Technology Assessment of Next Generation Sequencing in Personalized Oncology

Minisymposium

5 september 2018

NKI-AVL

Valesca Retèl

Edwin Cuppen

T A O N G

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Welcome!

- Start writing project September 2015
- Start TANGO 31 December 2016
- Start most PhD students summer 2017
- Stakeholders/advisors (patients representatives, ZIN, RIVM, datasteward)
- AVG

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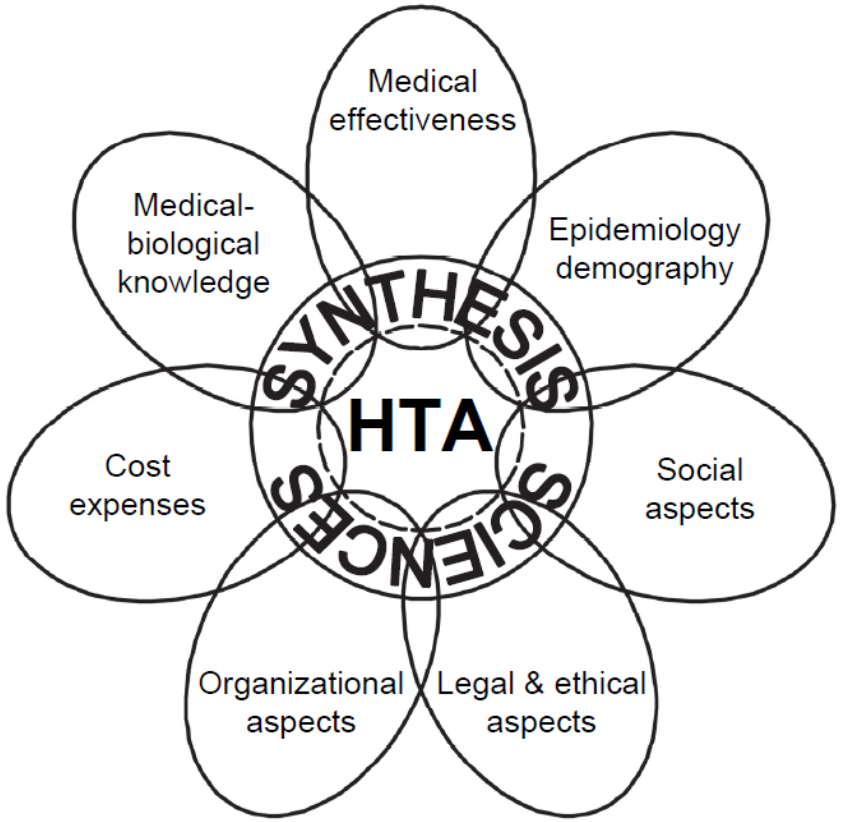
Technology Assessment

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

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



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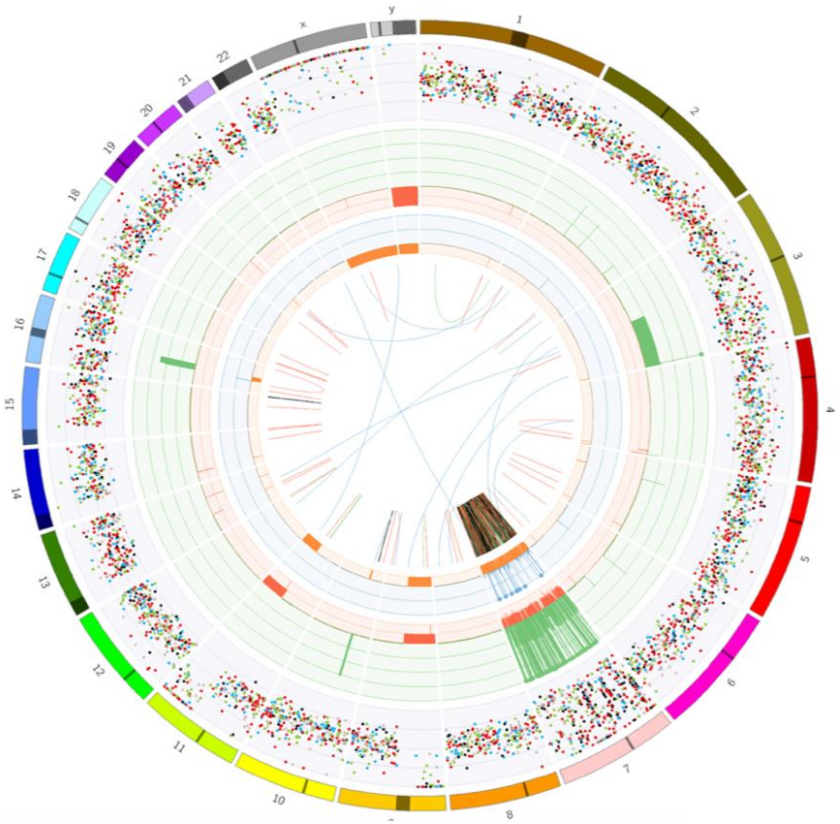
Next Generation in Oncology

- 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.



Hartwig MEDICAL FOUNDATION

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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:

-QoL↓

-Health care costs↑

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

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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: 1,2,3

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

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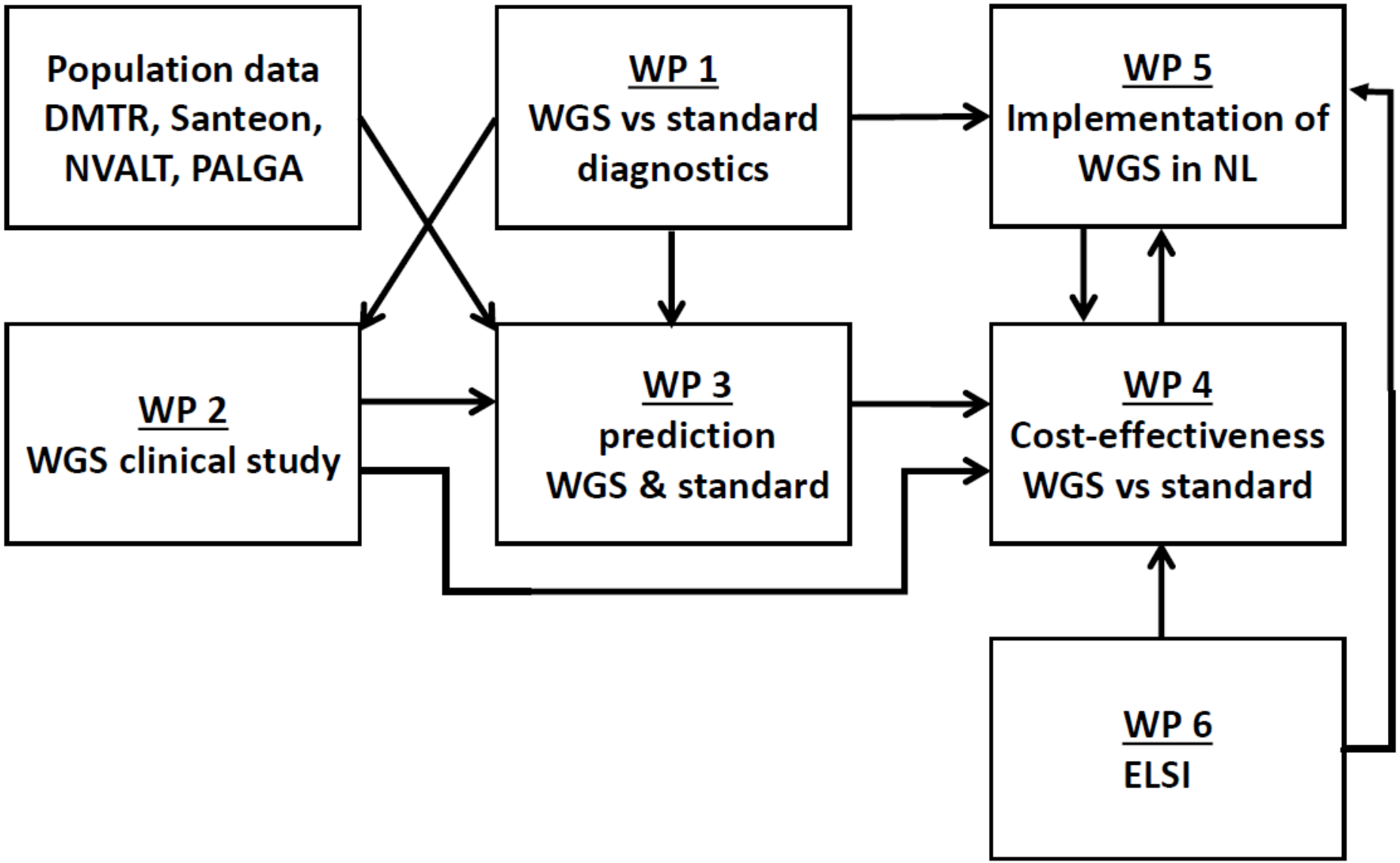
Overwiew TANGO



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Programme

TIJD	INHOUD	SPREKERS
12.30-13.00	Ontvangst met broodje	
13:00-13.15	Opening Update TANGO en doel van deze bijeenkomst	Edwin & Valesca
13:15-14.15	Milestones & preliminaire resultaten per work package	WP1: Edwin, Geert & Clémence WP1: Marc & Rogier WP2: Joachim & Joanne WP3: Veerle
14.15-14.30	Pauze	
14.30-15.30	Milestones & preliminaire resultaten per work package	WP4: Manuela & Martijn WP5: Erik & Michiel WP6: Corrette, Sjef & Collin
15.30-15.45	Pauze	
15.45-16.00	Potential Value of WGS_lung	Paul Roepman (Clinical Molecular Biologist HMF)
16.00-16.15	Diagnostic Pathway Lungcancer	Joachim Aerts/ Joanne Mankor
16.15-16.45	Interactieve sessie m.b.t. scenario's over WGS in 2025 met TANGO, stakeholders, adviseurs & patient advocates	Martijn & Michiel
16.45-17.00	Afsluiting	Edwin & Valesca
17.00	Borrel	

Work package 1/ Medical part

Molecular diagnostics by whole genome sequencing versus current diagnostics

Work package 1/ Medical part

WP leaders: E. Cuppen PhD, M.J. Van de Vijver MD, PhD

PhD candidate: R. Butter MD

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Contents

- Aims
- Milestones
- Progress milestones
- Upcoming

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Aims

- Implementation of WGS in the routine clinical landscape
- Incremental value of WGS versus current diagnostics
- Treatment decisions bases on WGS (→ WP2)

Milestones

- Activate centers to include non-small cell lung cancer (NSCLC)
- Acces to WGS data from Hartwig Medical Foundation
- Retrospective collection of regular diagnostic data
- Merging and analysis of data
- Collaboration with PATH

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Progress milestones (1/7): Activate centers

- In collaboration with WP2
- Progress inclusions presented by Joanne Mankor (WP2)

Progress milestones (2/7): Access to WGS data

- Access to NSCLC data through Erasmus UMC
- Upcoming: Data request via Amsterdam UMC

Progress milestones (3/7): Collection regular data

- High volume including centers
- Acces via Biobank Data requests

Progress milestones (4/7): Collection regular data

- VCF files gene panels/ next generation sequencing
- Mutation, translocations, mutational load
- Immunohistochemistry for PD-L1
- Clinical data for WP2 → To be specified

Progress milestones (5/7): Collection regular data

Centre	NSCLC	Melanoma
EMC	26	53
Meander	28	2
NKI-AvL	71	29
UMCU	1	19
VUmc	6	46
Totaal	**132**	**149**

*Numbers inlcude sequenced patients, with or without immunotherapy

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Progress milestones (6/7): Merging data

- Idea is cBioPortal
- Precise method at the end of/ after collection of data

Progress milestones (7/7): Collaboration PATH

- Collaboration TANGO-PATH
- Overlap reporting in PALGA/ Molecular Tumor Boards
- Specify plans in 2019

Upcoming

- Collection of regular data
- Get familiar with WGS data HMF
- Merging and analysing data

- Needs attention: Acces from Biobank Acces Boards

Work Package 1
Molecular Tumor Diagnostics by Whole Genome Sequencing versus Current Diagnostics

Microcosting WGS & Standard Care Utilization

Edwin Cuppen, PhD
Geert Frederix, PhD
Clémence Pasmans, MSc

UMC Utrecht
Julius Center

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Overview Work Package 1

Molecular tumor diagnostics by WGS versus current diagnostics

What do we have to organize to implement WGS in routine procedures?
- optimization PALGA setup (sample logistics, data exchange) to handle NGS/WGS data
  Rogier Butter (Marc vd Vijver) with PATH project

What is the direct added value of measuring differently?
- identification potential added therapeutic value of WGS (retrospective analysis)
  Rogier Butter (Marc vd Vijver)

Can we make better decisions when we have more (WGS) data?
- identification of a WGS-based classifier that predicts treatment outcome
  together with WP2: Joanne Mankor (Joachim Aerts)

What is the effect on the costs for diagnostics?
- comparison total costs of WGS vs current diagnostics (input WPs 3-5)
  Clémence Pasmans (Geert Frederix) with PATH project

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Table of Contents

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Goal, Milestones and Context

- Goal
  - To compare the total costs of current diagnostics and Whole Genome Sequencing (WGS) and to assess current practice patterns
- Milestones
  - Microcosting of WGS – Hartwig Medical Foundation (HMF)
  - Assessing healthcare resource utilization and costs
- Context
  - To guide future decision-making on the added value and implementation of WGS
  - Costing outcomes will be used as input to all other Work Packages

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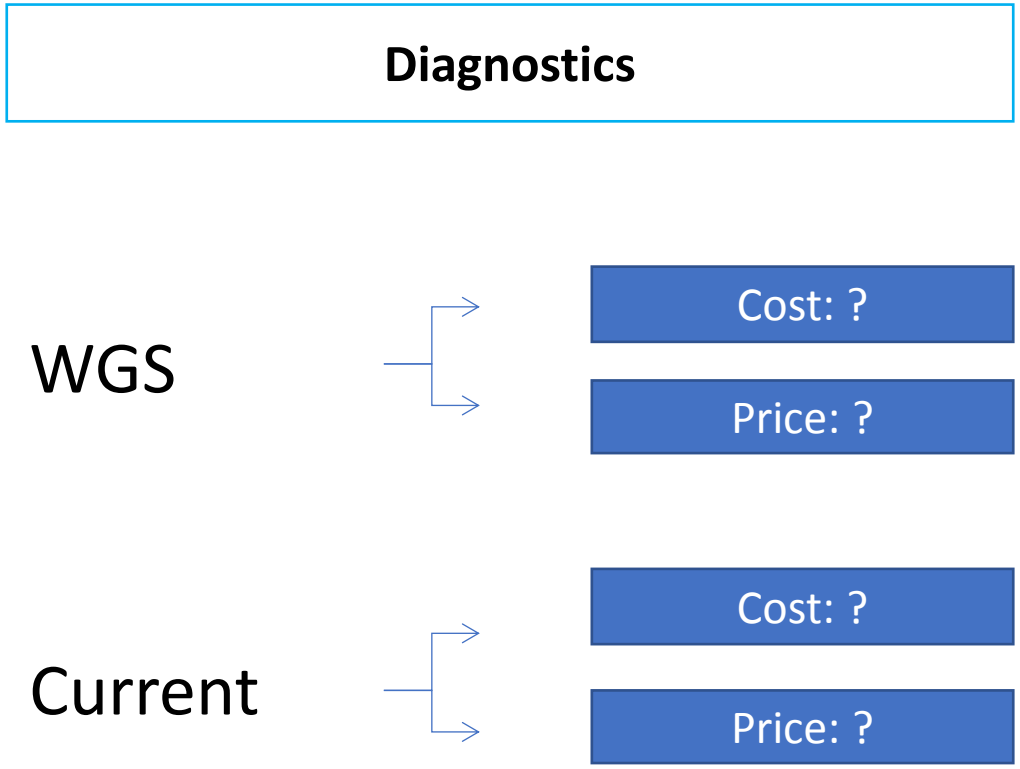
Overview Diagnostics

Microcosting WGS & Standard Care Utilization



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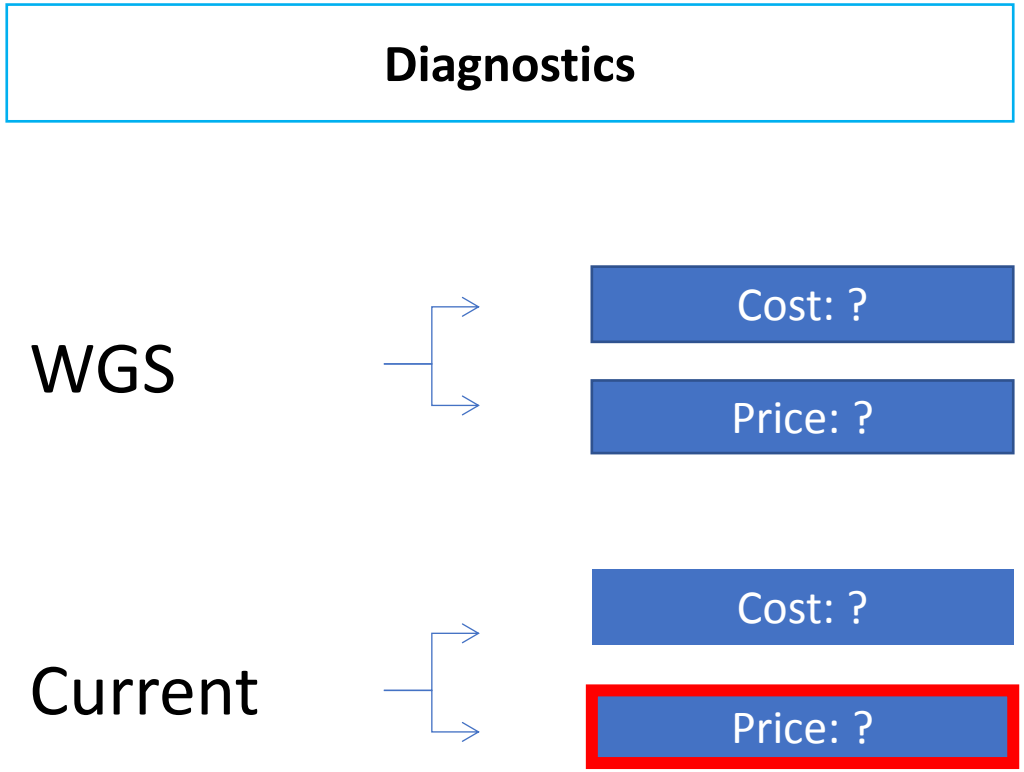
Overview Diagnostics

Microcosting WGS & Standard Care Utilization



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Preliminary Results

Current Diagnostics 1/4

- Data inclusion
  - University Medical Center Utrecht (UMC Utrecht)
  - Advanced Non-Small Cell Lung Cancer (NSCLC)
  - Years 2016 – 2017
  - → Eligible: N = 130
- Patient characteristics

Table 1
Patient characteristics of included patients.

