Erasmus MC
Universitair Medisch Centrum Rotterdam

Cancer Institute

CPCT, DRUP: wat is bereikt en hoe nu verder?

Martijn Lolkema, MD/PhD
Medical Oncologist
Erasmus MC Cancer Institute

Disclosures

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- Grants for research (to Institute): JnJ/ Astellas/ MSD/ Sanofi
- Advisory role: Roche/ Bayer/ Amgen/ JnJ/ Sanofi/ Servier/ Pfizer/ Incyte

Center for Personalized Cancer Treatment

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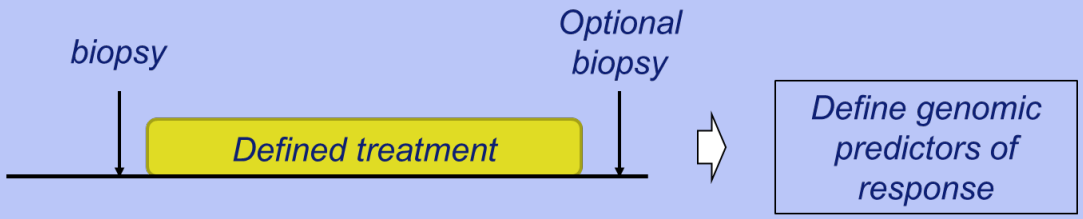
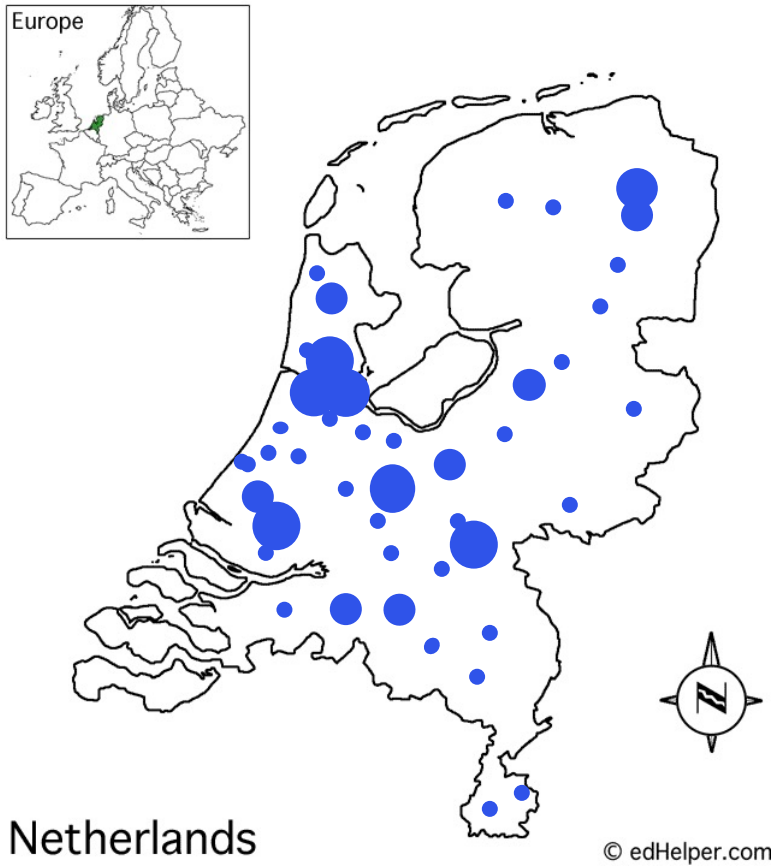
Metastatic cancer patients:





44 sites in the Netherlands with almost comprehensive geographical coverage

Per site 2-1000 patients included over 6 year period

Almost 6000 pts included as of sep 2018

Hartwig Medical Foundation: whole genome sequencing

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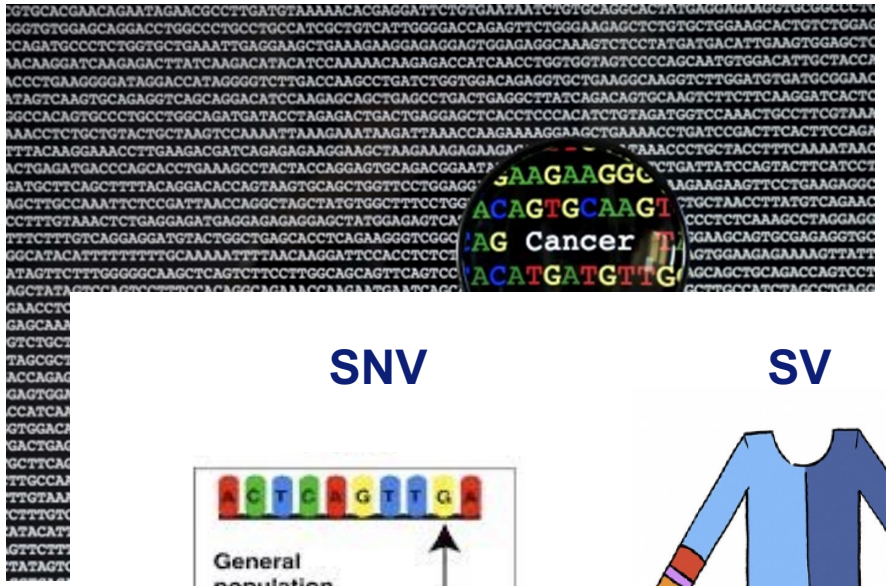
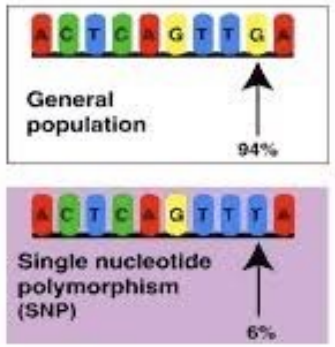
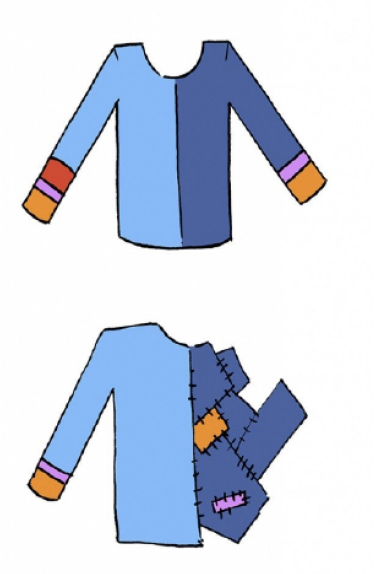


