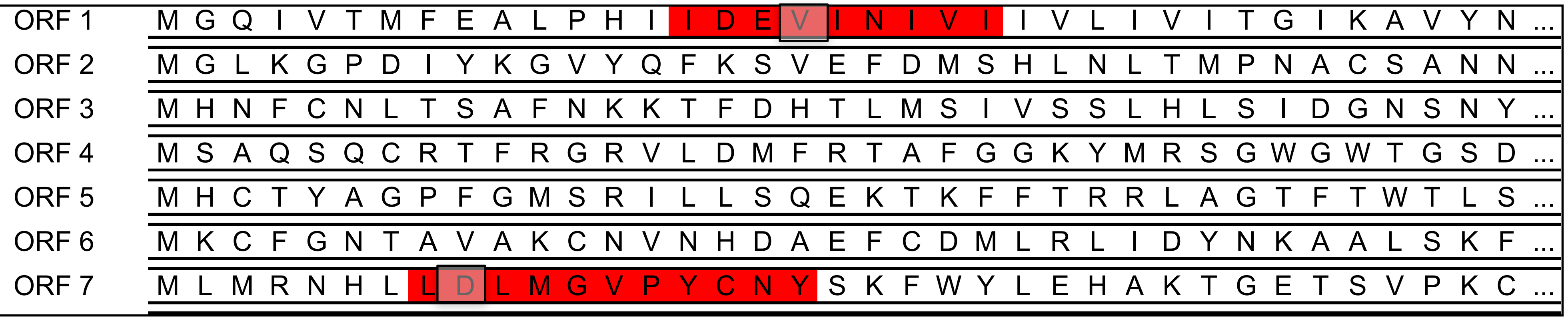
→ Predict binding peptides using machine learning

Find function F_i in $F_1, F_2, F_3, \ldots$

F_i (Sequence) ≈ Affinity

Many different approaches (ANN, SVM, HMM, LP, ...)

T cell epitope mapping



ORF 1 M G Q I V T M F E A L P H I I D E V I N I V I I V L I V I T G I K A V Y N ...
ORF 2 M G L K G P D I Y K G V Y Q F K S V E F D M S H L N L T M P N A C S A N N ...
ORF 3 M H N F C N L T S A F N K K T F D H T L M S I V S S L H L S I D G N S N Y ...
ORF 4 M S A Q S Q C R T F R G R V L D M F R T A F G G K Y M R S G W G W T G S D ...
ORF 5 M H C T Y A G P F G M S R I L L S Q E K T K F F T R R L A G T F T W T L S ...
ORF 6 M K C F G N T A V A K C N V N H D A E F C D M L R L I D Y N K A A L S K F ...
ORF 7 M L M R N H L L D L M G V P Y C N Y S K F W Y L E H A K T G E T S V P K C ...

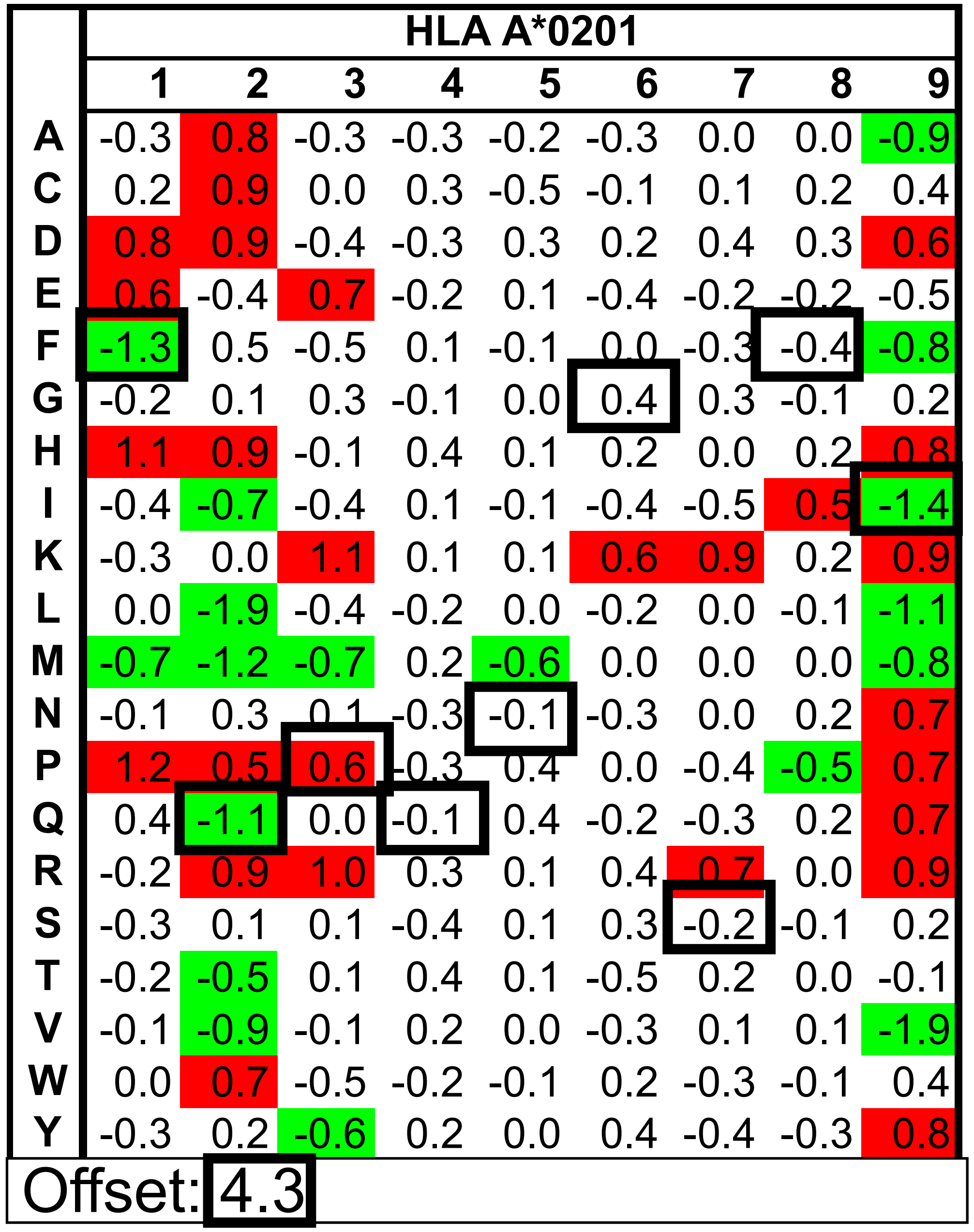
Slide from: **Bjoern Peters** (LIAI)

Calculate scoring matrix from affinities

Machine learning PSSM = Minimize the difference between predicted and measured binding affinities by varying the matrix values

N peptides with measured binding affinities

log (IC50)	Peptide
0.50	FQPQNGSFI
0.72	ISVANKIYM
2.37	RVYEALYYV
3.42	FQPQSGQFI
3.46	LYEKVKSQL
4.07	FKSVEFDMS
4.18	FQPQNGQFH
4.24	VLMLPVWFL
4.39	YMTLGQVVF
4.40	EDVKNAVGV
4.90	VFYEQMKRF
...	