Patient Characteristics	N	%
Total (year of diagnosis)		
2016	54	42
2017	76	58
Histology		
Adenocarcinoma	83	64
Adenosquamous Carcinoma	1	1
Large Cell Unspecified Carcinoma	6	5
Large Cell Neuroendocrine Carcinoma	6	5
Squamous Cell Carcinoma	18	14
Non PA proven lung cancer	16	12
Follow-up (days)		
Mean	167	
Median	132	
Range	1 - 712	

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Preliminary Results

Current Diagnostics 2/4

Healthcare resource utilization and costs

Table 2

Representation of healthcare resource utilization and costs.

Cost per healthcare resource	Mean	Median	Range	% Treated
Laboratory	€ 1.251	€ 1.014	€ 0 - 5789	96,2
Oncolytic drugs	€ 3.170	€ 99	€ 0 - 34162	50,8
Inpatient care	€ 8.222	€ 4.121	€ 0 - 46582	89,2
Outpatient care	€ 1.834	€ 1.596	€ 87 - 8850	100,0
Imaging	€ 1.629	€ 1.165	€ 0 - 8877	93,1
Radiotherapy	€ 651	€ 277	€ 0 - 3997	63,9
Revalidation	€ 38	€ 0	€ 0 - 1317	7,7
Surgery	€ 27	€ 0	€ 0 - 987	48,5
Other	€ 2	€ 0	€ 0 - 80	8,5
Total	**€ 16.825**	€ 13.443	€ 167 - 64420	**100**

Preliminary Results

Current Diagnostics 3/4

Healthcare resource utilization and costs: Laboratory in detail

Table 3

Detailed representation of healthcare resource utilization and costs.

Cost per healthcare resource	Mean	Median	Range	% Treated
Laboratory				
Pathology	€ 297	€ 240	€ 0 - 1317	68,5
Mutation Analysis	€ 801	€ 397	€ 0 - 4407	55,4
Other Laboratory	€ 152	€ 98	€ 0 - 908	93,1
Total	**€ 1.251**	€ 1.014	€ 0 - 5789	**96,2**

Preliminary Results

Current Diagnostics 4/4

Clinical course: € 16825 / 100 %

Diagnostics: € 1251 / 7,4 %

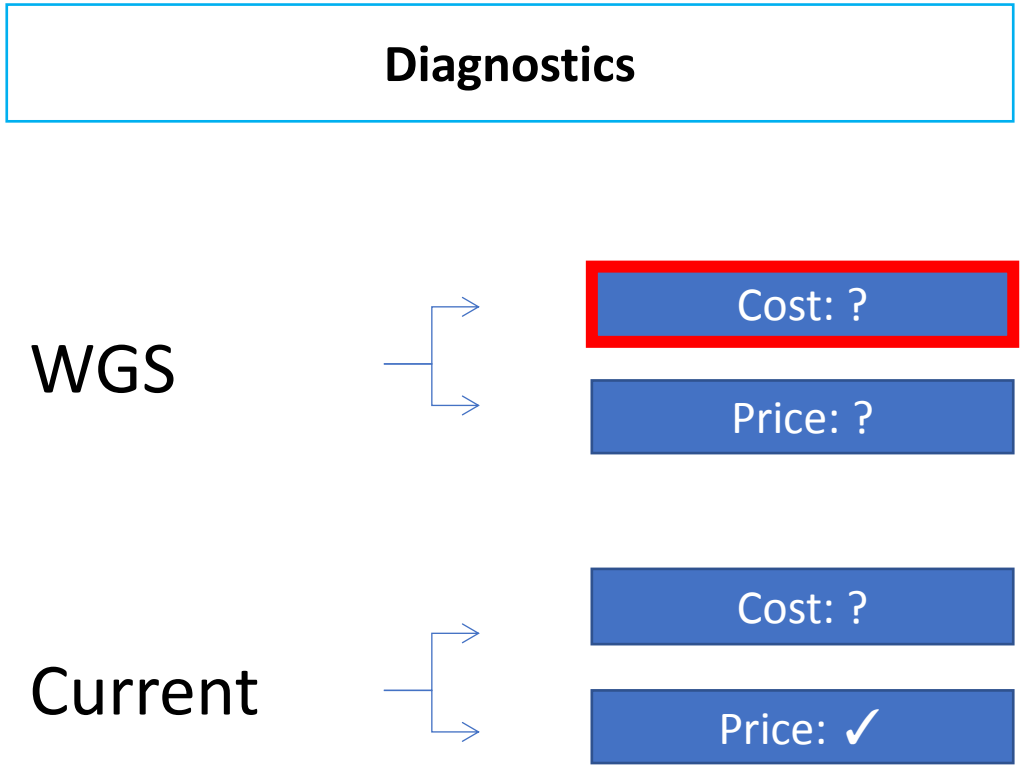
- Pathology: € 297 / 1,8 %
- Mutation Analysis: € 801 / 4,8 %
- Other: € 152 / 0,9 %

Care: € 15574 / 92,6 %

- Oncolytic drugs: € 3170 / 18,8 %
- Inpatient Care: € 8222 / 48,9 %
- Outpatient Care: € 1834 / 10,9 %
- Imaging: € 1629 / 9,7 %
- Radiotherapy: € 651 / 3,9 %
- Revalidation: € 38 / 0,2 %
- Surgery: € 27 / 0,2 %
- Other: € 2 / 0,0 %

Overview Diagnostics

Microcosting WGS & Standard Care Utilization



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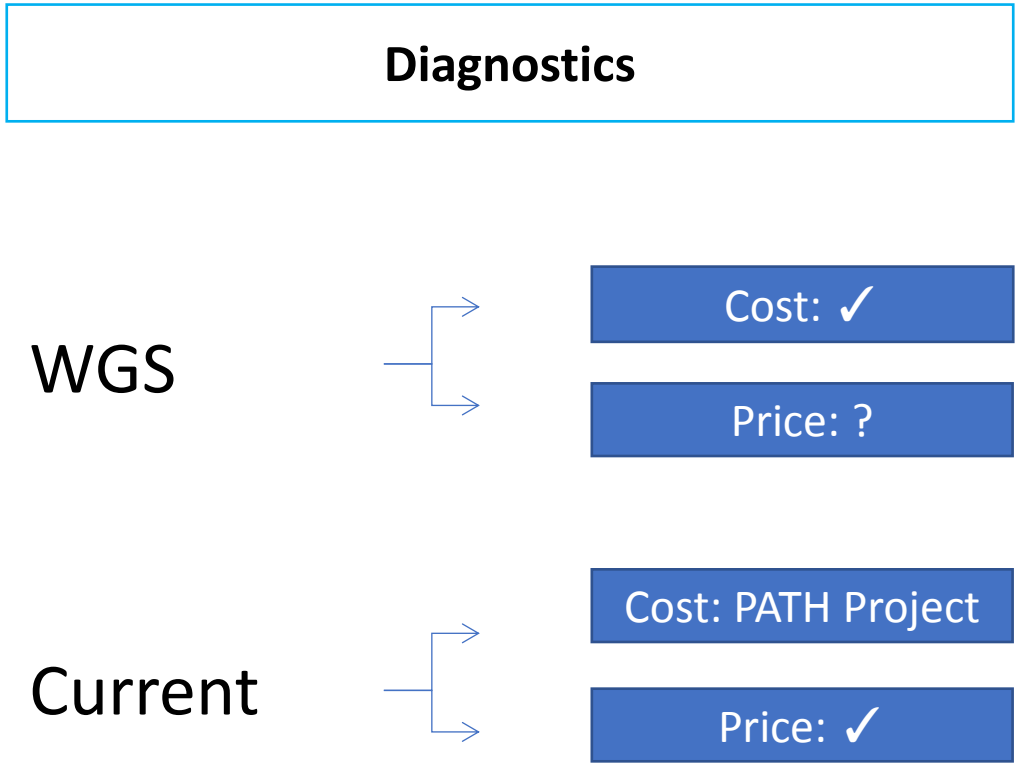
Preliminary Results

WGS

- Microcosting WGS
  - Activity-based costing (ABC) methodology
    - Process costs: Capital, maintenance, software (ICT), operational
  - Cost driver WGS
    - Sample sequencing consumables: 63 – 77 % of total costs per cancer patient

Overview Diagnostics

Microcosting WGS & Standard Care Utilization



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Next steps

- Final cost results for:
  - WGS (HMF)
  - Current diagnostics (PATH)
- Collect healthcare resource utilization data from:
  - Netherlands Cancer Institute
  - Rijnstate
- Compare total costs of current diagnostics and WGS

Work Package 2
Treatment selection based on WGS vs current diagnostics

Joachim Aerts, MD, PhD

Emile Voest, MD, PhD

Joris van de Haar, PhD candidate AvL

Joanne Mankor, PhD candidate Erasmus MC

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Table of Contents

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Goals, Milestones and Context

Goals

- Demonstrate the value of WGS for immune- and targeted treatment selection for NSCLC
- Identify potential biomarkers for patient stratification

Milestones

- Patient accrual in CPCT-02
- Access to and analyses of WGS data generated by HMF
- Collection of clinical data

Context

- Clinical outcome and potential biomarkers: modelling of cost-effectiveness

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NSCLC in CPCT-02 for TANGO

311 NSCLC patients included in CPCT-02

Biopsies excluded due to
28 no biopsy done
85 low tumor percentage
2 low tumor purity

196 biopsies suitable for WGS

Treatment:
17 tyrosine kinase inhibitors (TKI)
36 chemotherapy
29 no treatment
17 other
43 pending

53 treated with ICB: WGS

31 WGS and clinical data available for analysis

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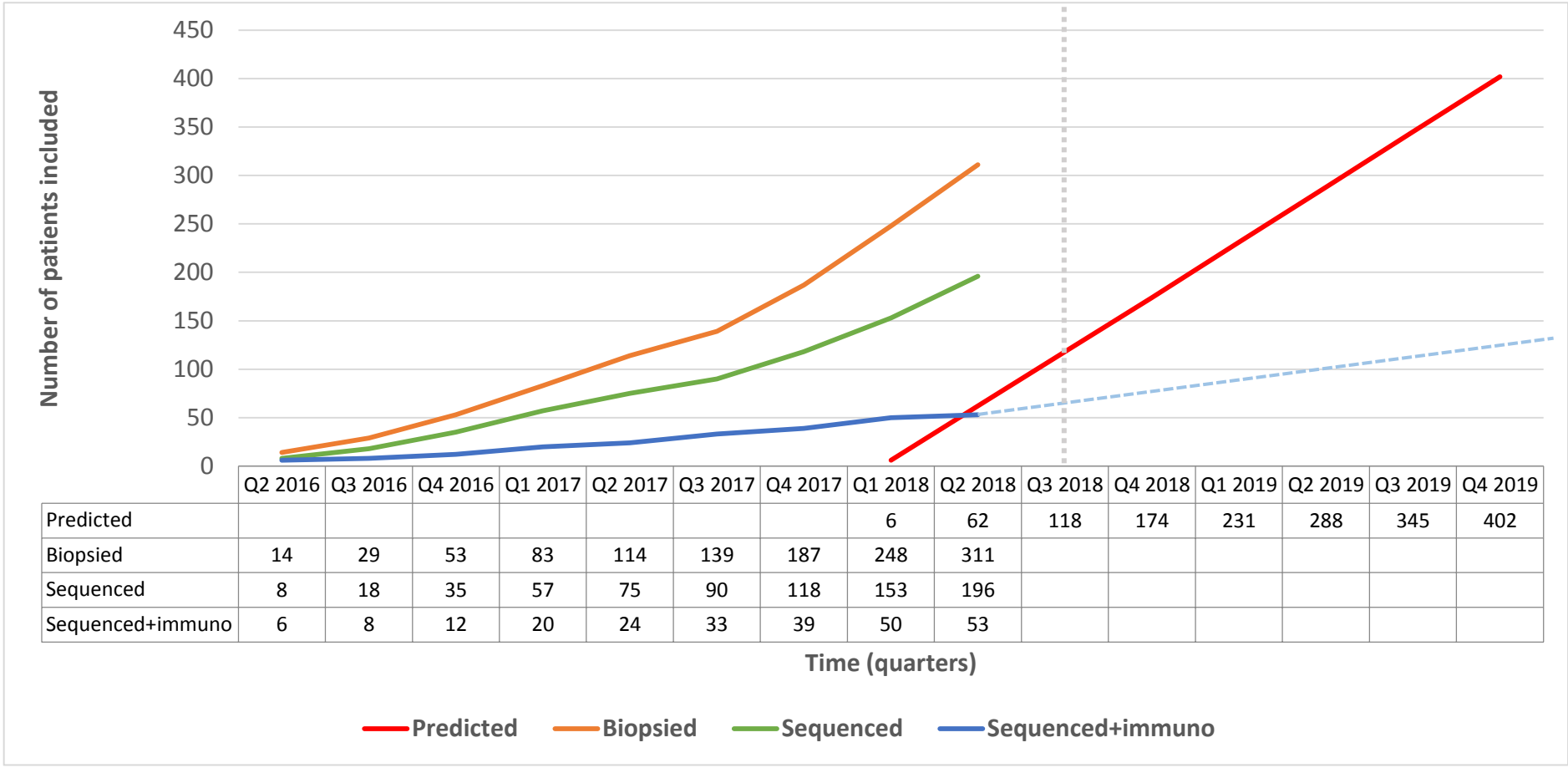
NSCLC in CPCT-02 for TANGO



	Q2 2016	Q3 2016	Q4 2016	Q1 2017	Q2 2017	Q3 2017	Q4 2017	Q1 2018	Q2 2018	Q3 2018	Q4 2018	Q1 2019	Q2 2019	Q3 2019	Q4 2019
Predicted								6	62	118	174	231	288	345	402
Biopsied	14	29	53	83	114	139	187	248	311						
Sequenced	8	18	35	57	75	90	118	153	196						
Sequenced+immuno	6	8	12	20	24	33	39	50	53						

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Go/ no-go requirements

- ICB is effective for a subgroup of patients
- A biomarker that predicts response in a subgroup of patients is discovered
- A biomarker that predicts which patients will not respond is discovered
- A biomarker that predicts which patients will not respond is discovered and therefore WGS can be budget neutral or cost saving

