New advances in the diagnosis of neutropenia conditions

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NNN Retreat

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Neutropenia: diagnostic categories

Primary

Genetic

Do not rely only on clinical diagnosis without genetics

Secondary

Autoimmune/ Inflammatory

Other condition
eg: infection
medication
marrow stress

Unknown "Idiopathic"

Why is diagnosis important?

- Guides medical care

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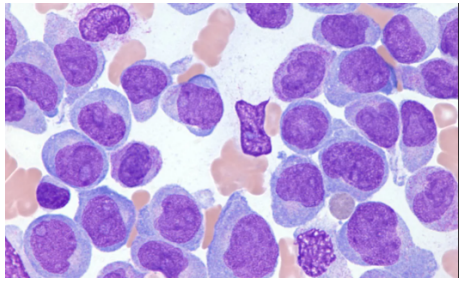
- Guides medical care
- Informs surveillance to prevent complications

Germline Predisposition

Clonal Hematopoiesis



MDS/Leukemia

Diagnosis

Surveillance
Risk Stratification

Intervention
Prevention

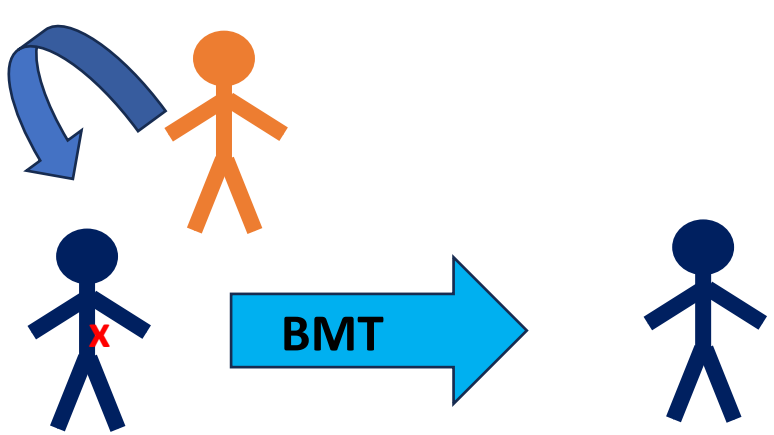
Treatment

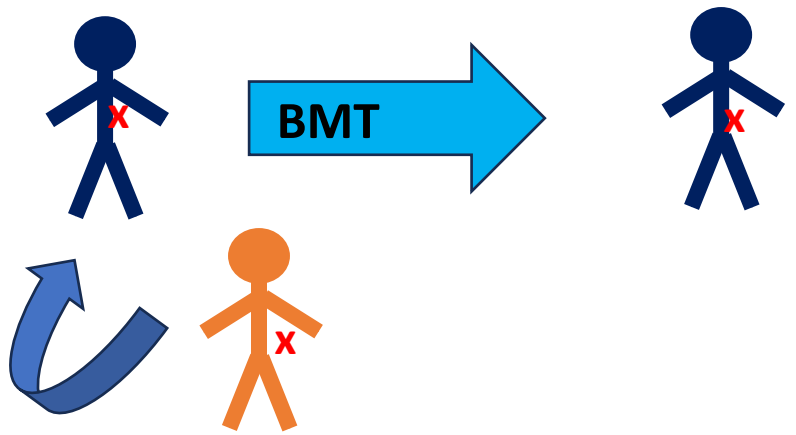
Why is diagnosis important?

- Guides medical care
- Informs surveillance to prevent complications
- Treatment decisions

Why is diagnosis important?

- Guides medical care
- Informs surveillance to prevent complications
- Treatment decisions
- Transplant donor choice





Why is diagnosis important?

