Improving relapse detection in neuroblastoma via eco-evolutionary informed machine learning

10 June 2022

CIRM - DSCE 2022

Group C

Early relapse detection Relapse time estimation in neuroblastoma metastasis

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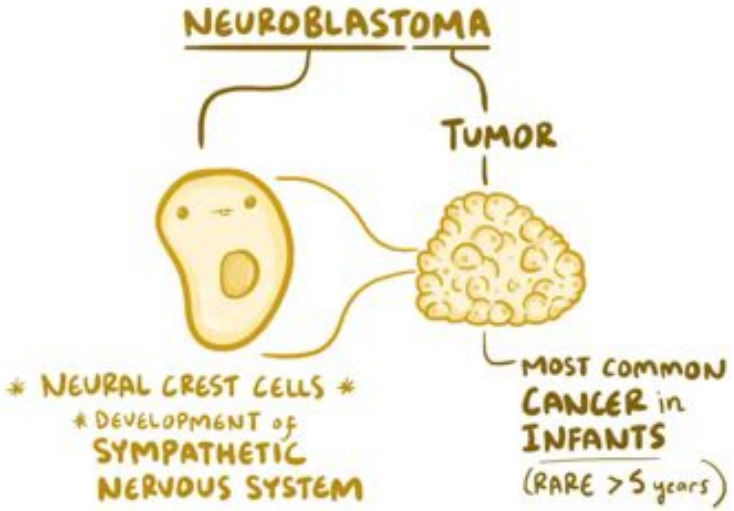
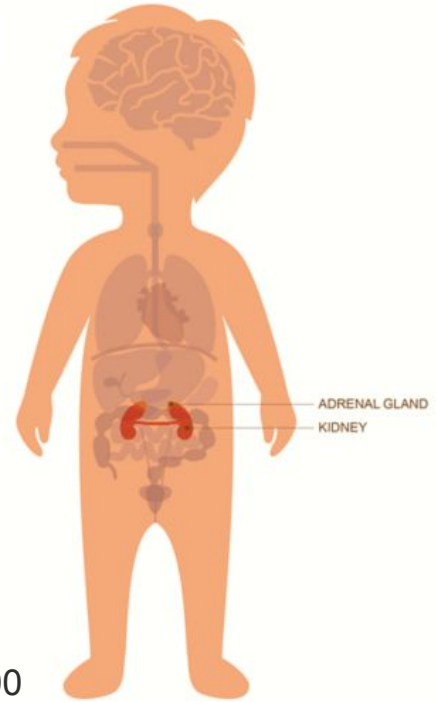
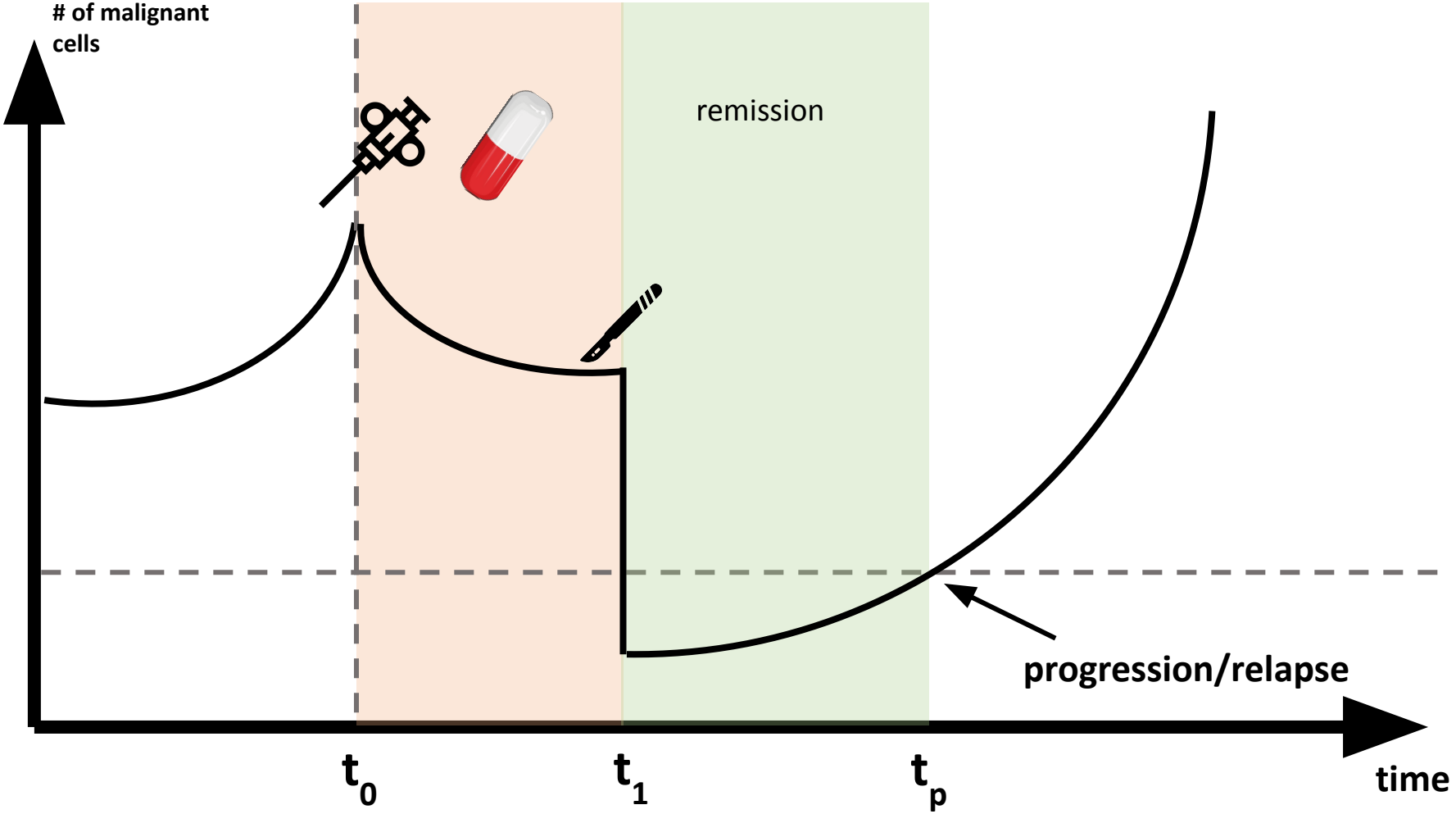
Introduction

