Personalised medicine in digestive cancers

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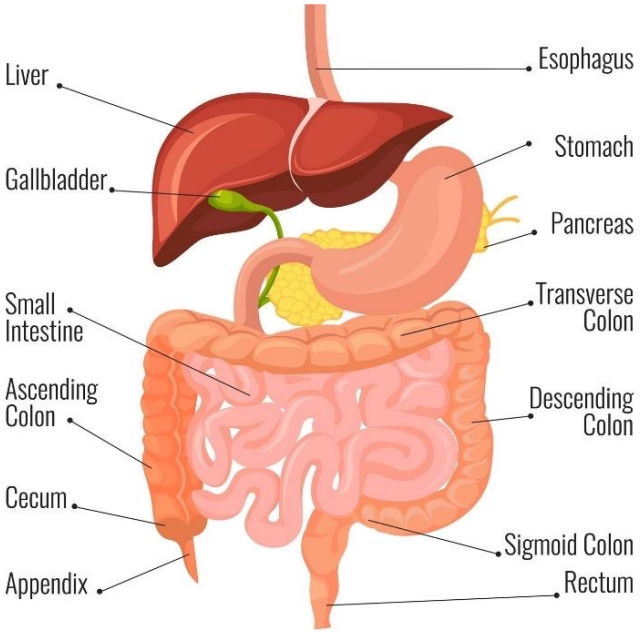
Outline

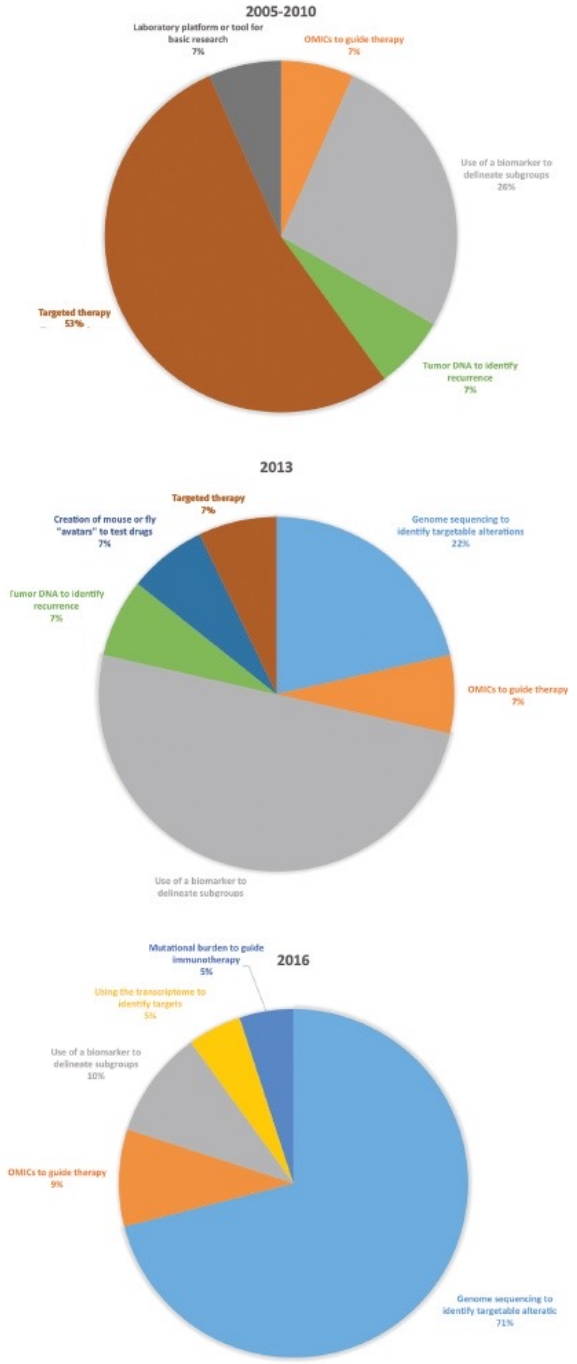


- Personalised medicine: definition
- ESCAT level of evidence
- Agnostic Biomarkers
- Upper GI Biomarkers
- Lower GI Biomarkers
- Personalised medicine: a different perspective

What is personalised medicine (in oncology)?

"The goal of precision medicine is to deliver the right cancer treatment to the right patient at the right dose and the right time. "

Schwartzberg et al 2017 asco.org/edbook
ASCO EDUCATIONAL BOOK



Use of the term ‘Precision Oncology’ over time

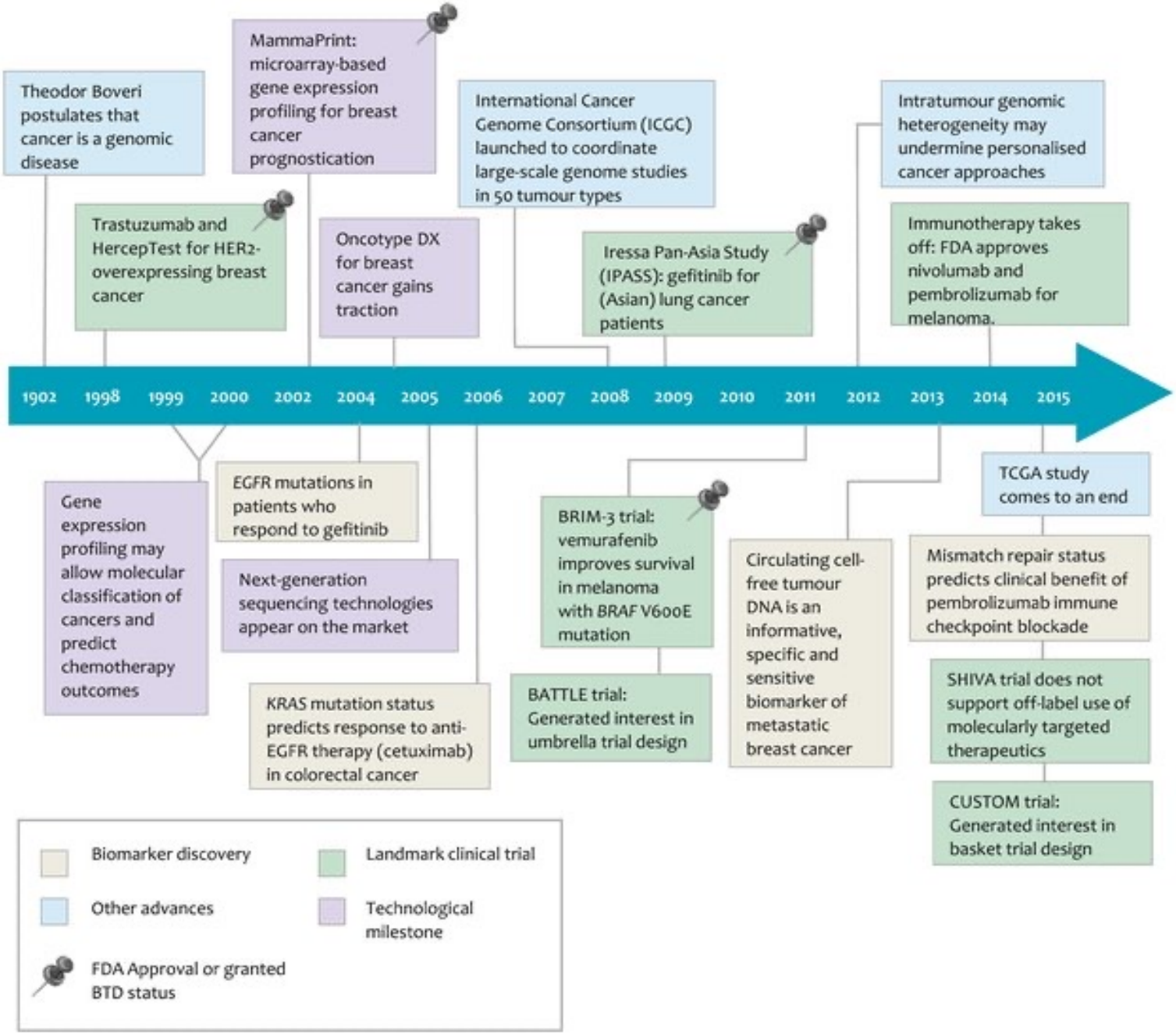
Google Scholar query for the term “precision oncology” over 3 time-intervals

2005-2010 **Use of targeted therapies** → vascular endothelial growth factor (VEGF) inhibitors (bevacizumab) or *BCR/ABL1* inhibitors (imatinib). This use has largely ceased.

2013 **Using data from analyses of biomarkers**.
Examples: the use of crizotinib in patients with lung cancer harbouring EML4-ALK rearrangements
adjuvant chemotherapy guided by genomic testing e.g. the Oncotype DX panel in women with breast cancer

2016 **Using data from next-generation sequencing** to **guide therapies**, a definition that was used in 15 of 21 articles reviewed, all published since January 1, 2016.