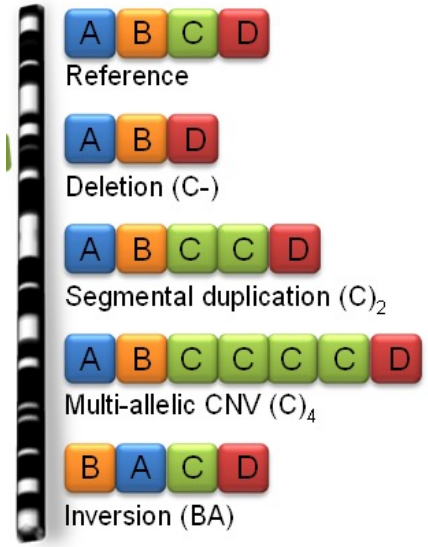
SNV



SV



CNV



https://www.hartwigmedicalfoundation.nl/

Compounding all data

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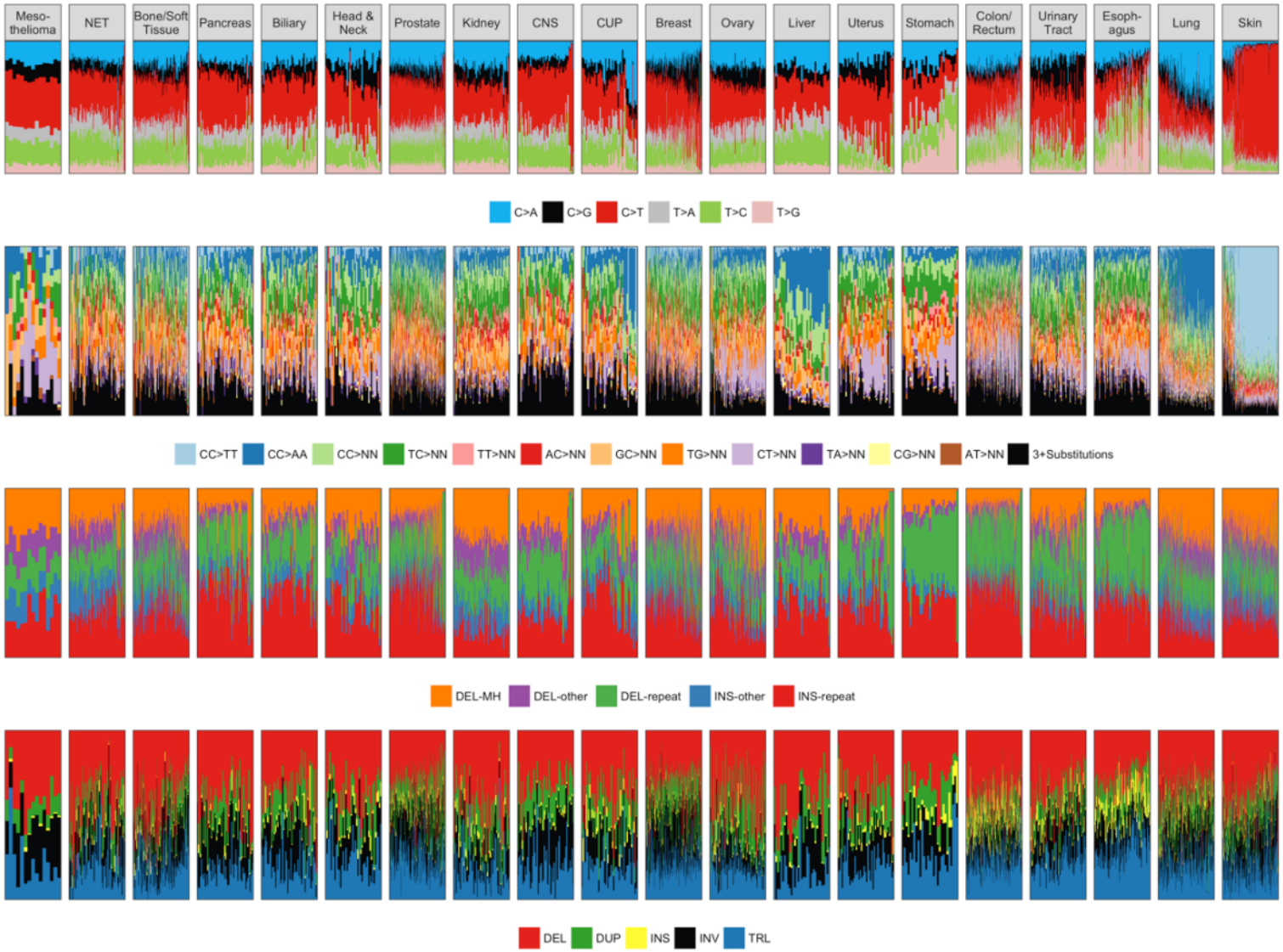

Conclusions on WGS as a tool

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- Global analysis shows: limited intra-biopsy heterogeneity in biopsies of metastatic disease, driver genes can be identified.
  Priestley et al Nat 2019

- Analysis of repeat biopsies shows limited genetic drift over time: “1 biopsy is all it takes”
  Van de Haar et al Nat Med 2021

- WIDE study analysis shows that WGS captures all findings we have in the routine diagnostics (and more).
  To be published: presented at ESMO 2020

Disease specific analysis example: the Prostate Cancer Genome

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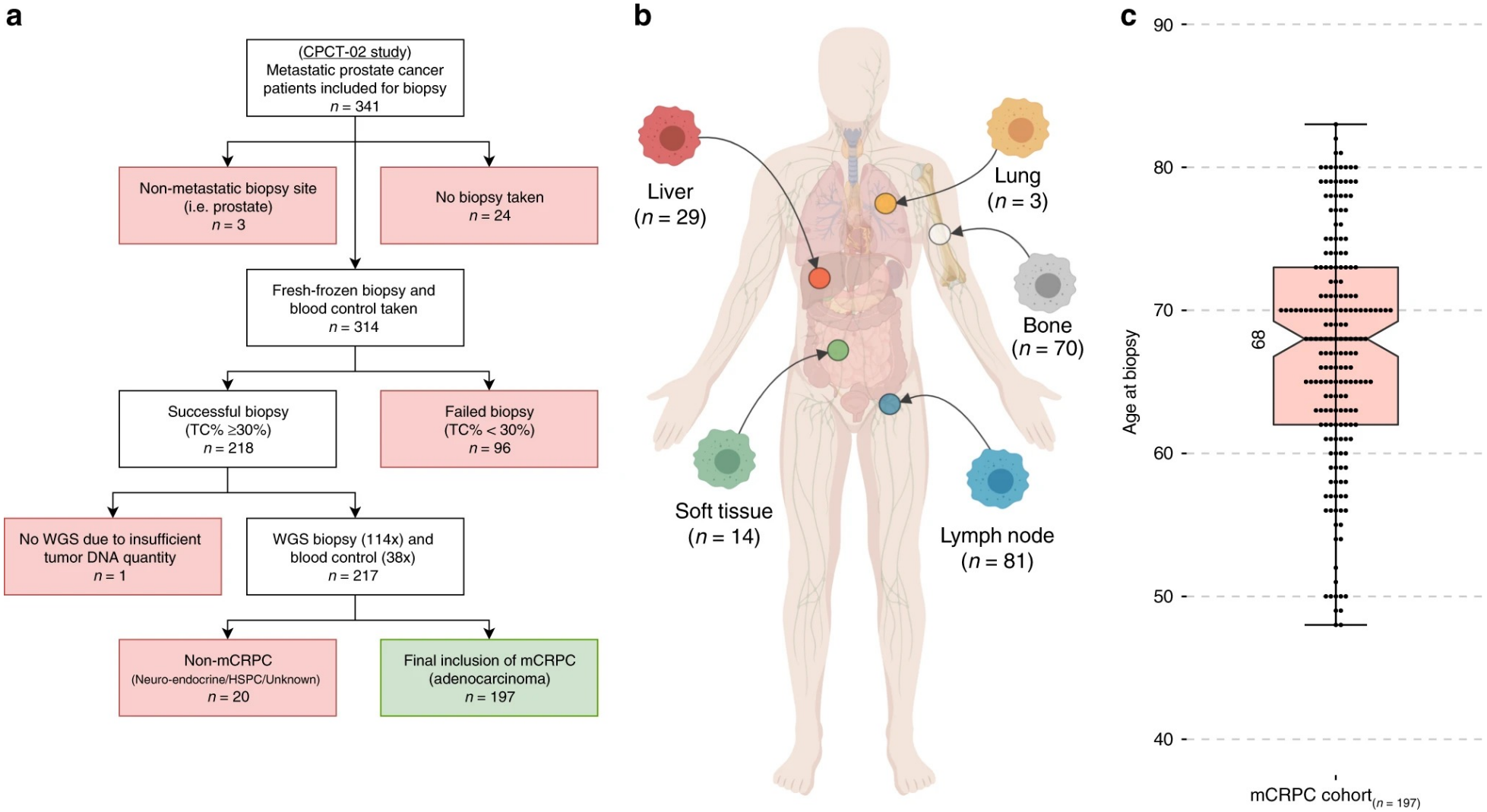

The Genes Involved

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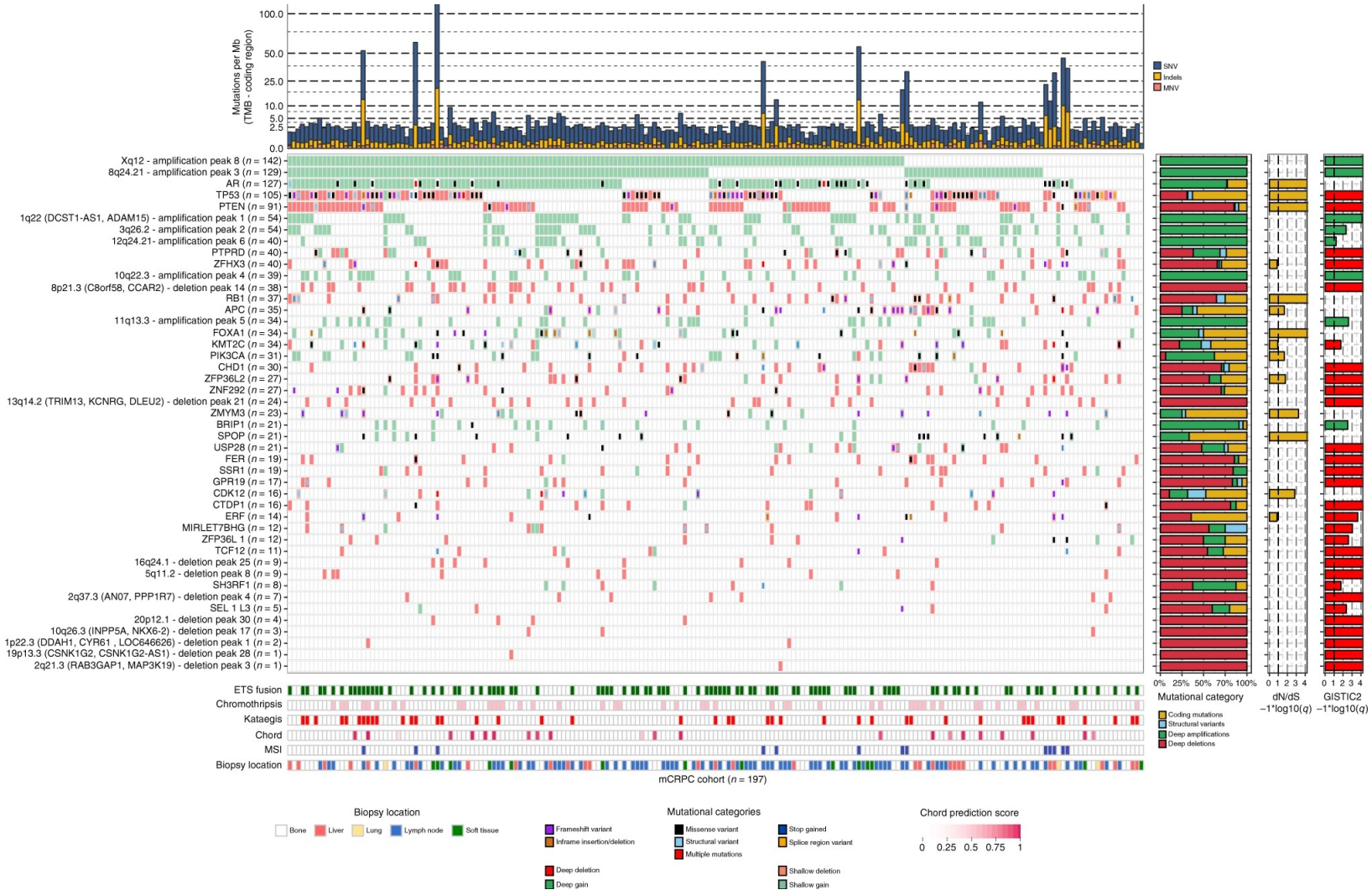

AR, TP53, PTEN, RB1, APC

More amplifications compared to deletions

Relatively modest number of SNVs

So we identified the usual suspects…..