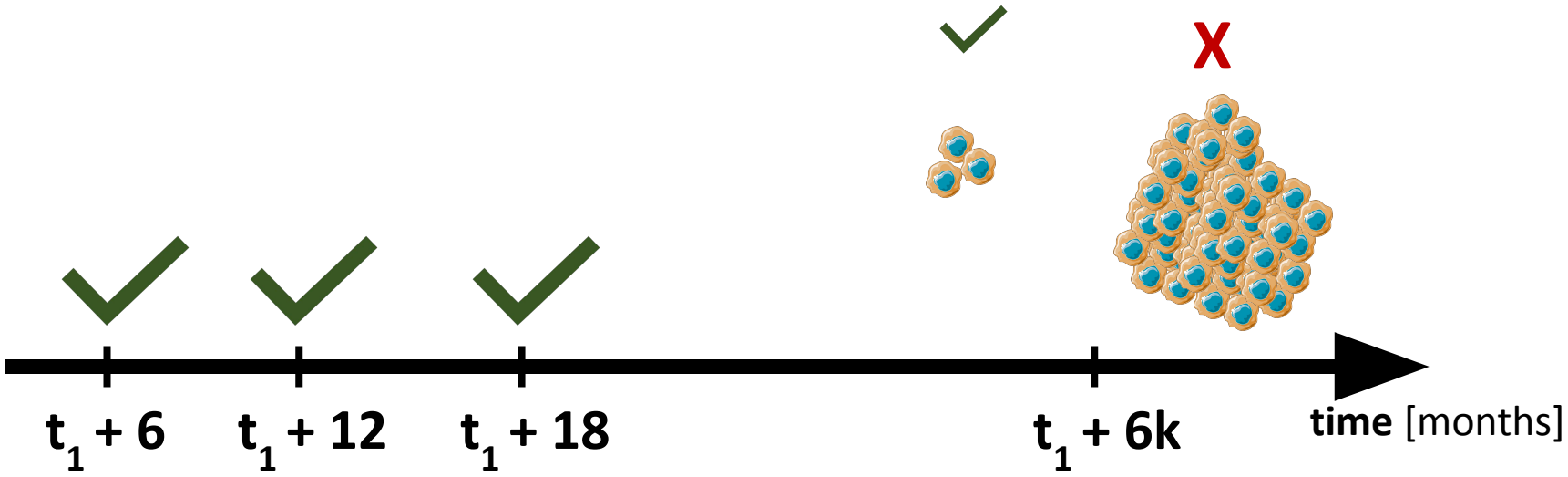
Neuroblastoma is a cancer that develops from immature nerve cells found in several areas of the body





Survival of children with recurrent neuroblastoma is very poor, with minimal 40,000 being killed every year in the world.

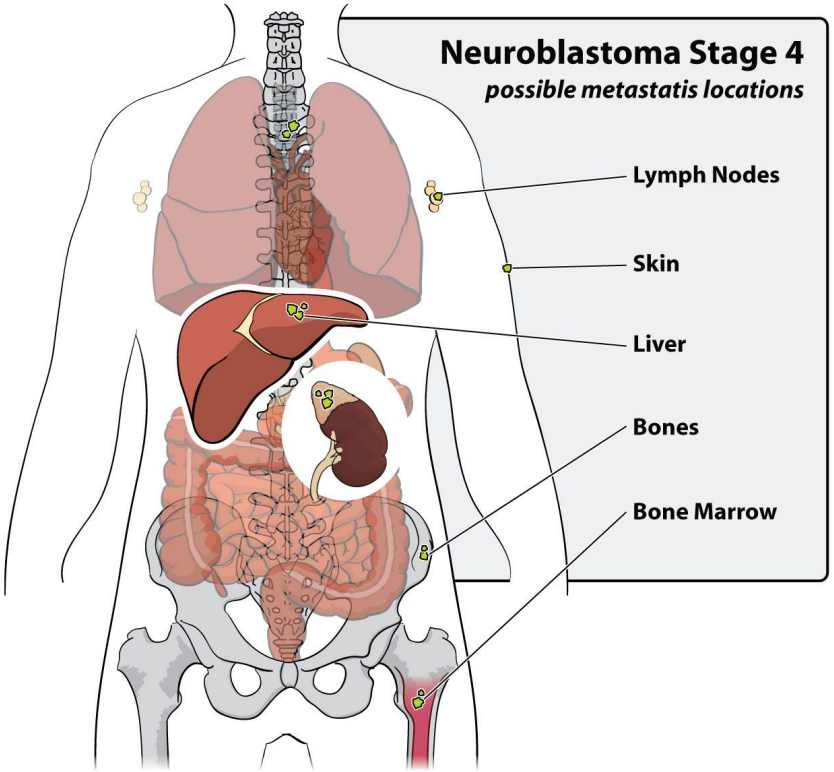

# of malignant cells
remission
progression/relapse
t_0
t_1
t_p
time



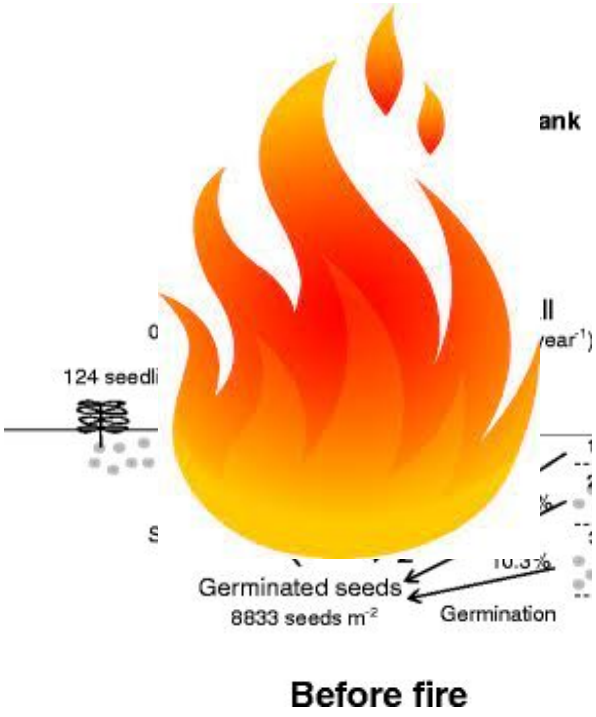
Current solution : Screening each 6 months

Problem : In 6 months the tumor has time to become huge and very problematic

Eco-Evolutionary approaches to Neuroblastoma



Soil seed banking in cancer?



