A simulator of cancer-cell evolution toward a simulation-based personalized medicine

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Cancer Genome Medicine

- Calling program of DNA alterations – ***cisCall*** (Kato et al, 2018, *Genome Medicine*)

Kato *et al. Genome Medicine* (2018) 10:44
https://doi.org/10.1186/s13073-018-0547-0

Genome Medicine

METHOD Open Access

A computational tool to detect DNA alterations tailored to formalin-fixed paraffin-embedded samples in cancer clinical sequencing

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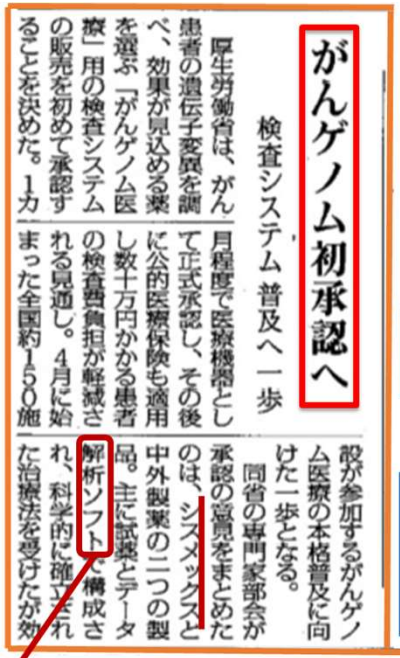
Technology transfer



がんゲノム初承認へ

検査システム 普及へ一歩

厚生労働省は、がん患者の遺伝子変異を調べ、効果が見込める薬を選ぶ「がんゲノム医療」用の検査システムの販売を初めて承認することを決めた。1カ月程度で医療機器として正式承認し、その後に公的医療保険も適用し数十万円かかる患者の検査費負担が軽減される見通し。4月に始まった全国約150施設が参加するがんゲノム医療の本格普及に向けた一歩となる。

同省の専門家部会が承認の意見をまとめたのは、シスメックスと中外製薬の二つの製品。主に試薬とデータ解析ソフトで構成され、科学的に確立された治療法を受けたが効果がなくなった患者や、確立された治療法がない希少がん、小児がんなどの患者が対象になる。シスメックスの製品は1～4種類、中外製薬の製品は3～4種類の遺伝子を調

The Mainichi
(毎日新聞)
Dec. 15, 2018

OncoGuide™
NCC onco-panel system

Combination Medical Device of
1) **Software**, and
2) Reagents

***cisCall* and *cisInter*, which we developed**

First Medical Device approved by the Japanese government in cancer genome medicine

However, **not all** patients show drug response

- Only 3/9 responsive on our first genome medicine project (Tanabe et al, 2016, *Mol. Cancer*)

tugHall (tumor gene-Hallmark) simulator

(Nagornov and Kato, 2020, *Bioinformatics*)

Bioinformatics, 36(11), 2020, 3597–3599
doi: 10.1093/bioinformatics/btaa182
Advance Access Publication Date: 14 March 2020
Applications Note

