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Decision Support Systems for Protontherapy

Prof. Philippe Lambin

U.H. Maastricht

Herceptin:

Δ « Companion biomarker »

Tirapazamin:

Biomarker +

Protontherapy

Biomarker -

Our hypothesis

Protontherapy mode[...] [...]er *the strict conditions* th[...] population has been sel[...]

...wi[...] [...]actorial Decision

The "one size fits all philosophy will not work with protons

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The Dutch aproach for protontherapy

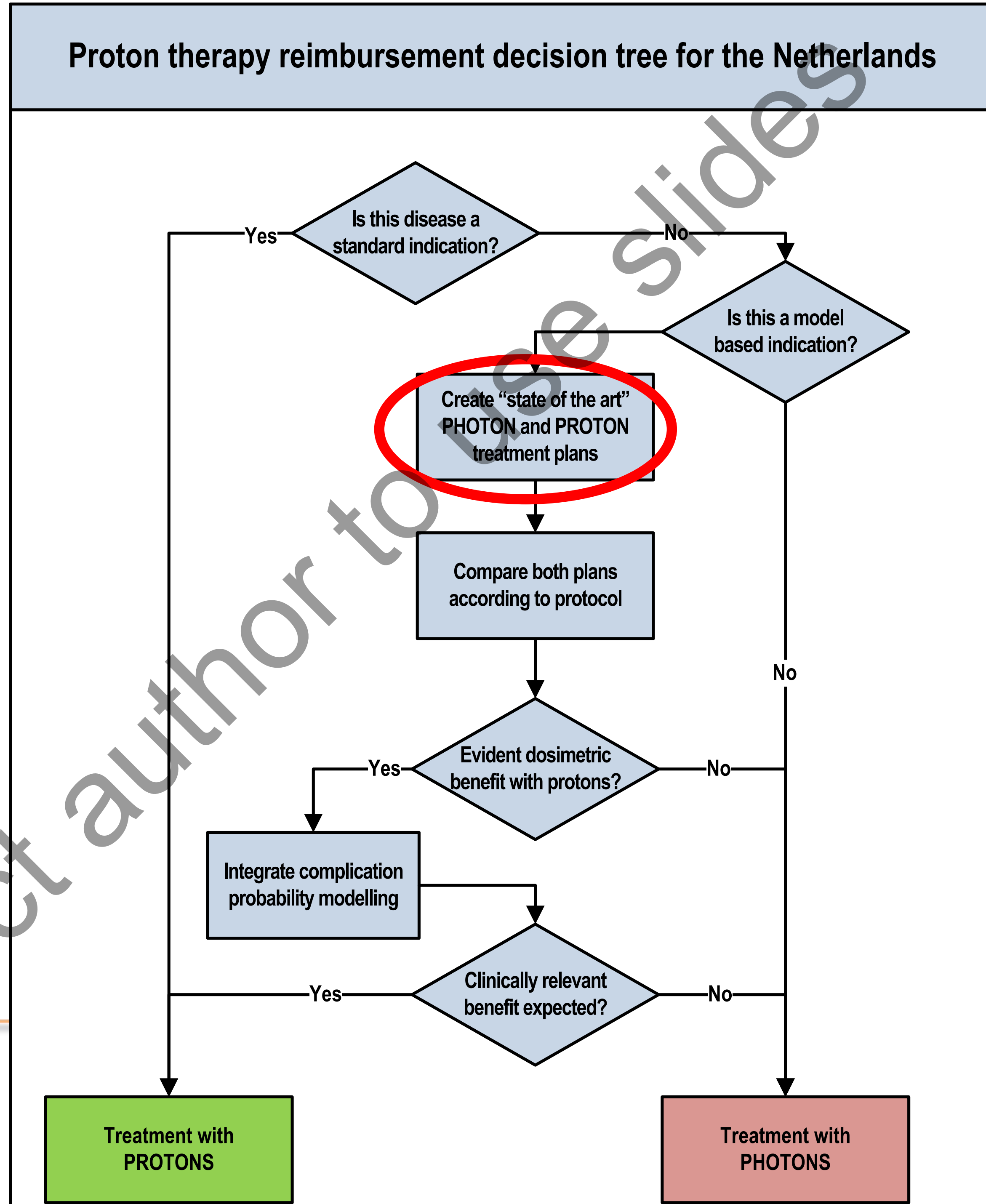
1. **The standard indications*** (pediatric, melanoma of the eyes…): fully reimbursed

2. **The trial patients**: externally funded

3. **The model based indications*** (head & neck, lung, breast, prostate, *reirradiations*…): need an accredited Decision Support System (DSS)