Whole genome correlates of response to immune checkpoint blockade in lung cancer

TANGO mini-symposium

September 5th 2018

Joris van de Haar, MD, Msc

PhD-student Voest & Wessels laboratories

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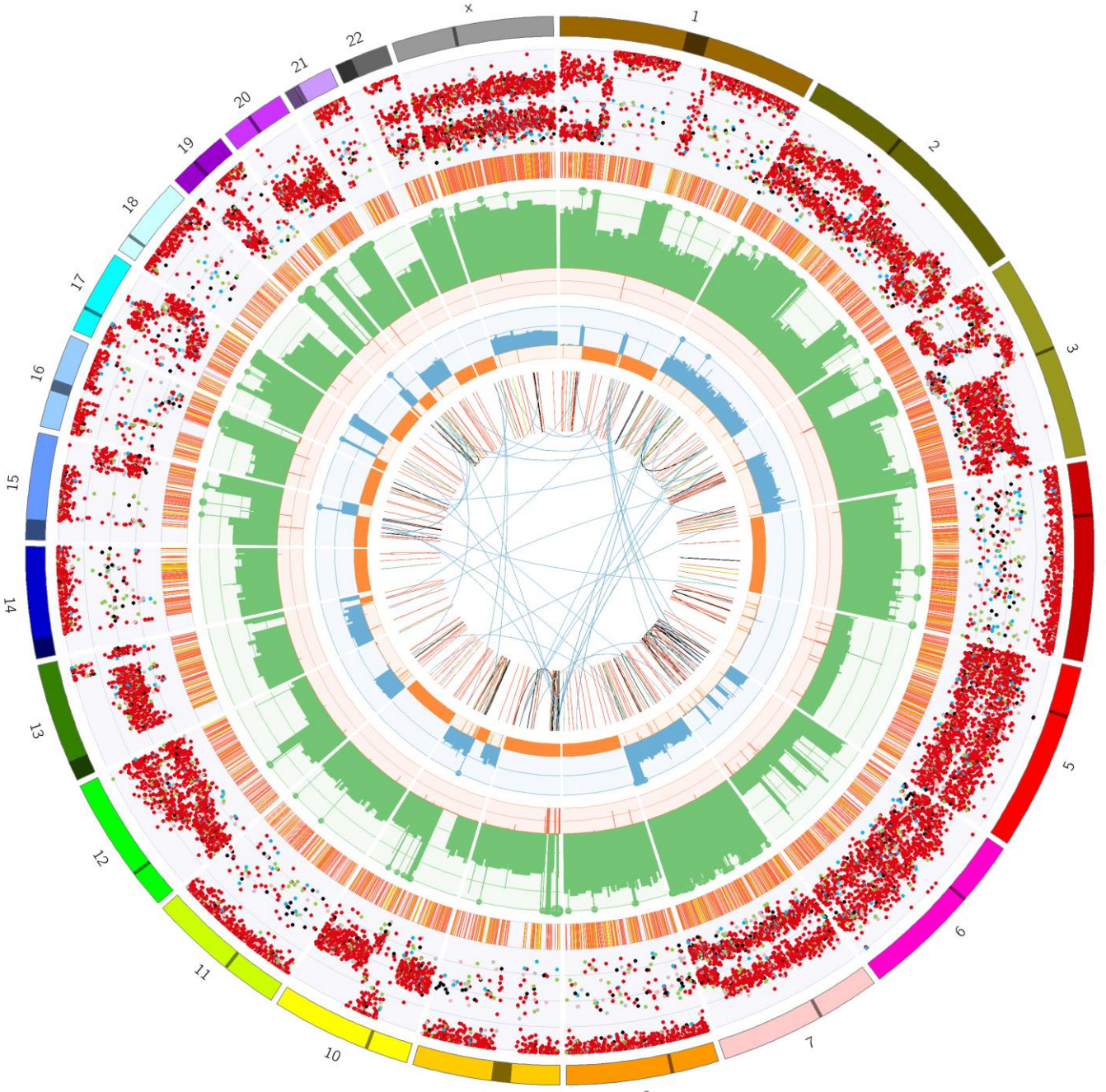
All patients with WGS data *(n = 41; July 2018)*

Age	
<50	3 (7.3%)
50-65	20 (48.8%)
>65	18 (43.9%)
Gender	
♂	24 (58.5%)
♀	17 (41.5%)
Response (RECIST at 8 weeks)	
CR	0 (0.0%)
PR	10 (24.4%)
SD	12 (29.3%)
PD	9 (22.0%)
Not evaluable	1 (2.4%)
Pending	9 (22.0%)
Treatment	
Anti-PD-(L)1	41 (100%)

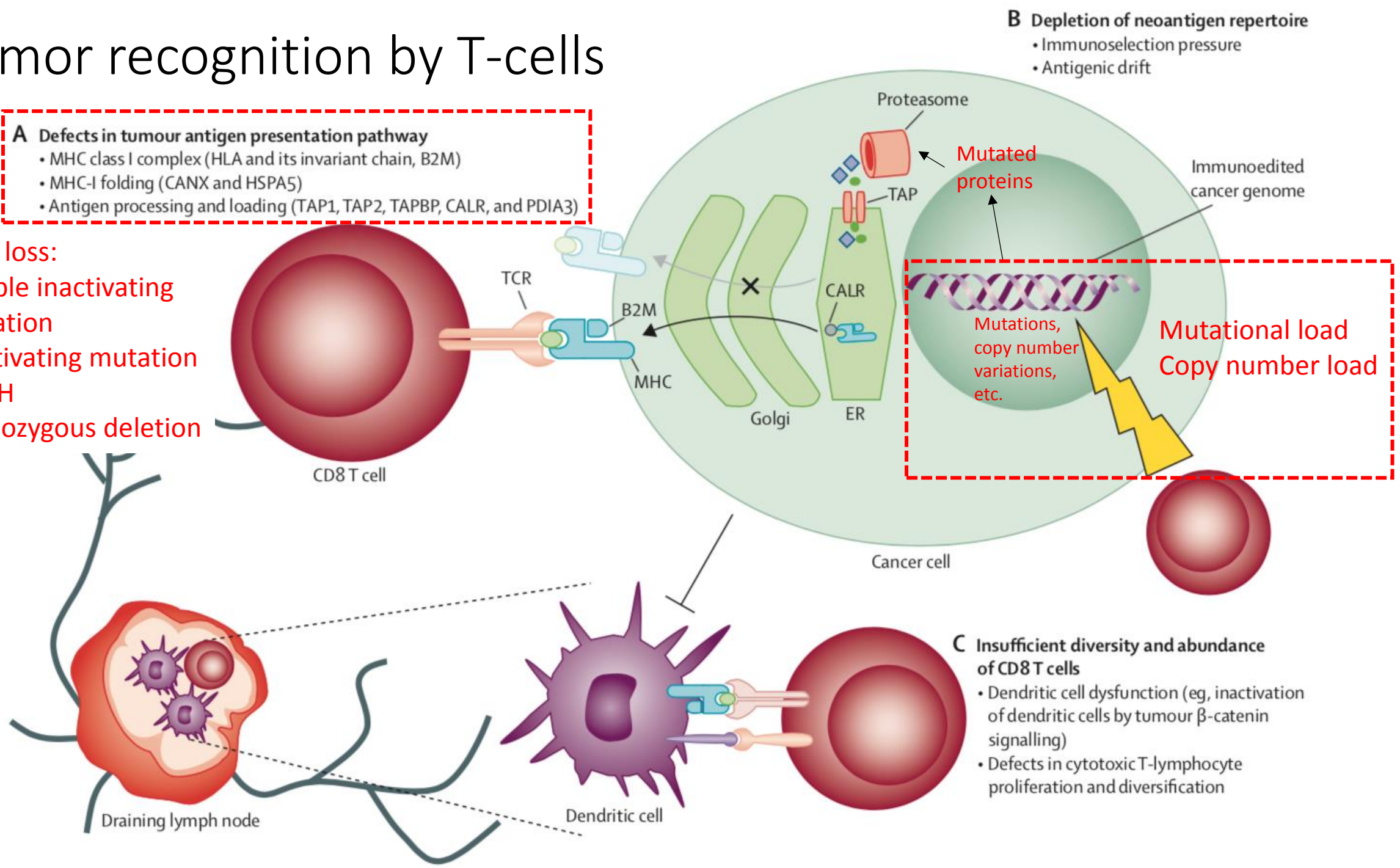
Whole genome sequencing (WGS)

Unprecedented depth of 130X:



The biology behind immunotherapy response

Tumor recognition by T-cells

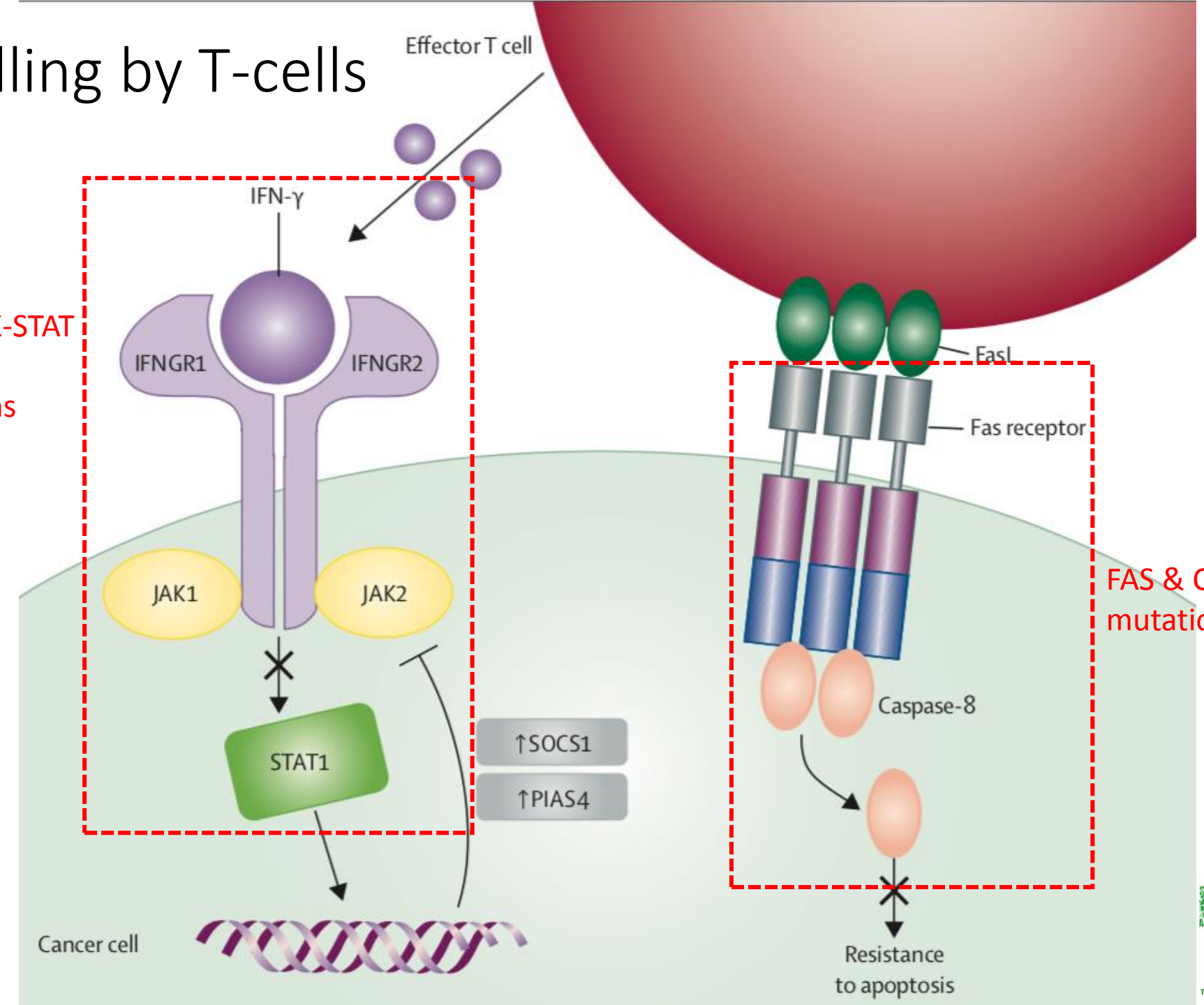


Biallelic loss:

- Double inactivating mutation
- Inactivating mutation + LOH
- Homozygous deletion

Tumor killing by T-cells

IFNG-JAK-STAT pathway mutations



FAS & Caspase-8 mutations

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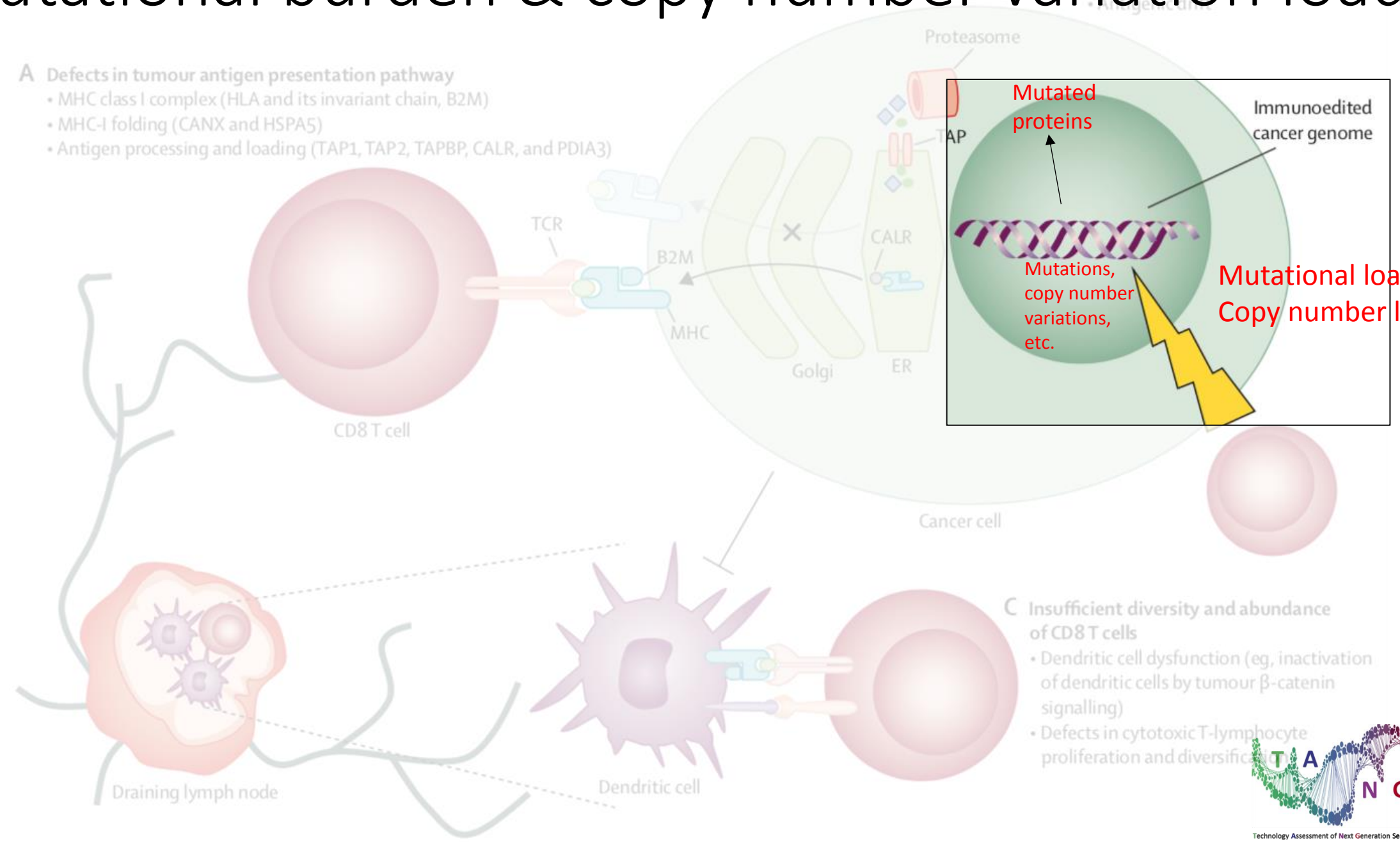
Mutational burden & copy number variation load



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Preliminary results

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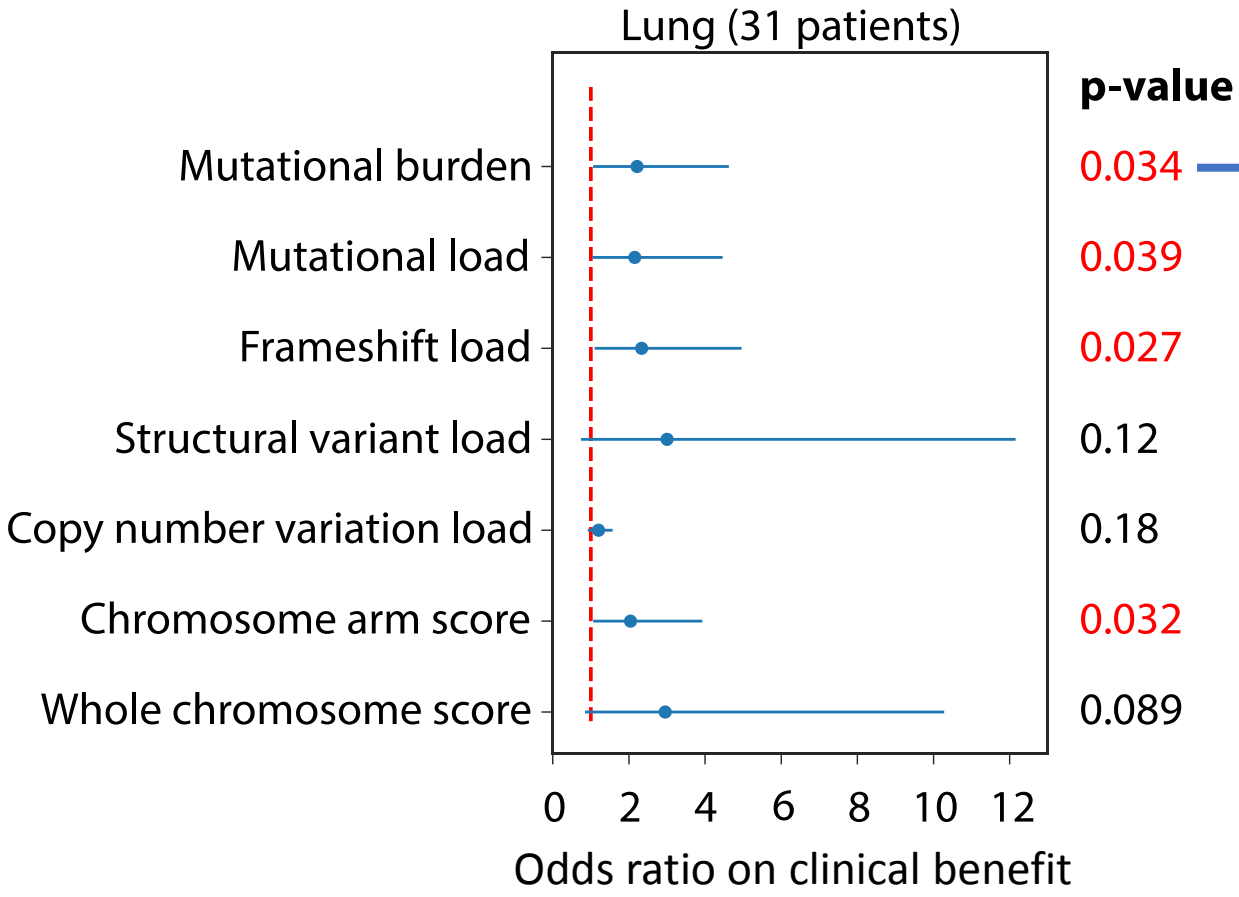
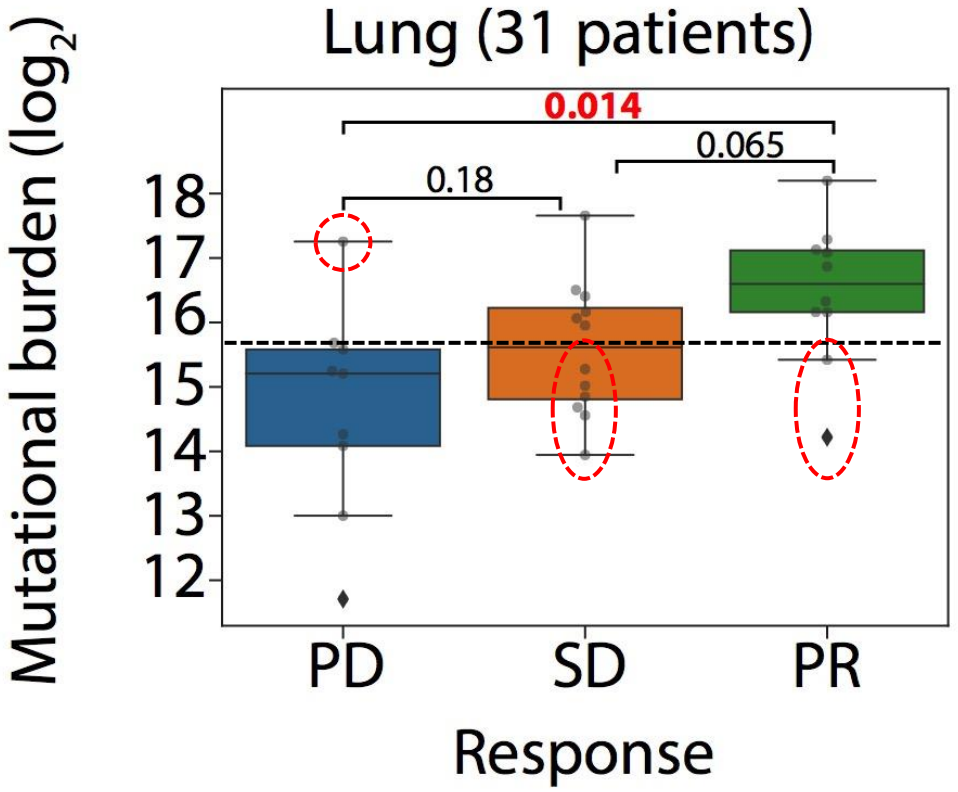
Mutational burden & chromosomal instability