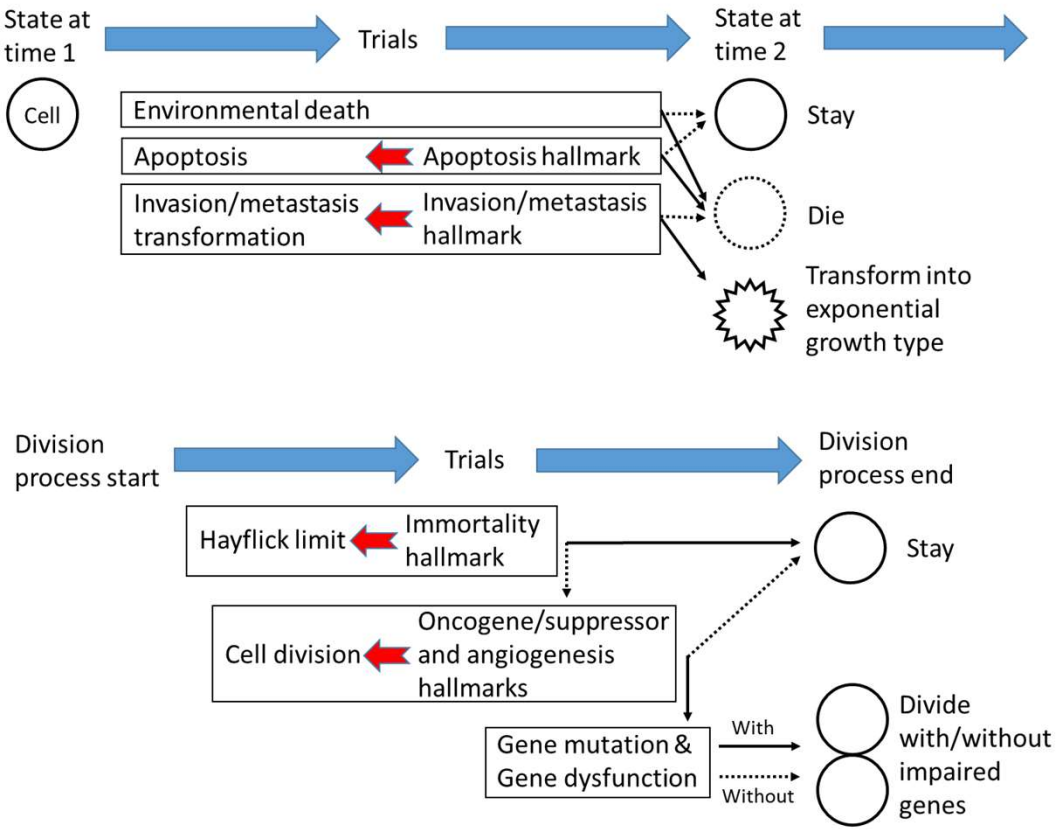
Genetics and population analysis

tugHall: a simulator of cancer-cell evolution based on the hallmarks of cancer and tumor-related genes

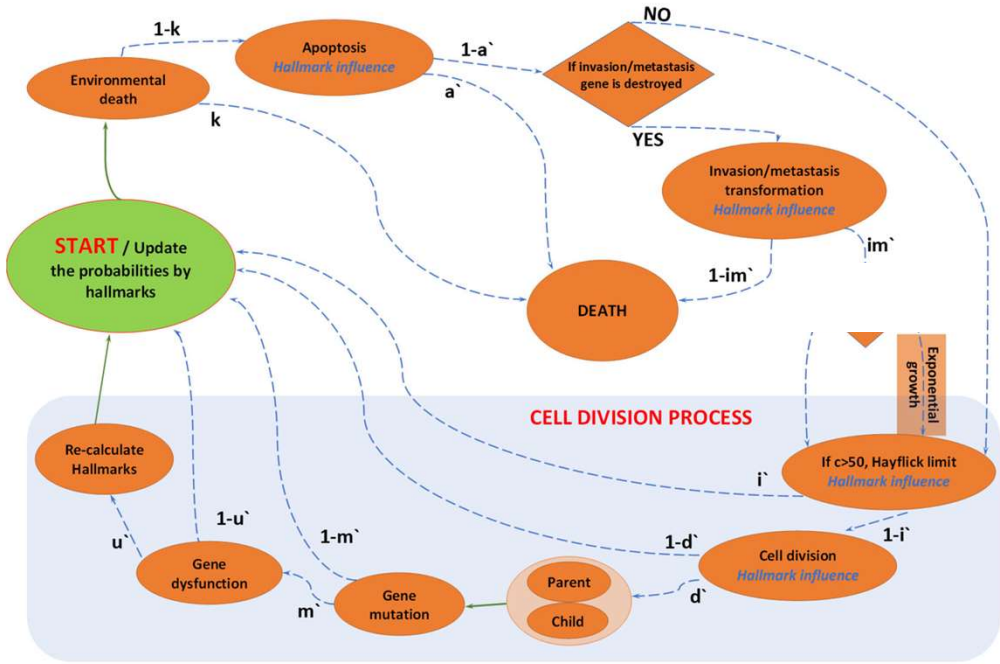
Iurii S. Nagornov and Mamoru Kato*

Trial probability	Cancer hallmark	Gene mutations
Cell's next states are determined by the probabilities	interference with the trial probabilities	determine degree of hallmark interference

The algorithm



State transition



(Nagornov and Kato, 2020, *Bioinformatics*)

Trials	Condition	Probability	Event
Environmental death	Every time step	• $k' = k_0$	Death
		• $1 - k'$	Nothing
Apoptosis	Every time step	• $a' = a - H_a = \sigma(s_0 \times (x - 0.5)) - H_a$, where $x = impaired\_gene\_density$	Death
		• $1 - a'$	Nothing
Invasion/ metastasis transformation	$im' \neq 0$	• $im' = H_{im} < 1$	Nothing
		• $im' = H_{im} = 1$	Transfor exponen growth
		• $1 - im'$	Death
Hayflick limit (immortalization)	$c > c_{max}$	• $i' = i_0 - H_i$	Stop divi process
		• $1 - i'$	Start divi trial
Cell division	Every time step	• $d' = \begin{cases} d - E' \times N, \text{ when logistic growth} \\ d, \text{ when exponential growth} \end{cases}$, where $d = d_0 + H_d$ and $E' = E_0 / (1 + F_0 \times H_b)$	Division
		• $1 - d'$	Nothing
Gene mutation	Cell division happens	• $m' = m_0 \times CDS\_length$	Mutation
		• $1 - m'$	Nothing
Gene dysfunction	Gene mutation happens	• $u' = \begin{cases} u_{o,0}, \text{ for oncogene} \\ u_{s,0}, \text{ for suppressor} \end{cases}$	Gene dysfuncti
		• $1 - u'$	Nothing