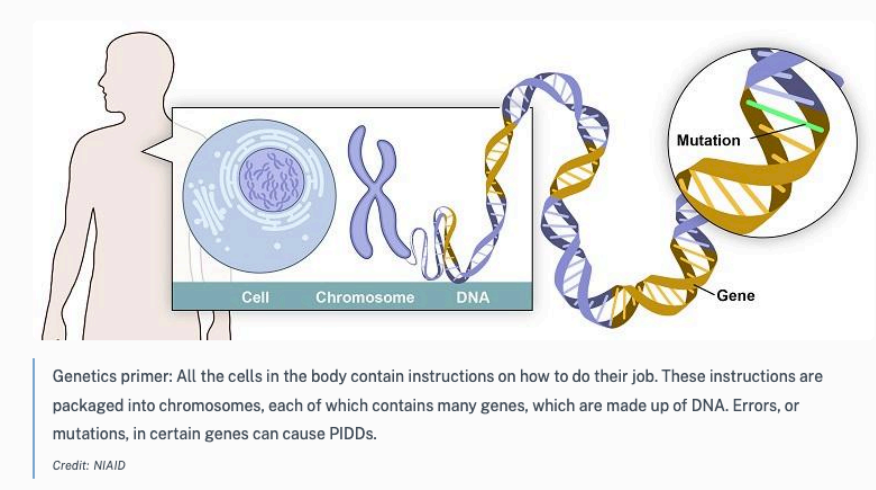
- Guides medical care
- Informs surveillance to prevent complications
- Treatment decisions
- Transplant donor choice
- Family planning/counseling

Diagnosis: importance of genetics!

- Distinguish genetic neutropenia versus acquired/secondary neutropenia
- Identify correct genetic neutropenia conditions (don’t just rely on clinical findings)
- Informs donor evaluation prior to transplant

Genetics basics

- Genes:
  - Encode information that specify traits
    - eg: eye color, height, skin pigmentation, blood cell production
  - Present on the chromosomes within all your cells
    - Everyone has 2 copies of each chromosome (except for sex chromosomes: XY in males)
    - 23 pairs of chromosomes = 46 total chromosomes
  - Inherited from your parents (randomly)



Genetics primer: All the cells in the body contain instructions on how to do their job. These instructions are packaged into chromosomes, each of which contains many genes, which are made up of DNA. Errors, or mutations, in certain genes can cause PIDDs.

Credit: NIAID

Genetic mutations

- A mutation refers to a change in a gene that alters it ability to encode information

  “The fat **c**at”

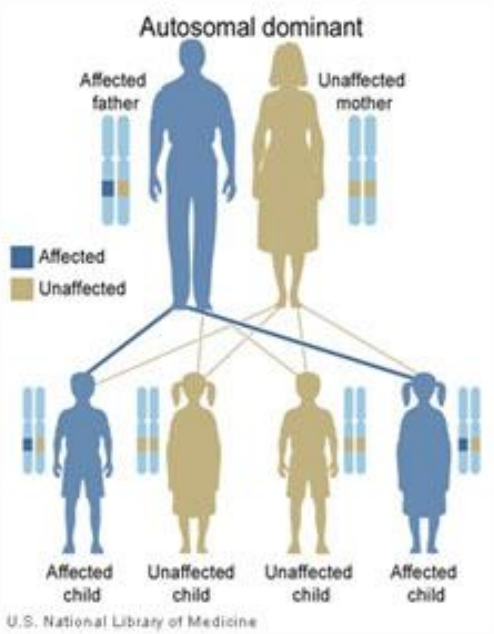
  -> ”The fat **h**at”

  -> “The fat **d**at”

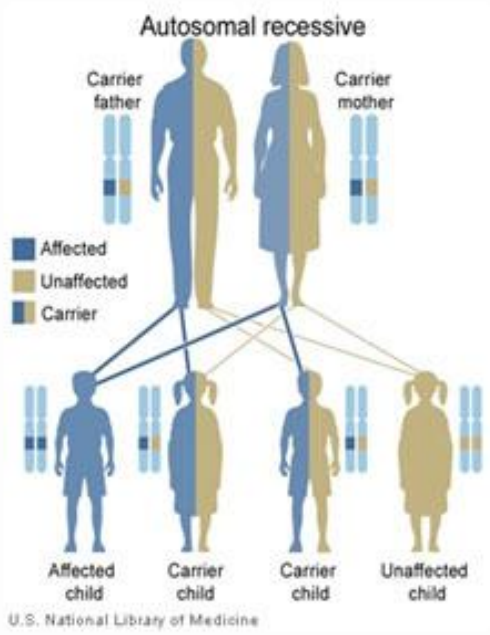
  -> “The fat _at”

