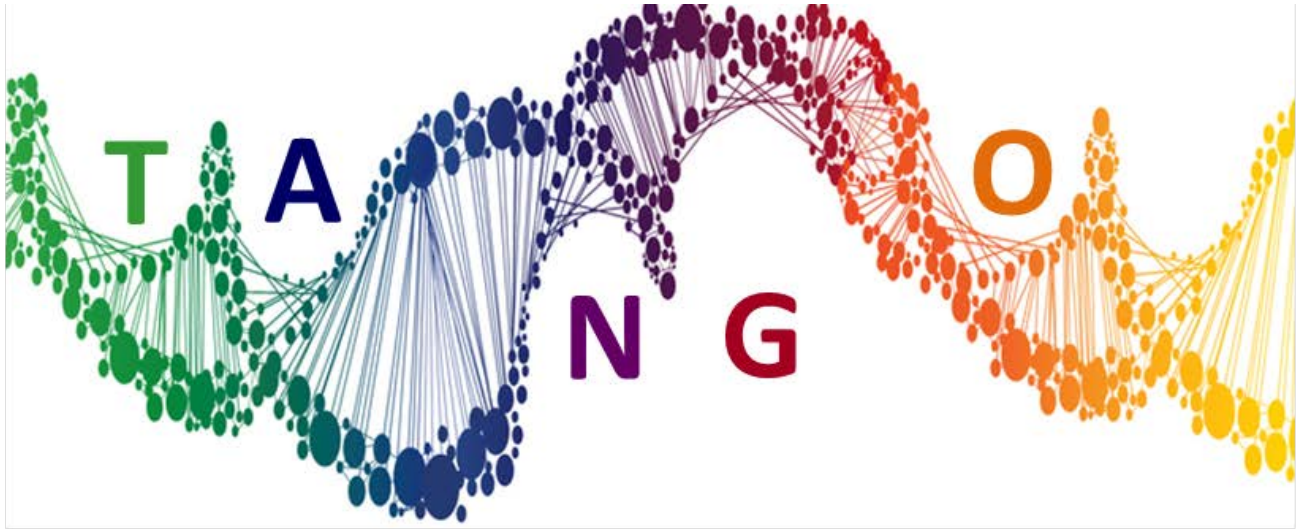


Technology Assessment of Next Generation Sequencing in Personalized Oncology

2nd TANGO symposium

October 30, 2019

Valesca Retèl

Edwin Cuppen

ZonMw

KWF KANKER BESTRIJDING

Zilveren Kruis

achmea

T A O N G

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Welcome!

TIME	PRESENTATION	SPEAKERS
13.00-13.10	Welcome	Edwin/ Valesca
13.10-13.25	Microcosting of WGS versus standard diagnostics	Clémence/Geert
13.25-13.45	Validation of whole genome sequencing against routine molecular tests	Rogier/Marc
13:45-14:15	Genomic and transcriptomic correlates of response to immune checkpoint blockade	Joanne/Joris/ Joachim/Emile
14:15-14.35	The lifetime gain of targeted and immunotherapy in NSCLC - a systematic review and modelling study	Martijn/Manuela
14:35-14.55	Time to treatment	Michiel/Erik
14.55-15.25	Pause	
15:25-15:45	When new information becomes available: should doctor's recontact?	Noor/Annelien/ Corrette/Wim
15:45-16:05	Results Scenarios	Michiel/ Martijn
16:05-16:25	Discussion on the results of the scenarios and perspective on implementing WGS as standard diagnostics in the Netherlands	Stakeholders (RIVM/ZonMw/ ZINL/ Patients
16:25-16:45	Survival pattern and Time to next treatment regimens	Zakile/Veerle
16:45-17:00	Closing Session	Edwin/ Valesca
17:00-18:00	Indonesian buffet & drink	All

Photo-moment

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Rationale

- Large variability of sequencing/NGS tests in the Netherlands
- Increased use of immunotherapy, while this is effective for only a small part of the patients

Consequences:

-Survival

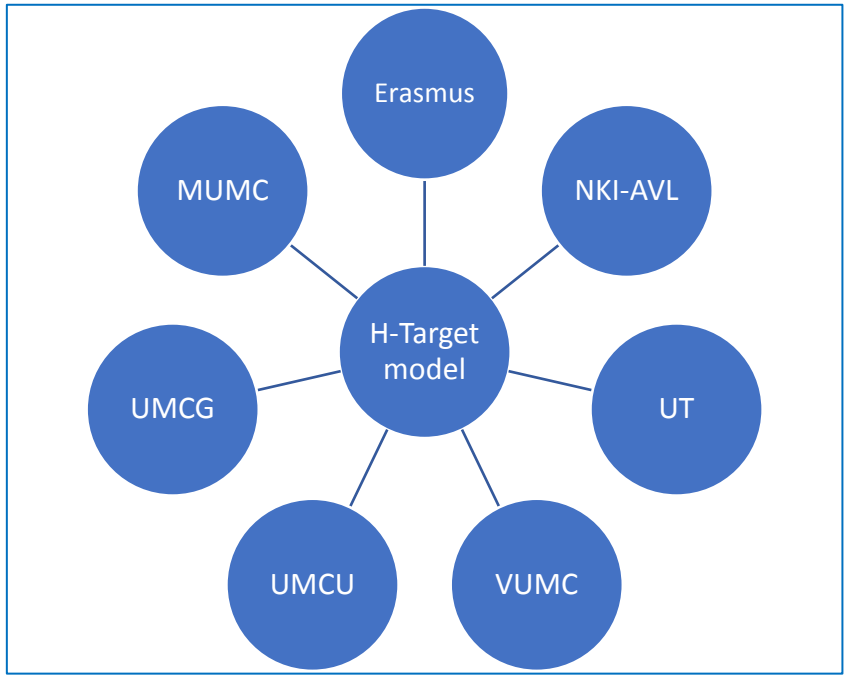
-QoL

-Health care costs

How can we optimize the use of NGS in the Netherlands?

Technology Assessment of Next Generation Sequencing in Personalized Oncology

HTA-network meets CPCT



+

CPCT
Center for Personalized Cancer Treatment

=

TANGO
Technology Assessment of Next Generation Sequencing in Personalized Oncology

€1.9M grant

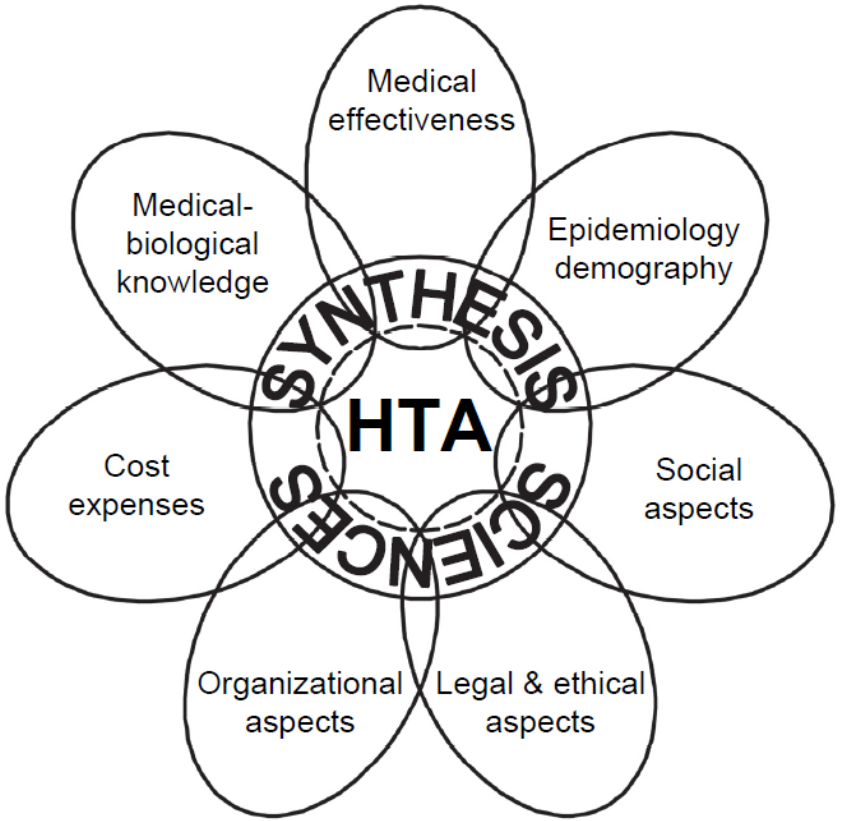
ZonMw
Zilveren Kruis
KWF KANKER BESTRIJDING
achmea

TANGO

Technology Assessment

HTA: broad evaluation of new or existing health technologies
-Clinical effectiveness
-Financial (cost-effectiveness)
-Patient related
-Ethical/legal
-Organizational

→ Information for policy making
→ Decision making for groups of patients



TA**NGO**

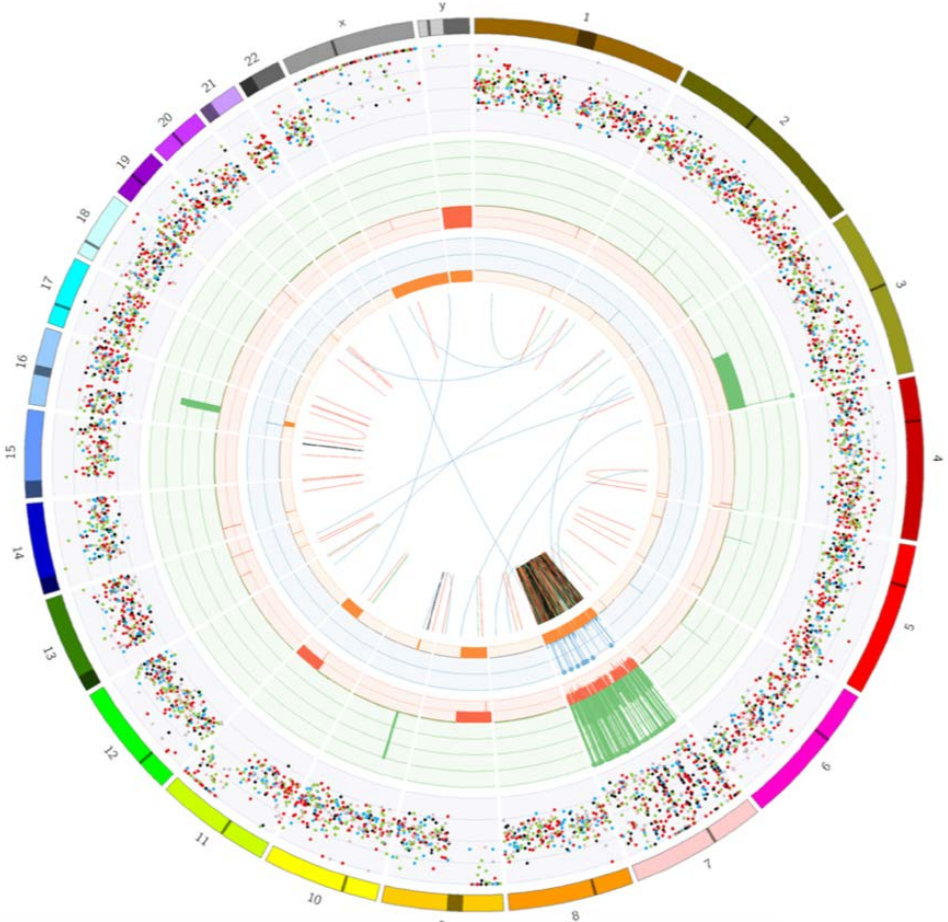
Next Generation sequencing in Oncology

- Tests for all relevant mutations in 1 experiment
- To prescribe the most optimal therapy
- This could improve survival with less toxicity

- Assist in controlling healthcare costs :

→ Offering (often expensive) treatment to only those likely to benefit.

-> Whole genome sequencing: complete tumor DNA



Hartwig
MEDICAL FOUNDATION

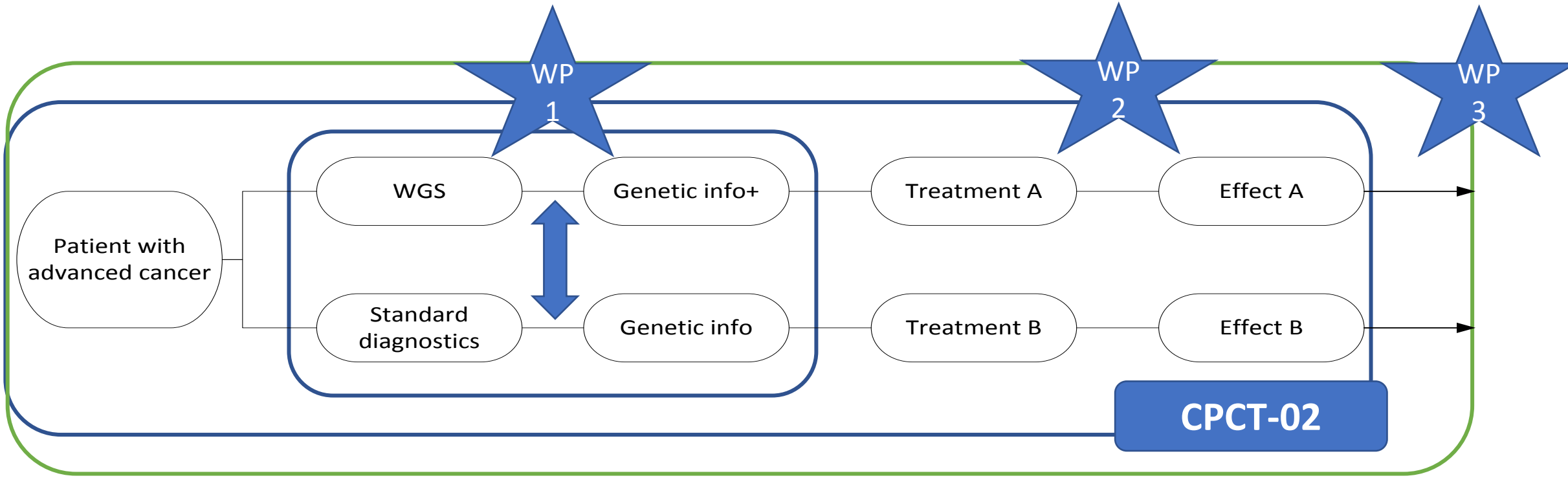
Purpose TANGO

A) to expand molecular profiling of tumors in order to improve immune- and targeted treatment selection and outcomes in patients with advanced NSCLC (and melanoma) **WP**: 1,2

B) to project long-term outcomes like cost-effectiveness, budget impact, and relevant patient & organizational issues related to the introduction of WGS compared to standard diagnostics. **WP**: 3,4,5,6

Technology Assessment of Next Generation Sequencing in Personalized Oncology

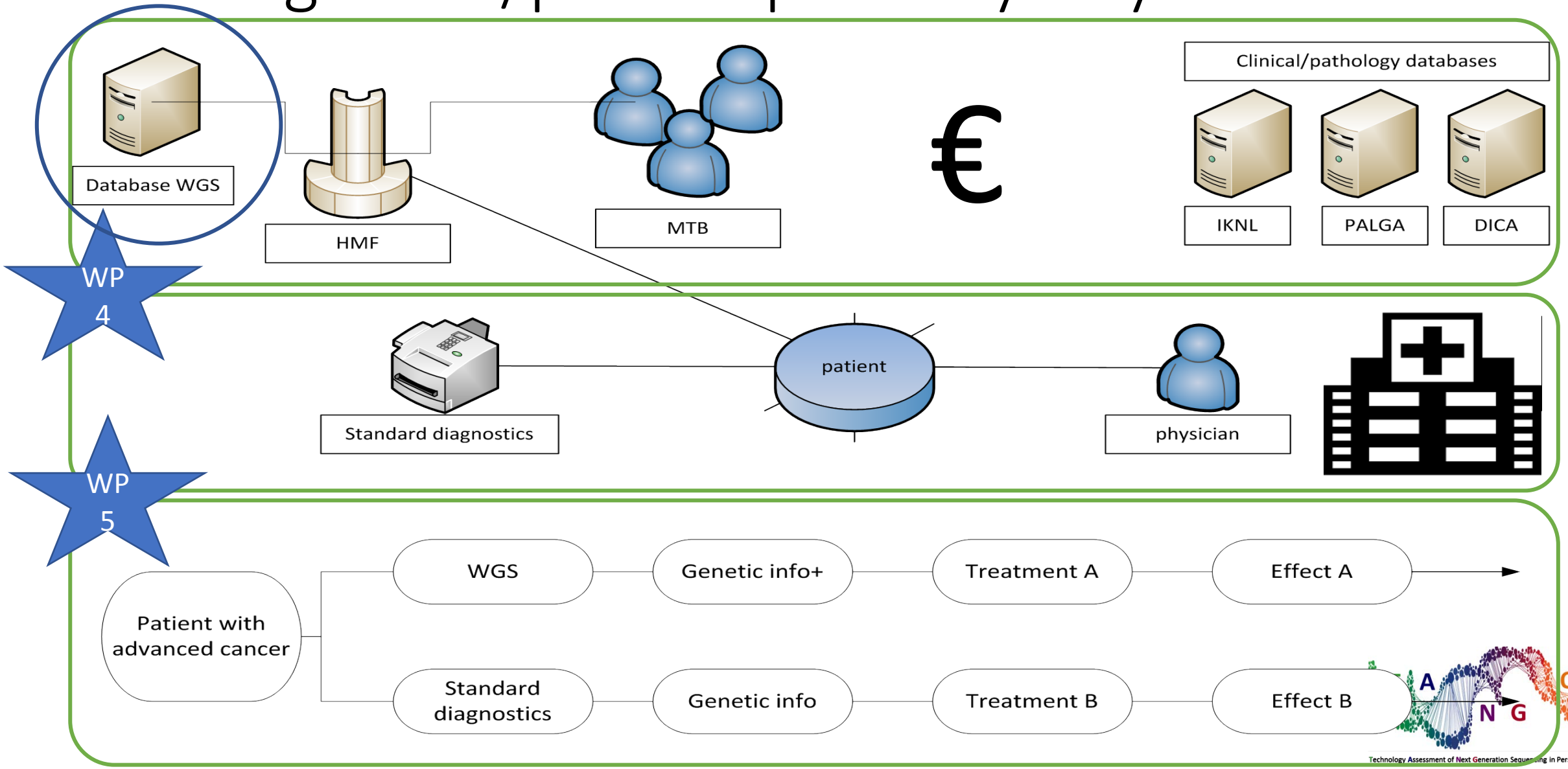
Diagnostic/patient pathway – micro level



WP1	diagnostic pathway	-> based on CPCT-02
WP2	diagnostics + treatment + survival	-> based on CPCT-02
WP3	diagnostics + treatment longer FU	-> based on registry data

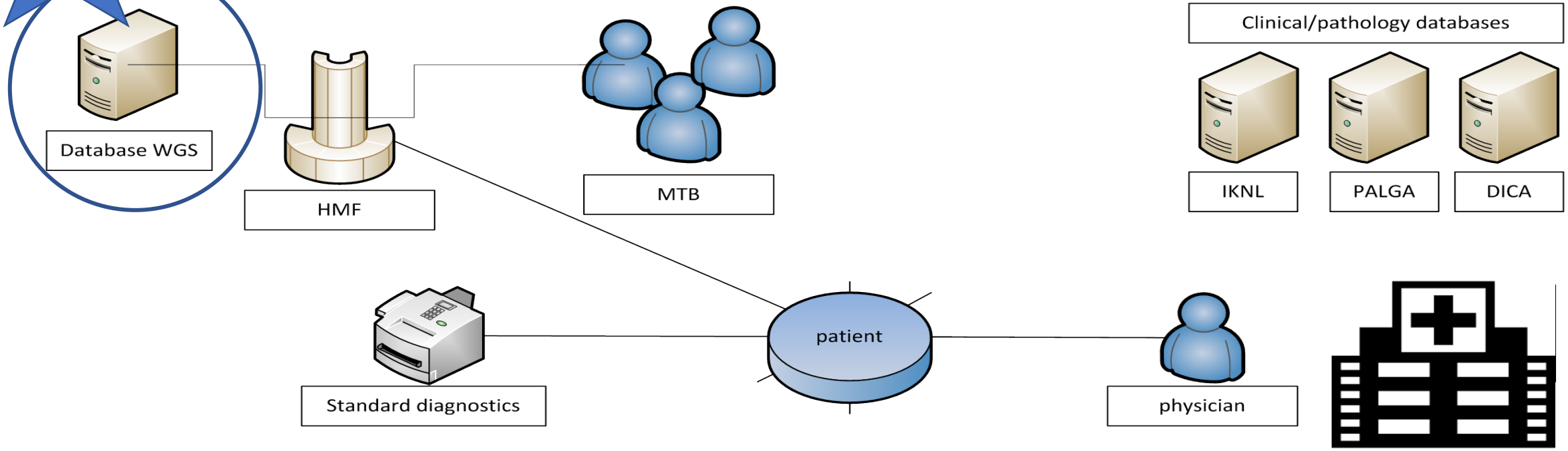
Technology Assessment of Next Generation Sequencing in Personalized Oncology

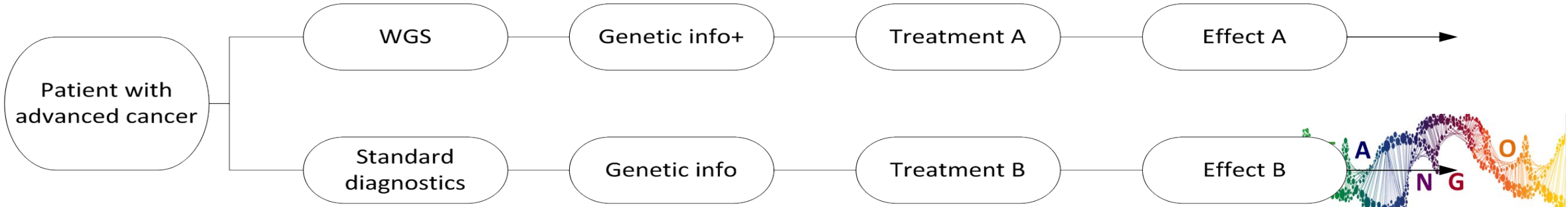
Diagnostic/patient pathway – system level



