Cancer Diagnosis:

Beyond tissue type, the genomics of cancer and heritable cancer risk

Dr Neil Watkins

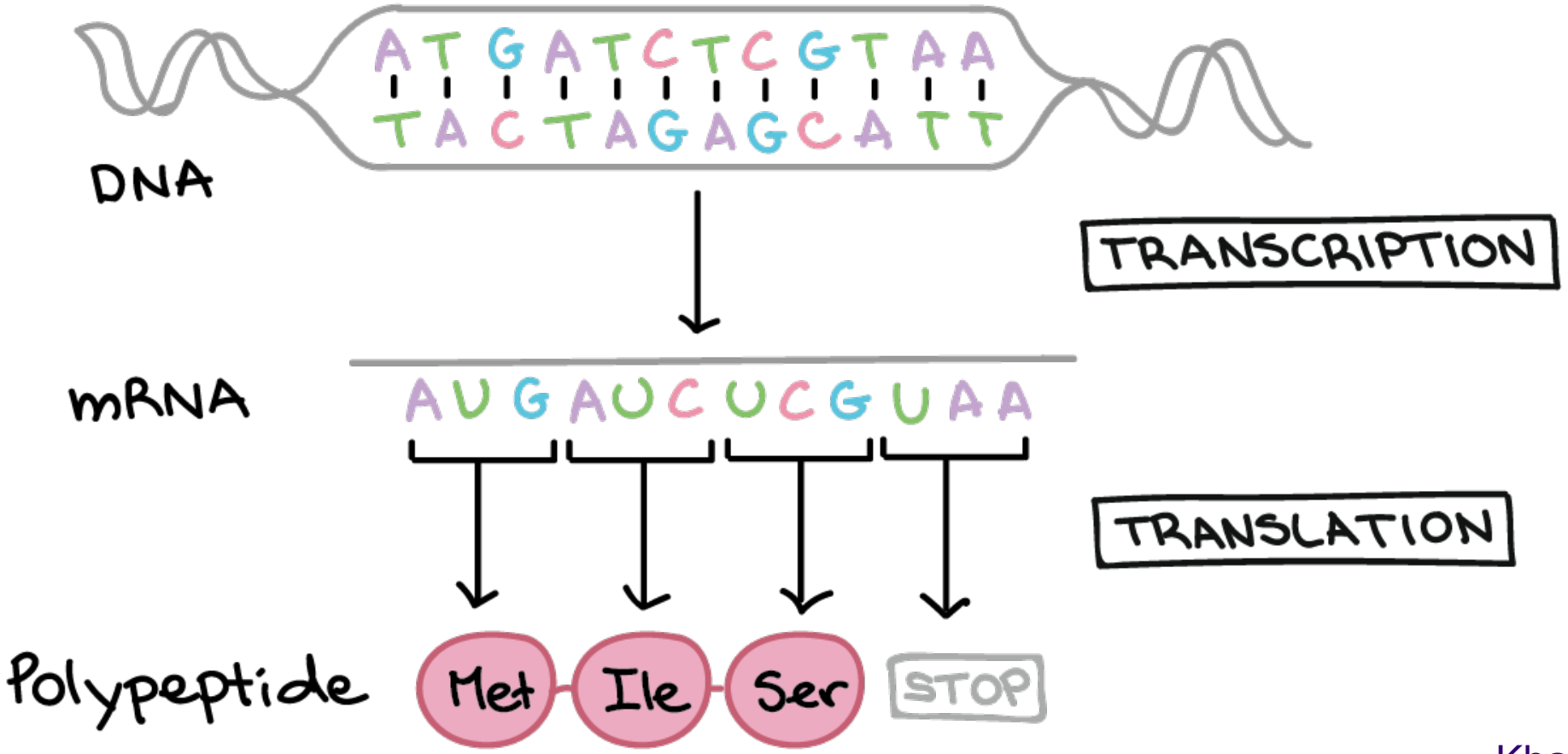
26/02/2026

LifeStrands
Empowering lives with Genomics

PASO MEDICAL
Treatment·Research·Support

Concepts

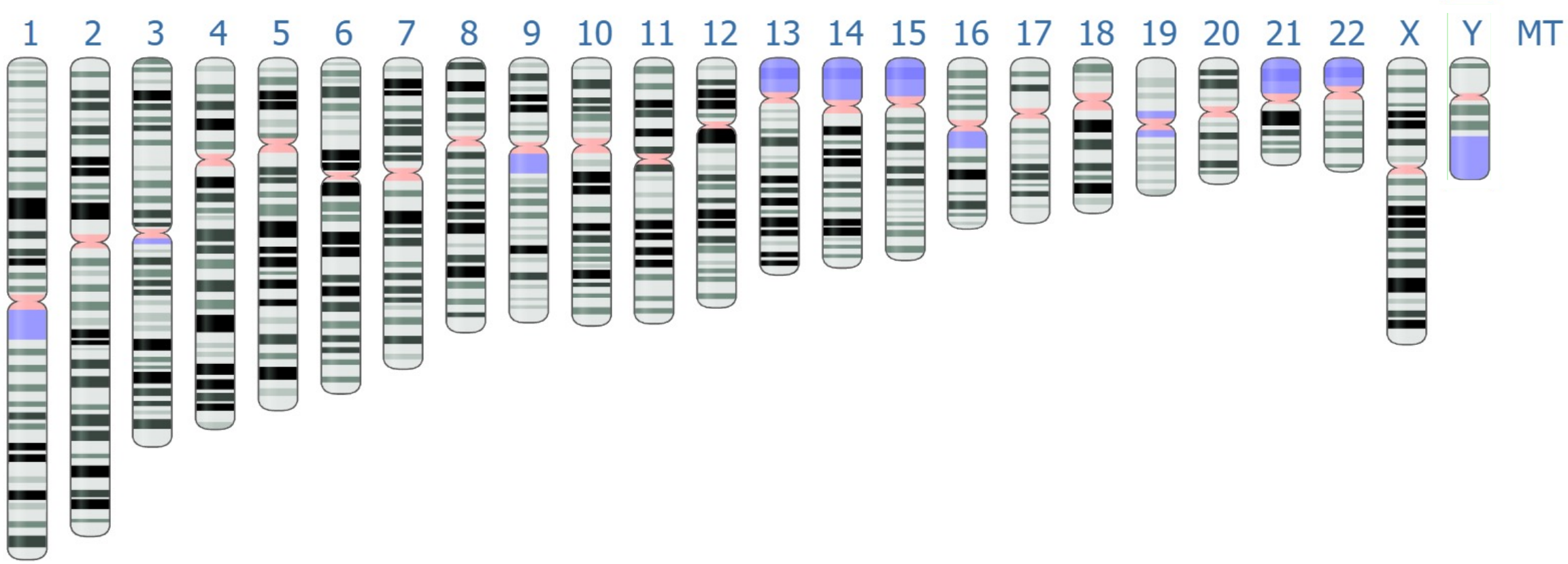
Central Dogma of Molecular Biology



Khan Academy

Concepts

Reference Human Genome



Definitions

