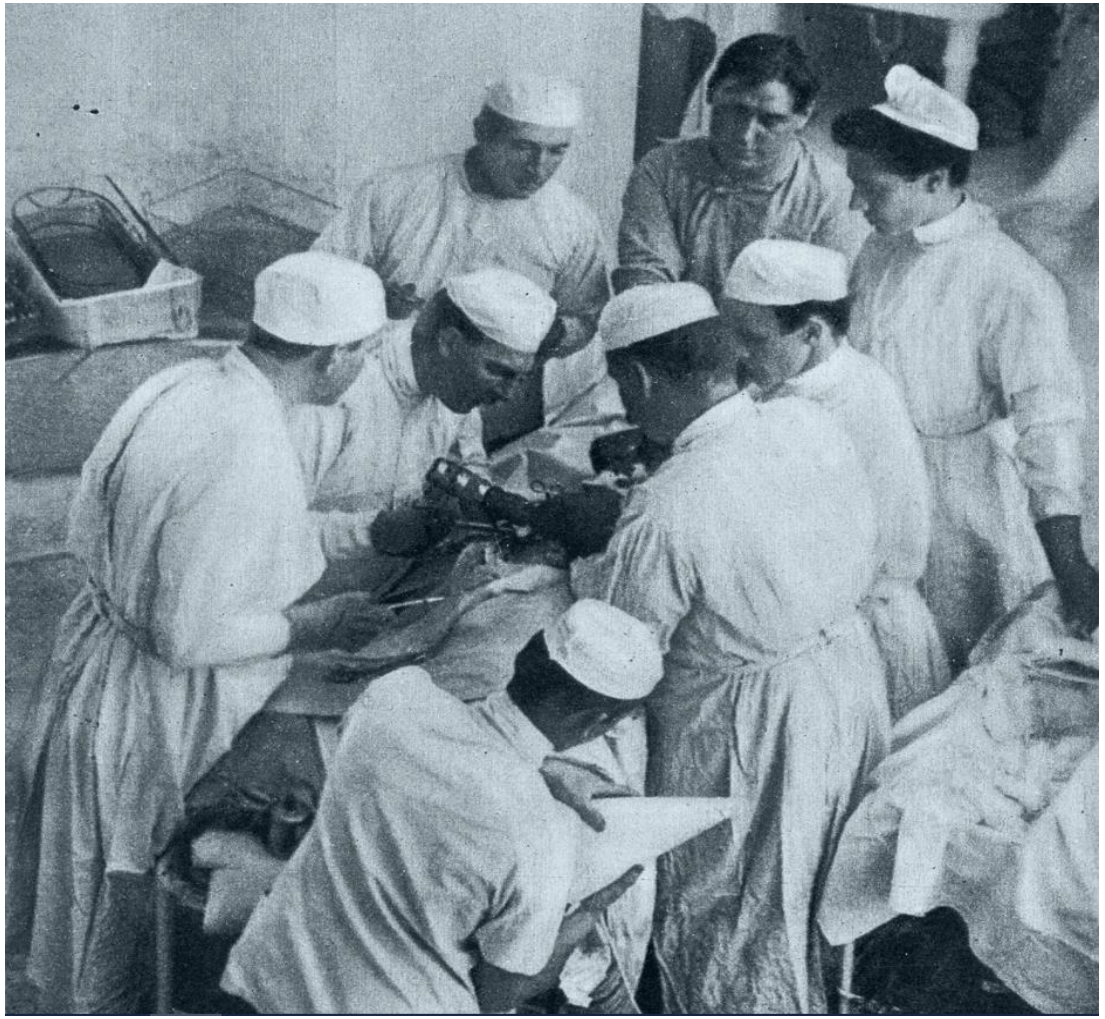
Regionaalhaigla

MOLEKULAADIAGNOSTIKA ONKOLOOGIAS

ANU PLANKEN

Onkoloogia evolutsioon

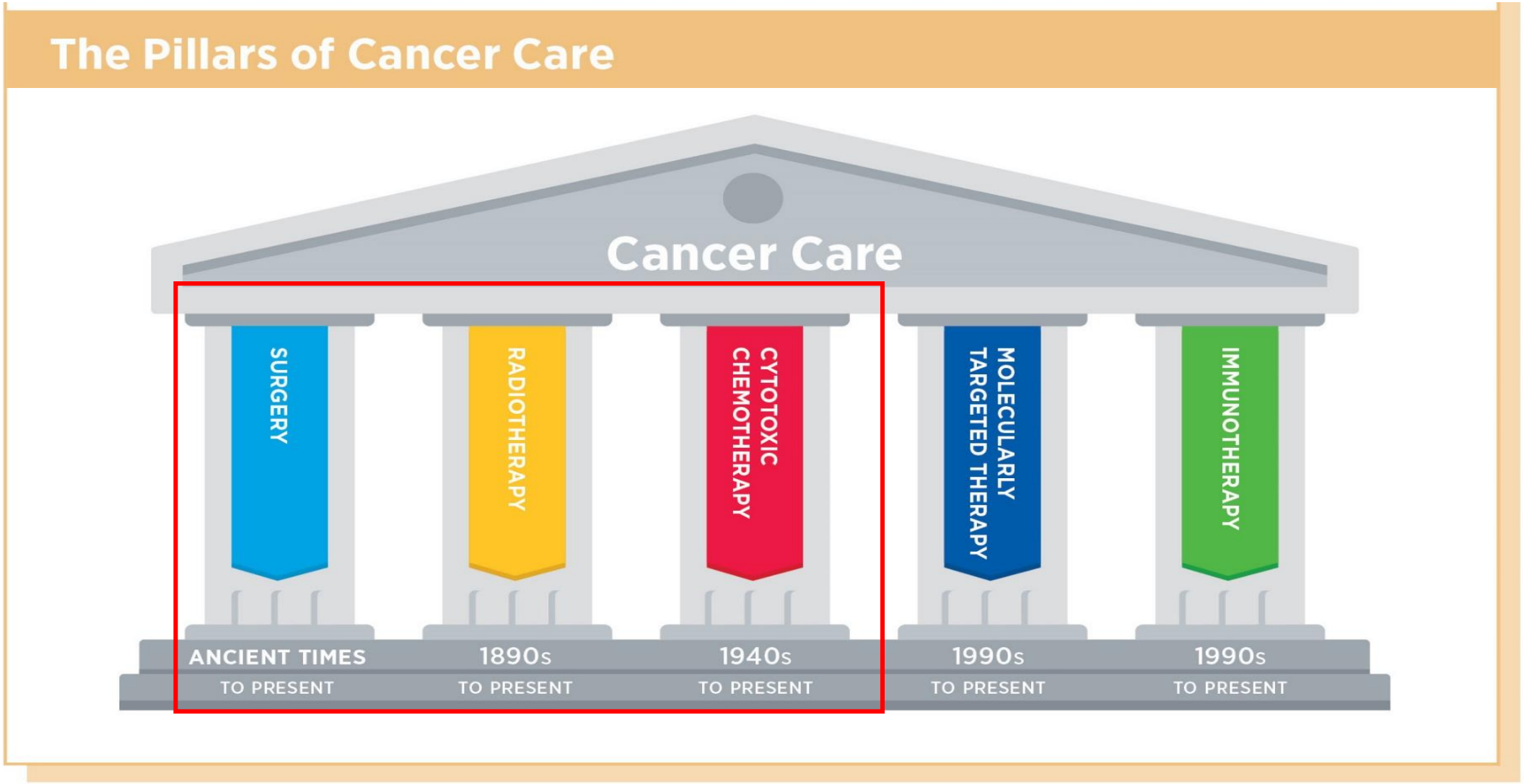
1882 “Halsted’i mastektoomia”