Responsible implementation – ELSI

WP 6

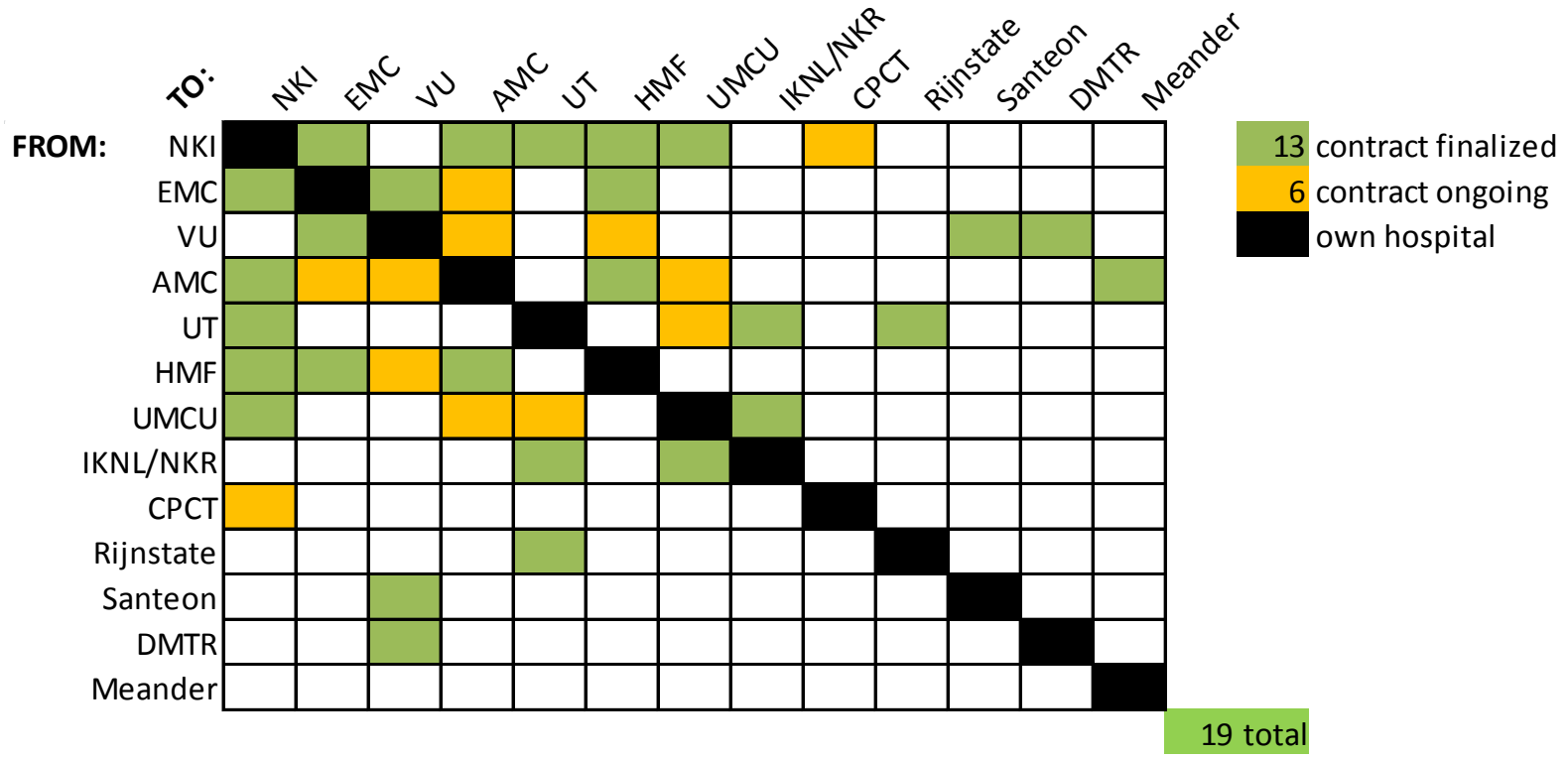




Technology Assessment of Next Generation Sequencing in Personalized Oncology

Developments since Oct 2018

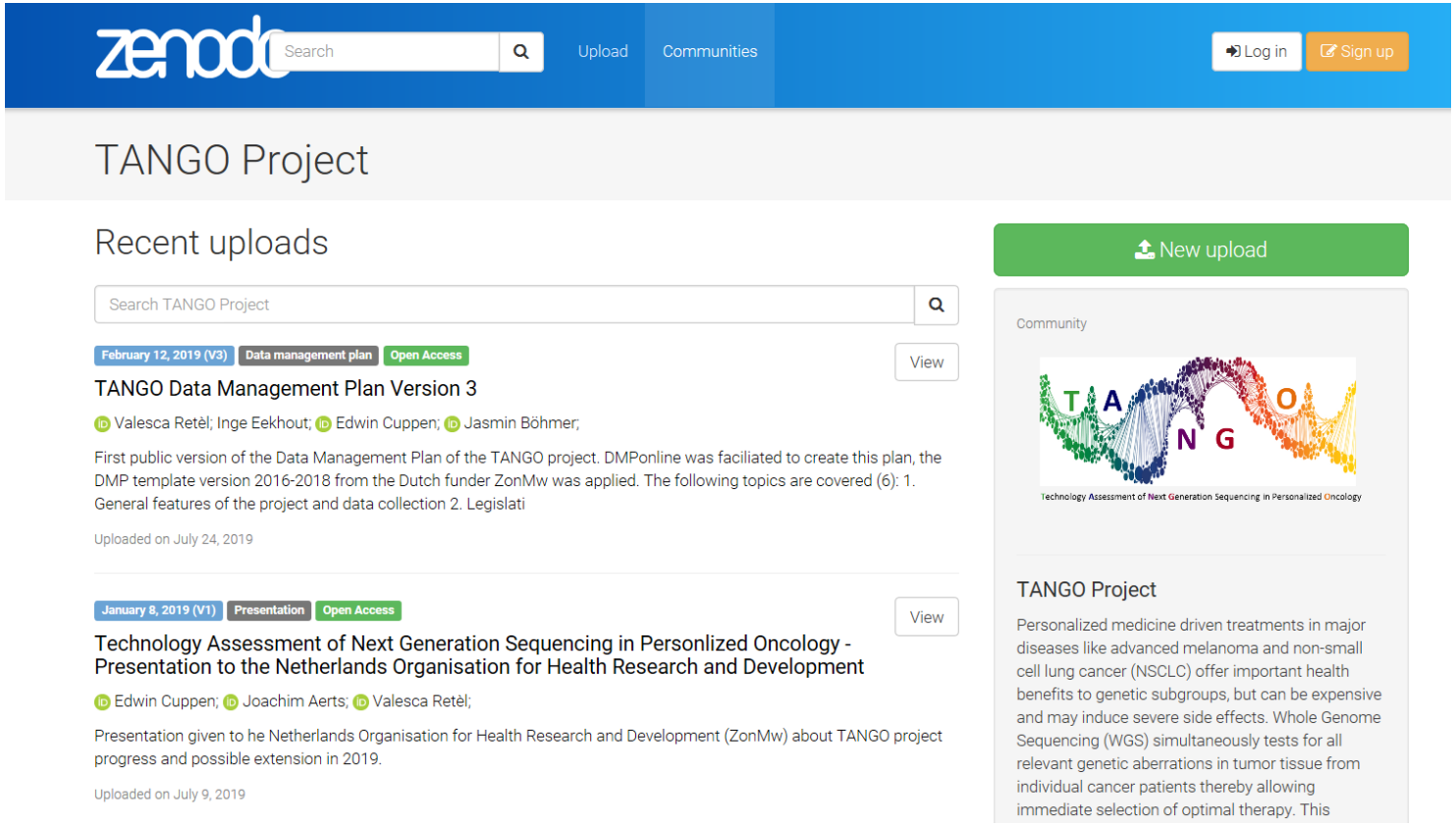
- January 2019: start melanoma
- TANGO extended till February 15th 2021
- 19 Data transfer agreements



Technology Assessment of Next Generation Sequencing in Personalized Oncology

Website ZENODO: tango-wgs

https://zenodo.org/communities/tango-wgs/



Version 4 DMP available

T A N G O
Technology Assessment of Next Generation Sequencing in Personalized Oncology

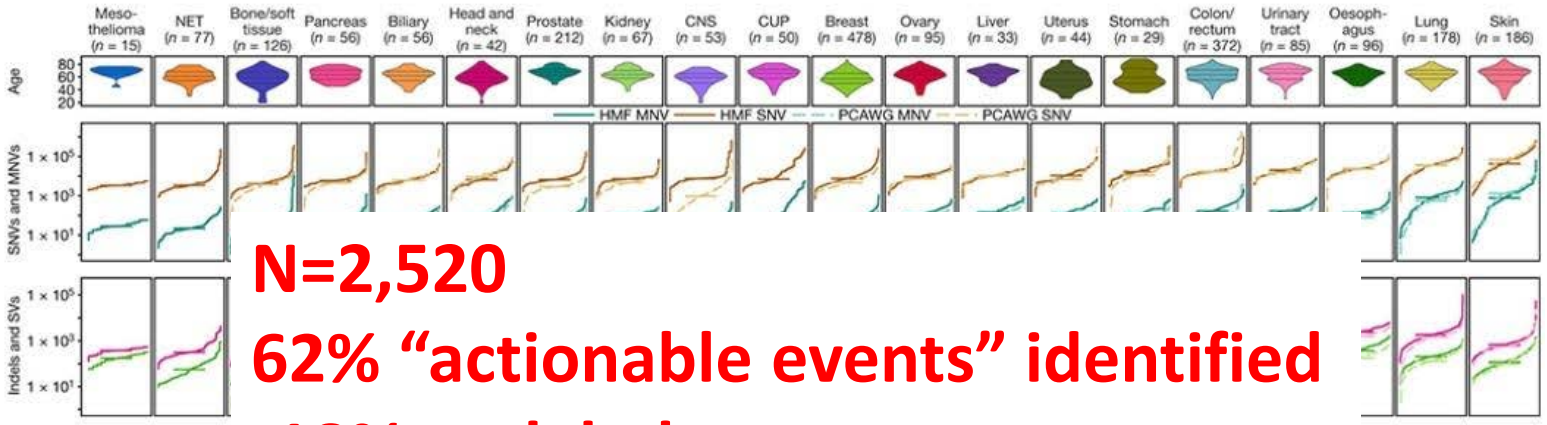
Publications TANGO

- WP 1 Microcosting (Clémence)
  - **Pasmans e.a**. Micro-costing Diagnostics in Oncology: From Single-Gene Testing to Whole Genome Sequencing
- WP5 System dynamics (Michiel)
  - **van de Ven e.a.**: Variation in the time to treatment for stage III and IV Non-Small Cell Lung Cancer patients
- WP6 ELSI-legal(Colin, Sjef en Corrette)
  - **Mitchell e.a**.: Experts reflecting on the duty to recontact patients and research participants; why professionals
  - **Ploem e.a.**: A duty to recontact in the context of genetics: futuristic or realistic?
- WP6 ELSI-ethical (Noor)
  - **Giesbertz e.a.** : a duty to recontact in genetics: context matters

Congratulations!

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Publications related to TANGO-I



N=2,520

62% "actionable events" identified

-18% on-label

-13% off-label

-31% clinical trials

CPCT-02

nature
International journal of science

Letter | Published: 30 September 2019

The Drug Rediscovery protocol facilitates the expanded use of existing anticancer drugs

D. L. van der Velden, L. R. Hoes, […] E. E. Voest

DRUP Study

Article

Pan-c
metas

https://doi.org/10.1038/s41586-019-1689-y

Received: 9 September 2018

Accepted: 20 September 2019

Published online: 23 October 2019

Open access

Peter Priestley[1,2,12], Jonathan Baber[1,2,12], Martijn P. Lolkema[3,4], Neeltje Steeghs[3,5], Ewart de Bruijn[1], Charles Shale[2], Korneel Duyvesteyn[1], Susan Haidari[1,3], Arne van Hoeck[6], Wendy Onstenk[1,3,4], Paul Roepman[1], Mircea Voda[1], Haiko J. Bloemendal[7,8], Vivianne C. G. Tjan-Heijnen[9], Carla M. L. van Herpen[8], Mariette Labots[10], Petronella O. Witteveen[11], Egbert F. Smit[3,5], Stefan Sleijfer[3,4], Emile E. Voest[3,5] & Edwin Cuppen[1,3,6*]

TANGO

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Publications related to TANGO-II

DRUP Study

Editorial

Personalised reimbursement: a risk-sharing model for biomarker-driven treatment of rare subgroups of cancer patients

Annals of Oncology

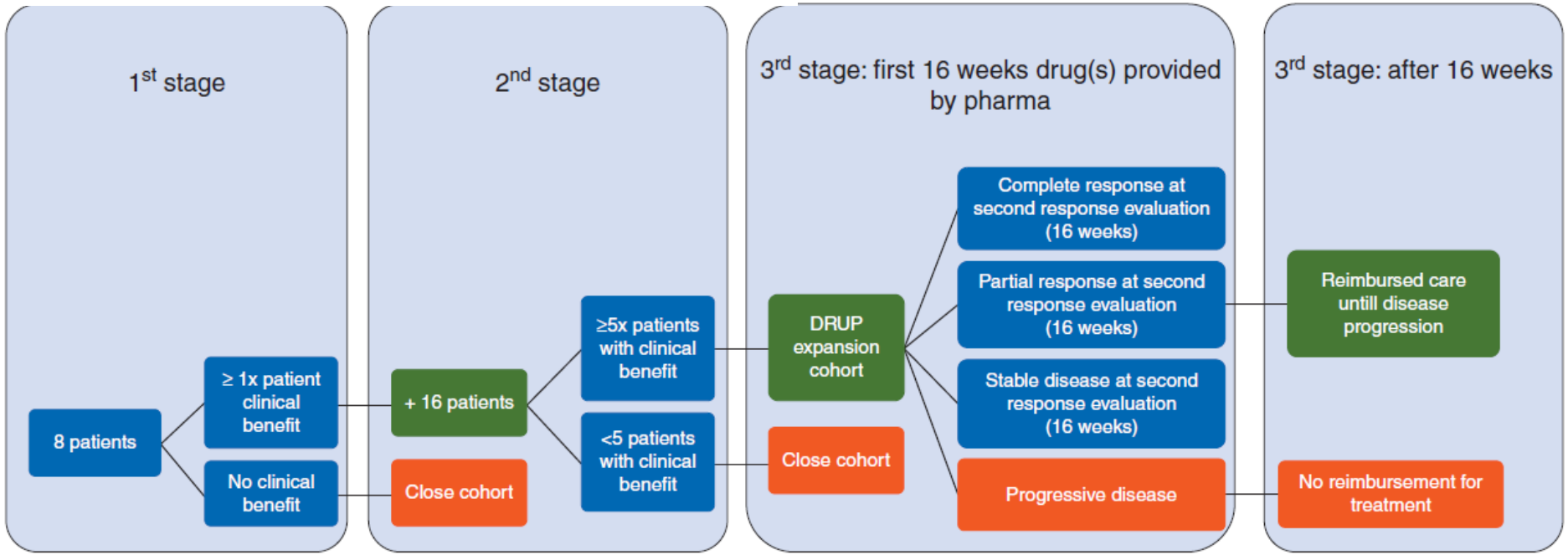


Figure 1. A performance-based, personalised reimbursement scheme after 16 weeks of clinical benefit at stage III, when the effectiveness is proven for an individual patient, commercial medication will be reimbursed by payers.

deVolkskrant

Columns & Opinie Video Wetenschap Mensen De Gids Cultuur & M

ANALYSE NIEUW FARMACEUTISCH VERGOEDINGSMODEL

Experiment met nieuwe betaalregeling dure anti-kankermedicijnen is stap naar 'no cure, no pay' in de zorg

Zorgpartijen en farmaceutische bedrijven gaan experimenteren met een nieuw no cure no pay-model. Medicijnen worden daarbij alleen vergoed als ze na 16 weken aanslaan. De hoop is dat dure medicijnen op deze wijze beschikbaar blijven, en dat artsen ze kunnen voorschrijven aan uitbehandelde patiënten die er wellicht baat bij hebben.

Michiel van der Geest 13 juni 2019, 5:00

Waalwijk van Doorn ea, Annals of Oncol, 2019

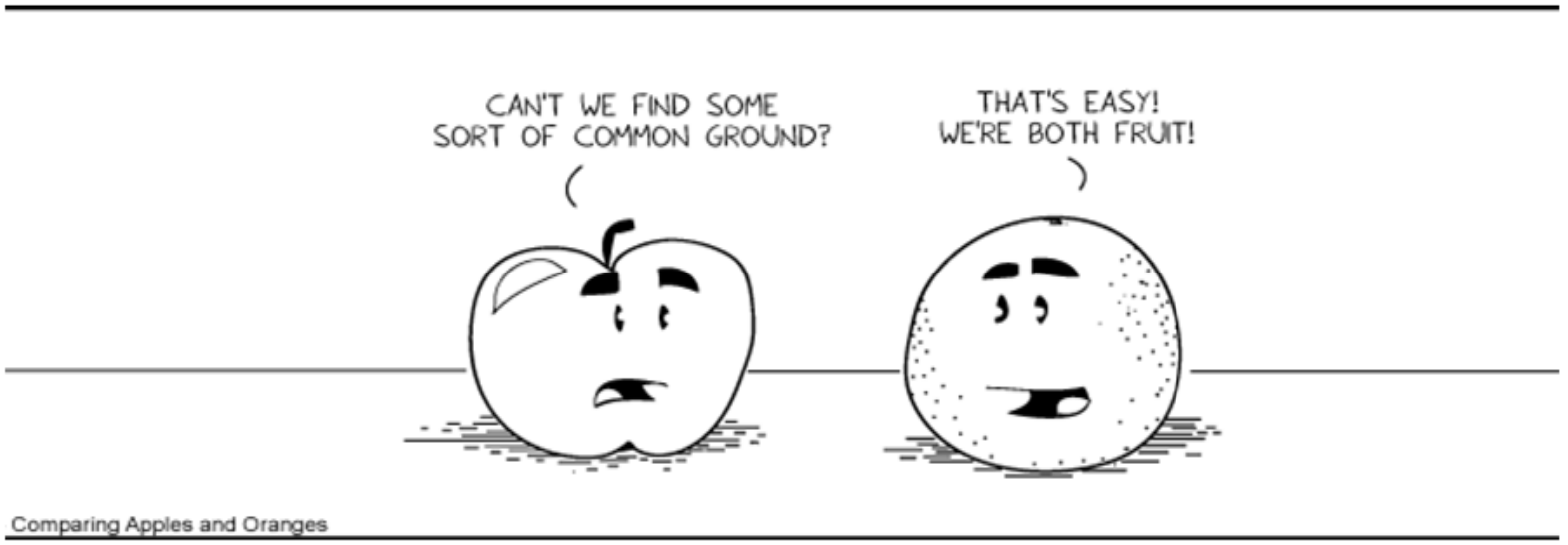
Next plans

- Design paper TANGO
- Paper on HTA-modeling approaches
- ISPOR presentations
- ..

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Microcosting diagnostics in oncology

Collaboration and transparency to enable valid comparisons



G.W.J.Frederix@umcutrecht.nl

@GeertFrederix

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Background

- Technology Assessment of Next Generation sequencing in personalized oncology (**TANGO studie**)
    - Objective (WP1)

        1) Microcosting Whole Genome Sequencing

- Predictive Analysis for Therapy: PATH to Optimising Access to Personalised Cancer Therapy in the Netherlands (**PATH studie**)
    - Objective:

        1) DEA organizational effectiveness
        2) Cost-effectiveness predictive diagnostics

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Collaboration

- Added value current diagnostics and WGS
- Price diagnostics essential in this comparison (unit costs)
- Collaboration is needed to ensure valid and comparable outcomes
- A big THANKS to Bastiaan Tops (PATH project) and Clemence Pasmans (TANGO project) for making these outcomes possible

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Objective study

- Calculate and compare total costs of WGS and different diagnostic techniques in the treatment of specific oncologic diseases

PAT
Predictieve Analyse voor THerapie

TANGO

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Method 1/2

- Data availability
  - Dutch pathology laboratories, Hartwig Medical Foundation (HMF)

- Micro-costing design
  - Measurement plan
  - Detailed and discussed

- Cost allocation
- Capital costs, maintenance costs, operational costs, software costs

PAT
Predictieve Analyse voor THerapie

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Method 2/2

- Analyses

1) Base case analysis

- *Primary outcome*
  Total costs per patient and per technique
- *Secondary outcome*
  Total cost per patient per most used combination of techniques (NSCLC, melanoma, CRC and GIST)

2) Sensitivity analysis

- Vary different unit costs: Cost drivers varied: utilization platforms and cost of consumables

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Result 1/4 – measurement plan

Maintenance costs
Annual maintenance costs additional equipment (other years)[e]
Annual maintenance costs platform (other years)[e]
Annual maintenance costs

Capital costs
Additional equipment initial costs[b]
Platform initial costs[b]
Annual capital costs additional equipment[c]
Annual capital costs platform[c]

Operational costs
Sample preparation and quality control consumables per sample[b]
Consumables per sample[b]
Data processing (per CPU hour / IT infra per tumor normal)[g]
Data storage (per GB storage per year)[g]
Personnel sample preparation and primary data analysis per sample[h]
Personnel data interpretation and report per sample[i]

Software costs
Aqcuisition software costs[b]
Annual software management / maintenance costs[f]
Annual software costs

PATH
Predictieve Analyse voor THerapie

TANGO

U

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Technology Assessment of Next Generation Sequencing in Personalized Oncology