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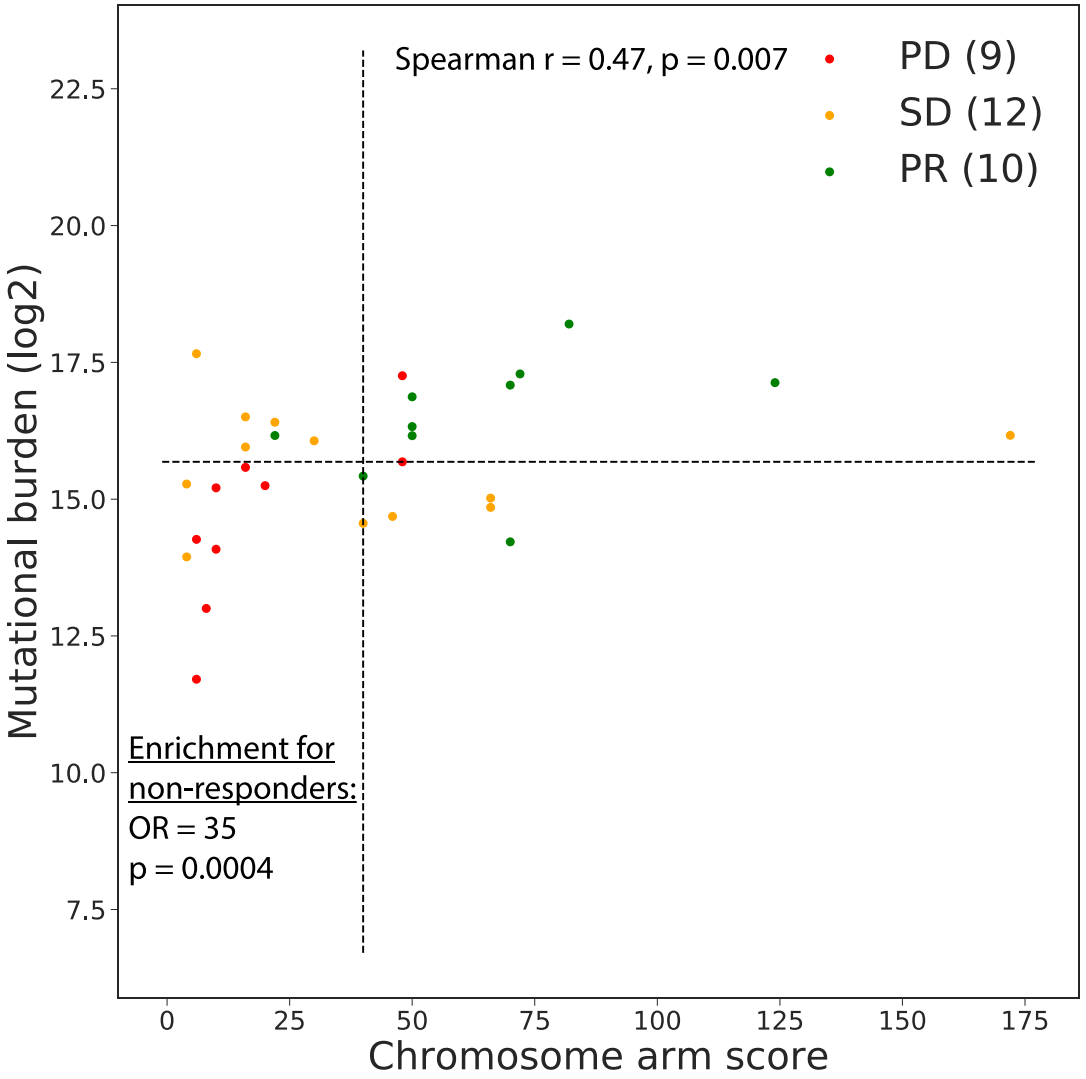
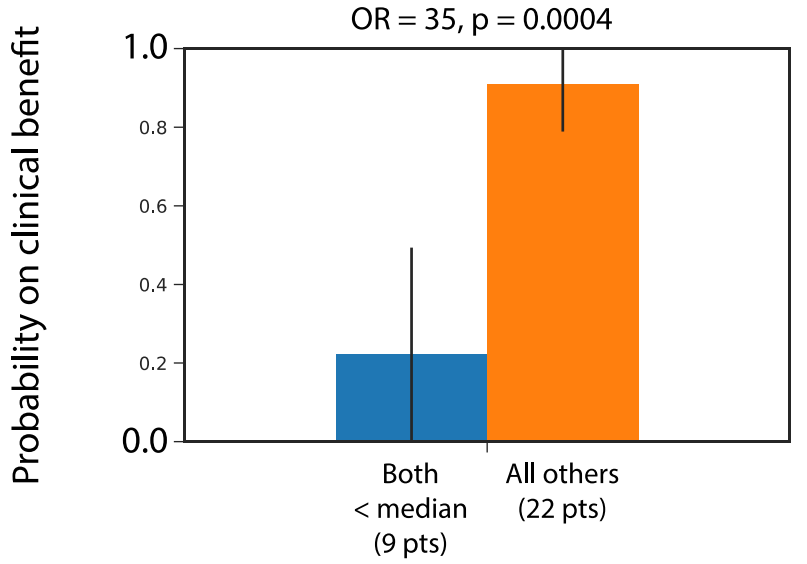
Mutational burden & chromosome arm score are **complementary biomarkers**





Mutational burden & Chromosome arm score

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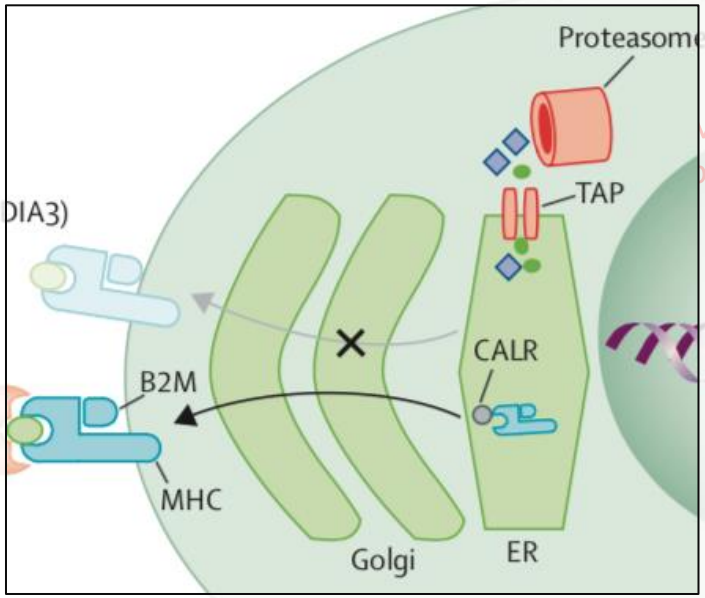
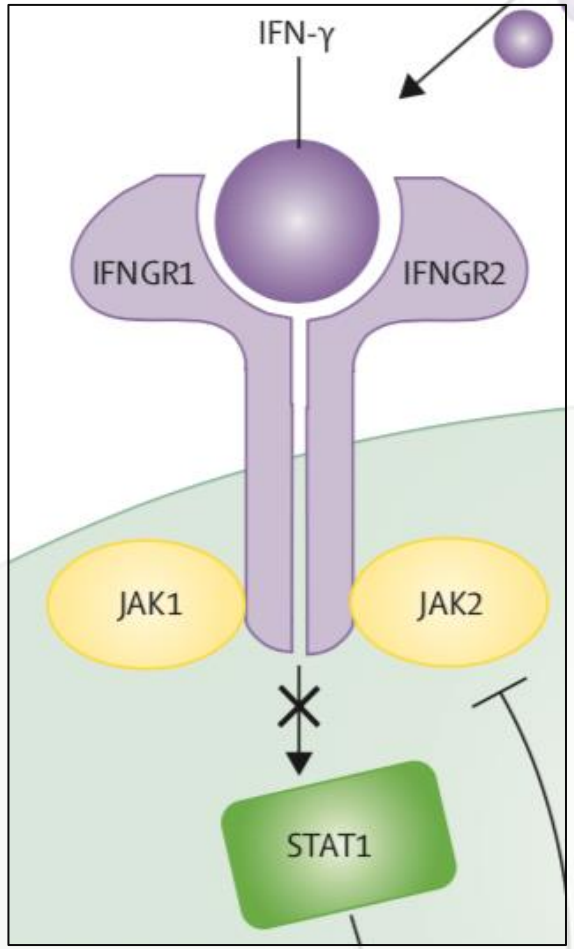
Defects in tumor antigen presentation pathway

Gene	Biallelic loss (#)
B2M	0
CANX	0
HSPA5	0
TAP1	0
TAP2	0
TAPBP	0
CALR	0
PDIA3	0



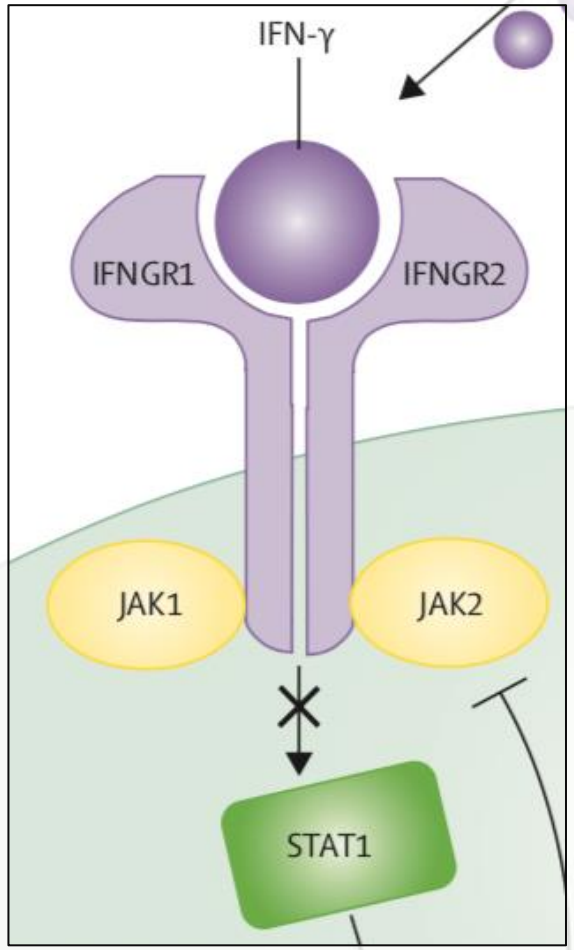
Defects in T-cell killing pathways

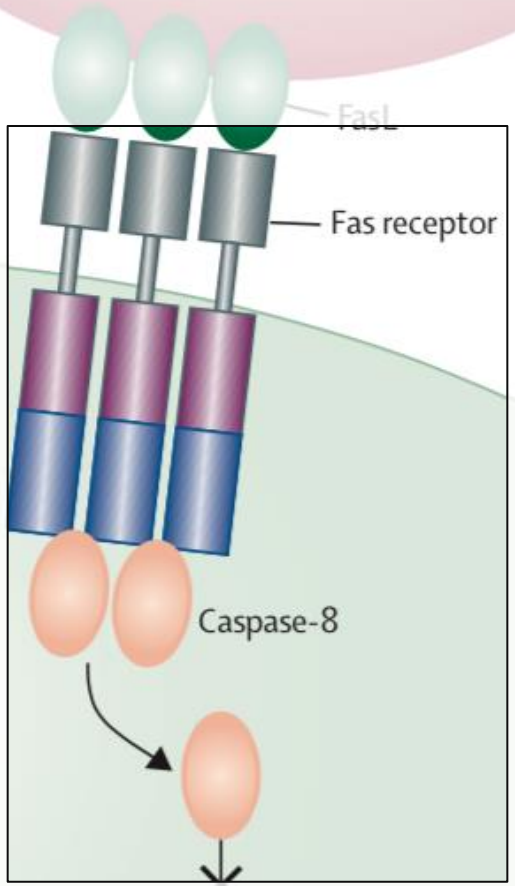
Gene	Biallelic loss (#)
IFNGR1	0
IFNGR2	0
JAK1	0
JAK2	0
STAT1	0



Defects in T-cell killing pathways

Gene	Biallelic loss (#)
IFNGR1	0
IFNGR2	0
JAK1	0
JAK2	0
STAT1	0





Gene	Biallelic loss (#)
FAS (receptor)	0
CASP8	0

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Conclusions

- We identified mutational burden and chromosome arm score as **complementary biomarkers** for anti-PD1 response in lung cancer

- These biomarkers enable accurate and highly significant patient stratification:

  Correct classification of:

  - **10 out of 10** (100%) partial responses
  - **10 out of 12** (83%) stable diseases
  - **7 out of 9** (78%) progressive diseases

- Genomic inactivation of ‘essential genes’ for anti-PD1 response is rare in lung cancer

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Future perspective

More samples with WGS are needed to:

- Validate mutational burden and chromosome arm score as complementary biomarkers
- Determine optimal cutoffs for patient stratification
- Identify additional genomic biomarkers (e.g. combinations of mutational signatures)

Additional clinical data is needed to:

- Analyze responses of later time points (3 months, 6 months, progression free survival, overall survival);
- Add important clinical parameters, like PD1 protein expression status, tumor histology, performance status

RNA-sequencing follows, which enables patient stratification based on:

- Immune checkpoint expression levels
- Inflammatory, cytolytic, and stemness gene expression signatures
- Computational estimates of immune cell infiltration

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TANGO WP3
Prediction of population-based long-term health benefits and harms

V. Coupé, M. Joore, T. Feenstra

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Main initial objective

Predict long-term health outcomes of WGS-based care versus current diagnostics-based care for the Dutch advanced NSCLC and melanoma patient population

Strategies:

1. Current diagnostics and treatment for melanoma and NSCLC (reference)
2. WGS and WGS-based treatment
3. Hypothetical strategies varying in cut-offs for immunotherapy selection
4. Extension of strategy 3, optimizing response monitoring to allow for early detection of treatment failure and potential switching of treatment.

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Data requirements

- The National Cancer Register (NCR)
- The Dutch Melanoma Treatment Registry (DMTR)
- Santeon (NSCLC)
- Tumor growth data: longitudinally collected CT scans performed in the follow-up of metastatic melanoma and NSCLC patients

Main steps

Outline of main steps (both for melanoma and NSCLC):

1. Mathematically model the growth of multiple metastases within an individual patient, making a distinction between prognostic subgroups.
2. Include modelled tumor growth in microsimulation framework
3. Link growth of metastases within an individual to progression-free survival (PFS) and calibrate the model
4. Reproduce PFS in the first and subsequent lines, and time to death
5. Simulate different diagnosis and treatment strategies and compare long-term PFS and overall survival (OS) outcomes.