Trials and hallmarks

- Apoptosis hallmark

$$a' = a - H_a = \sigma(s_0 \times (x - 0.5)) - H_a,$$

where $x = impaired\_gene\_density$

- Oncogene/suppressor and angiogenesis hallmarks

$$d' = \begin{cases} d - E' \times N, \text{ when logistic growth} \\ d, \text{ when exponential growth} \end{cases},$$

where $d = d_0 + H_d$ and

$$E' = E_0 / (1 + F_0 \times H_b)$$

Hallmark variable and mutations

- Linear combination simply for interpretability

A) The oncogene/suppressor hallmark variable, H_d, for example:

$$H_d = w_1^d \cdot g_1^d + w_2^d \cdot g_2^d + w_3^d \cdot g_3^d + w_4^d \cdot g_4^d$$

Let $(w_1^d, w_2^d, w_3^d, w_4^d) = (0.1, 0.2, 0.3, 0.4)$

When $(g_1^d, g_2^d, g_3^d, g_4^d) = (1, 1, 0, 0)$

$$H_d = 0.1 \cdot 1 + 0.2 \cdot 1 + 0.3 \cdot 0 + 0.4 \cdot 0 = 0.3$$

H_d interferes with a probability value of the cell division trial:

$$d' = d_0 + H_d = 0 + 0.3 = 0.3$$

of parameters?

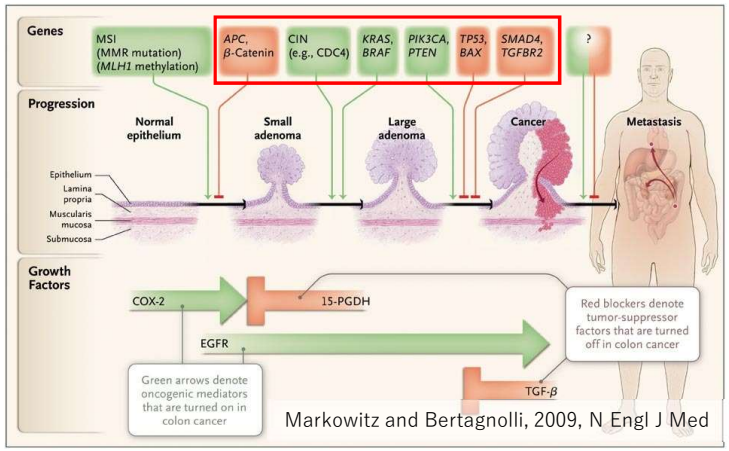
- Only 7
- + hallmark weights

cf. 20-30 parameters in Standard Model of particle physics

Information on gene mutations

The first trial toward simulation-based personalized medicine (1)

1. Pick out colorectal cancer and focus on 4 classical genes (*APC*, *KRAS*, *TP53*, *PIK3CA*)



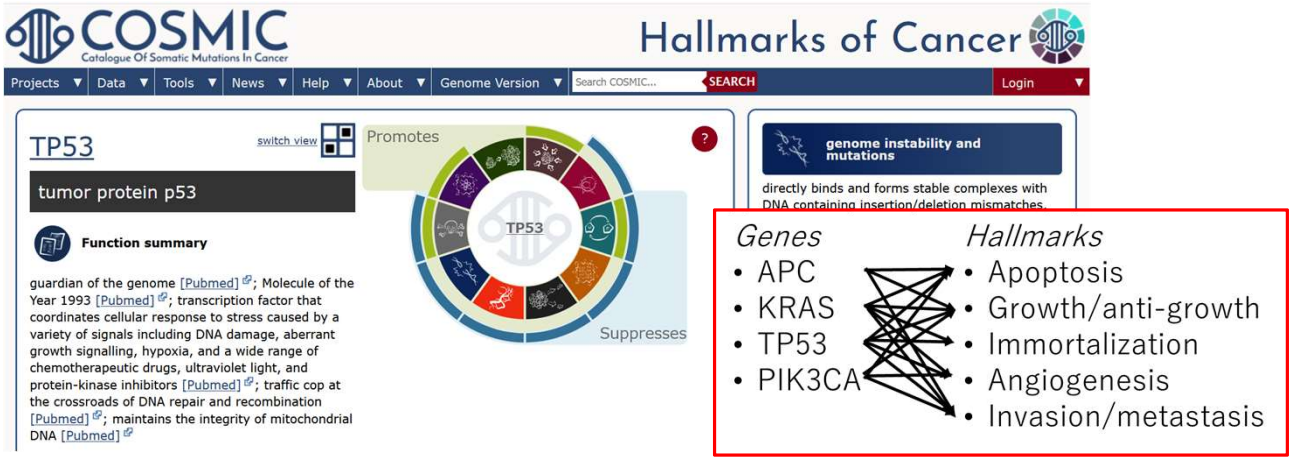
Markowitz and Bertagnolli, 2009, N Engl J Med