Patterns of inheritance

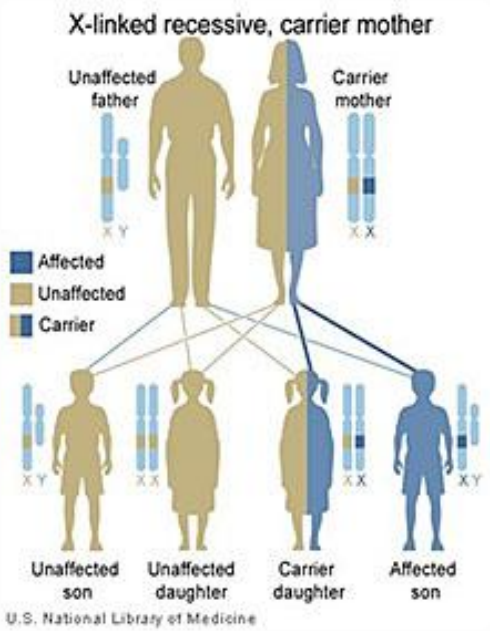
Autosomal Dominant



Autosomal Recessive



X-Linked Recessive



De novo

https://www.niaid.nih.gov/diseases-conditions/pidds-genetics-inheritance

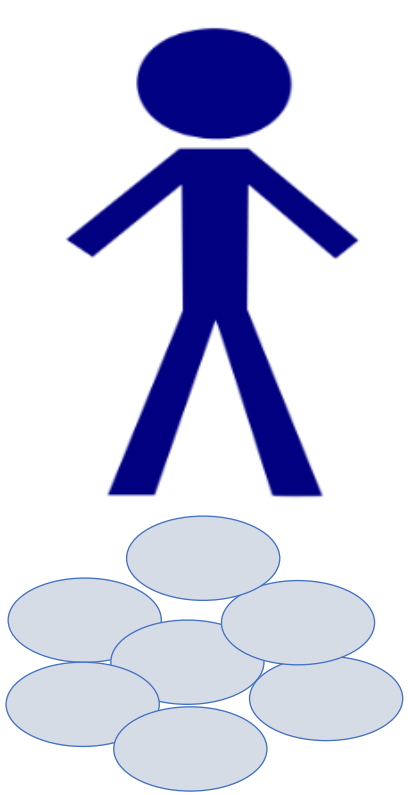
Different types of genetic testing available

- Individual gene sequencing
  - Hard to predict which gene based on clinical findings
- Targeted panel of genes
  - Different “neutropenia panels” each include different sets of genes
  - Analysis is complicated
- Whole exome sequencing
  - Can miss certain types of mutations
  - Analysis is complicated
- Whole genome sequencing (expensive and hard to get)

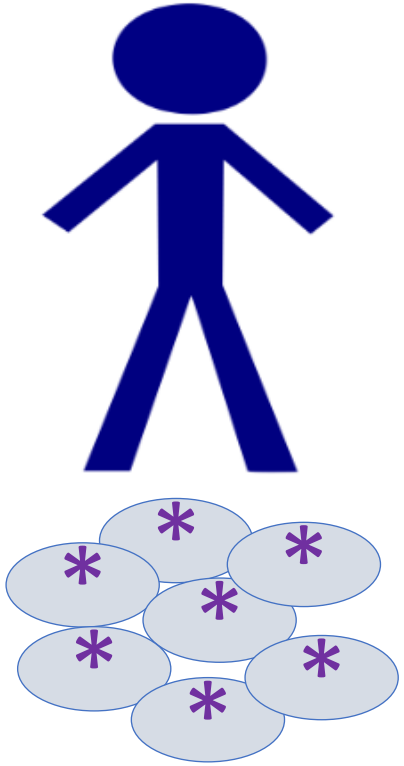
***If diagnosis is not found, consult with expert in neutropenia conditions