* Equipoise, ALARA… Only if there is no Dose escalation

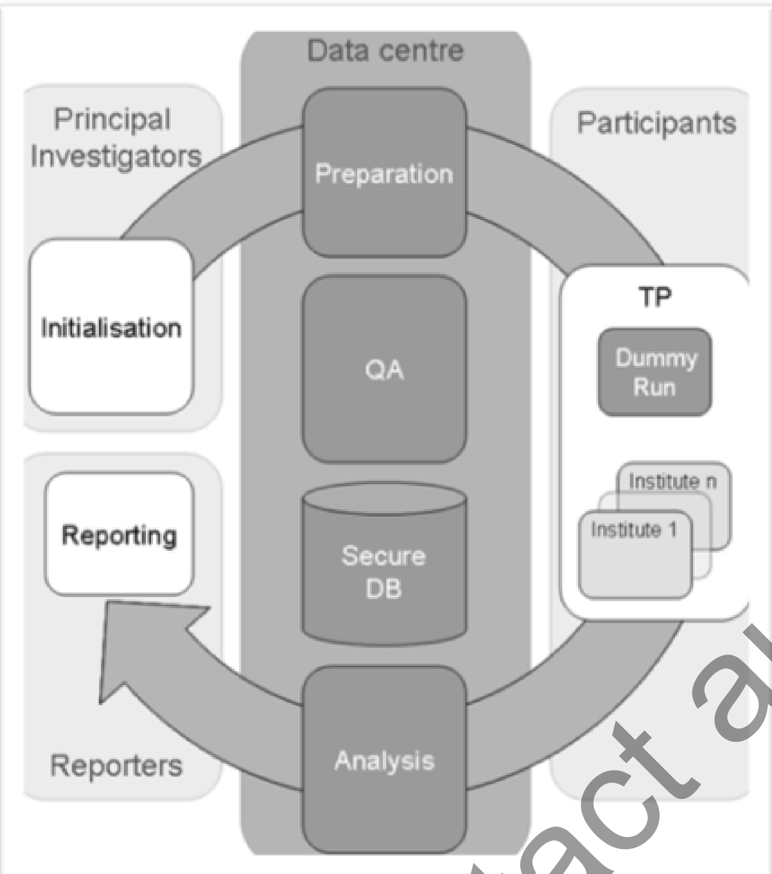
ALARA principle

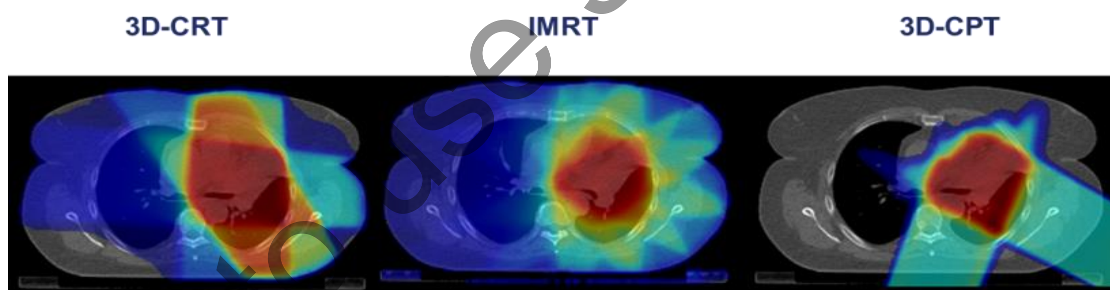


zonPTC
Zuid-Oost Nederland Protonen Therapie Centrum

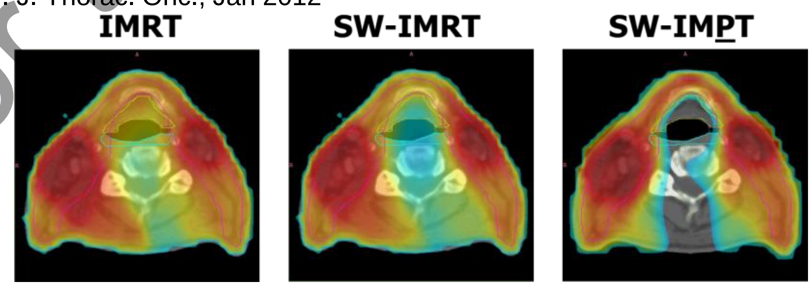
Past: In Silico clinical trials

Radiation Oncology COllaborative COmparison

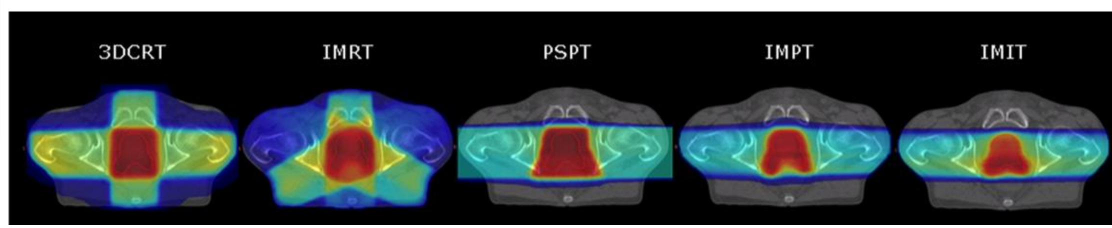




Roelofs, et al. J. Thorac. Onc., Jan 2012

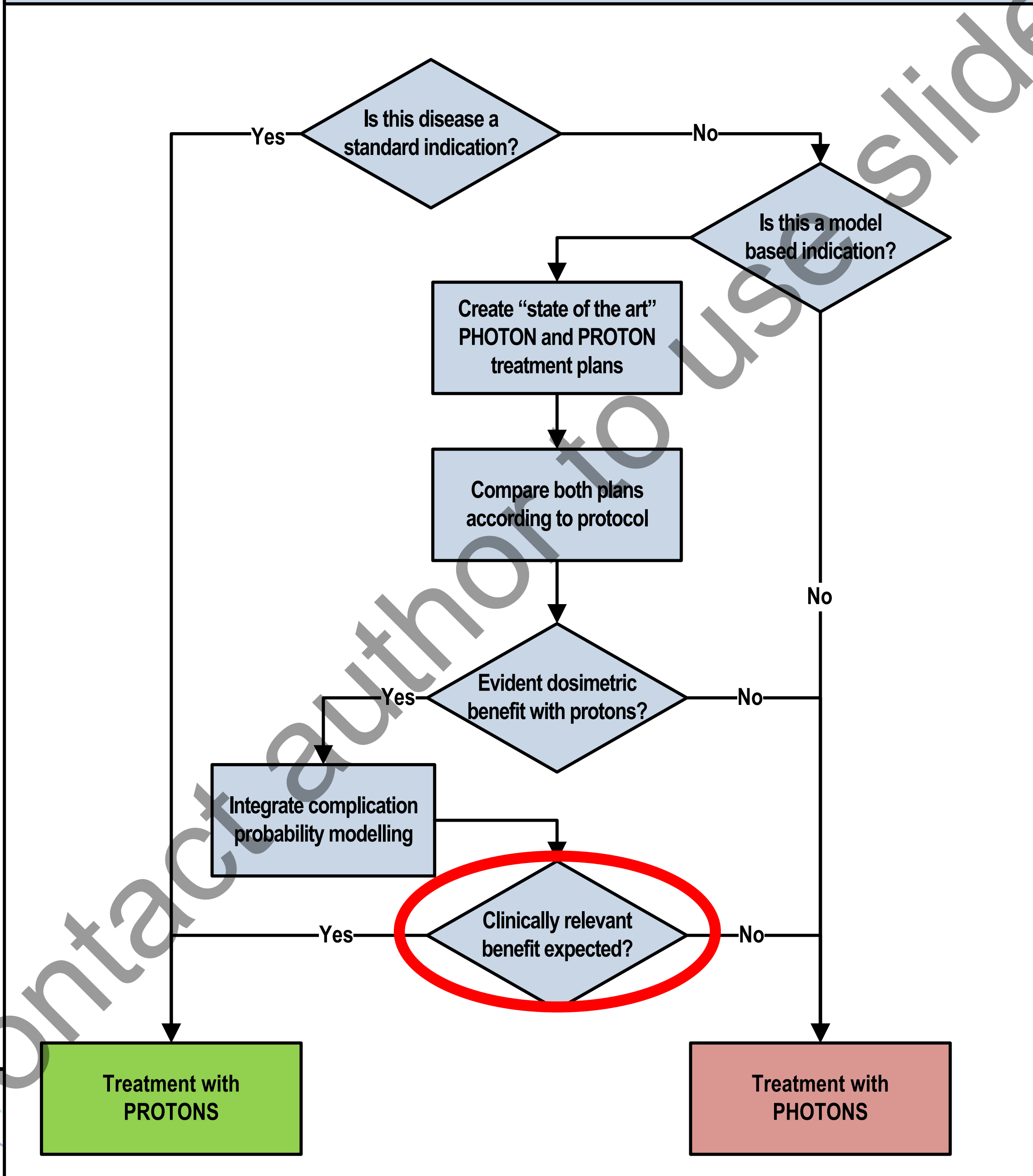


Van der Laan, et al. Acta Oncol. Apr 2013



Roelofs et al,, *2015*

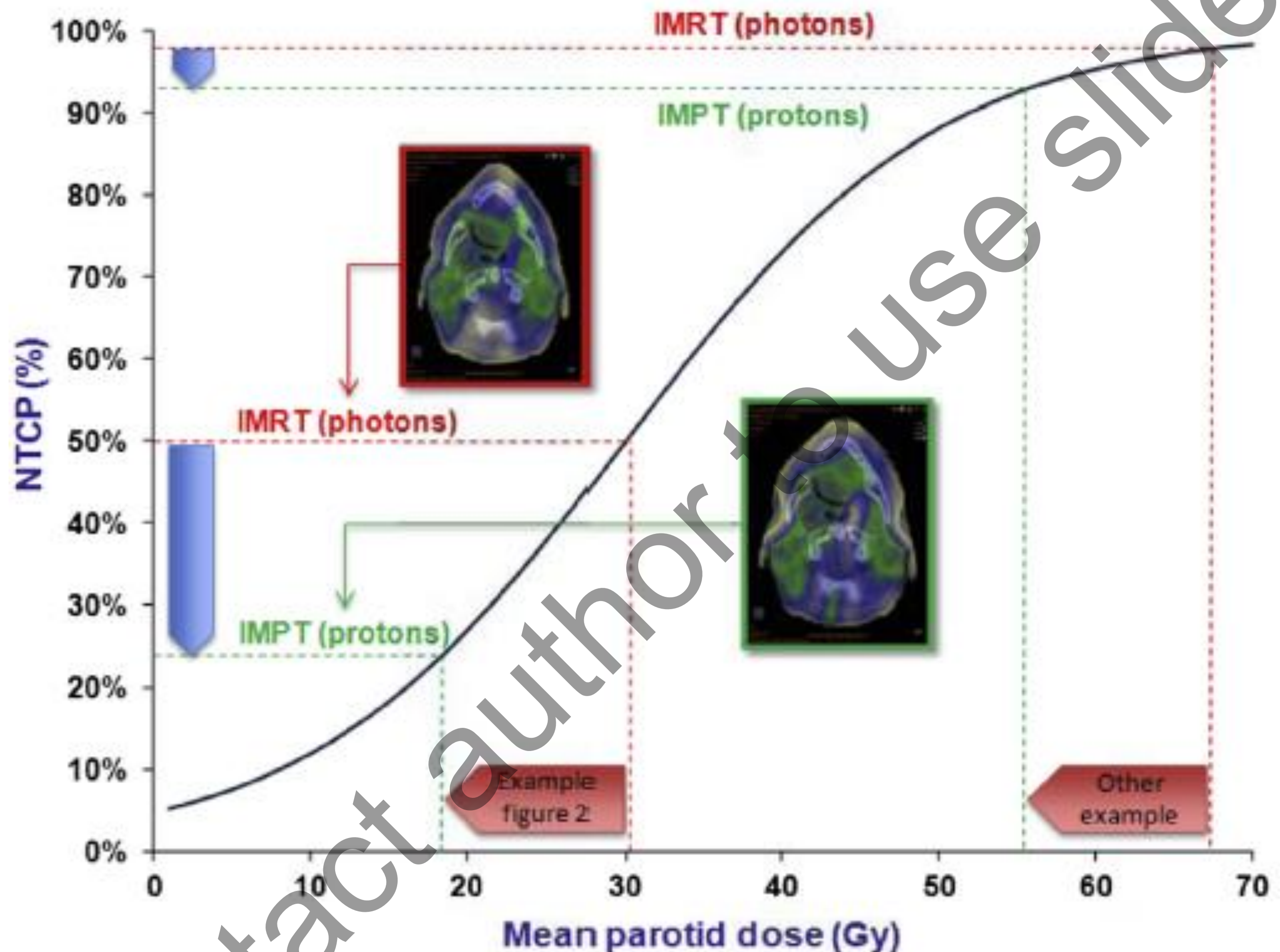
Proton therapy reimbursement decision tree for the Netherlands



Multifactorial Decision Support System

Lambin et al. Nature Rev. Clin. Oncol.

Selection of patients for protons



Langendijk JA, et al., Radiother Oncol. 2013 Jun

How to get

the data

To build the predictive models?

Data selection

Conventional Clinical Research	Rapid Learning Health Care
High data quality	Low data quality
Low data quantity	High data quantity
Controlled • Selected patients • “EORTC-RTOG grade” QA/Protocol	**Reality** • Unselected patients • “Clinical grade” QA/Protocol

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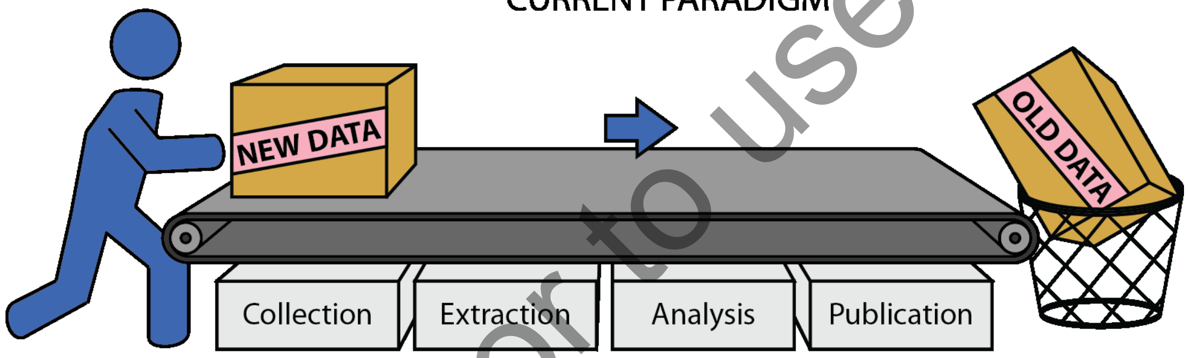
CURRENT PARADIGM



Modified from Deasy et al.