Result 2/4 – outcomes

	Techniques																		
	IHC		FISH	Pyro seq	HRM		Sanger				NGS			Cobas	Biocartis				WGS
Additional equipment	Light microscope, Leica	Light microscope, Leica	Hybridizer (DAKO, Agilent)								Ion Chef + PCR apparatus	Ion Chef + PCR apparatus	Ion Chef + PCR apparatus		Idylla console	Idylla console	Idylla console	Idylla console	Biomek 4000
Platform	Ventana, Roche	Ventana, Roche	Fluorescence microscope, Leica	Pyromark Q24, Qiagen	LC480, Roche	LC480, Roche	Applied Biosystems, ThemoFisher	Applied Biosystems, ThemoFisher	Applied Biosystems, ThemoFisher	Applied Biosystems, ThemoFisher	IonTorrent PGM, ThermoFisher	IonTorrent PGM, ThermoFisher	MiSeq, Illumina	Cobas, Roche	Idylla, Biocartis	Idylla, Biocartis	Idylla, Biocartis	Idylla, Biocartis	NovaSeq 6000, Illumina
Platform type	ALK, ROS1	PD-1, PD-L1	ALK, ROS1, RET	EGFR+KRAS hotspots (6 amplicons)	EGFR+KRAS+BRAF hotspots (8 amplicons)	BRAF+NRAS (3 amplicons)	ABI3500 (10 amplicons: EGFR, KRAS, BRAF, ERBB2, MET)	ABI3500 (3 amplicons: BRAF, NRAS)	ABI3500 (6 amplicons: KRAS, NRAS, BRAF)	ABI3500 (9 amplicons: KIT, PDGFRA, BRAF)	PGM: 316 chip, cancerhotspot panel v2	PGM: 318 chip, cancerhotspot panel v2	MiSeq: 2x150 bp micro v2 kit, cancer hotspot panel v2	BRAF	BRAF	EGFR	KRAS	BRAF+NRAS	
Utilization	30%	30%	24%	8%	56%	28%	54%	54%	54%	54%	32%	32%	32%	0,3%	60%	60%	60%	60%	60%
Actual annual throughput	7020	7020	1498	666	1747	1747	18870	18870	18870	18870	666	1331	1331	117	624	624	624	624	2995
Capital costs																			
Additional equipment initial costs[b]	€ 50.000,00	€ 50.000,00	€ 6.679,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 9.000,00	€ 9.000,00	€ 9.000,00	€ 0,00	€ 5.000,00	€ 5.000,00	€ 5.000,00	€ 5.000,00	€ 80.000,00
Platform initial costs[b]	€ 15.000,00	€ 15.000,00	€ 70.000,00	€ 70.944,00	€ 65.000,00	€ 65.000,00	€ 136.500,00	€ 136.500,00	€ 136.500,00	€ 136.500,00	€ 61.897,00	€ 61.897,00	€ 95.811,00	€ 64.060,37	€ 45.000,00	€ 45.000,00	€ 45.000,00	€ 45.000,00	€ 761.000,00
Annual capital costs additional equipment[c]	€ 6.318,94	€ 6.318,94	€ 1.521,42	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 2.050,12	€ 2.050,12	€ 2.050,12	€ 0,00	€ 631,89	€ 631,89	€ 631,89	€ 631,89	€ 17.970,17
Annual capital costs platform[c]	€ 1.895,68	€ 1.895,68	€ 8.846,52	€ 16.160,45	€ 8.214,62	€ 8.214,62	€ 23.164,25	€ 23.164,25	€ 23.164,25	€ 23.164,25	€ 14.099,62	€ 14.099,62	€ 21.824,94	€ 8.095,87	€ 10.250,62	€ 10.250,62	€ 10.250,62	€ 10.250,62	€ 170.941,23
Capital costs per sample or per tumor normal[d]	€ 1,17	€ 1,17	€ 6,92	€ 24,28	€ 4,70	€ 4,70	€ 1,23	€ 1,23	€ 1,23	€ 1,23	€ 24,26	€ 12,13	€ 17,93	€ 29,66	€ 17,44	€ 17,44	€ 17,44	€ 17,44	€ 242,69
Maintenance costs																			
Annual maintenance costs additional equipment (other years)[e]	€ 5.000,00	€ 5.000,00	€ 200,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 900,00	€ 900,00	€ 900,00	€ 0,00	€ 500,00	€ 500,00	€ 500,00	€ 500,00	€ 3.000,00
Annual maintenance costs platform (other years)[e]	€ 500,00	€ 500,00	€ 1.000,00	€ 6.500,00	€ 3.148,00	€ 3.148,00	€ 3.655,00	€ 3.655,00	€ 3.655,00	€ 3.655,00	€ 6.100,00	€ 6.100,00	€ 11.867,00	€ 5.200,00	€ 4.000,00	€ 4.000,00	€ 4.000,00	€ 4.000,00	€ 64.000,00
Annual maintenance costs	€ 4.950,00	€ 4.950,00	€ 1.060,00	€ 5.200,00	€ 2.833,20	€ 2.833,20	€ 3.132,86	€ 3.132,86	€ 3.132,86	€ 3.132,86	€ 5.600,00	€ 5.600,00	€ 10.213,60	€ 4.680,00	€ 3.650,00	€ 3.650,00	€ 3.650,00	€ 3.650,00	€ 53.600,00
Maintenance costs per sample or per tumor normal[d]	€ 0,71	€ 0,71	€ 0,71	€ 7,81	€ 1,62	€ 1,62	€ 0,17	€ 0,17	€ 0,17	€ 0,17	€ 8,41	€ 4,21	€ 7,67	€ 17,14	€ 5,85	€ 5,85	€ 5,85	€ 5,85	€ 87,87
Software costs																			
Aqcuisition software costs[b]							€ 2.000,00	€ 2.000,00	€ 2.000,00	€ 2.000,00	€ 20.000,00	€ 20.000,00	€ 20.000,00						
Annual software management / maintenance costs[f]																			€ 400,00
Annual software costs							€ 2.000,00	€ 2.000,00	€ 2.000,00	€ 2.000,00	€ 3.500,00	€ 3.500,00	€ 3.500,00						€ 400,00
Software costs per sample or per tumor normal[d f]	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,11	€ 0,11	€ 0,11	€ 0,11	€ 5,26	€ 2,63	€ 2,63	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,00	€ 0,16
Operational costs																			
Sample preparation and quality control consumables per sample[b]	€ 69,10	€ 60,96	€ 79,60	€ 319,05	€ 46,13	€ 23,07	€ 19,30	€ 5,79	€ 11,58	€ 17,37	€ 106,48	€ 106,48	€ 140,57	€ 251,74	€ 140,00	€ 250,00	€ 190,00	€ 250,00	€ 100,00
Consumables per sample[b]					€ 3,57	€ 3,57					€ 120,29	€ 81,19	€ 33,75	€ 7,78					€ 4.000,00
Data processing (per CPU hour / IT infra per tumor normal)[g]	€ 0,10	€ 0,10	€ 0,10	€ 0,10	€ 0,10	€ 0,10	€ 0,10	€ 0,10	€ 0,10	€ 0,10	€ 0,01	€ 0,01	€ 0,01	€ 0,10	€ 0,10	€ 0,10	€ 0,10	€ 0,10	€ 200,00
Data storage (per GB storage per year)[g]	€ 0,01	€ 0,01	€ 0,01	€ 0,01	€ 0,01	€ 0,01	€ 0,01	€ 0,01	€ 0,01	€ 0,01	€ 0,05	€ 0,05	€ 0,05	€ 0,01	€ 0,01	€ 0,01	€ 0,01	€ 0,01	€ 24,00
Personnel sample preparation and primary data analysis per sample[h]	€ 20,59	€ 20,59	€ 32,71	€ 37,14	€ 28,58	€ 28,58	€ 37,38	€ 37,38	€ 37,38	€ 37,38	€ 50,82	€ 42,08	€ 42,08	€ 33,02	€ 28,05	€ 28,05	€ 28,05	€ 28,05	€ 50,00
Personnel data interpretation and report per sample[i]	€ 10,21	€ 10,21	€ 14,43	€ 16,98	€ 12,90	€ 12,90	€ 12,90	€ 12,90	€ 12,90	€ 12,90	€ 14,26	€ 14,26	€ 14,26	€ 12,90	€ 16,29	€ 16,29	€ 16,29	€ 16,29	€ 33,33
Operational costs per sample or per tumor normal[d]	€ 100,01	€ 91,87	€ 126,85	€ 373,28	€ 91,29	€ 68,23	€ 69,69	€ 56,18	€ 61,97	€ 67,76	€ 291,91	€ 244,07	€ 230,72	€ 305,54	€ 184,45	€ 294,45	€ 234,45	€ 294,45	€ 4.407,33
Total costs per cancer patient[j]	€ 101,88	€ 93,74	€ 134,48	€ 405,37	€ 97,62	€ 74,56	€ 71,19	€ 57,68	€ 63,47	€ 69,26	€ 329,85	€ 263,04	€ 258,96	€ 352,34	€ 207,74	€ 317,74	€ 257,74	€ 317,74	€ 4.738,05

Result 3/4 – outcomes

IHC		FISH	Pyro seq	HRM		Sanger			
ALK, ROS1	PD-1, PD-L1	ALK, ROS1, RET	EGFR+KRAS hotspots (6 amplicons)	EGFR+KRAS+BRAF hotspots (8 amplicons)	BRAF+NRAS (3 amplicons)	ABI3500 (10 amplicons: EGFR, KRAS, BRAF, ERBB2, MET)	ABI3500 (3 amplicons: BRAF, NRAS)	ABI3500 (6 amplicons: KRAS, NRAS, BRAF)	ABI3500 (9 amplicons: KIT, PDGFRA, BRAF)
€ 101,88	€ 93,74	€ 134,48	€ 405,37	€ 97,62	€ 74,56	€ 71,19	€ 57,68	€ 63,47	€ 69,26

NGS			Cobas	Biocartis					WGS
PGM: 316 chip, cancerhotspot panel v2	PGM: 318 chip, cancerhotspot panel v2	MiSeq: 2x150 bp micro v2 kit, cancer hotspot panel v2	BRAF	BRAF	EGFR	KRAS	BRAF+NRAS		
€ 329,85	€ 263,04	€ 258,96	€ 352,34	€ 207,74	€ 317,74	€ 257,74	€ 317,74		€ 4.738,05[a]

[a] – 4 genomes (2 samples x 2 genomes (tumor and blood)

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Result 4/4 – outcomes

Table 3. Costs of frequently applied combinations of techniques per cancer type.[a]

	NGS	Sanger	HRM	IHC	FISH	WGS	Total cost per cancer patient
	PGM 316, 318 chip; MiSeq	ABI3500 (10/3/6/9 amplicons)	BRAF+NRAS	ALK+ROS1	ALK+ROS1+RET		
NSCLC[b c]							
Test 1	€ 283,95			€ 203,77			€ 487,72
Test 2[d]	€ 283,95				€ 242,07		€ 526,01
Test 3[d]		€ 71,19			€ 242,07		€ 313,26
Melanoma[b]							
Test 1	€ 283,95						€ 283,95
Test 2			€ 74,56				€ 74,56
Test 3		€ 57,68					€ 57,68
CRC[b]							
Test 1	€ 283,95						€ 283,95
Test 2		€ 63,47					€ 63,47
GIST[b]							
Test 1	€ 283,95						€ 283,95
Test 2		€ 69,26					€ 69,26
All							
						€ 4.738,05	€ 4.738,05

PAT Predictieve Analyse voor THerapie

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Conclusion/discussion

- Detailed overview of costs diagnostics in oncology
- Adaptable and transparent framework
- Currently no comparable prices available in literature
- Essential part for upcoming evaluations
- Outcomes of today are not the outcomes of tomorrow (prices change framework is detailed snapshot of that time, we should keep that in mind)

Disclaimer: Complete economic evaluations should take place to fully assess added value

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Questions?

G.W.J.Frederix@umcutrecht.nl

@GeertFrederix

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Work Package 1

Performance of WGS

WP Leaders: Marc van de Vijver, Edwin Cuppen

PhD Candidate: Rogier Butter

Amsterdam UMC
Universitair Medische Centra

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Technology Assessment of Next Generation Sequencing in Personalized Oncology

Objectives

- Performance of WGS compared to current tests
- Molecular Tumor Boards (TMBs) for interpretation of WGS results → Collaboration PATH

Objective

- **Performance of WGS compared to current tests**

- Molecular Tumor Boards (TMBs) for interpretation of WGS results → Collaboration PATH

Methods

- Patients with NSCLC and Melanoma included in CPCT-02
- Succesfully performed WGS
- Independent of (immuno)therapy

Methods

- Routine predictive tests
- Retrospective collection

- Agreement WGS + Routine test

Inclusions of NSCLC and Melanoma patients independent of (immuno)therapy

	NSCLC	Melanoma
Amsterdam UMC	8	35
Erasmus MC	30	72
Meander	44	8
NKI-AvL	143	36
UMC Utrecht	2	24
Total	227	175
Total All centers	**318**	**276**

Progress NSCLC and Melanoma ± 60%

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Technology Assessment of Next Generation Sequencing in Personalized Oncology

Different gene panels among centers for NSCLC, all using next generation sequencing

Center	Gene panels during study period	Techniques	Covered genes
Amsterdam UMC	1	NGS (IonTorrent)	+/- 50
Erasmus MC	3	NGS (IonTorrent)	23, 41, 41
Meander	UMC Utrecht	UMC Utrecht	UMC Utrecht
NKI-AvL	2	NGS (Illumina) Massarray (Sequenom)	51 8
UMC Utrecht	1	NGS (IonTorrent)	54

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Technology Assessment of Next Generation Sequencing in Personalized Oncology

Basic characteristics: Prevalence of mutated genes in routine testing consistent with literature

Genes %	Prevalence Centers	Percentage Literature
EGFR	39%	30%
KRAS	22%	30%
CDKN2A	9%	2%
BRAF	9%	6%
TP53	53%	50%
MET ampl	6.3%	3%
ERBB2	5%	4%
PIK3CA	8%	3%

Skoulidis and Heymach; Nature Reviews 2019/Lee ea; J Thor Oncol 2010;

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Plan: Paired analysis of mutation data routine practice and WGS

- Selection of genes present in all gene panels
- Distinguish subgroups:
  - Biopsy same time + site
  - Biospy different time + same site
  - Both different
- Paired analysis of WGS and routine testing

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T A N G O
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Objective

- Performance of WGS compared to current tests

- **Molecular Tumor Boards (TMBs) for interpretation of WGS results**

  → Collaboration PATH

Collaboration with PATH project

- Inventarisation of MTBs through the Netherlands
- Method for use in MTBs

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Molecular Tumor Board in Amsterdam UMC every 2 weeks

- AMC, Vumc, Spaarne
- Vumc, NKI-AvL
- Intention for uniform MTB
- Inventarising relevant cases

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T A N G O
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Objectives

1. Validation of WGS

2. Implementation of Molecular Tumor Boards (TMBs)

Perspectives

- End 2019 completion datacollection
- Start 2020 start data analysis

Genomic and transcriptomic correlates of response to immune checkpoint blockade

WP2:
Jessica Notohardjo, Fons van den Eertwegh (Amsterdam UMC)
Joris van de Haar, Emile Voest (AvL)
Joanne Mankor, Joachim Aerts (Erasmus MC)

Hartwig MEDICAL FOUNDATION

CPCT Center for Personalized Cancer Treatment

TANGO Technology Assessment of Next Generation Sequencing in Personalized Oncology

Objectives work package 2

- Demonstrate the value of WGS for immunotherapy treatment selection for NSCLC and melanoma
  - Discovery of genomic and transcriptomic correlates of response
  - Identify potential biomarkers for patient stratification

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Inclusion CPCT-02 for TANGO

509 NSCLC patients included in CPCT-02

148 biopsies suitable for WGS

102 treated with immunotherapy

34 treated with targeted therapy

412 melanoma patients included in CPCT-02

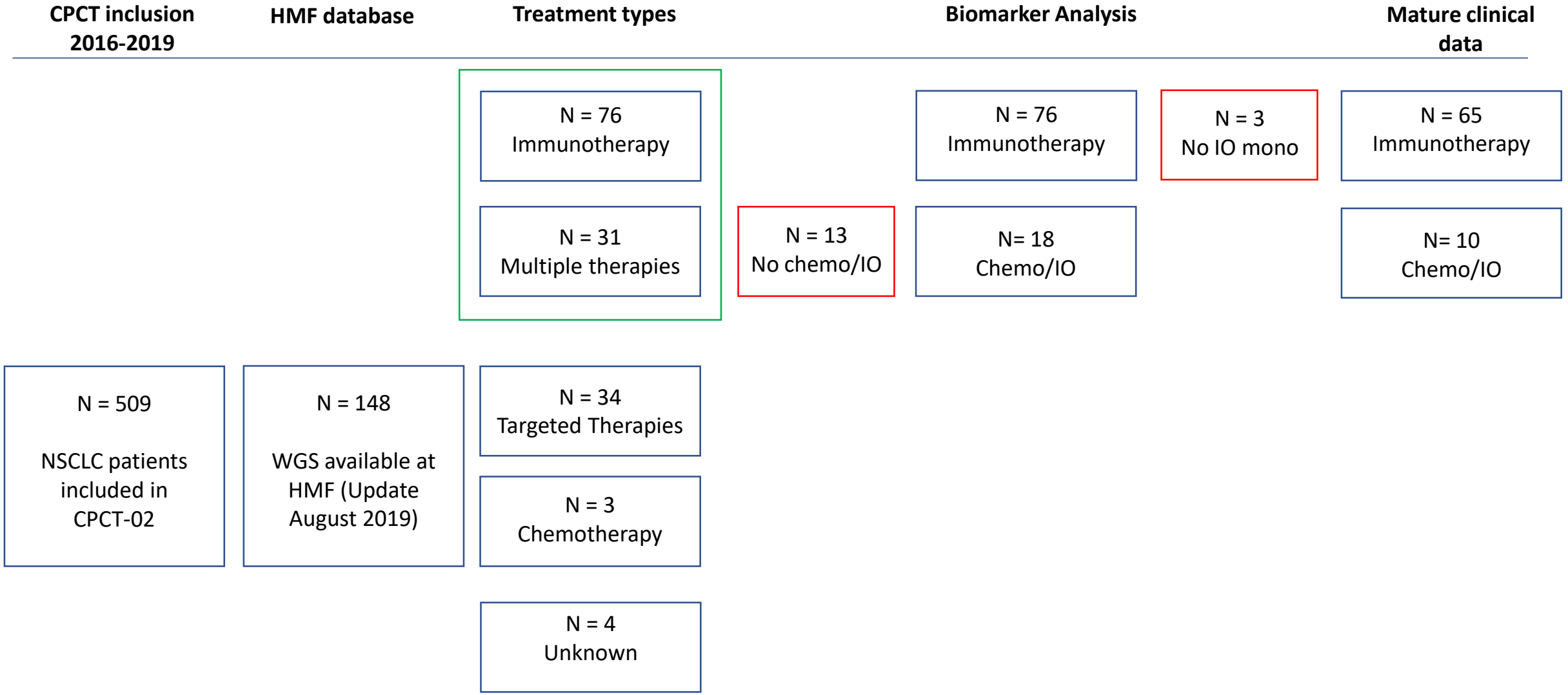
243 biopsies suitable for WGS

185 treated with immunotherapy

49 treated with targeted therapy

WGS and clinical data available for analysis

Technology Assessment of Next Generation Sequencing in Personalized Oncology



Technology Assessment of Next Generation Sequencing in Personalized Oncology

Patient characteristics

Patient characteristics	N= 75
WGS and IO monotherapy WGS and IO combination therapy	65 10
ECOG - 0 - 1 - ≥ 2	59 14 (23,7%) 25 (59,5%) 10 (16,9%)
Smoking - current or former - Never - NA	66 48 (72,7%) 3 (4,5%) 13 (19,7%)
Histology - Adeno - SCC - NOS	61 41 (76,2%) 9 (14,8%) 11 (18,0%)
PD-L1 TPS (%) - <1% - 1-49% - ≥ 50%	48 25 (52,1%) 15 (31,3%) 8 (16,7%)
Line of Tx - 1 - 2 - ≥ 3	64 10 (15,6%) 50 (78,1%) 4 (6,3%)

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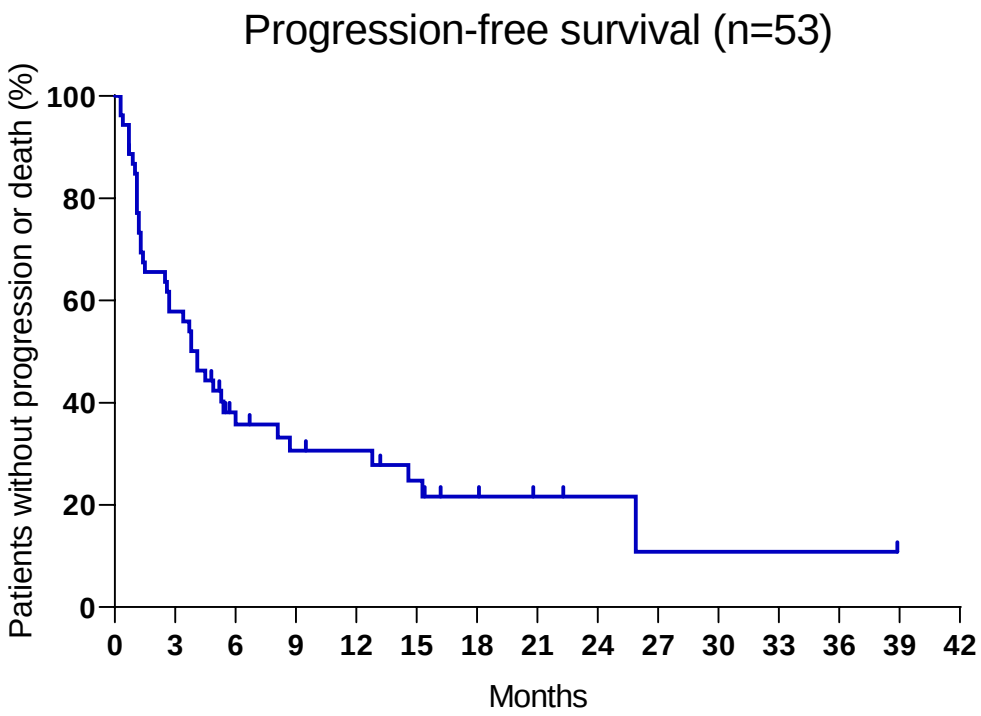
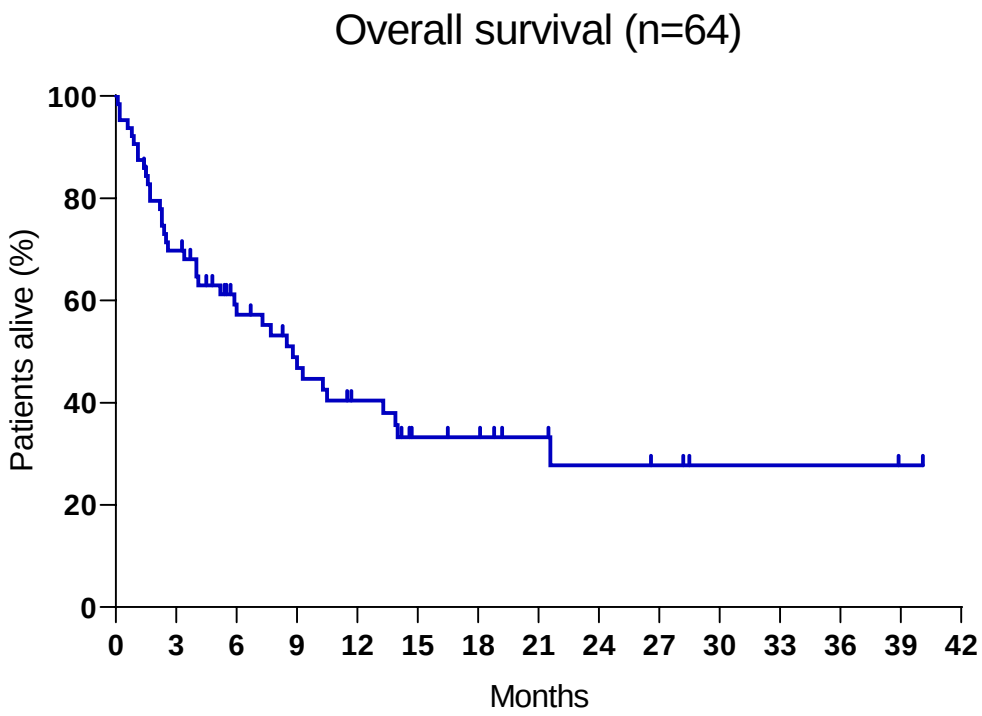
PFS and OS in the TANGO NSCLC cohort (immuno monotherapy)





	Median PFS *mo*	**1-YR PFS**	**Median OS *mo***	**1-YR OS**
Immunotherapy (n=53)	4.1	30%	8.8	40%

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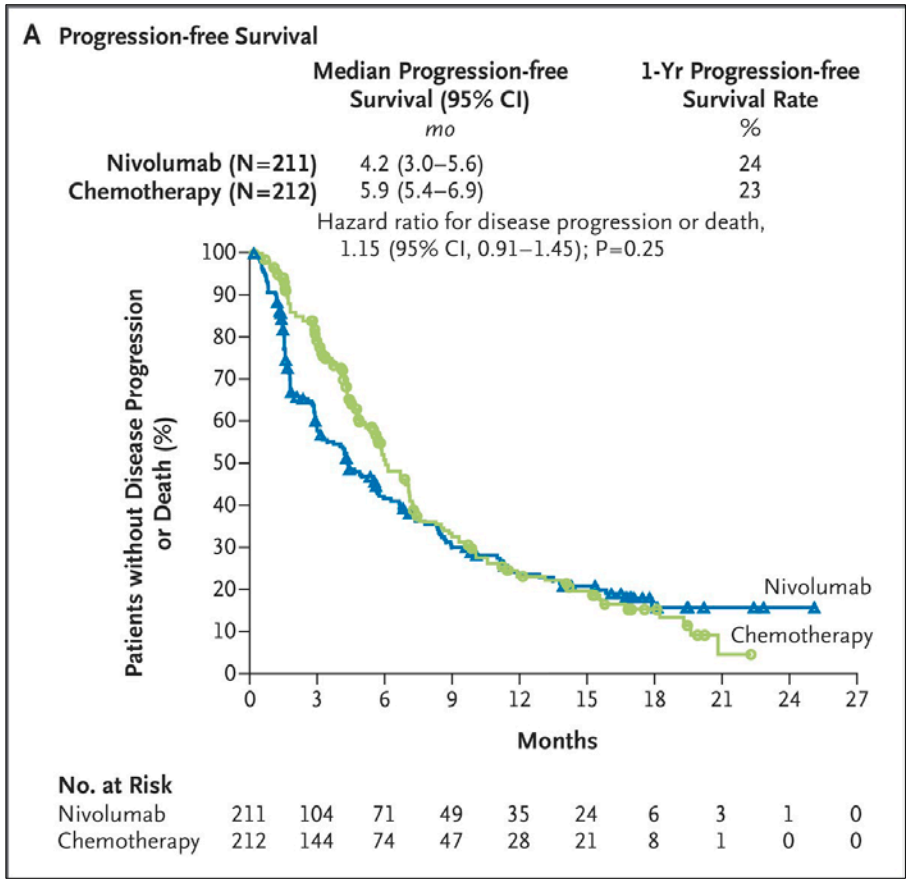
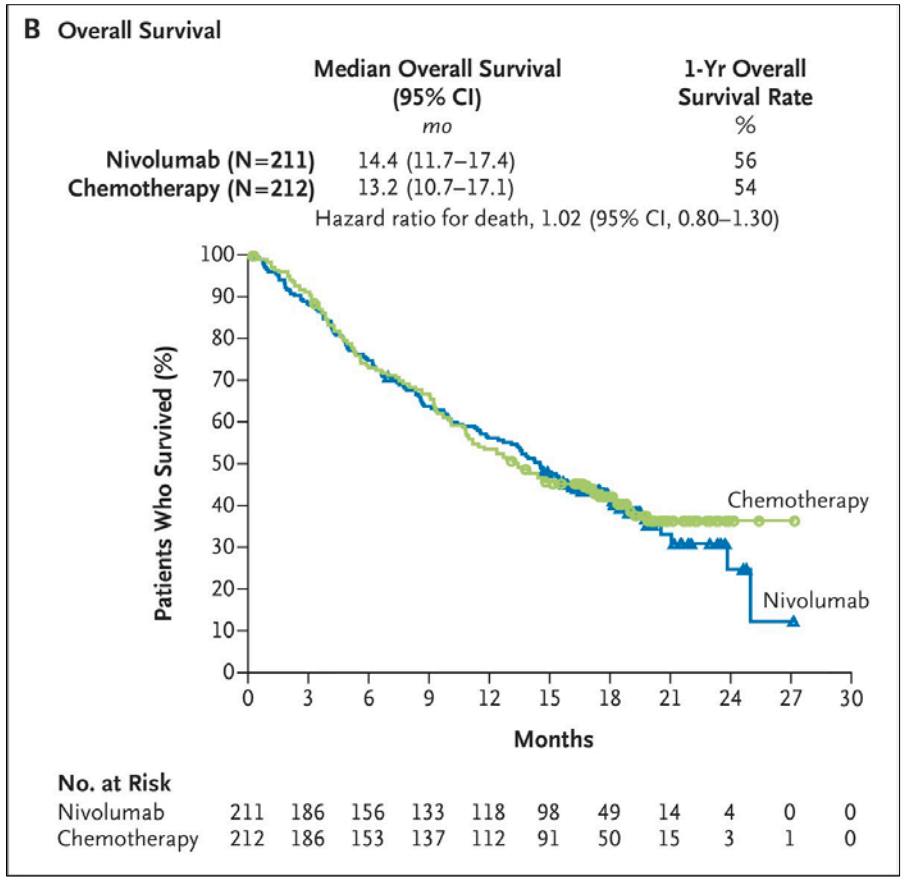
Real life data compared to clinical studies