***Beware the “variant of unknown clinical significance” (VUS)

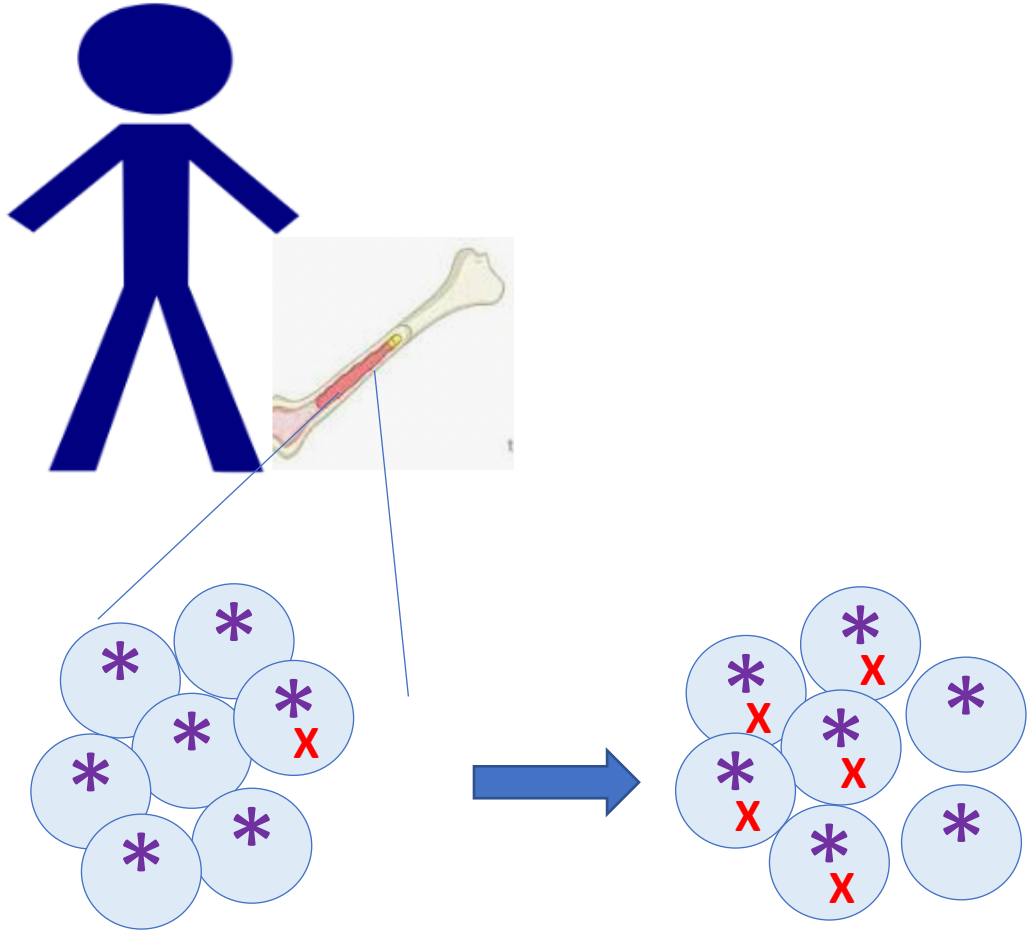
Mutations: inherited (germline) vs acquired (somatic)