Aran, et al. (2017).

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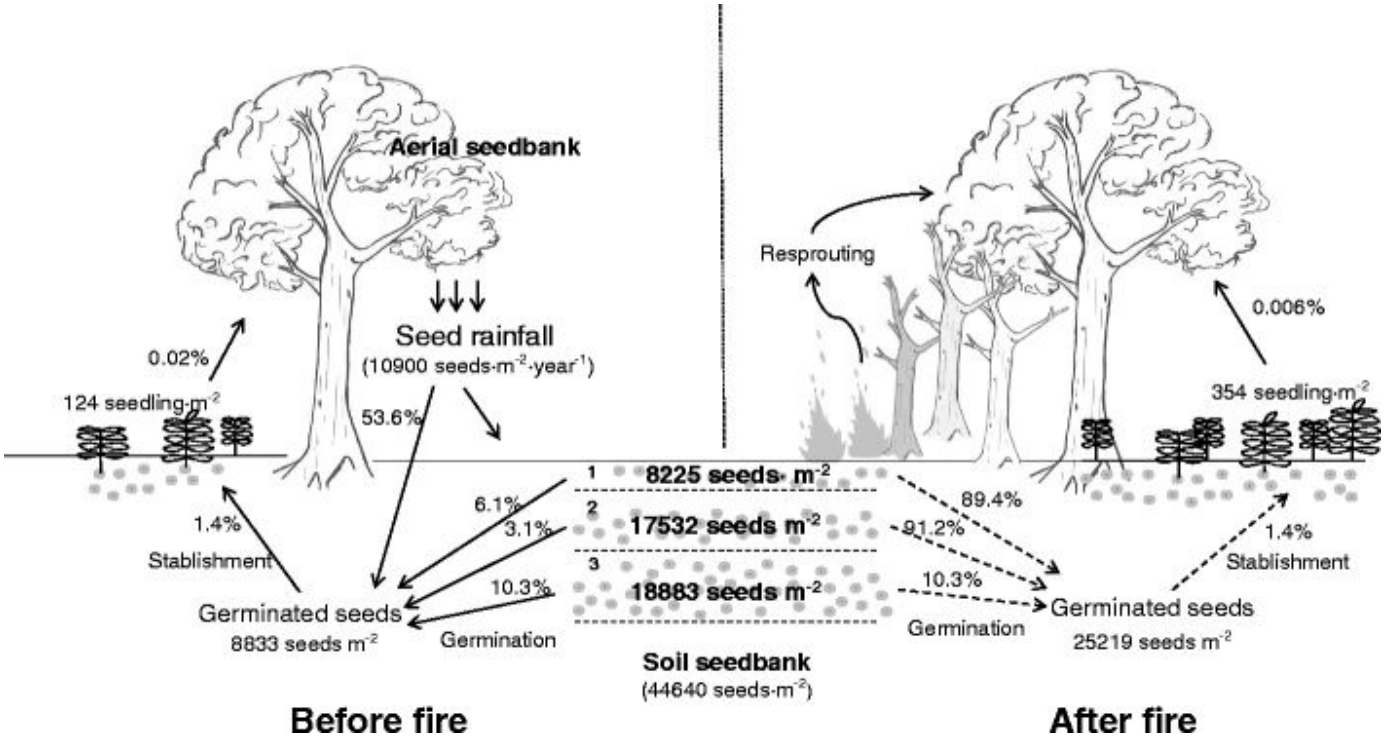

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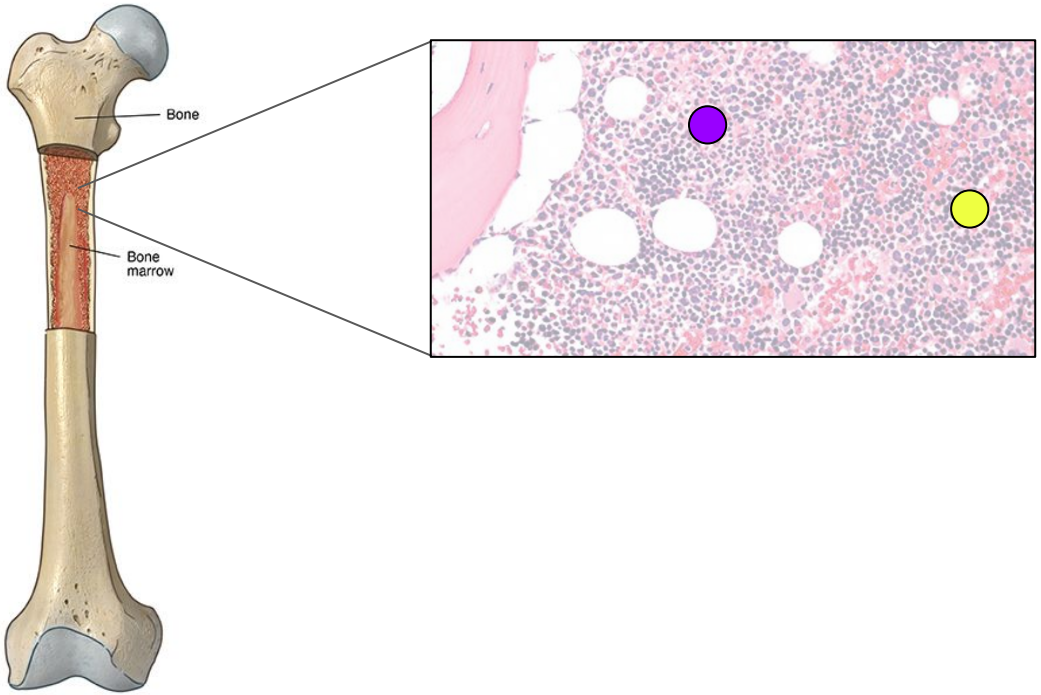
What is the role of normal cell turnover and microenvironment on time to (metastatic) relapse?