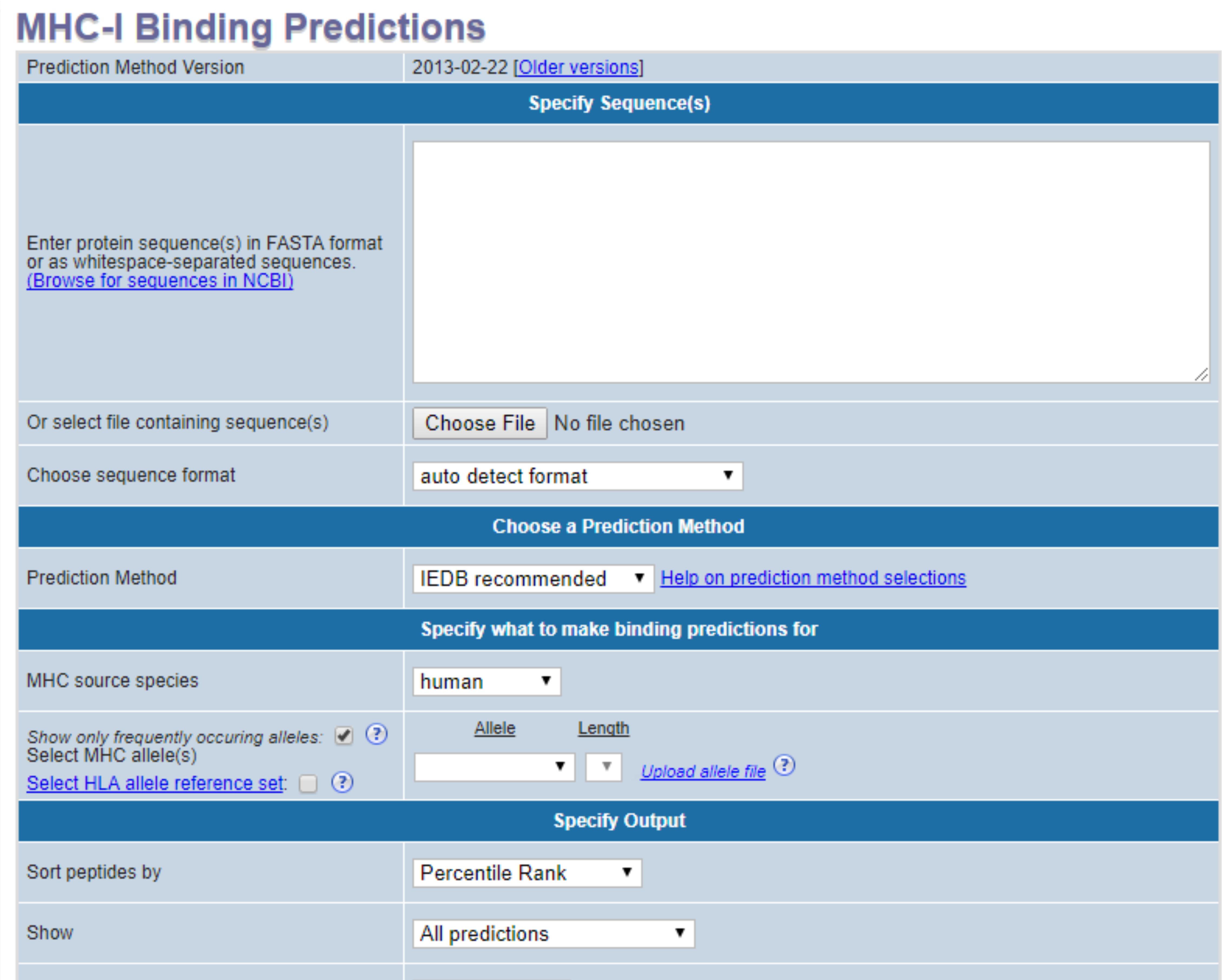


HLA A*0201

	1	2	3	4	5	6	7	8	9
A	-0.3	0.8	-0.3	-0.3	-0.2	-0.3	0.0	0.0	-0.9
C	0.2	0.9	0.0	0.3	-0.5	-0.1	0.1	0.2	0.4
D	0.8	0.9	-0.4	-0.3	0.3	0.2	0.4	0.3	0.6
E	0.6	-0.4	0.7	-0.2	0.1	-0.4	-0.2	-0.2	-0.5
F	-1.3	0.5	-0.5	0.1	-0.1	0.0	-0.3	-0.4	-0.8
G	-0.2	0.1	0.3	-0.1	0.0	0.4	0.3	-0.1	0.2
H	1.1	0.9	-0.1	0.4	0.1	0.2	0.0	0.2	0.8
I	-0.4	-0.7	-0.4	0.1	-0.1	-0.4	-0.5	0.5	-1.4
K	-0.3	0.0	1.1	0.1	0.1	0.6	0.9	0.2	0.9
L	0.0	-1.9	-0.4	-0.2	0.0	-0.2	0.0	-0.1	-1.1
M	-0.7	-1.2	-0.7	0.2	-0.6	0.0	0.0	0.0	-0.8
N	-0.1	0.3	0.1	-0.3	-0.1	-0.3	0.0	0.2	0.7
P	1.2	0.5	0.6	-0.3	0.4	0.0	-0.4	-0.5	0.7
Q	0.4	-1.1	0.0	-0.1	0.4	-0.2	-0.3	0.2	0.7
R	-0.2	0.9	1.0	0.3	0.1	0.4	0.7	0.0	0.9
S	-0.3	0.1	0.1	-0.4	0.1	0.3	-0.2	-0.1	0.2
T	-0.2	-0.5	0.1	0.4	0.1	-0.5	0.2	0.0	-0.1
V	-0.1	-0.9	-0.1	0.2	0.0	-0.3	0.1	0.1	-1.9
W	0.0	0.7	-0.5	-0.2	-0.1	0.2	-0.3	-0.1	0.4
Y	-0.3	0.2	-0.6	0.2	0.0	0.4	-0.4	-0.3	0.8