V.Prasad and RP Gale
ascopost.com/issues/january-25-2017



Precision oncology timeline

Syn et al 2017 exp opin on drug met

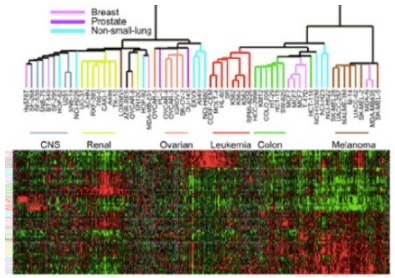
What is a biomarker?

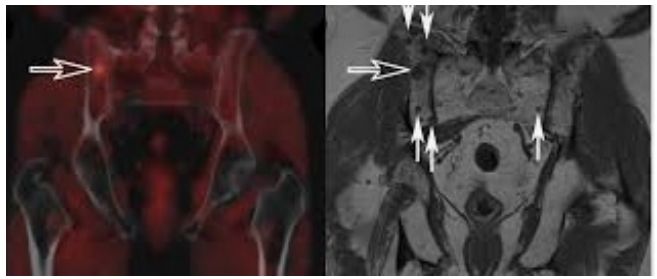
"A characteristic that is objectively measured and evaluated as an indicator of a physiological or pathogenic process or pharmacologic response to therapeutic intervention "

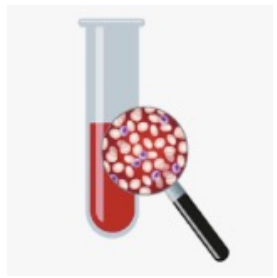
1998 NIH Biomarkers definition Working Group

A quantifiable parameter providing insight into a biologic process

Discovery → **Confirmation** → **Validation** → **Adoption**







What is a biomarker?

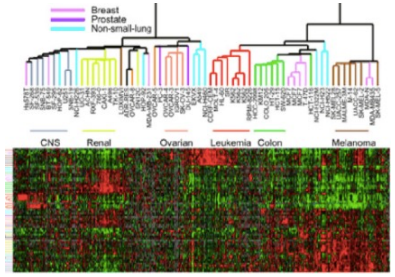
Prognostic

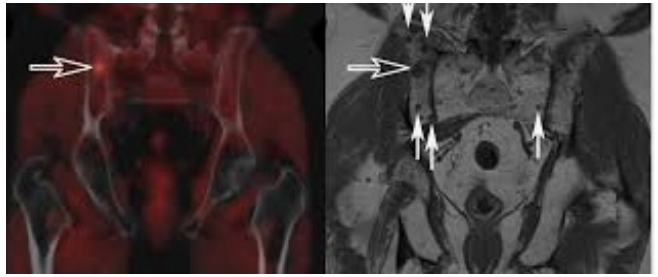
- Indicates likely the course of the disease, **indipendently of treatemnt**
- Inform about an estimate of **outcome** probability
- **Not a predictor of treatment benefit**

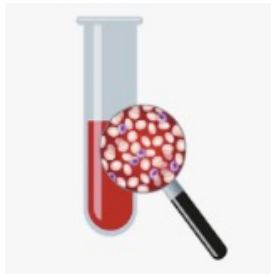
Predictive

- Associated with response / lack of **benefit to a treatment**
- Inform about **treatment efficacy** in a specific population

Discovery → **Confirmation** → **Validation** → **Adoption**







Ravello trial

Report from NGS Panel

Genomic Signatures

Microsatellite status - MSI-High

Tumor Mutational Burden - TMB-High (61 Muts/Mb)

Gene Alterations

For a complete list of the genes assayed, please

KRAS wildtype
NRAS wildtype
FBXW7 S668fs*39
PTEN Y76del
RNF43 G659fs*41, R145*
STK11 E57fs*106
ARID1A T1917A, G276fs*87
ASXL1 G645fs*58
CDH1 F462fs*19
CIC T1541fs*79
CREBBP V95fs*29
FAM46C A232T
FLCN H429fs*39, W306*
KDM6A R1351*
MLH1 R226*
MLL2 P2354fs*30
MSH3 splice site 1897-1G>A, K383fs*32
MSH6 Y524fs*1, F1088fs*2, R361H
SDHA R379C
TP53 R248Q

Gene Alterations (unknown significance)

APC N944T	***ARID1A*** G187S	***AXIN1*** G265fs*149	***AXL*** H292fs*5
BCOR R1136C	***BRCA2*** A2351T and S1437N	***CBL*** T231I	***CD22*** splice site 1771+2T>C
EPHA3 K713T	***EPHB4*** V330M	***ERBB4*** R1273Q	***FGFR4*** N228S and R54C
HGF G375D and R178Q	***ID3*** S49T	***JAK3*** I955T	***KDM5A*** E1137fs*13 and R1051Q
LTK R647Q	***MPL*** R390C	***MTOR*** R2193C	***NF1*** R1396H
NKX2-1 S233G	***P2RY8*** A188T	***PARP1*** S507fs*17	***PDGFRB*** L726fs*7 and V886M
PIK3C2B E1507fs*12	***PIK3CA*** P397H	***PIM1*** P309L	***POLD1*** A223T and R465W
RET L1048fs*11	***RNF43*** G360D	***SDHA*** P477S	***SGK1*** M17I
SOX9 M109V	***SPOP*** A303V	***STK11*** E223K	***TET2*** S1776F
TSC1 R908W	***WT1*** E479K	***ZNF703*** A514S	

MSI-High
Chromatin remodeling

Patient 2001

Site: Naples (Pascale)

Annals of Oncology 0: 1–8, 2018
doi:10.1093/annonc/mdy263

Not all biomarkers have clinical implications

SPECIAL ARTICLE

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

J. Mateo[1], D. Chakravarty[2], R. Dienstmann[1], S. Jezdic[3], A. Gonzalez-Perez[4], N. Lopez-Bigas[4,5], C. K. Y. Ng[6], P. L. Bedard[7], G. Tortora[8,9], J. -Y. Douillard[3], E. M. Van Allen[10], N. Schultz[2], C. Swanton[11], F. André[12*] & L. Pusztai[13]

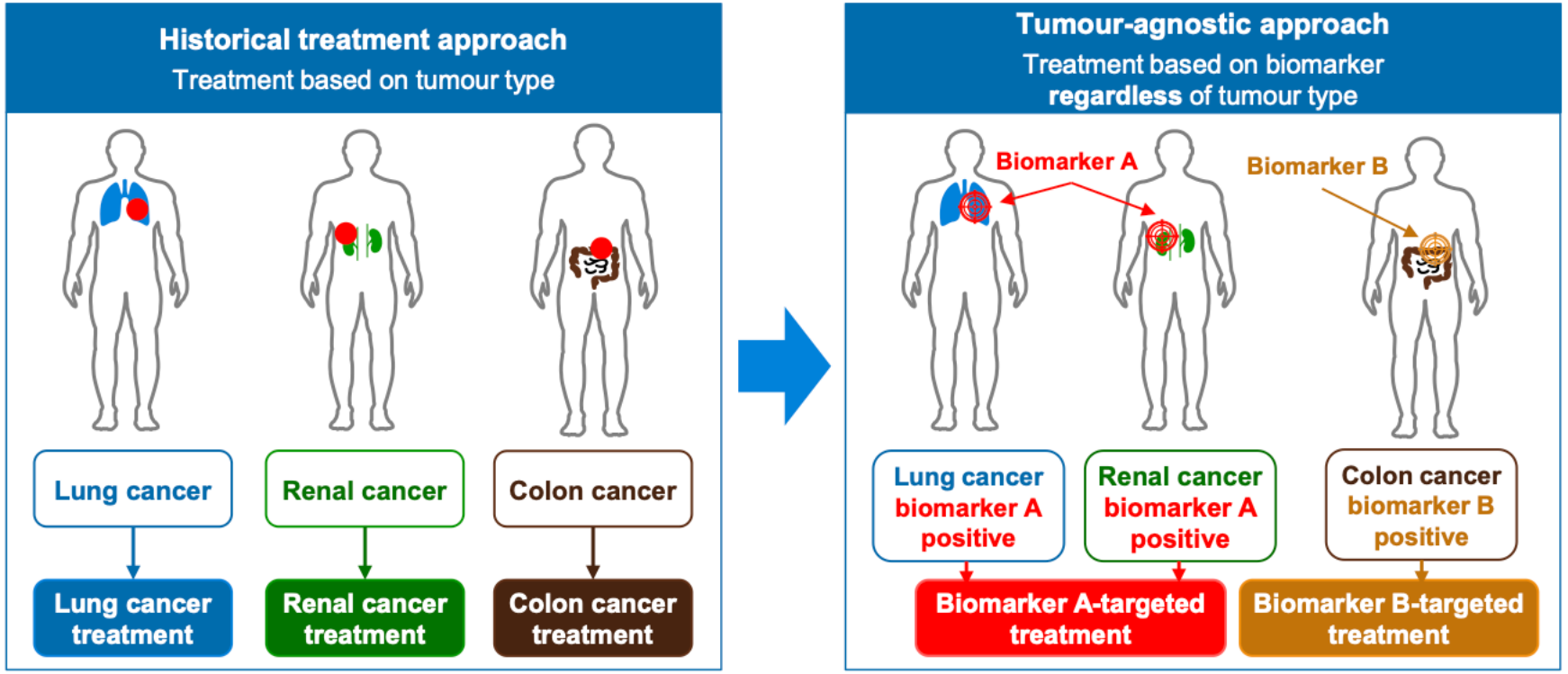
This first version of the ESMO Scale of Clinical Actionability for molecular Targets (ESCAT) defines six levels of clinical evidence