Comparison Primary Prostate Cancer

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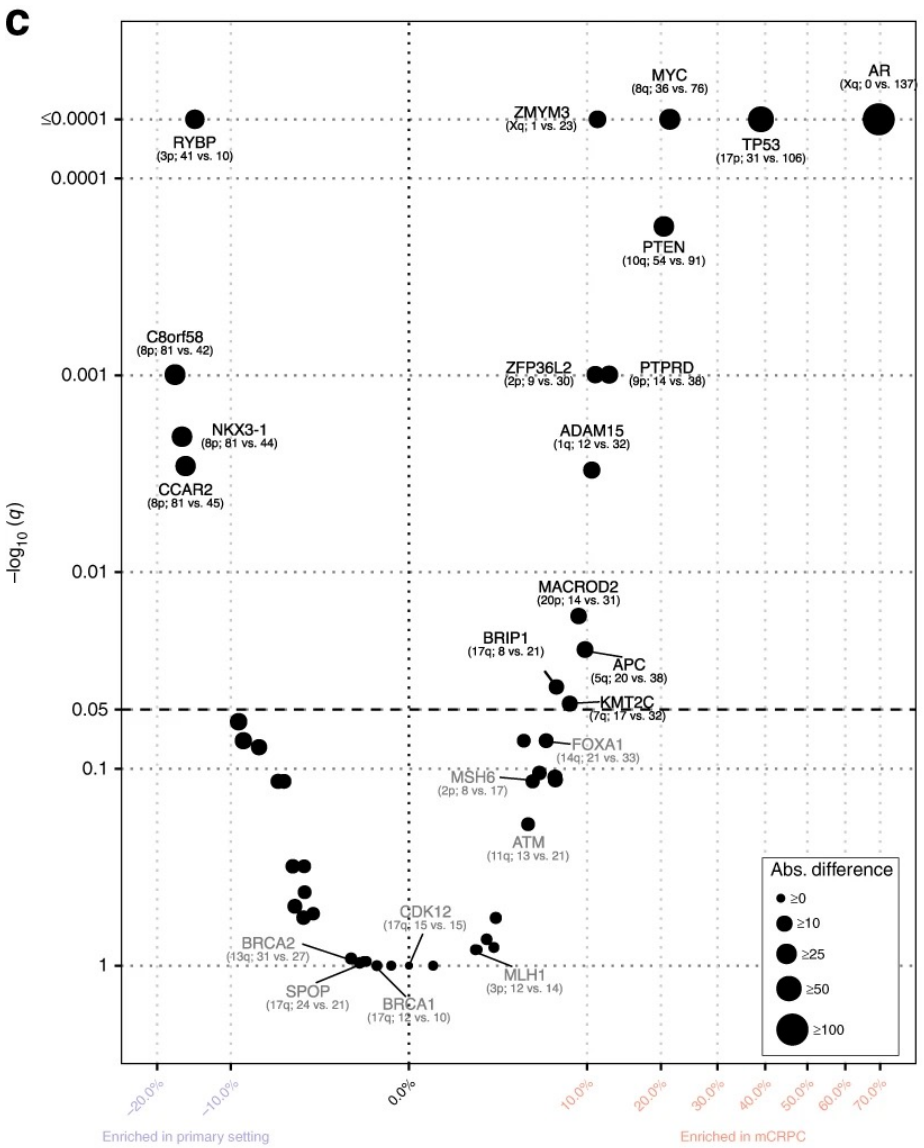
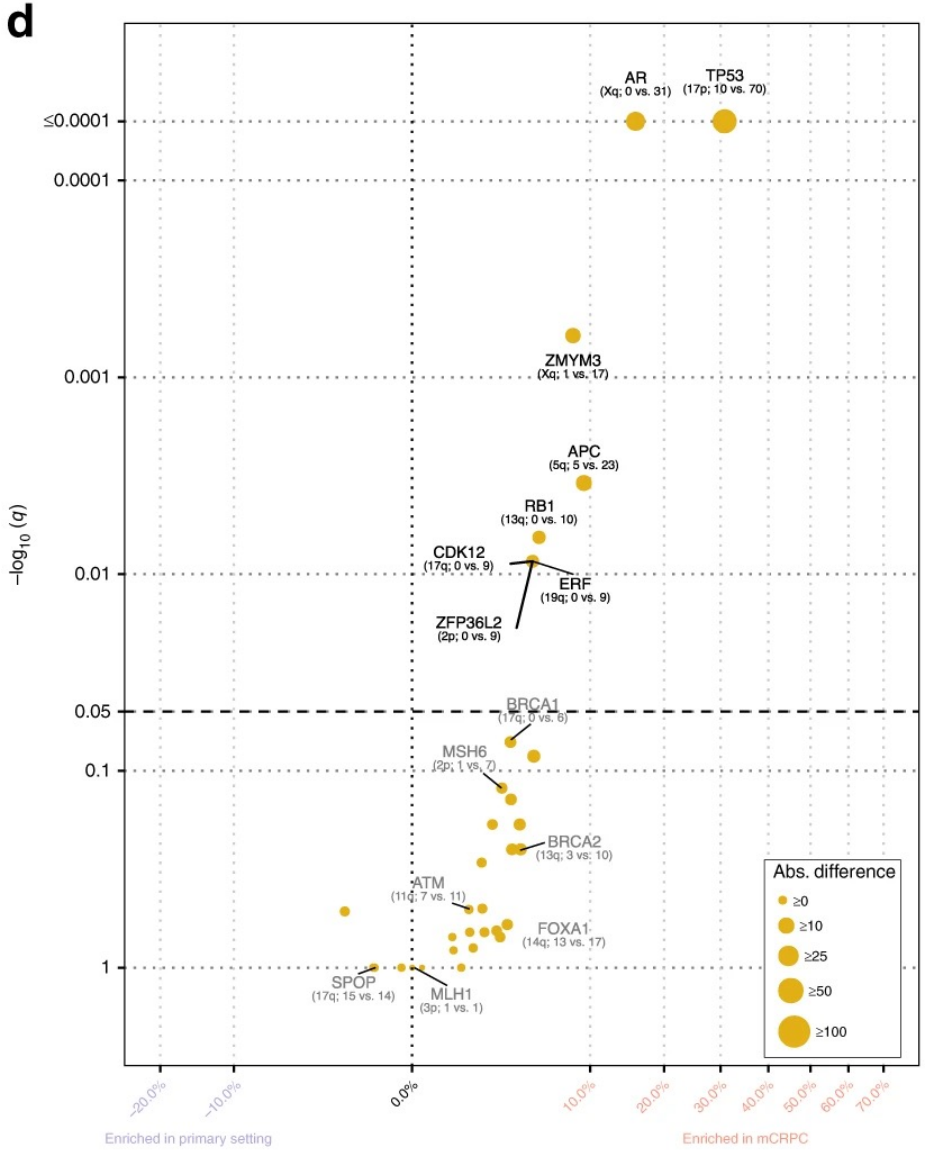
All mutations



Coding mutations



Comparison Primary Prostate Cancer (II)