Offset: 4.3

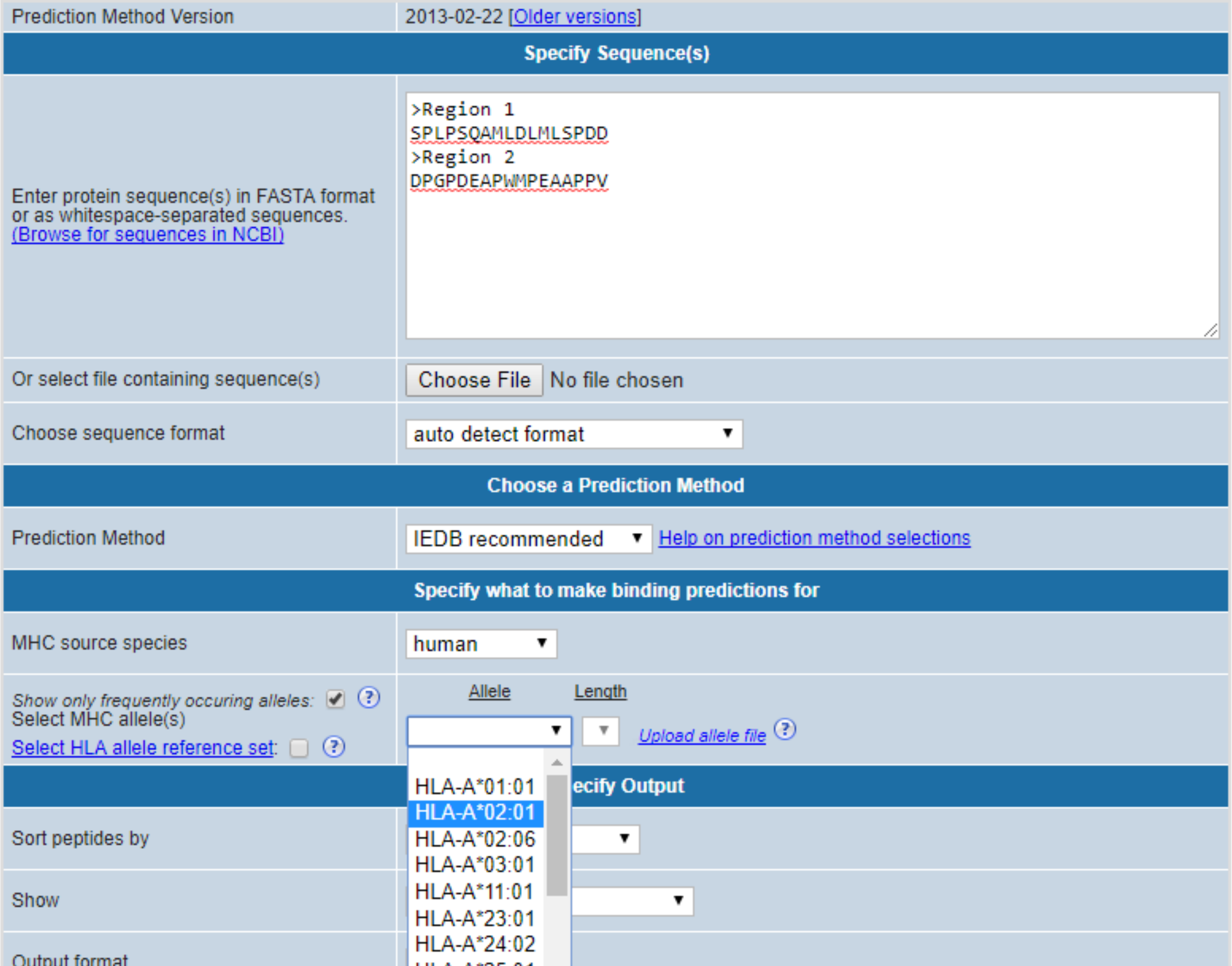
http://tools.iedb.org/mhci/



MHC-I Binding Predictions

Prediction Method Version	2013-02-22 [Older versions]
Specify Sequence(s)	
Enter protein sequence(s) in FASTA format or as whitespace-separated sequences. (Browse for sequences in NCBI)	
Or select file containing sequence(s)	Choose File No file chosen
Choose sequence format	auto detect format ▾
Choose a Prediction Method	
Prediction Method	IEDB recommended ▾ Help on prediction method selections
Specify what to make binding predictions for	
MHC source species	human ▾
Show only frequently occuring alleles: ☑ ? Select MHC allele(s) Select HLA allele reference set: ☐ ?	Allele ▾ Length ▾ *Upload allele file* ?
Specify Output	
Sort peptides by	Percentile Rank ▾
Show	All predictions ▾

http://tools.iedb.org/mhci/



Prediction Method Version	2013-02-22 [Older versions]

Specify Sequence(s)

Enter protein sequence(s) in FASTA format or as whitespace-separated sequences. (Browse for sequences in NCBI)	>Region 1 SPLPSQAMLDLMLSPDD >Region 2 DPGPDEAPWMPEAAPPV
Or select file containing sequence(s)	Choose File No file chosen
Choose sequence format	auto detect format ▼

Choose a Prediction Method

Prediction Method	IEDB recommended ▼ Help on prediction method selections

Specify what to make binding predictions for

MHC source species	human ▼
Show only frequently occuring alleles: ☑ ? Select MHC allele(s) Select HLA allele reference set: ☐ ?	Allele ▼ Length ▼ Upload allele file ?

HLA-A*01:01
HLA-A*02:01
HLA-A*02:06
HLA-A*03:01
HLA-A*11:01
HLA-A*23:01
HLA-A*24:02

ecify Output

Sort peptides by	▼
Show	▼
Output format	

HLA binding Prediction on IEDB

Peptides:

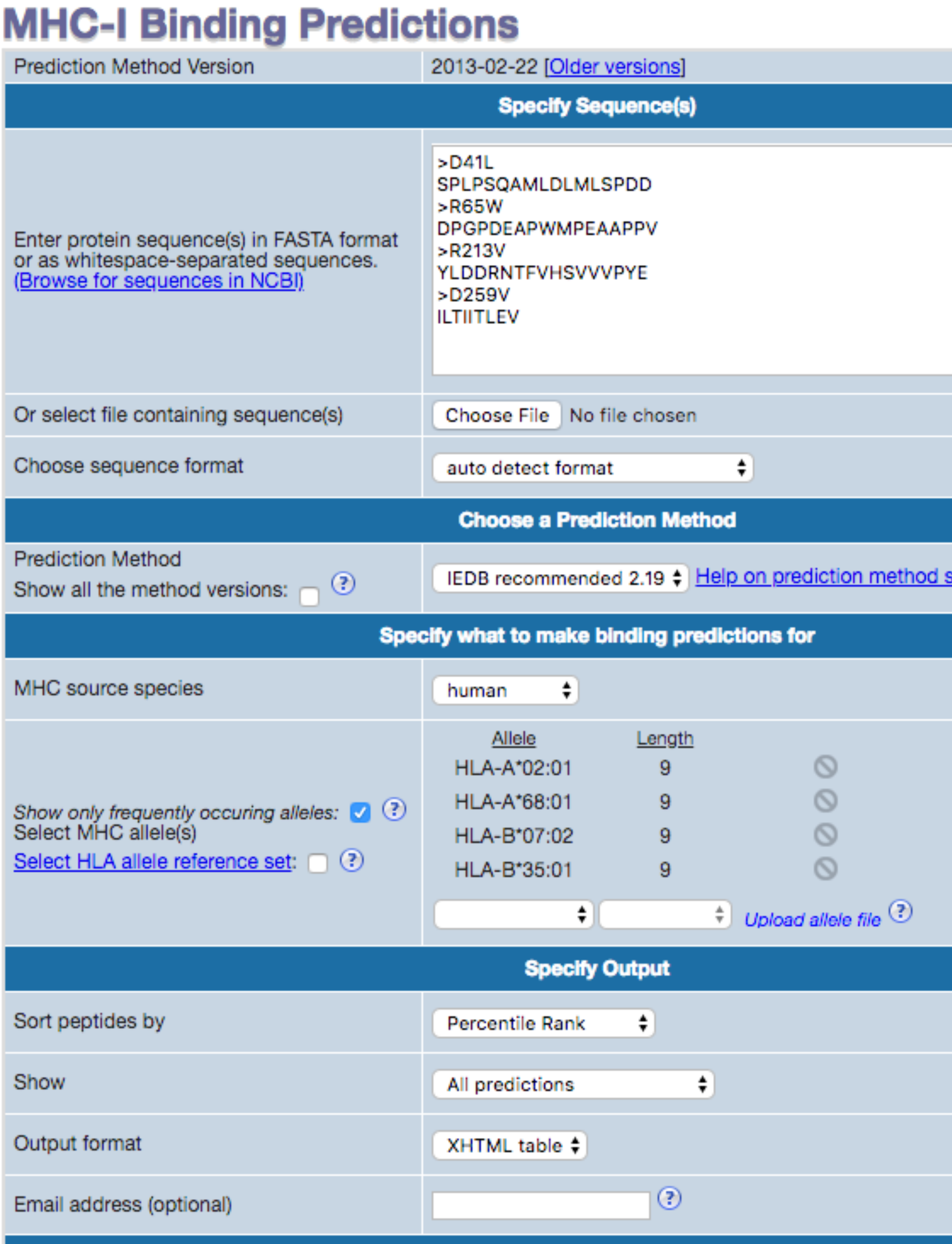
>D41L
SPLPSQAMLD**L**MLSPDD
>R65W
DPGPDEAP**W**MPEAAPPV
>R213V
YLDDRNTF**V**HSVVVPYE
>D259V
ILTIITLE**V**

HLA Alleles:

HLA-A*02:01
HLA-A*68:01
HLA-B*07:02
HLA-B*35:01

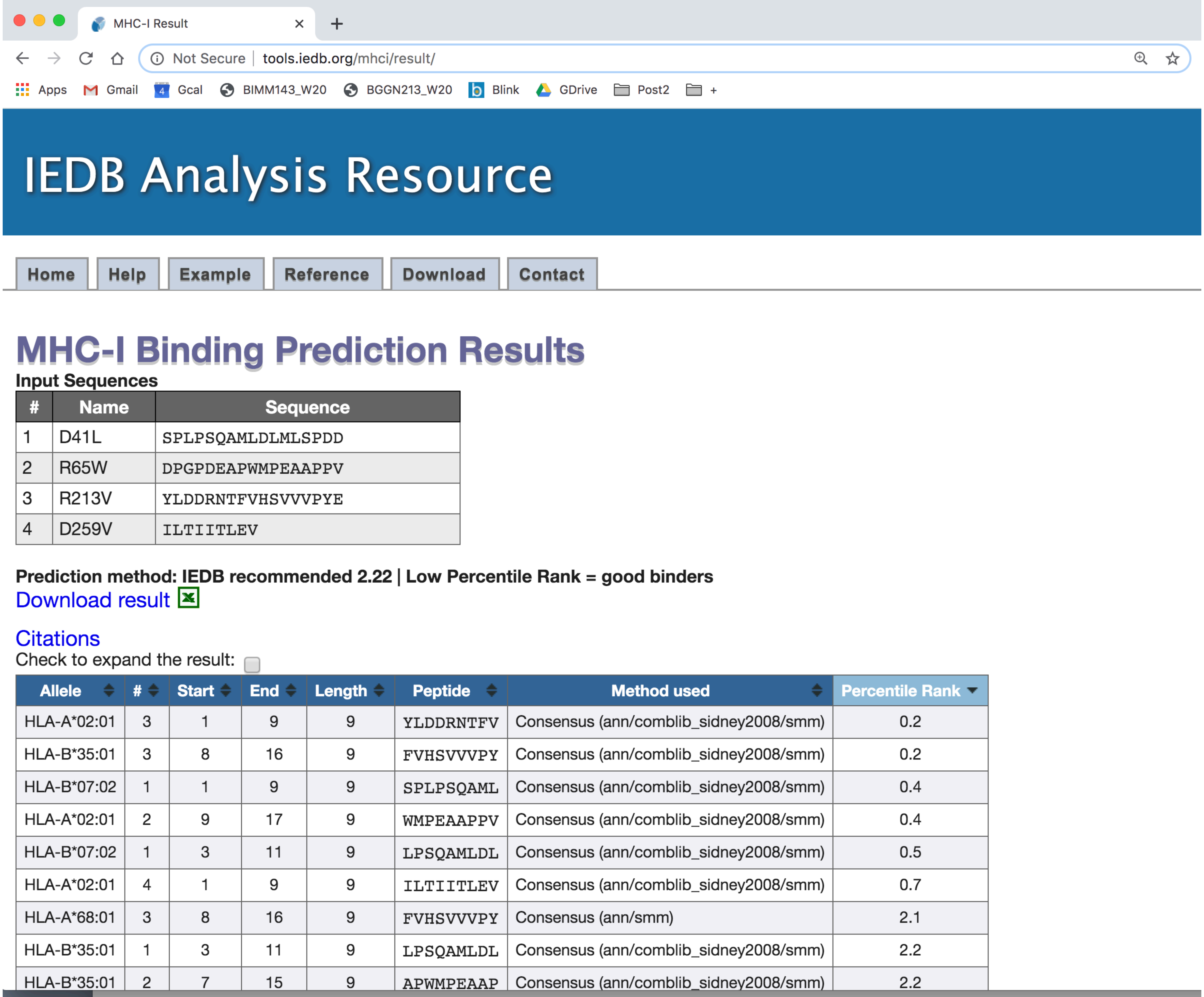
Length:

9



MHC-I Binding Predictions

Prediction Method Version	2013-02-22 [Older versions]
Specify Sequence(s)	
Enter protein sequence(s) in FASTA format or as whitespace-separated sequences. (Browse for sequences in NCBI)	>D41L SPLPSQAMLDLMLSPDD >R65W DPGPDEAPWMPEAAPPV >R213V YLDDRNTFVHSVVVPYE >D259V ILTIITLEV
Or select file containing sequence(s)	Choose File No file chosen
Choose sequence format	auto detect format
Choose a Prediction Method	
Prediction Method Show all the method versions: ☐	IEDB recommended 2.19 Help on prediction method s
Specify what to make binding predictions for	
MHC source species	human
Show only frequently occuring alleles: ☑ Select MHC allele(s) Select HLA allele reference set: ☐	Allele / Length: HLA-A*02:01 9 HLA-A*68:01 9 HLA-B*07:02 9 HLA-B*35:01 9 *Upload allele file*
Specify Output	
Sort peptides by	Percentile Rank
Show	All predictions
Output format	XHTML table
Email address (optional)	



MHC-I Binding Prediction Results

Input Sequences

#	Name	Sequence
1	D41L	SPLPSQAMLDLMLSPDD
2	R65W	DPGPDEAPWMPEAAPPV
3	R213V	YLDDRNTFVHSVVVPYE
4	D259V	ILTIITLEV

Prediction method: IEDB recommended 2.22 | Low Percentile Rank = good binders

Download result

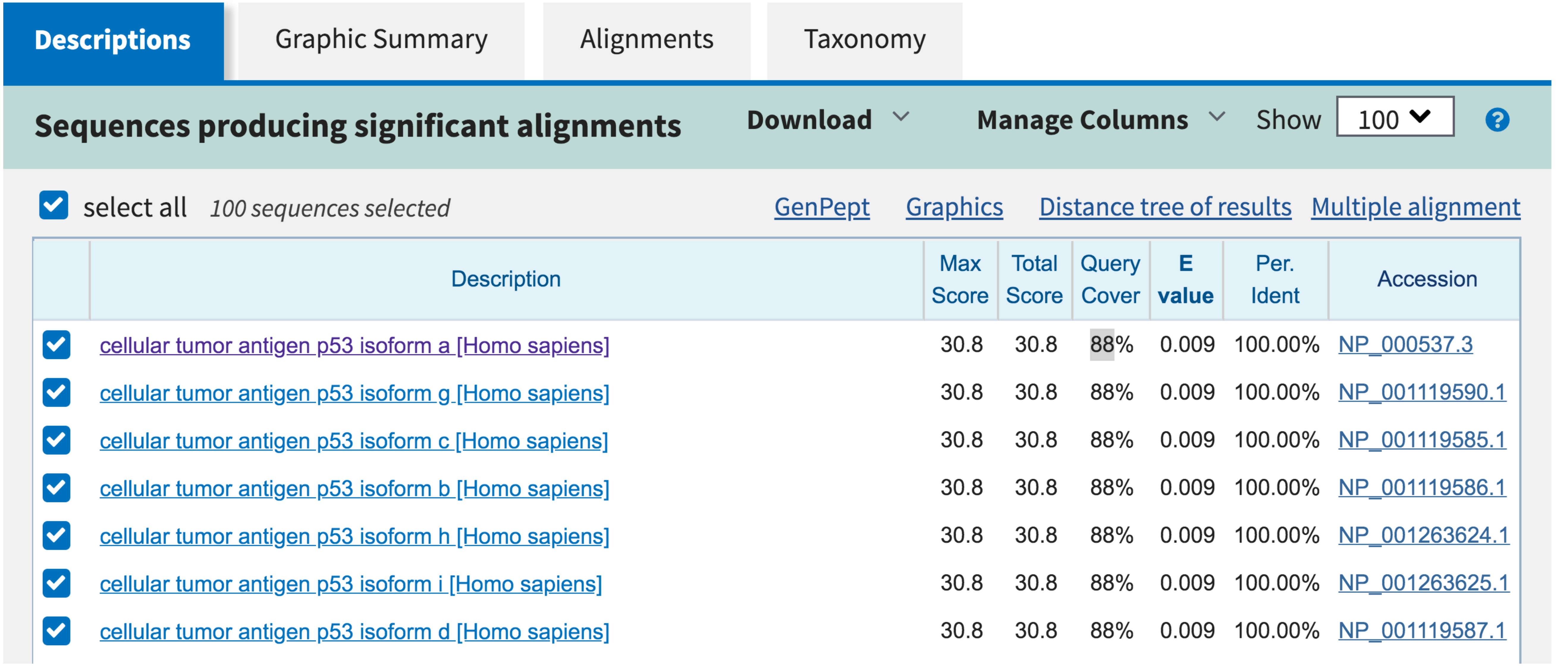
Citations

Check to expand the result: ☐

Allele	#	Start	End	Length	Peptide	Method used	Percentile Rank
HLA-A*02:01	3	1	9	9	YLDDRNTFV	Consensus (ann/comblib_sidney2008/smm)	0.2
HLA-B*35:01	3	8	16	9	FVHSVVVPY	Consensus (ann/comblib_sidney2008/smm)	0.2
HLA-B*07:02	1	1	9	9	SPLPSQAML	Consensus (ann/comblib_sidney2008/smm)	0.4
HLA-A*02:01	2	9	17	9	WMPEAAPPV	Consensus (ann/comblib_sidney2008/smm)	0.4
HLA-B*07:02	1	3	11	9	LPSQAMLDL	Consensus (ann/comblib_sidney2008/smm)	0.5
HLA-A*02:01	4	1	9	9	ILTIITLEV	Consensus (ann/comblib_sidney2008/smm)	0.7
HLA-A*68:01	3	8	16	9	FVHSVVVPY	Consensus (ann/smm)	2.1
HLA-B*35:01	1	3	11	9	LPSQAMLDL	Consensus (ann/comblib_sidney2008/smm)	2.2
HLA-B*35:01	2	7	15	9	APWMPEAAP	Consensus (ann/comblib_sidney2008/smm)	2.2