ESCAT levels of evidence

1. **ESCAT Tier I**: **Target suitable for routine use** and recommend specific drug when specific molecular alteration is detected
2. **ESCAT Tier II**: Investigational targets likely define a patient population that benefits from a targeted drug, additional data are needed
3. **ESCAT Tier III**: clinical benefit previously demonstrated in other tumour types or for related molecular targets
4. **ESCAT Tier IV**: Preclinical evidence of actionability
5. **ESCAT Tier V**: Evidence of relevant antitumour activity, not resulting in clinical meaningful benefit as single treatment but supporting development of co-targeting approaches
6. **ESCAT Tier X**: **Lack of evidence for actionability**.

Mateo et al 2018 Ann of Onc

Tumor Agnostic biomarkers



Tumor-agnostic therapy uses the same drug to treat all cancer types that have the genetic mutation (change) or biomarker that is targeted by the drug. It is a type of targeted therapy.

Rosas Oncol Ther 2020

Agnostic biomarkers

Several biomarkers have agnostic indication : MSI, TRK, TMB and, recently, BRAF

MSI-H / dMMR

NTRK

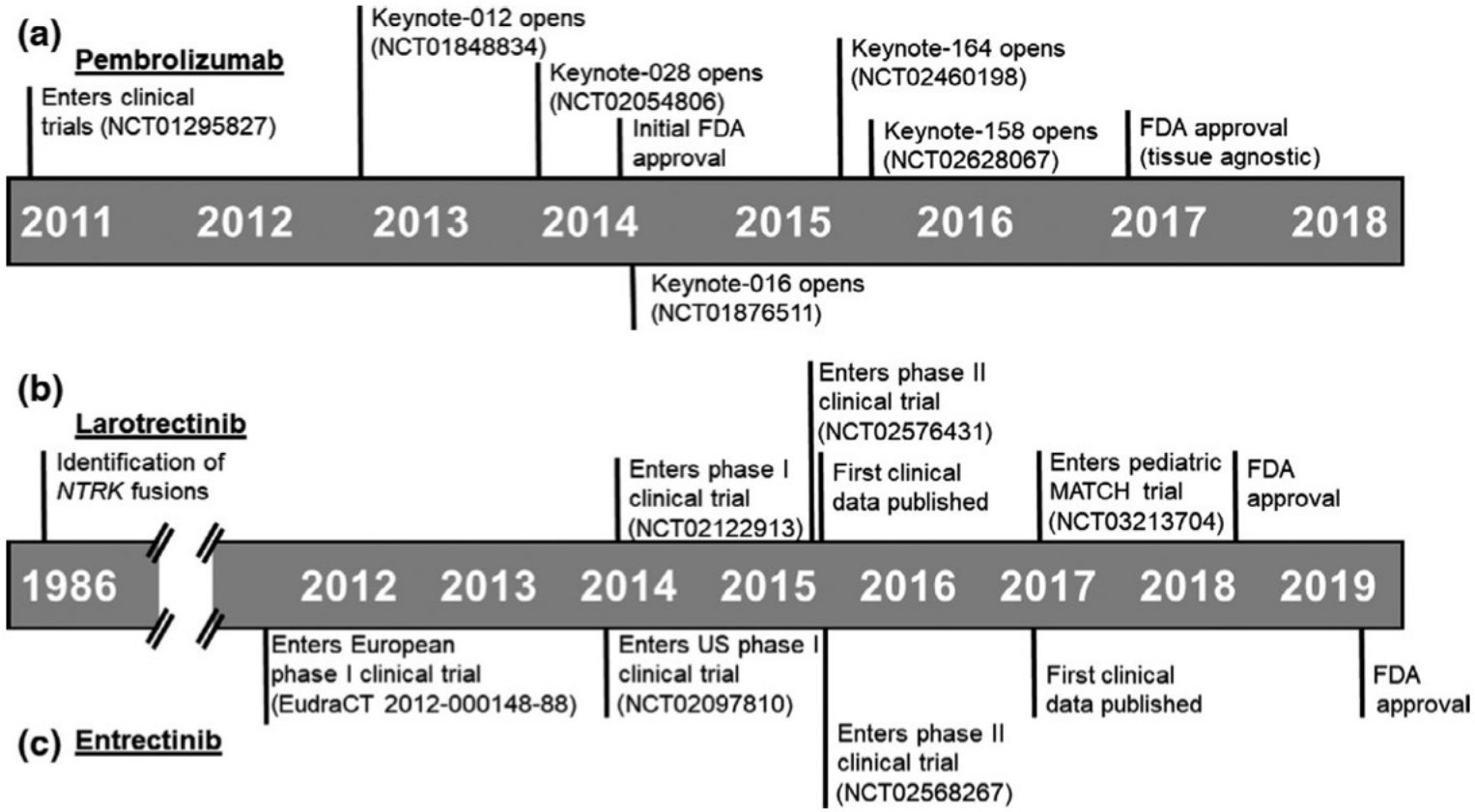
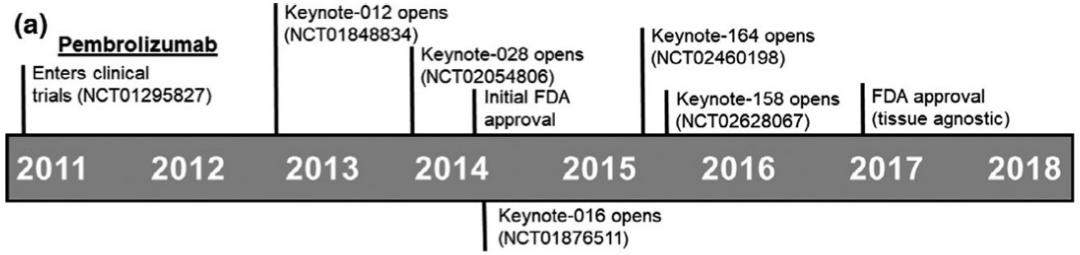


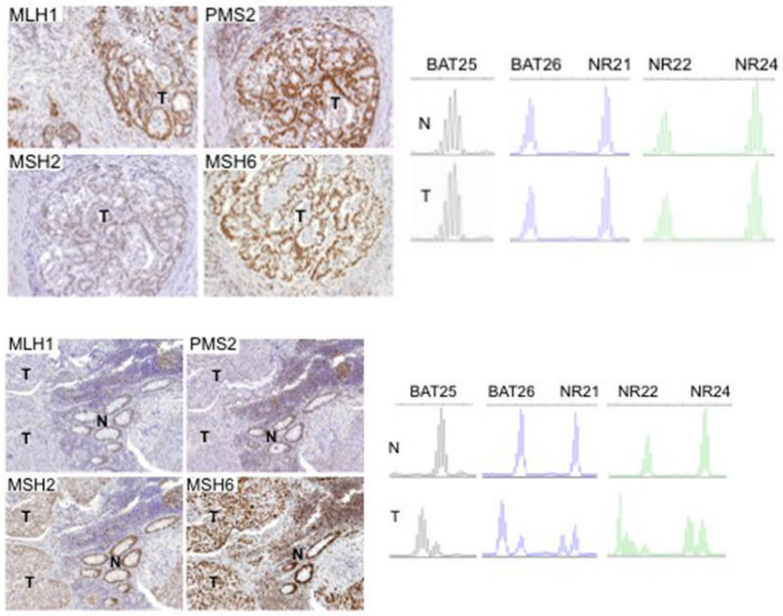
Figure 1 Clinical drug development timeline for FDA-approved tissue-agnostic therapies. Timeline of clinical development for current FDA-approved tissue-agnostic therapies including (**a**) pembrolizumab, (**b**) larotrectinib, and (**c**) entrectinib. FDA, US Food and Drug Administration.

MSI d-MMR



Techniques: IHC / PCR / NGS

IHC PCR



ESMO biomarker factsheet

MSI-H cancer cells may have a defect in the ability to correct mistakes that occur when DNA is copied in the cell.