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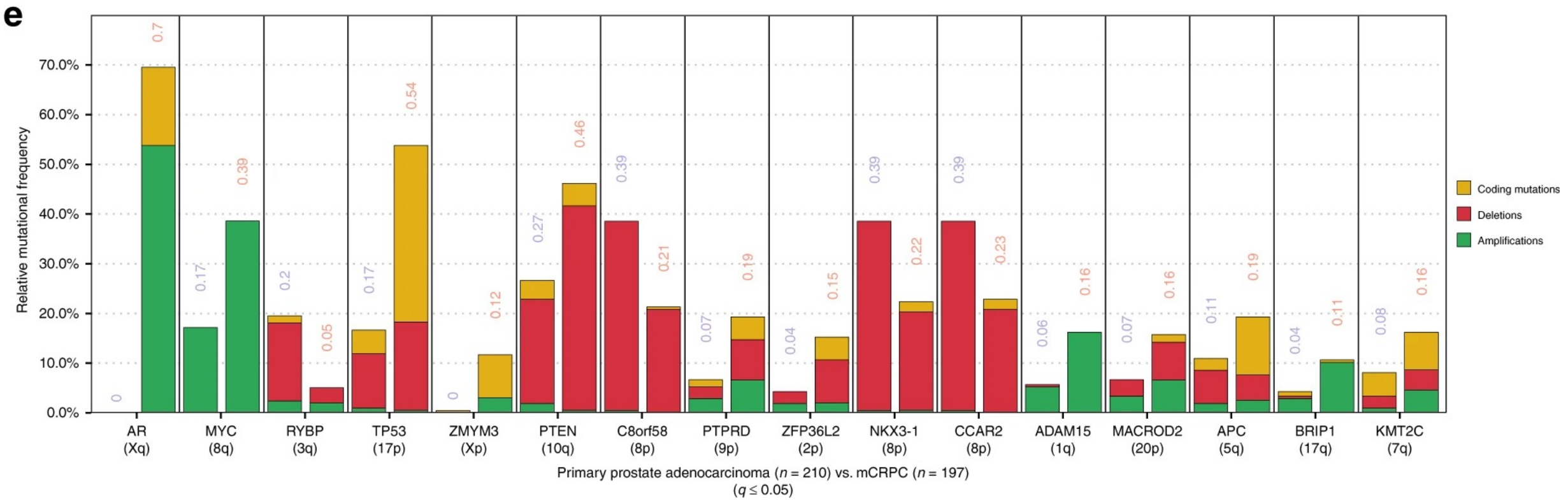

Androgen Receptor Alterations in mCRPC

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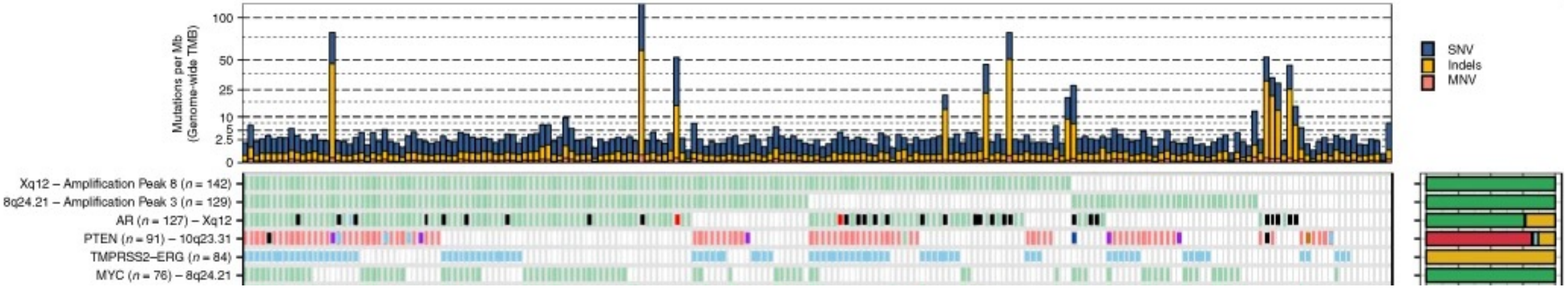

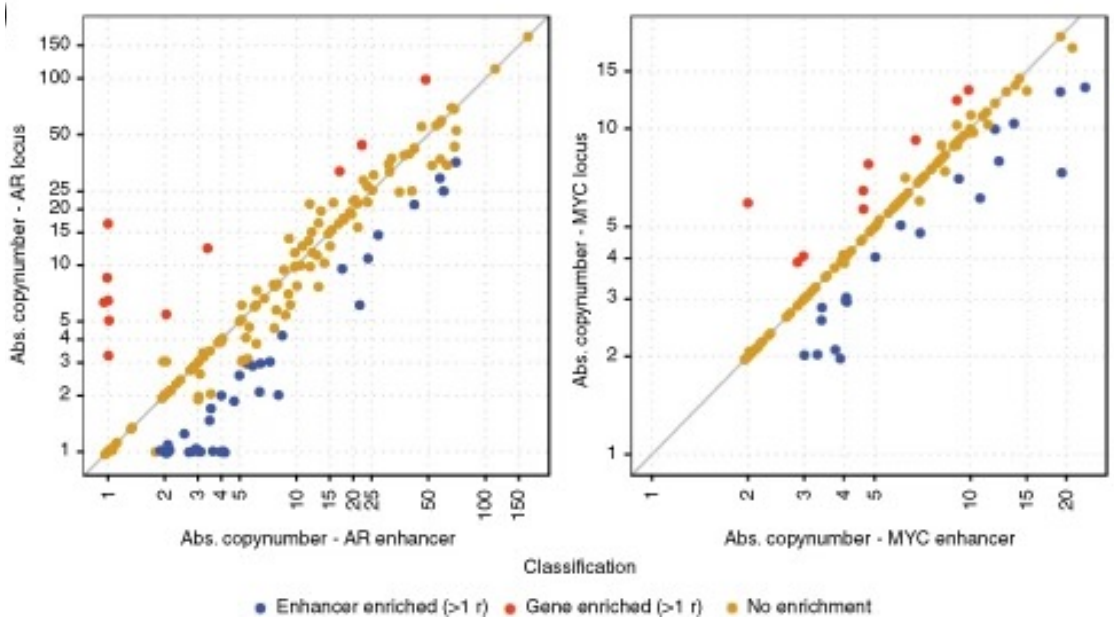

Clinically Relevant Patient Clustering

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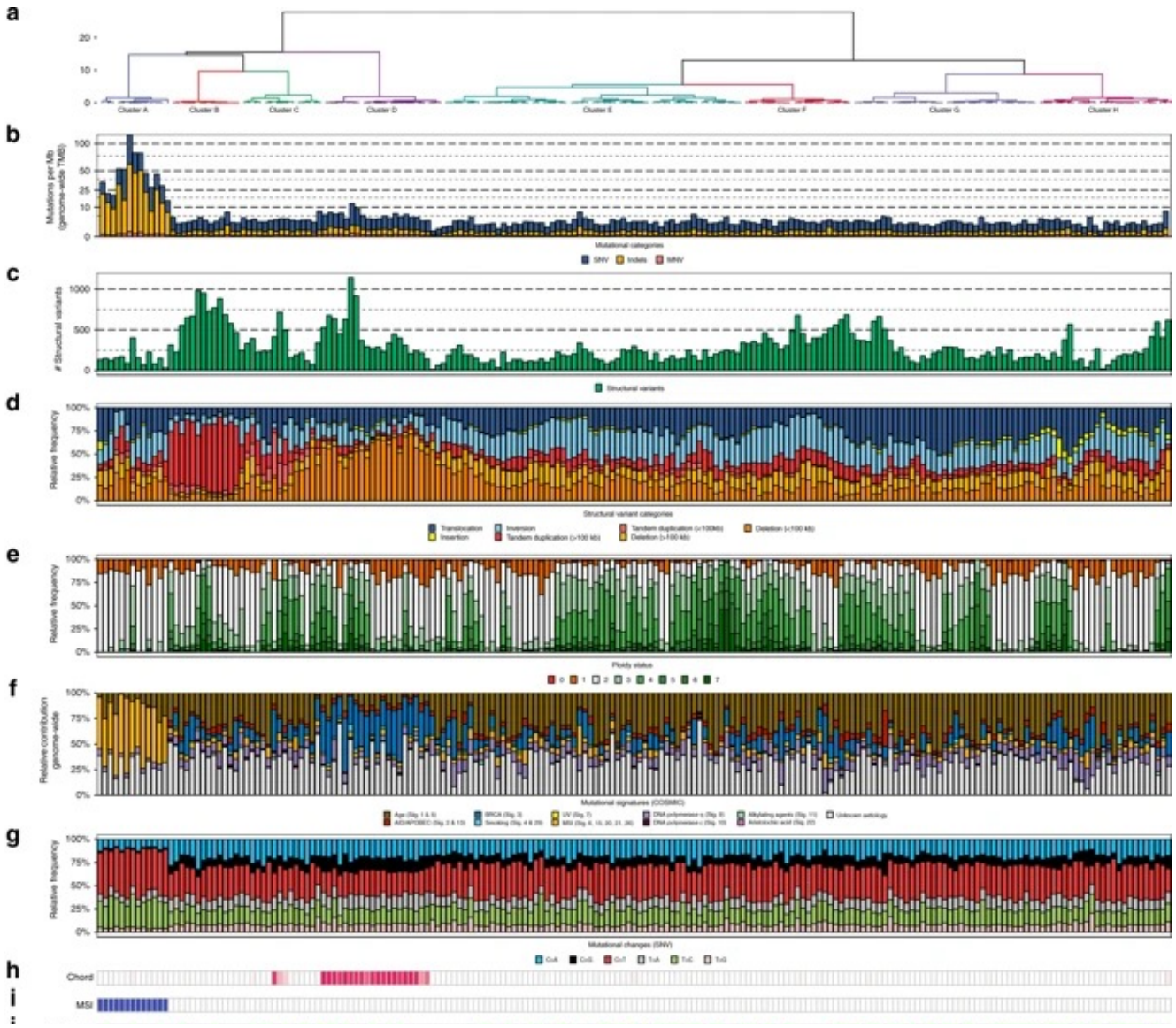

Other variables

Clustering variables

Number of mutations

Number of Structural Variants

Type of Structural Variants

Ploidy

Signature of mutations

Context of mutations

CHORD score

MSI score

What can we learn from these data?