unaffected



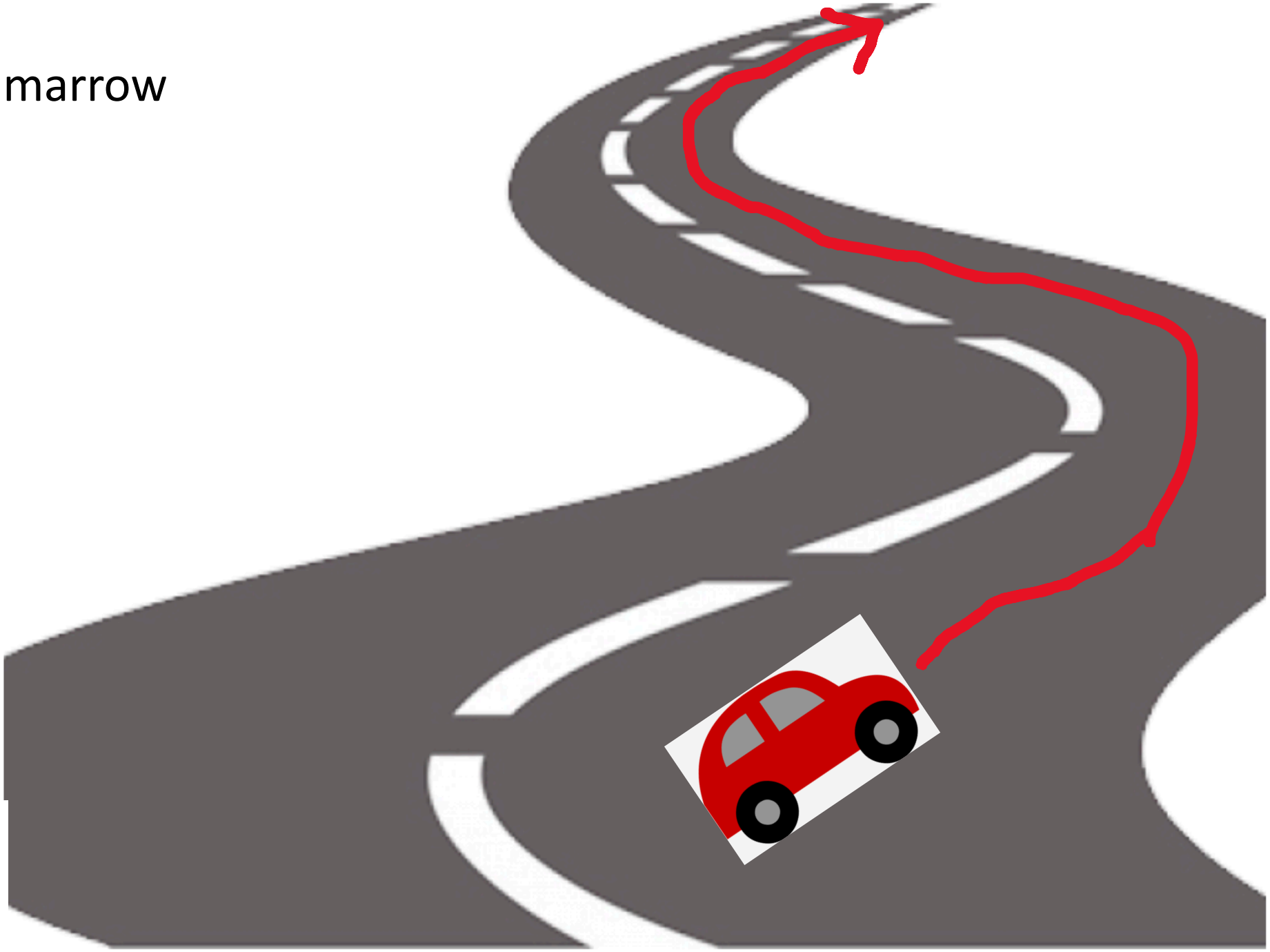
mutations in all cells of the body



somatic mutations in bone marrow

“clone”