Workflow:

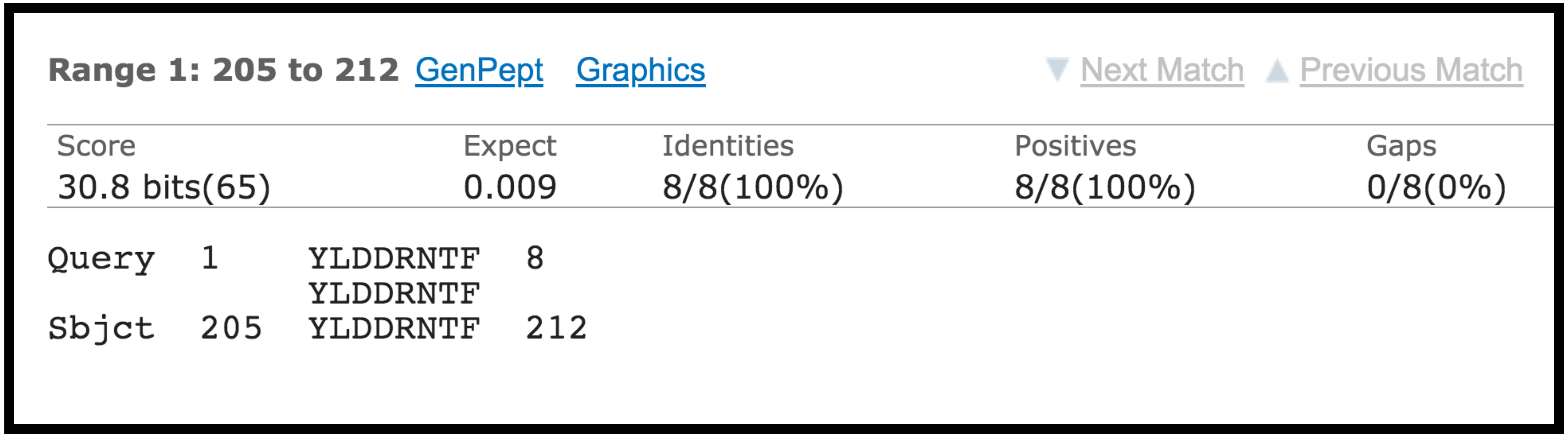
- **Step 1**: Identify sequence regions that contain all **9-mer** peptides that are **only** found in the tumor
    - What are the tumor specific amino-acids?
    - What peptides include these amino acids?
- **Step 2**: Run HLA binding prediction to identify 9-mer peptides in the sequence regions unique to the tumor to select peptides that can be **presented to T cells** in this patient
- **Step 3**: Determine if the identified peptides are specific for the tumor (i.e. are they found anywhere else?)
    - **Which peptide would you choose?**



Sequences producing significant alignments

☑ select all *100 sequences selected*

	Description	Max Score	Total Score	Query Cover	E value	Per. Ident	Accession
☑	cellular tumor antigen p53 isoform a [Homo sapiens]	30.8	30.8	88%	0.009	100.00%	NP_000537.3
☑	cellular tumor antigen p53 isoform g [Homo sapiens]	30.8	30.8	88%	0.009	100.00%	NP_001119590.1
☑	cellular tumor antigen p53 isoform c [Homo sapiens]	30.8	30.8	88%	0.009	100.00%	NP_001119585.1
☑	cellular tumor antigen p53 isoform b [Homo sapiens]	30.8	30.8	88%	0.009	100.00%	NP_001119586.1
☑	cellular tumor antigen p53 isoform h [Homo sapiens]	30.8	30.8	88%	0.009	100.00%	NP_001263624.1
☑	cellular tumor antigen p53 isoform i [Homo sapiens]	30.8	30.8	88%	0.009	100.00%	NP_001263625.1
☑	cellular tumor antigen p53 isoform d [Homo sapiens]	30.8	30.8	88%	0.009	100.00%	NP_001119587.1

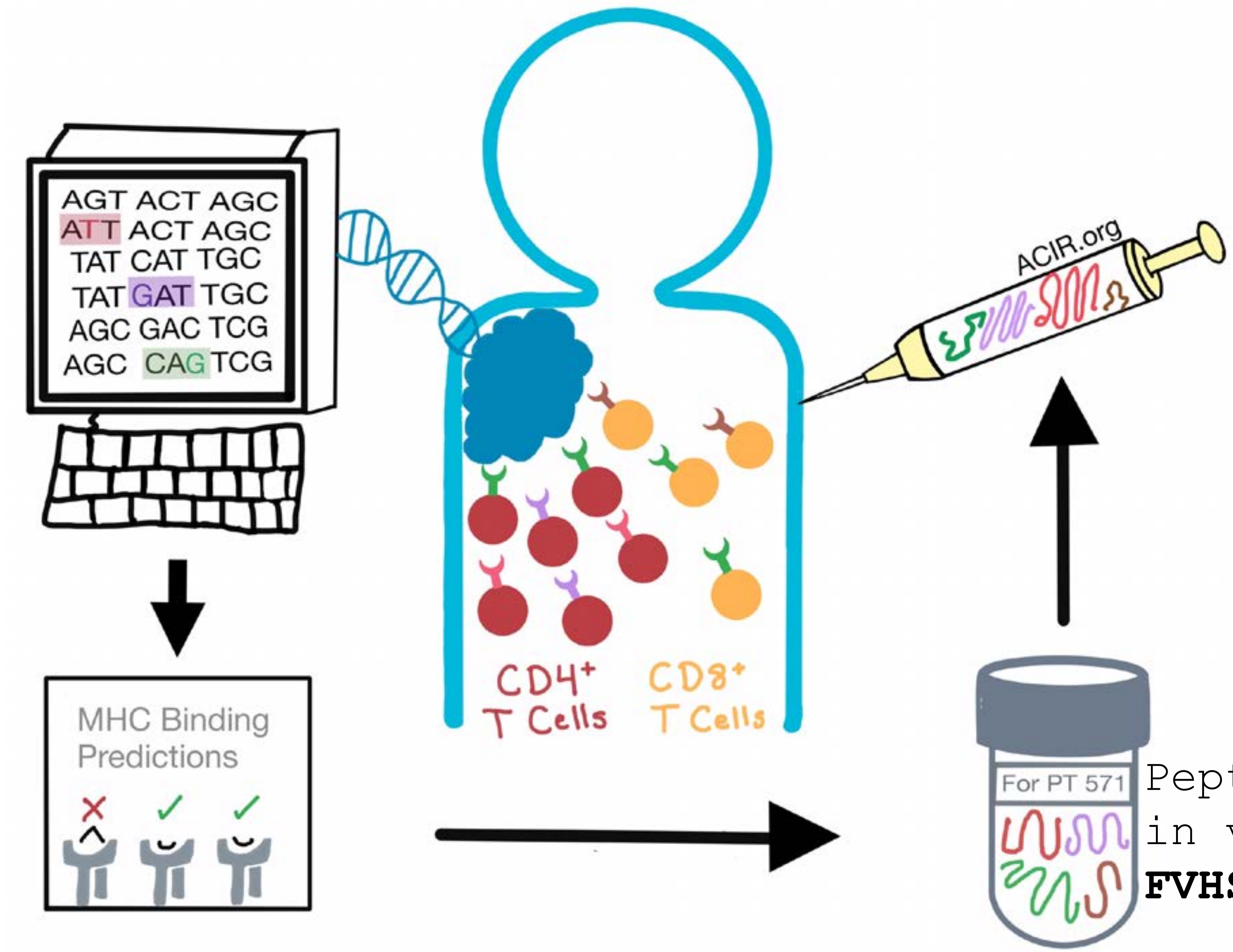


Range 1: 205 to 212

Score	Expect	Identities	Positives	Gaps
30.8 bits(65)	0.009	8/8(100%)	8/8(100%)	0/8(0%)

```
Query  1    YLDDRNTF  8
            YLDDRNTF
Sbjct  205  YLDDRNTF  212
```