MSI-H = microsatellite instability
dMMR = deficient mismatch repair

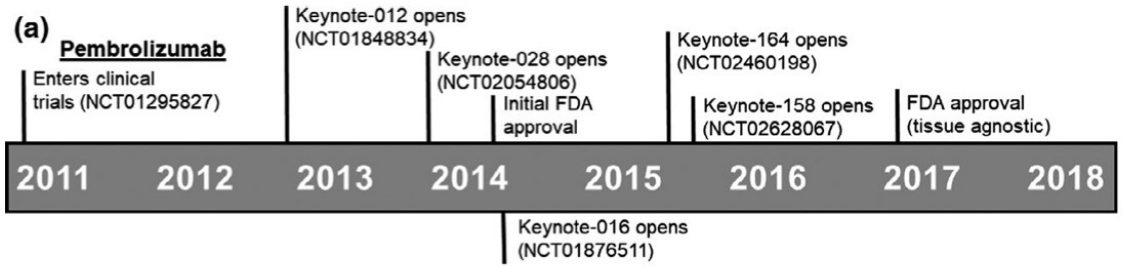
Causes of dMMR/MSI-H:

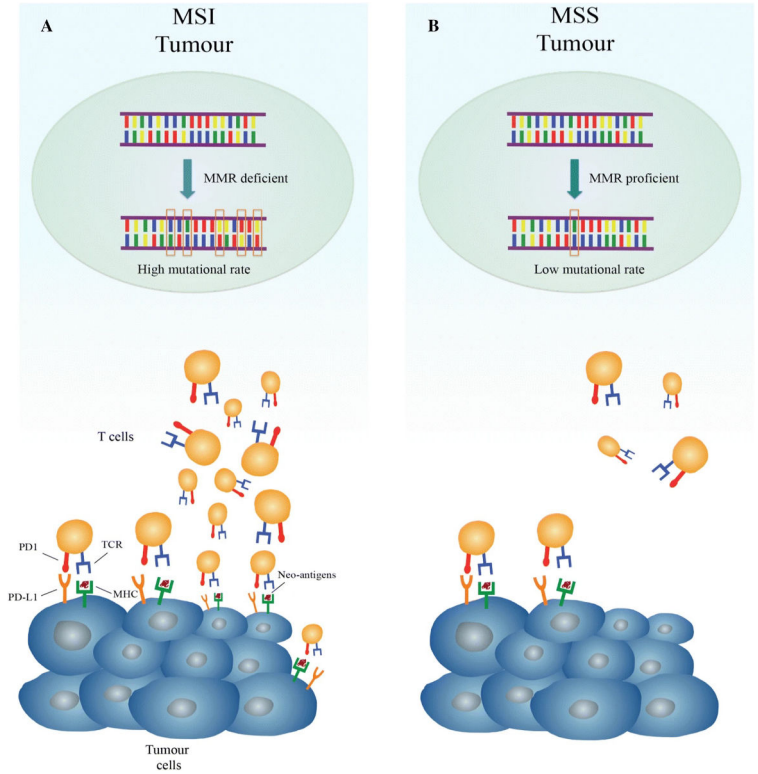
– Mutation in DNA repair proteins (Can occur in Lynch syndrome)
– Inactivation of DNA repair proteins

Frequency

- CRC 15%
- Gastric 15%
- Duodenal 10%
- esophageal 5% (Barret)
- Pancreas 1%

MSI d-MMR





Ratti et al 2021

Impairment in mismatch repair causes:

– ↑↑↑ mutations in tumors

– Some mutations (neo-antigens) may be targeted by immune system

Checkpoint inhibitors (i.e Pembrolizumab) can facilitate immune system response in MSI-H/dMMR cancers

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring,

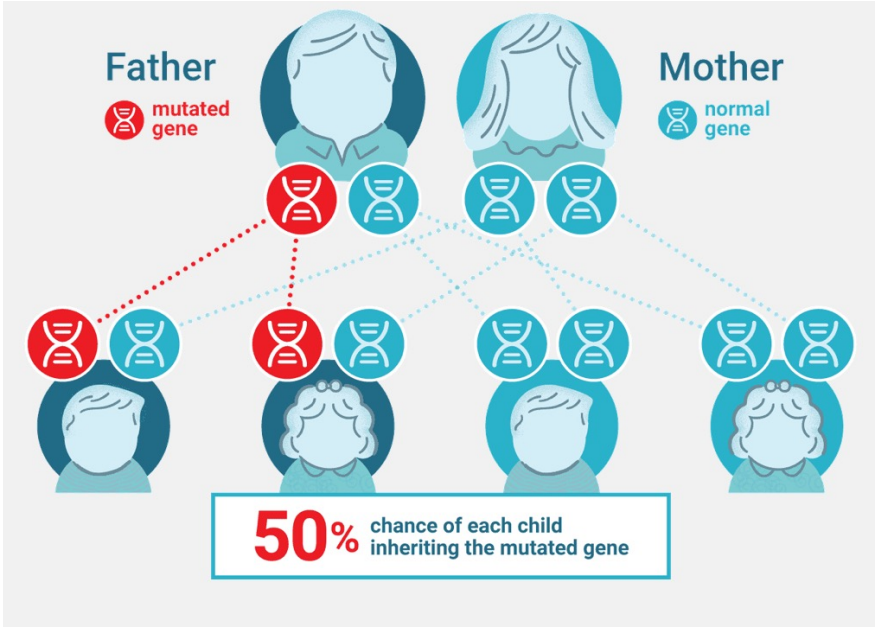
dMMR- MSIH (pooled data) - immunotherapy			
Cancer type	N	ORR	Duration response
CRC	90 (40%)	36%	1.6-22.1
Biliary	11 (7.4%)	46%	11.6-19.6
Gastric	9 (6%)	27%	5.8-22.1
Pancreatic	6 (4%)	56%	2.6-9.2
Esophageal	1 (0.7%)	na	18.2

Lynch Syndrome

MSI is also a diagnostic marker: useful to screen/ diagnose Lynch Syndrome

- Lynch syndrome, **hereditary** nonpolyposis colon cancer
- It is a common form of hereditary CRC (3–5% of CRC)
- Caused by autosomal dominant mutations to MMR genes (*MLH1, MSH2, MSH6* or *PMS2* and *EPCAM* gene that inactivates *MSH2)*

- In addition to CRC , Lynch syndrome is associated with other cancers, i.e endometrial, ovarian and gastric cancer.