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- WGS can be used as a tool to stratify patients into relevant subgroups
- Numbers count! To study genomes we need more data
- In specific diseases we can make a real difference if we identify subgroups: in prostate cancer 20-25% of patients have actionable mutations and could benefit from alternative treatments.

Using Genomic Analyses for Patients

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Hartwig MEDICAL FOUNDATION

- Indication is determined by Phase I Unit MTB
  - Considerations:
    - Adequate physical condition (ECOG 0-1)
    - Amenable for biopsy
    - No previous molecular testing
    - Lab results
    - Tumor type

- Fresh frozen biopsy → Whole Genome Sequencing via Hartwig Medical Foundation
- Additional 2 FFPE samples for extra tests and PD analysis (pre-treatment biopsy)

- Actionability according to ESCAT and OncoKb

Genomic Analysis on fresh Biopsy

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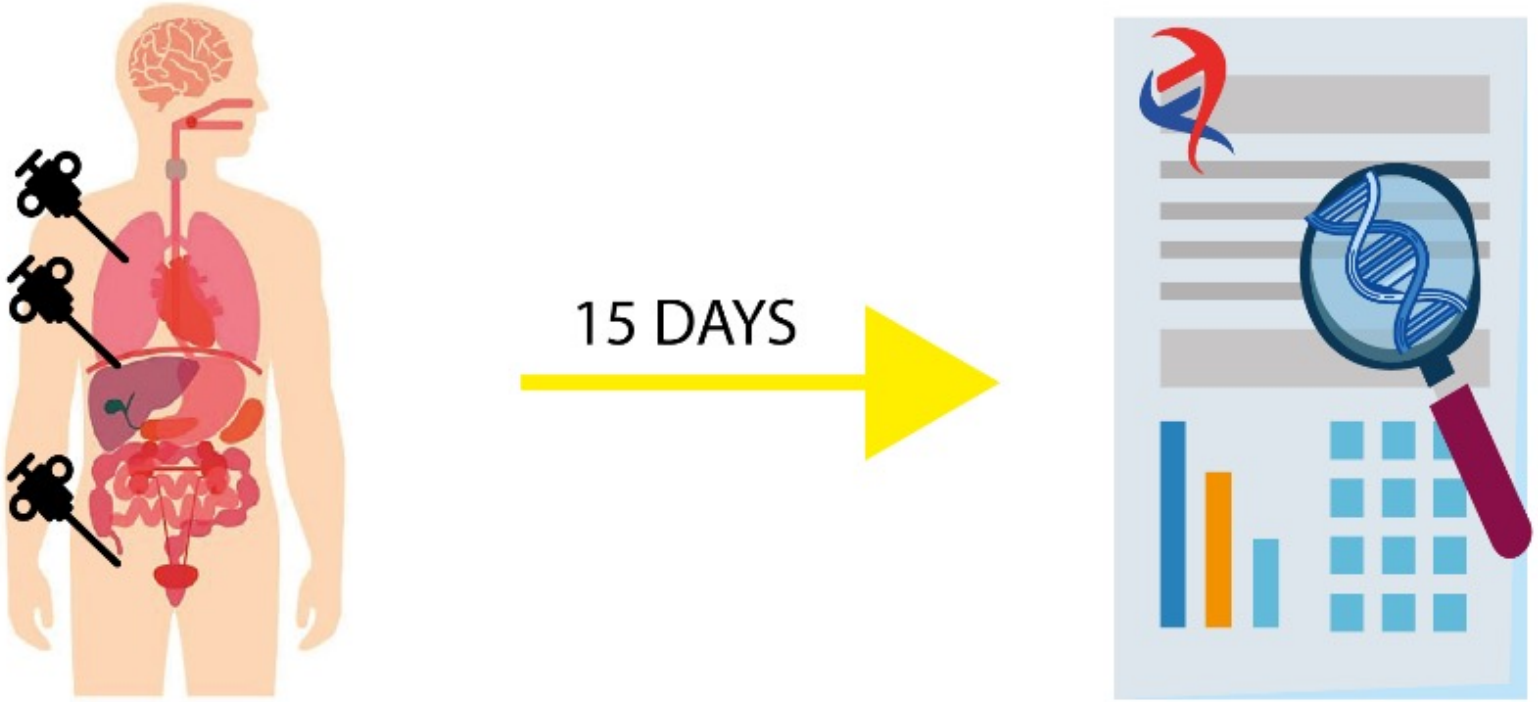

Essential analysis: MTB

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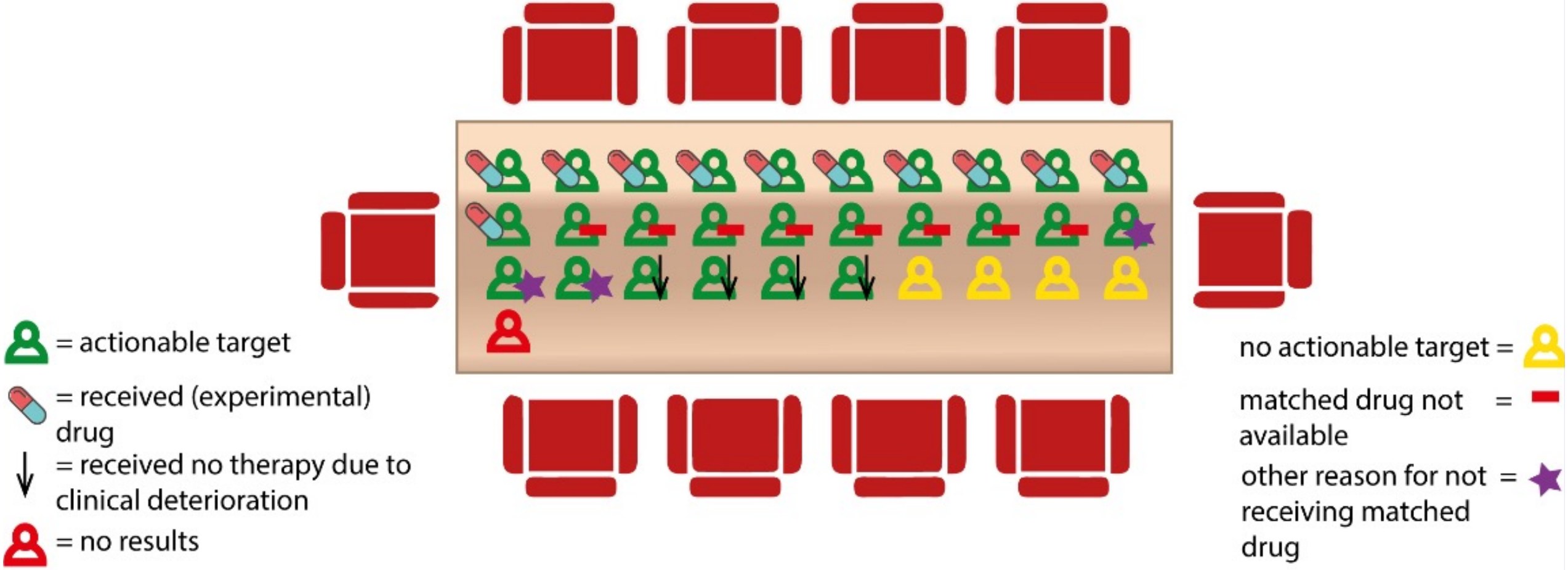

Case	TCP(%)	Organ of biopsy site	ESCAT I	ESCAT II	ESCAT III	ESCAT IV	ESCAT X	OncoKb Level 1
1	45%	Soft tissue				CDKN2A HZD		
2	17%	Liver				SMARCA4		TMB high
3	92%	Liver				PTEN		TMB high
4	76%	Liver			PIK3CA		HNRNPA2B1 - ETV1	
5	89%	Soft tissue					FUS-DITT3	
6	24%	Liver			CDK4 AMP	PTEN HZD		
7	64%	Liver				WHSC1L1 - FGFR1		TML high
8	82%	Liver			KRAS			
9	33%	Liver		KRAS		MAP2K4		
10	64%	Cervix			PIK3CA			TMB high
11	15%	Thoracic wall				ARID1A		
12	15%	Liver			PIK3CA		CDKN1B	
13	41%	Soft tissue			NRAS			
14	51%	Liver			HRD	CDKN2A HZD		
15	15%	Liver				Viral insert	SMAD4	
16	29%	Lymphnode			PIK3CA	Viral insert		TMB high
17	77%	Lymphnode			PTEN HZD			
18	49%	Soft tissue					SS18-POU5F1	
19	NE	Lymphnode		NRAS				
20	12%	Soft tissue				CDKN2A HZD		
21	NE	Lymphnode						
22	98%	Bone				Viral insert		TMB high
23	79%	Skin					FBXW7	
24	37%	Lung				ATR		
25	17%	Liver				ADAM9-BRAF CDKN2A HZD		
26	63%	Liver					CDKN1B	
27	76%	Soft tissue				KIT		
28	85%	Bone						MSI
29	49%	Soft tissue						TMB high
30	14%	Liver				BAP1		
31	18%	Lung						TML high