20..

https://static.scientificamerican.com/sciam/assets/media/multimedia/msktimeline/index.html
https://breastcancer-news.com/2017/06/09/cancer-free-future-leveraging-ai-technology-research/

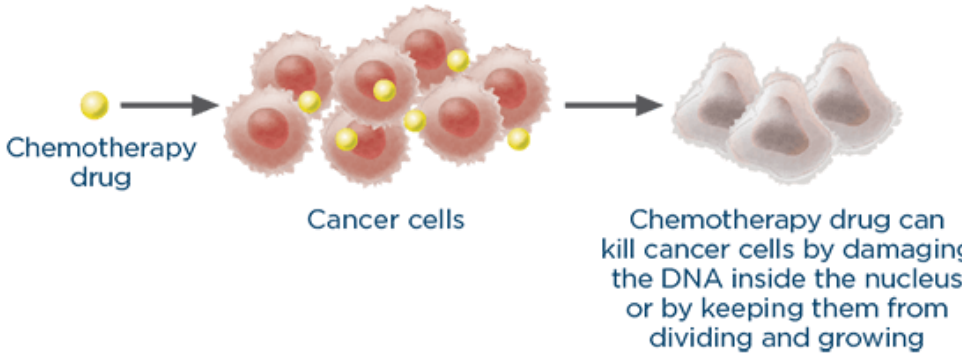
Onkoloogiline ravi



American Association for Cancer Research (AACR) Cancer Disparities Progress Report 2020

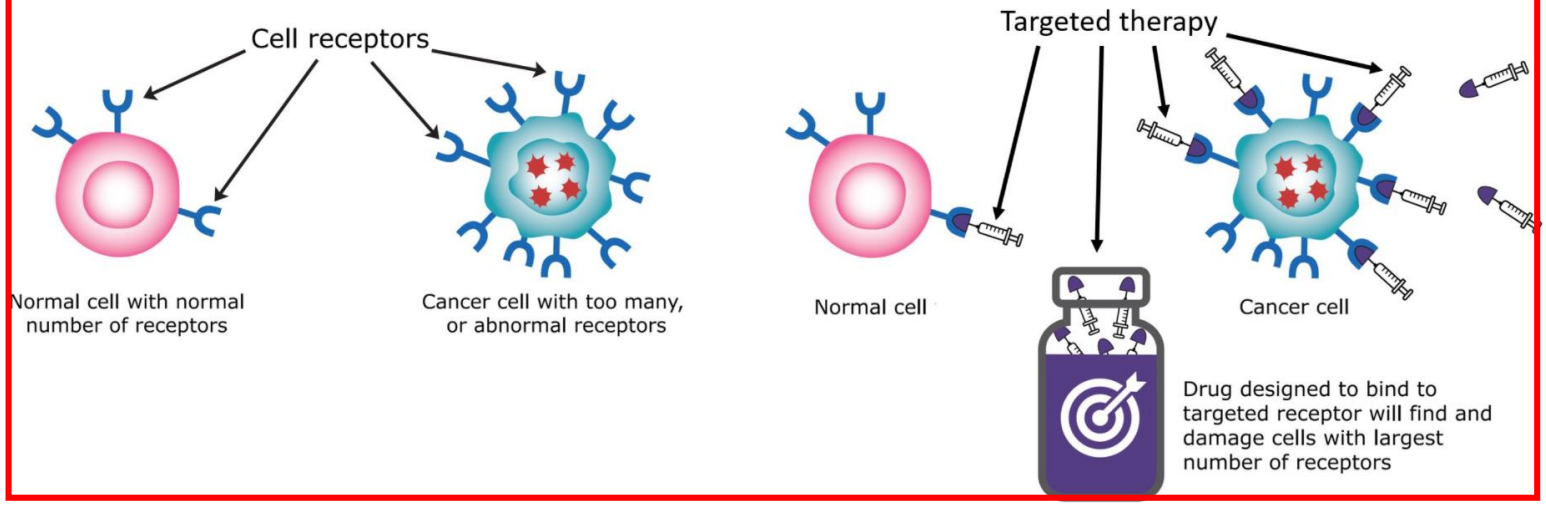
Onkoloogiline ravi

Keemiaravi



- Tapab kõiki kiiresti paljunevaid rakke
- Tõsised kõrvaltoimed
- Enamasti veenikaudne ravi
- Tekib resistentsus