2. This time, set other parameters than the weight parameters based on literature-based values
   - ✓ Can be estimated in the future

Supplementary Table 1. The variables.

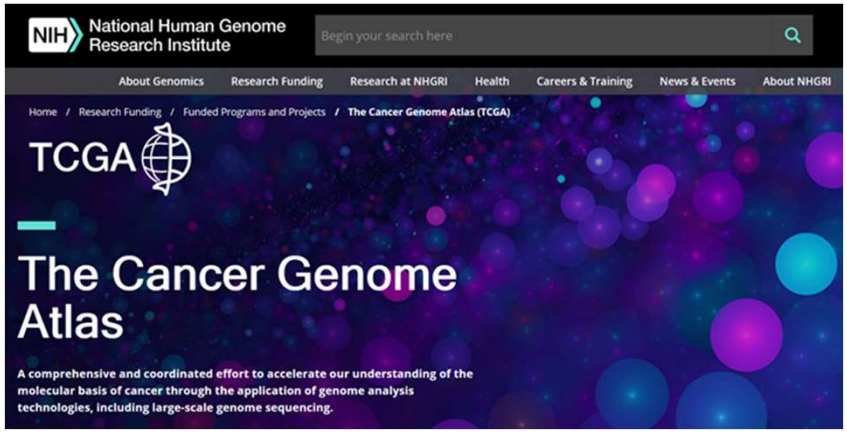
Variable type	Notation	Description	Per	Interfered by hallmarks	Time change	Notation as parameter	Possible initial values for parameter
Cell	c	Cell division counter	-	No	Dynamic	-	-
	c_{max}	Maximum cell division number by Hayflic limit	-	No	Static	($c_{max,0}$)	50
	k	Probability of cell death by environments	τ	No	Static	k_0	{0.1, 0.2, ..., 0.9}
	d	Cell division rate	τ	Yes	Dynamic	(d_0)	0.1 for τ, arbitrarily time unit
	im	Probability of invasion/metastasis transformation	τ	Yes	Dynamic	-	-
	a	Probability of cell death by apoptosis	τ	Yes	Dynamic	s_0	{10, 15, 20, 30, 40, 90}
	i	Probability of cell division stop by Hayflic limit	τ	Yes	Dynamic	(i_0)	1
	m	Mutation rate per bp	division	No	Static	m_0	{$\mathbf{10^{-6}}$, 10^{-7}, 10^{-8}, $\mathbf{10^{-9}}$, $\mathbf{10^{-10}}$}
	u_o	Probability of dysfunction of a oncogene	mutation	No	Static	$u_{o,0}$	{1/1, 1/10, 1/100}
	u_s	Probability of dysfunction of a suppressor	mutation	No	Static	$u_{s,0}$	{1/1, 1/10, 1/100}
External	N/M	Number of cells with logistic/exponential growth	-	No	Dynamic	-	-
	E	Environmental resource limitation	-	No	Static	E_0	{10^{-1}, 10^{-2}, $\mathbf{10^{-3}}$, 10^{-4}, 10^{-5}}
	F	Reduction effect to E by angiogenesis	-	Yes	Static	F_0	{10^1, 10^2, 10^3, 10^6}
	T	Time counter	-	-	-	-	-