Reference Human Genome

Germline Genome of an individual at fertilization

Variant DNA sequence that is different to the reference genome

Definitions

Reference Human Genome

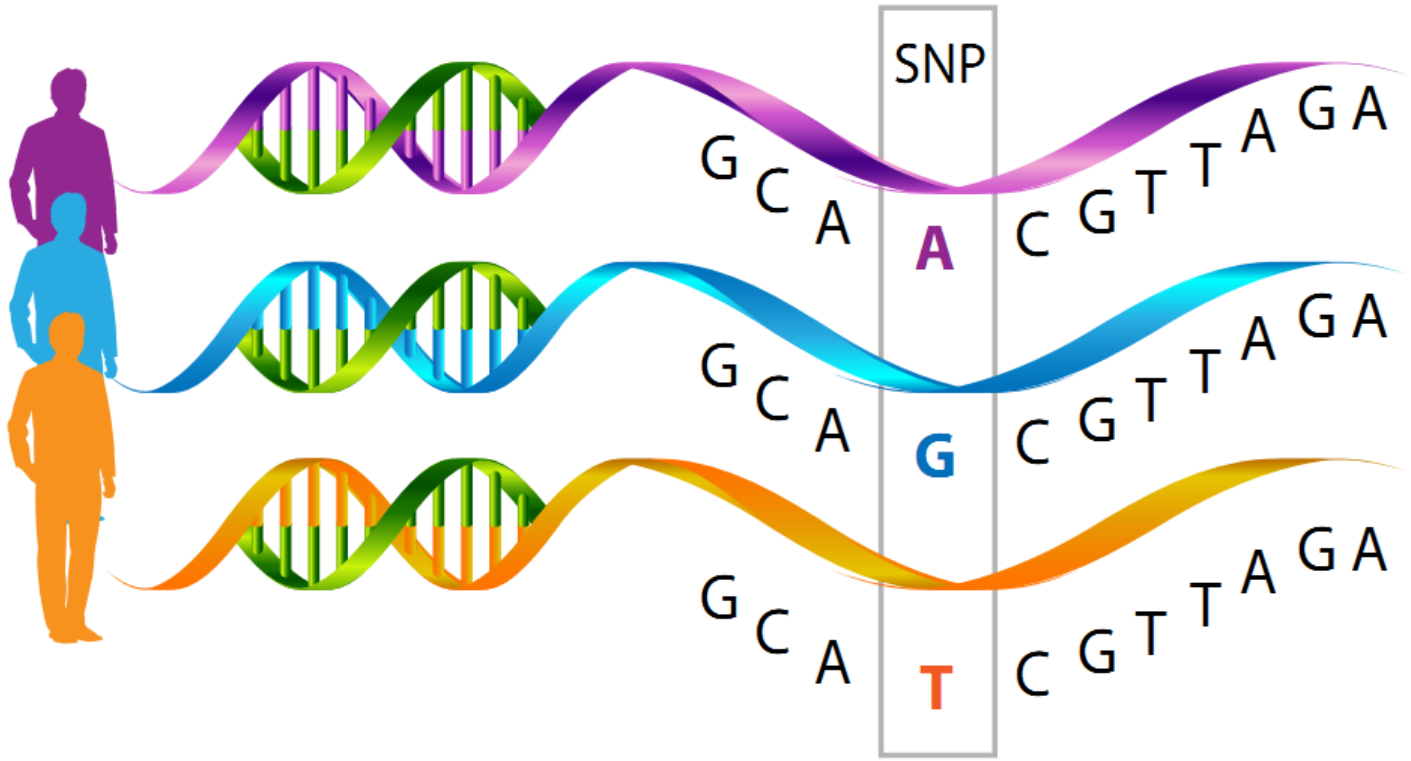
“Germline” Sequence of a control sample distinct from the tumour

Peripheral blood white cells

Definitions

Germline Variants

Single Nucleotide Polymorphism (SNP)