Sihtmärklaud ravimid

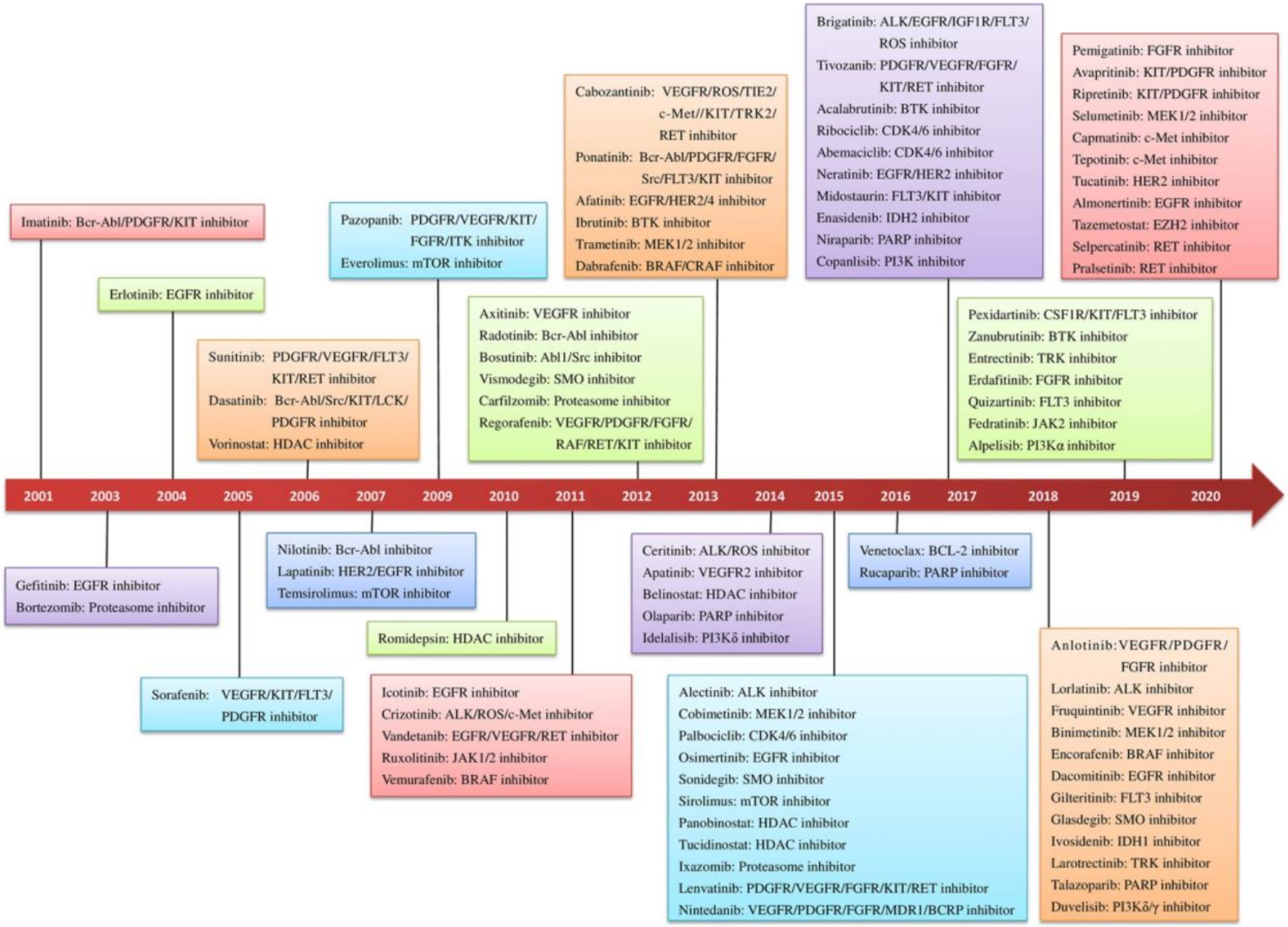


- Tapab vaid rakke kus vastav geneetiline mutatsioon
- Leebed kõrvaltoimed ja hästi talutav
- Enamasti tablettravi
- Tekib resistentsus

2019 seisuga **64** sihtmärklaud ravimit **24** molekulaarse muutuse vastu

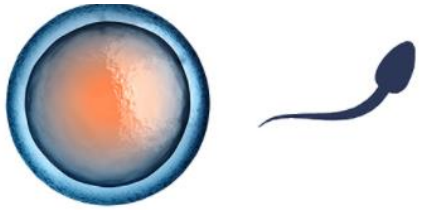
https://www.facingourrisk.org/uploads/targeted-therapy.JPG
https://www.lungevity.org/for-patients-caregivers/navigating-your-diagnosis/treatment-options/chemotherapy

Sihtmärklaud ravimid 2001-2021

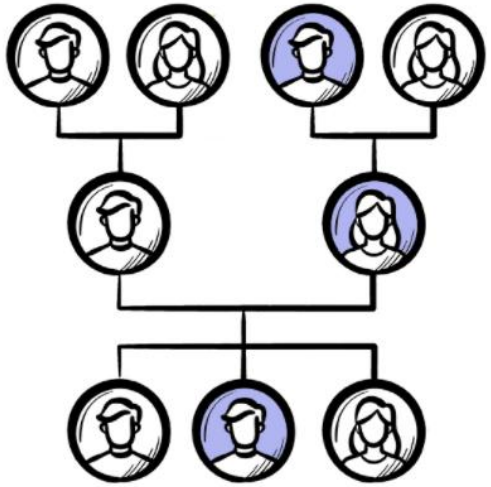


Small molecules in targeted cancer therapy: advances, challenges, and future perspectives

Iduliini vs somaatilised muutused

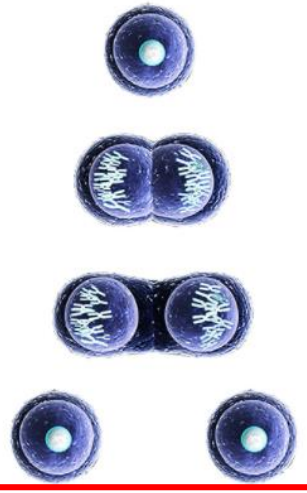


Iduliini mutatsioonid -10%



- Pärilikud ehk iduliini mutatsioonid esinevad sugurakkudes
- Tõstavad riski haigestuda teatud kasvajatesse
- n.BRCA1/2 ↑ 50% rinna/munasarjavähi risk