3. Limit search space of the weight parameters by COSMIC knowledge-based hallmark genes



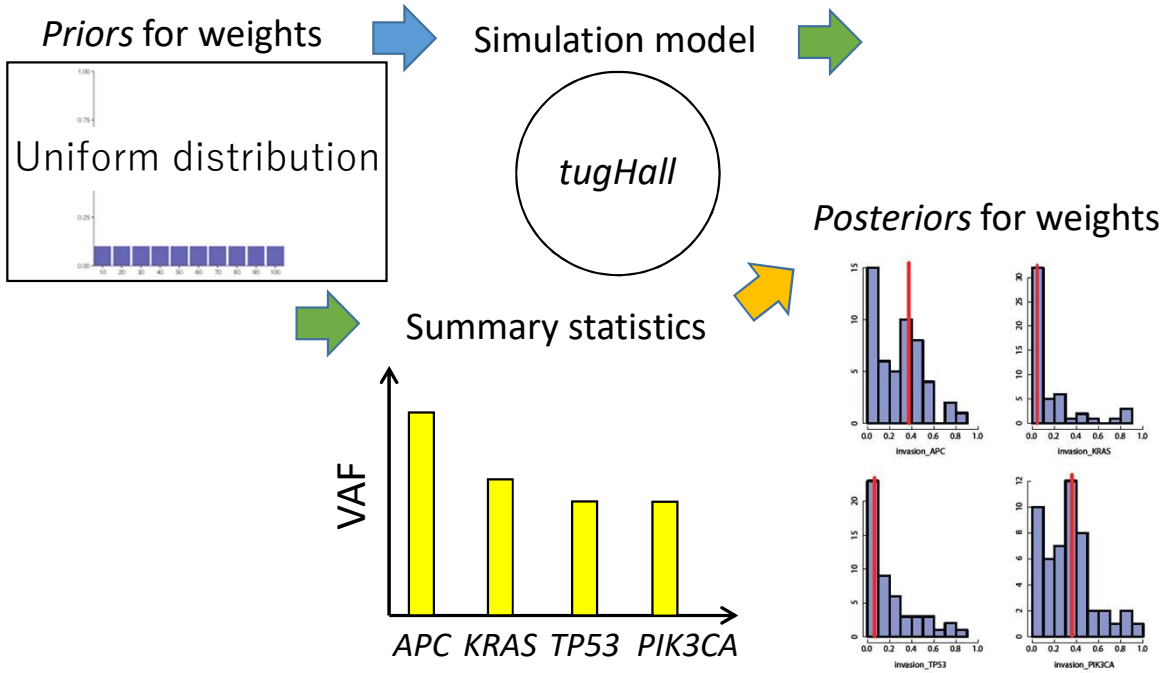
The first trial toward simulation-based personalized medicine (2)

4. Select a colorectal cancer patient from TCGA arbitrarily
   - ✓ With APC VAF of ~50% to circumvent the tumor purity issue



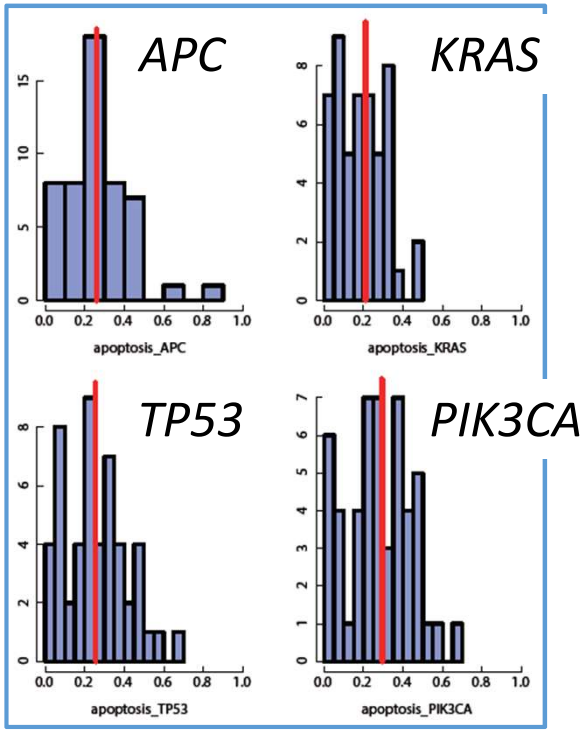
Patient: TCGA-COAD, 73-year-old Male — *APC*, *KRAS*, *TP53*, *PIK3CA*

5. Weight parameter estimation by ABC
   - ✓ ABC: Approximate Bayesian Computation
   - ✓ Latest method to estimate parameters used in complex simulation models
   - ✓ Often used in population genetics
   - ✓ We used it before in a β-coalescent model (Kato et al, 2017, Royal Society Open Science)