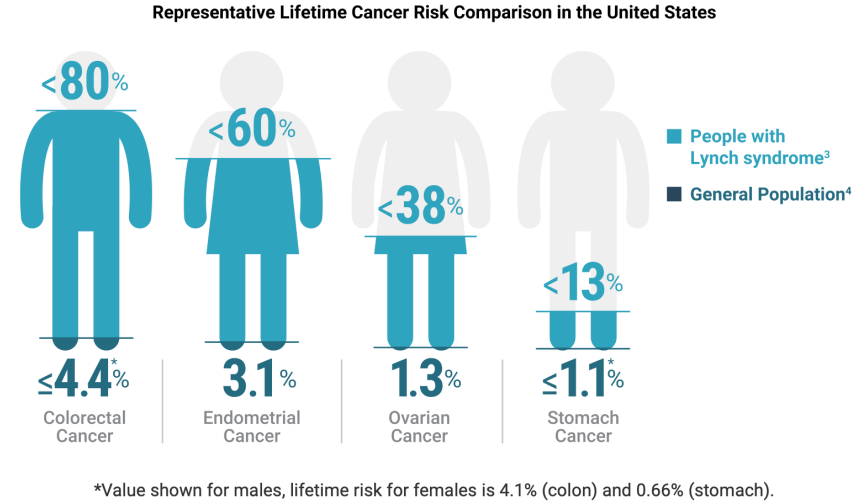
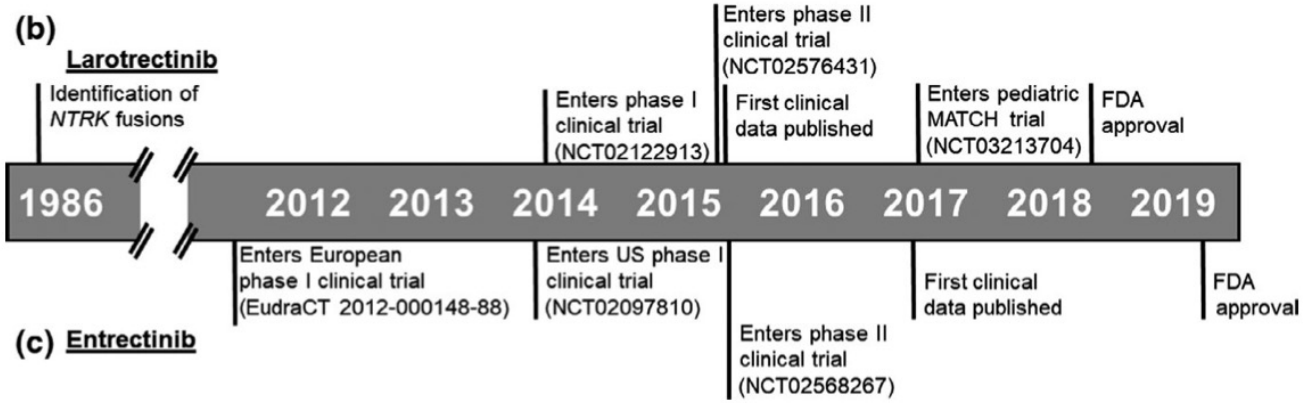
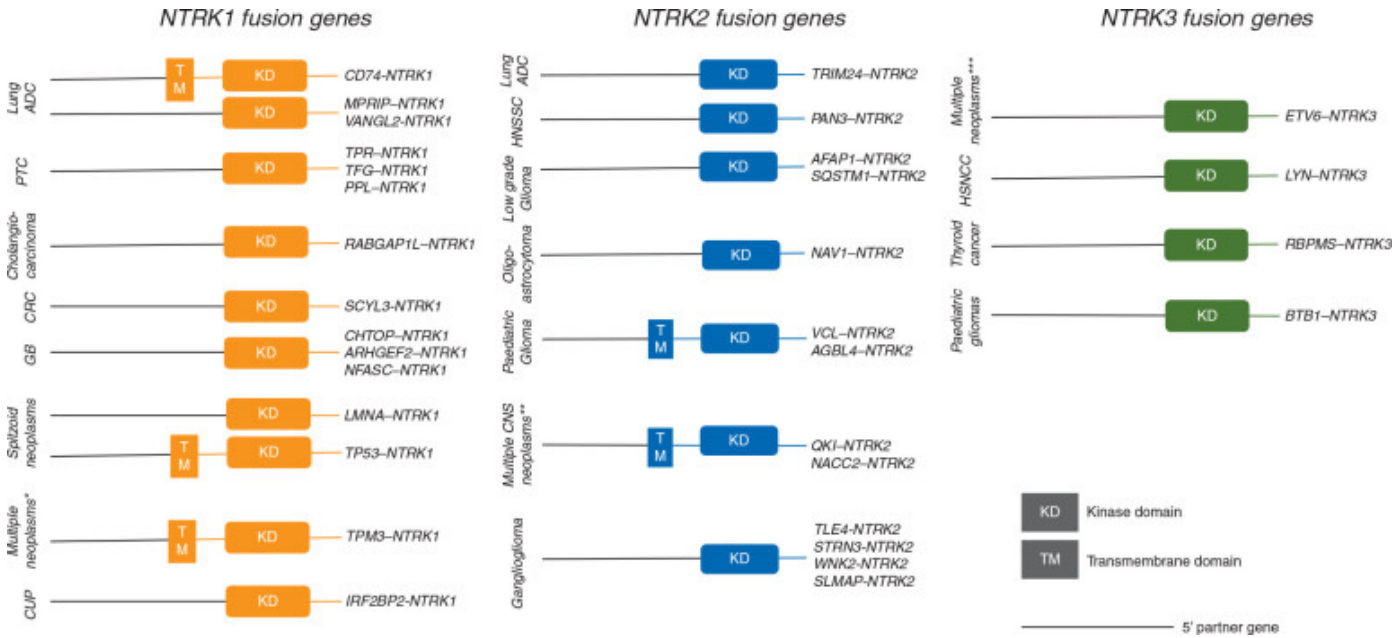


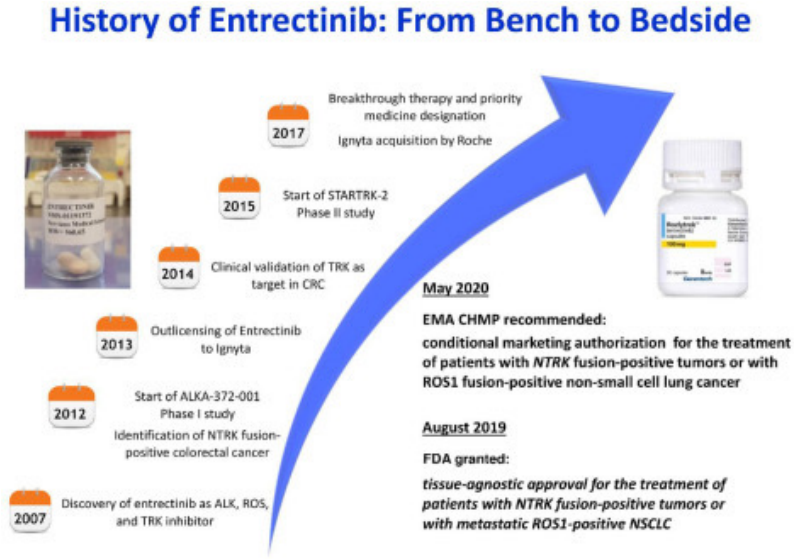
Image Source: Itapromega.it, last accessed 2.6.22

NTRK



1982: an inversion within chromosome 1 resulting in a fusion oncogene that was named *TRK* (tropomyosin receptor kinase)



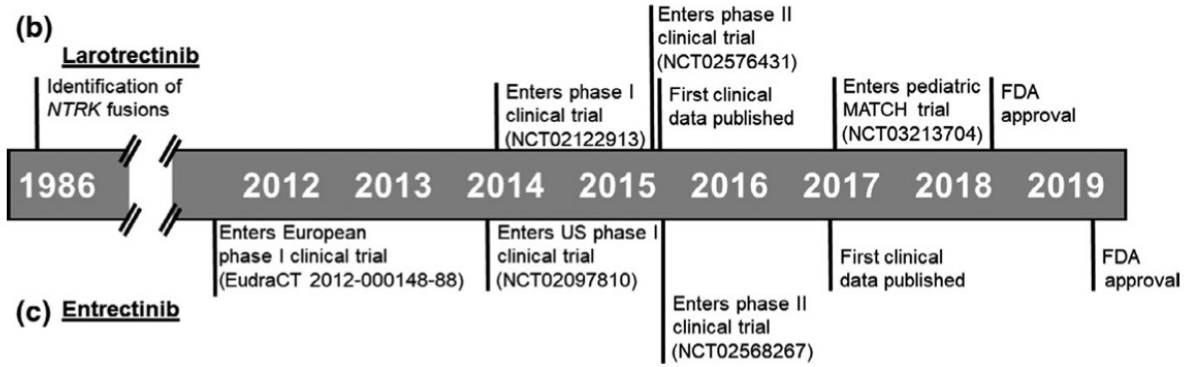


Frequency

<1%

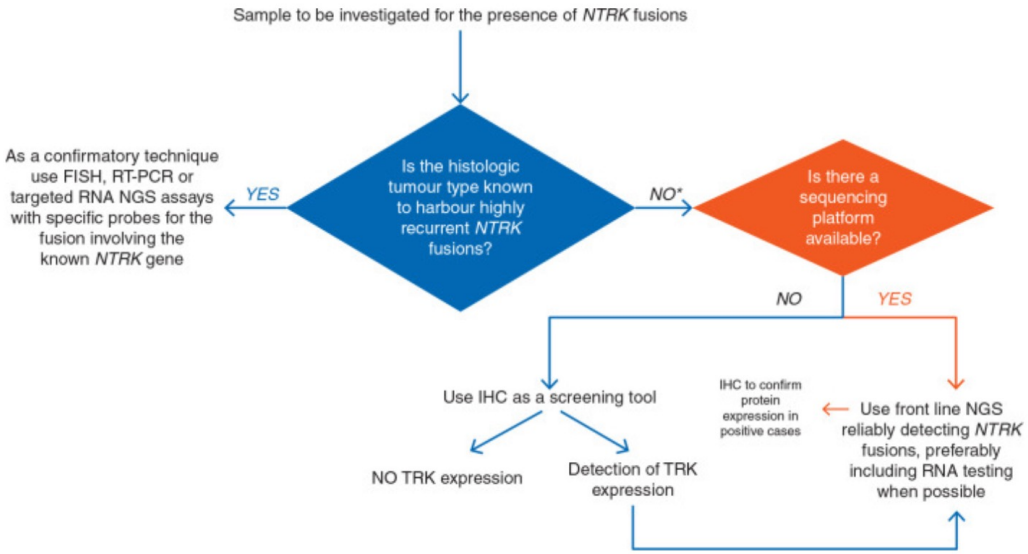
More common in MSI tumors

NTRK



Who? any malignancy at an advanced stage, in particular if it has been proven wild type for other known genetic alterations tested in routine practice, and especially if diagnosed in young patients'.