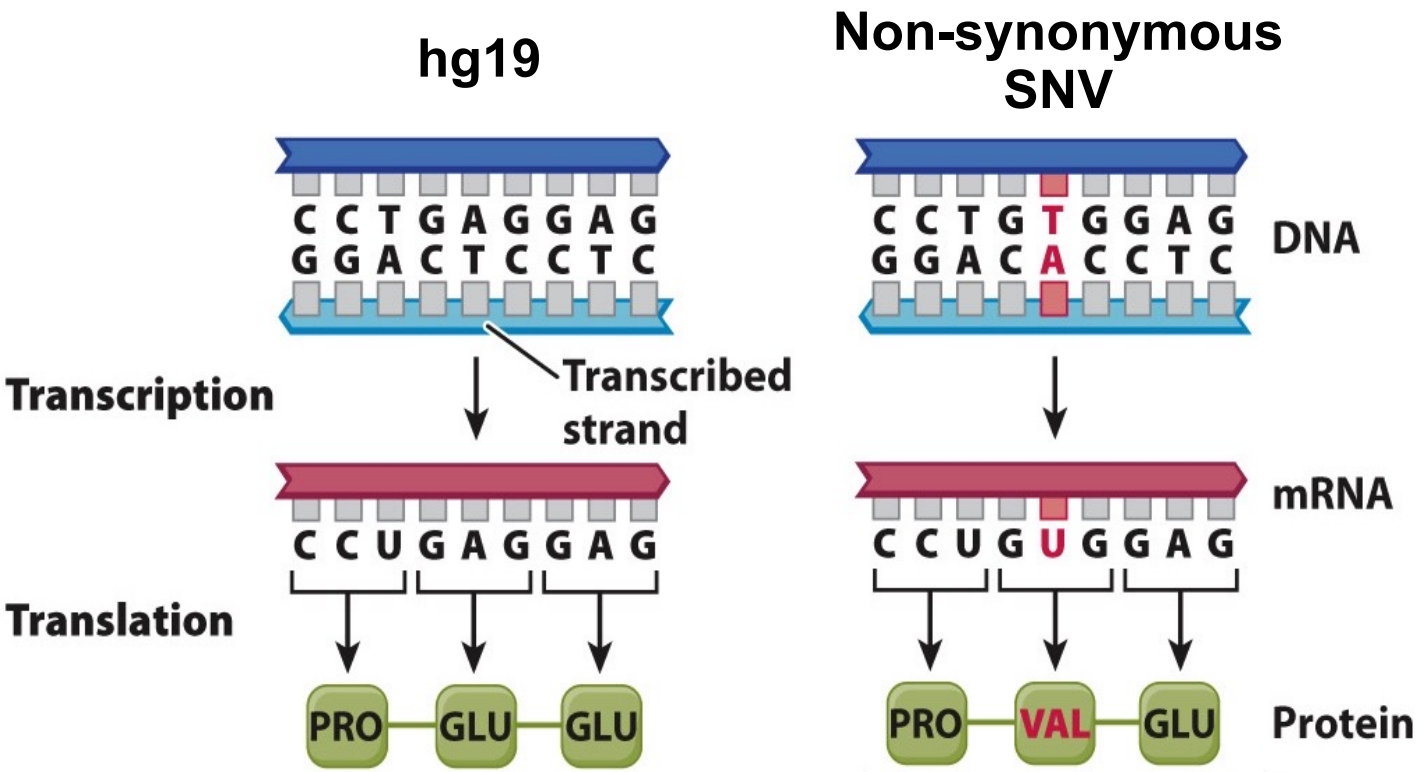
Human genetic and phenotypic variation

genome.gov

Definitions

Germline Variants

Single Nucleotide Variant (SNV)



Human genetic and phenotypic variation

“Missense Variants”

ACMG Classification

Pathogenic
Likely pathogenic
Variant of unknown significance (VUS)
Likely benign
Benign

genome.gov
Richards et al, Genet Med, 2015; 17:405-424

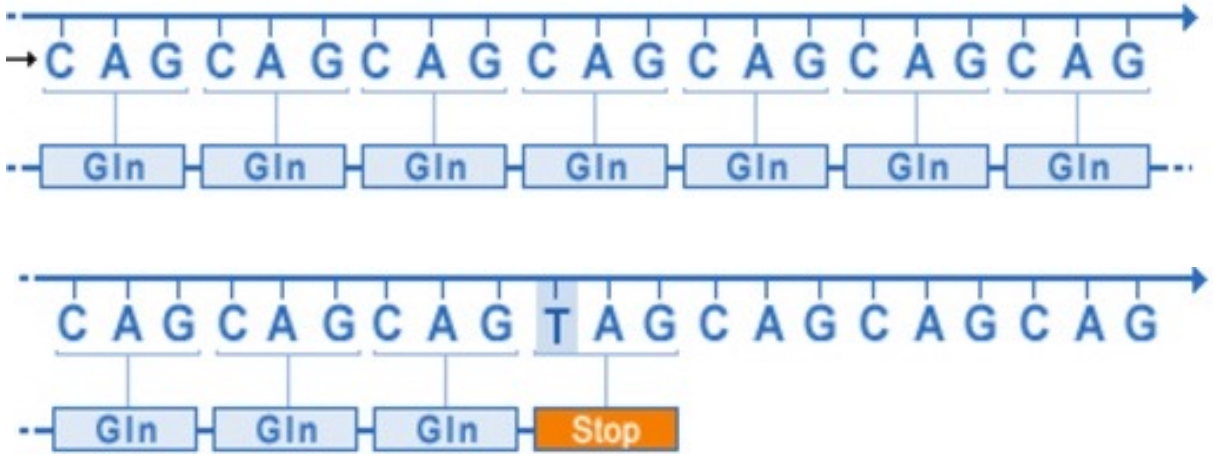
Definitions

Germline Variants

Single Nucleotide Variant (SNV)

Human genetic and phenotypic variation

Nonsense



“Nonsense Variants”

ACMG Classification
Pathogenic
Likely pathogenic
Variant of unknown significance (VUS)
Likely benign
Benign