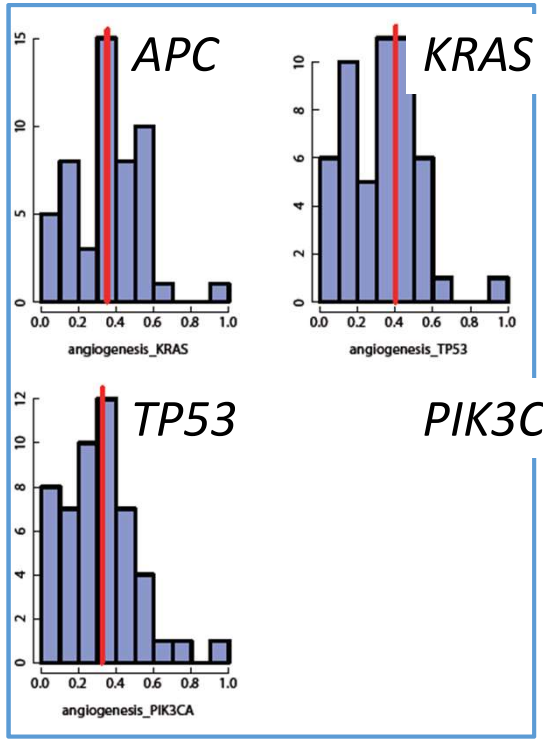


Posterior and MAP estimation for the weight parameters of this patient

Apoptosis hallmark



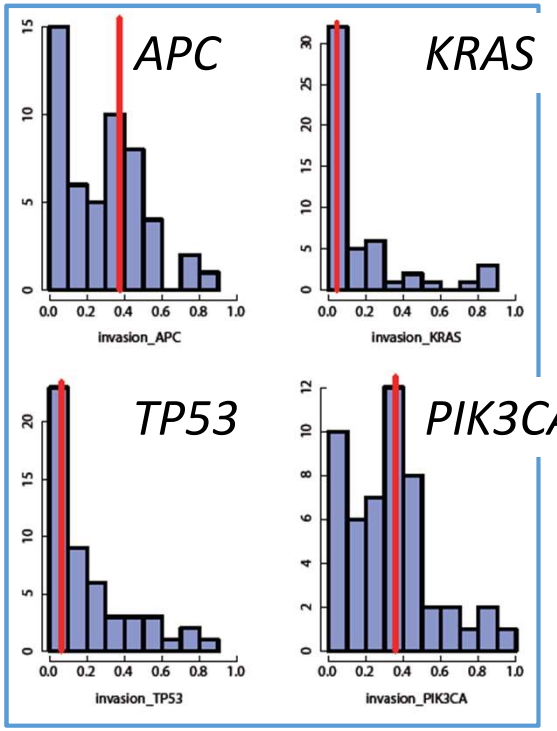
Angiogenesis hallmark



(Growth/anti-growth and Immortalization hallmarks)

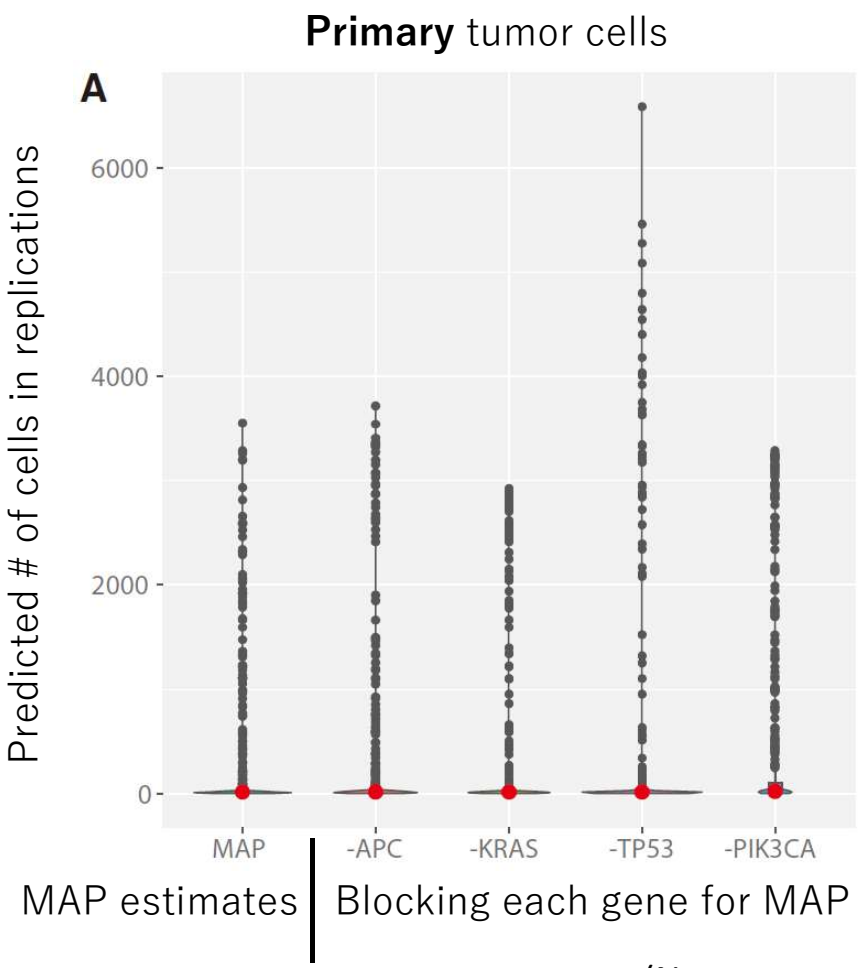
...