Personalized Vaccines for Cancer Immunotherapy



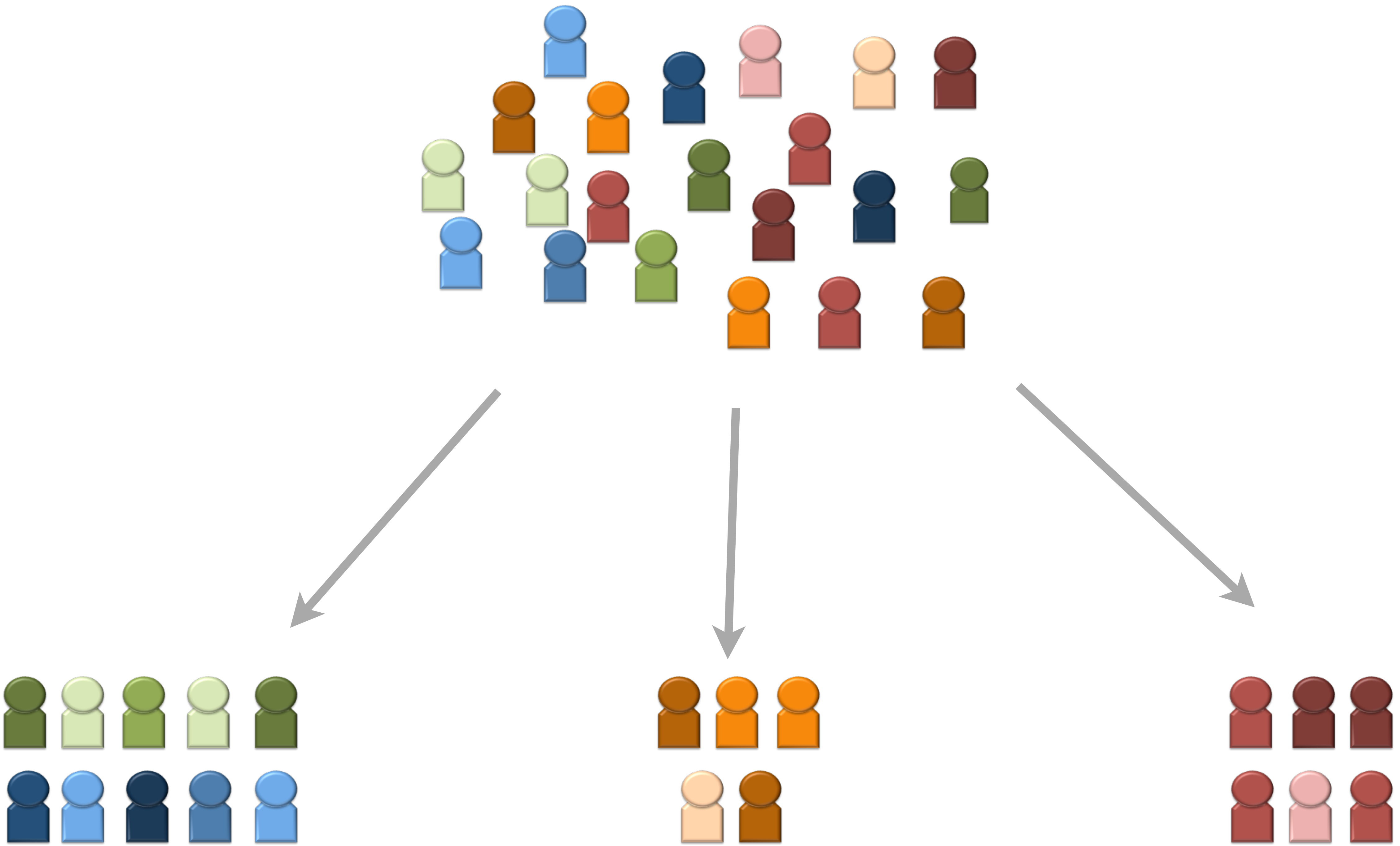
Peptide included in vaccine: **FVHSVVVPY**

Slide from: **Bjoern Peters** (LIAI)

Bonus Slides
(For Reference)

Genetic and genomic approaches can identify a cancers molecular signature to usefully stratify tumors for treatment