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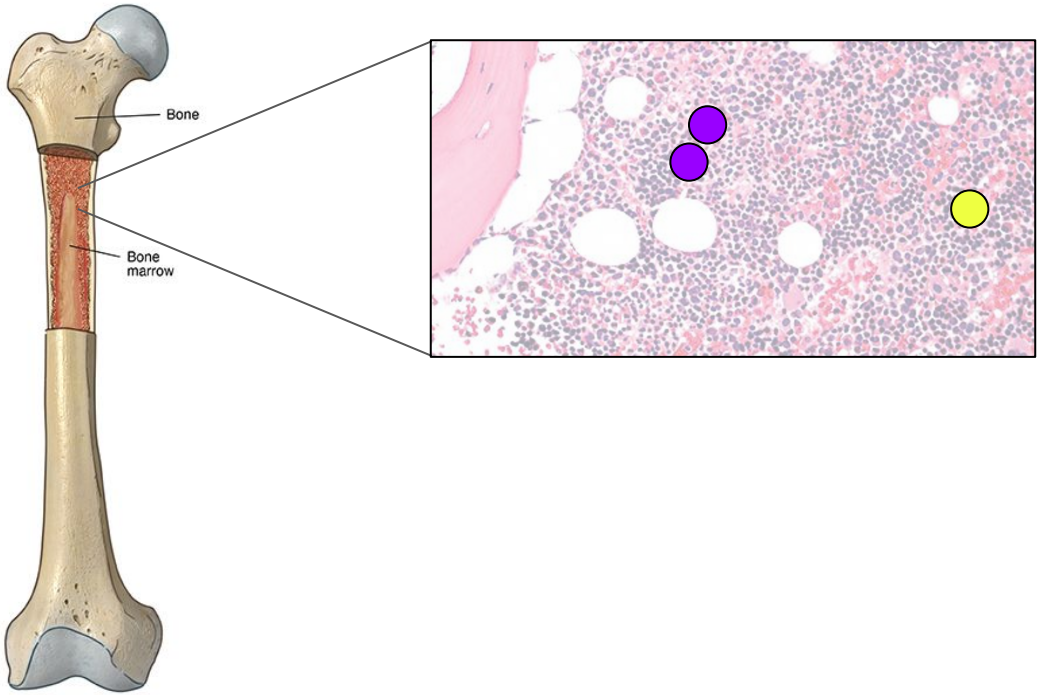

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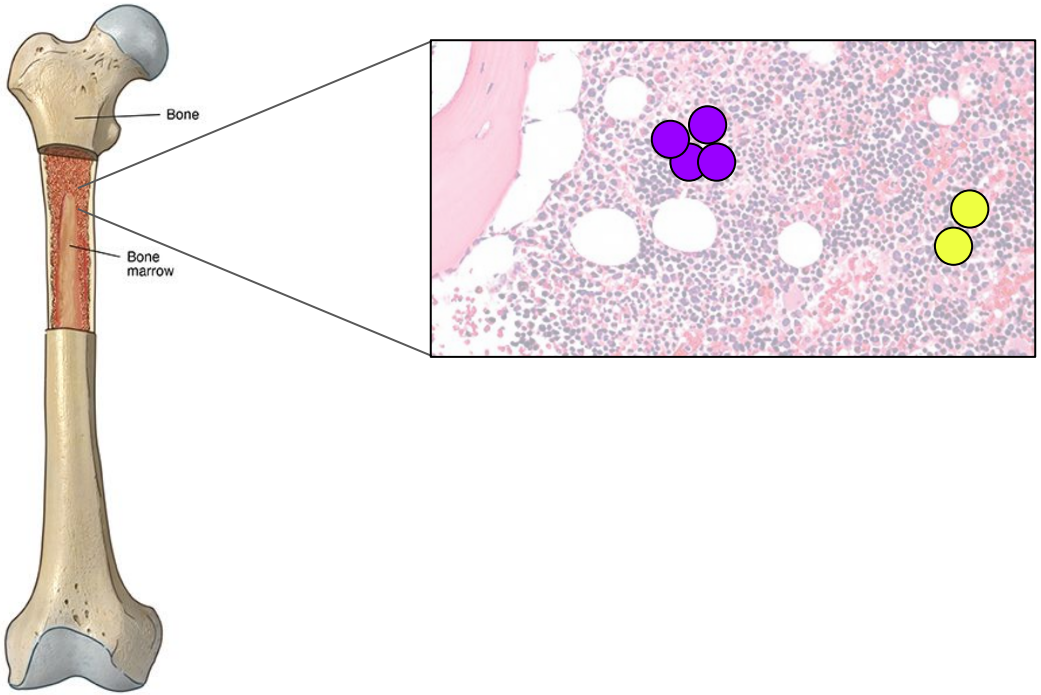

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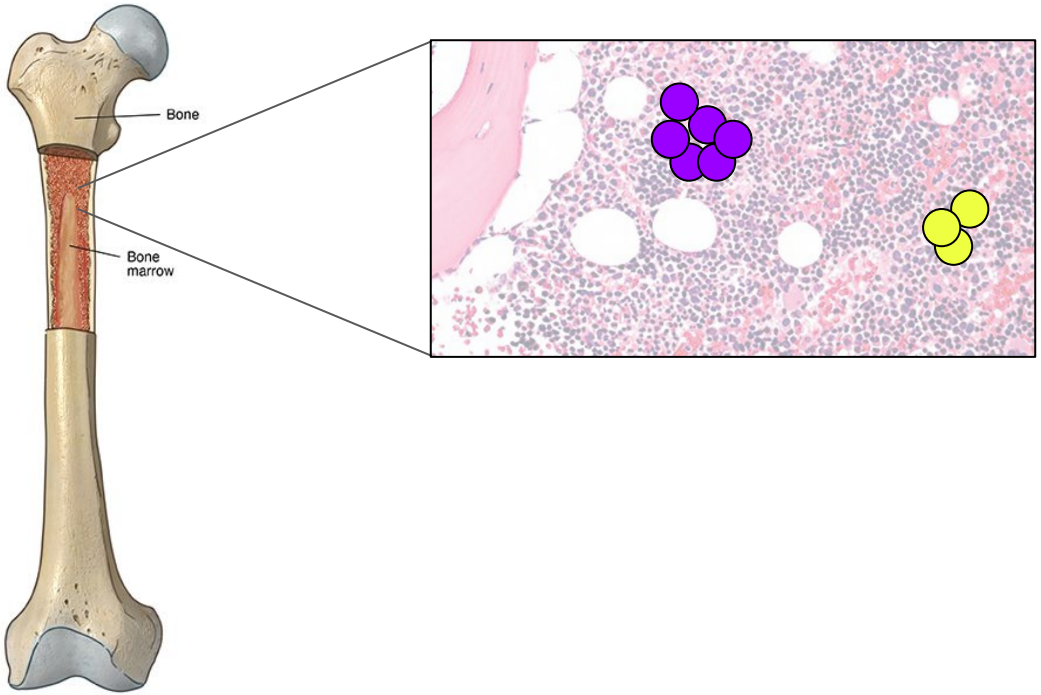