Techniques: IHC / FISH / RT-PCR/ RNA-and DNA-based NGS



Summary of the ESMO Translational Research and Precision Medicine Working Group recommendation

Marchio Ann of Onco 2021

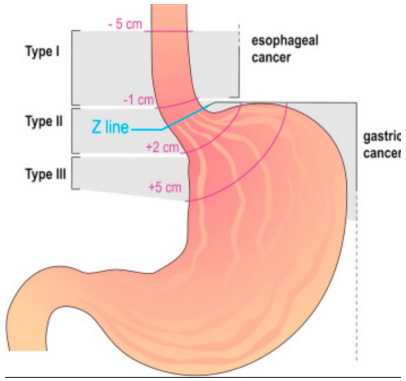
2 generations of TRK inhibitors

	EMA and FDA approved		Second Generation inhibitors			
	Larotrectinib	Entrectinib	Taletrectinib (DS-6051b/A8-106)	Repotrectinib (TPX-0005)	Selitrectinib (LOXO-195)	ICP-723
Targets	TRK A/B/C	TRK A/B/C, ROS1, ALK	TRK A/B/C, ROS1	TRK A/B/C, ROS1, ALK	TRK A/B/C	TRK A/B/C, ROS1
IC50 against TRK in vitro, nmol/L	9.8-25	0.1-1.7	3-20	<0.2	<5	Not reported
CNS penetration (Brain to plasma ratio in mice)	0.03-0.23	0.6-1	Not reported	0.028-0.057	0.017-0.025	Not reported
ORR %	74%	61%	Not reported	7/13 patients with NTRK mutation	9/20 patients with NTRK mutation	4/6 (dose escalation)
PFS, mo	29.4	13.8	Not reported	Not reported	Not reported	Not reported
Sensitivity to NTRK secondary mutation	No	No	Yes	Yes	Yes	Yes

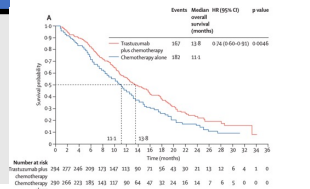
Harataka Clin Lung Cancer 2021, Drilon ASCO 2022, Wei ASCO 2022

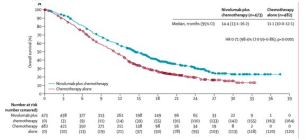
2022 ASCO ANNUAL MEETING #ASCO22

UPPER GI - Esophageal and Gastric cancer



Biomarker	Stage/ Prevalence	Technique	Actionability
HER2	IV / 15-25%	IHC , FISH, NGS	Anti-HER2
PDL1 (CPS)	IV	IHC	ICI
EBV	IV / 10%	ISH , PCR	NA
MSI	IV / 10%	IHC, PCR	ICI
NTRK	IV / <1%	IHC, NGS	Anti-NTRK





UPPER GI - Esophageal and Gastric cancer

Is it useful to order a NGS panel?

There is **no current need to perform tumour multigene NGS** in patients with mGC in daily practice.
Detection of MSI and NTRK fusions should be done using cheap standard methods.

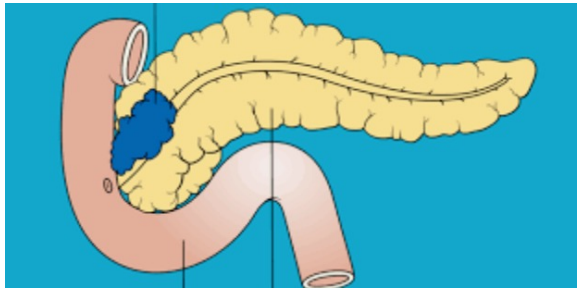
F. Mosele et al Ann of Onc 2020

Table 7. List of genomic alterations level I/II/III according to ESCAT in metastatic gastric cancer (mGC)

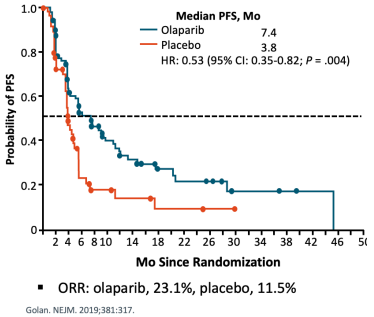
Gene	Alteration	Prevalence	ESCAT	References
ERBB2	Amplifications	16%	IA	The Cancer Genome Atlas Research Network. *Nature.* 2014[102] Bang Y-J, et al. *Lancet.* 2010[103]
	Hotspot mutations	3%	IIIA	Hyman D, et al. *Nature.* 2018[55]
	MSI-H	8%	IC	The Cancer Genome Atlas Research Network. *Nature.* 2014[102] Marcus L, et al. *Clin Cancer Res.* 2019[97]
NTRK	Fusions	2%	IC	Drilon A, et al. *N Engl J Med.* 2018[48]
EGFR	Amplifications	6%	IIB	Maron S, et al. *Cancer Discov.* 2018[104]
MET	Amplifications	3%	IIB	Lennerz J, et al. *J Clin Oncol.* 2011[105]
	Mutations	1.3%	IIIA	Lee J, et al. *Oncotarget.* 2015[107]
PIK3CA	Hotspot mutations	7%	IIIA	Juric D, et al. *J Clin Oncol.* 2018[90]
FGFR2	Amplifications	4%	IIIA	Van Cutsem E, et al. *Ann Oncol.* 2017[109] Loriot Y, et al. *N Engl J Med.* 2019[110]
ATM	Mutations	3%	IIIA	Bang Y-J, et al. *Lancet Oncol.* 2017[108]
BRCA1/2	Mutations	1%–5%	IIIA	Balasubramaniam S, et al. *Clin Cancer Res.* 2017[63]
ROS1	Fusions	<1%	IIIA	Shaw A, et al. *Ann Oncol.* 2019[46]
RET	Fusions	<1%	IIIA	Oxnard G, et al. *J Thorac Oncol.* 2018[106]
ERBB3	Hotspot mutations	3%	IIIB	Hyman D, et al. *Nature.* 2018[55]

ESCAT, European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets; MSI-H, microsatellite instability-high.

UPPER GI - Pancreatic cancer



Biomarker	Stage/ Prevalence	Technique	Actionability
BRCA 1-2	IV 3 % Germline Somatic	PCR, NGS	Platinum +/- olaparib
HER2	IV / <1%	IHC , FISH , NGS	Anti-HER2 (trial, off label)
MSI	IV / 5%	IHC, PCR	ICI
NTRK	IV / <1%	IHC, NGS	Anti-NTRK



UPPER GI - Pancreatic cancer

Is it useful to order a NGS panel?

It is not currently recommended to perform tumour multigene NGS in patients with advanced PDAC in daily practice.

Considering the unmet medical needs and the high number of alterations ranked as level IIeIV, ESMO considers it is the mission of clinical research centres and their networks **to propose multigene sequencing to patients with advanced PDAC in the context of molecular screening programmes, in order for patients to get access to innovative drugs.**

If multigene sequencing is not carried out, detection of MSI and NTRK fusions should be done using cheaper standard methods, pending drugs are approved and reimbursed.

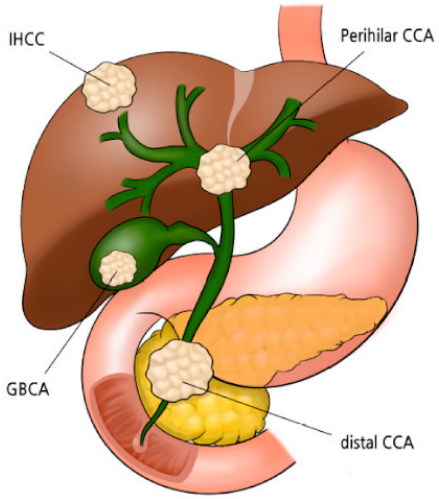
F. Mosele et al Ann of Onc 2020

Table 8. List of genomic alterations level I/II/III according to ESCAT in advanced pancreatic ductal adenocarcinoma (PDAC)

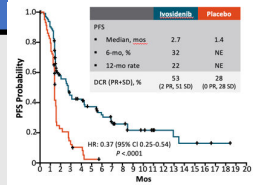
Gene	Alteration	Prevalence	ESCAT	References
BRCA1/2	Germline mutations	1%–4%	IA	The Cancer Genome Atlas Research Network. *Cancer Cell.* 2017[111] Golan T, et al. *N Engl J Med.* 2019[112]
	Somatic mutations	3%	IIIB	Shroff R, et al. *JCO Precis Oncol.* 2018[113]
	MSI-H	1%–3%	IC	Pihlak R, et al. *Cancers.* 2018[115] Marcus L, et al. *Clin Cancer Res.* 2019[97]
NTRK	Fusions	<1%	IC	Cocco E, et al. *Nat Rev Clin Oncol.* 2018[114] Doebele RC, et al. *Lancet Oncol.* 2020[50]
KRAS	Mutations	90%	IIIA	Zeitouni D, et al. *Cancers.* 2016[116]
PIK3CA	Hotspot mutations	3%	IIIA	Heestand G, et al. *Oncotarget.* 2015[117] Payne S, et al. *J Clin Oncol.* 2015[118]
BRAF^{V600E}	Mutations	3%	IIIA	Hyman D, et al. *N Engl J Med.* 2015[119]
MDM2	Amplifications	2%	IIIA	Azmi A, et al. *Eur J Cancer.* 2010[120]
ERBB2	Amplifications/ mutations	1%–2%	IIIA	Waddell N, et al. *Nature.* 2015[121] Harder J, et al. *Br J Cancer.* 2012[122] Hyman D, et al. *Nature.* 2018[55]
NRG1	Fusions	1%	IIIA	Jones M, et al. *Clin Cancer Res.* 2019[123]
ALK	Fusions	<1%	IIIA	Singhi A, et al. *J Natl Compr Canc Netw.* 2017[124]
RET	Fusions	<1%	IIIA	Drilon A, et al. *J Clin Oncol.* 2018[91]
ROS1	Fusions	<1%	IIIA	Pishvaian M, et al. *J Clin Oncol.* 2018[125]

ESCAT, European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets; MSI-H, microsatellite instability-high.