Stratify tumors based on molecular patterns

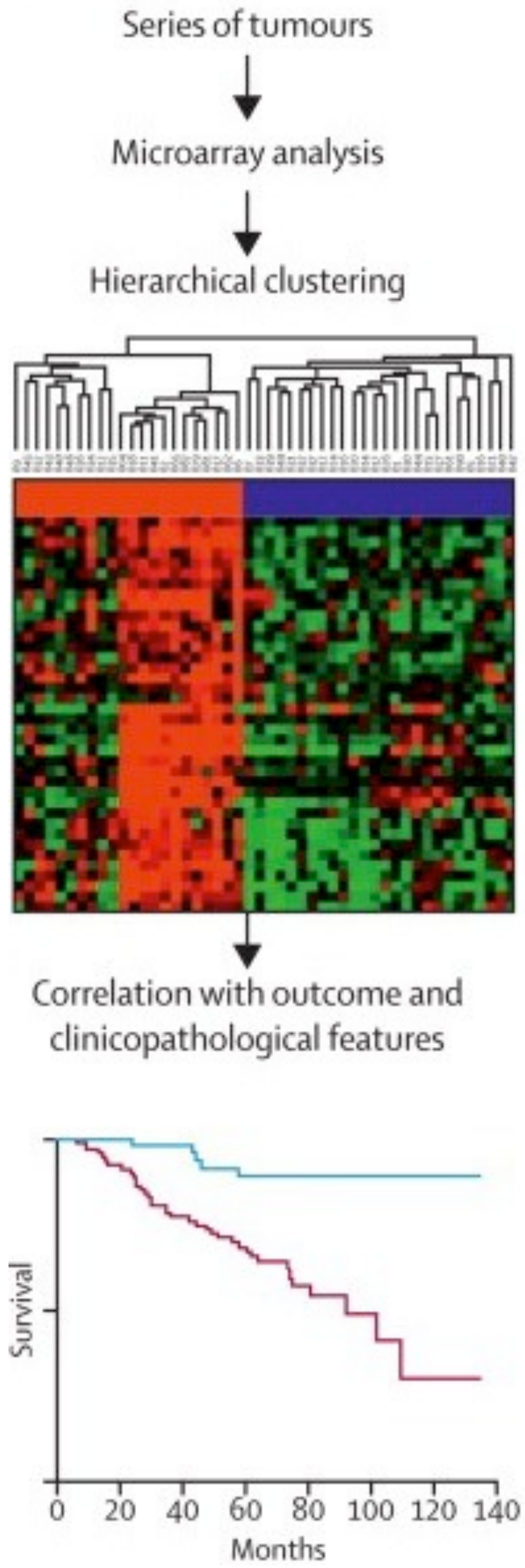


Good prognosis
Favorable response

Bad prognosis
Unfavorable response

Increased toxicity

Stratify tumors based on molecular patterns



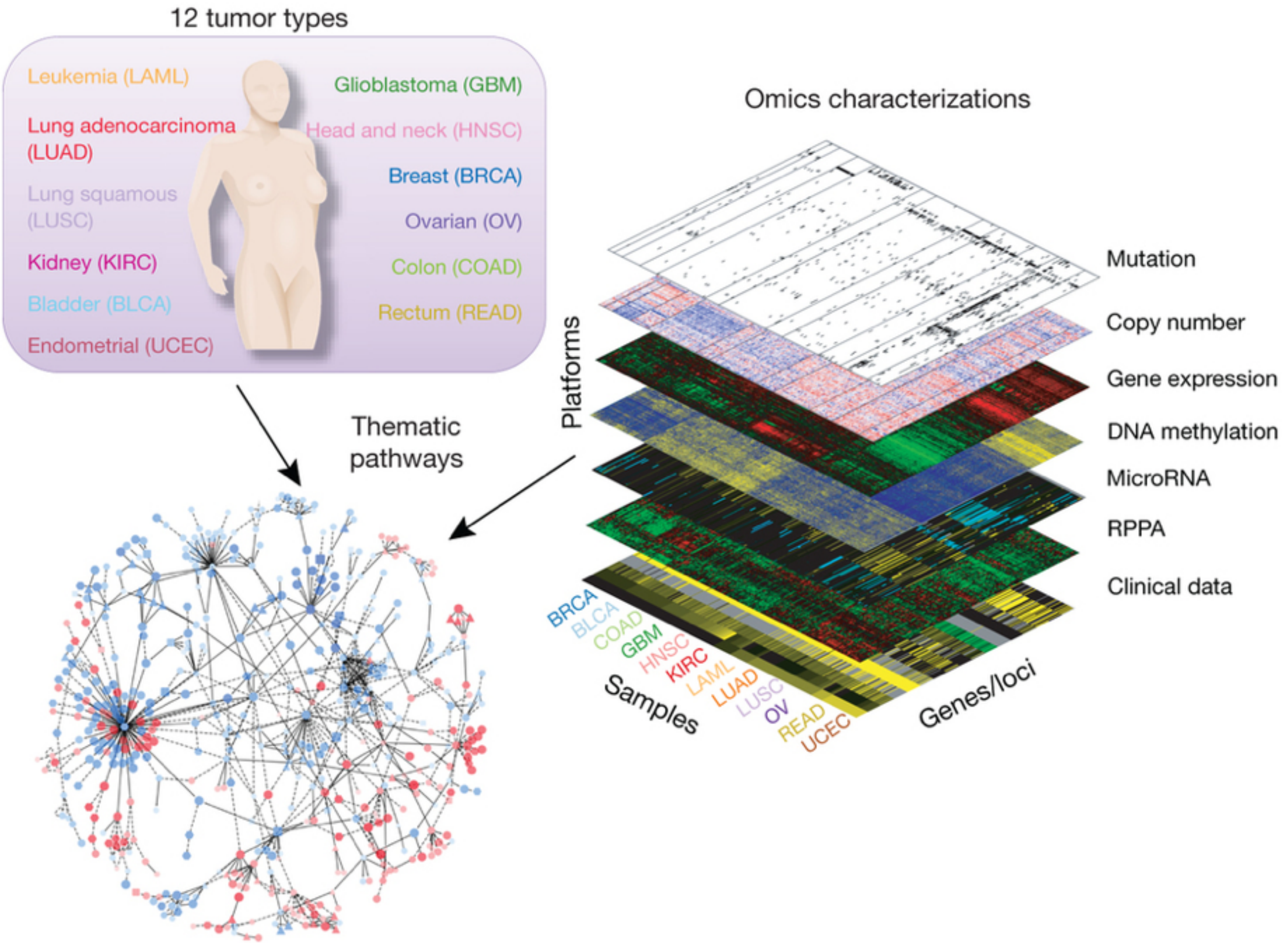
Series of tumours

Microarray analysis

Hierarchical clustering

Correlation with outcome and clinicopathological features

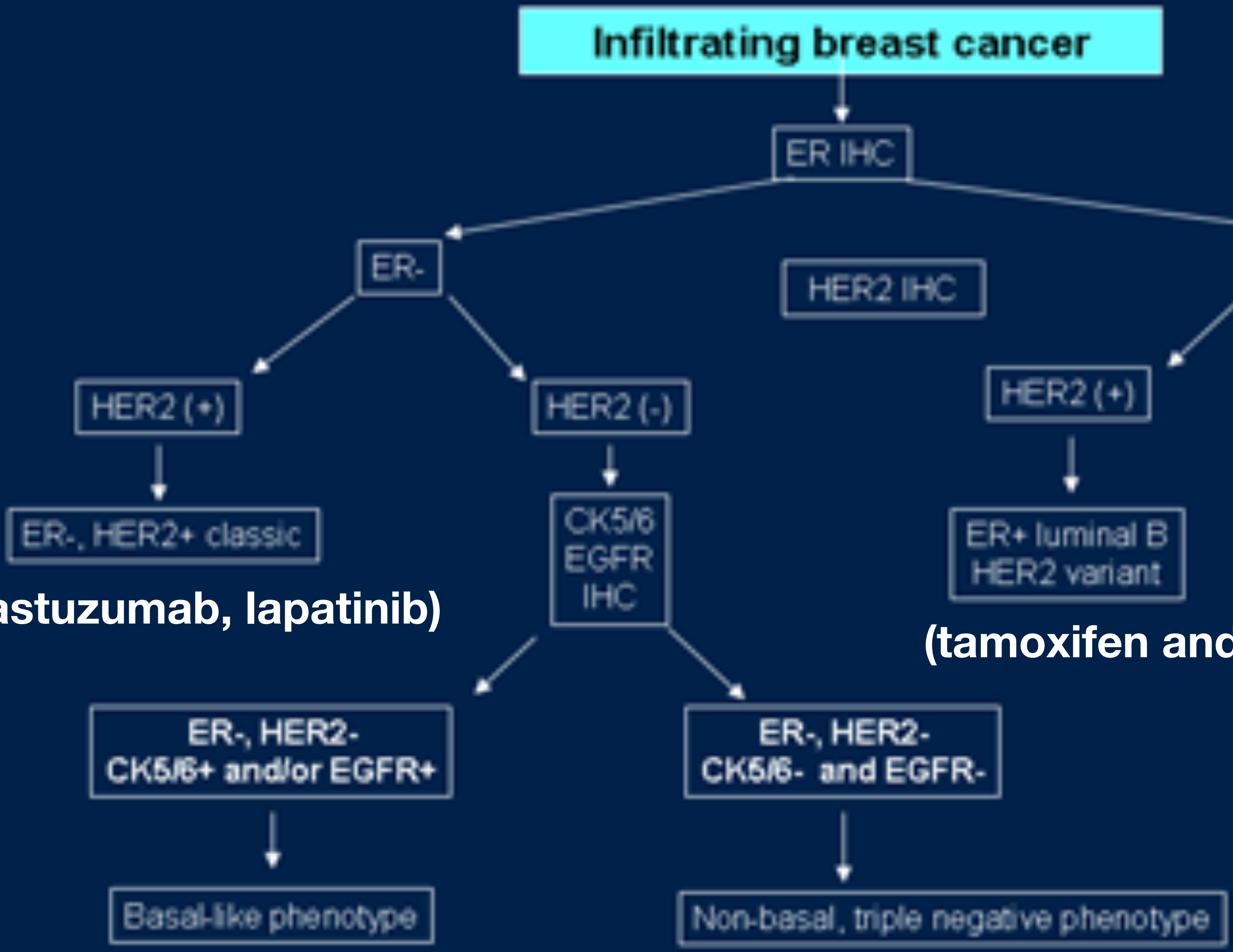
TCGA Pan-Cancer project



For example, breast cancer may be classified into various types based upon which proteins are expressed on the surface of the tumor cells. Breast tumors that express human epidermal growth factor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR), or are triple negative (do not express HER2, ER, or PR) behave differently and have different prognoses. Tumors that are HER2 positive are treated with medications that bind to HER2 (e.g. trastuzumab, lapatinib) and inhibit its activity. ER and PR are hormone receptors, and ER/PR positive tumors are treated with antihormonal therapies (e.g. tamoxifen and aromatase inhibitors). Triple negative tumors have the poorest prognosis and are unlikely to respond to HER2-targeted therapies or antihormonal therapies. Such cancers are usually treated very aggressively with chemotherapy.