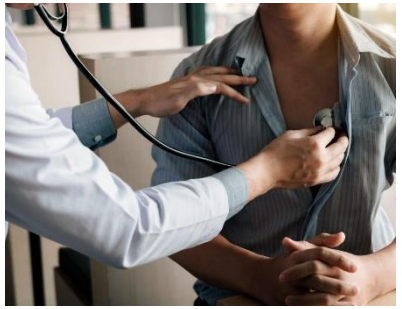
Somaatilised mutatsioonid – 90%

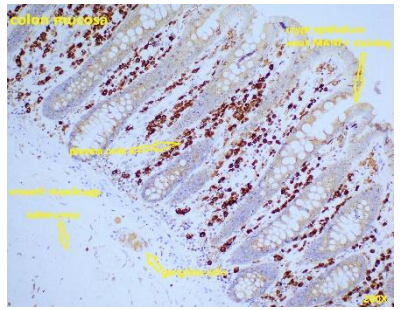


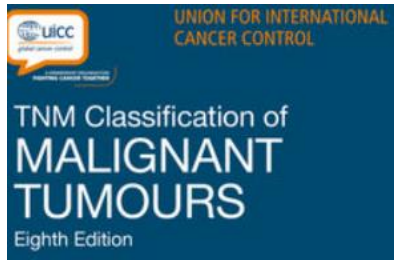
- Somaatilised mutatsioonid esinevad kasvajarakkudes
- Ei pärandu vanemalt lapsele
- Võimalik ravida “sihtmärklaud rvimitega” n.BRAF mutatsioon ja dabrafenib melanoomi ravis

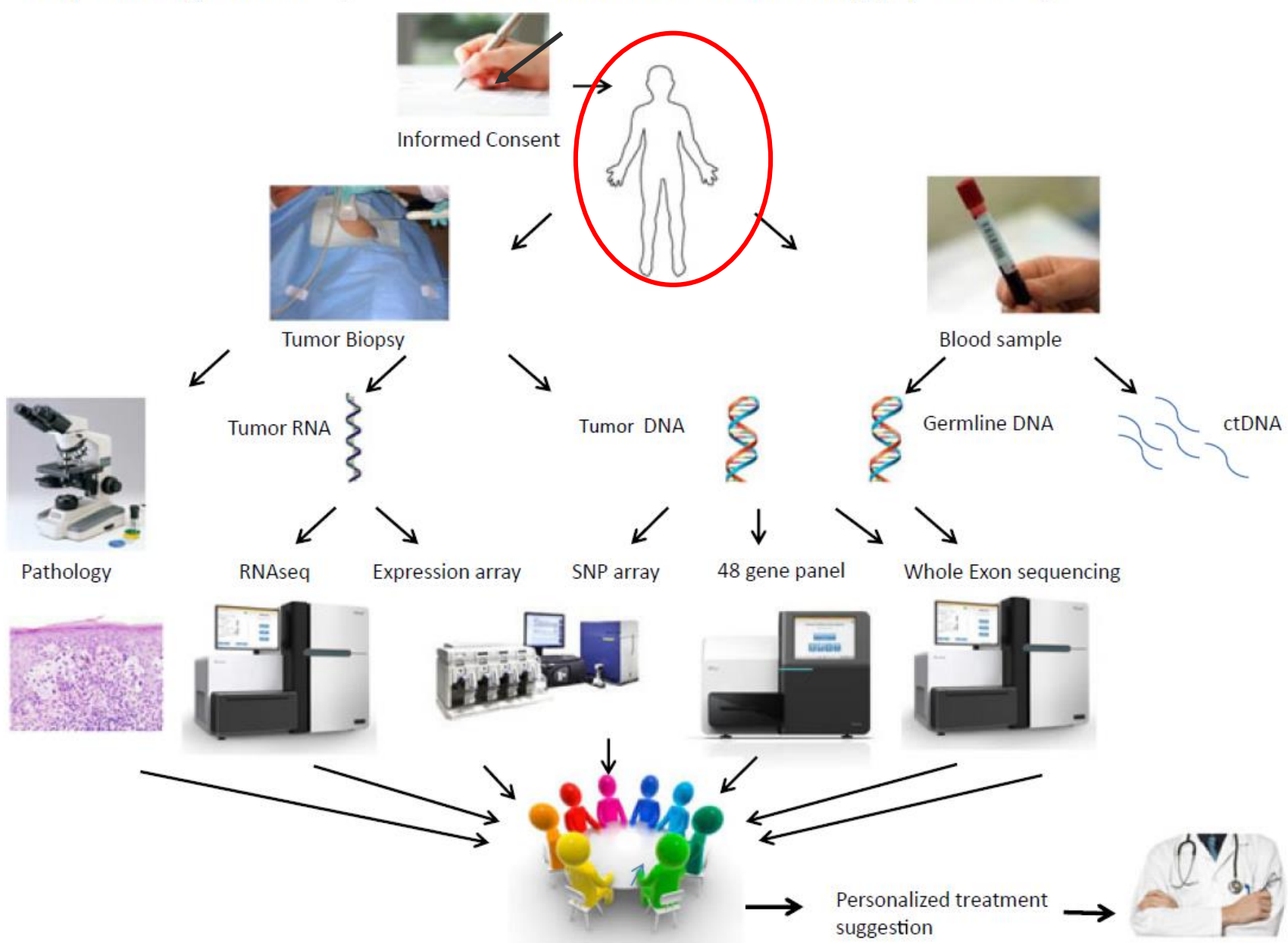
https://www.cancertodaymag.org/Pages/cancer-talk/Misunderstandings-About-Cancer-DNA-Tests.aspx

Personaliseeritud onkoloogia





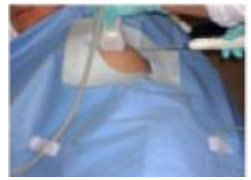




Personalized oncology: Genomic screening in phase 1. 2014 APMIS. 122. 10.1111/apm.12293.