Healthy marrow

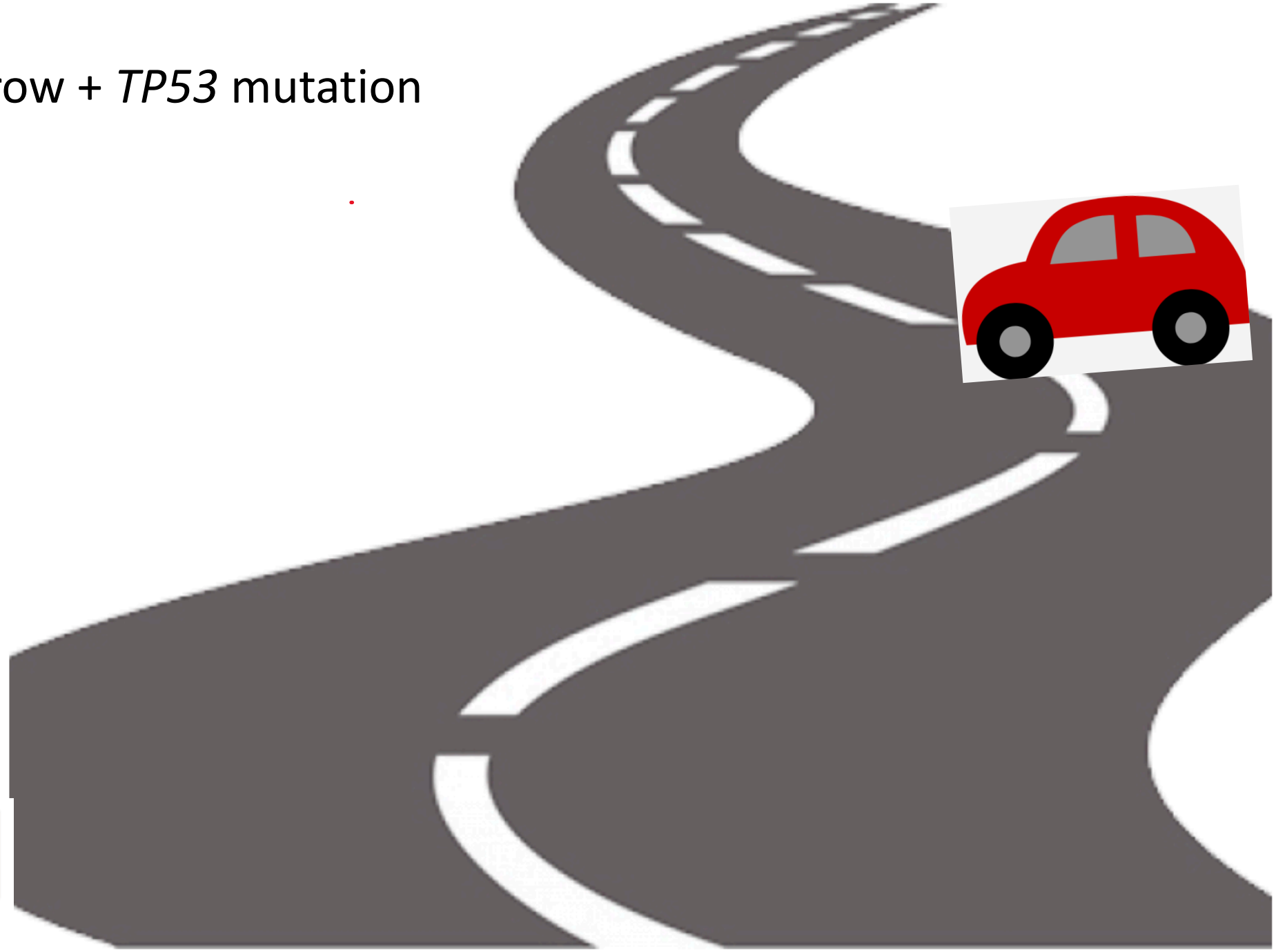


SDSR
Shwachman-Diamond Syndrome Registry

SDS Marrow

SDSR
Shwachman-Diamond Syndrome Registry

SDS Marrow + *TP53* mutation



SDSR
Shwachman-Diamond Syndrome Registry

Leukemia

SDSR
Shwachman-Diamond Syndrome Registry

SDS + EIF6 mutation =>

Improved ribosome function

Restores bone marrow function

Potential therapeutic target

Also: Alan Warren, Patrick Revy, Jean Donadieu, Roberto Valli and colleagues

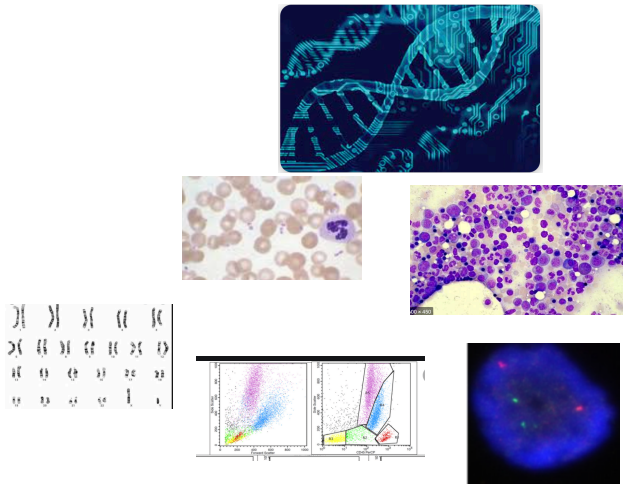
SDSR

Shwachman-Diamond Syndrome Registry

SDSR
Shwachman-Diamond Syndrome Registry

Bone marrow transplant

MDS X AML



SDS Board

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Email: sdsregistry-dl@childrens.harvard.edu