Reasons for adaptation of WP3 content

- Ongoing experience with MAICARE tumor growth model: registry data (eg DMTR) not detailed enough.
- Search for more detailed tumor data (eg longitudinal CTs in BRAF+ melanoma, EGFR+ NSCLC): hard to obtain!
- Detailed tumor growth data available for Nivolumab treated NSCLC & melanoma (NKI) and start of collaboration with radiology NKI

Adaptation of WP3 content

Predict long-term health outcomes of optimization of diagnostics and monitoring in immunotherapy in advanced NSCLC and melanoma

Strategies:

1. Current diagnostics and immunotherapy for melanoma and NSCLC (reference)
2. Optimize CT-based monitoring to define optimal moment for halting immunotherapy in non-responders.
3. If possible: selection of immunotherapy based on WGS (link CPCT)

If possible and agreed upon; impact of monitoring strategies on cost-effectiveness of immunotherapy

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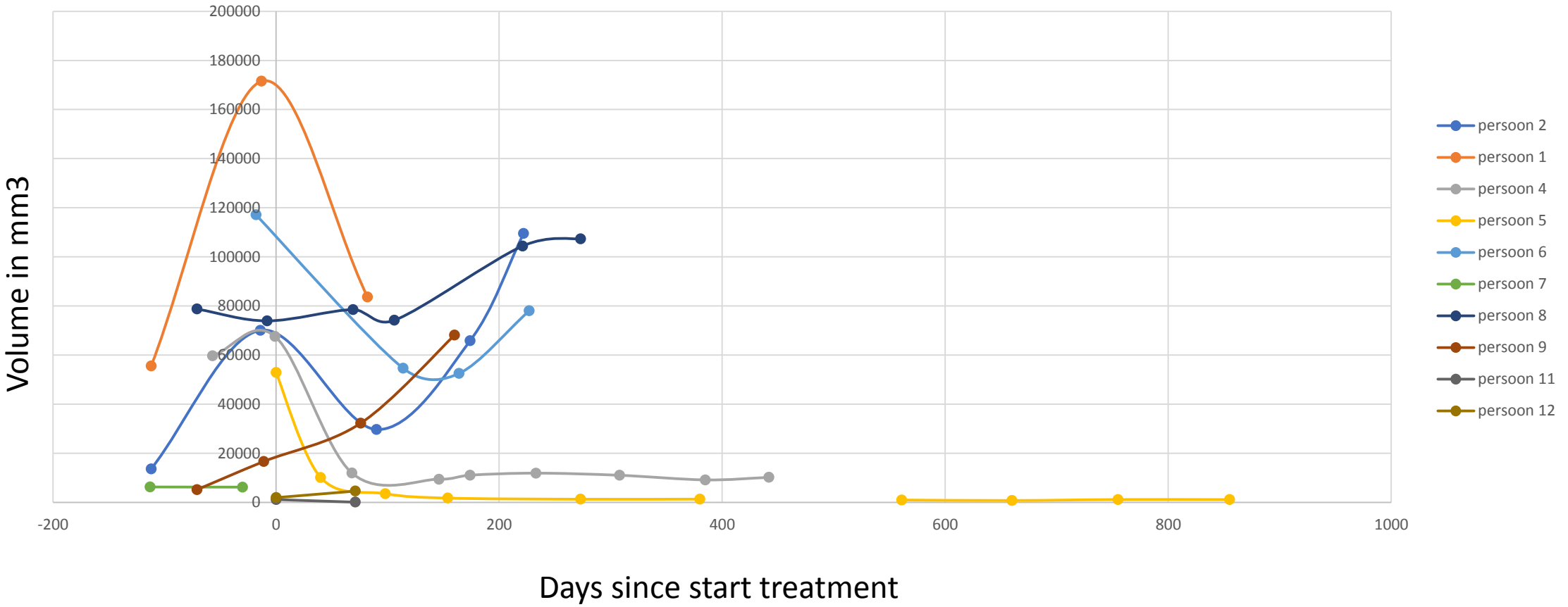
Preliminary tumor growth data Nivolumab

10 patients



Technology Assessment of Next Generation Sequencing in Personalized Oncology

Related project

Simulation of detection of oligo-recurrences in NSCLC

Background:

- Oligo-recurrences often treated with curative intent,
- If additional metastases present: no benefit from curative treatment

Aim: To develop a decision model to select patients for curative treatment in oligo-recurrent disease.

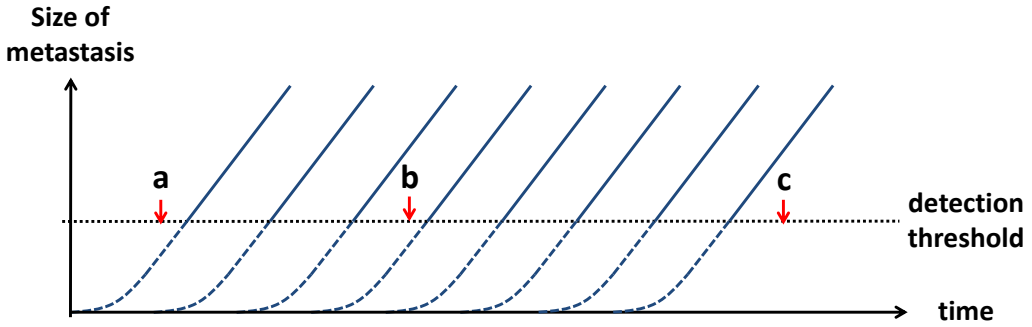
Method:

- Simulation development and growth of metastases in stage I NSCLC
- Simulation starts after curative treatment of primary tumour
- Recurrences detected through surveillance or symptoms.
- Output model gives features preditive for presence of undetected metastases in oligo-recurrent disease.
- Data from two Dutch stage I NSCLC cohorts & literature

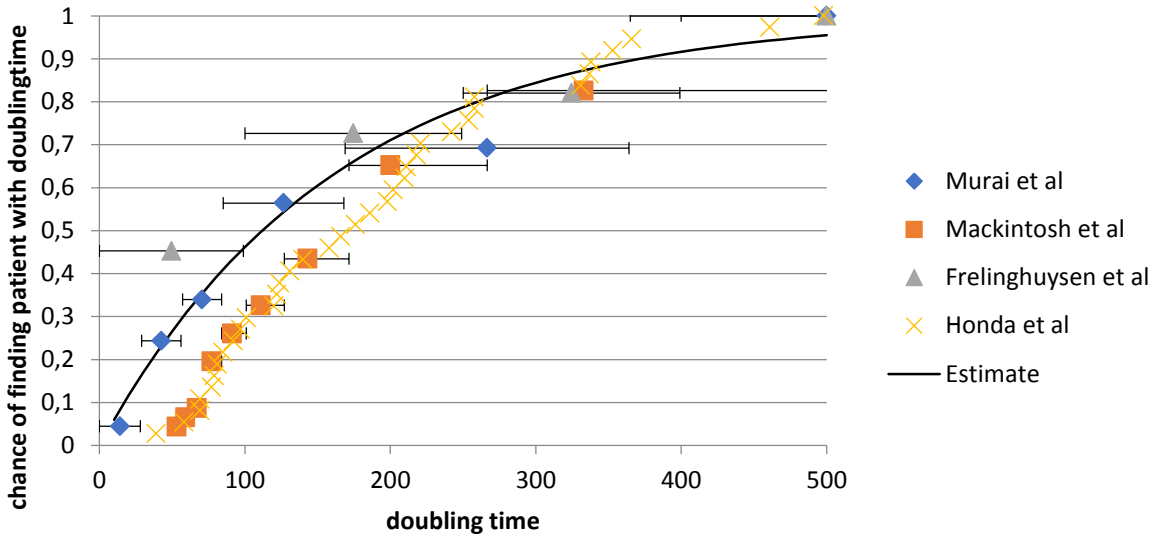
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Related project

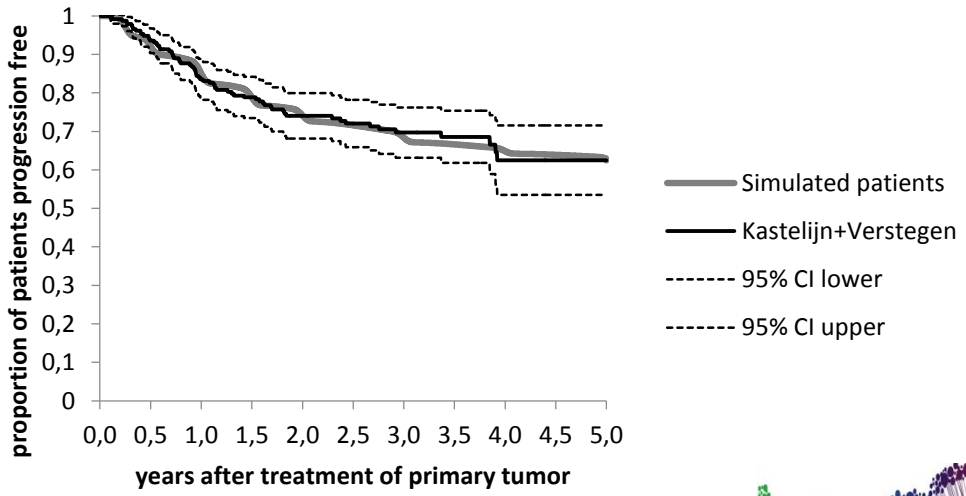
Simulation of detection of oligo-recurrences in NSCLC



'CDF' of VDTs



Progression Free Survival



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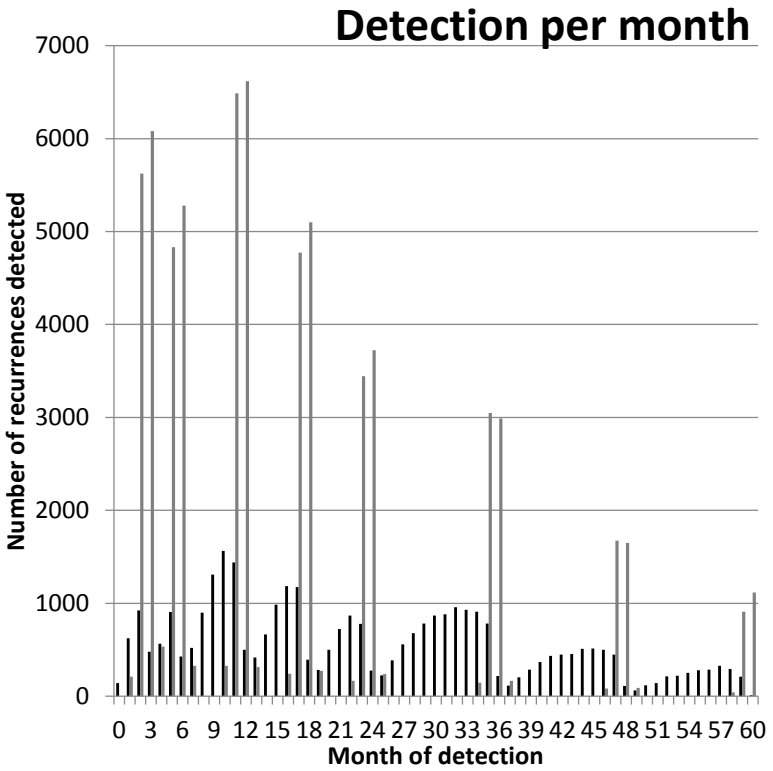
Results



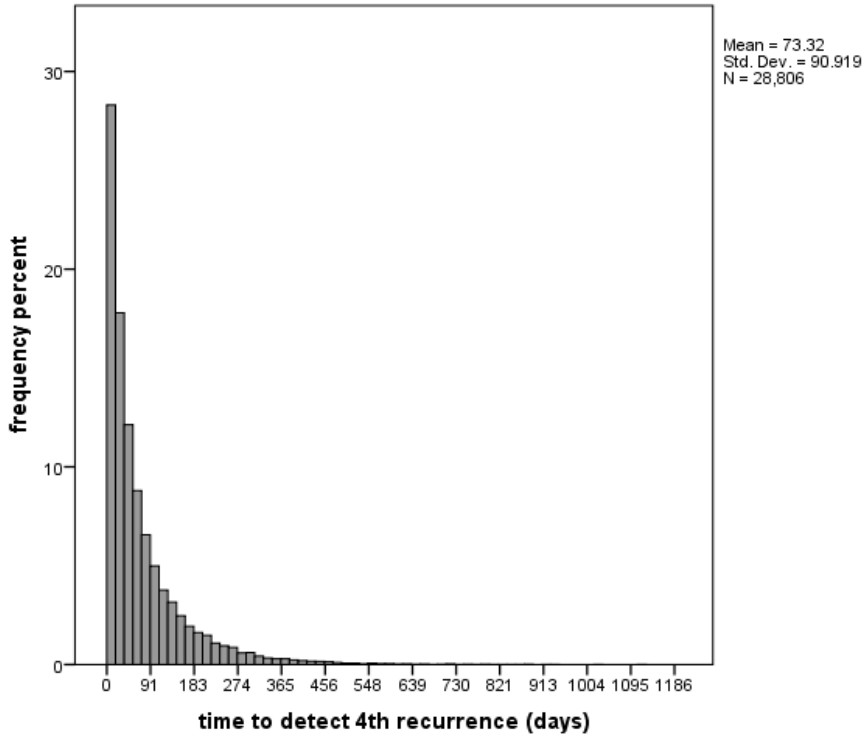


Table 3. Prevalence of oligo⁺ within patients with detected oligo metastases in the Base Case scenario, within all subgroups (indicated by oligo+).

	Asymptomatic			Symptomatic		
Metastases detected:	1	2	3	1	2	3
Small (<6mm)	0.91	0.92	0.93	0.88	0.88	0.83
Medium (6-8mm)	0.08	0.61	0.81	0.08	0.71	0.84
Large (>8mm)	0.00	0.02	0.19	0.00	0.00	0.24

Prevalence of oligo⁺ (% of patients with detected oligo metastases). Grey fields represents the low risk group.

Technology Assessment of Next Generation Sequencing in Personalized Oncology

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+

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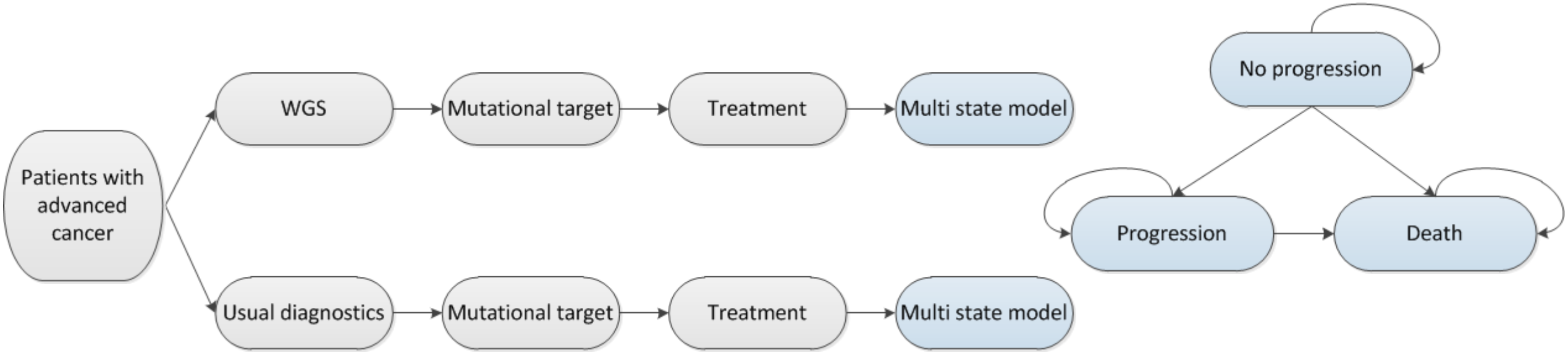
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Overview progress WP4

Milestones ZonMw		What is done	What still needs to be done
1. Cost-effectiveness analysis	***Model structure***	• Developed	• Validation by experts
	Model inputs • Effects NSCLC • Effects Melanoma • QoL • Costs (with WP1)	• Syst. review/meta-analysis, survival modelling • DMTR dataset (collaboration EUR) • Questionnaires CPCT-02 • Costs NGS and WGS from WP1	• NVALT, Santeon, IKNL • DMTR data-analyses • Data collection & analysis • Literature
	Model analysis		• Autumn 2018
2. Scenario analysis	***Methods*** (with WP5)	• Literature review • Mindmap	
	Data collection		• Autumn 2018
3. Wider public benefits	***Methods***	• Mindmap (Scenario analysis) • Model (Cost-effectiveness analysis)	
	Data collection		• Autumn 2018 (Scenario analysis)
4. Heterogeneity	***Methods***	• Model (Cost-effectiveness analysis)	tbd
5. Budget impact analysis	***Methods (with WP1&5)***	• Model (Cost-effectiveness analysis)	tbd

Results (1): cost-effectiveness analysis
model structure

- Hybrid: decision tree (grey) + multi state model (blue)