Open source data of publications: www.cancerdata.org

HOME DATA LINKS ABOUT

About CancerData

The *CancerData* site is an effort of the Medical Informatics and Knowledge Engineering team (*MIKE* for short) of Maastro Clinic, Maastricht, The Netherlands. Our activities in the field of medical image analysis and data modelling are visible in a number of projects we are running. Please refer to the Links for more information.

Open source driven
CancerData is build using Free and Open Source Software (FOSS) only. Refer to this page for more information on the used software.
In return, we offer tools for image analysis and more. Have a look at the file manager (ps: allow popups).

Contact us
Please use the Contact form for feedback or more information.

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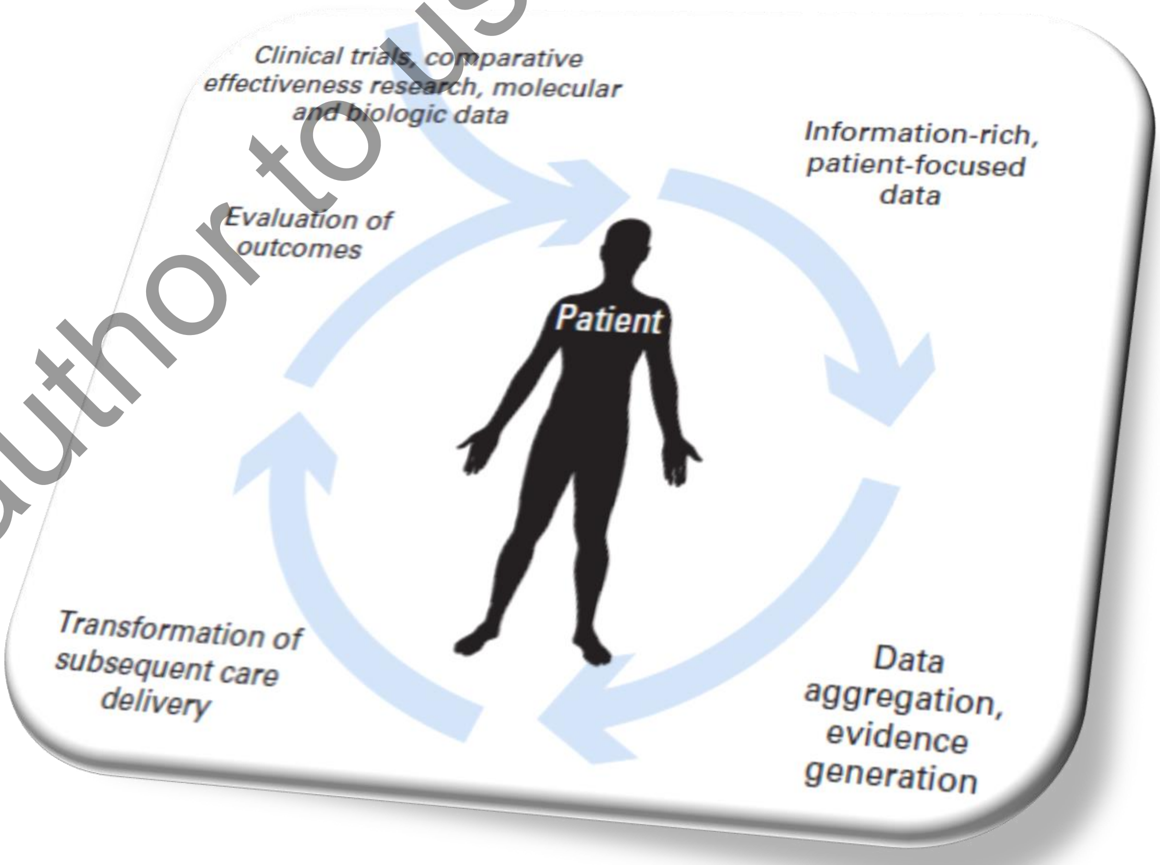
Rapid Learning

In [..] rapid-learning [..] data routinely generated through patient care and clinical research feed into an ever-growing [..] set of coordinated databases.

•*Abernethy, J Clin Oncol 2010;28:4268*

•[..] rapid learning [..] where we can learn from each patient to guide practice, is [..] crucial to guide rational health policy and to contain costs [..].

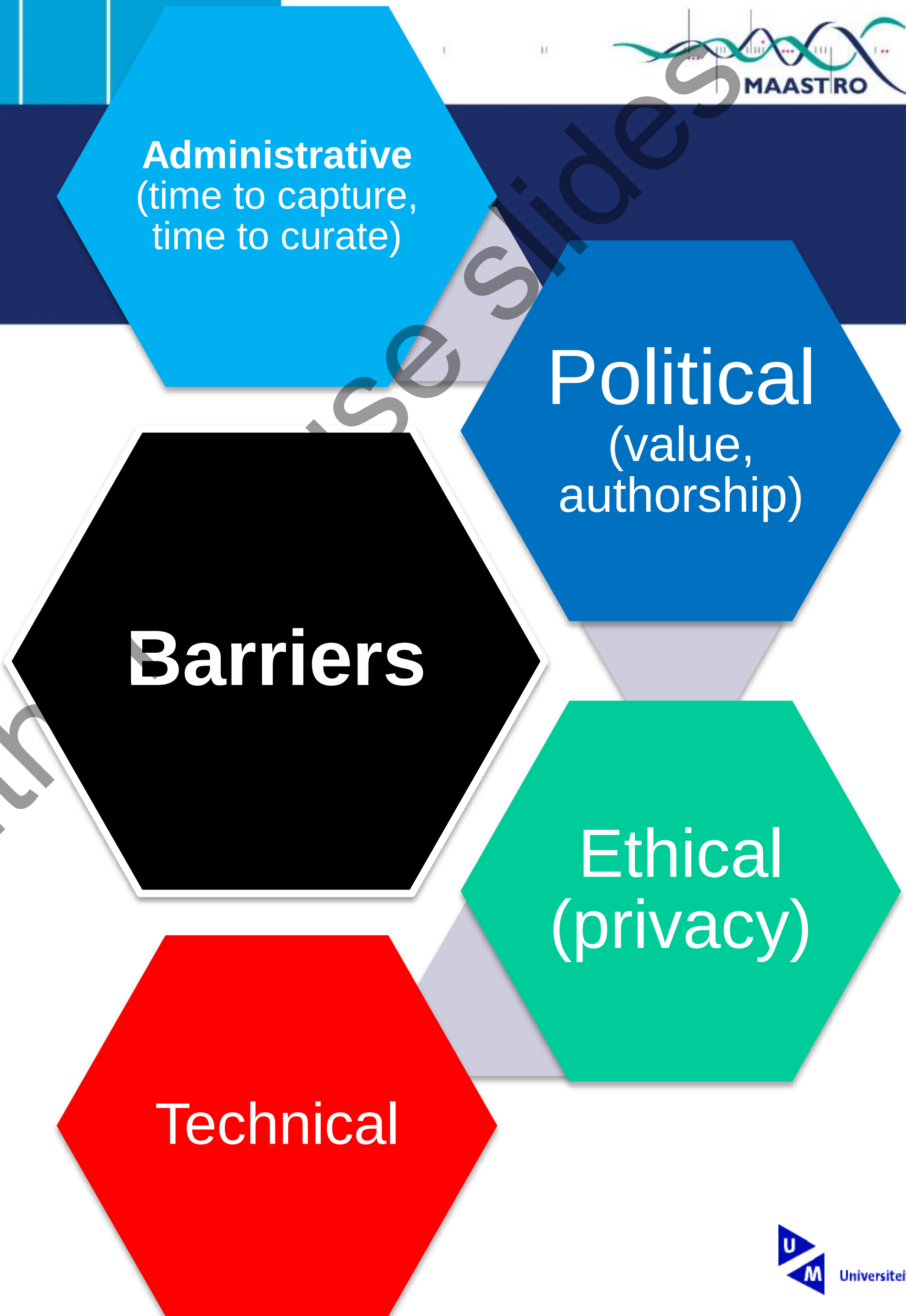
•*Lancet Oncol 2011;12:933*



Sharing data

[..] the problem is not really technical […]. Rather, the problems are **ethical, political, and administrative**.
Lancet Oncol 2011;12:933

Solutions: Distributed learning from federated databases



Data warehousing for research


Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

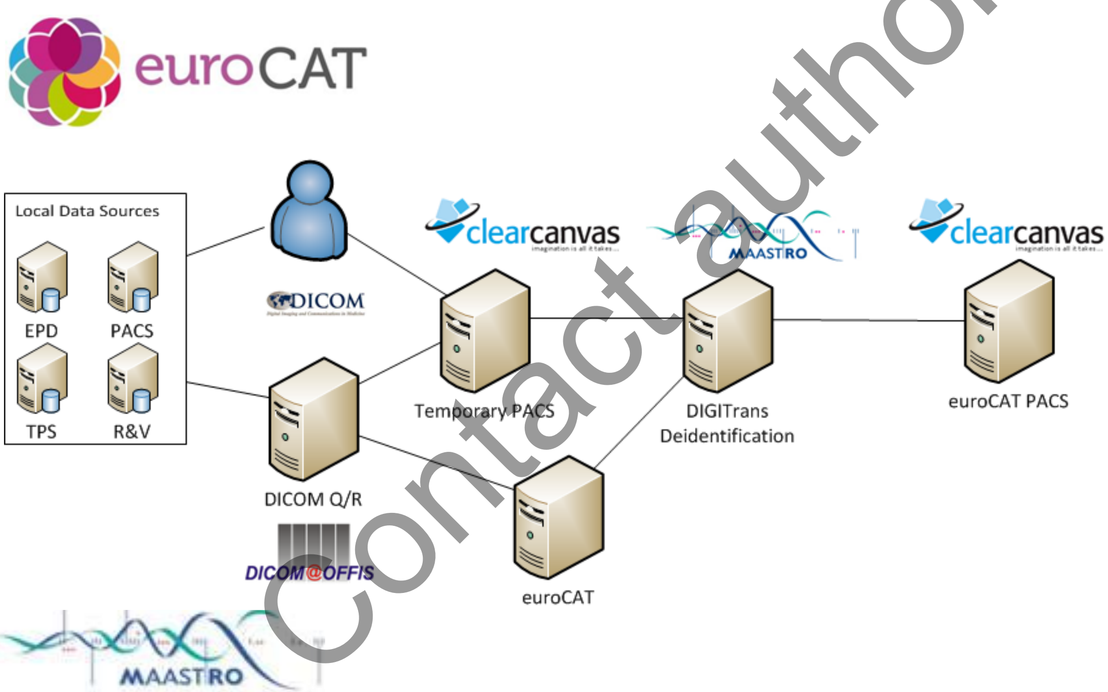
journal homepage: www.thegreenjournal.com