1st line nivolumab in KN-024 (PD-L1>50%), Reck et al. NEJM 2016

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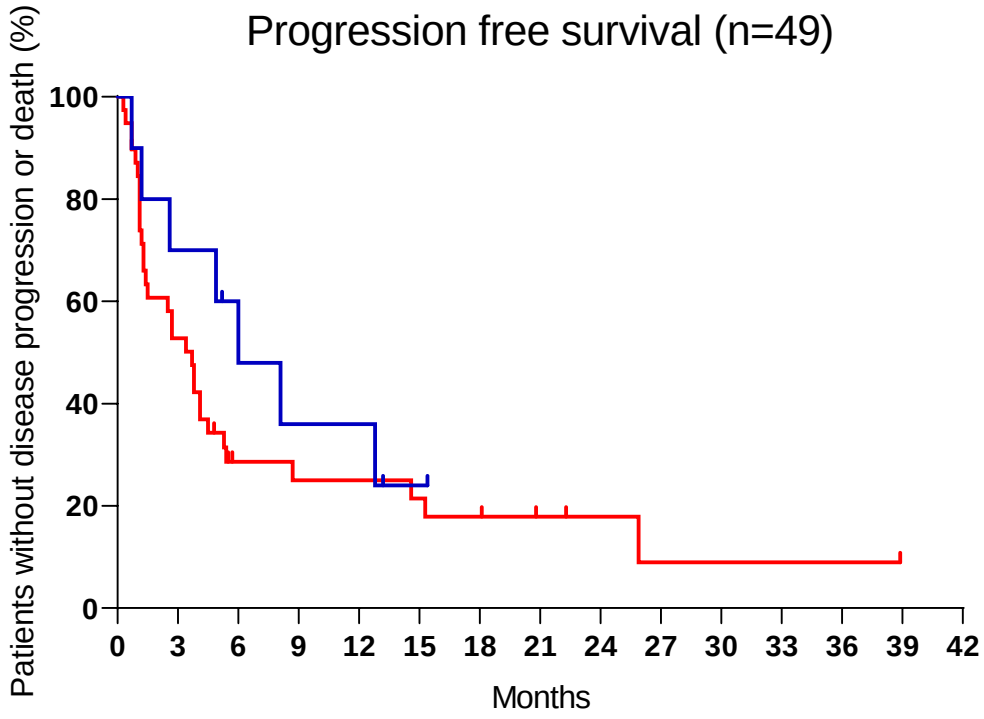
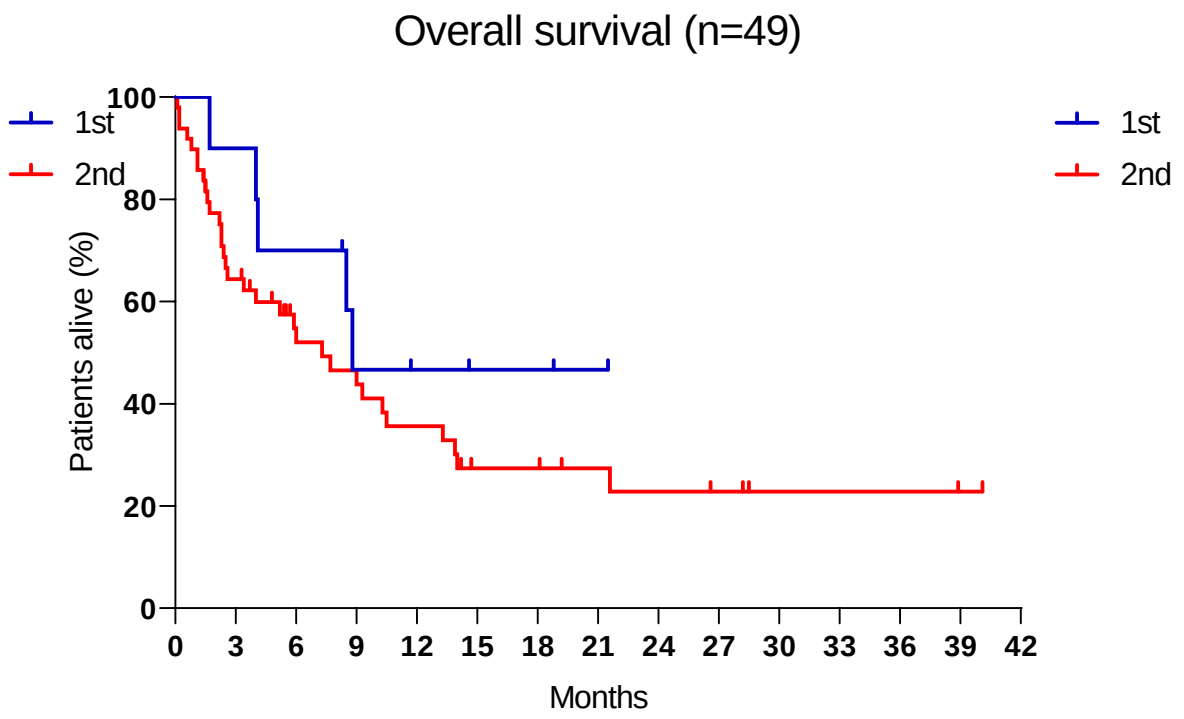
PFS and OS depends on line of treatment





line of Tx	Median PFS *mo*	1-YR PFS	Median OS *mo*	1-YR OS
1st line (n=10)	6	36%	8.8	47%
2nd line (n=39)	3.7	25%	7.3	33%

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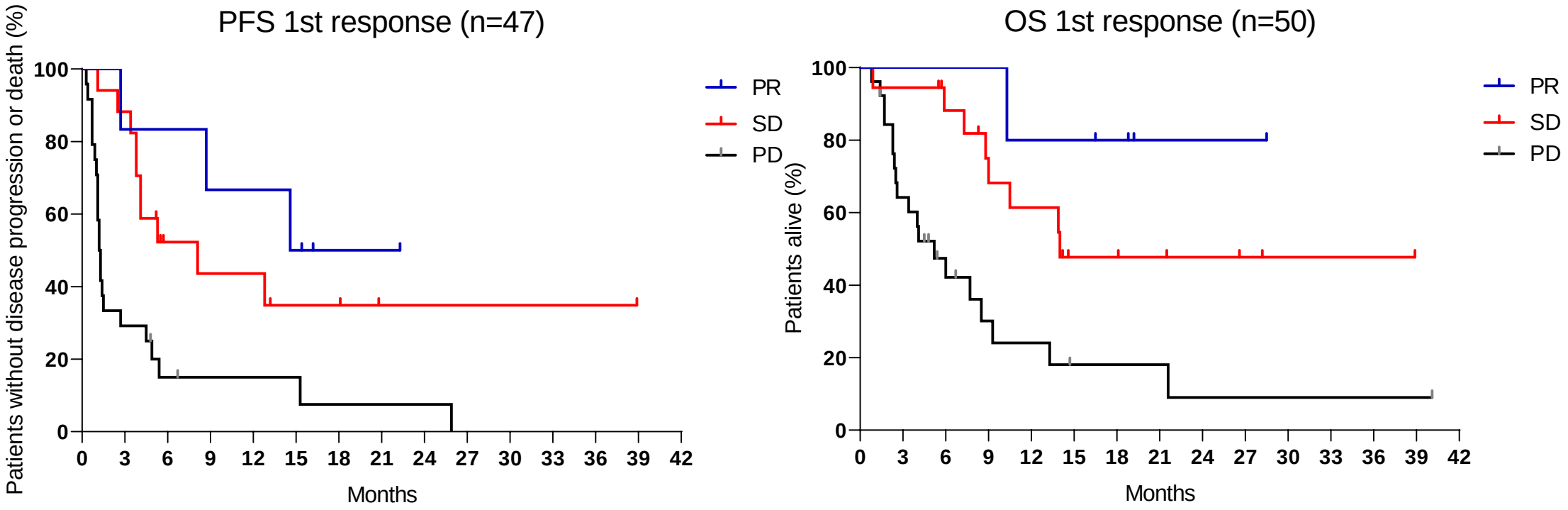
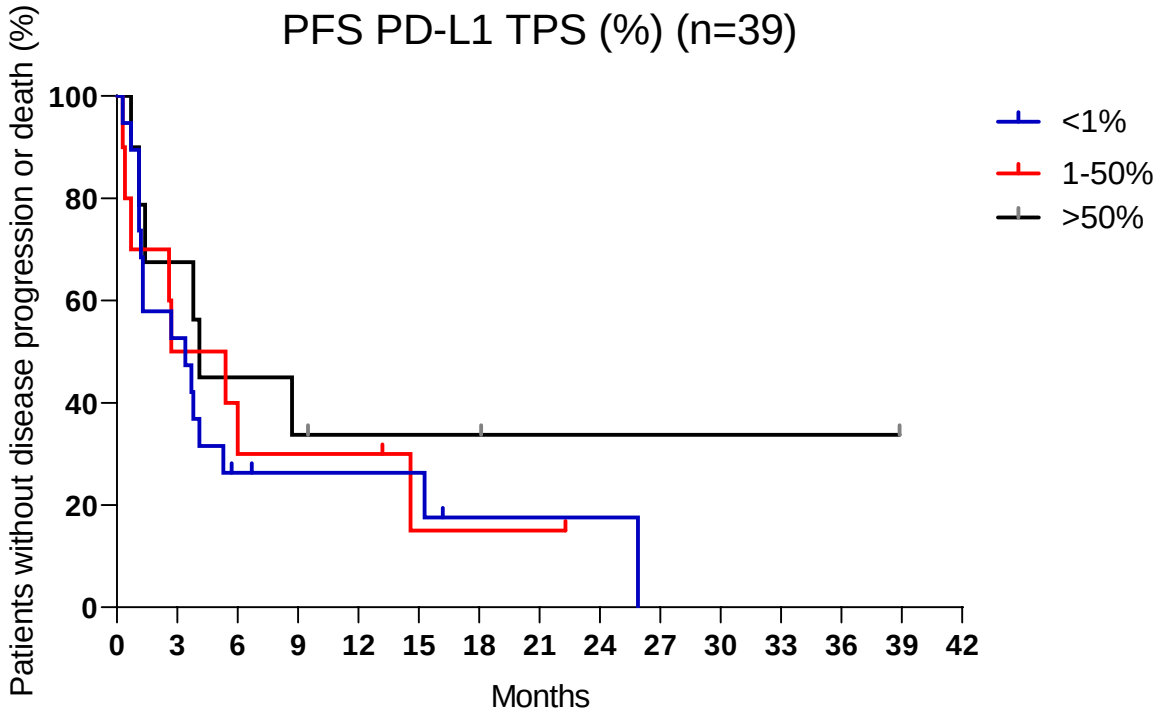
PFS and OS compared to 1st response evaluation in CPCT/HMF database

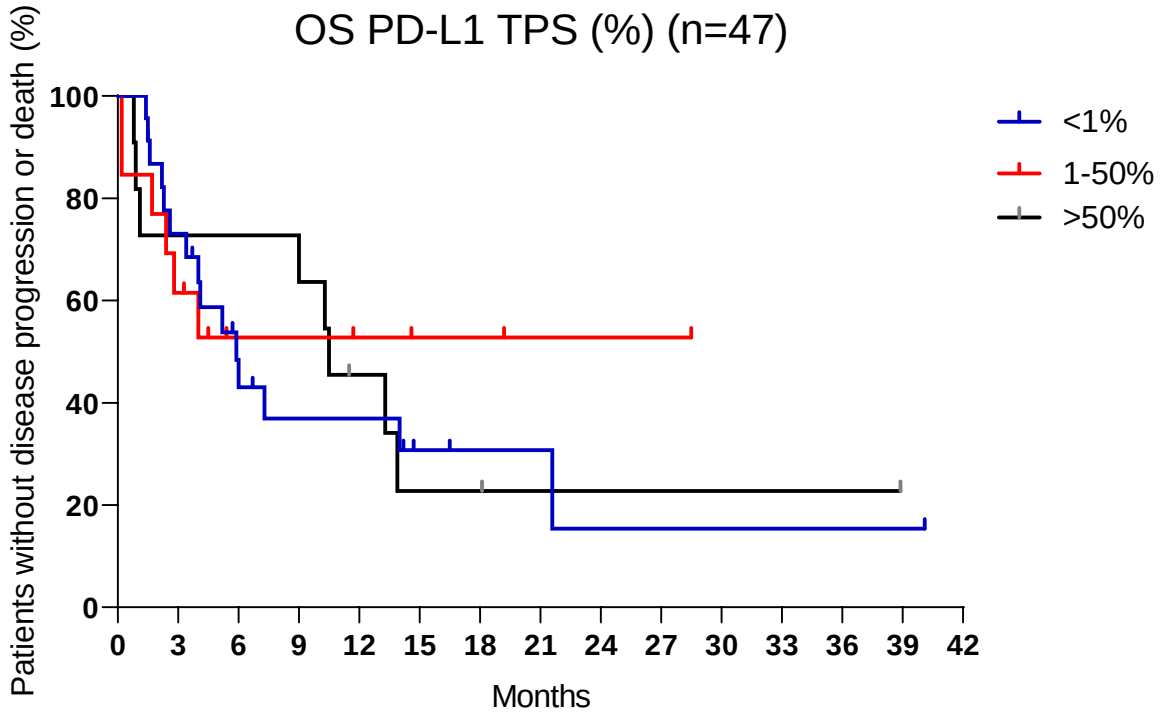


1st response	Median PFS *mo*	1-YR PFS	Median OS *mo*	1-YR OS
PR (n=6)	18.45	67%	Not reached	80%
SD (n=18)	8.1	43%	14	61%
PD (n=26)	1.25	15%	5.2	24%

Technology Assessment of Next Generation Sequencing in Personalized Oncology

PFS in PD-L1 expression subgroups





PD-L1 TPS (%)	**Median PFS *mo***	**1-YR PFS**	**Median OS *mo***	**1-YR OS**
<1% (25)	3.1	23%	5.2	35%
1-50% (15)	4.1	28%	4.5	53%
>50% (8)	4.0	33%	10.5	45%

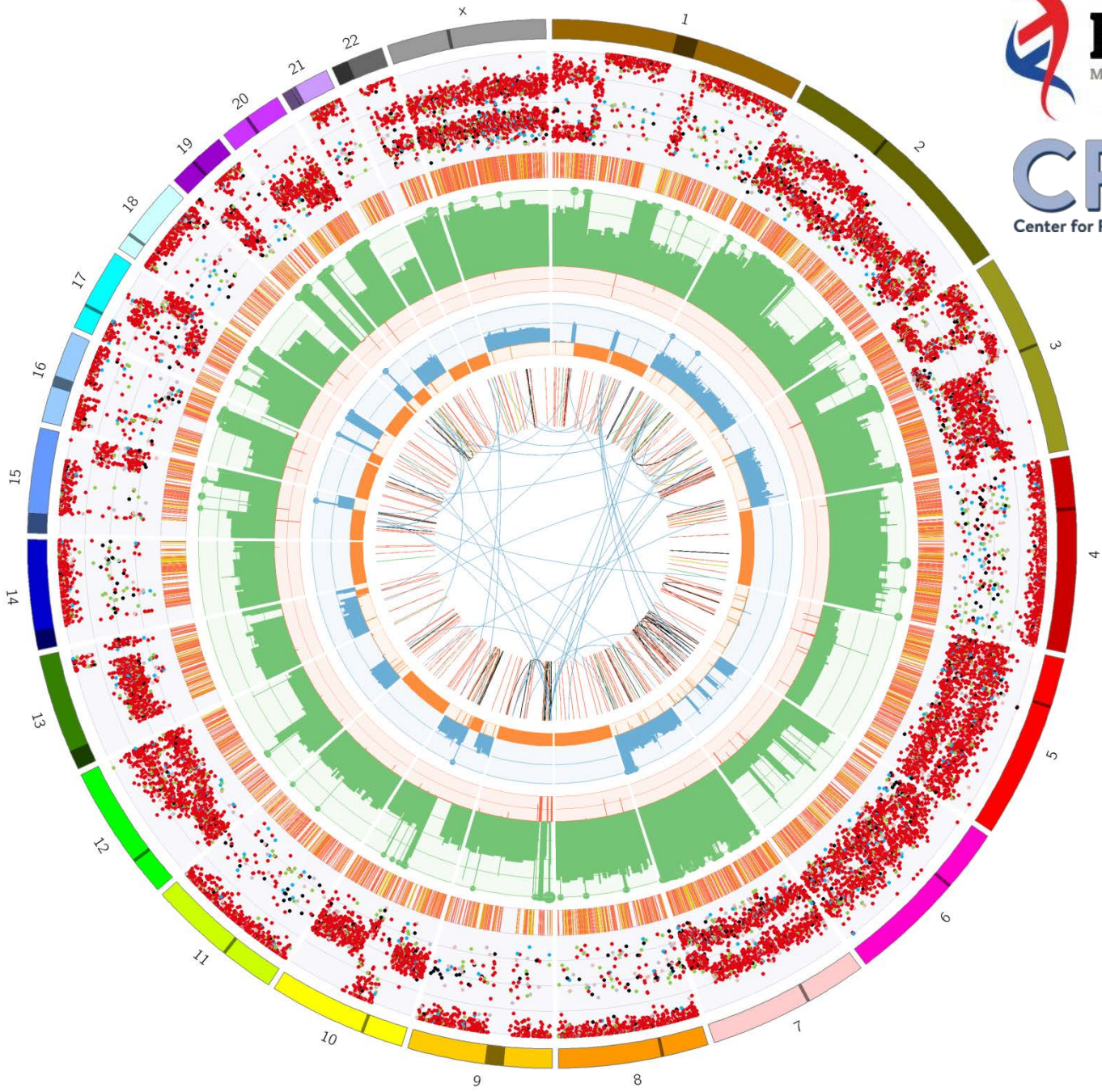
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Part II: WGS and RNAseq analysis in TANGO

Whole genome sequencing of tumor-normal pairs

High sequencing depth:
- ~100-130X for tumor
- ~ 30X for germline

Information
1. Mutations
2. Indels
3. Structural variants
4. Copy number variations



RNA-sequencing of tumors

~60% of patients

Information
1. Immune signatures
2. Differential expression analysis

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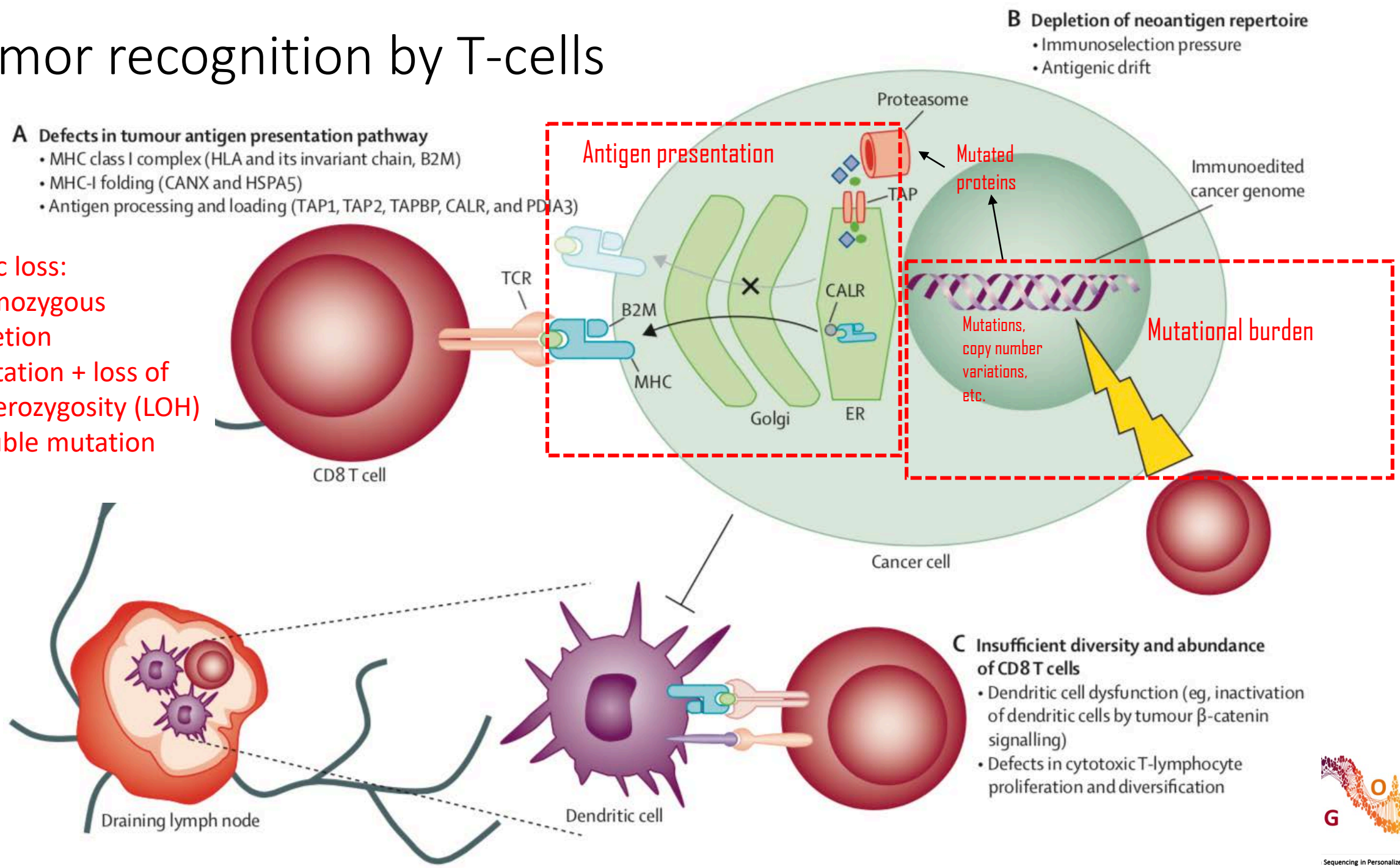
N G O