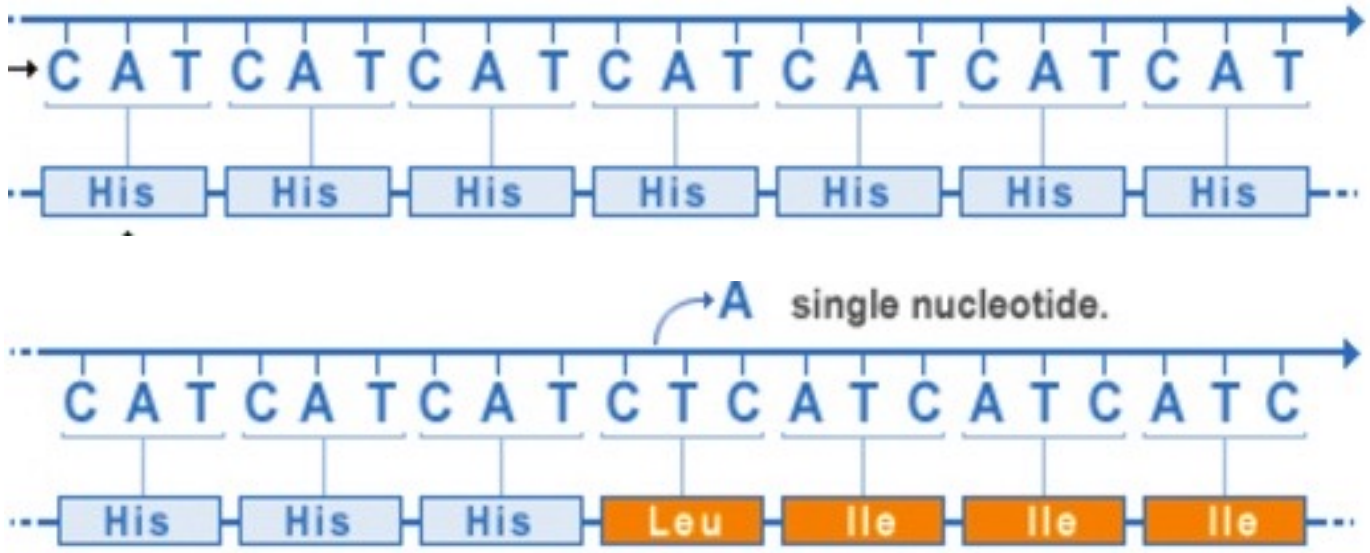
genome.gov

Definitions

Germline Variants

Insertions/Deletions (InDel)

Deletion Frameshift



“Frameshift Variants”

ACMG Classification
Pathogenic
Likely pathogenic
Variant of unknown significance (VUS)
Likely benign
Benign

genome.gov

Conventions

Variants

Amino Acid Consequence

Examples

KRAS p.G12D
TP53 p.R213*
BRCA1 p.E1000fs

Pathogenic Germline Variants

Cancer Predisposition

10% of patients with adult solid tumours have a pathogenic or likely pathogenic germline variant

Huang et al, Cell, 2018; 173:355-370

Pathogenic Germline Variants

Cancer Predisposition

Inherited Family history

De Novo No family history

Pathogenic Germline Variants

Cancer Predisposition

86 well characterised genes

Most are tumour suppressors

Most are loss-of-function mutations

Most inherited in autosomal dominant fashion

Family History

Cancer Predisposition

Some cancers have increased risk for relatives with no germline genes identified

- Prostate
- Testicular
- Colonic polyps

Pathogenic Germline Variants

Common Genes

BRCA2 1:225

Females	**Males**
Breast	Prostate
Ovarian/fallopian tube	Pancreatic
Pancreatic	Breast
Endometrial	

Pathogenic Germline Variants

Lynch Syndrome (1:276)

MLH1, MSH2, MSH6, PMS2, EPCAM

Females
Colorectal
Endometrial
Ovarian

Males
Colorectal
Prostate

Small intestine
Pancreas
Ureter/renal pelvis
Cholangiocarcinoma
Gastric

Pathogenic Germline Variants

Common Genes

BRCA1 1:500

Females	**Males**
Breast	Prostate
Ovarian/fallopian tube	Pancreatic
Pancreatic	Breast
Endometrial	

Definitions

Reference Human Genome

Germline Genome of an individual at fertilization
Control sample distinct from the tumour

Somatic Genomic variants accumulated by the cancer

Somatic Variants

Classification

Horak Classification

Oncogenic
Likely oncogenic
Variant of unknown significance (VUS)
Likely benign
Benign

Horak et al, Genet Med, 2022; 24:4986-998

Somatic Variants

Classification

Tumour Suppressor

Oncogene

Somatic Variants

Classification

Tumour Suppressors

Cell cycle
Cell death
DNA repair
Growth suppression

"Brakes"

Loss-of-function

Horak et al, Genet Med, 2022; 24:4986-998

Somatic Variants

Examples

Tumour Suppressors

TP53
BRCA1
RB1
APC

Horak et al, Genet Med, 2022; 24:4986-998

Somatic Variants

Classification

Oncogenes

Growth signals
Receptors
Transcription factors
Entry into cell cycle

"Accelerators"