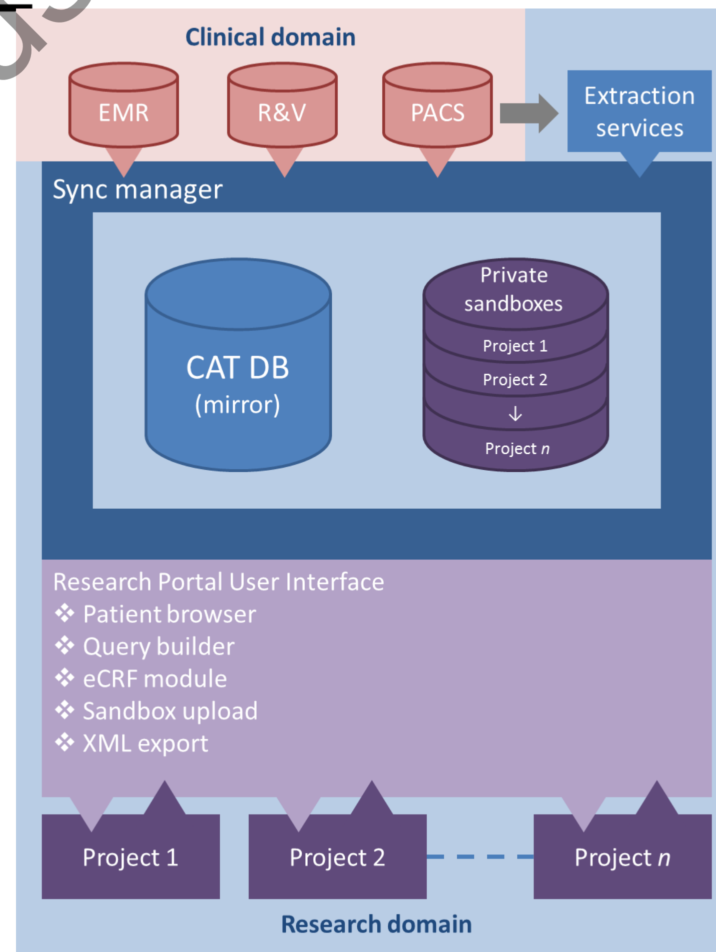
Original article

Benefits of a clinical data warehouse with data mining tools to collect data for a radiotherapy trial

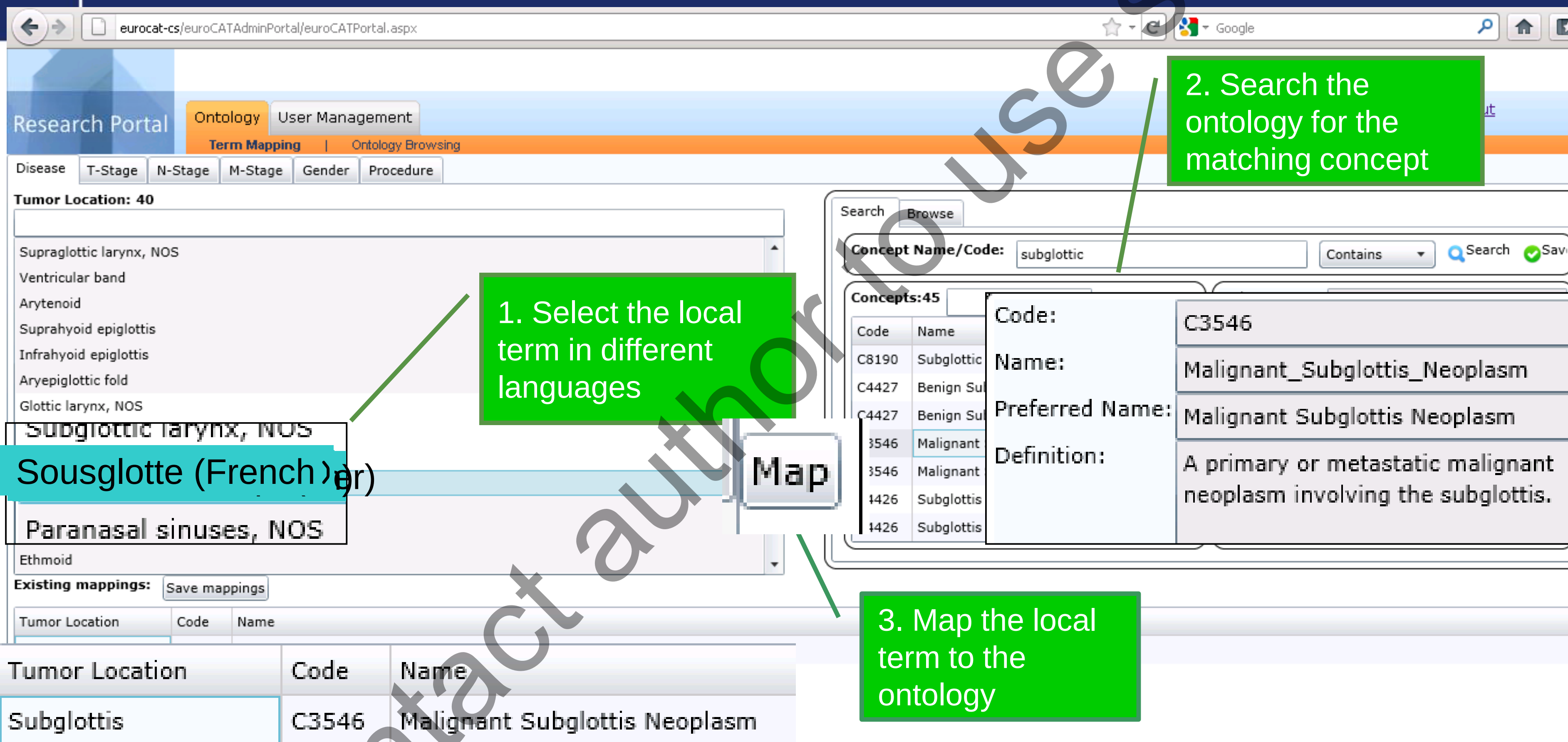
Erik Roelofs [a,*,1], Lucas Persoon [a,1], Sebastiaan Nijsten [a], Wolfgang Wiessler [b], André Dekker [a,1], Philippe Lambin [a,1]

[a] Department of Radiation Oncology (MAASTRO Clinic), Maastricht University Medical Centre (MUMC+), The Netherlands; [b] Siemens Healthcare, Malvern, PA, USA





Ontology mapping
(To be done once)



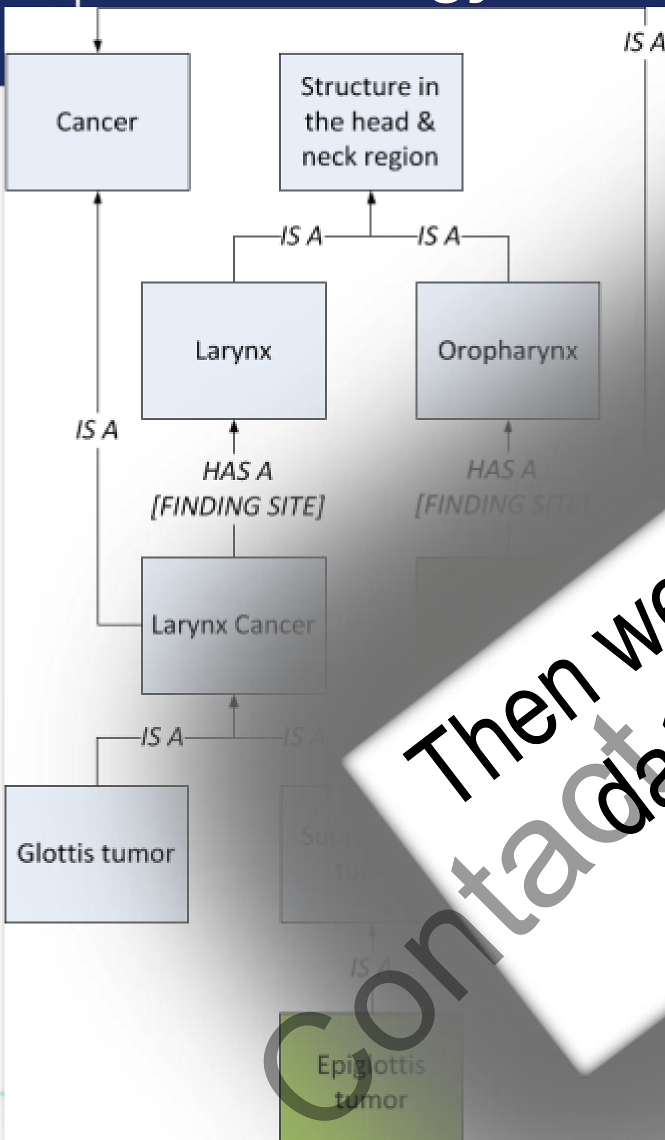
1. Select the local term in different languages