t of Next Generation Sequencing in Personalized Oncology

Tumor recognition by T-cells

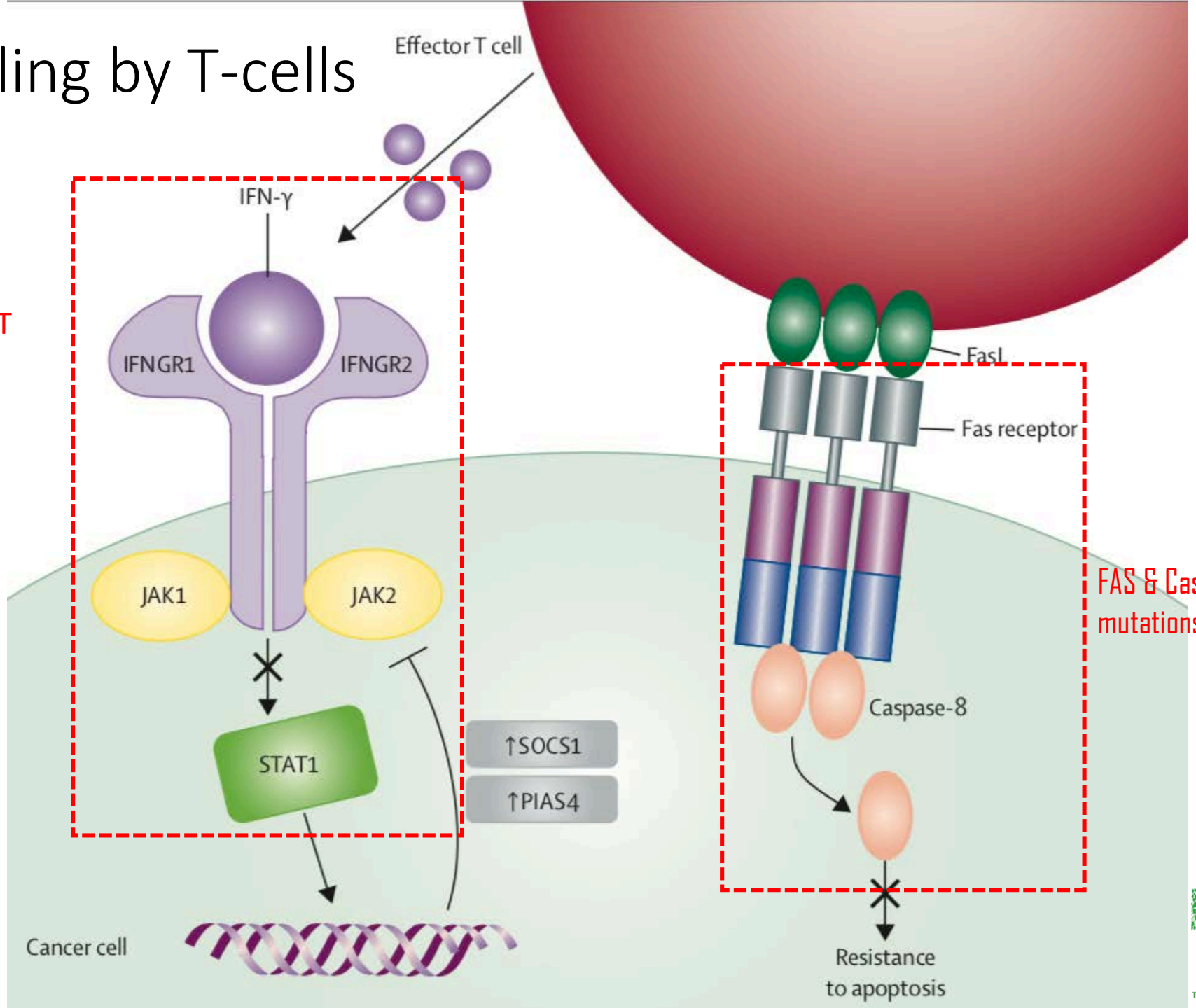
Biallelic loss:
- Homozygous deletion
- Mutation + loss of heterozygosity (LOH)
- Double mutation



Sequencing in Personalized Oncology

Tumor killing by T-cells

IFNG-JAK-STAT pathway mutations

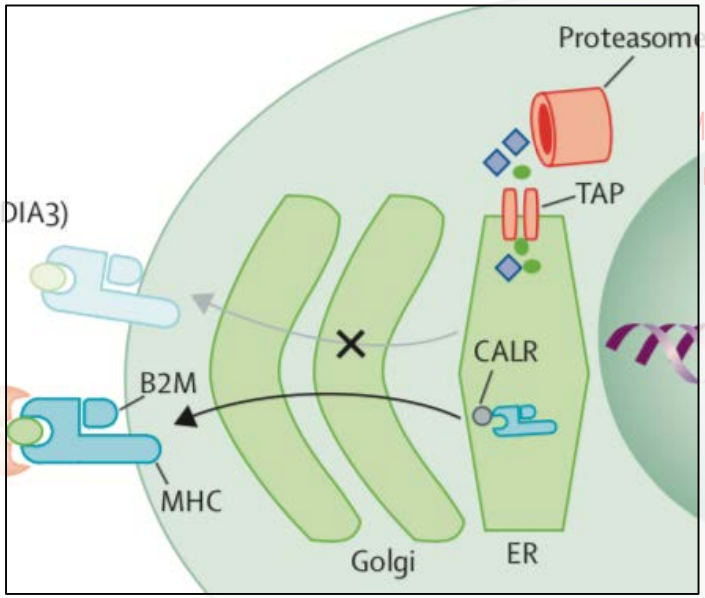


FAS & Caspase-8 mutations

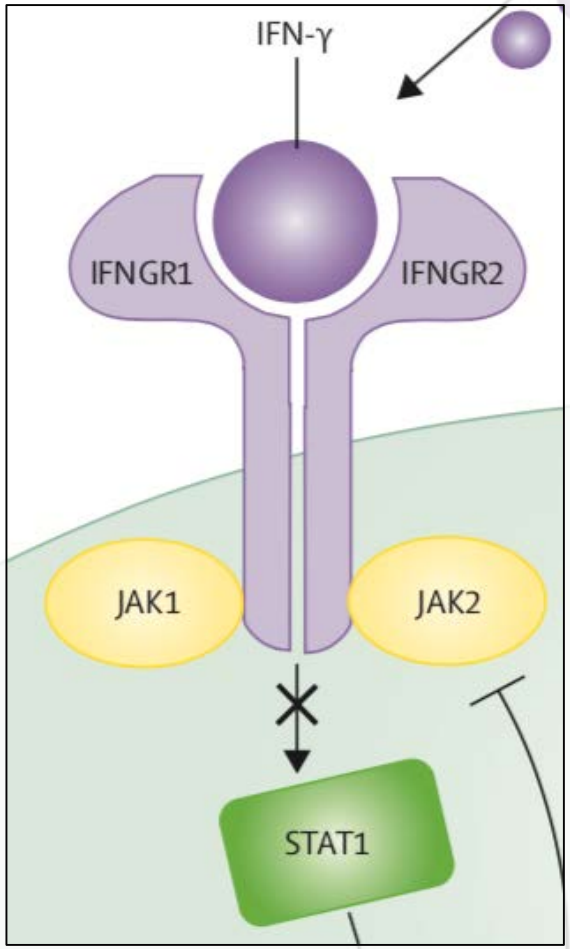
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Defects in tumor antigen presentation pathway

Gene	Biallelic loss (#)	Response	No response
B2M	0	0	0
CANX	0	0	0
HSPA5	0	0	0
TAP1	0	0	0
TAP2	0	0	0
TAPBP	0	0	0
CALR	0	0	0
PDIA3	0	0	0



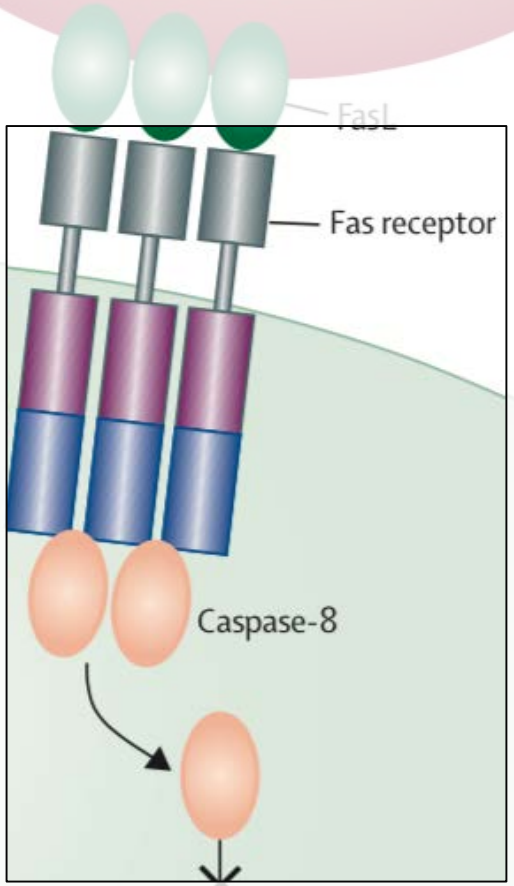
Defects in T-cell killing pathways



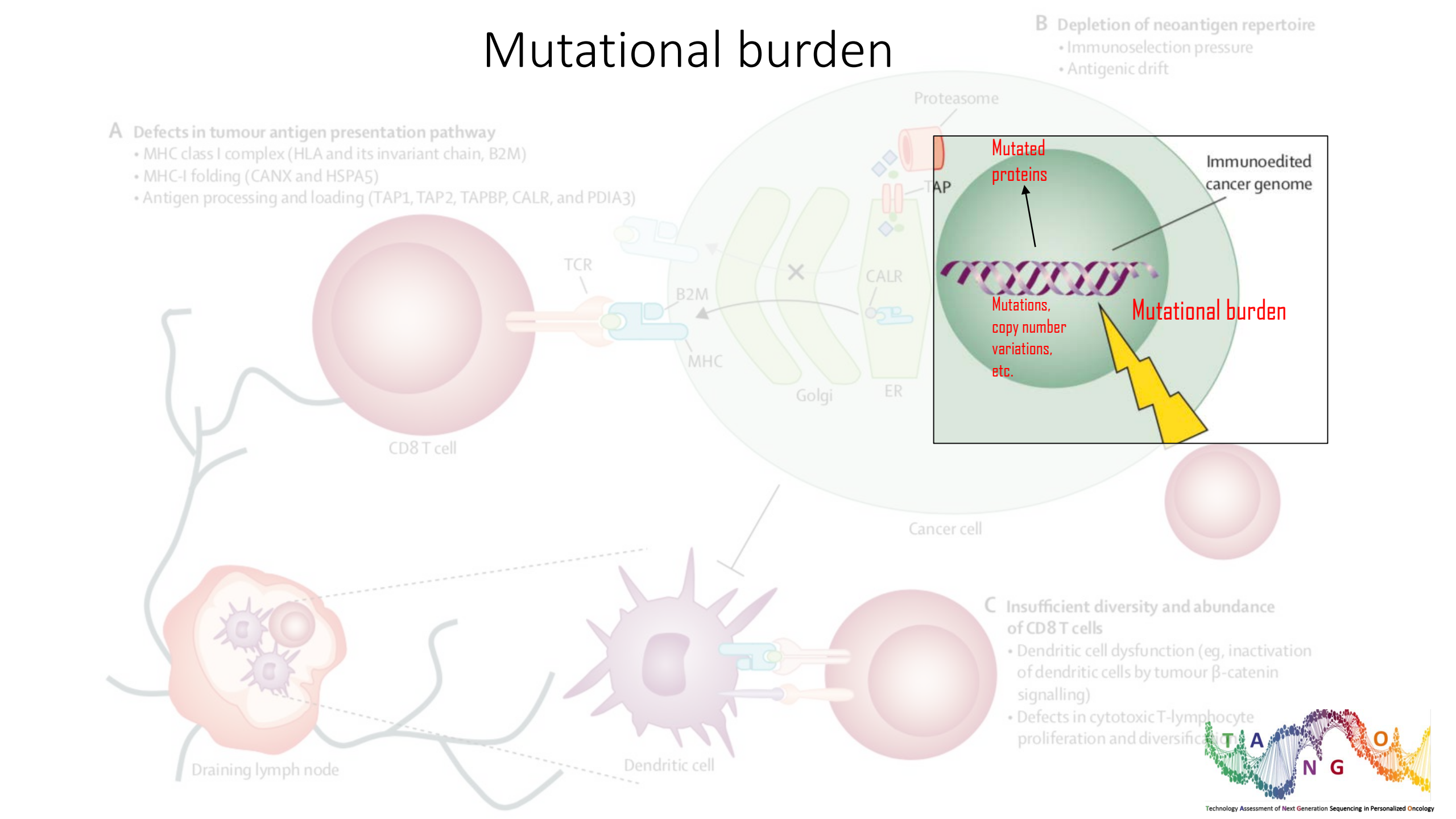
Gene	Biallelic loss (#)	Response	No response
IFNGR1	0	0	0
IFNGR1	0	0	0
JAK1	0	0	0
JAK2	1	1 (SD)	0
STAT1	0	0	0

Defects in T-cell killing pathways

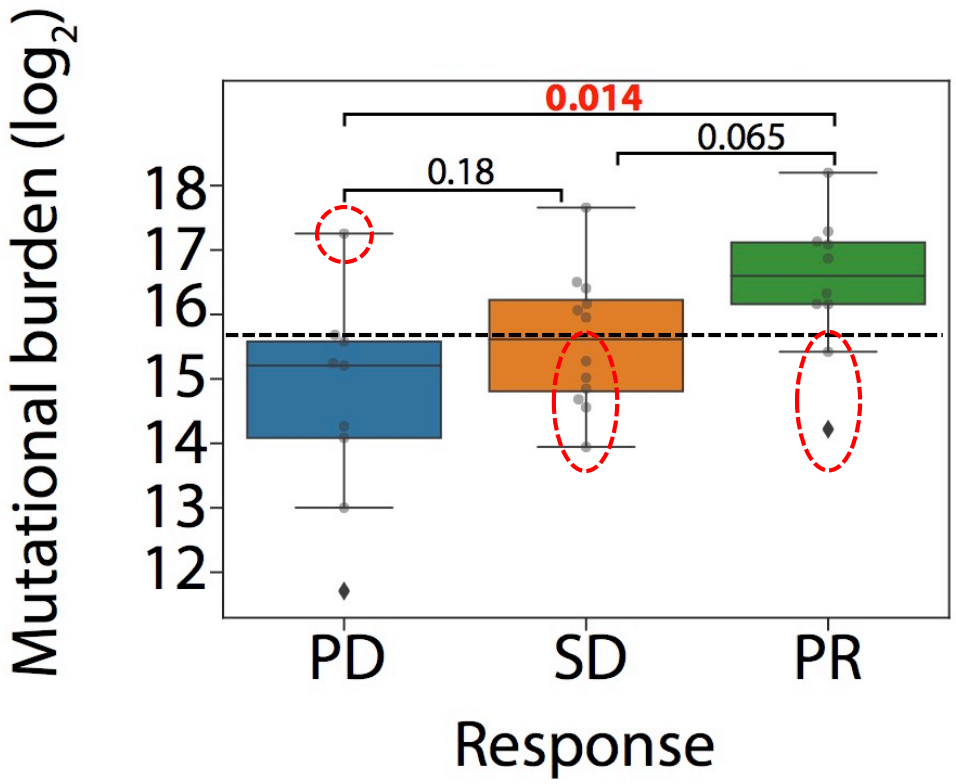
Gene	Biallelic loss (#)	Response	No response
FAS (receptor)	0	0	0
CASP8	0	0	0



Mutational burden



Mutational burden is a biomarker for a-PD1 response in NSCLC



Can we improve this classification with other genomic information?

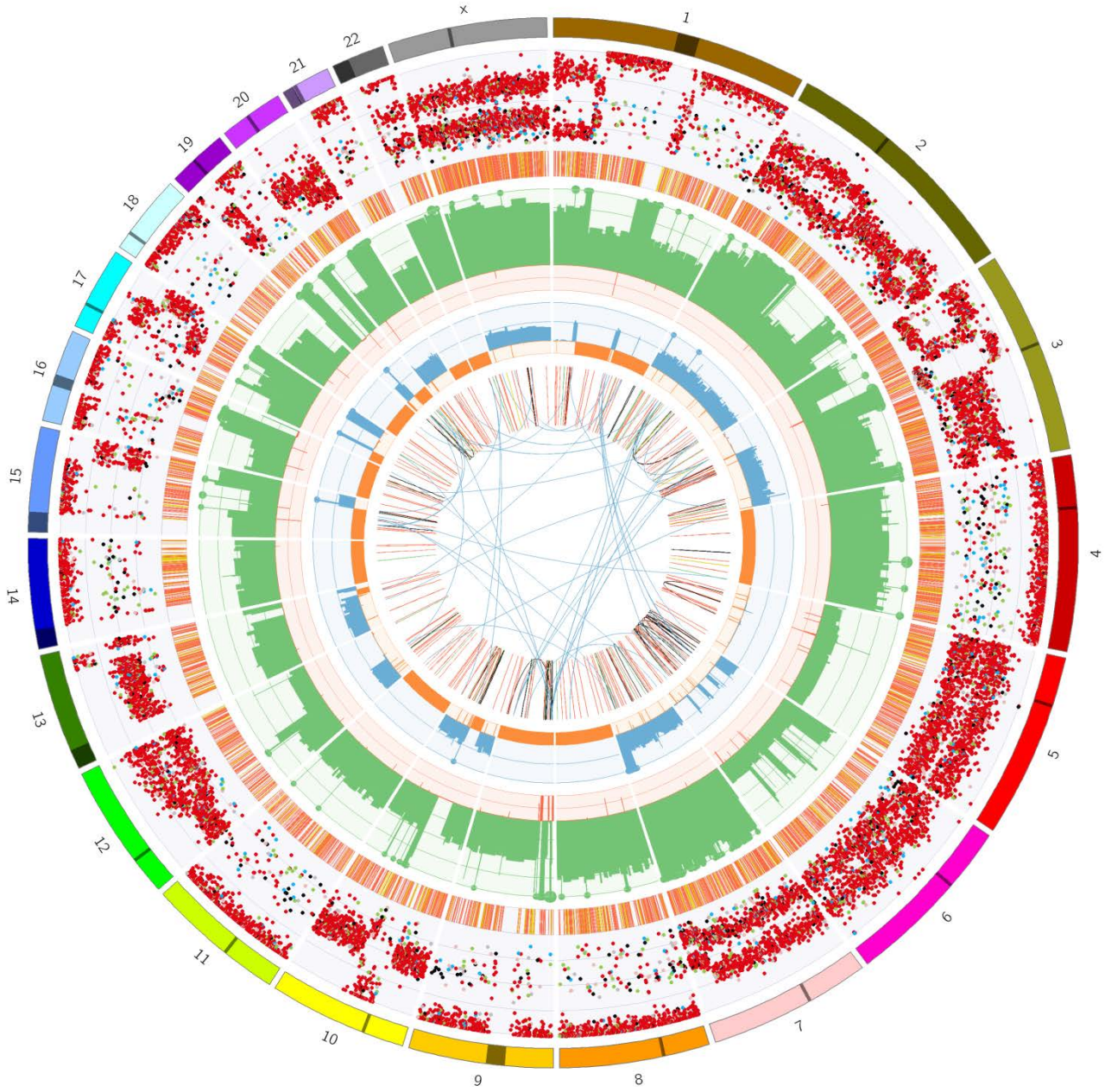
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Conclusions I

- Extensive work in model systems has shown that loss of antigen presentation, IFNg-signaling, or FAS-signaling results in resistance to PD-1 blockade
- However, genomic loss of these pathways is extremely rare in lung cancer
- Thus, most patients must be resistant to PD-1 blockade through other mechanisms

Technology Assessment of Next Generation Sequencing in Personalized Oncology

WGS-based detection of aneuploidy



Aneuploidy = Abnormal number of chromosomes

TANGO

Technology Assessment of Next Generation Sequencing in Personalized Oncology

How could aneuploidy affect tumor immunogenicity?

Nature 2017

LETTER

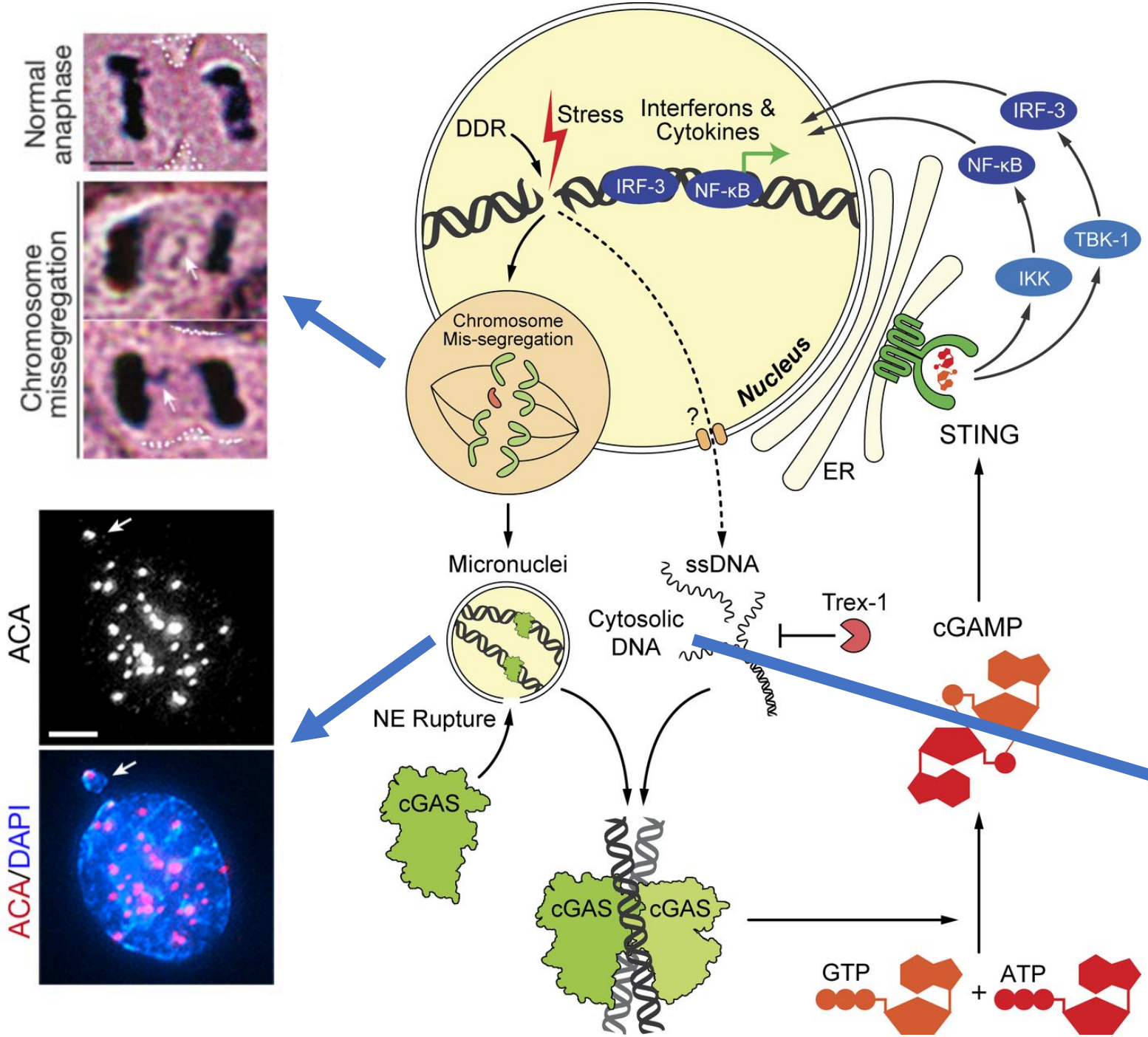
doi:10.1038/nature23449

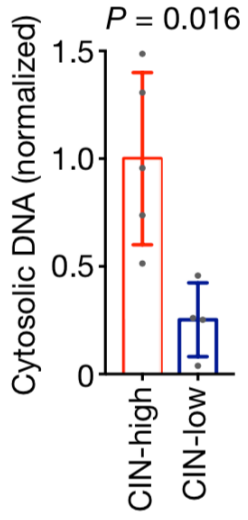
cGAS surveillance of micronuclei links genome instability to innate immunity