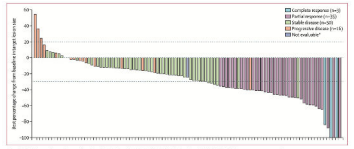
UPPER GI - Biliary cancer

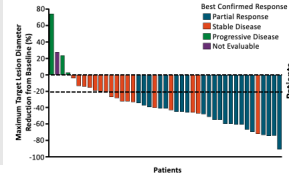


Biomarker	Stage/ Prevalence	Technique	Actionability
IDH	IV / 20%	NGS	Ivosidenib
FGFR	IV / 11%	NGS	Anti-FGFR Pemigatinib
BRAF	IV /	NGS	Anti-BRAF
HER2	IV / <1%	IHC , FISH , NGS	Anti-HER2 (trial, off label)
MSI	IV / 5%	IHC, PCR	ICI
NTRK	IV / <1%	IHC, NGS	Anti-NTRK



IDH





Anti BRAF

UPPER GI - Biliary cancer

Is it useful to order a NGS panel?

Tumour multigene NGS could be used to detect level I actionable alterations in cholangiocarcinoma.

Given that they are unlikely to be cost-effective in these cases, larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (including off-label use of drugs) and pending a ranking of additional alterations using a valid ranking system.

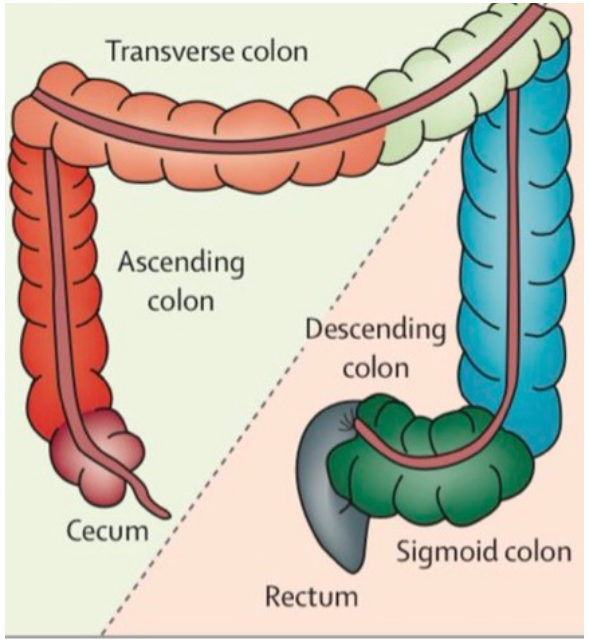
Table 10. List of genomic alterations level I/II/III according to ESCAT in advanced cholangiocarcinoma (CC)

Gene	Alteration	Prevalence	ESCAT	References
IDH1	Mutations	20%	IA	Abou-Alfa G. K, et al. *Ann Oncol.* 2019[129]
FGFR2	Fusions	15%	IB	Vogel A, et al. *Ann Oncol.* 2019[130]
	MSI-H	2%	IC	Marabelle A, et al. *J Clin Oncol.* 2020[131]
NTRK	Fusions	2%	IC	Doebele RC, et al. *Lancet Oncol.* 2020[50]
BRAF^{V600E}	Mutations	5%	IIB	Wainberg Z, et al. *J Clin Oncol.* 2019[132]
ERBB2	Amplifications Mutations	10% 2%	IIIA	Javle MM, et al. *J Clin Oncol.* 2017[133]
PIK3CA	Hotspot mutations	7%	IIIA	André F, et al. *N Engl J Med.* 2019[72]
BRCA 1/2	Mutations	3%	IIIA	De Bono J, et al. *N Engl J Med.* 2020[93]
MET	Amplifications	2%	IIIA	Camidge D, et al. *J Clin Oncol.* 2018[52]

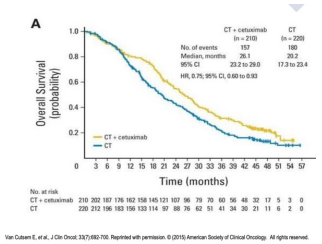
ESCAT, European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets.

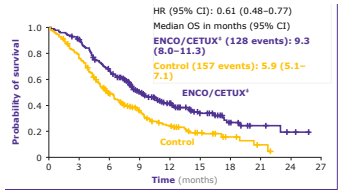
F. Mosele et al Ann of Onc 2020

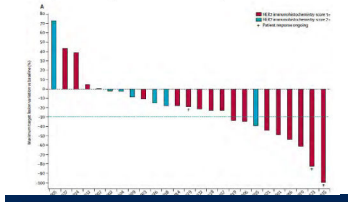
Lower GI - Colorectal cancer

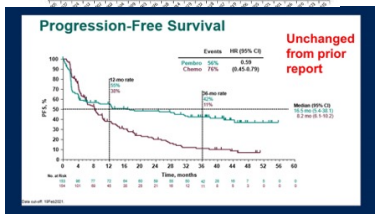


Biomarker	Stage/ Prevalence	Technique	Actionability
RAS WT	IV / 50%	PCR, Sanger, pyroseq, BEAMing, NGS	Anti-EGFR (left-sided+) No anti-EGFR RAS G12C (trial)
RAS MUT	IV / 50%		
BRAF MUT V600E	IV / 8-15%	’’ ’’	Lack of benefit of anti-EGFR Anti-BRAF, Encorafenib
HER2	IV / 5%	IHC , NGS	Lack of benefit of anti-EGFR Anti-HER2 (off label)
MSIH	I-III / 15% IV / 5%	IHC, PCR	Lack of benefit from 5-FU-therapy ICI (trial) Benefit from ICI
NTRK	IV / <1%	IHC, NGS	Anti-NTRK
MGMT	IV /	IHC	Temozolamide (trial, off label)









Lower GI - Colorectal cancer

Is it useful to order a NGS panel?

Since most level I alterations **are hotspot mutations in KRAS, NRAS and BRAF, and considering that MSI status is determined by IHC or PCR**, **there is no need to test samples using multigene NGS in the context of daily practice.**

Nevertheless, **multigene NGS can be an alternative to PCR tests only if it does not generate extra cost compared with standard techniques** already implemented in routine.

Patients with mCRC can present oncogenic alterations for which drugs are being developed and **it is therefore recommended for clinical research centres to include patients in molecular screening programmes to propose access to innovative agents in clinical trials.**

F. Mosele et al Ann of Onc 2020

Table 5. List of genomic alterations level I/II/III according to ESCAT in metastatic colorectal cancer (mCRC)

Gene	Alteration	Prevalence	ESCAT	References
KRAS *NRAS*	Mutations (resistance biomarker)	44% 4%	Not applicable	Van Cutsem E, et al. *J Clin Oncol.* 2015[79] Douillard J-Y, et al. *N Engl J Med.* 2013[80] Sorich M, et al. *Ann Oncol.* 2015[81]
BRAF^{V600E}	Mutations	8.5%	IA	https://doi.org/10.1093/annonc/mdw235 Kopetz S, et al. *N Engl J Med.* 2019[82]
	MSI-H	4%—5%	IA	Overman M, et al. *Lancet Oncol.* 2017[83] Le DT, et al. *J Clin Oncol.* 2020[84]
NTRK1	Fusions	0.5%	IC	Demetri G, et al. *Ann Oncol.* 2018[85] Doebele RC, et al. *Lancet Oncol.* 2020[50]
ERBB2	Amplifications	2%	IIB	Meric-Bernstam F, et al. *Lancet Oncol.* 2019[86] Sartore-Bianchi A, et al. *Lancet Oncol.* 2016[87]
PIK3CA	Hotspot mutations	17%	IIIA	Juric D, et al. *J Clin Oncol.* 2018[90]
ATM	Mutations	5%	IIIA	Wang C, et al. *Transl Oncol.* 2017[92] De Bono J, et al. *N Engl J Med.* 2020[93]
MET	Amplifications	1.7%	IIIA	https://clinicaltrials.gov/ct2/show/NCT03592641[94]
AKT1^{E17K}	Mutations	1%	IIIA	Hyman D, et al. *J Clin Oncol.* 2017[76]
	TMB-high in MSS	1%	IIIA	Fabrizio D, et al. *J Gastrointest Oncol.* 2018[89]
RET	Fusions	0.3%	IIIA	Drilon A, et al. *J Clin Oncol.* 2018[91]
ALK	Fusions	0.2%	IIIA	Yakirevich E, et al. Clin Cancer Res 2016[88]

ESCAT, European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets; MSI-H, microsatellite instability-high; MSS, microsatellite stable.