2. Search the ontology for the matching concept

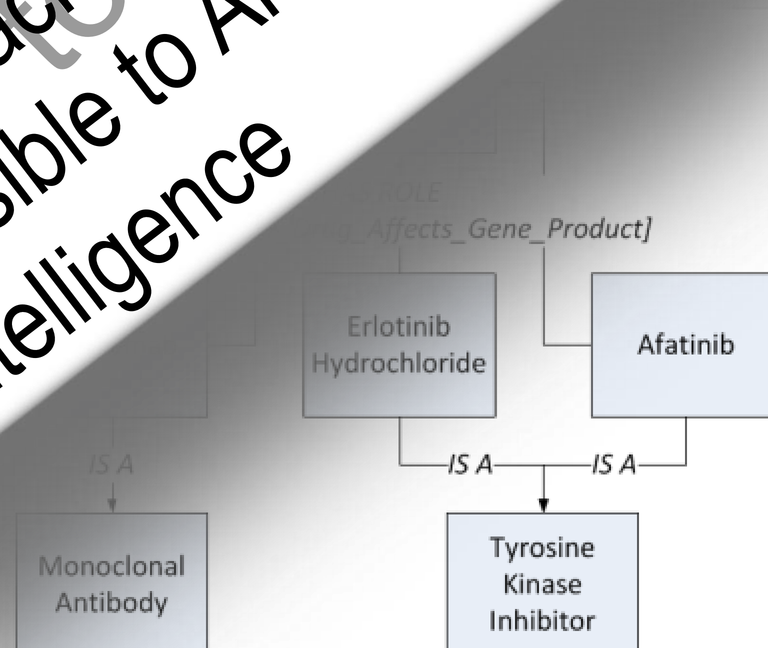
3. Map the local term to the ontology

4. See the result of your mapping

An ontology is more than a dictionary



Ontolog
relati



Then we have "machine readable data" accessible to Artificial Intelligence

MAASTRO's euroCAT approach

Technical

An IT Infrastructure

To make radiotherapy centers

Under their full control

Political

Administrative

Semantic interoperable/ machine readable

While the data stays inside the hospital

Ethical

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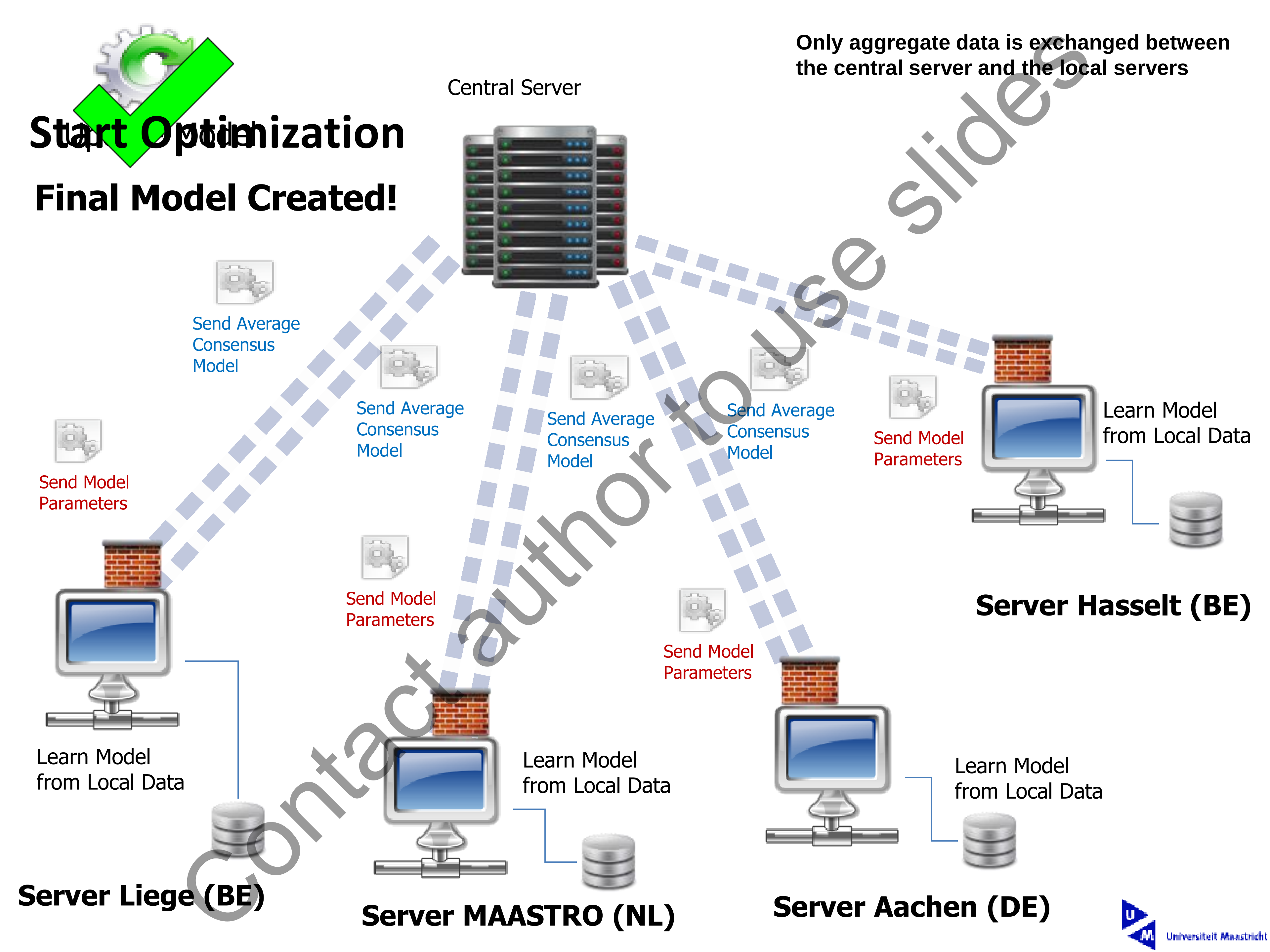
Only aggregate data is exchanged between the central server and the local servers
Start Optimization
Final Model Created!
Central Server
Send Average Consensus Model
Send Average Consensus Model
Send Average Consensus Model
Send Average Consensus Model
Send Model Parameters
Send Model Parameters
Send Model Parameters
Send Model Parameters
Learn Model from Local Data
Server Hasselt (BE)
Learn Model from Local Data
Server Liege (BE)
Learn Model from Local Data
Server MAASTRO (NL)
Learn Model from Local Data
Server Aachen (DE)
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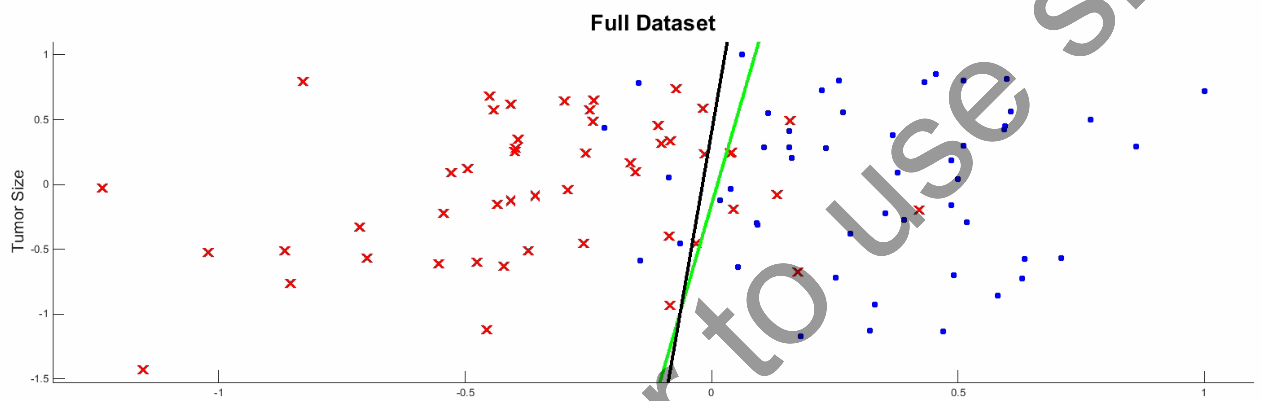
Visualization of Distributed Learning: Support Vector Machines