Karen J. Mackenzie[1]*, Paula Carroll[1]*, Carol-Anne Martin[1], Olga Murina[1], Adeline Fluteau[1], Daniel J. Simpson[1], Nelly Olova[1], Hannah Sutcliffe[1], Jacqueline K. Rainger[1], Andrea Leitch[1], Ruby T. Osborn[1], Ann P. Wheeler[1], Marcin Nowotny[2], Nick Gilbert[1], Tamir Chandra[1], Martin A. M. Reijns[1] & Andrew P. Jackson[1]

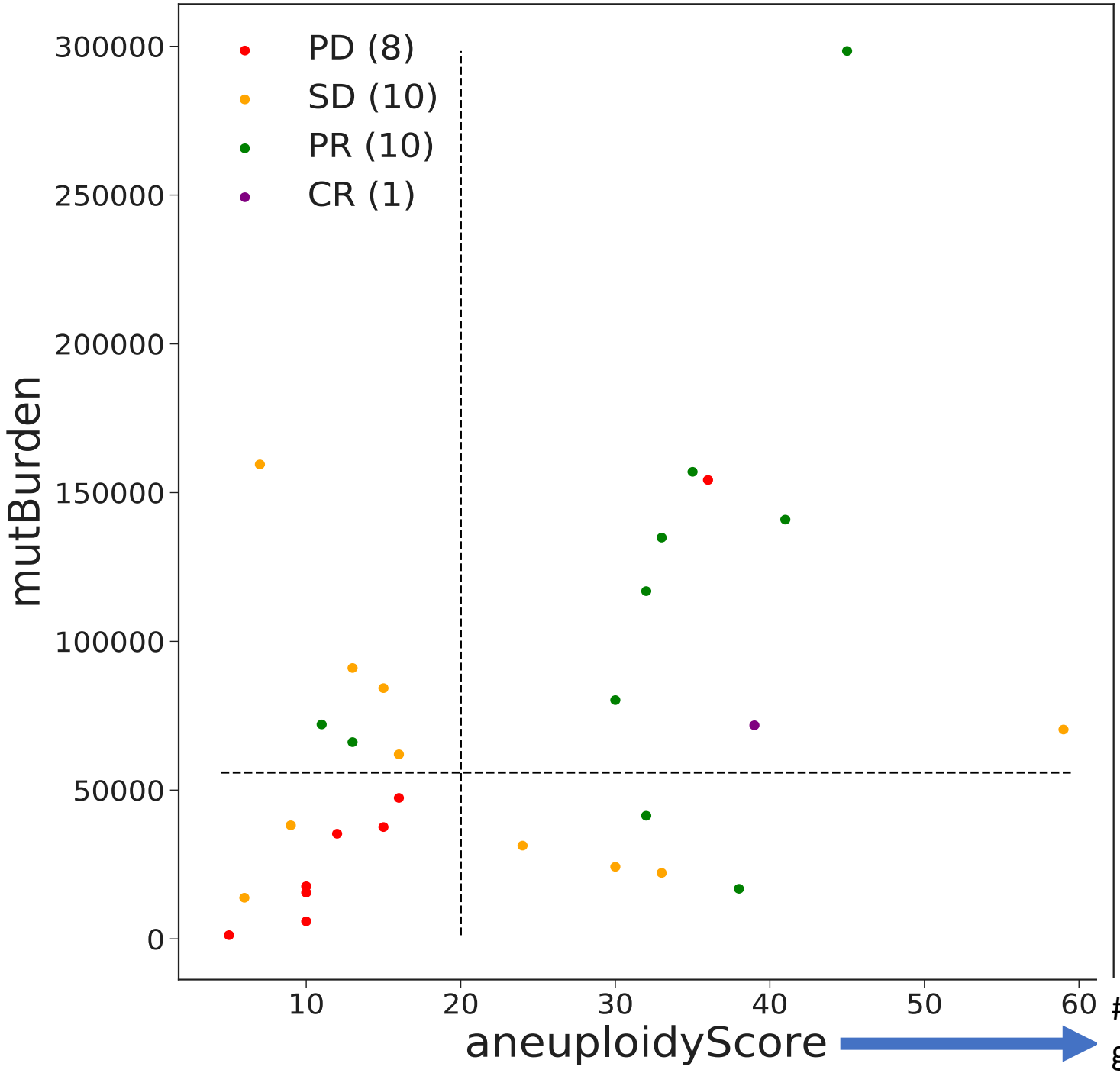
Chromosomal instability leads to innate immune response and type I interferon production

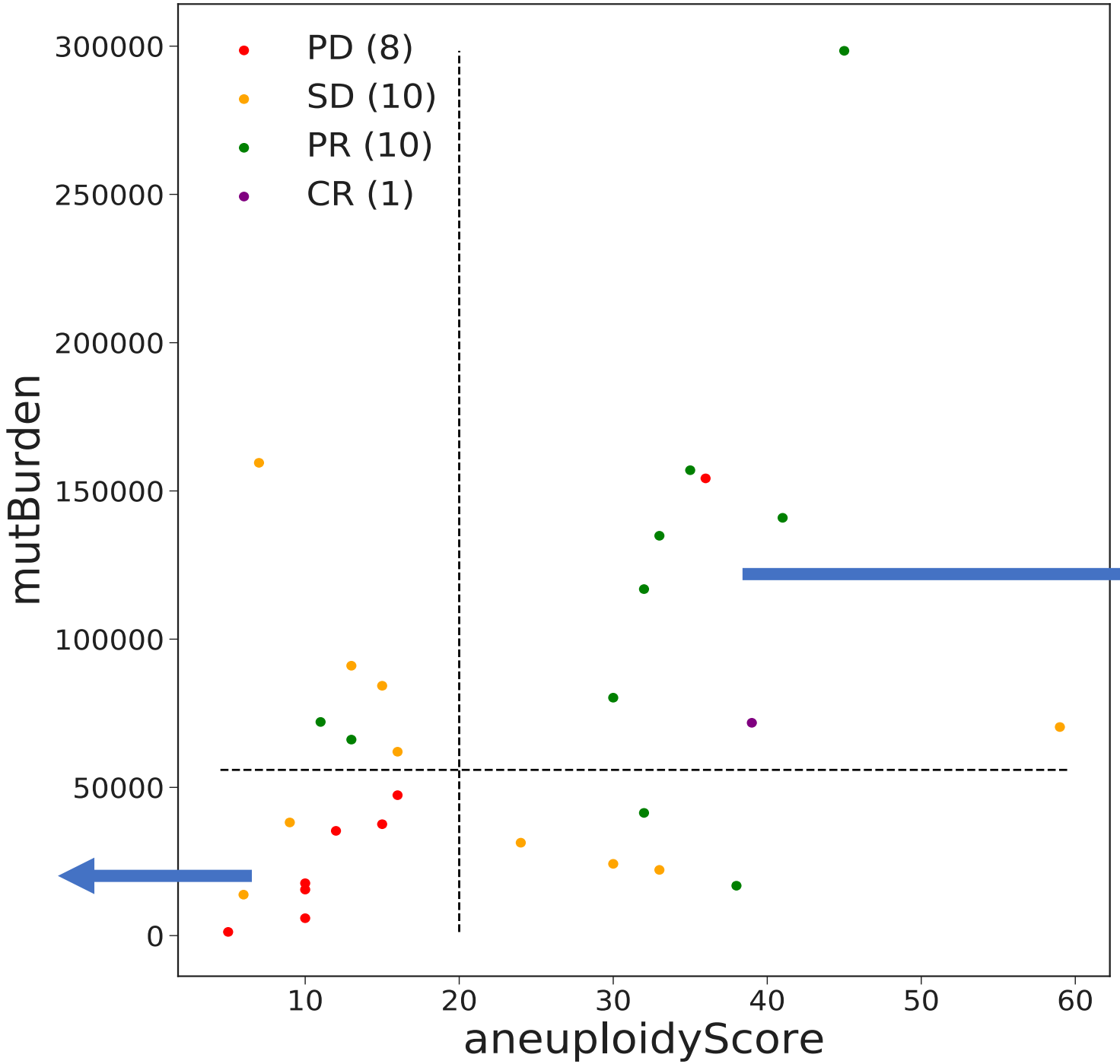
Chromosomal instability contributes to the immunogenicity of tumors by activation of innate immune signaling via cGAS-STING


Normal anaphase
Chromosome missegregation
ACA
ACA/DAPI
DDR
Stress
Interferons & Cytokines
IRF-3
NF-κB
Chromosome Mis-segregation
Nucleus
?
ER
STING
TBK-1
IKK
Micronuclei
ssDNA
Trex-1
Cytosolic DNA
cGAMP
NE Rupture
cGAS
cGAS
cGAS
GTP
+
ATP


P = 0.016
Cytosolic DNA (normalized)
1.5
1.0
0.5
0
CIN-high
CIN-low


N G O
of Next Generation Sequencing in Personalized Oncology


PD (8)
SD (10)
PR (10)
CR (1)
mutBurden
300000
250000
200000
150000
100000
50000
0
10
20
30
40
50
60
aneuploidyScore
# of chromosome arm gains or losses



Enrichment for responders:
OR = 14
P-value = 0.0169

Enrichment for Non-responders:
OR = 63
P-value = 0.0002

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Technology Assessment of Next Generation Sequencing in Personalized Oncology

Validation cohort

- Erik van Werkhoven (statistician NKI): 50 patients needed for >80% power
- 31 samples CPCT
- 19 additional samples from NKI (Kim Monkhorst & Karlijn Hummelink)
  - DNA isolation is planned

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Conclusions II

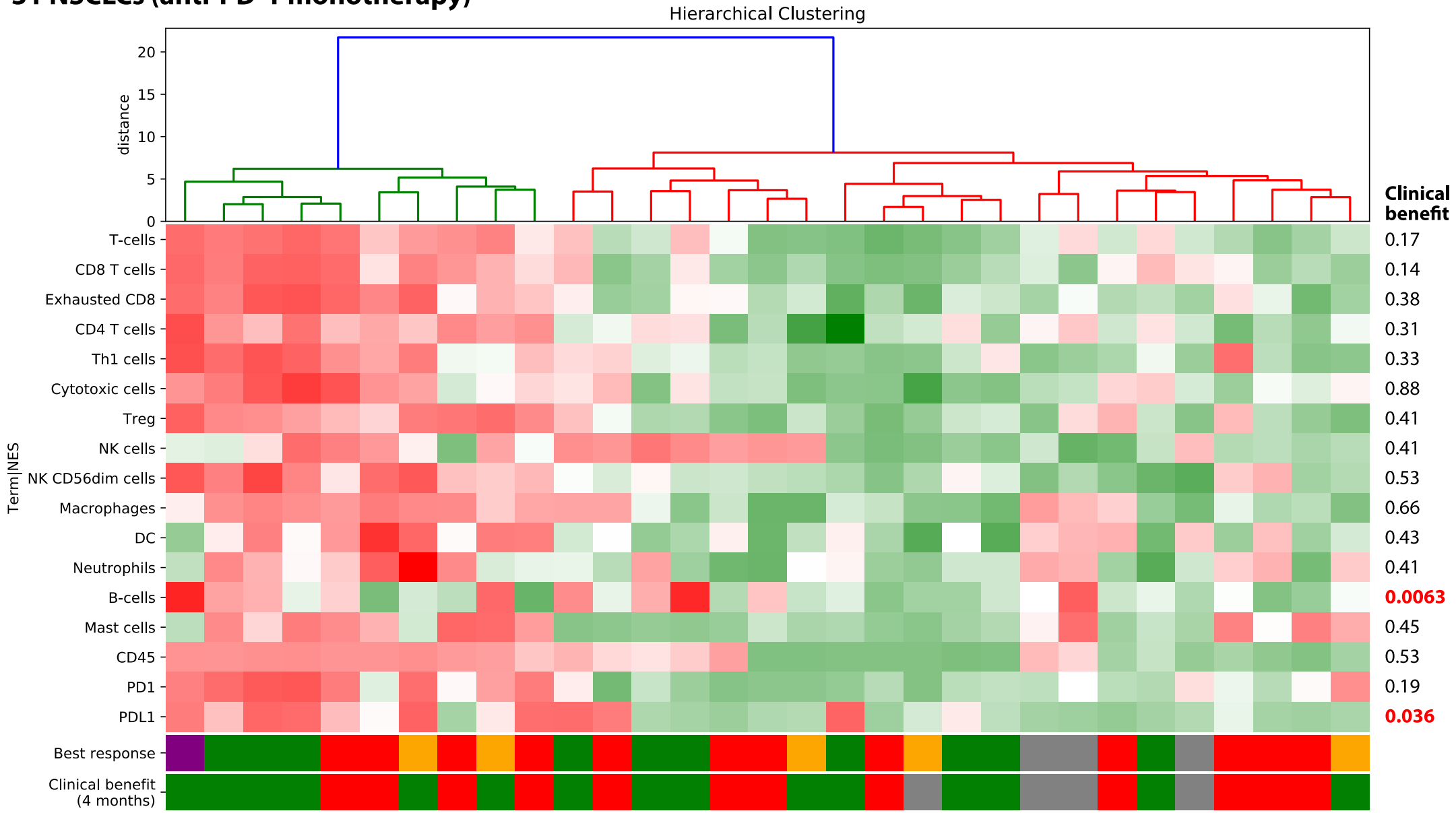
- In a small discovery cohort, mutational burden and aneuploidy correlates to response to PD-1 blockade in NSCLC
- Aneuploidy seems a biomarker complementary to mutational burden
- Validation in an independent cohort is needed and ongoing

Technology Assessment of Next Generation Sequencing in Personalized Oncology

RNA-seq analysis

- Some genes are expressed only in specific immune cells
- Expression of such genes is used to characterize the immune infiltrate

31 NSCLCs (anti-PD-1 monotherapy)



- Not a clear link between inflammation and response
- B-cells (tertiary lymphoid structures?)
- PDL1

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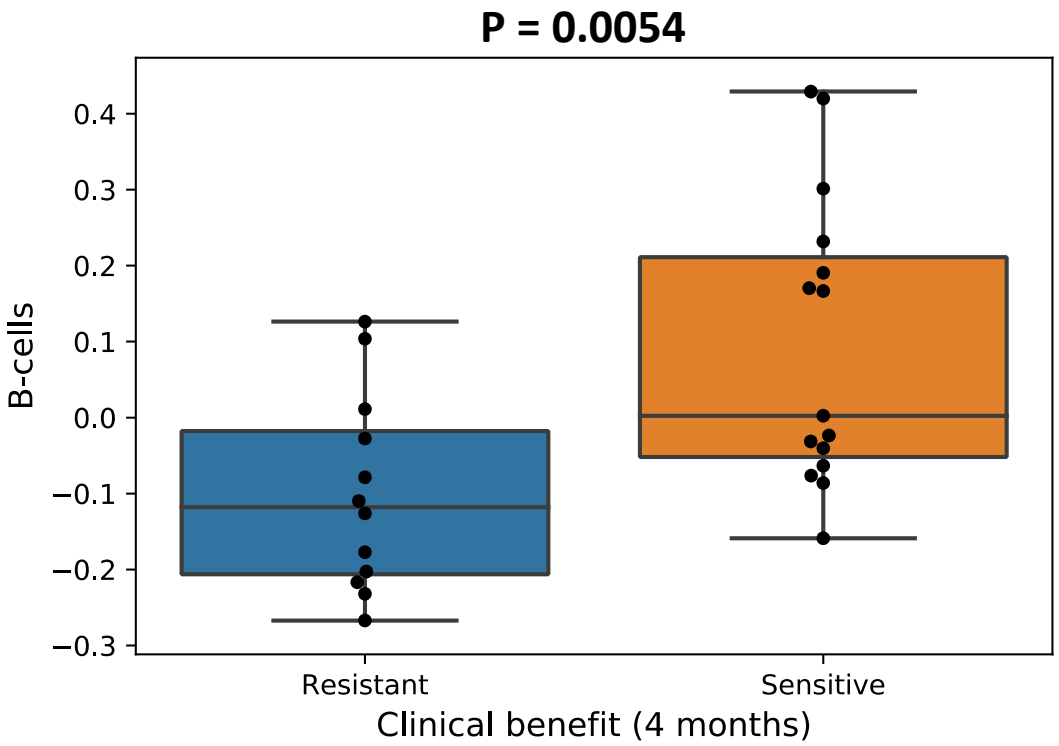
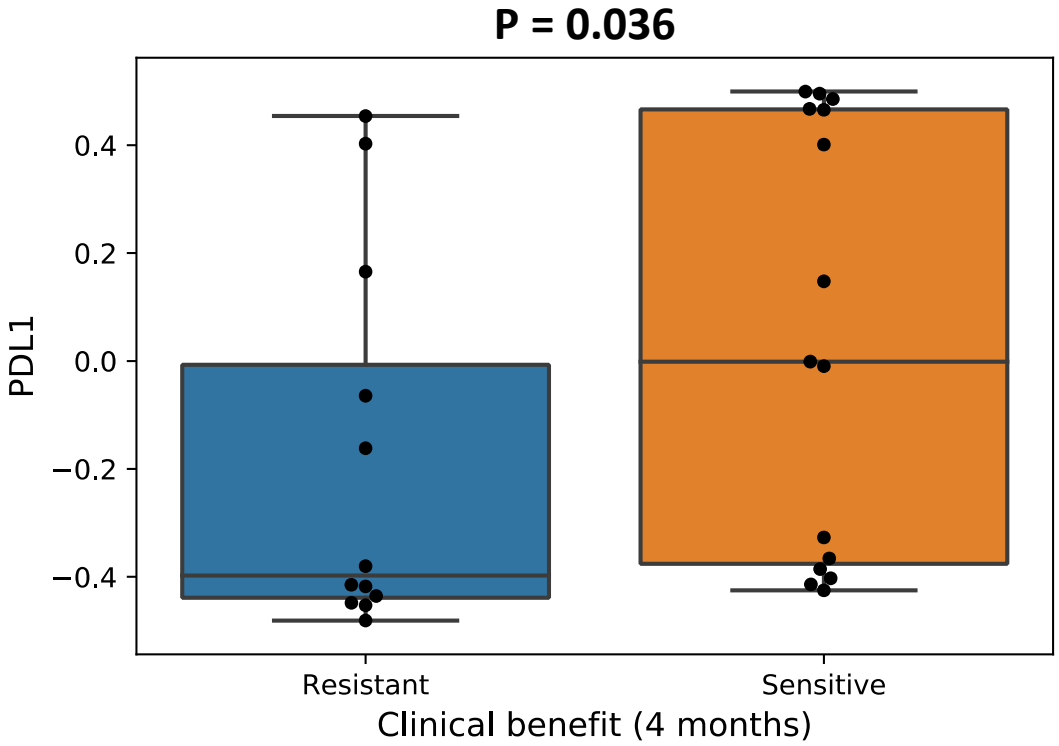
Technology Assessment of Next Generation Sequencing in Personalized Oncology

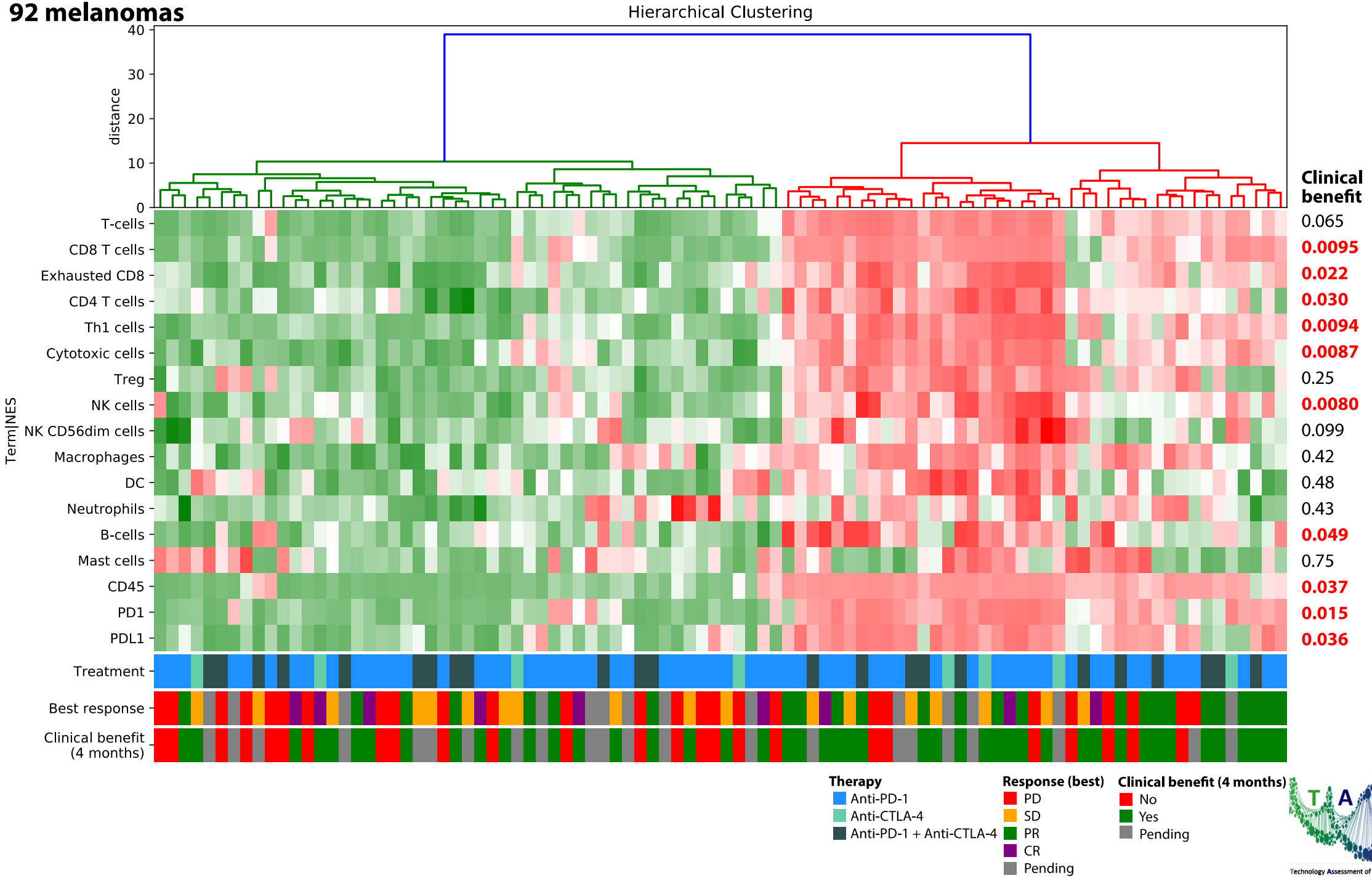
B-cells and PDL1 RNA-expression correlate to response





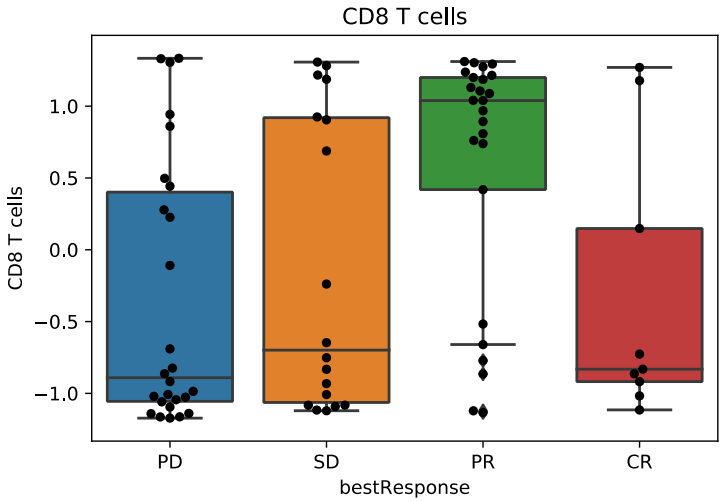
Technology Assessment of Next Generation Sequencing in Personalized Oncology