Gain-of-function

Horak et al, Genet Med, 2022; 24:4986-998

Somatic Variants

Examples

Oncogenes

KRAS
EGFR
HER2
MYC

Horak et al, Genet Med, 2022; 24:4986-998

Somatic Variants

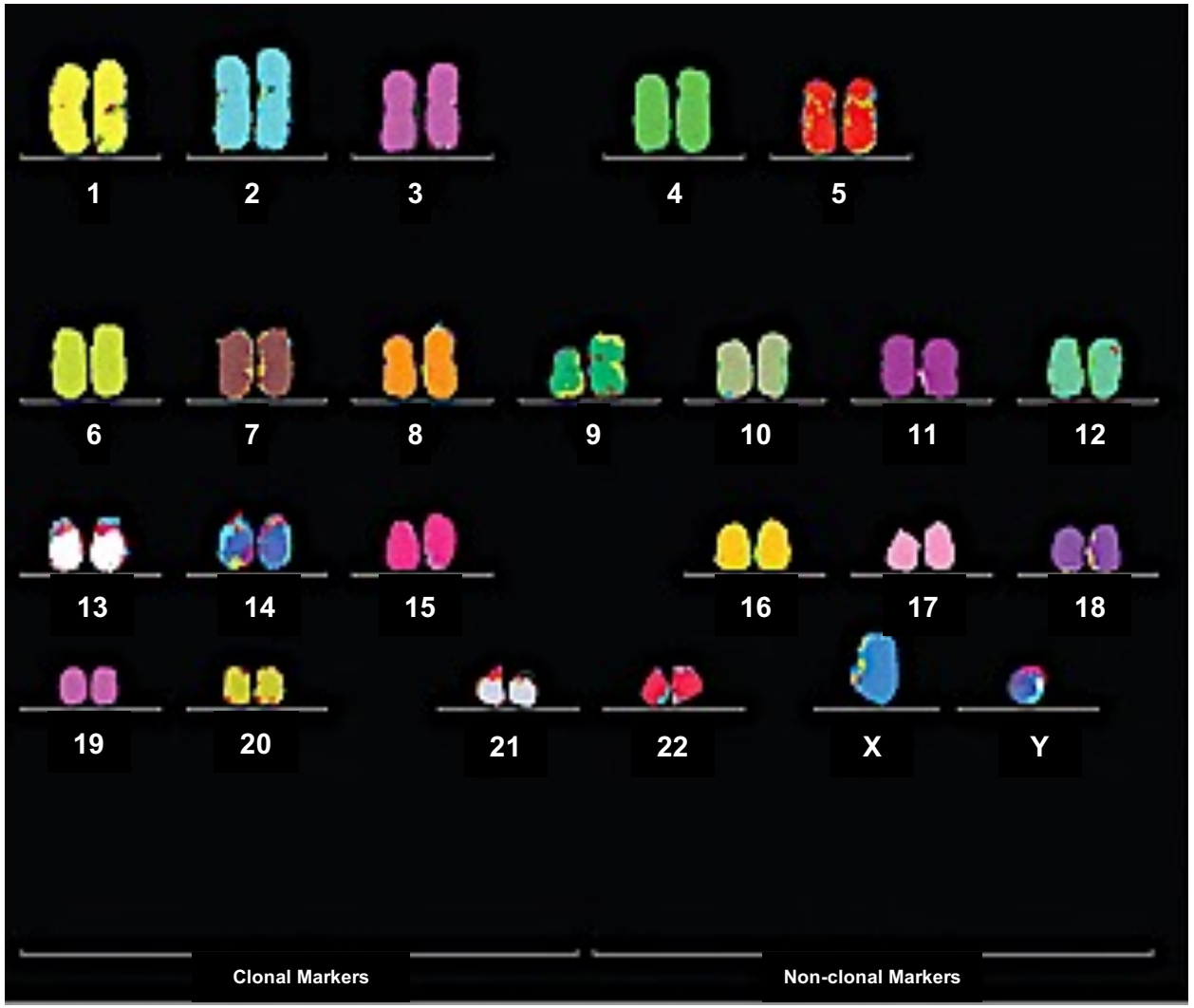
Examples

KRAS p.G12D
TP53 p.R213*
BRCA1 p.E1000fs
HER2 amplification (22 copies)
RB1 deletion (0 copies)