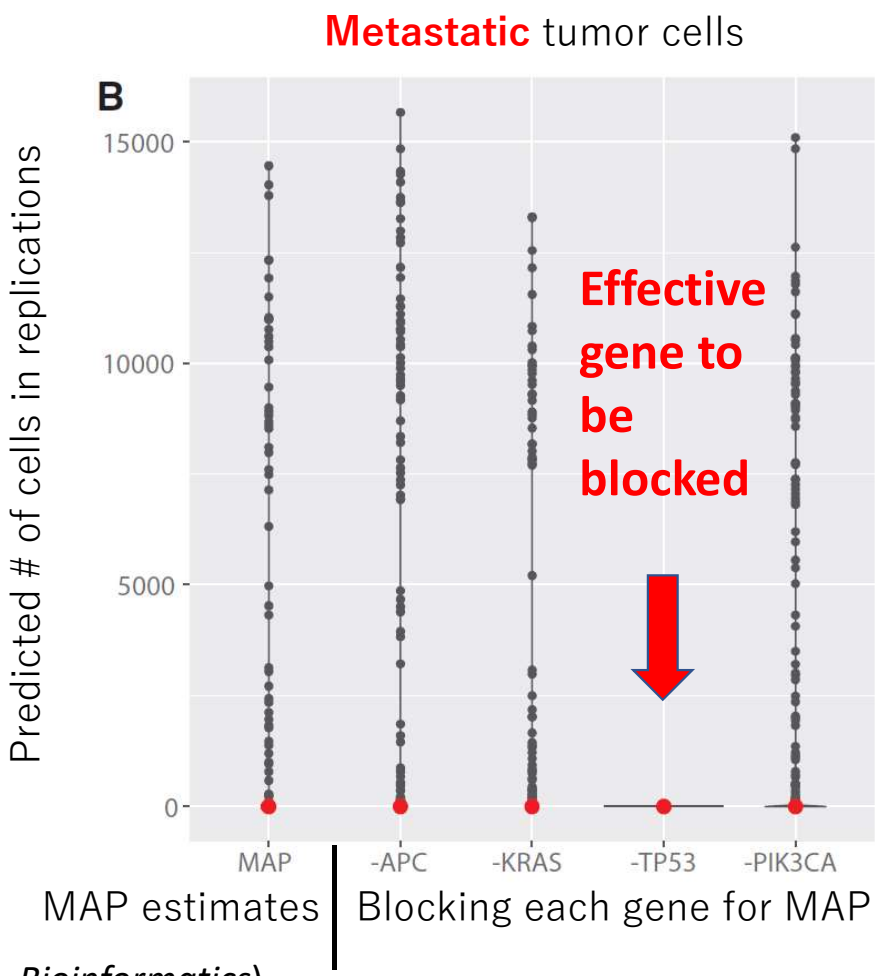
Invasion/metastasis hallmark



: MAP estimate

Artificially blocking each gene in our simulator





(Nagornov and Kato, 2020, *Bioinformatics*)

Possible mechanism on this blocking

Preliminary analysis of **mechanisms revealed in our simulator**

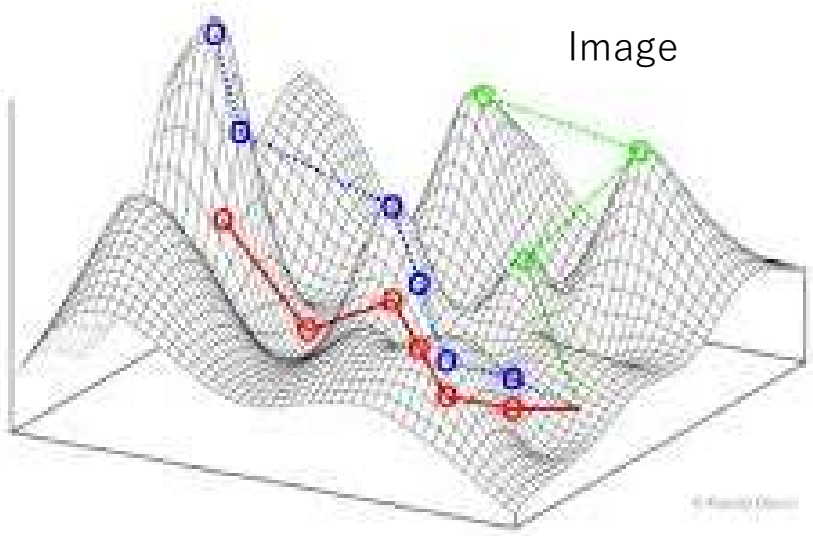
- Efficient and dead-end orders of gene dysfunctions for cell proliferation?
- Blocking TP53 seems to inhibit efficient paths for cell proliferation **in this patient**