DRUP study status

- Study was launched in September 2016
- 34 participating hospitals, of which 27 are open for inclusion

Participating sites			
Currently open for inclusion (*n* = 27)			
• AVL	• Haaglanden MC	• NWZ	• UMC Maastricht
• Amphia	• Isala	• OLVG	• UMC Radboud
• Deventer ZH	• Martini	• Reinier de Graaf	• UMC Utrecht
• Erasmus	• Maxima MC	• Rijnstate	• VieCuri
• ETZ	• MC Leeuwarden	• Spaarne Gasthuis	• VUMC
• Franciscus	• Meander	• UMC Groningen	• Zuyderland
• Gelderse Vallei	• Nij Smellinghe	• UMC Leiden	
In preparation (*n* = 6)			
• AMC	• Haga ziekenhuis	• Treant Zorggroep	• ZG Twente
• Gelre Ziekenhuizen	• Maasstad Zkh		

DRUP and the Dutch health authorities

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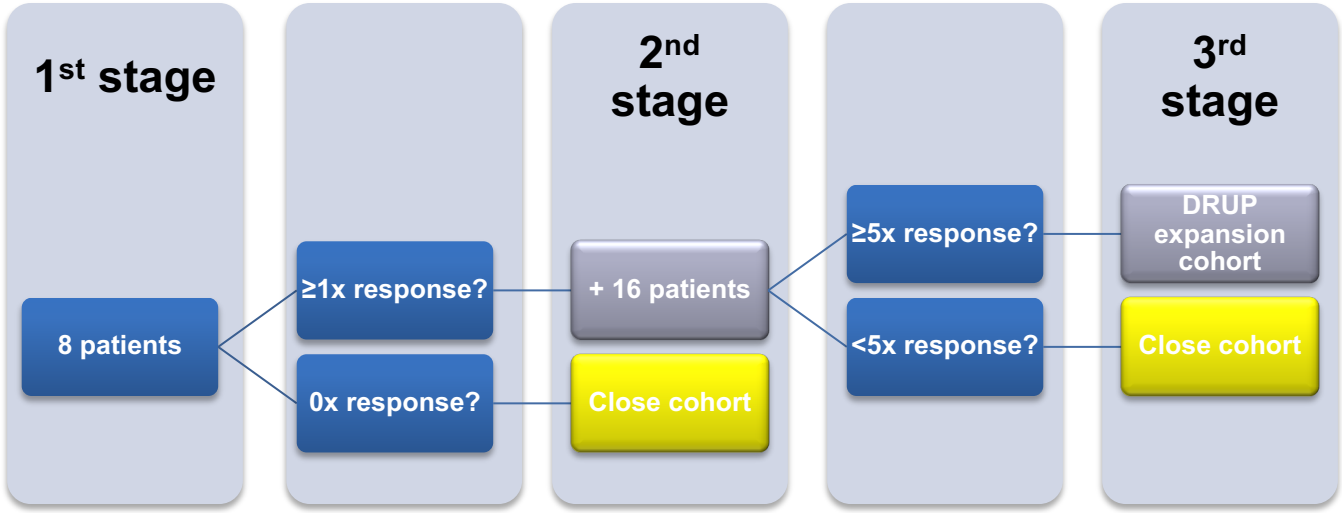
In collaboration with ZIN/CBG and the Dutch Health insurers

→ Create third stage within DRUP for successful cohorts

- Example: patient access program MSI cohort



Vd Velden et al Nature 2019

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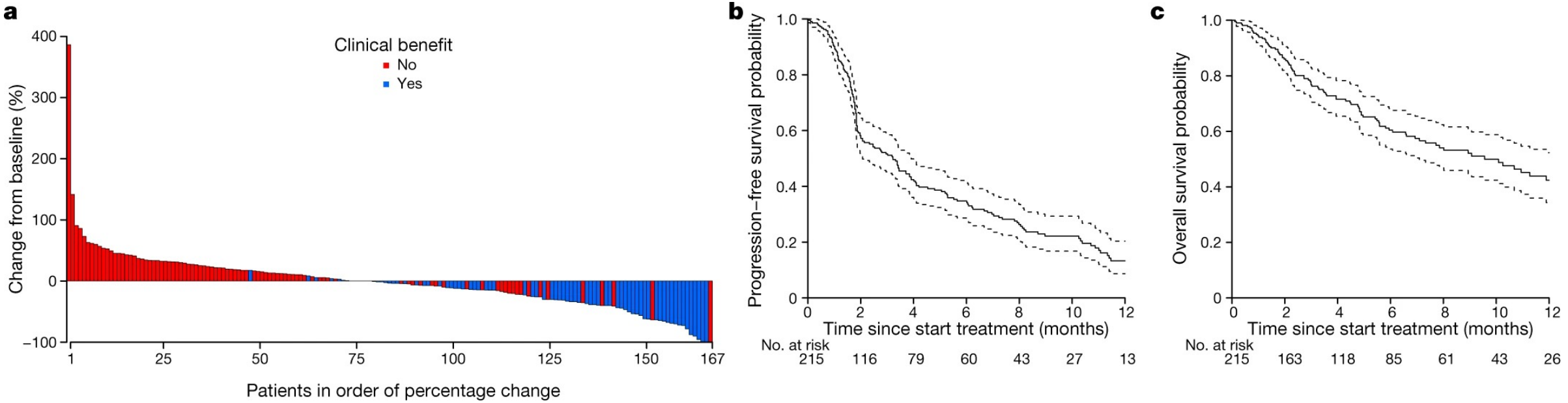
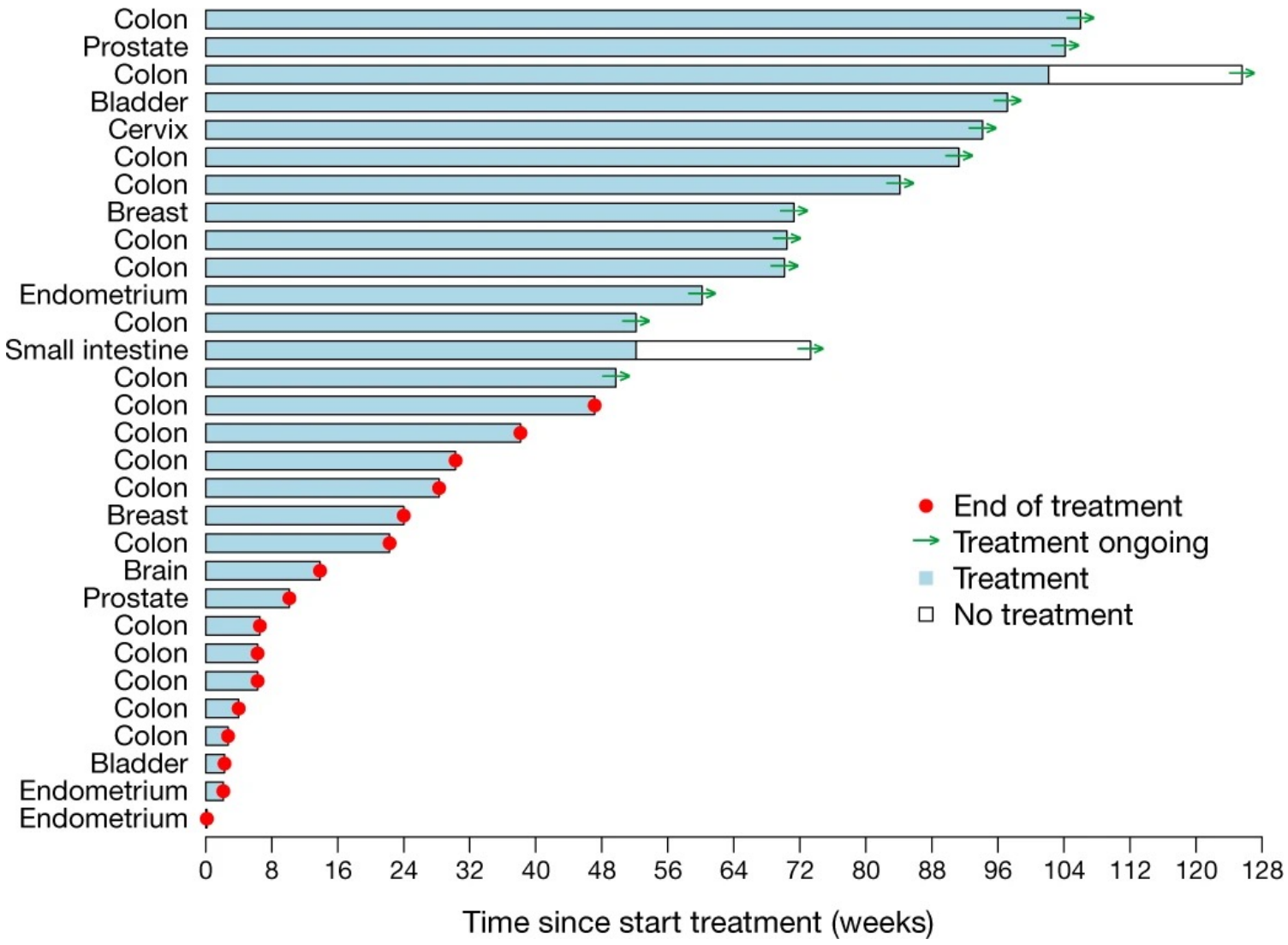