Horak et al, Genet Med, 2022; 24:4986-998

Somatic Variants

Classification
Chromosomal

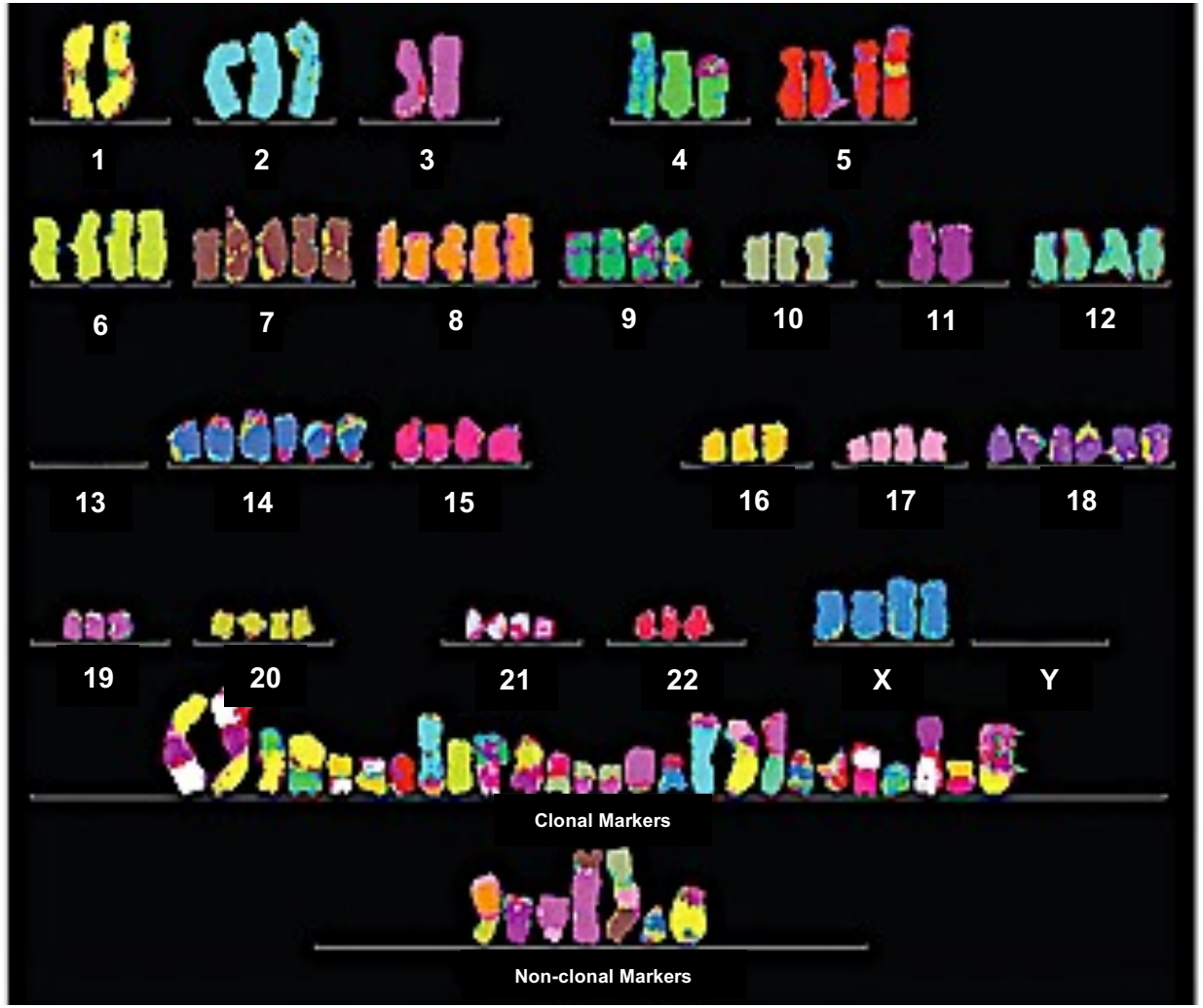


vcresearch.berkeley.edu

Somatic Variants

Classification

Chromosomal

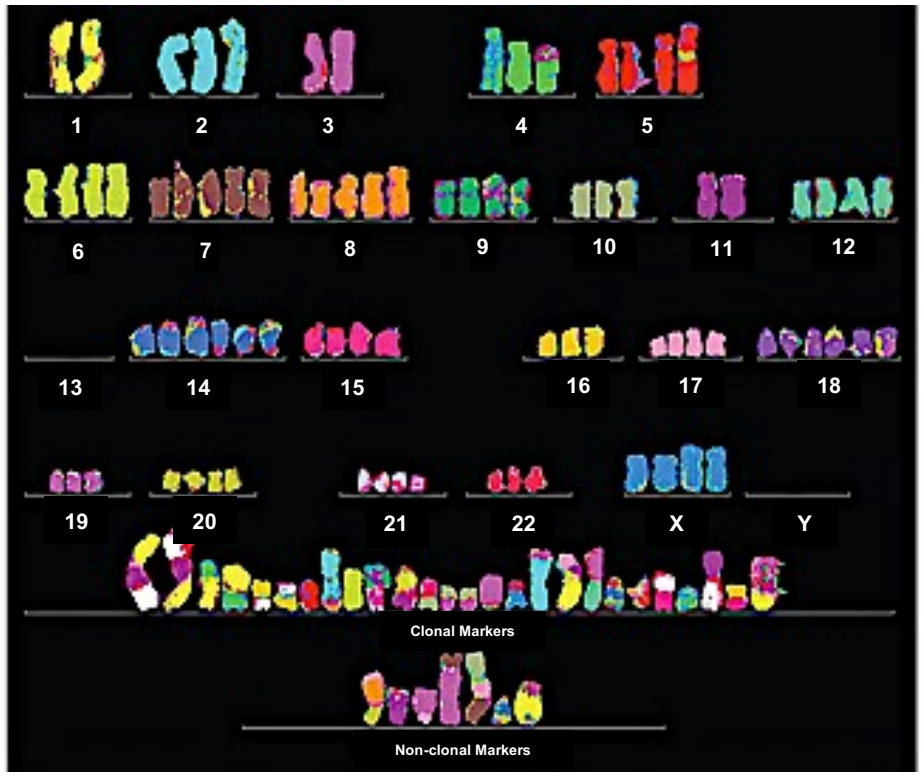


vcresearch.berkeley.edu

Somatic Variants

Classification

Chromosomal



Consequences

Deletion

Amplification