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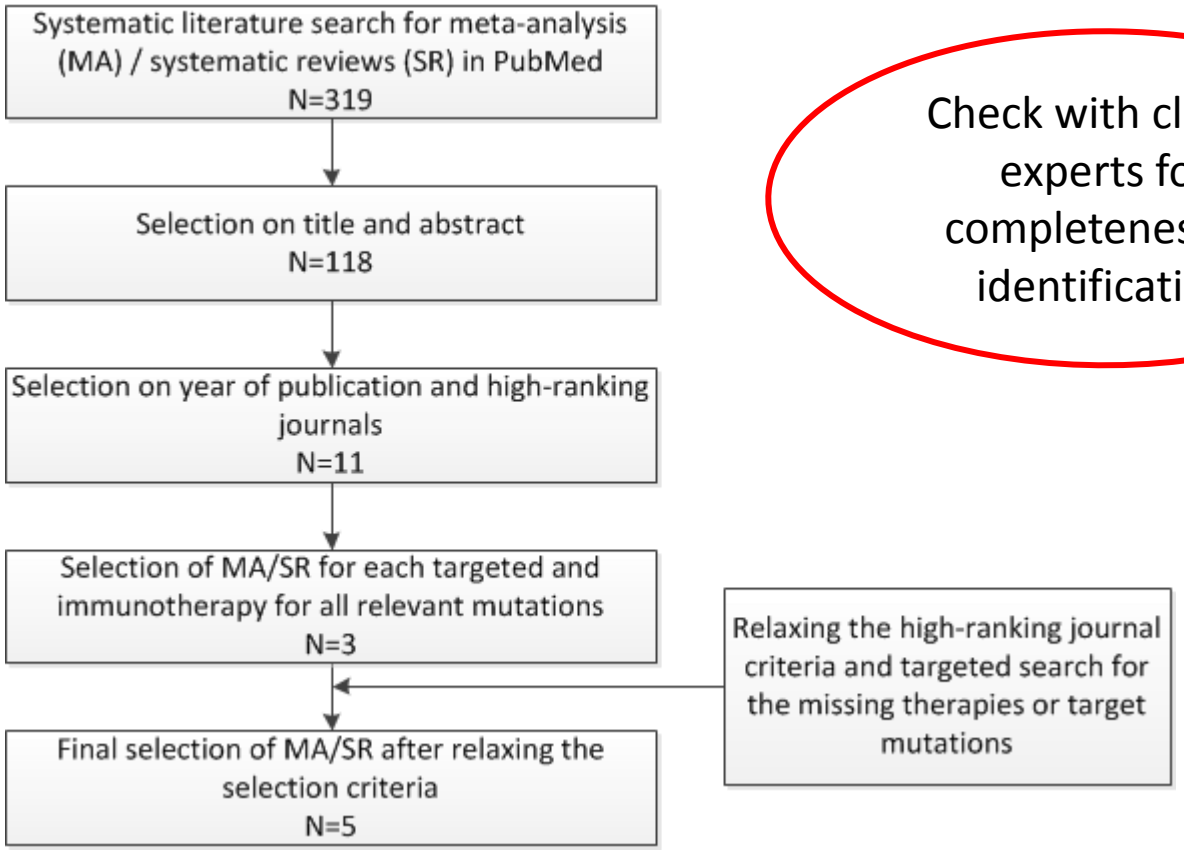
Results (1): cost-effectiveness analysis

review of reviews for effectiveness of treatments for NSCLC



Check with clinical experts for completeness of identification

- Identified trials
  - PD-1/L1 n=8
  - EGFR n=26
  - ALK n=10
  - ROS1 n=2
  - BRAF n=3
  - KRAS n=2
  - MET n=3
  - RET n=2
  - Other n=3

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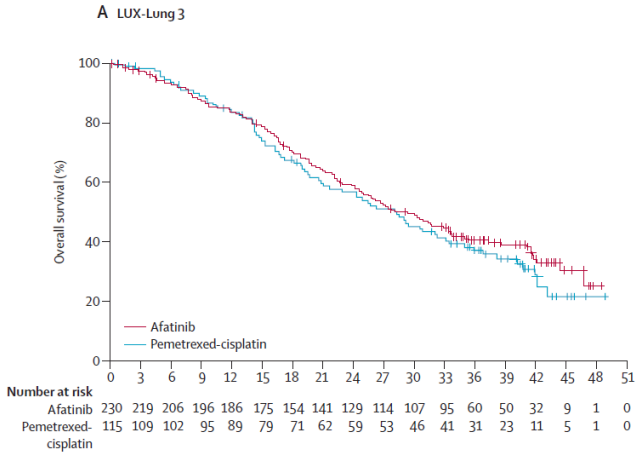
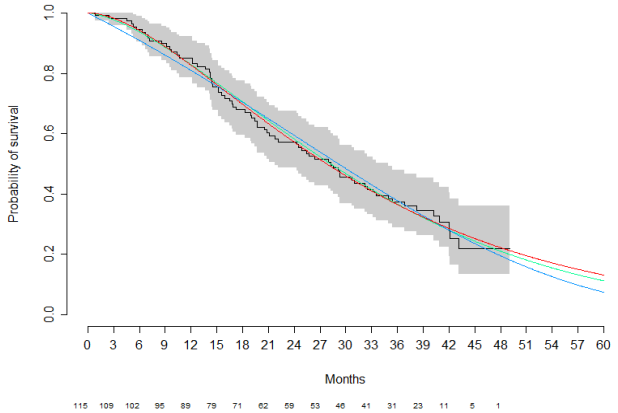
Results (1): cost-effectiveness analysis

effects NSCLC



Approximation original patient time-to-event data from digitized KM-curve



Pool obtained HR TT & IT **(interventions)**

Pool survival models **(Common comparator)**

CEA Model

- Therapeutic effect → transition probabilities model
  - PFS & OS chemotherapy-arm per target **(common comparator)**
  - Relative effect PFS & OS targeted & immunotherapy Hazard ratios **(interventions)**

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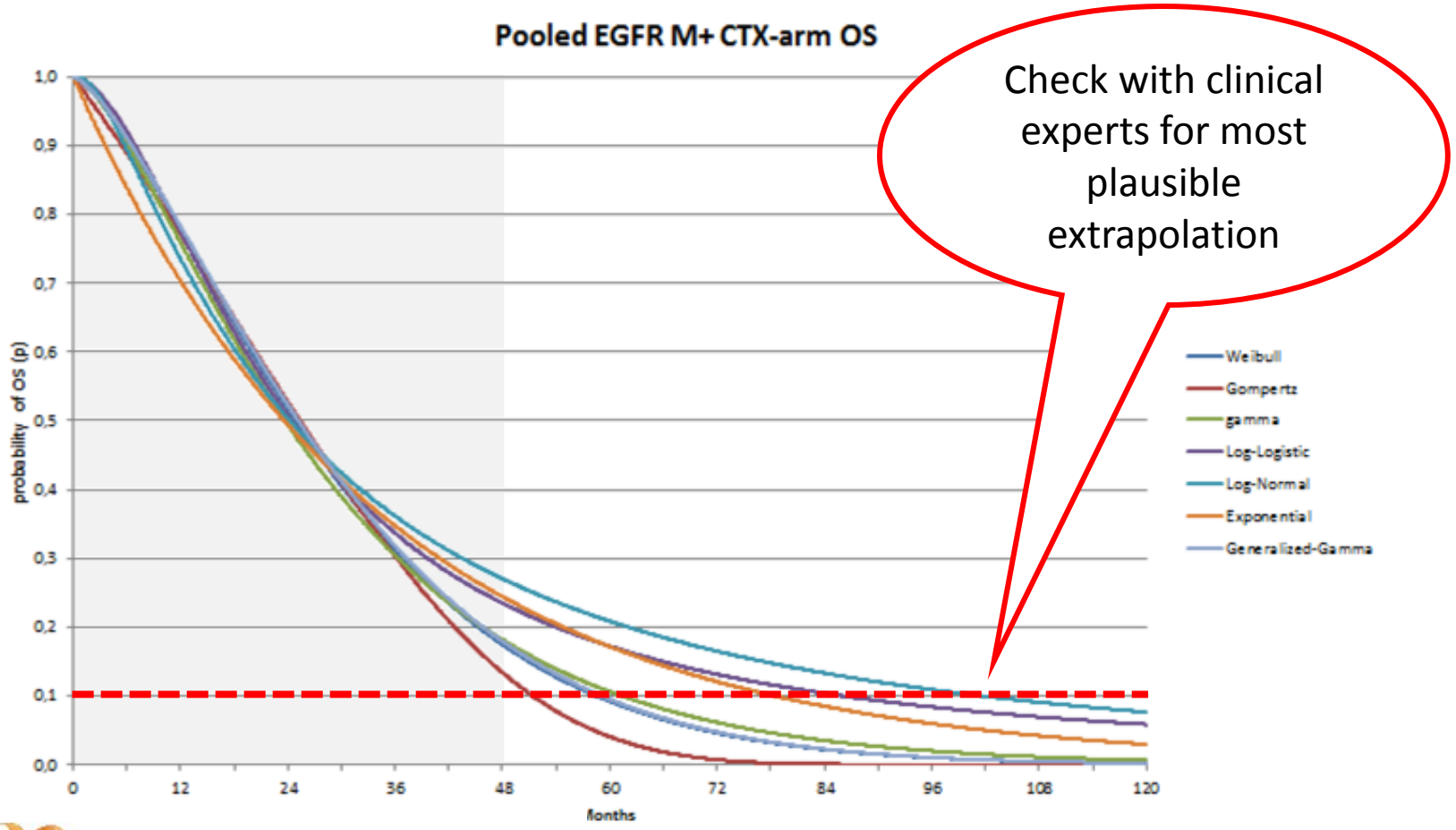
Results (1): cost-effectiveness analysis

effects NSCLC



- Example pooled survival models
  - Seven trials
  - Positive EGFR mutation
  - OS chemotherapy
- Observed (grey)
- Extrapolated (white)
  - 10% OS

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Planning (1): cost-effectiveness analysis
what needs to be done

- Model structure: validation
- Effects NSCLC: retrieving data from Santeon, NVALT (Alternative: IKNL)
- Effects Melanoma: DMTR data analysis (collaboration with EUR)
- Utilities/QoL: data collection and analysis
  - Questionnaires CPCT-02 study (amendment protocol accepted)
  - Start NKI 4 weeks: 10 questionnaires sent, 7 questionnaires received!
- QoL questionnaires EMC (optional)
- Costs: WP1, literature
- Model analysis: autumn 2018

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Remaining tasks per milestone (#)

- Scenario drafting / analysis (2) → next presentation
- Wider public benefits (3)
  - Same methodology as scenario paper
  - Data collection start autumn 2018
- Heterogeneity (4)
  - CEA model
  - Analysis to be decided
- Budget impact analysis (5) (collaboration with WP1+5)
  - CEA model
  - Analysis to be decided

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Technology Assessment of Next Generation Sequencing in Personalized Oncology

Overview papers WP4

Milestone (#)	Title	Paper
CEA (1)	***Effect estimates of targeted and immunotherapies on the lifetime progression free and overall survival in locally advanced non-small cell lung cancer***	A
CEA (1)	***Early cost-effectiveness of whole genome sequencing as a diagnostic tool in patients with locally advanced cancer***	B
Scenarios (2)	***Future scenarios and management of WGS developments concerning therapeutic effects on a macro level***	C*
Wider public benefits (3)	*Wider costs and benefits of the use of WGS as a diagnostic tool in patients with locally advanced cancer*	D
Heterogeneity (4)	*The expected value of individualized care (EVIC) of WGS: the optimal design of further research towards molecular diagnostics*	E
BIA (5)	*Budget impact of the use of WGS*	F**

Bold, started with writing any part of the paper
*WP4+5, work together on this topic
**paper BIA (with WP1+5)

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

Work Package 5
Nation-wide organization of WGS

Michiel van de Ven

Maarten Ijzerman

Valesca Retèl

Wim van Harten

Erik Koffijberg

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Rationale and aim

- **Rationale: WGS** is a complex intervention & disruptive technology
  - Large scale facilities, such as the HMF, have a major impact on health outcomes and costs of clinical oncology services, healthcare delivery and patient pathways (system level impact)
  - Implementation requires adaptation of professionals and reallocation of healthcare resources
- **Aim**: provide insights into the (requirements for) optimal (cost-effective) 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 in the NL?*
- **Analysis** to support health policy decisions and planning of services requires evidence on
  - The availability of WGS services, the # of facilities offering clinical oncology services, prescription of advanced molecular drug treatment, adoption of clinical guidelines (e.g. the use of biomarker panels), etc.

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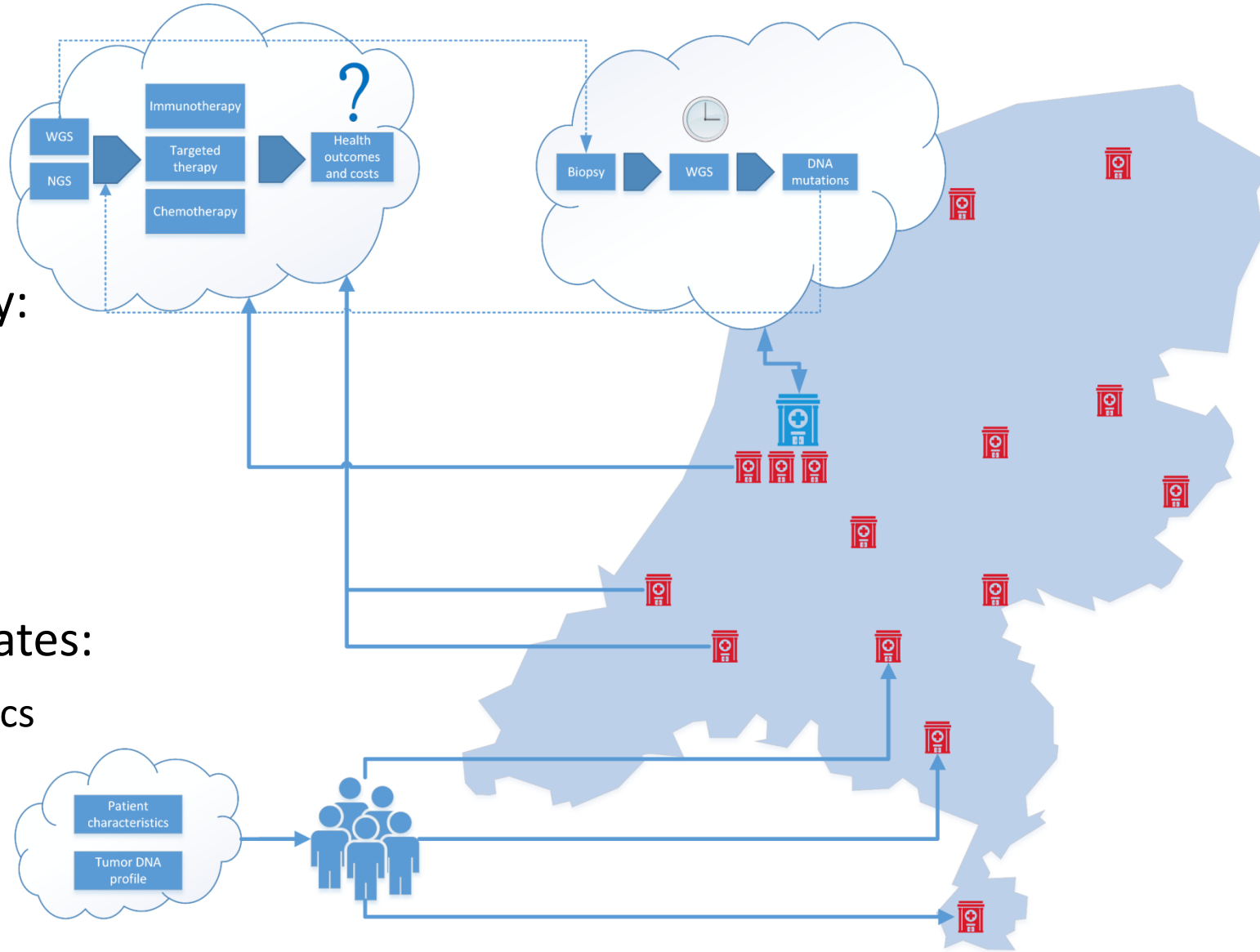
Conceptual model

The problem is characterized by:

- Heterogeneity
- Dependencies
- Non-linearity

The simulation model incorporates:

- Patient and hospital characteristics
- Patient pathways and delays
- Health outcomes and costs
- Resource availability



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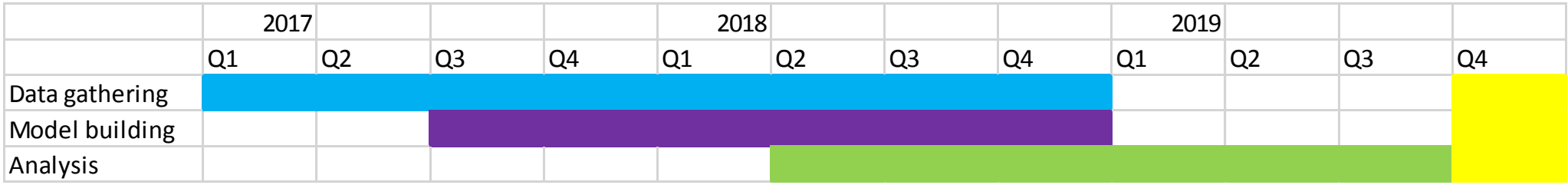
Progress so far

- Conceptual model
- Real-world evidence on first-line treatments and delays in advanced NSCLC
- Referral patterns advanced NSCLC
- International survey on the future of WGS