92 melanomas

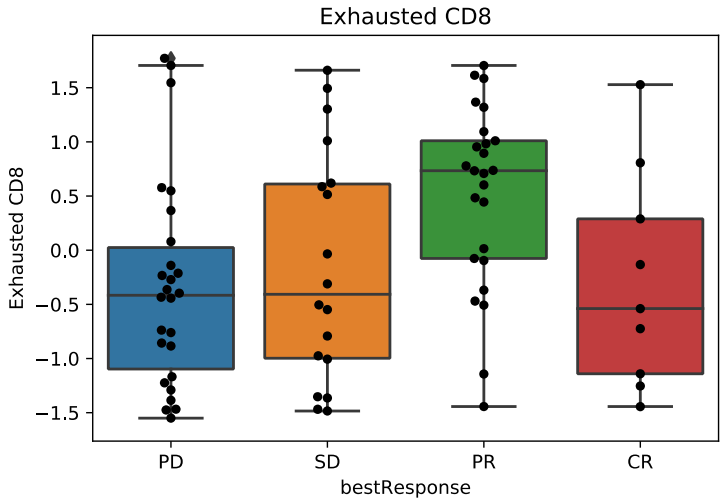


Technology Assessment of Next Generation Sequencing in Personalized Oncology

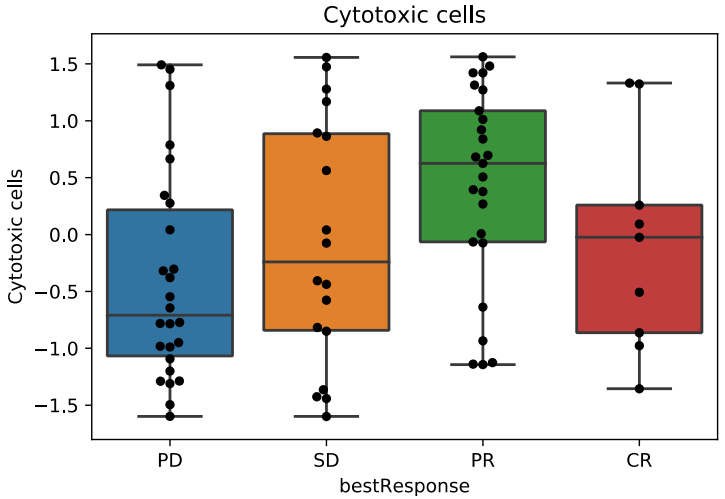
Melanoma, 78 patients



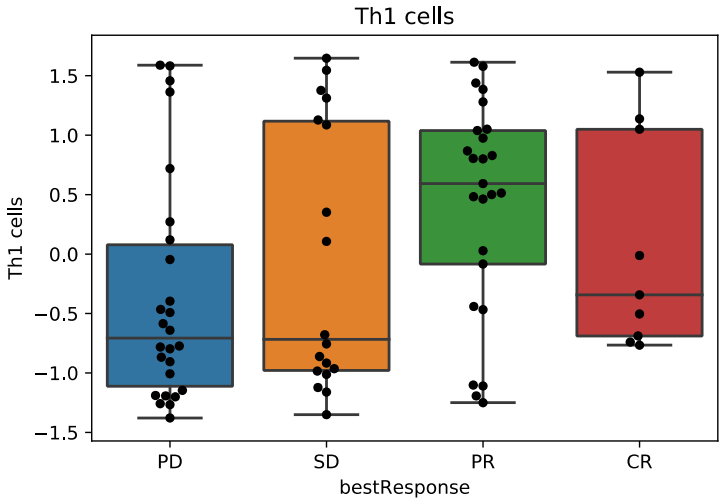
PD vs PR/CR: **p = 0.0053**



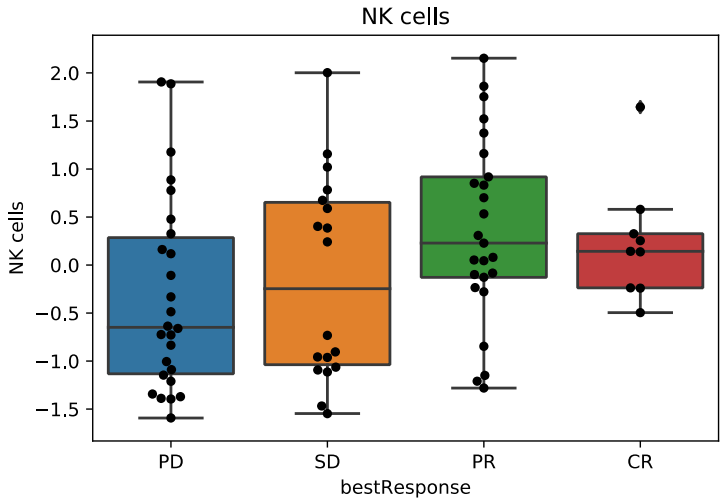
PD vs PR/CR: **p = 0.0099**



PD vs PR/CR: **p = 0.0076**



PD vs PR/CR: **p = 0.0057**



PD vs PR/CR: **p = 0.0094**

Responders show increased inflammation:

- Cytotoxic cells
- CD8 T cells
- NK cells
- Th1 cells

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Conclusions III

- Unlike in melanoma, general inflammation/infiltration is not linked to better responses to PD1 blockade in lung cancer
- A B-cell expression signature correlates to response to PD1 blockade in lung cancer
- This might reflect the presence of tertiary lymphoid structures
- T- and NK-cell signatures correlate to response to PD1 blockade in melanoma

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Survival pattern and time to next treatment for different treatment regimens

WP3

Leaders: V. Coupé, M. Joore, and J. Wilschut

PhD student: Z. Mfumbilwa

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Objectives WP3

- Cost-effectiveness of WGS-based selection for immunotherapy with/without radiological features

- Real-world patterns of treatment choice & TTNT and OS in Melanoma and NSCLC

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Outline

- Santeon Data:
  - Advanced NSCLC
  - Patients characteristics
  - Overall survival for first line
  - Next step

- DMTR data
  - Advanced Melanoma
  - Patients characteristics
  - Overall survival for first line
  - Next step: Model description

- This work is part of inputs for model WP3/ 4/ 5

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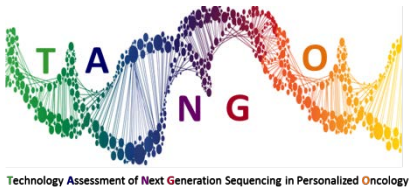
SANTEON: Non-small Cell Lung Cancer

Collaboration of Six independent run hospitals in the Netherlands



Santeon: Patients Characteristics

- Stage IIIB/IV NSCLC
- Period: 2008 – 2014
- Total patients: 2982

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Santeon: Patients Characteristics

- Best supportive care (BSC): 60%
- Observed median OS: 2.3 months for BSC and 9 months for Systemic
- Probability of Treated:
  - Year diagnosis
  - Age, PS, and Comorbidities

Santeon: Next step

- Parametric survival model: Chemotherapy
  - Time to second line treatment
  - Overall survival

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DMTR: DUTCH MELANOMA TREATMENT REGISTRY

DICA: Dutch Institute for Clinical Auditing

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DMTR: Patients Characteristics

- Melanoma: IIIB / IV

- Registration:
  Dec 2011 – Dec 2017

- Latest follow up:
  Mar 2019
  Median follow up: 2.8 yrs

- Total Nu. Patients: 3959

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DMTR: Patients Characteristics

Patients characteristics per first line treatment regimen were presented

DMTR: MUTATIONS

- 92.0% Had BRAF mutation tested
- Test used: mostly with NGS or Sanger sequencing.
- Mutation proven: BRAF 57.2 % (of tested)

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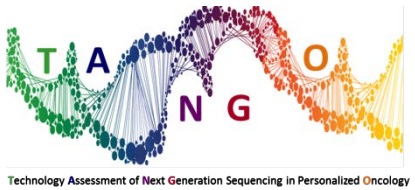
Factor associated with treatment choice & OS

Preliminary analysis of first line treatment choice and overall survival was presented



DMTR: Next step

- Parametric survival model:
- Time to second line treatment
  - Overall survival

Work Package 4

Tumour-overarching early cost-effectiveness modelling

prof. dr. Manuela Joore

dr. Valesca Retèl

prof. dr. Carin Uyl-de Groot

prof. dr. Wim van Harten

drs. Martijn Simons

Maastricht UMC+

T A N G O

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Main goal WP4

Potential value of whole genome sequencing as molecular diagnostic compared to standard diagnostics in advanced cancer patients

- Cost-effectiveness analysis for Non-small cell lung cancer and Melanoma
- Future scenario analysis
- Wider public benefits

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Technology Assessment of Next Generation Sequencing in Personalized Oncology

Cost-effectiveness analysis (part 1)

Data overview

	Literature	Real world data	Actions	Source
Model structure	• Conceptualisation	• % mutations (WGS) • Frequency diagnostic tests	• Data expected Q1, 2020 • Collaboration WP5	• WP1 • WP5
Effectiveness	• Survival, targeted and immunotherapy	• OS, PFS chemo, erlotinib, gefitinib, BSC	• Collaboration WP3	• DMTR, Santeon, WP3 • Literature
Costs	• Costs diagnostic tests • Costs treatment	• Productivity losses, informal care	• Data analysis ~June 2020 • Literature review	• WP1 • Medicijnkosten.nl • CPCT-02 biopsy study • Literature
Utilities		• HRQoL, utilities,	• Data analysis ~June 2020 • Literature review	• CPCT-02 biopsy study • Literature

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TANGO

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Cost-effectiveness analysis
Non-small cell lung cancer

Research question

- What is the cost-effectiveness of WGS versus standard diagnostics in patients with locally advanced and metastatic Non-small cell lung cancer?

Approach

- Model-based
- Lifetime time horizon
- Societal perspective

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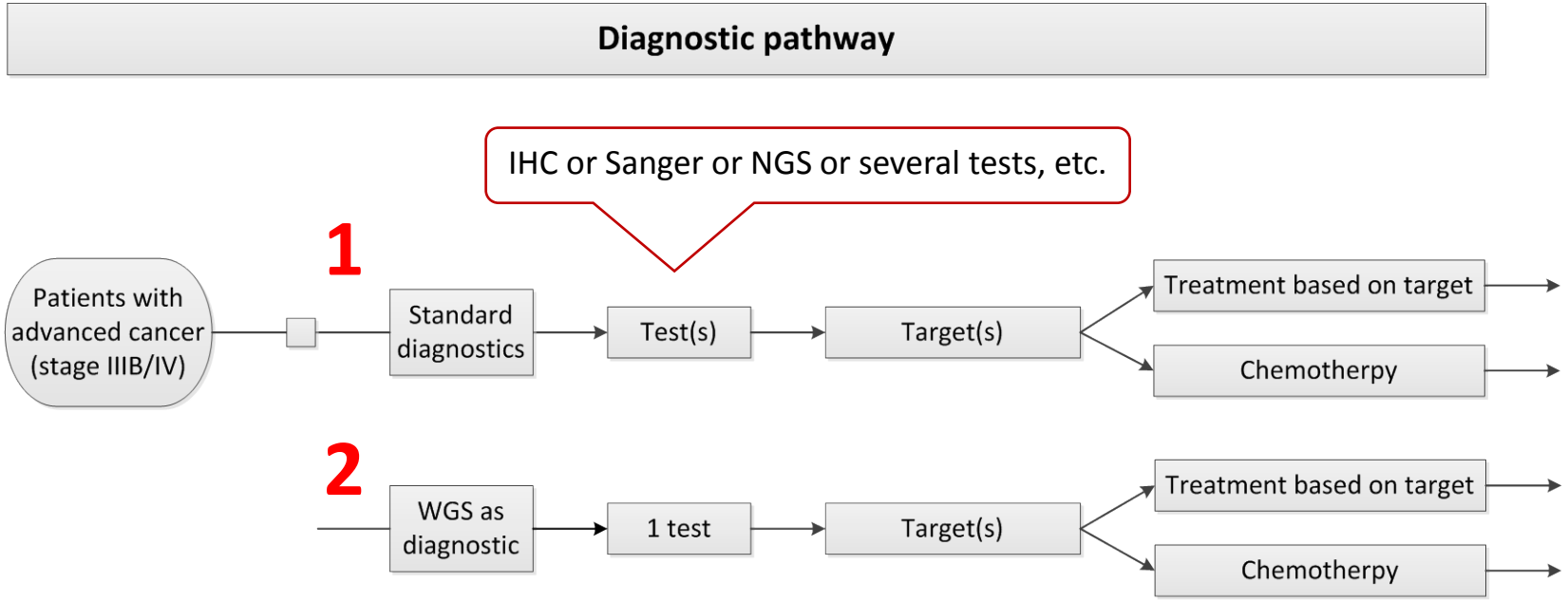
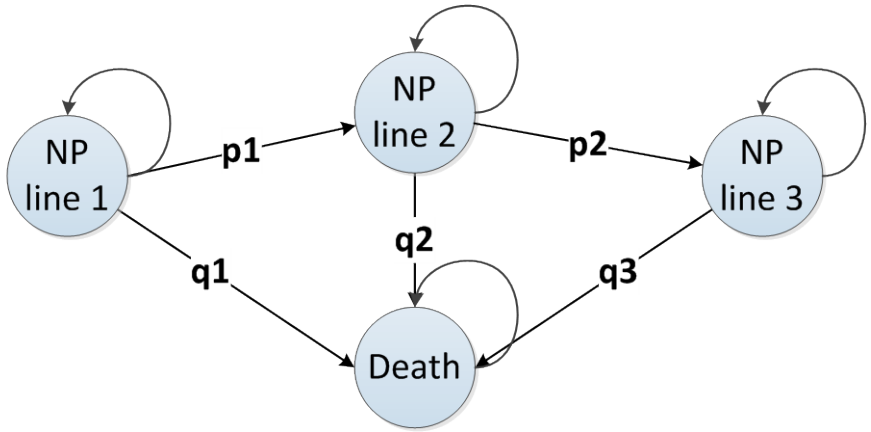
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Cost-effectiveness analysis
Model structure





Data

- **WP1:** cost molecular tests
- **WP5:** number of tests being performed
- **Literature**: treatment costs

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TANGO
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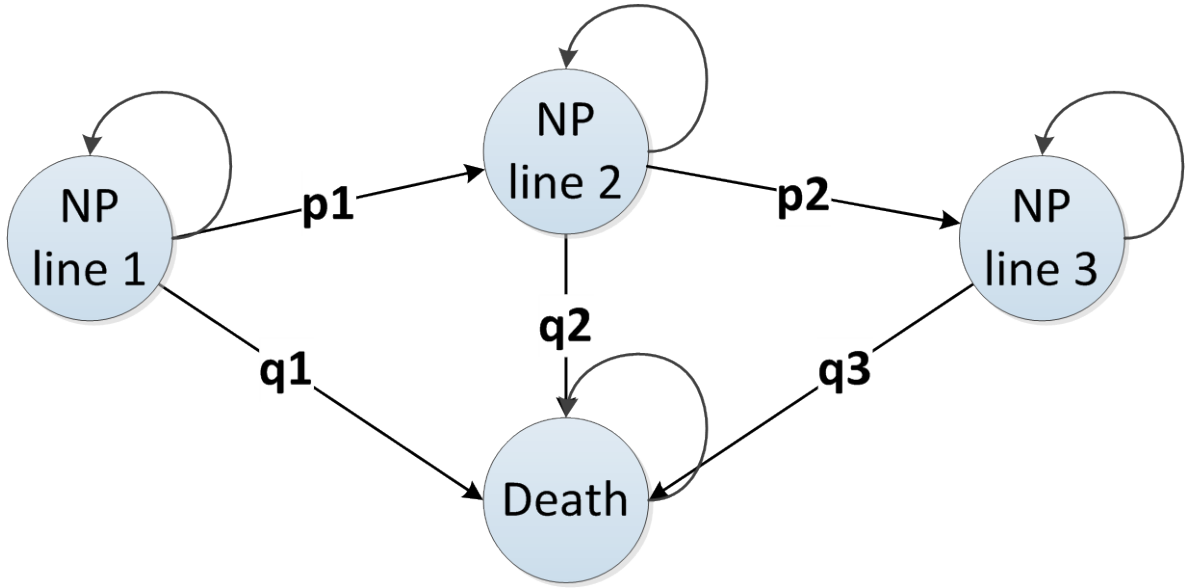
Cost-effectiveness analysis

Disease model



Data

- **WP3, Santeon:** OS, PFS
  1. Chemotherapy ✔
  2. Erlotinib / gefitinib ✔
  3. Best supportive care ✔
  4. Other targeted therapies ✖
  5. Immunotherapies ✖

→ **Systematic review**

Legend

NP, no progression

p, probability for progression

q, probability for dying

1-3, line of treatment administration

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Systematic review (part 2)
objective

First objective:

(1) To obtain estimates of OS benefit of targeted therapies and immunotherapies for patients with advanced Non-small cell lung cancer

Additional objective:

(2a) To compare observed median OS gain with modelled mean OS gain

(2b) To explore the impact of trial characteristics on the difference between median and mean OS gain

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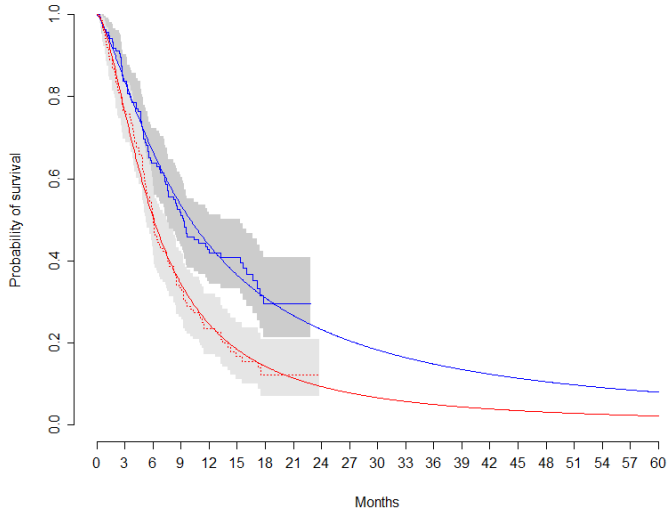
Systematic review
methods

Number of hits
- n=668

Clinical trials included
- EGFR (n=12)
- ALK (n=5)
- PD-L1 (n=10)

Data extraction



Long term OS
- EGFR-TKI,
- ALK-TKI,
- Immunotherapies

CEA Model

First objective

Comparison
- Observed median OS
- Modelled mean OS

Relations
- Trial characteristics

Additional objective

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Systematic review

To conclude

(1) Long term OS estimates for EGFR-TKI, ALK-TKI and immunotherapies

(2a) No differences median vs. mean OS gain for EGFR-TKI and ALK-TKI

Differences median vs. mean OS gain for immunotherapy

(2b) Mean OS gain was larger than median OS gain in trials with

- Immunotherapy treatment strategy
- Low % treatment switchers
- Older population

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Systematic review
Discussion

Using this OS data obtained from literature in the CEA model requires assumptions

- How do we link the trial data with the Santeon data?
- How is the effectiveness of targeted therapies and immunotherapies when patients are selected based on WGS results?
- Address this with scenario analyses

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Main goal WP4
Next steps

Cost-effectiveness analysis

- Implement diagnostic trajectory based on data WP1 and WP5 and calculate costs
- Link diagnostic data with real world data and literature including scenario analysis
- Further implementation of cost-effectiveness models → patient-level

Implement results of the future scenario analysis and explore wider public benefits

Quality of life data analysis

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Cost-effectiveness analysis

Data overview

	Literature	Real world data	Actions	Source
Model structure	✓ Conceptualisation	• % mutations (WGS) • Freq. diagnostic tests	• Data expected Q1, 2020 • Collaboration WP5	• WP1 • WP5
Effectiveness	✓ Survival, targeted and immunotherapy	• OS, PFS chemo, erlotinib, gefitinib, BSC	• Collaboration WP3	• DMTR, Santeon, WP3 • Literature
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Utilities		• HRQoL, utilities,	• Data analysis ~June 2020 • Literature review	• CPCT-02 biopsy study • Literature

- 3 centres included
- 173 patients included
- 350 questionnaires received (T0, T1, T2)
- ~38% immuno, ~23% targeted, ~22% chemo

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WP5: Nationwide organization of WGS

Maarten IJzerman, Erik Koffijberg, Valesca Retèl, Wim van Harten, Michiel van de Ven

University of Twente

Technology Assessment of Next Generation Sequencing in Personalized Oncology

WP5 objective

- **Aim of WP 5**: provide insights into the (requirements for) optimal implementation of WGS from a system level perspective – to support health services planning.
    - *What difficulties in the process of the implementation of WGS need to be overcome to achieve the optimal cost-effective implementation in the Netherlands?*

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Required evidence

- To support health policy decisions and planning of services, more detailed information is required about
  - The availability of WGS services
  - The use of molecular profiling and its costs and its delays
  - Prescription of advanced molecular drug treatment
  - Possible future developments regarding the implementation of WGS
  - …

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Progress so far

1. Simulation model to evaluate implementation scenarios developed to a large extent
2. Published article 'Variation in the time to treatment for stage III and IV non-small cell lung cancer patients for hospitals in the Netherlands' has been published in Lung Cancer
3. Analysis ongoing for article 'Uncovering the real-world pre-treatment diagnostic pathway of advanced non-small cell lung cancer with routinely gathered data'
4. Data collection and analysis ongoing for article 'Where do we go with Whole Genome Sequencing in oncology? Using scenario drafting to explore future developments'

Technology Assessment of Next Generation Sequencing in Personalized Oncology

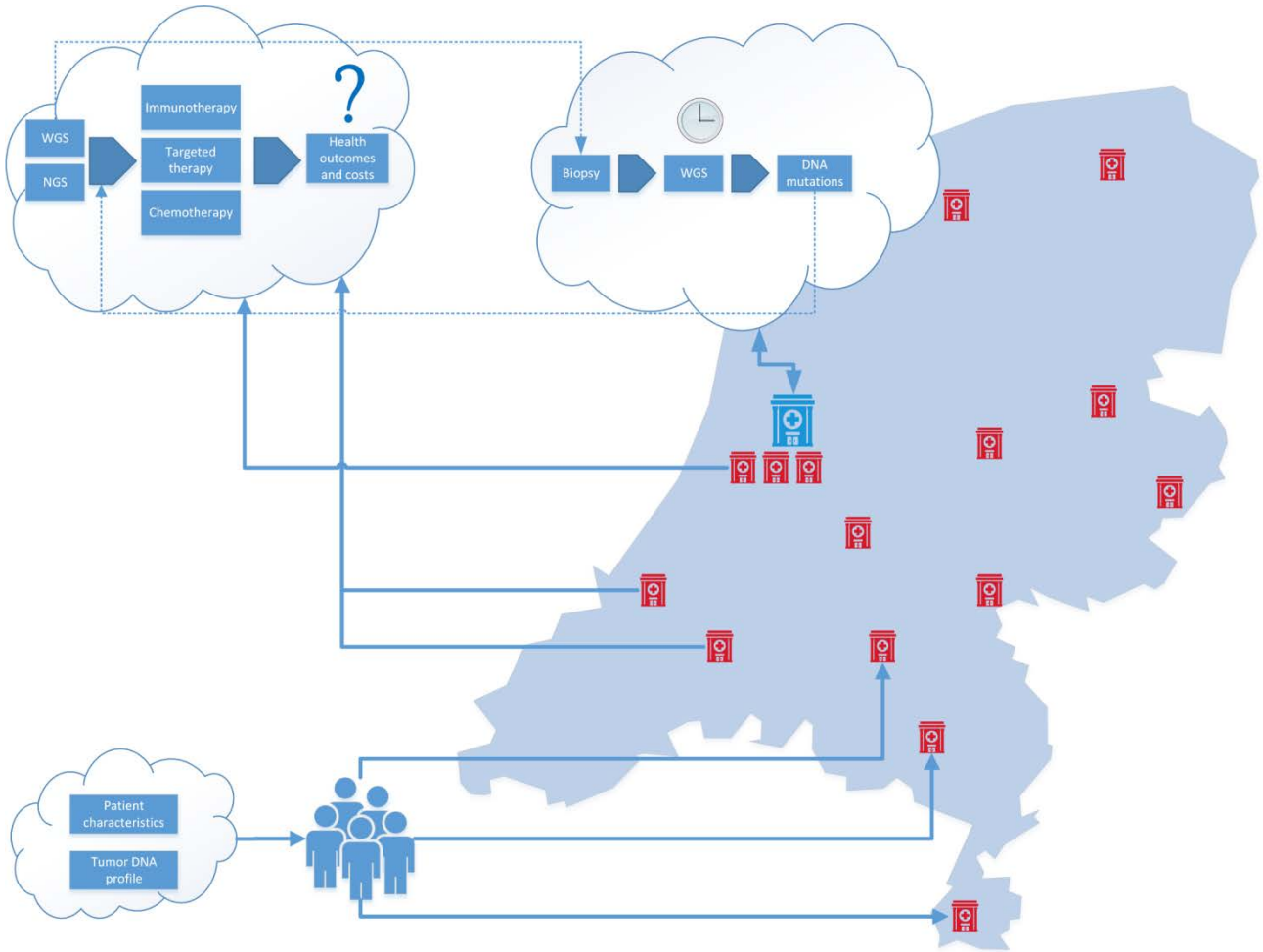
1. Simulation model

To evaluate the implementation WGS on a national level, evidence is combined into a **dynamic (agent-based) simulation model** that includes (practice variation in) patient pathways, delays, and costs.