Fusions

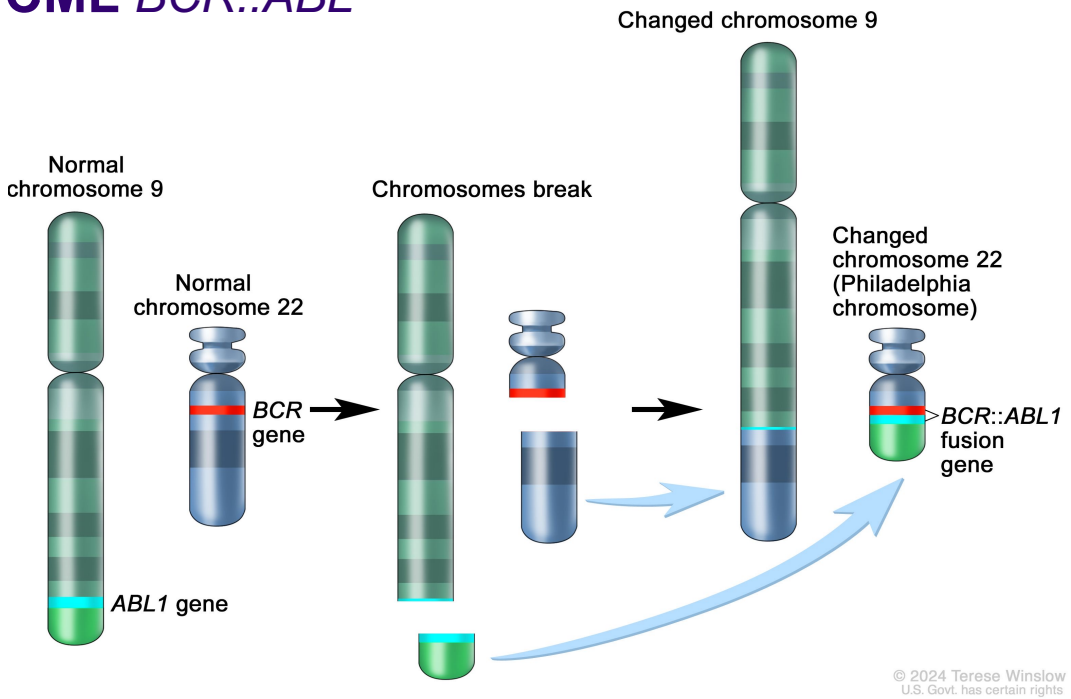
vcresearch.berkeley.edu

Somatic Variants

Classification

Fusions

CML *BCR::ABL*



"Frankenstein" Oncogene



Somatic Variants

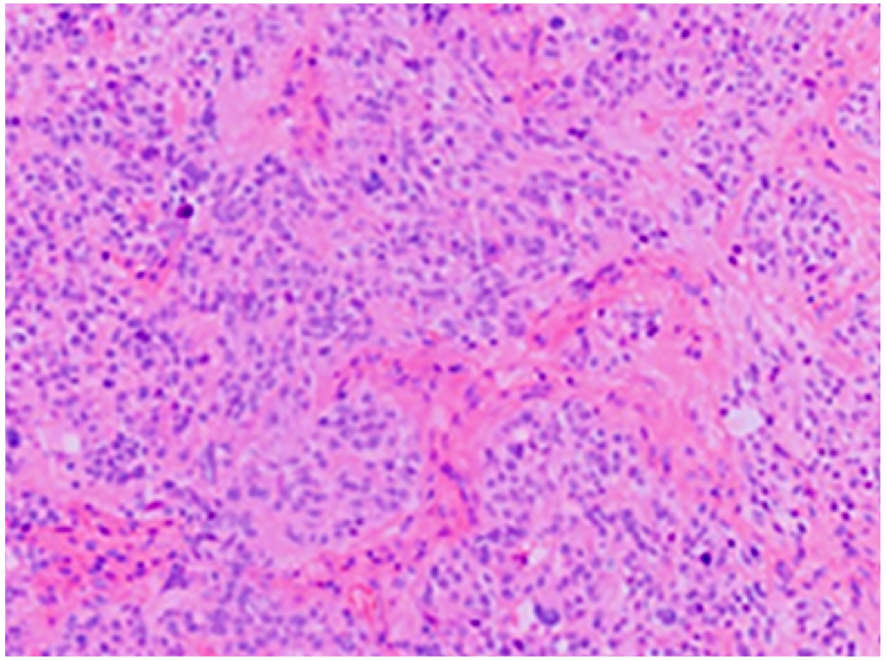
Significance

Diagnostic

44-year-old previously well woman with no family history with a right occipital lobe brain tumour.