MSI cohort: swimmers plot



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Patients with bi-allelic BRCA1/2 inactivation respond to olaparib treatment across histologic tumor types

Authors and affiliations

Hanneke van der Wijngaart[1,2], Louisa R. Hoes[2,3], J. Maxime van Berge Henegouwen[2,4], Daphne L. van der Velden[5], Laurien J. Zeverijn[2,3], Paul Roepman[6], Erik van Werkhoven[7], Wendy W. J. de Leng[8], Anne M. L. Jansen[8], Niven Mehra[9], Debbie G. J. Robbrecht[10], Mariette Labots[1], Derk Jan A. de Groot[11], Ann Hoeben[12], Paul Hamberg[13], Hans Gelderblom[4], Emile E. Voest[2,3], Henk M. W. Verheul[9]

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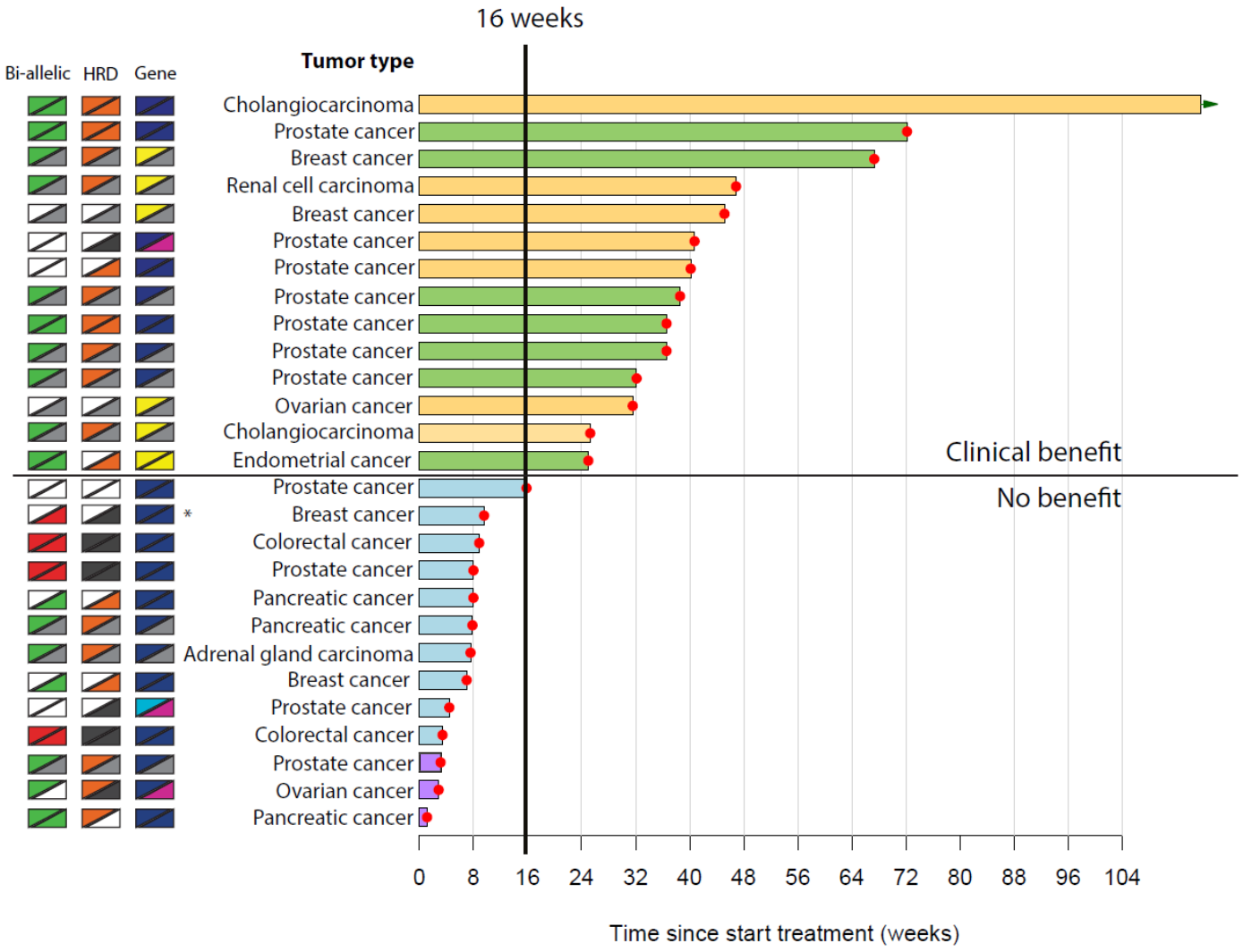

Color legend molecular details

- Pre-enrollment / Baseline biopsy
- BRCA1 variant
- BRCA2 variant
- No BRCA variant detected
- Bi-allelic loss
- Mono-allelic loss
- HRD signature high
- HRD signature low
- * Functional HRD
- BRCA 1 exon 1 deletion
- No WGS results available
- Unknown

Color legend clinical response

- Partial response as best response
- Stable disease as best response
- Progressive disease as best response
- Not evaluable

DRUP lessons learned

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- DRUP is a unique resource to optimize drug usage in oncology
- For the obvious cohorts some efficacy can be observed but further refinement is necessary
- Many european countries are adopting this type of platform.

Primary Tumor Unknown: a use case for WGS

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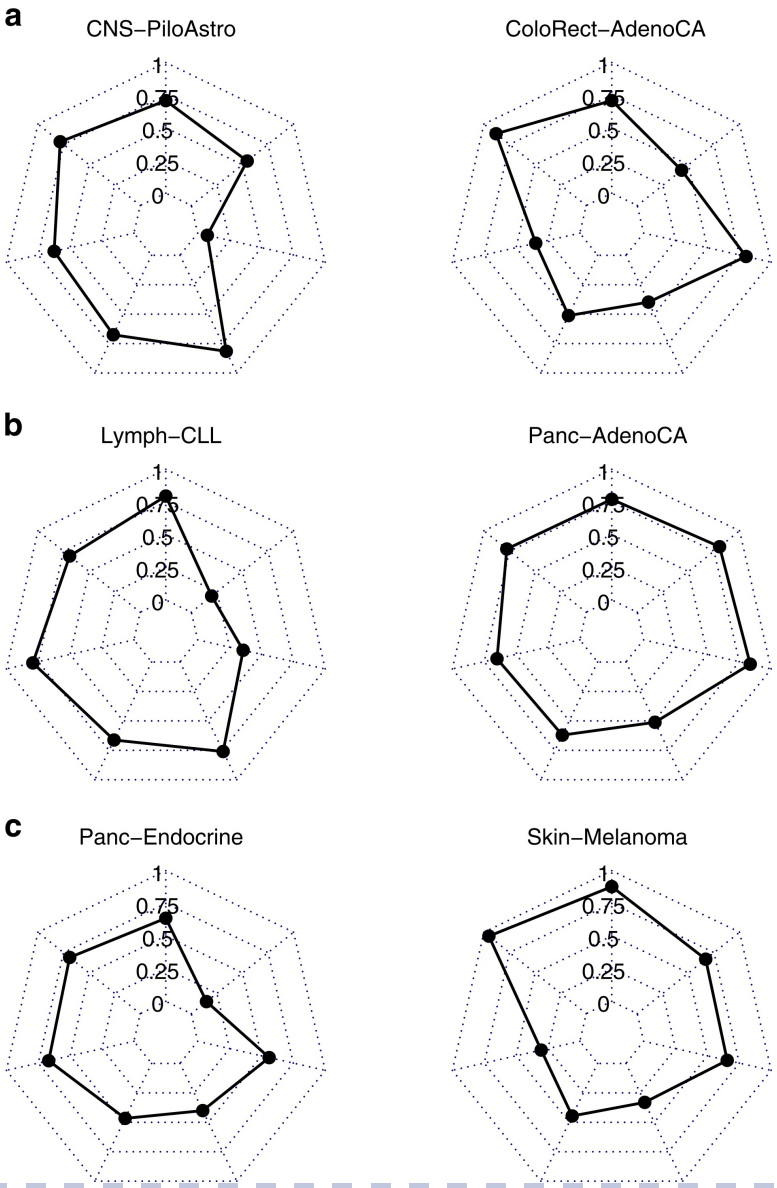

Jiao et al, Nat Comm 2020: **A deep learning system accurately classifies primary and metastatic cancers using passenger mutation patterns**

Prospective use of WGS to classify PTO patients

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Diagnose PTO (a)
en WHO 0-1*
en niet
behorend tot een gunstige subgroep (b)

Verwijzing naar PTO Centrum (alwaar aanwezigheid toegewijd PTO specialist);
Beoordeling patiënt
Check eerder verrichte diagnostiek
Biopt t.b.v. WGS (c)
Bespreken WGS rapport in MDO (d)