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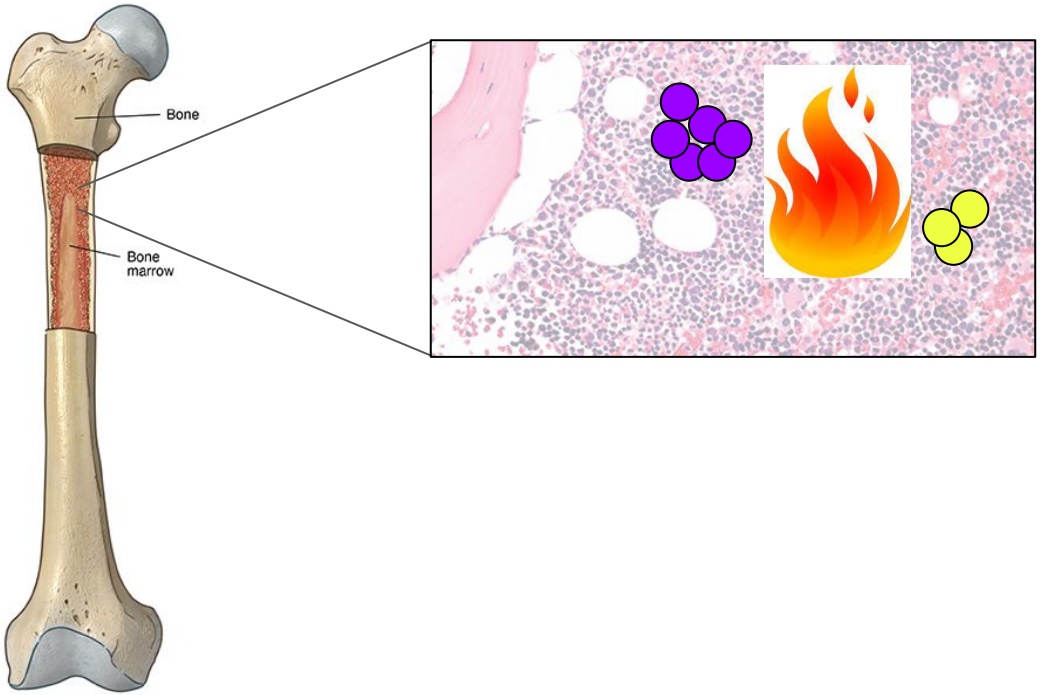

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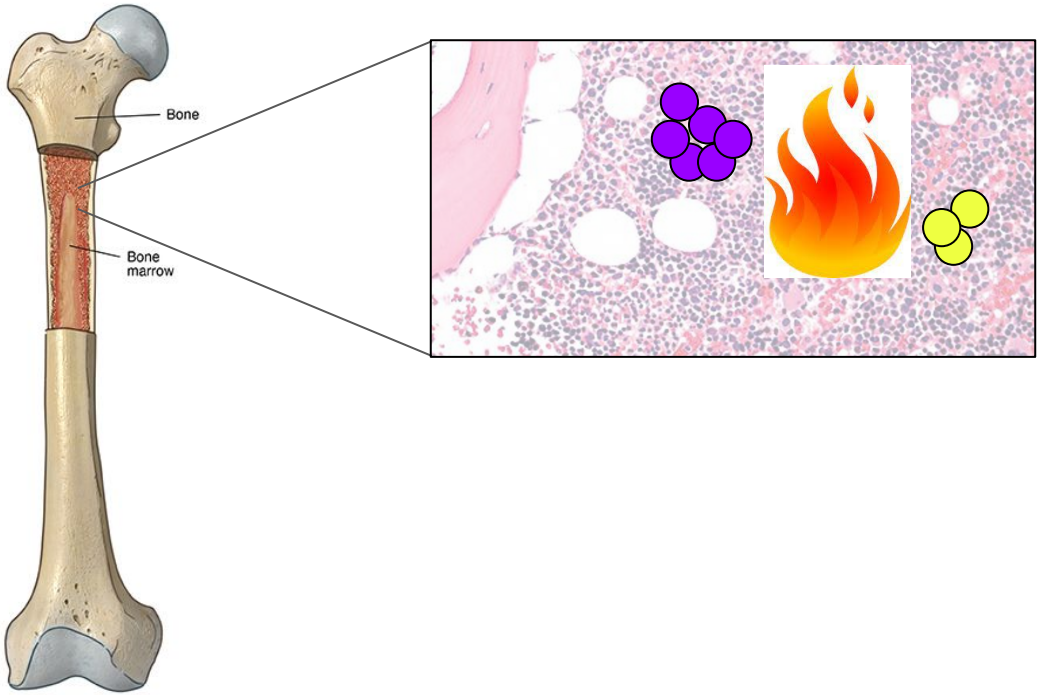
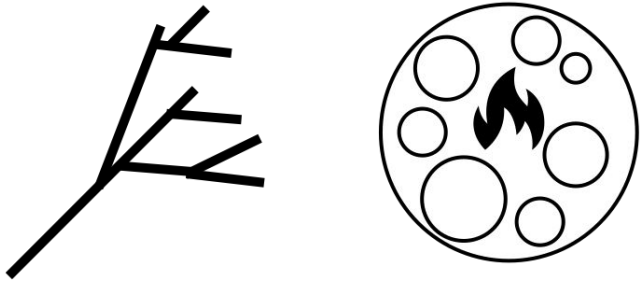


Normal cell turnover?

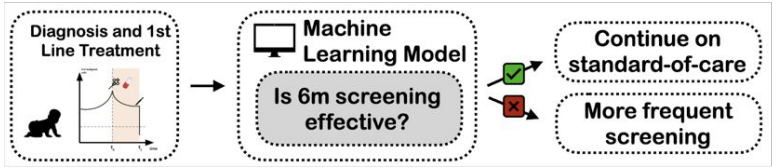
Inflammation?