Histopathology

High grade glioma
High cellularity
Microvascular proliferation

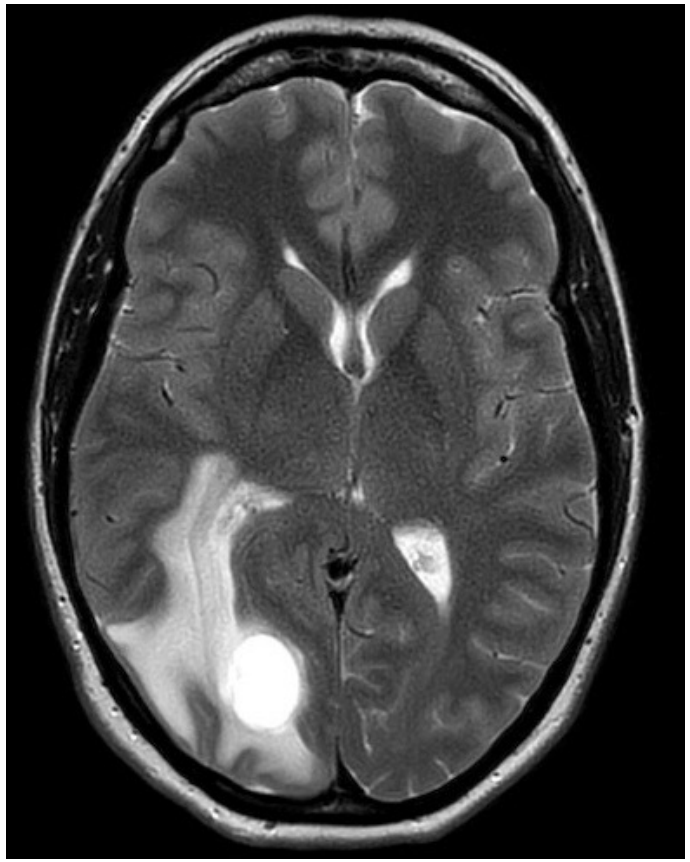


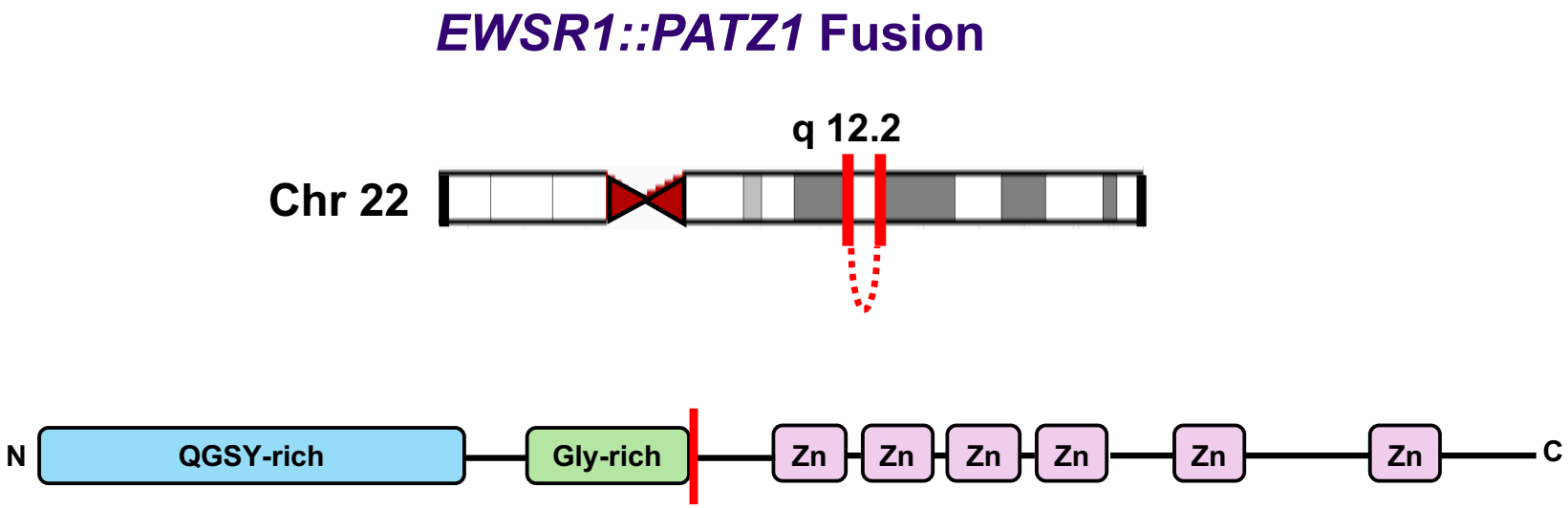


Somatic Variants

Significance

Diagnostic

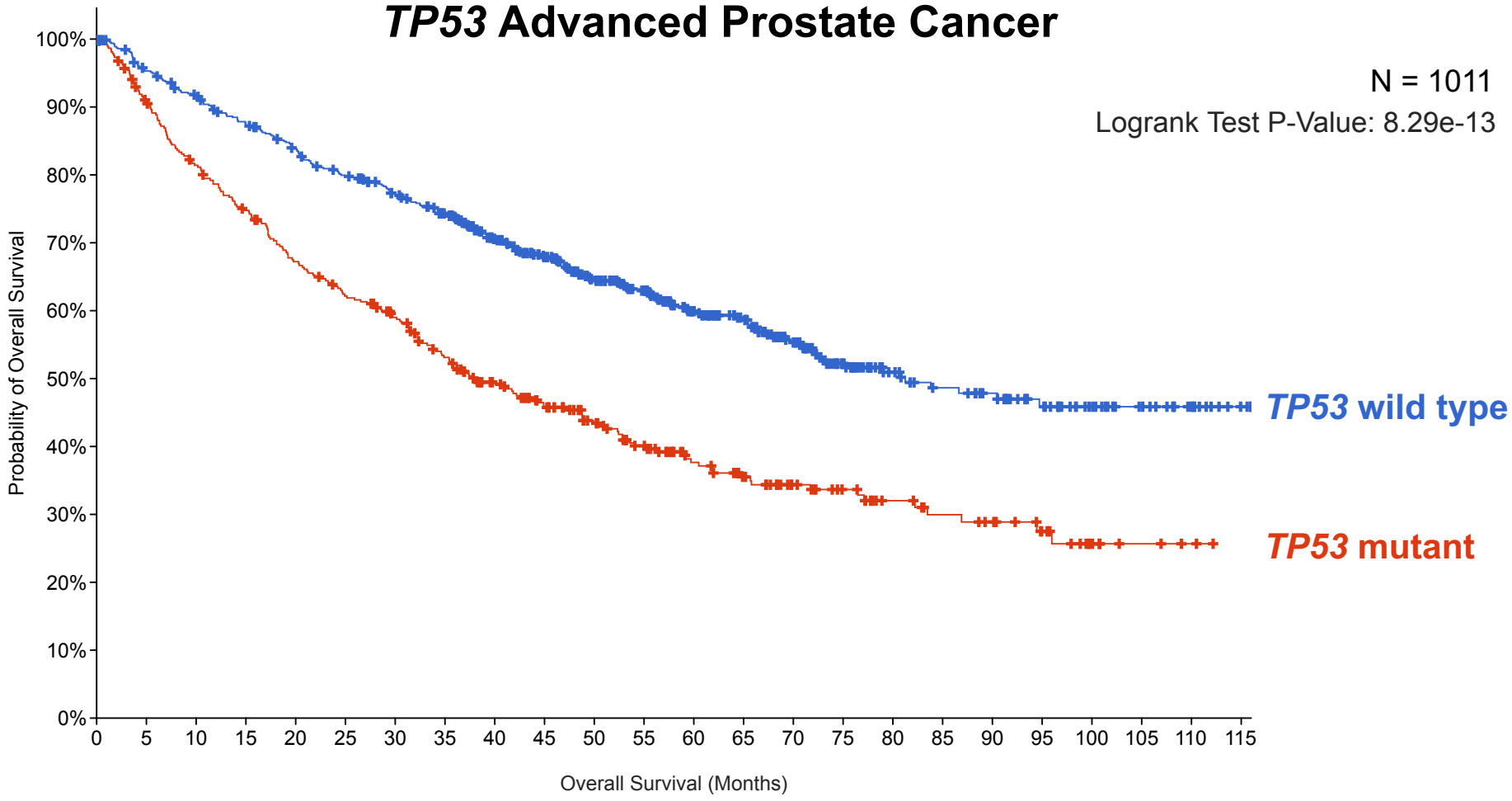




Somatic Variants

Significance

Prognostic



cbioportal.org

LifeStrands

PASO MEDICAL Treatment·Research·Support

Somatic Variants

Significance

Classification

Endometrial Cancer

p53abn	dMMR	*POLE*mut	NSMP
15 - 20%	15 - 25%	7 - 9%	50 - 55%
Subtype with a poor prognosis.	Subtype with an intermediate prognosis.	Subtype with a good prognosis.	Subtype with an intermediate prognosis.*
○ Chemoradiotherapy ○ Chemoradiotherapy + DDR targeting agent	○ Radiation therapy ○ Radiation therapy + PD-L1|PD-1 inhibitor	○ No adjuvant treatment /de-escalation of therapy	○ Chemoradiotherapy ○ Radiation therapy + Hormonal therapy
CIN high	MSI (+)	Ultramutated	CNV low

Galant et al, Int J Mol Sci, 2024; 25(11), 5893

Somatic Variants

Significance

Therapy

A previously well 76-year-old woman with de-novo metastatic pancreatic adenocarcinoma.

GP2::NTRK1 fusion