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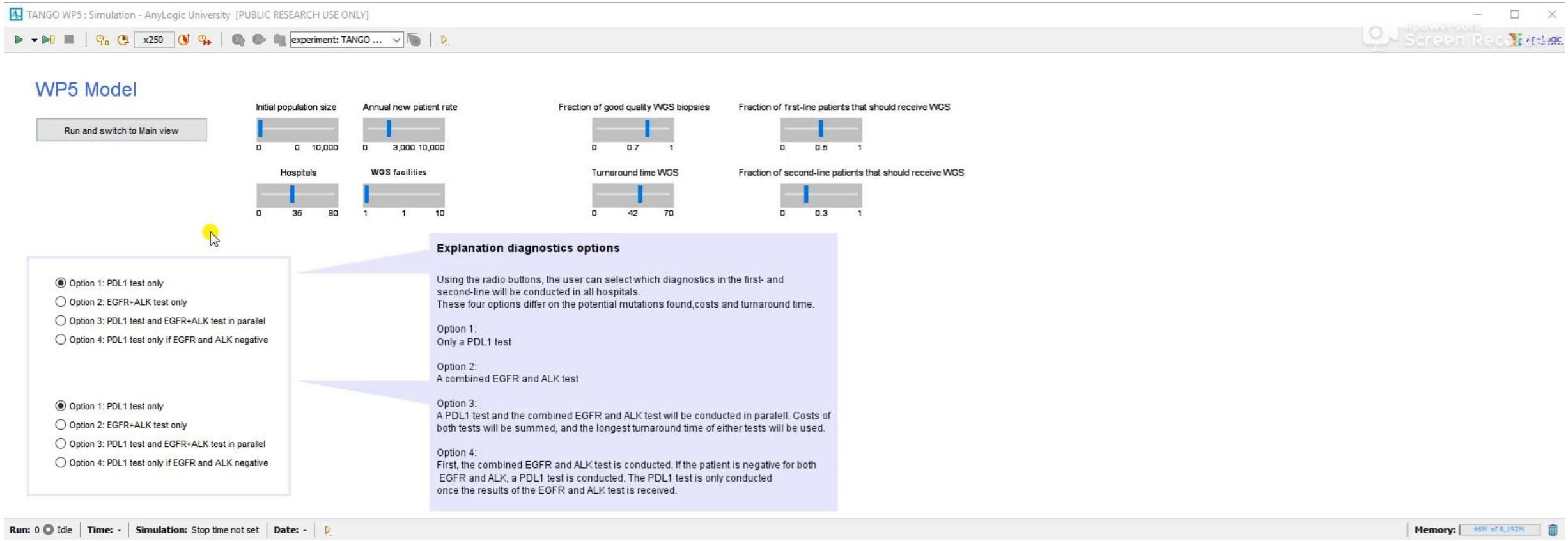
Conceptual model



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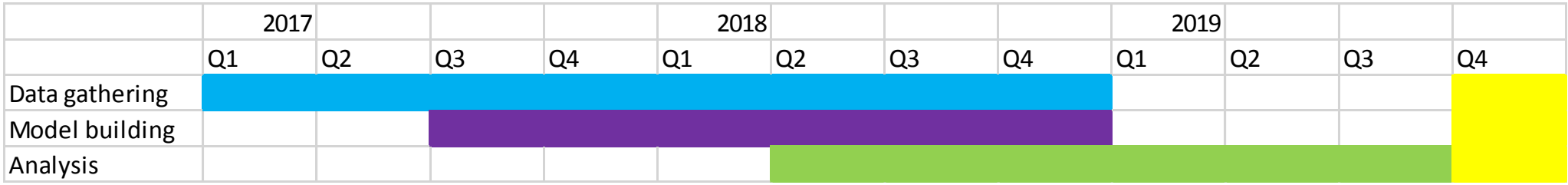

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Real-world evidence on first-line treatments and delays in advanced NSCLC

- Relevance:
  - Variation in care across hospitals means effect of WGS on health and costs will not be the same in each hospital

- Variation across hospitals and across hospital types in:
  - Initial diagnostics
  - First-line treatments
  - Time from diagnosis until start first-line treatment

- Patient-level data from all 79 hospitals in the Netherlands that treated advanced NSCLC in 2016

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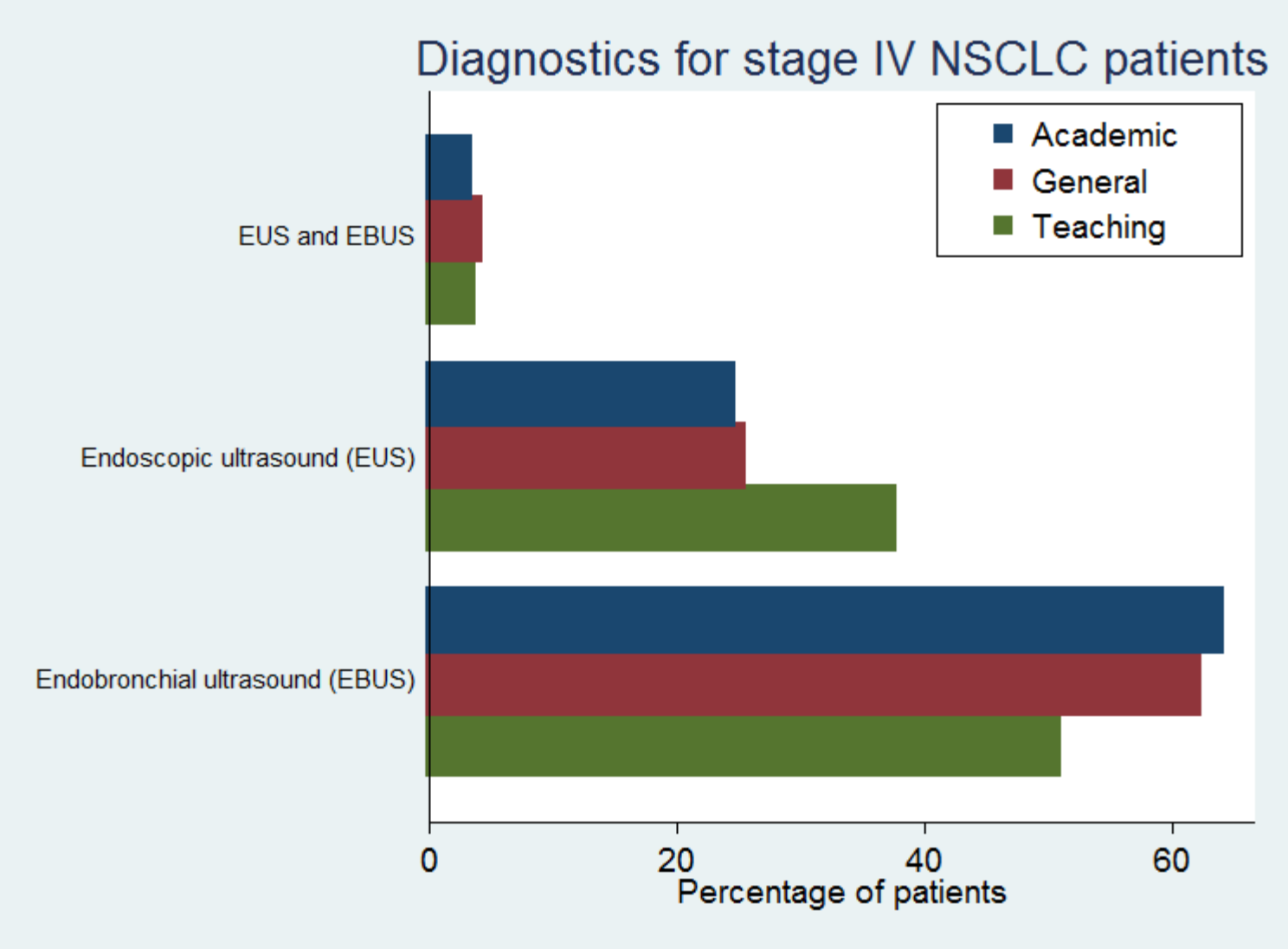
Real-world evidence on diagnostics



Source: NCR (2016)

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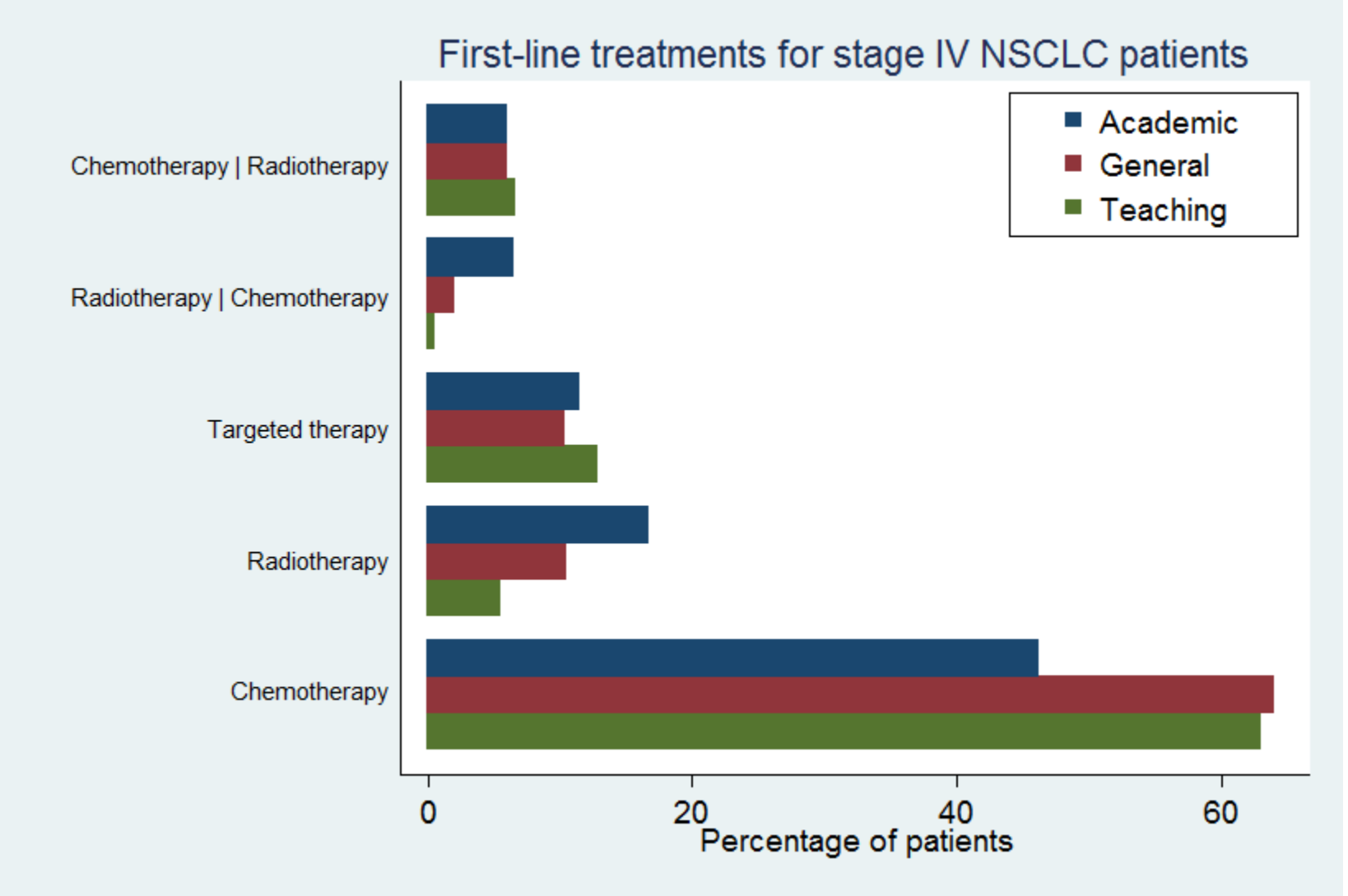
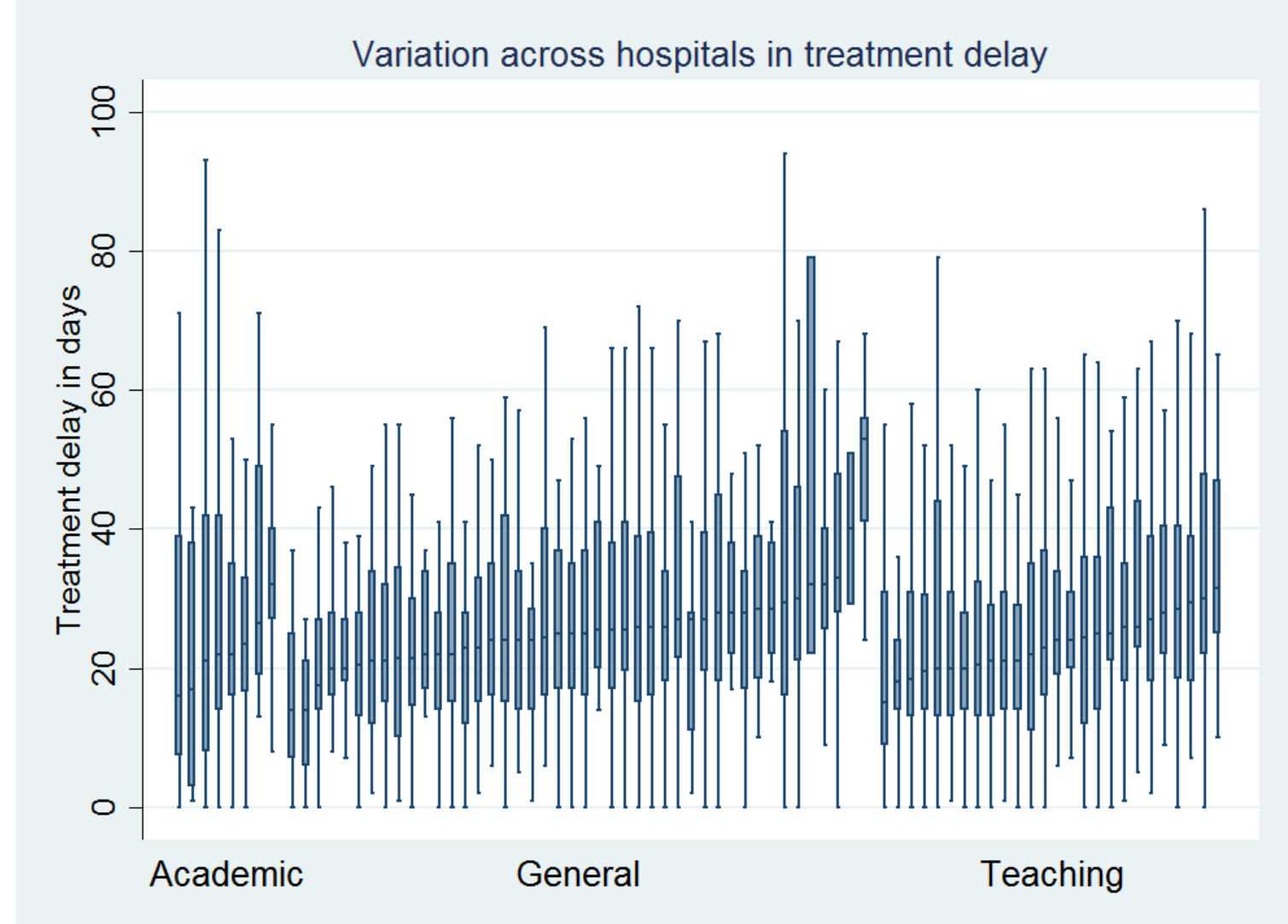
Real-world evidence on first-line treatments



Source: NCR (2016)

Real-world evidence on treatment delay



Source: NCR (2016)

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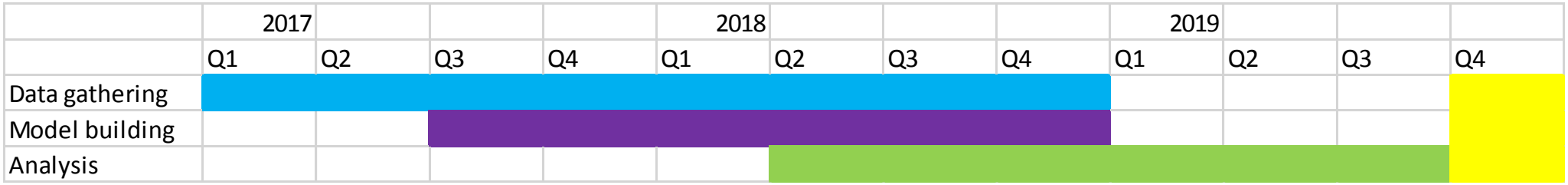

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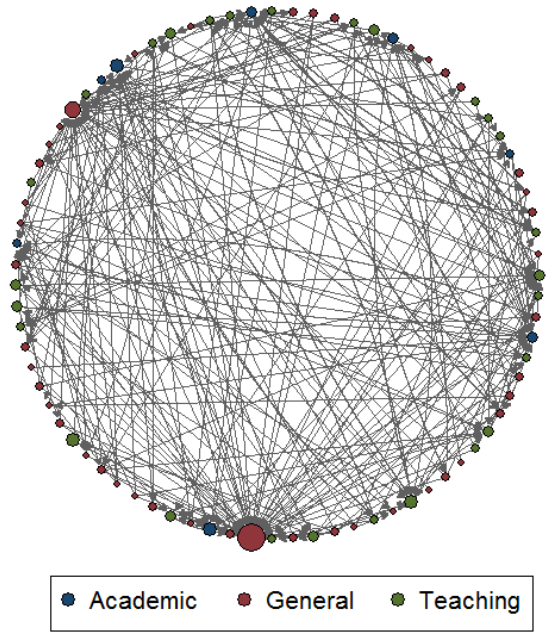
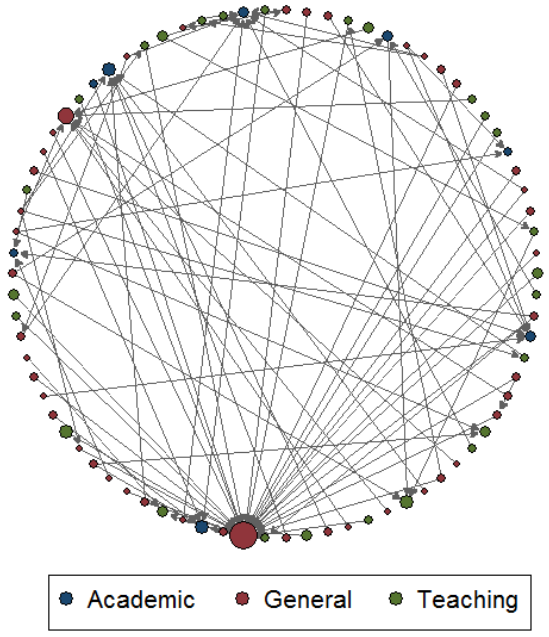
Referral patterns advanced NSCLC