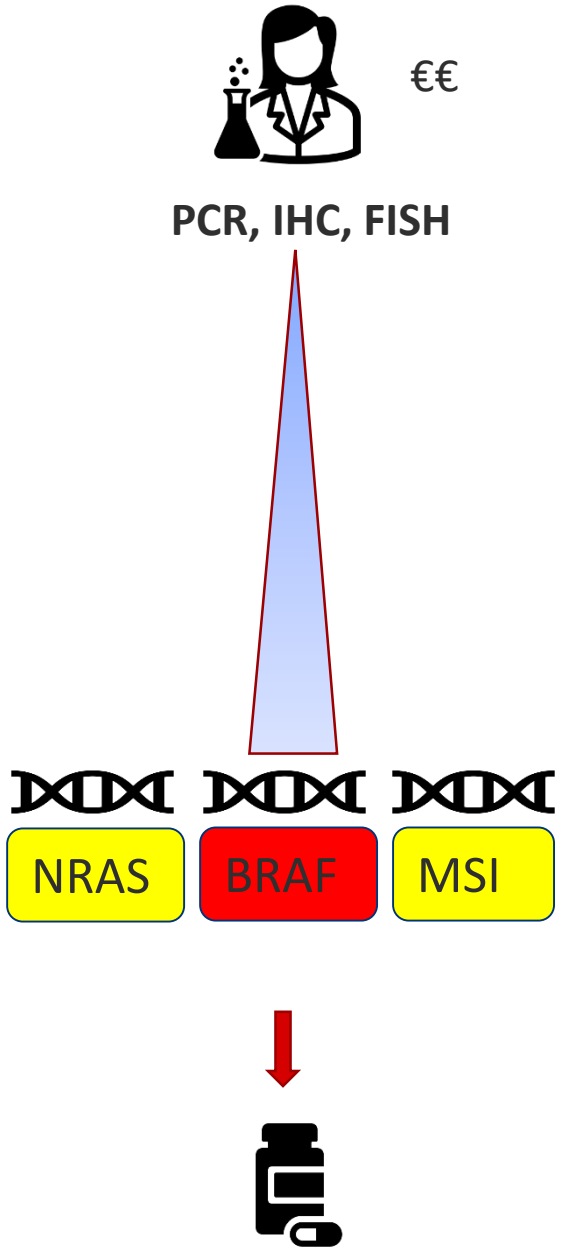
Mõisted

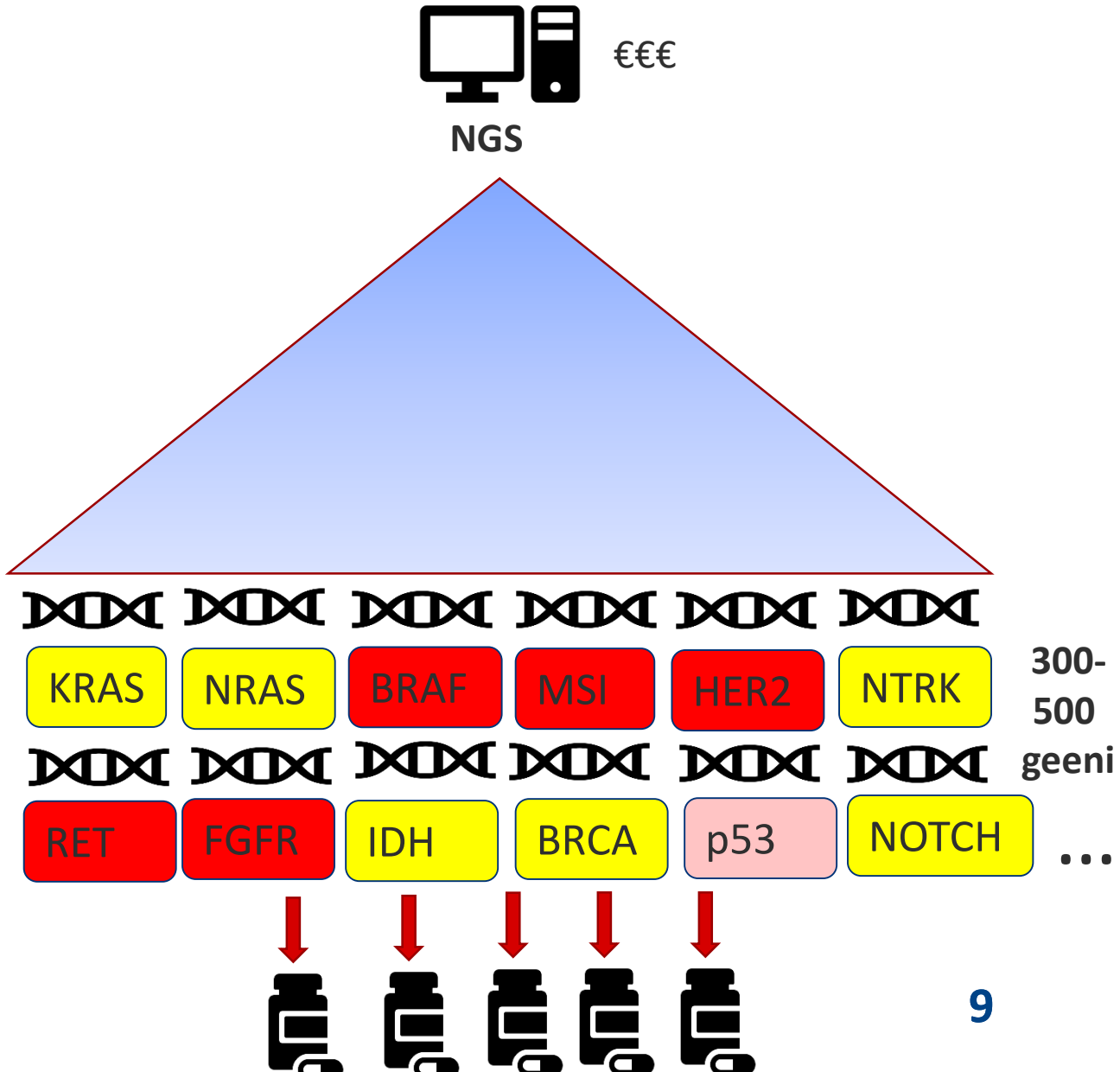
- Molekulaarne analüüs
- Mutatsioonide määramine
- Kasvajakoe profileerimine vs verest nn. “liquid biopsy”