Personalised medicine: a different perspective

Anatomy (Tumor location) is a biomarker

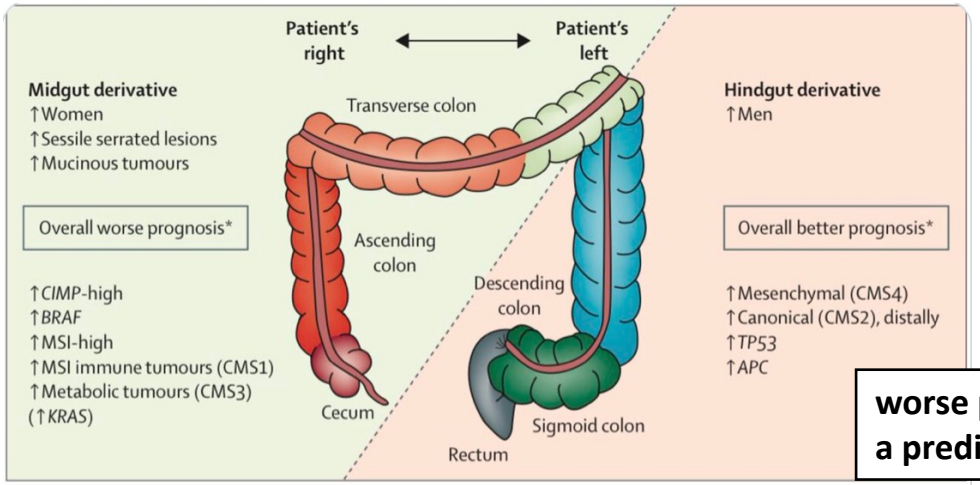
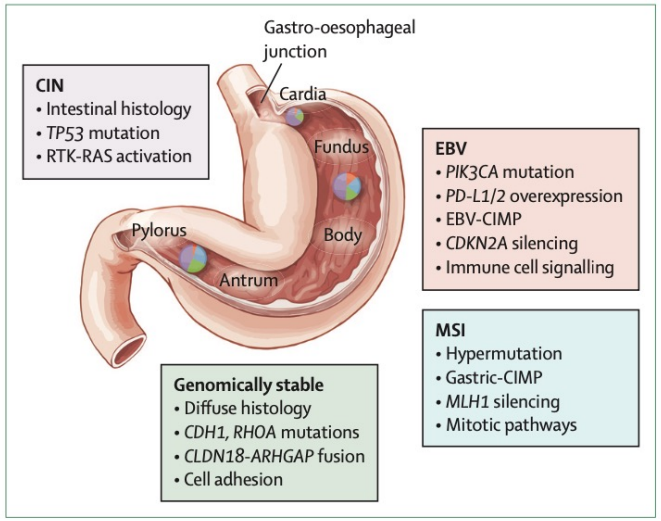


Figure 4: **Differences in right-sided versus left-sided colon and rectum**

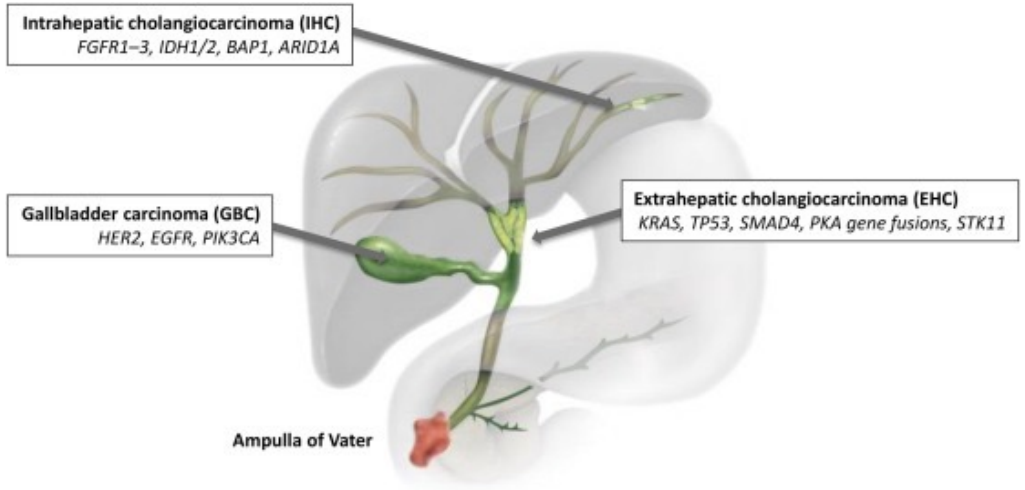
Prognostic and predictive value of primary tumour side in patients with *RAS* wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials[†]

worse prognosis for OS, PFS and ORR for patients with right-sided tumours and **a predictive effect of tumour side.**

Dekker et al Lancet 2019



Van Cutsem et al Lancet 2016



Althauda A et al Cancer Treat Rev 2020

Personalised medicine: a different perspective

DPYD is a biomarker

Dihydropyrimidine dehydrogenase (DPYD) is a polymorphic gene encoding for DPD, involved in fluoropyrimidines (5FU, capecitabine) catabolism

The estimated prevalence of DPYD deficient genotypes in the European population is <8%.

Test for DPYD before 5FU administration to prevent severe toxities !!!
(dose modifications, in rare cases avoid 5FU)

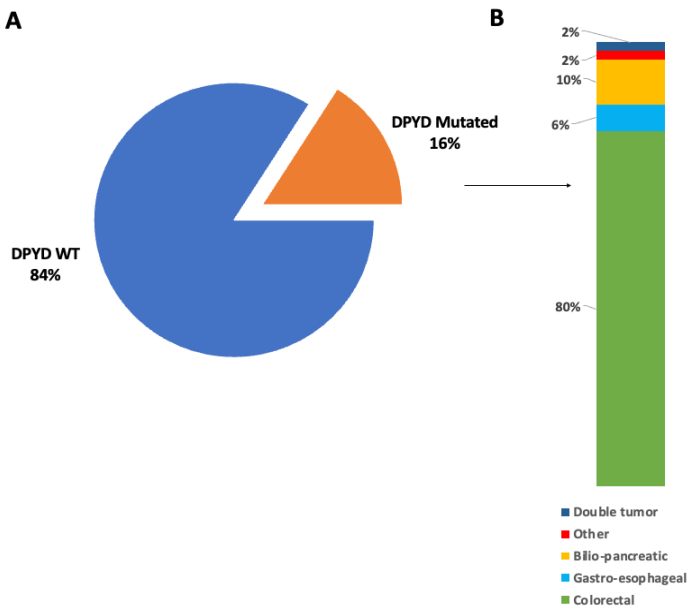


Figure 1 A. Prevalence of DPYD deleterious variants in the overall population
B. Tumor type of patients carrier of DPYD deleterious variants

DPYD variants	N (%)
c.2194G>A(*6)	37 (12%)
c.1905+1G>A(*2A)	6 (2%)
c.1129-5923C>G	4 (1%)
c.2846A>T	2 (<1%)
c.1679T>G(*13)	1 (<1%)

Table 1. DPYD deleterious variants in the overall population

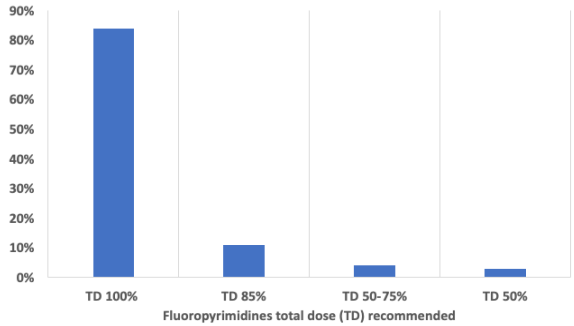


Figure 2. Fluoropyrimidine dose recommended according to DPYD status

Cardone et al. 2021

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 2915–2922, 2017
doi:10.1093/annonc/mdx411
Published online 2 August 2017

REVIEW

DPYD genotype-guided dose individualization to improve patient safety of fluoropyrimidine therapy: call for a drug label update

L. M. Henricks[1,2], F. L. Opdam[1,2], J. H. Beijnen[3,4], A. Cats[5] & J. H. M. Schellens[1,2,4*]

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EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine Share

Press release 30/04/2020

Take home message

- Personalised medicine is the key to ensure comprehensive care

  (type of treatment, setting (trial?), dose, duration)
- Not all biomarkers translate into clinical practice
- Some biomarkers implicate genetic counselling (hereditary syndrome)
- Relevance of molecular tumor board (to integrate knowledge and perspectives)
- Academic research is the place to discover / validate novel biomarkers and to develop clinical trials

Thank you! Questions?

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