- Hospital planning and policy can also affect other hospitals
- Considering those effects helps with optimal implementation WGS

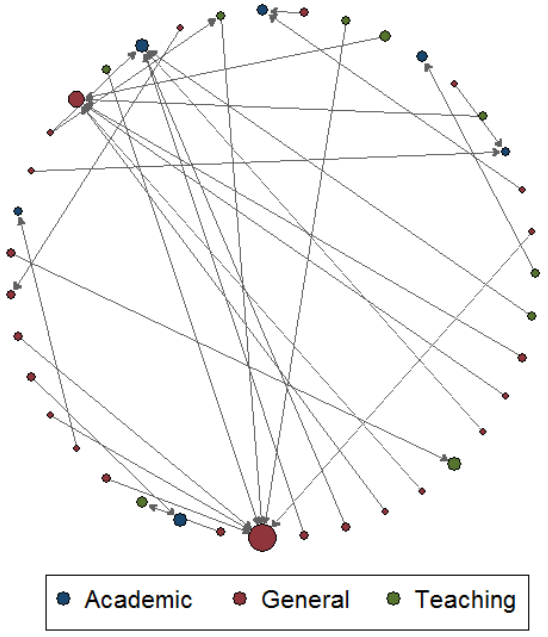
All referrals



At least 5% of hospital's volume



At least 25% hospital's volume



Source: NCR (2016)

Technology Assessment of Next Generation Sequencing in Personalized Oncology

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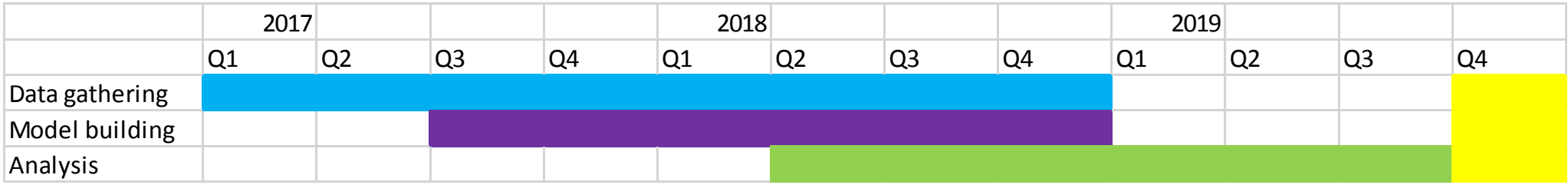

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International survey on the future of WGS

- Goal: Learning from others' approaches in implementing WGS
- Survey among members of the OECI
- 10 hospitals from NL, BE, IT, NO, CZ, PO, AT, HU
- Reported job titles:
  - Pathologist
  - Oncologist
  - Pulmonologist
  - Associate professor
  - Medical physicist
  - MD
  - Senior researcher

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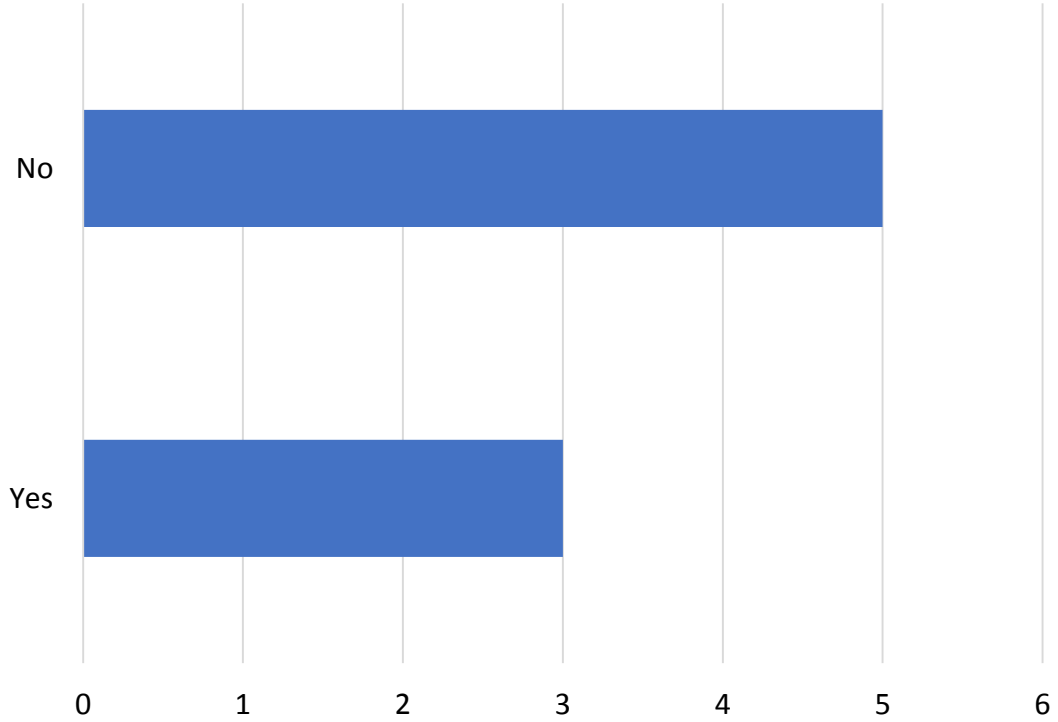
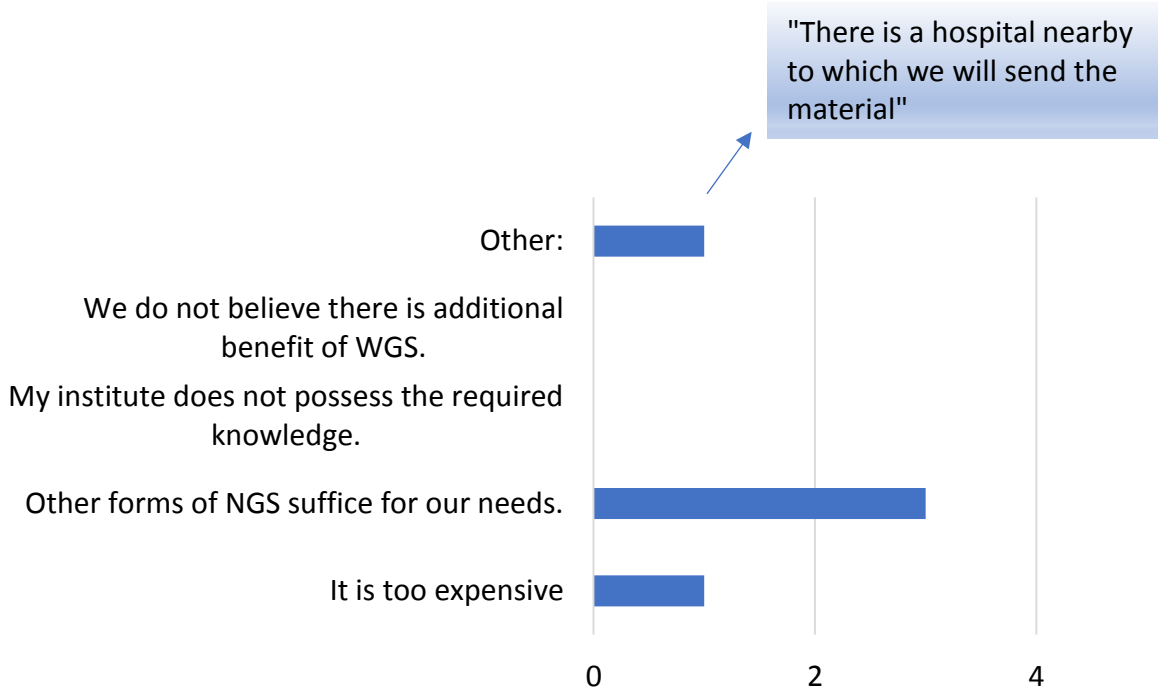
International perspective on the future of WGS

According to your expectations, will your institution use WGS in the future?



Future: five years from now

What is / are the reason(s) that your institute will not be conducting or using WGS?



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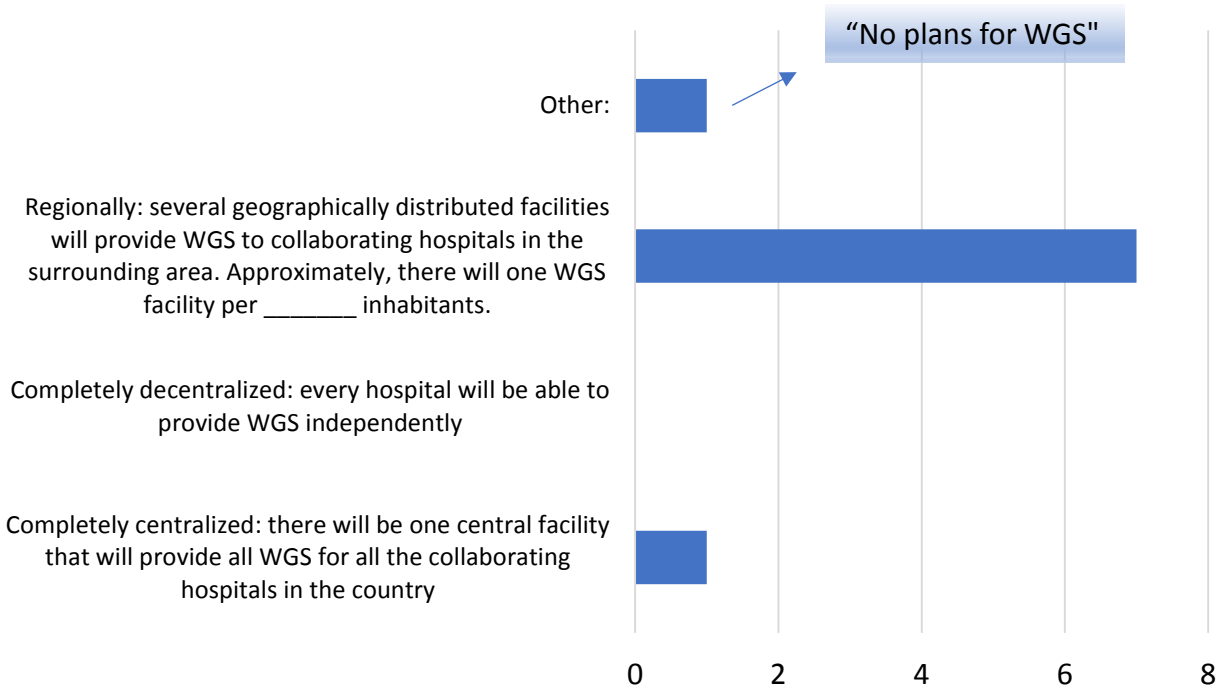
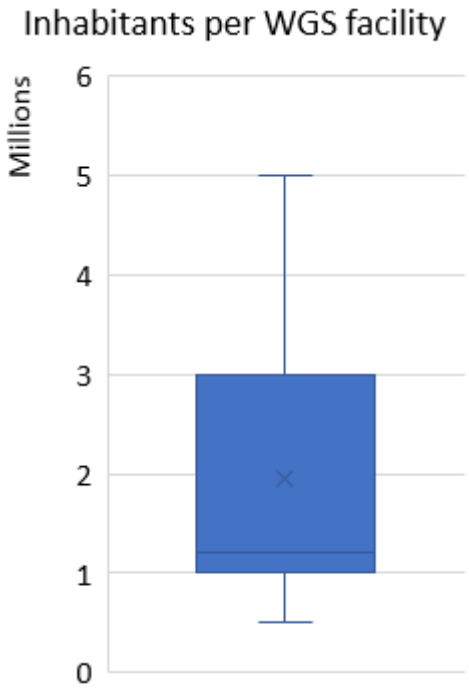
International perspective on the future of WGS

According to your expectations, how will WGS services be organized in your country in the future?



Regional organization:



Future: five years from now

Next steps

- Populating simulation model with empirical data
  - Care pathways and delays (WP5)
  - Survival and QoL data (WP3 & 4)
  - Cost data (WP1)

- Drafting and analysis of scenarios that impact implementation of WGS (with WP4)
- Survey on (choices in) diagnostic pathway of advanced NSCLC (with WP1)

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?

Milestones

- Juridisch artikel voor European Journal of Health Law (EJHL)

  A duty to recontact in the context of genetics: futuristic or realistic? status: ingediend, deze week gereviseerde versie terug naar Editors (zie volgende sheets)

- Empirisch artikel voor European Journal of Human Genetics (of soortgelijk blad)

  Views of professionals on the duty to recontact; status: laatste versie voor indiening gereed (zie volgende sheets)

- Juridisch artikel voor T. voor Gezondheidsrecht (over de mogelijke ontwikkeling van verplichting tot ‘recontact’ naar Nederlands recht); status: wordt komende maanden geschreven (uitvoerig aandacht voor positie van wetenschappelijk onderzoeker)

- Nog nader vast te stellen: afsluitend artikel of rapport (zie laatste sheet)

Resultaten juridisch artikel EJHL (1)

- There are, at least at this point in time, no grounds for the existence of a general duty that would be legally enforceable. This seems to be also the consensus in the international literature on the topic. Furthermore, there are no jurisdictions in which such a duty has been accepted, either by the legislator or by the courts.

- However, a judge might today or tomorrow come to the conclusion that in a specific situation, a caregiver (or laboratory professional) owes a duty to inform his patient. This is most likely to occur in cases where, in case of significant findings, there is much at stake for patients whereas not much effort is needed to notify them. It could be argued that such a limited duty to warn is to be owed also to the relatives of (recently) deceased patients, or to patients participating in research.

Resultaten juridisch artikel EJHL (2)

- As suggested in the literature (Carrieri et al; Dheensa et al), as a first step to delineating responsibilities in the clinical setting, health professionals should routinely discuss recontacting with patients (including which new information should trigger the professional to initiate recontact), as part of the consent process for genetic testing, and patients should be informed that they are welcome to contact the team if a potentially relevant event occurs.

- Before doing so, health professionals should try to define what they might reasonably be able to do in terms of renewing contact with their patients, taking into account the specific circumstances (e.g. nature of the diagnosis/disease, available resources in terms of financial possibilities, IT arrangements etc.). After deciding what would be an appropriate/affordable policy for the time being, they should see to it that patients receive information about what options they have within that framework.

Voorlopige resultaten empirisch artikel (1)

- The interviewees confirmed that recontacting is occurring on an *ad hoc* basis and that it is increasingly emerging in clinical practice. They highlight the practical barriers to a more systematic approach to recontact due to limited resources. Some professionals do feel an ethical responsibility to recontact former patients if important new information is available. They mentioned the importance of obtaining patient preferences and of respecting the right not to know, and the difficulties associated with obtaining informed consent about future unknowns.

- Interviewees emphasised the differences between research and care, and also recognised that this difference may not be so clear. Some mentioned concerns at the current legal uncertainty, and a preference to develop professional standards prior to any legal duties was indicated. Basically, law should follow responsible practice, rather than the other way around.

Voorlopige resultaten empirisch artikel (2)

- When comparing the opinions of the interviewees with literature we conclude that a general duty to recontact in health care can be ruled out due to the lack of existing standards and the considerable burden it would place on time and resources. This also holds for research, where practical barriers and burden arguably may be even greater. A duty to recontact may be present in limited, specific circumstances if the benefit to the individual is significant and the burden on professionals is not too marked. It should be the professionals (clinicians and laboratory specialists) who consider when and how this applies.

- Finally, the immaturity of the field and lack of guidance on recontact will not prevent courts finding a legal duty in case of claims. In fact, an absence of standards on recontact can more easily give rise to legal claims and professional liabilities. Fortunately, courts are likely to give a wide margin of appreciation to varied practice and hear evidence from experts in the field, as they know that an unbalanced decision might result in professional decisions that are more controlled by the risk of legal liability than by the best interests of the patient.

Afsluitend artikel of rapportage

- Inhoudelijk: welke aanbevelingen kunnen uit een en ander worden afgeleid voor de huidige praktijk (zorg; onderzoek; mengvorm daarvan)
- Daarbij afstemming met ethiek deel (en zoveel mogelijk gezamenlijke aanbevelingen)
- Nog te bezien/te bespreken: specifiek op klinische oncologie/TANGO-gericht?
- Mede afhankelijk daarvan: artikel voor internationaal medisch tijdschrift? Rapport?

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Medewerkers

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TANGO
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Participating centers

CPCT
Center for Personalized Cancer Treatment

Hartwig
MEDICAL FOUNDATION

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Amsterdam UMC
Universitair Medische Centra

UMC Utrecht

Erasmus Universiteit Rotterdam
Instituut Beleid & Management Gezondheidszorg

azM
Maastricht University
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umcg

UNIVERSITY OF TWENTE.

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