- Uue põlvkonna sekveneerimine (Next Generation Sequencing- NGS)
- Üksikute geenide määramine
- Geenipaneelide testid (300-500 geeni korraga) (FMI, Illumina jt)
- Kogu genoomi/eksoomi analüüs

Üksikute geenide analüüs vs geenipaneelid





Tervishoiu toimetised

Terviseinfo
analüüsigrupp

Geenitestid kasvajate ravivalikutes

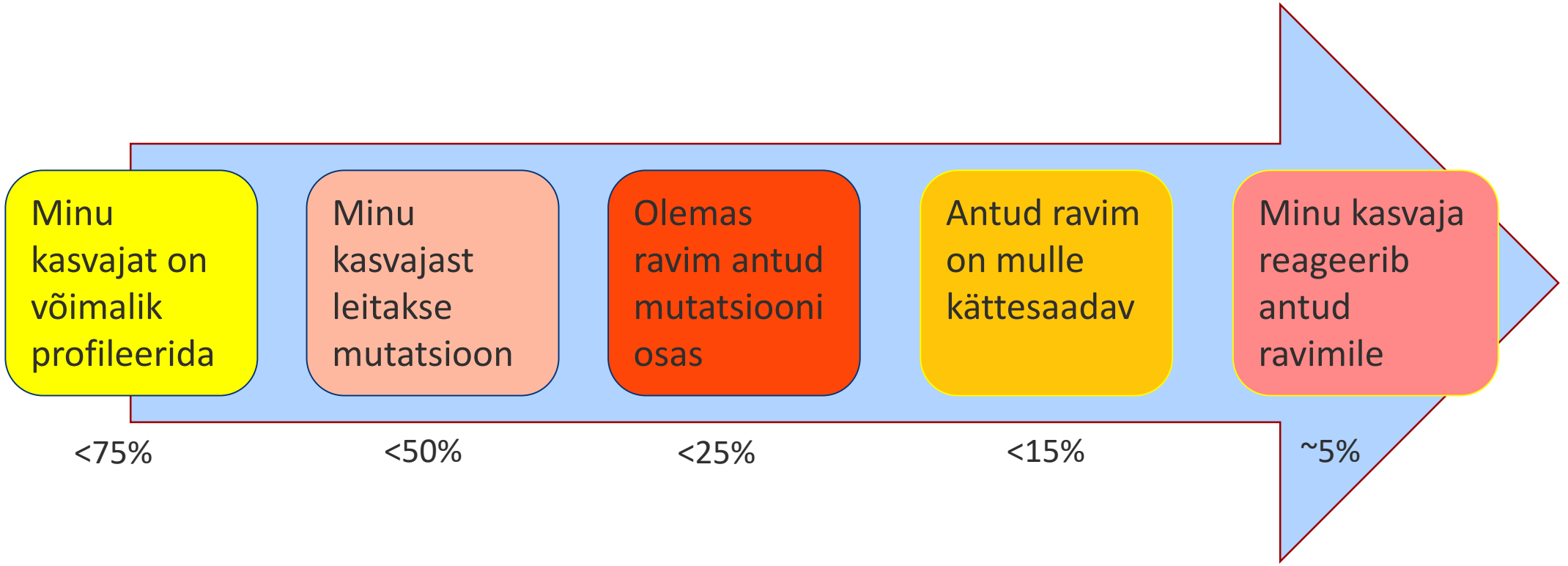
Tervisetehnoloogia hindamise raport TTH50

Milliseid patsiente testida?

Ei ole näidustatud	Teatud juhtudel näidustatud	Ei ole näidustatud
Varajases staadiumis/lokaalsed kasvajad, mille puhul tehakse tervistavat ravi	• IV st kopsuvähk • kolorektaalvähk • prostata • munasari • sapiteed	Kiirelt progres-seeruv kasvaja
	Haruldased kasvajad (n.CUP, sarkoomid)	Halb üld-seisund ECOG >3
	Kliinilised uuringud Standard ravi ammendunud	Oodatav elumus on lühike

EClinicalMedicine 2020 25 (DOI10.1016/j.eclinm.2020.100487)

Patsientide ootused ning nõustamine



- “Off label” ravimite kasutus ei ole soovitav, kui puudub riiklik regulatsioon
- “Basket/umbrella” uuringud pooleli

FOUNDATIONONE®CDx

TUMOR TYPE
Colon adenocarcinoma (CRC)
COUNTRY CODE
EE

REPORT DATE
29 Mar 2020
ORDERED TEST #
ORD-0773569-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT

DISEASE Colon adenocarcinoma (CRC)

MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHY
MEDICAL FACIL
ADDITIONAL RI
MEDICAL FACIL
PATHOLOGIST

SPECIMEN

SPECIMEN SITE Colon
SPECIMEN ID X202003723/1 P1 3
SPECIMEN TYPE Block
DATE OF COLLECTION 17 February 2020
SPECIMEN RECEIVED 11 March 2020

Genomic Signatures

Microsatellite status - MS-Stable
Tumor Mutational Burden - 6 Muts/Mb

Gene Alterations

For a complete list of the genes assayed, please refer to the Appendix.