Event Patient

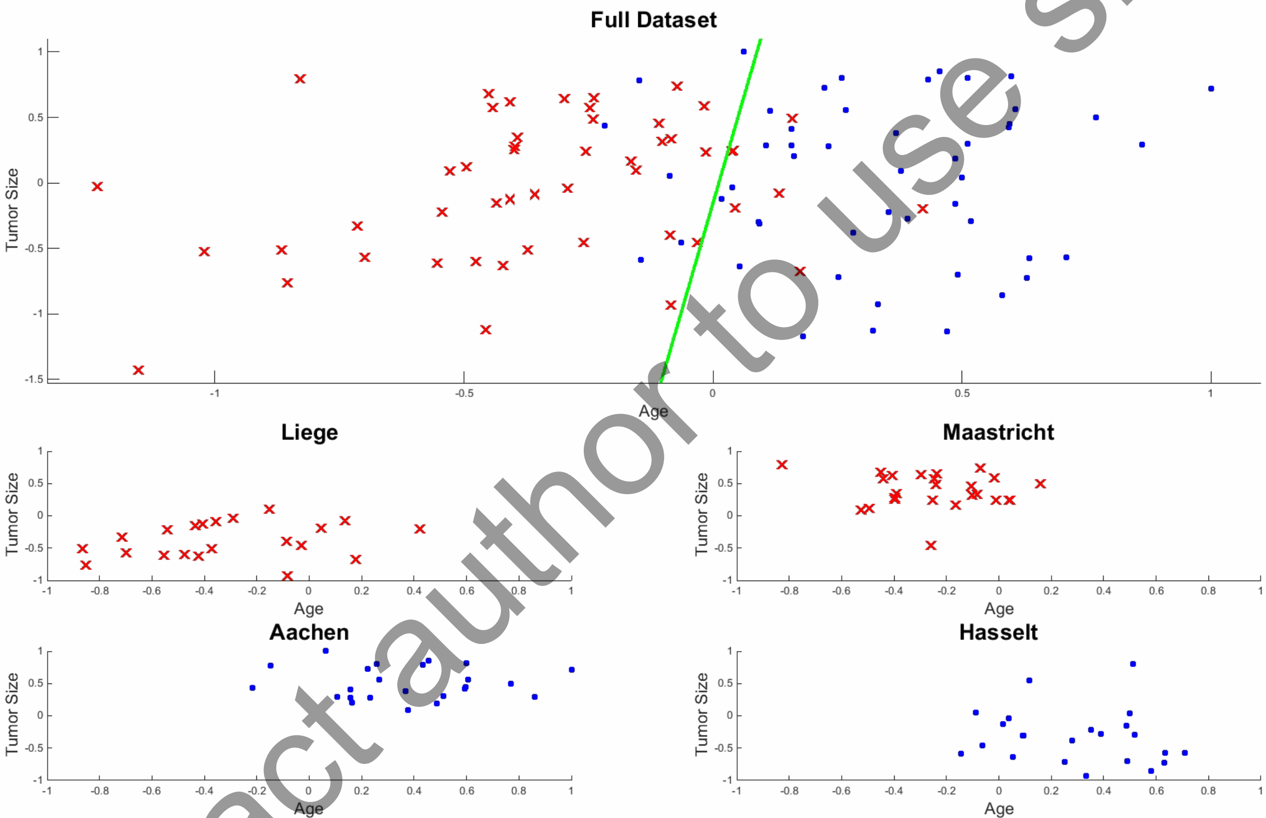
Non-Event Patient

Distributed Learning Solution

Centralized Learning Solution

Simulated Data

Visualization of Distributed Learning: Support Vector Machines (worst case scenario)



Event Patient

Non-Event Patient

Distributed Learning Solution

Centralized Learning Solution

Simulated Data

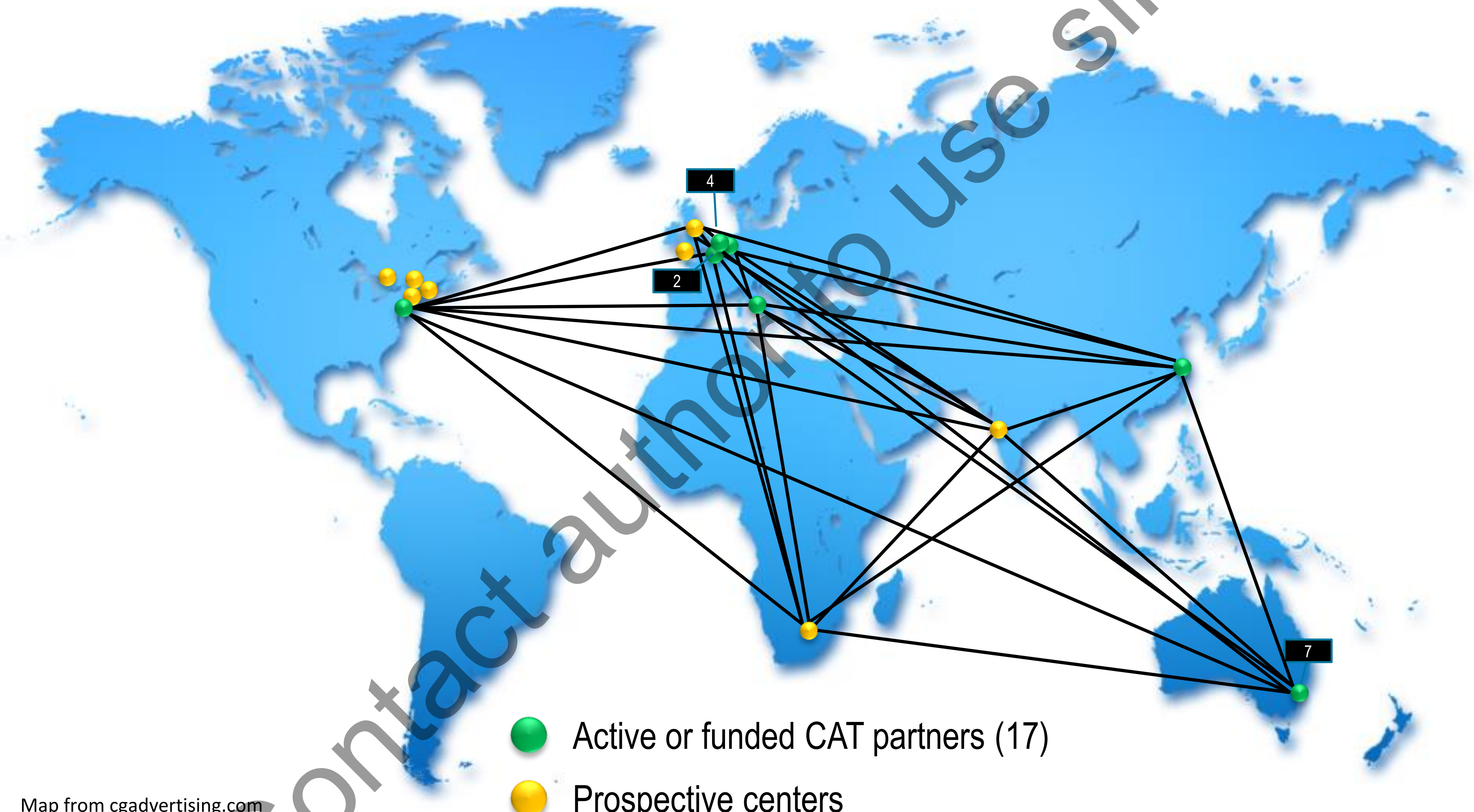
Results:
Distributed Learning vs. Centralized Learning

- Data from toxicity analysis, N = 259 (Nalbantov et al. 2015)
  - Data available at www.cancerdata.org
- Endpoint: Severe dyspnea (CTCAE dyspnea score $\geq$2)
- Predictors
  - Baseline dyspnea
  - FEV1 (in %)
  - Tumor location
  - Sequential chemotherapy
  - Cardiac comorbidity

	AUC
Centralized Learning	0.588
Distributed Learning	0.588

Clinical Data

Funded: euroCAT, duCAT, chinaCAT, VATE, ozCAT
New: ukCAT, indiaCAT



Map from cgadvertising.com

Can you give me

examples

of new knowldege coming from RLHC approaches

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ARTICLE IN PRESS

Radiotherapy and Oncology xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

Original article

Cardiac comorbidity is an independent risk factor for radiation-induced lung toxicity in lung cancer patients ☆

Georgi Nalbantov [a,*], Bas Kietselaer [b,c], Katrien Vandecasteele [d], Cary Oberije [a], Maaike Berbee [a], Esther Troost [a], Anne-Marie Dingemans [e], Angela van Baardwijk [a], Kim Smits [a], André Dekker [a], Johan Bussink [f], Dirk De Ruysscher [a,g], Yolande Lievens [d], Philippe Lambin [a]

[a] Department of Radiation Oncology (Maastro Clinic), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre; [b] Department of Cardiology; [c] Department of Radiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands; [d] Department of Radiation Oncology, Ghent University Hospital, Ghent, Belgium; [e] Department of Pulmonology, GROW - School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht; [f] Department of Radiation Oncology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; [g] Radiation Oncology, University Hospitals Leuven/KU Leuven, Leuven, Belgium

ARTICLE INFO

Article history:
Received 30 May 2013
Received in revised form 21 August 2013
Accepted 25 August 2013
Available online xxxx

Keywords:
Lung cancer
Cardiac comorbidity
Radiotherapy
Dyspnea
Radiation-induced lung toxicity

ABSTRACT

Purpose: To test the hypothesis that cardiac comorbidity before the start of radiotherapy (RT) is associated with an increased risk of radiation-induced lung toxicity (RILT) in lung cancer patients.
Material and methods: A retrospective analysis was performed of a prospective cohort of 259 patients with locoregional lung cancer treated with definitive radio(chemo)therapy between 2007 and 2011 (ClinicalTrials.gov Identifiers: NCT00572325 and NCT00573040). We defined RILT as dyspnea CTCv.3.0 grade ⩾2 within 6 months after RT, and cardiac comorbidity as a recorded treatment of a cardiac pathology at a cardiology department. Univariate and multivariate analyses, as well as external validation, were performed. The model-performance measure was the area under the receiver operating characteristic curve (AUC).
Results: Prior to RT, 75/259 (28.9%) patients had cardiac comorbidity, 44% of whom (33/75) developed RILT. The odds ratio of developing RILT for patients with cardiac comorbidity was 2.58 ($p < 0.01$). The cross-validated AUC of a model with cardiac comorbidity, tumor location, forced expiratory volume in

Results: Prior to RT, 75/259 (28.9%) patients had cardiac comorbidity, 44% of whom (33/75) developed RILT. The odds ratio of developing RILT for patients with cardiac comorbidity was 2.58 ($p < 0.01$). The cross-validated AUC of a model with cardiac comorbidity, tumor location, forced expiratory volume in 1 s, sequential chemotherapy and pretreatment dyspnea score was 0.72 ($p < 0.001$) on the training set, and 0.67 ($p < 0.001$) on the validation set.