The model will be used to:

- Evaluate the consequences of decentralizing WGS
- Calculate the consequences of possible future scenarios related to WGS

The model is largely developed, but needs to be tweaked to better reflect reality in e.g. care pathways.



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2. Variation in the time to treatment for stage III and IV non-small cell lung cancer patients

Date of diagnosis:

1. The date of the first confirmation of a tumor, or
2. The date of first hospital admission, or
3. The date of the first visit to outpatient clinic related to the tumor

Time to treatment → **Treatment initiation**

- Data from 2016 on 78 hospitals received from NCR
- Stage, histology, and performance status were correlated with time to treatment
- If patient is referred, time to treatment is expected to increase by at least one week

Table 1
Characteristics of the patient population.

Characteristics	Treated patients N (% or 95% CI)	Untreated patients N (% or 95% CI)	p-value
Patients	4,176 (55.1%)	3374 (44.9%)	N.A.
Median TTT (in days)	28 (IQR: 22)	–	N.A.
Mean age (in years)	65.4 (65.1, 65.7)	72.4 (72.1, 72.8)	0.000
Gender			
Male	56.0% (54.4%, 57.5%)	61.7% (60.1%, 63.3%)	0.000
Female	44.0% (42.5%, 45.5%)	38.3% (36.7%, 40.0%)	0.000
ECOG PS			
0-1	62.4% (61.0%, 63.9%)	23.2% (21.8%, 24.6%)	0.000
2+	8.0% (7.1%, 8.8%)	23.3% (21.9%, 24.7%)	0.000
Unknown	27.7% (26.3%, 29.1%)	52.7% (51.0%, 54.4%)	0.000
Missing	1.9% (1.5%, 2.3%)	0.9% (0.6%, 1.2%)	0.000
Tumor stage			
IIIA	23.6% (22.3%, 24.9%)	9.9% (8.9%, 10.9%)	0.000
IIIB	15.5% (14.4%, 16.6%)	7.9% (7.0%, 8.9%)	0.000
IV	60.9% (59.4%, 62.4%)	82.1% (80.8%, 83.4%)	0.000
Histology			
Squamous cell carcinoma	24.0% (22.7%, 25.3%)	16.2% (15.0%, 17.5%)	0.000
Adenocarcinoma	58.0% (56.5%, 59.5%)	42.3% (40.6%, 43.9%)	0.000
Large cell carcinoma	3.9% (3.3%, 4.5%)	5.6% (4.8%, 6.4%)	0.000
Other specified carcinoma	12.2% (11.1%, 13.2%)	12.2% (11.1%, 13.3%)	0.920
Unspecified malignant neoplasm	1.8% (1.4%, 2.3%)	23.6% (22.1%, 25.0%)	0.000
Other	0.1% (0.0%, 0.1%)	0.1% (0.0%, 0.1%)	0.831
Referral			
No	70.0% (68.6%, 71.4%)	82.2% (80.9%, 83.5%)	0.000
Yes	30.0% (28.6%, 31.4%)	17.8% (16.5%, 19.1%)	0.000

2. Variation in the time to treatment for stage III and IV non-small cell lung cancer patients

- Substantial variation among patients in the same hospital
- Substantial variation among hospitals (even after controlling for differences in patient population)
- In most hospitals, the median time to treatment is below the recommended maxima for time to treatment
- 50% of treatments started within 28 days
- 90% of treatments started within 58 days

What activities are conducted in this interval?

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3. Uncovering the real-world pre-treatment diagnostic pathway of advanced non-small cell lung cancer with routinely gathered data

- Previous research on care pathways:
  1. Report healthcare utilization (e.g. percentage of patients receiving a specific test), or
  2. Use the perception of professionals as the basis for the care pathways.
- Both approaches do not do justice to the complexity of the real world and do not provide much insight into the variation between patients in diagnostic pathways.
- Aim: To reconstruct real-world diagnostic pathways prior to treatment to inform the development of more efficient pathways
  - Where in the diagnostic pathway is the added value of WGS the largest?
- Endpoints:
  - (Most common) sequence of activities
  - Turnaround times of activities
  - Delays between activities
  - Costs of the pathways
- Results are input for cost-effectiveness model WP4

Technology Assessment of Next Generation Sequencing in Personalized Oncology

3. Uncovering the real-world pre-treatment diagnostic pathway of advanced non-small cell lung cancer with routinely gathered data

- Linking four datasets from the NKI-AVL:
  - DBC
  - Pathology (IHC and various forms of ISH tests)
  - Molecular pathology (sequencing and other forms of ISH tests)
  - Other diagnostics (e.g. imaging)
- From these datasets we can create one event log which includes an activity, which patient was involved and its execution times
- With the event log we can order the activities for each patient which results in diagnostic pathways

- Challenges:
  - Personalized medicine so many unique pathways!
  - Lack of structure in data

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4. Where do we go with Whole Genome Sequencing in oncology? Using scenario drafting to explore future developments

- Combined effort with WP4
- Objective: To define and gauge the likelihood of possible future developments that can facilitate or impede the implementation and adoption of WGS as a clinical diagnostic in oncology.
- The effects of these scenarios will be calculated with our simulation model
- Current status: data collection and analysis
- Preliminary results will be presented later today

Technology Assessment of Next Generation Sequencing in Personalized Oncology

WP 6 Ethische en juridische aspecten

Onderzoekers juridische deel:

Corrette Ploem, Colin Mitchell, Sjef Gevers (Amsterdam UMC)

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Vraagstelling

Centrale vraag (ook voor ethiek deel)

Wat als door nieuwe inzichten of technische ontwikkelingen in de genetica nieuwe informatie beschikbaar komt (of beschikbaar kan worden gemaakt) die relevant is voor (voormalige) patiënten: moet met hen dan opnieuw contact worden gezocht (‘responsibility to recontact’)?

Deelvragen o.a.

- Positie onderzoekers vergeleken bij die van hulpverleners?
- Gelden eventuele verantwoordelijkheden ook t.a.v. familieleden?
- Rechten en verantwoordelijkheden van patiënten in dit verband?
- Betekenis van e.e.a. in termen van mogelijke aansprakelijkheid?

Publicaties tot nu toe

- Juridisch artikel in European Journal of Health Law
- Juridisch artikel voor T. voor Gezondheidsrecht
- Empirisch artikel in European Journal of Medical Genetics

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BRILL
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EUROPEAN JOURNAL OF HEALTH LAW 25 (2018) 537-553

European Journal of Health Law

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A Duty to Recontact in the Context of Genetics: Futuristic or Realistic?

Corrette Ploem,[a] Colin Mitchell,[b] Wim van Harten[c] and Sjef Gevers[d]

[a] Academic Medical Center, Amsterdam, The Netherlands

[b] Doctoral student, Health Law, Amsterdam University Medical Center, Amsterdam, The Netherlands

[c] Professor, Quality Management and Governance, University of Twente, Twente, The Netherlands; Dept. Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

[d] Emeritus Professor of Health Law, University of Amsterdam, Amsterdam, The Netherlands

Abstract

Medical genetic testing, 'next generation sequencing', is increasingly generating data that could become useful for patients after they have been discharged from care. If new information is discovered that links a disease to a specific mutation, do health professionals have a legal duty to recontact their patients? Apart from other concerns (such as respecting the patient's right not to know), in many cases, this would require re-evaluation or re-analysis of the data. Taking such issues into account, we conclude that, at least at this point in time, it is not arguable that there is an unconditional duty of this kind. Health professionals should always do what can be reasonably expected from them to do justice to the patient's right to information. When there is reason to believe that recontacting would be of significant clinical relevance for the patient, they should do so, unless efforts and costs involved would be disproportional.

Keywords

genetic testing – duty to recontact – patient's right to information – updating previous test results

 | DOI:10.1163/15718093-12255399

ARTIKEL

Opnieuw contact zoeken met de patiënt: een artsenplicht?*

*Prof. mr. J.K.M. Gevers, mr. dr. M.C. Ploem & prof. dr. W.H. van Harten***

1. Inleiding

Zijn er omstandigheden waaronder een arts opnieuw contact moet zoeken met de patiënt, ook al is de behandeling afgerond of de hulpverleningsrelatie zelfs beëindigd? Deze vraag is zeker niet nieuw, maar de context waarin deze vraag zich aandient wel.
Er zijn altijd al situaties geweest waarin hulpverleners gehouden waren patiënten opnieuw te benaderen omdat er nieuwe informatie beschikbaar was gekomen die belangrijk bleek voor de bescherming van hun gezondheid. Voorbeelden zijn het waarschuwen van patiënten als implantaten achteraf gebrekkig blijken, indien van een eerder voorgeschreven geneesmiddel een gevaarlijke bijwerking bekend wordt of wanneer patiënten door ziekenhuisopname of via een bloedtransfusie mogelijk met een bepaalde ziekteverwekker besmet zijn geraakt.
Door de ontwikkelingen in de genetica, zoals 'next generation sequencing' (NGS), heeft het opnieuw contact zoeken met patiënten – in de internationale literatuur ook wel '*recontacting*' genoemd – een geheel nieuwe dimensie gekregen. Via NGS kan in één keer de sequentie van het hele genoom (whole genome sequencing/WGS) of het hele exoom (whole exome sequencing/WES) worden vastgelegd.[1] Het is overigens niet zo dat alle ruwe data die door sequencing beschikbaar komen direct ook geanalyseerd zullen (moeten) worden; het huidige Europese standpunt binnen de klinisch-genetische zorgverlening is dat gericht wordt gezocht naar 'kandidaat-genen' die verband houden met de ziekte of aandoening waarvoor hulp wordt gezocht.[2] Het punt is echter dat aan de hand van voortschrijdende

* Deze bijdrage is gebaseerd op onderzoek uitgevoerd in het kader van de projecten TANGO respectievelijk ELSI-Personalised Medicine (ELSI-PM), beide gefinancierd door ZonMw. Binnen het eerste project verscheen eerder C. Ploem, C. Mitchell, W. van Harten & S. Gevers, 'A Duty to Recontact in the Context of Genetics: Futuristic or Realistic?, Eur J Health Law 2018, p. 537-553. De auteurs danken de onderzoekers van TANGO en ELSI-PM voor hun waardevolle opmerkingen bij eerdere versies van dit artikel.

** Sjef Gevers is emeritus-hoogleraar gezondheidsrecht, Universiteit van Amsterdam. Corrette Ploem is universitair docent gezondheidsrecht bij de afdeling Sociale geneeskunde van het Amsterdam UMC en redacteur van dit blad. Wim van Harten is wetenschappelijk groepsleider in het NKI, hoogleraar aan de Universiteit Twente en voorzitter van de raad van bestuur van Rijnstate.

1 C. Ploem e.a., 'Invoering van *next generation sequencing* in de zorg', *Ned Tijdschr Geneeskd.* 2014, p. 172-175.

2 Zie aanbeveling 2 van de European Society of Human Genetics: 'When in the clinical setting either targeted sequencing or analysis of genome data is possible, it is preferable to use a targeted approach first in order to avoid unsolicited findings or findings that cannot be interpreted. Filtering should limit the analysis to specific (sets of) genes. Known genetic variants with limited or no clinical utility should be filtered out (if possible neither analyzed nor reported).' C.G. van El, M.C. Cornel e.a., 'Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics, *Eur J Hum Genet.* (22) 2013, p. S1-S5.

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Experts reflecting on the duty to recontact patients and research participants; why professionals should take the lead in developing guidelines☆

Colin Mitchell[a,*], Corrette Ploem[a], Valesca Retèl[b], Sjef Gevers[a,1], Raoul Hennekam[a,1]

[a] Amsterdam UMC, Meibergdreef 9, 1105AZ, Amsterdam, Netherlands
[b] Netherlands Cancer Institute—NKI, Amsterdam, Netherlands

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Duty of care

ABSTRACT

Sequencing technology is increasing the scale of information that could benefit patients who have been tested in the past. This raises the question whether professionals have a duty to recontact such patients or their families. There is currently no clear basis for a legal duty to recontact, and professional guidelines are limited. We conducted interviews with 14 senior professionals from the Netherlands and UK to obtain a range of opinions on what obligations are estimated to be possible or desirable. There was (near) consensus that a lack of resources currently inhibits recontacting in clinical practice, that recontacting is less desirable in research, that information on recontacting should be part of informed consent, and that a legal duty should follow professional standards. There was a diversity of opinions on the desirability of a more systematic approach, potential obligations in hybrid clinical-research projects, and who should bear responsibility for seeking updates. Based on the literature, legal framework and these interviews, we conclude that a general duty to recontact is unlikely, but that in specific circumstances a limited duty may apply if the benefit to the individual is significant and the burden on professionals not too extensive. The variation in opinion demonstrates that further deliberations are desirable. The development of guidelines—a process the European Society of Human Genetics has begun—is important to ensure that the courts, in deciding a recontacting case, can take into account what professionals consider responsible standards in this field.

1. Introduction

The debate over whether to update patients or research participants with changes in genetic knowledge goes back several decades (Knoppers, 2001; Letendre and Godard, 2004). Developments towards genomic medicine and the large number of 'hybrid' clinical-research projects using genome-sequencing technology greatly increases the scale of potentially significant test results for patients, research participants and their family members, due to consequences for treatment, prevention and reproductive choices. There is no legal basis that provides guidance for indications, timing, and procedures to healthcare professionals (HCPs) or researchers for re-analysing sequencing data, updating results and recontacting individual patients or research participants (Ploem et al., 2018; Otten et al., 2015; Carrieri et al., 2018). However, recontacting is already taking place on an *ad hoc* basis (Carrieri et al., 2017a, 2018; Sirchia et al., 2018; Dheensa et al., 2017), with nearly half of surveyed European genetic centres indicating that recontacting systems should be implemented (Sirchia et al., 2018). Currently, a variety of approaches are taken in clinical, research or hybrid clinical-research next-generation sequencing (NGS) initiatives to the possibility of updates in the future, whether patients/participants or their families may ask for such results or, whether they may be actively informed of new results. For example, in clinical exome/genome sequencing, patients are often informed that knowledge is likely to change and that they can ask their doctor for an update in the future, as well as the possibility that clinicians may recontact them (for example see the approach taken by the Amsterdam UMC). But patients may not always be asked about their recontacting preferences (Sirchia et al., 2018). In contrast, and frequently when NGS is applied in non-therapeutic research, participants may be informed that they will not

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* Corresponding author. Amsterdam UMC, Locatie AMC, Afdeling Sociale Geneeskunde, Kamernummer 205, Postbus 22660, 1100 DD, Amsterdam, Netherlands.
E-mail address: c.r.mitchell@amc.uva.nl (C. Mitchell).
[1] These authors contributed equally to this work.

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Belangrijkste gemeenschappelijke conclusies

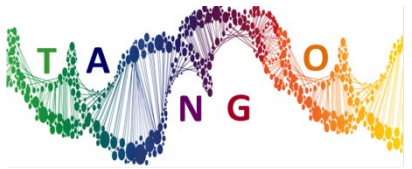
- ‘Duty to recontact’ heeft op dit moment geen juridisch ‘fundament’
- Tegen die achtergrond kan een dergelijke plicht tegenover de rechter niet worden afgedwongen
- Deze conclusie geldt niet alleen voor Nederland, maar ook voor ons omringende landen, zoals UK
- Tegelijkertijd is ook niet volledig uit te sluiten dat rechter *in concreet geval* tot vaststelling van recontact-plicht komt
- Denk hierbij m.n. aan situatie waarin veel voor betrokkene op het spel staat terwijl recontacten weinig inspanning van vergt
- Niettemin: vrees voor aansprakelijkheidsstelling begrijpelijk, maar kans daartoe vooralsnog beperkt
- Beroepsgroepen kunnen zelf aan ‘rechtszekerheid’ bijdragen door met richtlijnen te komen waarin ze duidelijk maken wat wel resp. niet van hen verwacht mag worden (vgl. VKGN-richtlijn ‘informeren van familieleden bij erfelijke ziekten)
- De kans is groot dat de rechter zulke richtlijnen in een concreet geval rond recontacting bij haar beoordeling zal betrekken

Laatste publicatie

- Recht en ethiek samen
- Breder oncologisch of medisch tijdschrift
- Ploem en Retel schrijven eerste versie
- Moet kort, krachtig en toegankelijk stuk worden, waarbij liefst TANGO-studie het vertrekpunt vormt en dat uitmondt in enkele praktische aanbevelingen, gericht op zowel medicus practicus/arts-onderzoeker als beroepsgroep(en)
- Suggesties die we kunnen meenemen?

Technology Assessment of Next Generation Sequencing in Personalized Oncology

WP6: Ethical part



Technology Assessment of Next Generation Sequencing in Personalized Oncology

Overview

- Ethical analyses → paper a duty to recontact in genetics: context matters
- Focus groups → analyses
- Joint paper

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COMMENT

A duty to recontact in genetics: context matters

Noor A. A. Giesbertz[1]*, *Wim H. van Harten*[2] *and Annelien L. Bredenoord*[3]

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Definition

Recontact patients (or participants) with new genetic information or developments that are relevant to their health or reproduction

(1) New screening recommendation or treatment possibility
(2) New technique or new genetic test
(3) New gene identified that may be relevant in relation to the disease
(4) Reclassification of variant

Ploem et al. 2018

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Arguments in favor and against

Arguments in favor	**Arguments against**
Respect for autonomy requires recontact	Respect for autonomy does not imply recontact (right not to know)
Beneficence or a duty to warn requires recontact	Recontact can have harmful consequences (principle of non-maleficence)
Technology developments can simplify and facilitate recontact	Recontact is not feasible
Empirical studies support a desire for recontact	Recontact poses an untenable burden on professionals
Protect against legal claims	Health professionals become vulnerable for legal claims
Recontact is part of (genetic) health care *	Recontact is the patient's responsibility*
Recontact engages participants **	Therapeutic misconception **

Adapted from Bredenoord et al 2011

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Weight of the arguments context-specific

- Strong arguments in favor and against
- Balance

"Considering the wide variety of recontact situations, the force of the arguments differs accordingly."

Giesbertz et al. 2019

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Factors

Information	• Validity • Severity and probability of the condition • Possibility to act • Compare with previous information • …
Costs and efforts	
Personal preferences	
Who is contacted	
Clinic or research setting	
Time	

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Focus groups

- Aim: to verify and further explore our framework with both professionals and oncology patients.

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Focus groups

- 3 focus groups with oncology patients and professionals
- Total n=25

- 1 patient group
  - n=12 (7 male, 5 female; age 48-71; ex-patients/family member)
- 2 professionals
  - n=6 (6 female)
  - n=7 (3 male, 4 female)
  - Professions: clinical geneticist, surgeon, laboratory specialist, pathologist, ethicist, mammacare/research nurse, social worker, oncologist

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Outline

- Introduction
- General thoughts
- Factors:

Information
Costs and efforts
Personal preferences
Who is contacted
Clinic or research setting
Time

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Work in progress (1)

- Patient group:
  - focus on receiving information
  - Importance of information for family members (comparison general discussion on informing family members of genetic test results)
  - Effect of information on people who had cancer vs. healthy people (family members)
  - Informed about the possibility to be recontacted / asked for permission

Work in progress (2)

Professionals

- Incomprehensive topic
- More focus on the harmful effects of information
  - On patients/participants
  - Costs and efforts
- Also focus on the harmfull effects of discussing recontact (too much information?)
- At the same time acknowledge importance of information in some situations

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Work in progress (3)

- Factors: hierarchy?
  - Patient preference
  - Information aspects

- …

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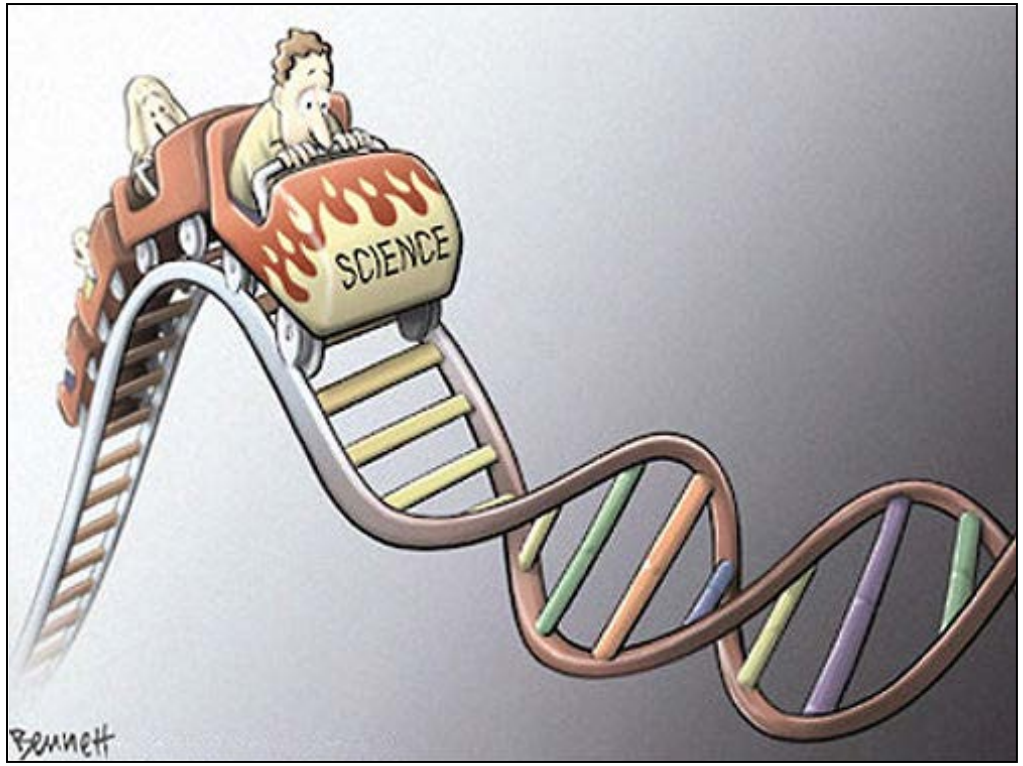
Closing session



Thank you all!

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Employees

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Deelnemende centra

Dit project (846001002) wordt mogelijk gemaakt door