KRAS wildtype
NRAS wildtype
ERRFI1 rearrangement exon 4
PTEN P248fs*5

3 Disease relevant genes with no reportable alterations: *BRAF, KRAS, NRAS*

2 Therapies approved in the EU
0 Therapies with Lack of Response
11 Clinical Trials

GENOMIC SIGNATURES	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Genomic Signatures section
Tumor Mutational Burden - 6 Muts/Mb	**No therapies or clinical trials.** see Genomic Signatures section

GENE ALTERATIONS	THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)		THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
KRAS - wildtype	Cetuximab	2A	none
0 Trials	Panitumumab	2A	
NRAS - wildtype	Cetuximab	2A	none
0 Trials	Panitumumab	2A	
ERRFI1 - rearrangement exon 4	none		none
1 Trial *see p. 6*			
PTEN - P248fs*5	none		none
10 Trials *see p. 7*			

☐ *NCCN category*

FOUNDATIONONE®CDx

TUMOR TYPE
Colon adenocarcinoma (CRC)

REPORT DATE
29 Mar 2020

ORDERED TEST # ORD-0773569-01

GENOMIC FINDINGS

GENE
KRAS

ALTERATION
wildtype

POTENTIAL TREATMENT STRATEGIES

Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab[46-49] or panitumumab[50-52] in patients with CRC. Therefore, these agents are indicated for treatment of patients with CRC lacking such mutations (NCCN Guidelines v2.2019).

FREQUENCY & PROGNOSIS

Approximately 50-65% of colorectal cancers (CRCs) have been reported to lack KRAS mutations[53-61]. Numerous studies have reported that KRAS wild-type status is associated with decreased metastasis, better clinicopathological features, and longer survival of patients with CRC[55-58,62-63].

FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[64-65]. No alterations in KRAS were identified in this case.

GENE
NRAS

ALTERATION
wildtype

POTENTIAL TREATMENT STRATEGIES

Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab[46-49] or panitumumab[50-52] in patients with CRC. Therefore, these agents are indicated for treatment of patients with CRC lacking such mutations (NCCN Guidelines v2.2019).

FREQUENCY & PROGNOSIS

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations[17,61,66-71]. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis[61] and longer survival[71-72] of patients with CRC.

FINDING SUMMARY

NRAS encodes a member of the RAS family of small GTPases that mediate transduction of growth signals. Activation of RAS signaling causes cell growth, differentiation, and survival by activating the RAF-MAPK-ERK, PI3K, and other pathways[64]. No alterations in NRAS were identified in this case.

GENE
ERRFI1

ALTERATION
rearrangement exon 4

POTENTIAL TREATMENT STRATEGIES

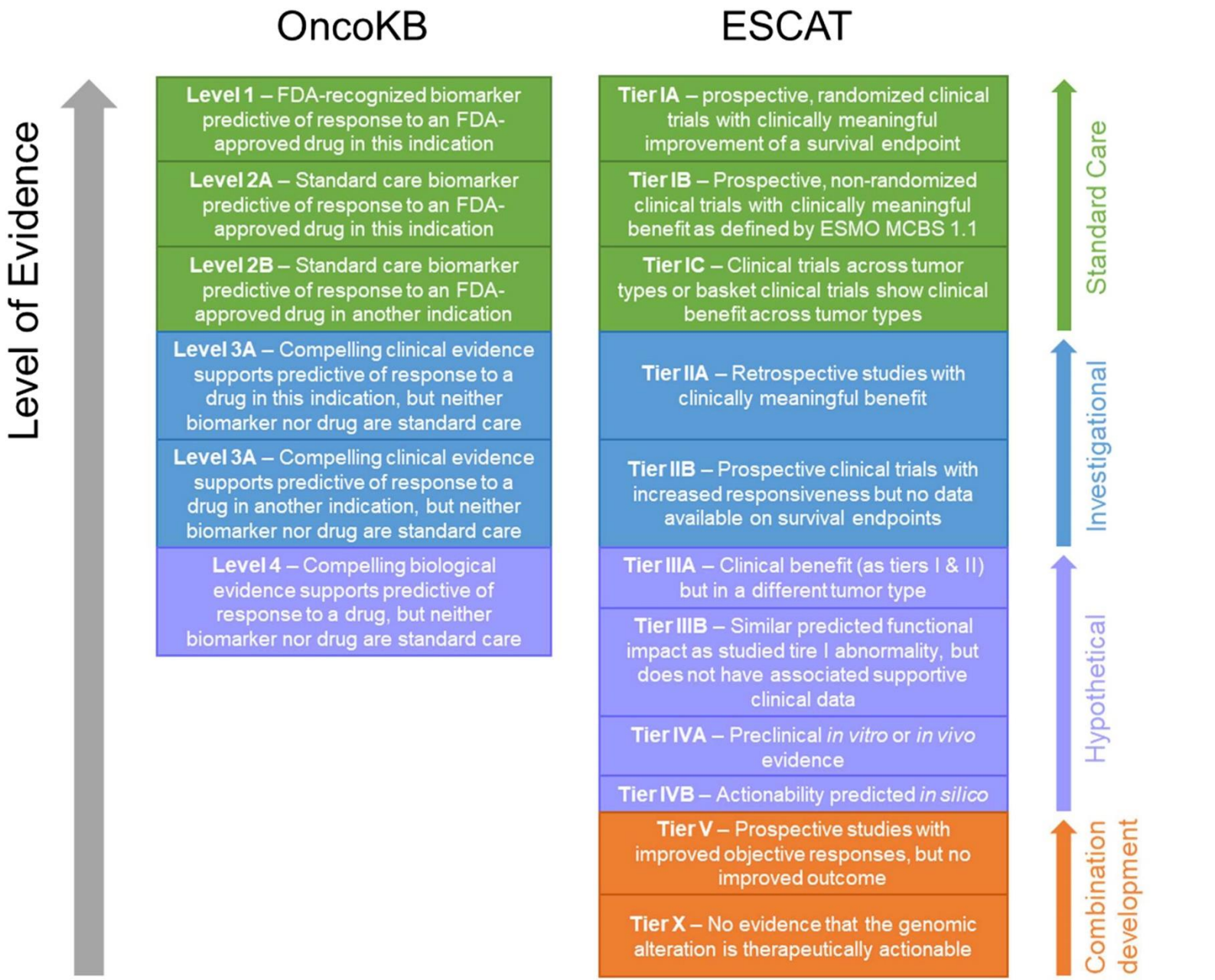
ERRFI1 loss or inactivating mutations may result in EGFR activation and predict sensitivity to ERBB tyrosine kinase inhibitors such as erlotinib, gefitinib, afatinib, and lapatinib, which are approved to treat lung or breast cancers. One patient with cholangiocarcinoma and an ERRFI1 loss of function mutation was reported to have a partial response to the EGFR inhibitor erlotinib[73]. In preclinical studies, the EGFR inhibitor gefitinib was reported to cause regression of tumors in ERRFI1 knockout mice[74] and inhibit signaling downstream EGFR in ERRFI1-depleted human cell lines[75].