Radiation-induced lung toxicity (RILT) is an important dose-limiting complication of radical thoracic radiotherapy (RT). While may permit (1) dose escalation for low-risk patients, potentially leading to better survival rates at reduced/similar levels of treat-

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One can extract *more* quantitative information from standard imaging

Radiology:

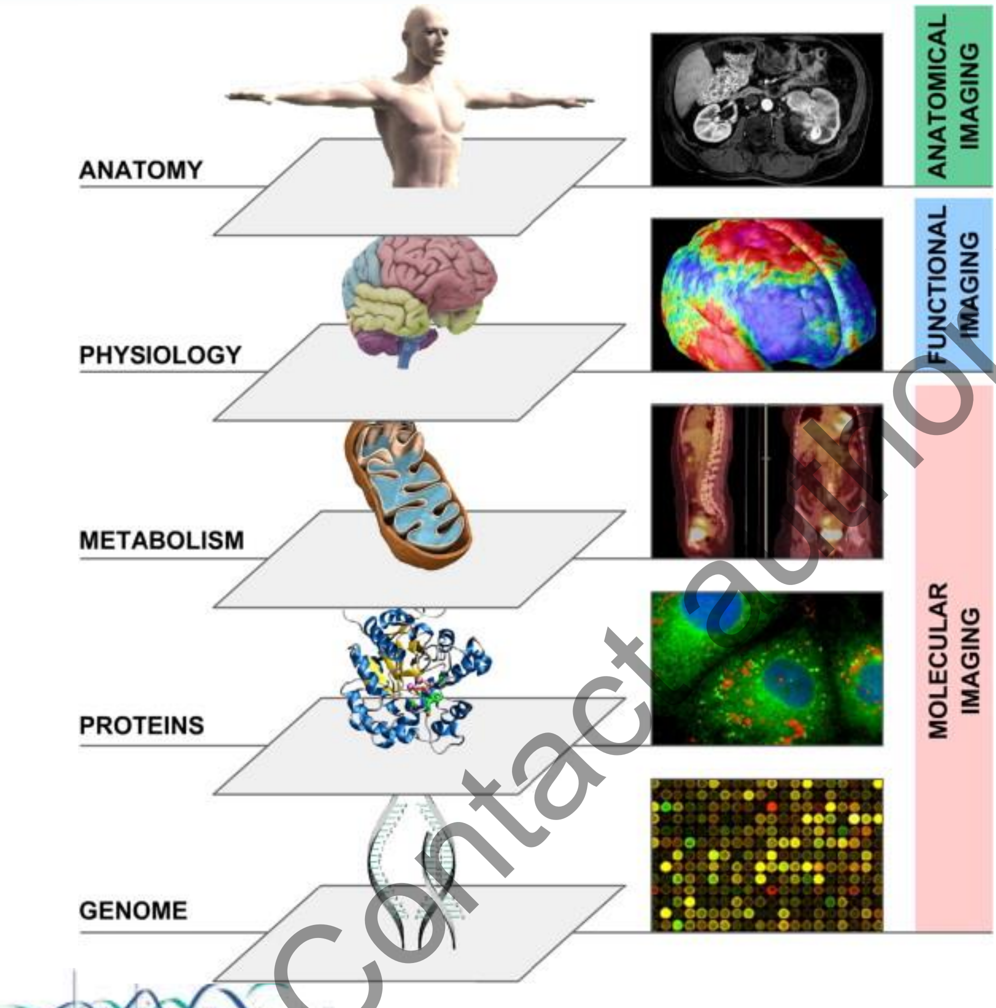
- Implicit knowledge
- Interpretability

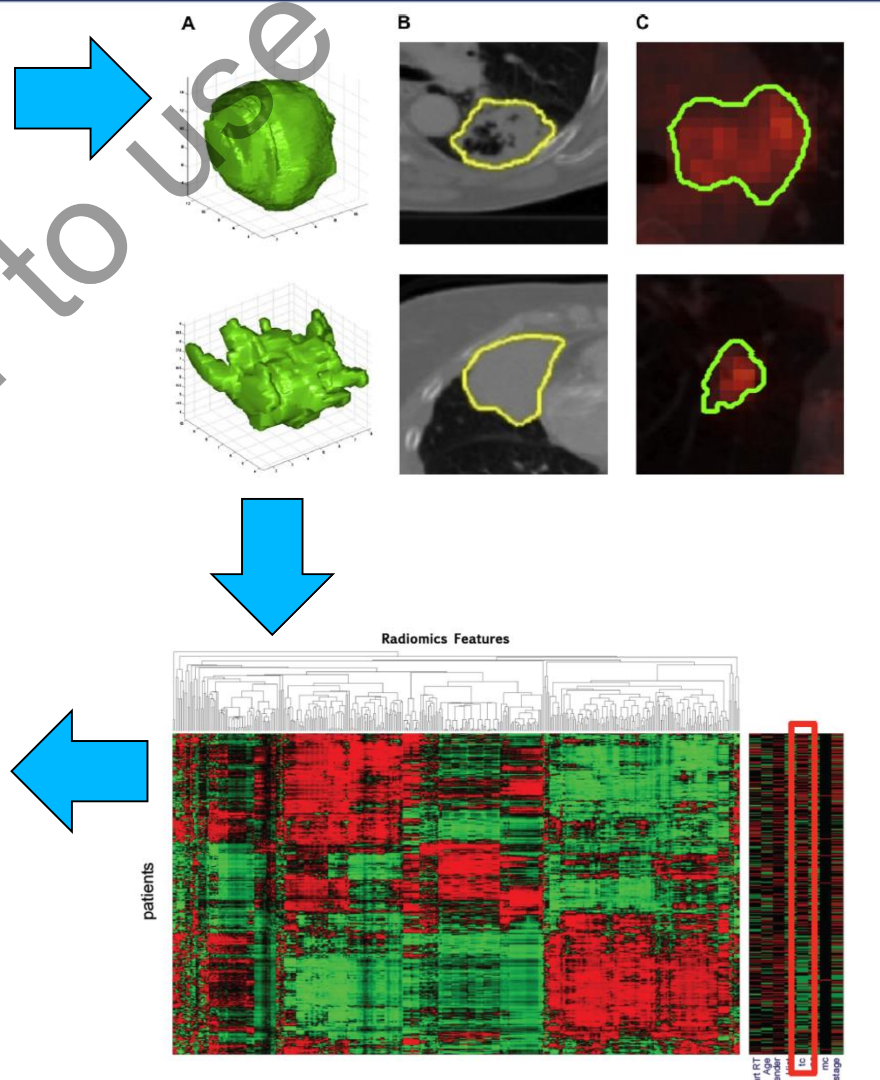
QUANTIFICATION

RADIOMICS
Extract *quantitative* features from images

Lambin et al. EJC, 2012; Aerts, Lambin et al. Nature Commun 2014

Entering the OMICS era… Radiomics





Lambin et al. EJC, 2012; Aerts, Lambin et al. Nature Commun 2014

Is this approach

ethical?

40 Years After Tuskegee: Reuniting Medical Research and Practice

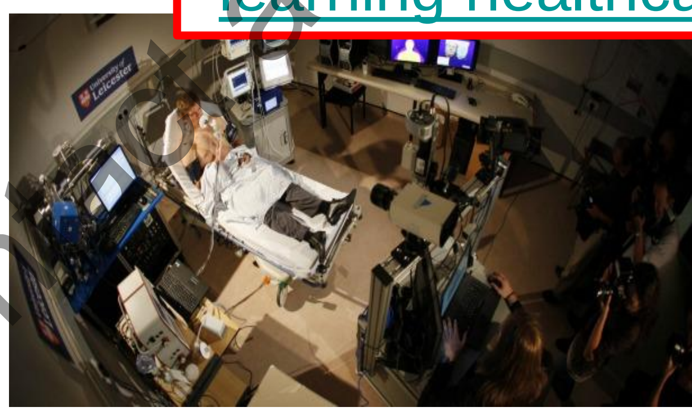
Ruth Faden (Bioethics) Jan 16 2013, 10:44 AM ET

the Atlantic

Guidelines to protect human research subjects impede efficient generation and exchange of knowledge.

..each episode of care we receive, should generate data and evidence that improve the care of patients who come after us; we then, in turn, benefit from what is systematically learned from the care received by patients who come before us.

care of patients who come after us; we then, in turn, benefit from what is systematically learned from the care received by patients who come before us. Through continuous, real-time learning, we can provide better care to more people, save lives, become smarter, and wring every dollar of value from the system. This is what the Institute of Medicine has dubbed the "learning healthcare system."