Patient:

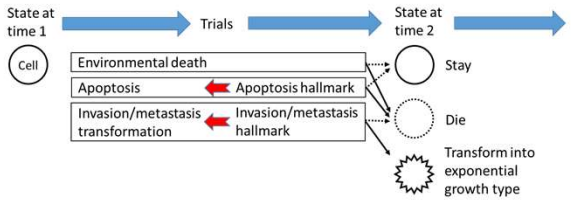
TCGA-COAD
73-year-old
Male

APC,
KRAS,
TP53,
PIK3CA

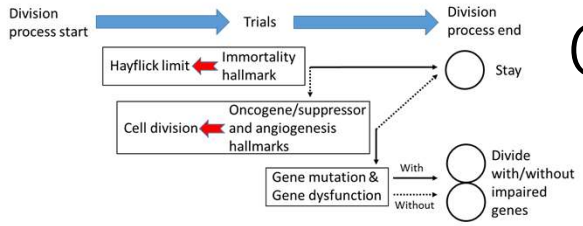
Image

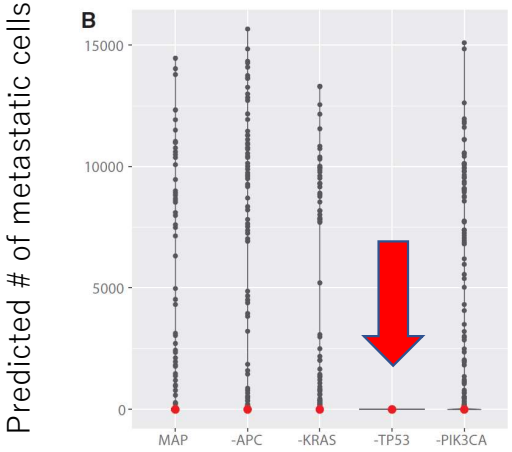


Simulation-based personalized medicine



tugHall





Patient:

TCGA-COAD
73-year-old
Male

APC,
KRAS,
TP53,
PIK3CA

(Nagornov and Kato, 2020, *Bioinformatics*)

Complementary

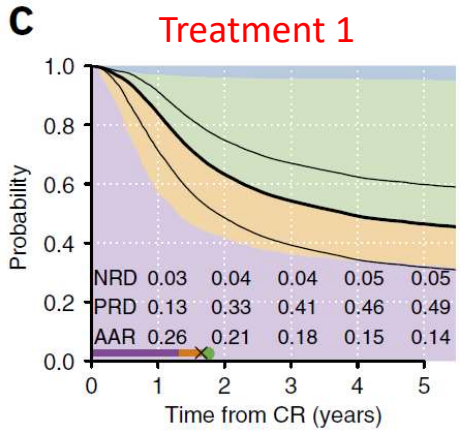
Statistics-based (incl. AI) personalized medicine

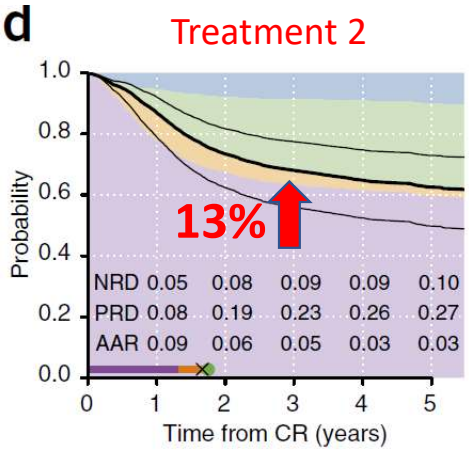
Patient:

PD8314a

49-year-old
Male
NK
NPM1,
DNMT3A,
IDH1

ELN favorable
Allo HSCT in CR2





(Gerstung et al, 2017, Nat Genet)

Summary and acknowledgments

- *tugHall*: cancer-cell evolution simulator involving gene information
- Applied tugHall to a colorectal-cancer patient in TCGA
  - Estimated parameters by the ABC method
- Blocking *TP53*, not other genes, is predicted to inhibit metastasis for this patient
- A possibility of simulation-based personalized medicine

■National Cancer Center Japan

- Division of Bioinformatics
  - ➢Iurii Nagornov
  - ➢Joe Nishino

END