FREQUENCY & PROGNOSIS

In the TCGA dataset, ERRFI1 mutation was observed in 1.3% of colorectal adenocarcinoma cases[17]. The prognostic significance of ERRFI1 in the context of colorectal cancer has not been an active area of investigation (PubMed, Jul 2019).

FINDING SUMMARY

The ERRFI1 gene (also known as MIG6 or RALT) encodes a tumor suppressor that negatively regulates the ERBB family of receptors[76-79], and is transcriptionally activated by RAS-RAF-ERK signaling[80]. ERRFI1 directly binds to the kinase domain of ERBB proteins and consequently antagonizes their oncogenic signaling and cell proliferation[76-79]. ERRFI1 also negatively regulates signaling by promoting EGFR endocytosis and degradation[81-82]. Knockout or depletion of ERRFI1 was shown to result in EGFR and ERBB2/ERBB3 activation[74,80,82-83], and disruption of the ERRFI1 gene promoted tumorigenesis in mice[74,84], whereas overexpression of ERRFI1 inhibited EGFR- or ERBB2-mediated signaling and oncogenic transformation in vitro[82,85-86]. ERRFI1 mutations that disrupt the region required for inhibition of ERBB receptor tyrosine kinase activity (amino acids 337-412), such as observed here, are predicted to be inactivating[76,78].



Abbreviations: ESCAT, European Society for Medical Oncology Scale for Clinical Actionability of Molecular Targets; ESMO MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; FDA, U.S. Food and Drug Administration.

Published in: Allen Li; Stephen M. Schleicher; Fabrice Andre; Zahi I. Mitri; *American Society of Clinical Oncology Educational Book* 4030-43.

Kasvajate molekulaarne nõukoda

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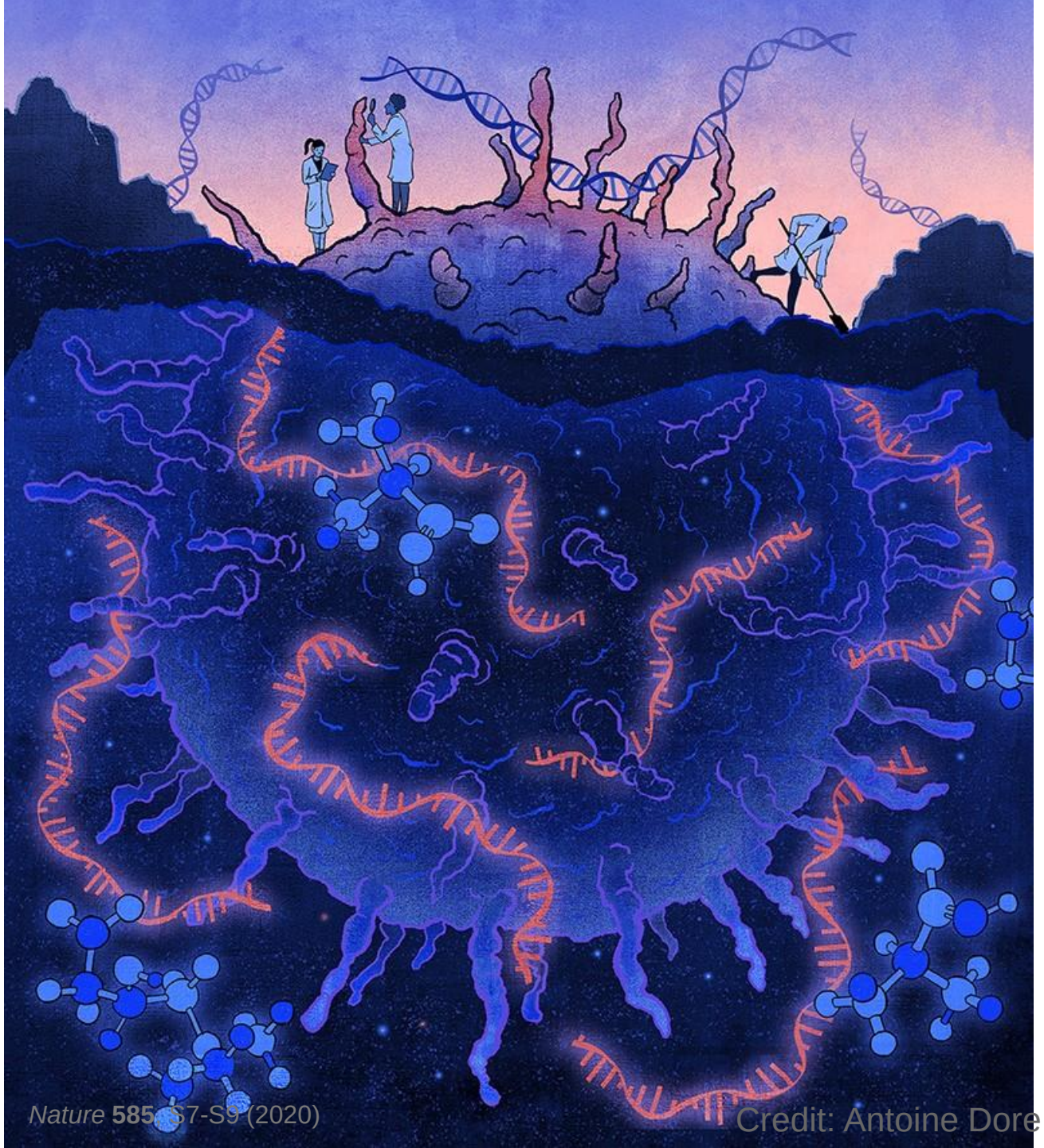
Institute for Molecular Medicine Finland
Nordic EMBL Partnership for Molecular Medicine
HiLIFE UNIT

Nature **585**, S16-S18 (2020)

Credit: Antoine Doré



Nature **585**, S7-S9 (2020)

Credit: Antoine Dore