Outline

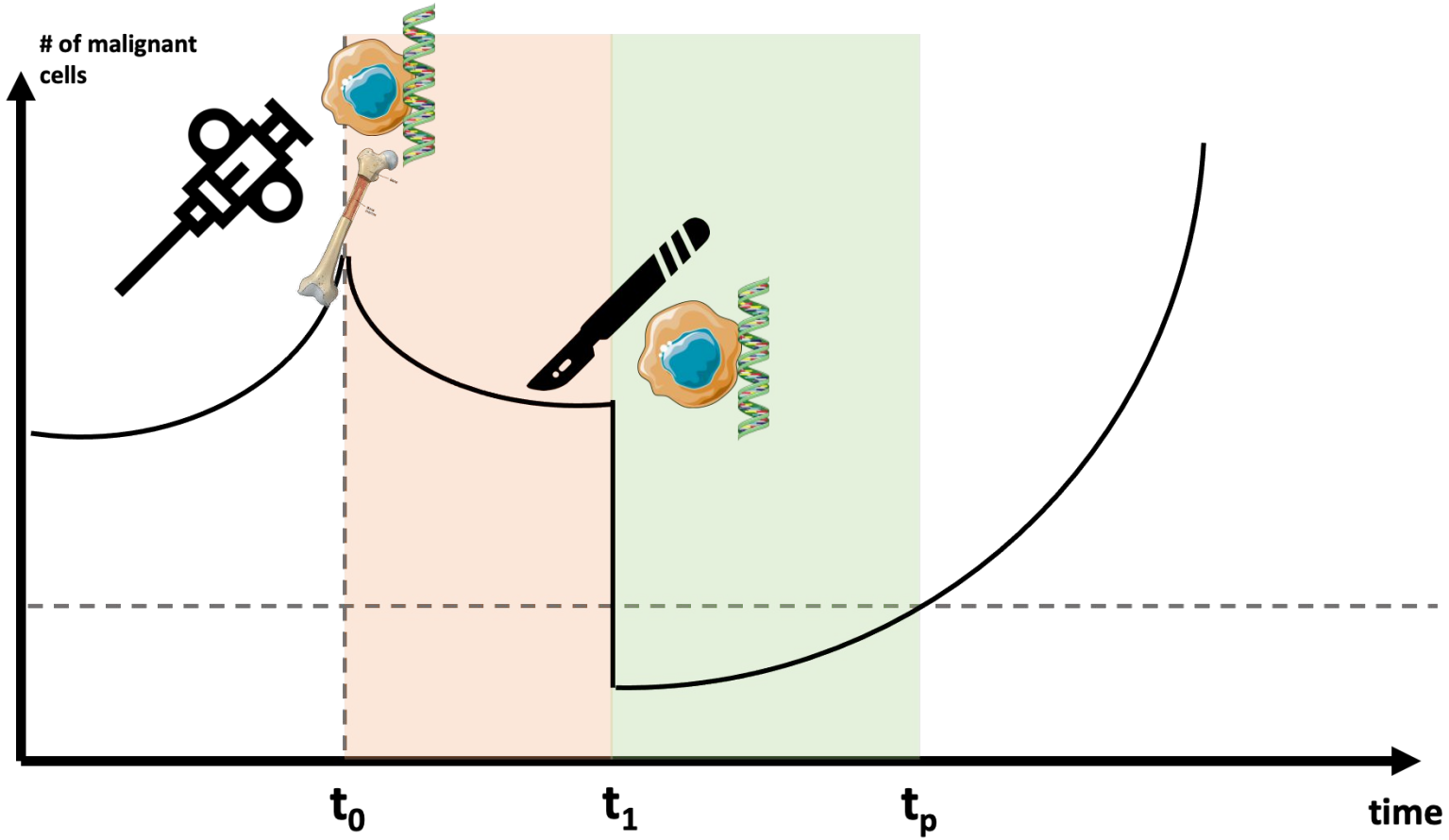
Aim 1: Characterize evolutionary and ecological processes driving relapse in neuroblastoma



Aim 2: Develop an eco-evolutionary informed machine learning model to guide screening intensification for earlier relapse detection



Data Collection



Aim 1: Characterize evolutionary and ecological processes driving relapse in neuroblastoma

Mathematical modelling

Most simple naive model: deterministic + start modelling after treatment

- After relapse $N(t) = N_0 \exp(rt)$ with N_0 estimated from treatment response (< 0.5 mm radius)

Next complicated: stochastic + start modelling from the first metastatic cell

- Stochastic model starting with beginning of the disease → TTP is a scalar
- random mutations that lead to mutant distribution → estimate of MRD → Estimate of TTP
- Try to infer patient-specific

Next complicated: Inter-patient heterogeneity

- What's more important? Inter- or intra-patient heterogeneity or demographic noise?
- Inter-tumour heterogeneity: Pick growth rate lambda from probability distribution

Next complicated: Using clonal structure (RNA clusters) to estimate relapse

Methods:

- Master equation: First hitting time
- Gillespie algorithm

Mathematical modelling

Mathematical model
$dS/dt = f(R,S)$
$dR/dt = f(R,S)$
$N=S+R$

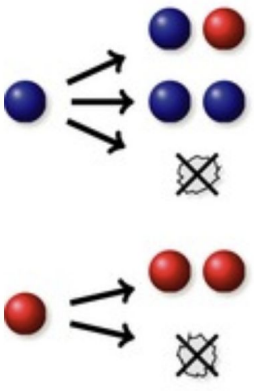
Estimation of surviving mutations

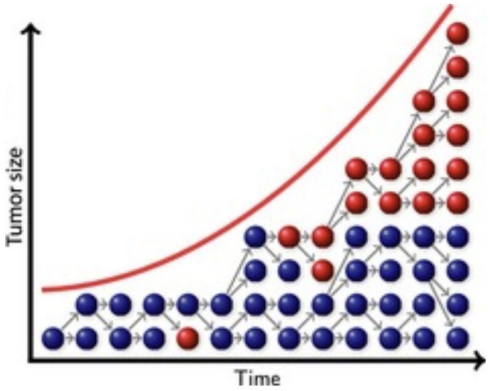
Estimate of time to relapse

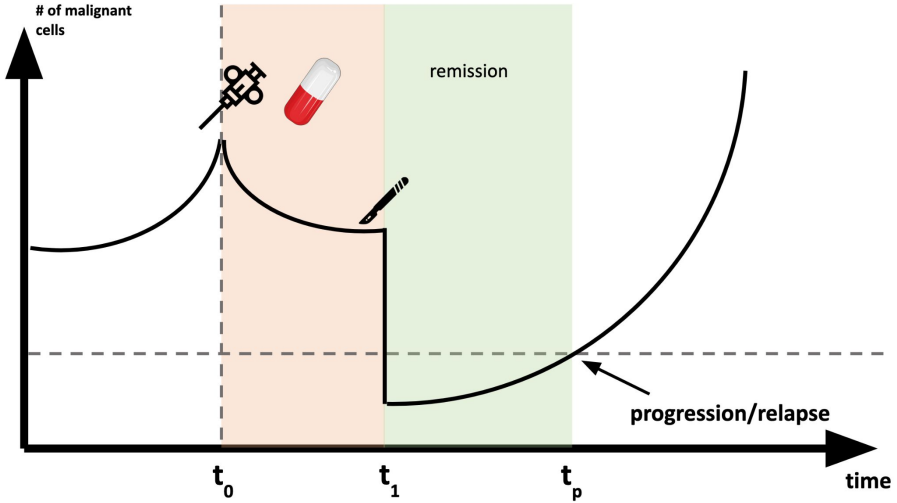
Methods:
- Mathematical analysis (starting from the Markov chain)
- Gillespie algorithm

$bX,\ X \rightarrow X+X$
$dX,\ X \rightarrow 0$
$Mu,\ X \rightarrow X+Y$
$bY,\ Y \rightarrow Y+Y$
$dY,\ Y \rightarrow 0$

Mathematical modelling







Parameter Estimation

Parameter Estimation

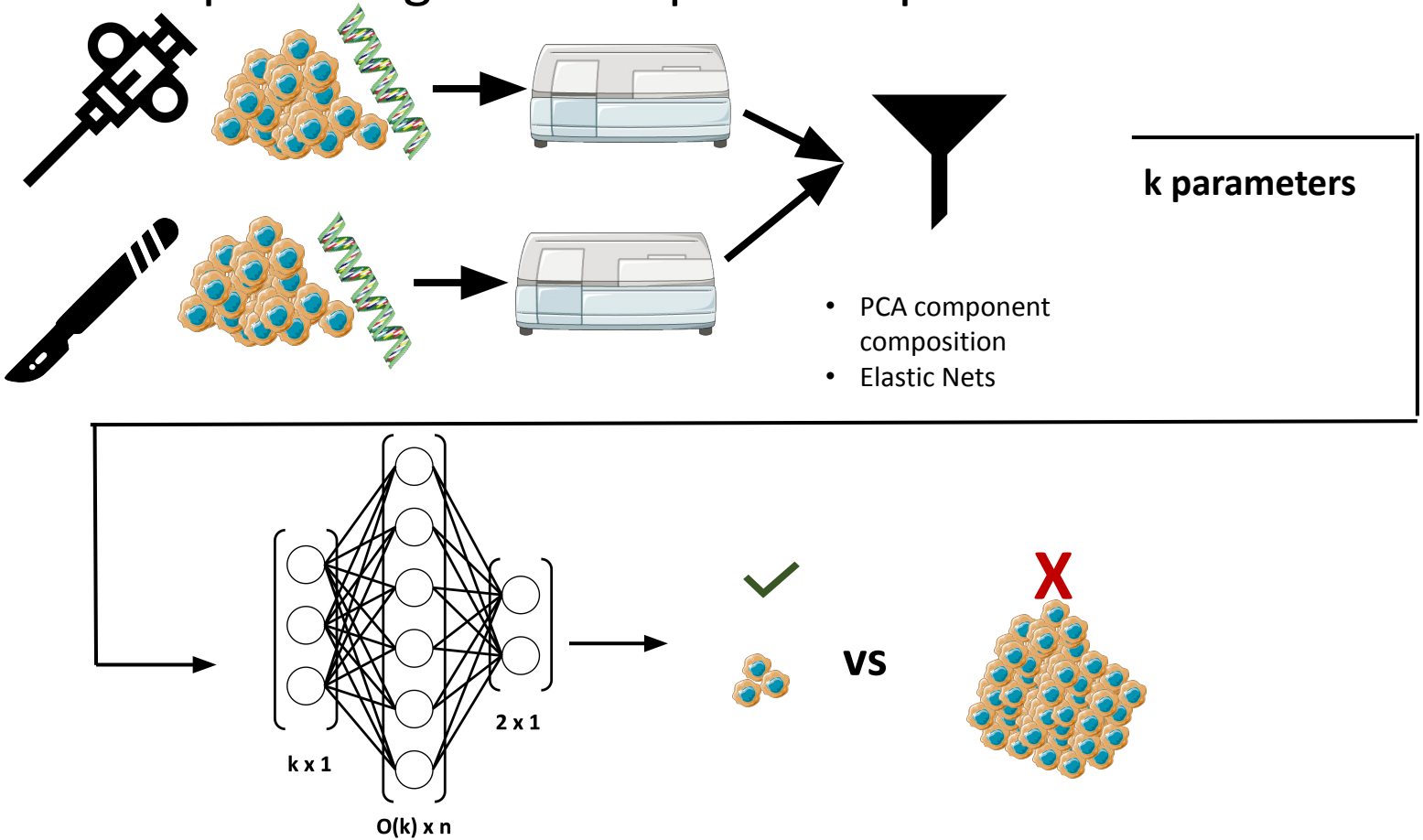
Mathematical model
- Compartment model
- Stochastic process

Estimation of surviving population

Estimation of time to relapse

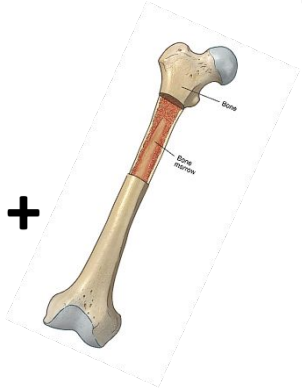
Aim 2: Develop an eco-evolutionary informed machine learning model to guide screening intensification for earlier relapse detection