As more has been learned about the molecular signature of various cancer subtypes, therapies that are specifically targeted to those signatures have been developed. Conventional chemotherapy acts on all rapidly dividing cells and does not distinguish between cancer cells and normal cells.

Classification of Breast Cancer



Infiltrating breast cancer

ER IHC

ER-

HER2 IHC

ER+

HER2 (+)

HER2 (-)

HER2 (+)

HER2 (-)

ER-, HER2+ classic

CK5/6
EGFR
IHC

ER+ luminal B
HER2 variant

ER+ luminal A

ER-, HER2-
CK5/6+ and/or EGFR+

ER-, HER2-
CK5/6- and EGFR-

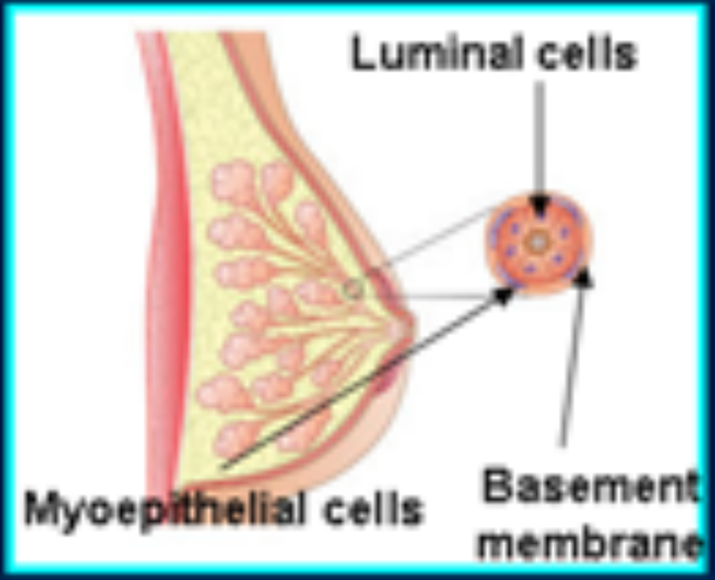
Basal-like phenotype

Non-basal, triple negative phenotype

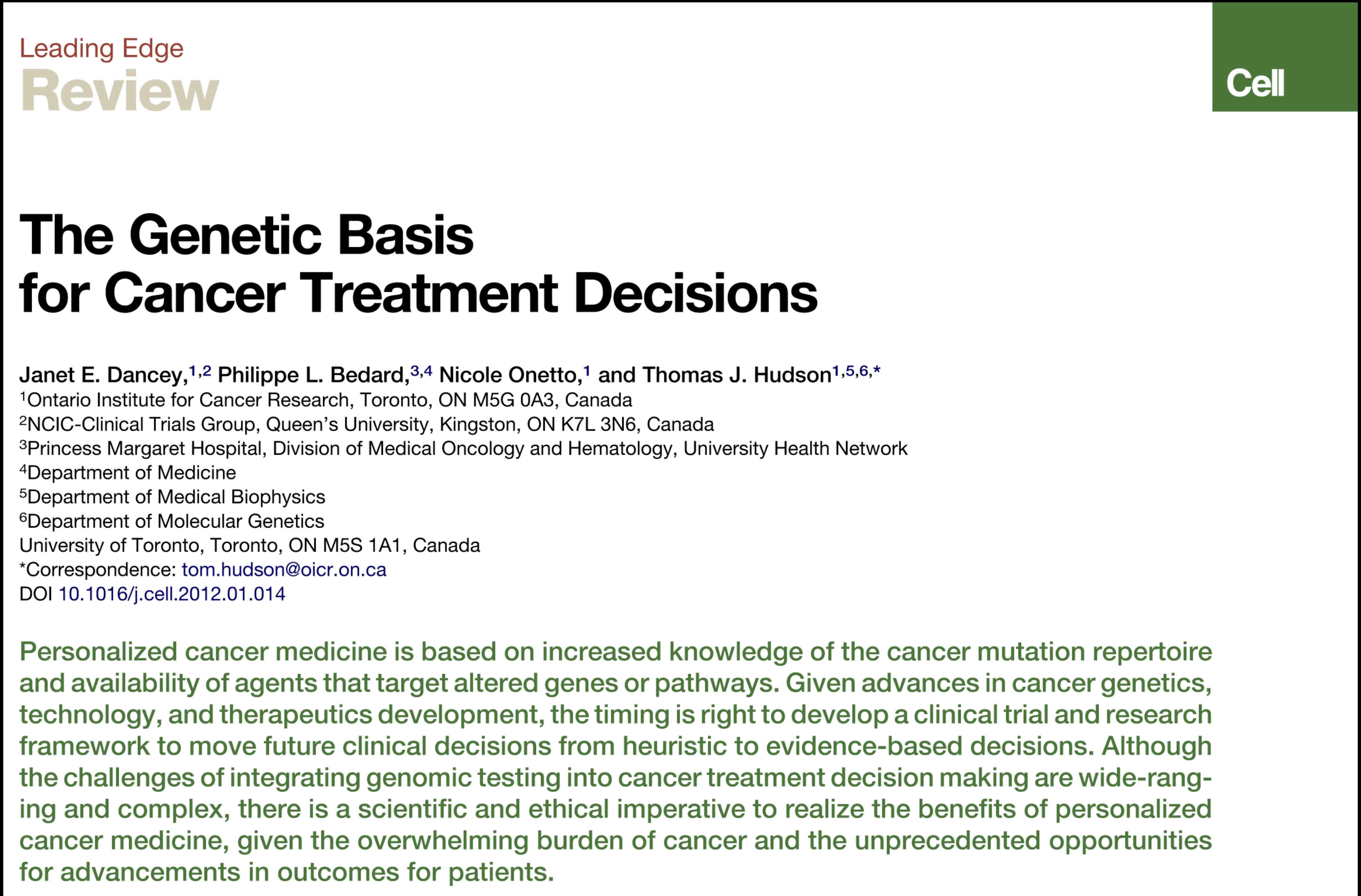
(trastuzumab, lapatinib)

(tamoxifen and aromatase inhibitors)

(aggressive chemotherapy)



Readings to find out more…



Leading Edge
Review

Cell

The Genetic Basis for Cancer Treatment Decisions

Janet E. Dancey,[1,2] Philippe L. Bedard,[3,4] Nicole Onetto,[1] and Thomas J. Hudson[1,5,6,*]
[1]Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada
[2]NCIC-Clinical Trials Group, Queen's University, Kingston, ON K7L 3N6, Canada
[3]Princess Margaret Hospital, Division of Medical Oncology and Hematology, University Health Network
[4]Department of Medicine
[5]Department of Medical Biophysics
[6]Department of Molecular Genetics
University of Toronto, Toronto, ON M5S 1A1, Canada
*Correspondence: tom.hudson@oicr.on.ca
DOI 10.1016/j.cell.2012.01.014

Personalized cancer medicine is based on increased knowledge of the cancer mutation repertoire and availability of agents that target altered genes or pathways. Given advances in cancer genetics, technology, and therapeutics development, the timing is right to develop a clinical trial and research framework to move future clinical decisions from heuristic to evidence-based decisions. Although the challenges of integrating genomic testing into cancer treatment decision making are wide-ranging and complex, there is a scientific and ethical imperative to realize the benefits of personalized cancer medicine, given the overwhelming burden of cancer and the unprecedented opportunities for advancements in outcomes for patients.

Your Turn

Read and share your thoughts on the following class *Readings*

- Calling cancer's bluff with neoantigen vaccines
- Can genomics help detect early cancer and monitor treatment effectiveness?
- The increasing cost of cancer therapies

https://bioboot.github.io/bimm194_W18/readings/