Identificatie
'tissue of origin'
(+/- bekende moleculaire variant (e))

Standaard therapie

→ *Retour verwijzend centrum*

Tumor-agnostische variant aanwezig (TRK fusies; MSI; BRCA 1/2 mutaties)

Gerichte therapie

→ *Retour verwijzend centrum, indien behandeling aldaar mogelijk is*

Relevante moleculaire variant(en) aanwezig

Behandeling in studieverband (fase 1/2 studies, o.a. DRUP)

→ *Indien optie in DRUP: Retour verwijzend centrum indien het participeert in DRUP-studie*

Geen relevante moleculaire variant(en) en geen 'tissue of origin'

→ *Fase 1 studie (f)*

→ *Indien geen studie beschikbaar: Retour verwijzend centrum*

Case report

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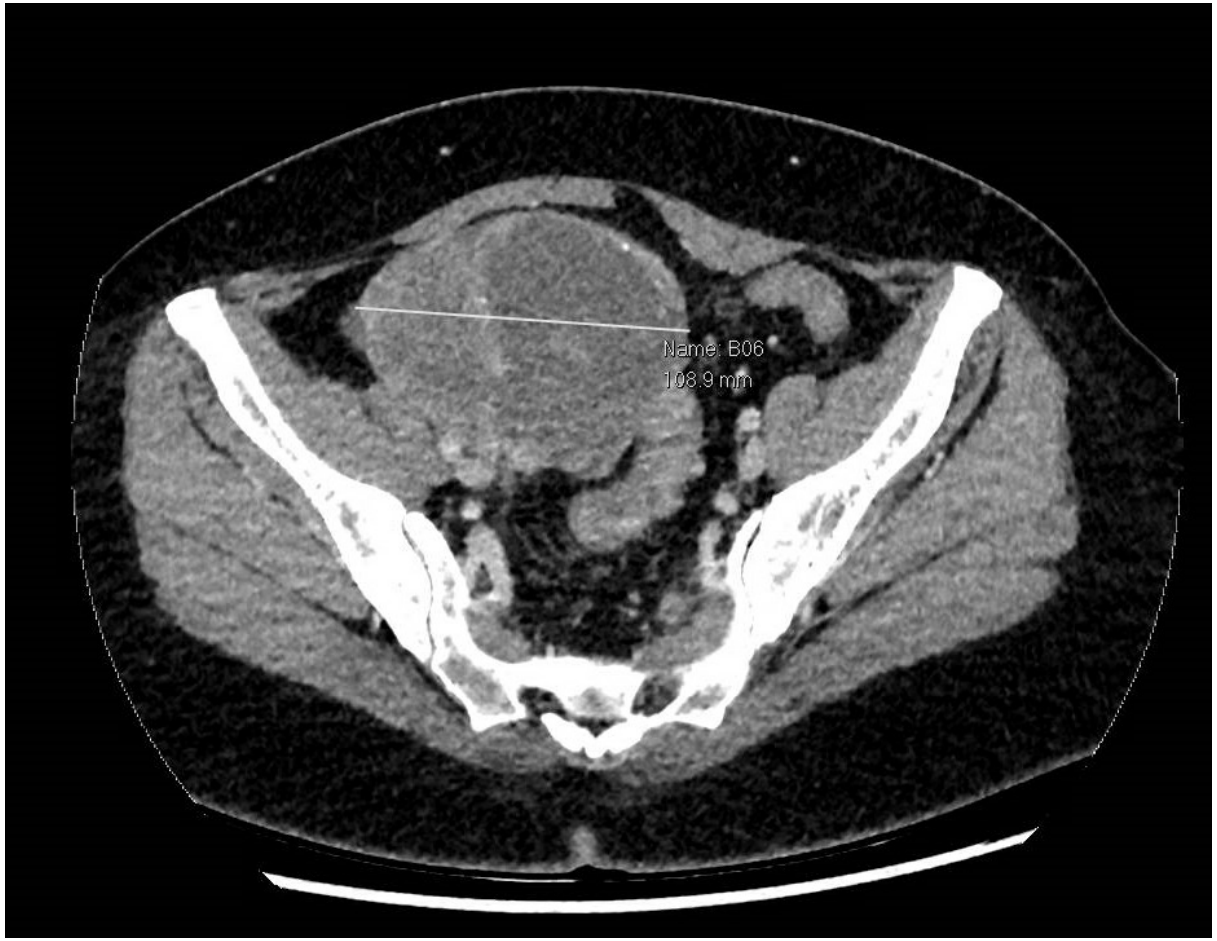
52 yo female patient with omental and ovarian metastases, no primary tumor identified.

Therefore no curative treatment options



WGS analysis

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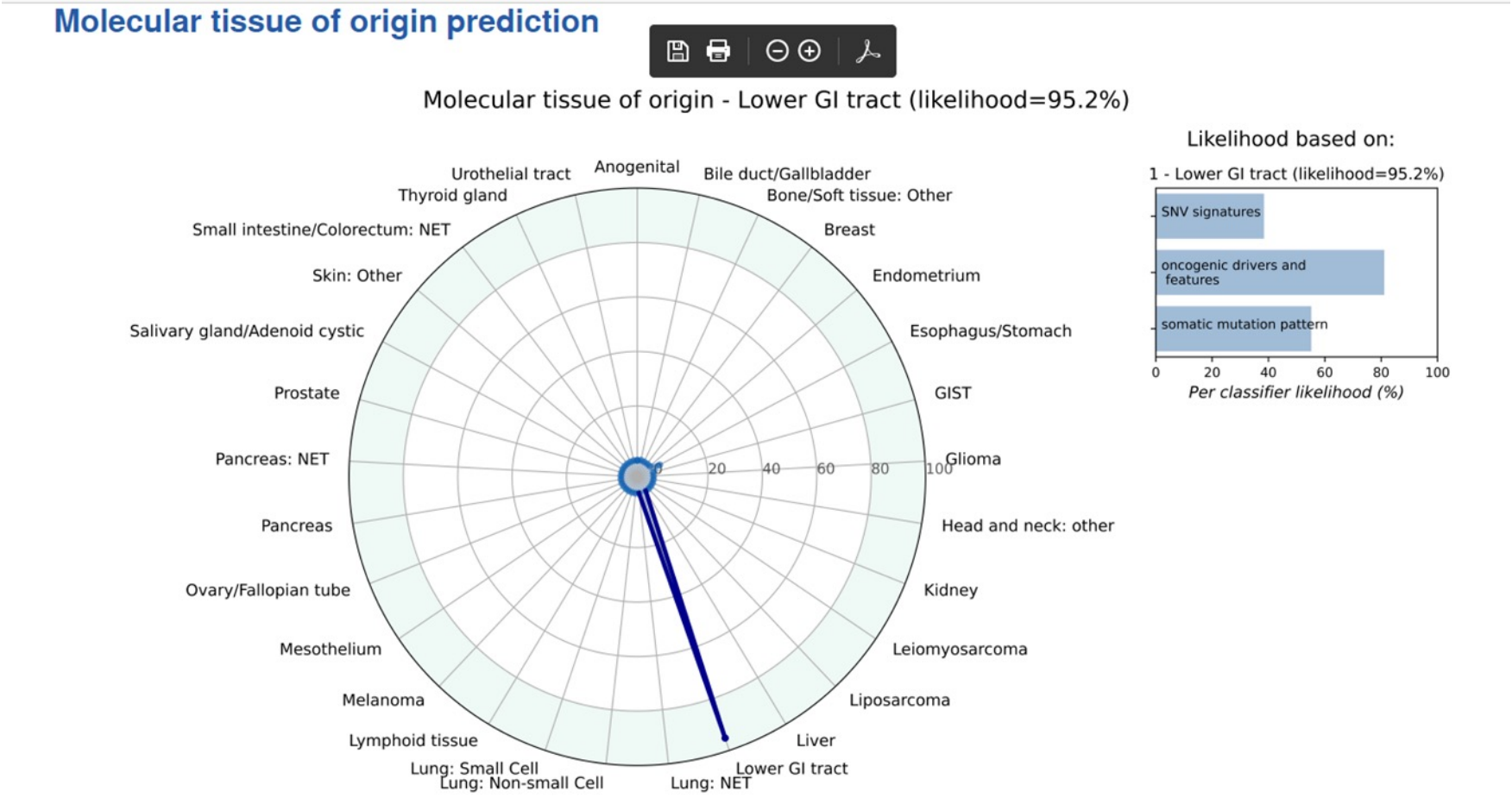

- Colorectal cancer: candidate for HIPEC, thus surgery and intent for long-term disease control.

Thank you for your attention

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Collaborators:
Hartwig Medical Foundation

- *Hans van Snellenberg*
- *Edwin Cuppen*
- *Koos van der Hoeven*
- *Many others*

Antoni van Leeuwenhoek Ziekenhuis

- *Emile Voest*
- *Many others*

Center for Personalized Cancer Treatment

- *Stefan Sleijfer*
- *Evelijn Bak*
- *All participating sites and many many datamanagers/ trial nurses etc*

Erasmus MC

- *Stefan Sleijfer*
- *Debbie Robbrecht*
- *Job van Riet*
- *Many others*

Twitter: @ErasmusOncology/ @MartijnLolkema