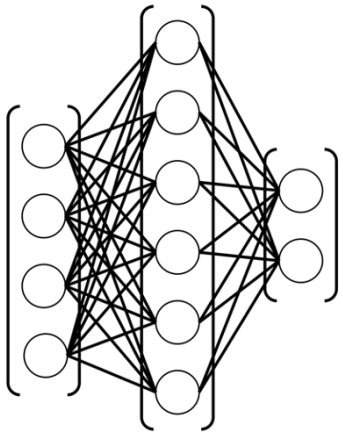
Sub Aim 2.1: Detection of patients with high risk large-tumor volume relapse using ultra deep DNAseq and dNNs

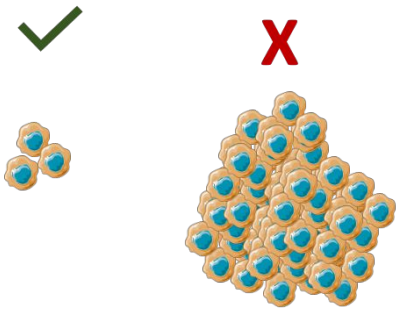


Sub Aim 2.2: Detection of patients with high risk large-tumor volume relapse with mathematical-model informed dNNs

$$M\left(\;\right) \longrightarrow (V, R_n, R_p)$$

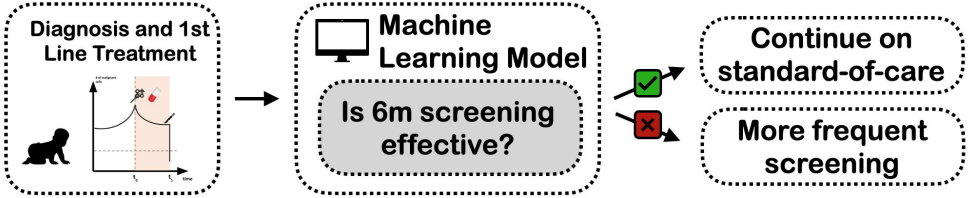






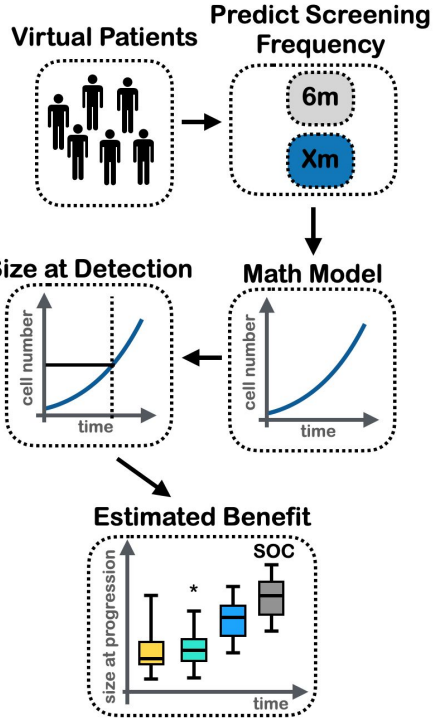
Sub Aim 2.3: Develop a protocol for model-guided screening intensification

Proposed Protocol



- We propose to use the ML model to guide when to intensify screening.
- Using the mathematical model from Aim 1 we will calibrate this protocol and estimate its potential benefit.

***In silico* validation and optimisation**



Budget

Retrospective cohort (200 patients; 3 years)

Running costs 3 years

- 200 patients —> 400 WGS (100x tumor, 30 x normal) —> 5000 € x 400 = 2 000 000 €
- Basic sample workup 400 x 1000 € = 400 000
- RNA Seq bone marrow 200 x 500 = 100 000

Staffing cost 3 years

- 1 bioinformatician/biologist PD 110 000 € /yr
- 1 mathematician PD 110 000 € /yr
- 1 pathologist (30%) PD 110 000 € /yr
- 1 research nurse (10%) = 30 000 E

Retrospective cohort total
2 500 000 + 1 020 000 = **3 520 000 Euros**

NIH NATIONAL CANCER INSTITUTE

erc European Research Council
Established by the European Commission

AACR American Association for Cancer Research

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Prospective cohort (100 patients; 5 years)

Staff
1 020 000 /3 x 5 = 1 700 000

Running costs (50 + 50 cohorts)

- WGS 200 x 5000 E = 1000 000
- RNA Seq bone marrow 100 x 500 = 50 000 E
- Workup 200 x 1000 = 200 000 E
- 25 x 25 MRIs = 625 x 500 E = 312 500 E

Total running costs

1 000000 + 200 000 + 50 000 + 312500 = 1 562 000

Total cost prospective study
1 562 000 + 1 700 000 = **3 262 000 Euros**

Budget - retrospective cohort (3 years)

Retrospective cohort (200 patients)

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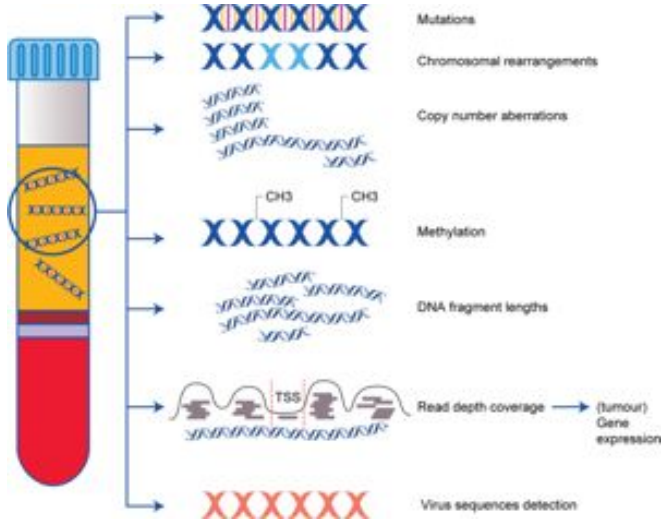
ctDNA

BJC
British Journal of Cancer
www.nature.com/bjc

REVIEW ARTICLE

Clinical relevance of blood-based ctDNA analysis: mutation detection and beyond

Laura Keller[1], Yassine Belloum[1], Harriet Wikman[1] and Klaus Pantel[1]



Conclusions

- Early detection of relapse can improve timing of secondary treatment

- Integrating eco-evolutionary approaches into machine learning may better inform models of neuroblastoma relapse and metastasis