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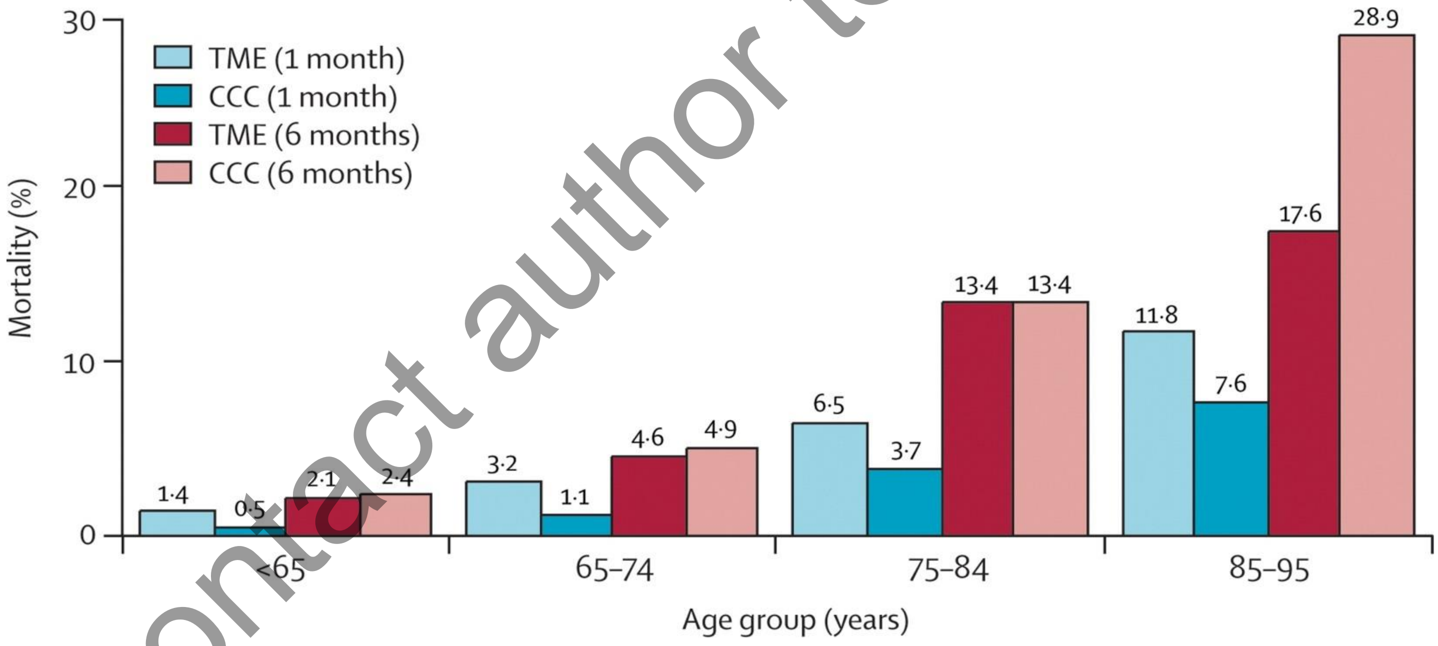
Rectum cancer: Mortality after surgery

6 month mortality >> 1 month mortality

Age and comorbidity related



Rutten et al. Lancet Oncology 2008; 9: 494

What about the biology?

E.g. The SNP TANC1 in prostate cancer (Nat genetics 2014) or mitochondrial DNA signature (unpublished)

What about the patient?

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About the 4th « P»: Participatory

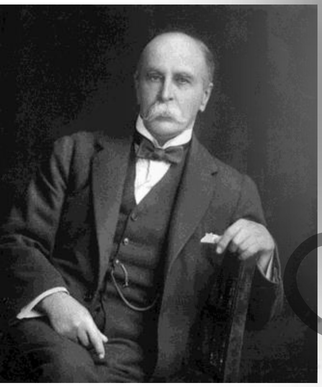
"The good phys... the

di...

the gre... ...an treats the patient

...has the disease".

Dr. William Osler, the father of modern medicine



The 5 P's of modern medicine

(from Leroy Hood)

« P » for Personalized

« P » for Preventive

« P » for Predictive

« P » for Participatory

Shared Decision Making with Decision aids (EL1)

Decision aids for people facing health treatment or screening decisions (Review)

Stacey D, Bennett CL, Barry MJ, Col NF, Eden KB, Holmes-Rovner M, Llewellyn-Thomas H, Lyddiatt A, Légaré F, Thomson R

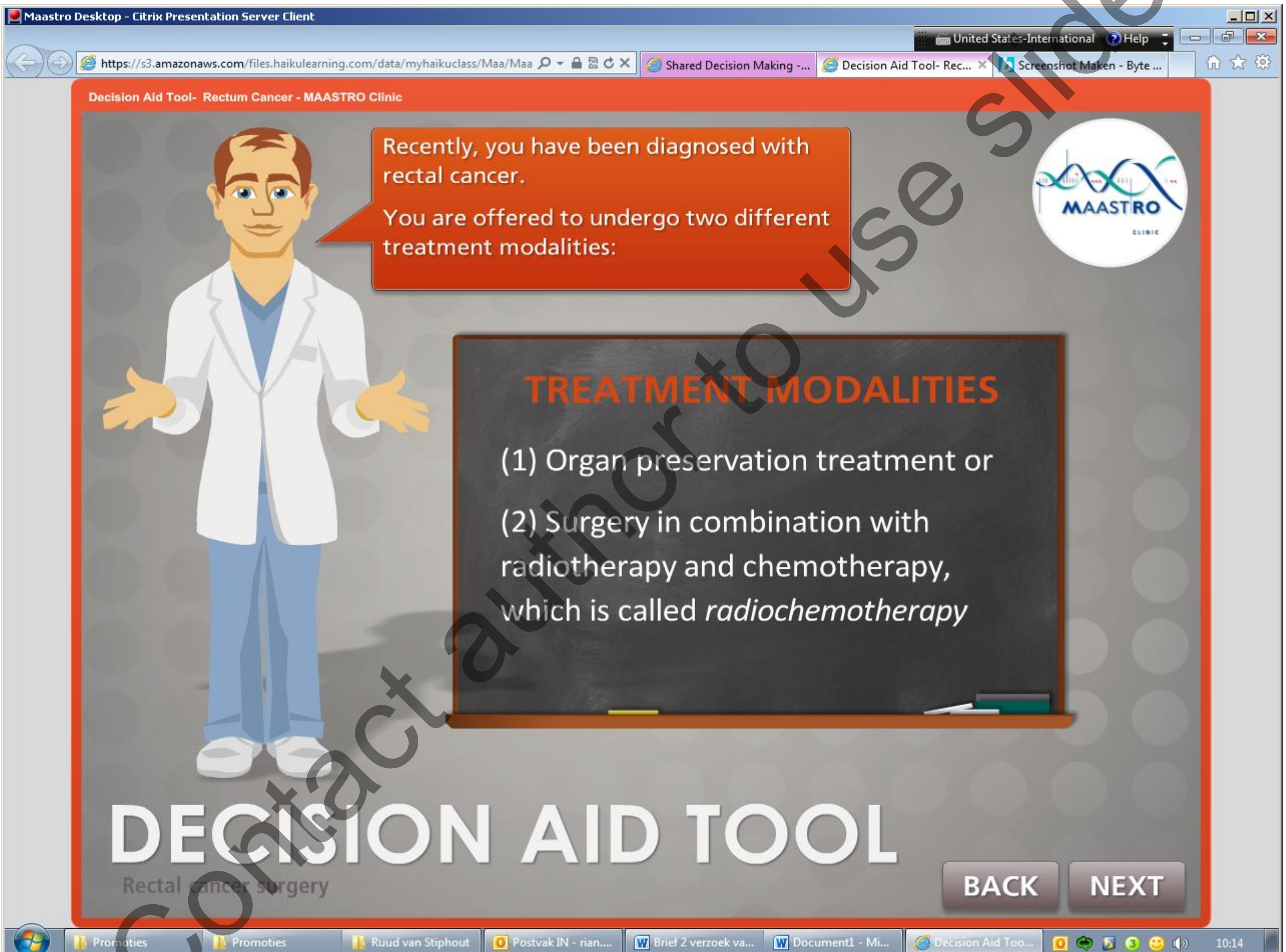
THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 5

http://www.thecochranelibrary.com

Study or subgroup	Decision Aid N	Mean(SD)	Usual Care N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Nagle 2008	167	16.25 (13.75)	171	15 (14.25)		7.5 %	1.25 [-1.74, 4.24]
Vandemheen 2009	70	10.4 (16.4)	79	17.9 (20.4)		5.8 %	-7.50 [-13.42, -1.58]
Vodermaier 2009	55	28.25 (20.75)	56	35 (20)		4.8 %	-6.75 [-14.33, 0.83]
Whelan 2004	94	12.5 (12)	107	17 (13)		7.3 %	-4.50 [-7.96, -1.04]
Wong 2006	136	19.38 (13.13)	159	36.67 (19.17)		7.1 %	-17.29 [-21.00, -13.58]
Subtotal (95% CI)	**1655**		**1702**			**100.0 %**	**-4.95 [-7.51, -2.39]**
Heterogeneity: $Tau^2 = 20.41$; $Chi^2 = 82.56$, df = 15 (P<0.00001); I^2 =82%							
Test for overall effect: Z = 3.79 (P = 0.00015)							
6 Total decisional conflict score							
Dolan 2002	41	20.75 (13)	37	25.75 (20.25)		3.6 %	-5.00 [-12.64, 2.64]
Laupacis 2006	53	17.5 (13.75)	54	25.25 (14.25)		4.9 %	-7.75 [-13.06, -2.44]
Legare 2008a	43	23 (14.25)	41	27 (15.25)		4.3 %	-4.00 [-10.32, 2.32]
Man-Son-Hing 1999	139	16.25 (11.25)	148	18.5 (13.5)		6.5 %	-2.25 [-5.12, 0.62]
Mathieu 2007	315	20.06 (14.51)	295	21.89 (14.51)		6.8 %	-1.83 [-4.13, 0.47]
McAlister 2005	205	15 (12.5)	202	17.5 (12.5)		6.7 %	-2.50 [-4.93, -0.07]
Montgomery 2003	50	27.1 (10)	58	44.2 (19.3)		4.7 %	-17.10 [-22.79, -11.41]
Montgomery 2007	198	23.6 (15.1)	201	27.8 (14.6)		6.4 %	-4.20 [-7.12, -1.28]
Morgan 2000	86	27.5 (37.5)	94	27.5 (37.5)		2.3 %	0.0 [-10.97, 10.97]
Mullan 2009	48	14.1 (17.89)	37	14.95 (12.68)		4.2 %	-0.85 [-7.35, 5.65]
Murray 2001a	57	32.5 (10)	48	40 (12.5)		5.5 %	-7.50 [-11.89, -3.11]
Murray 2001b	94	37.5 (12.5)	96	45 (15)		5.8 %	-7.50 [-11.42, -3.58]
Nagle 2008	167	17.75 (12.25)	171	16.25 (13.75)		6.5 %	1.50 [-1.27, 4.27]
Nassar 2007	98	4.6 (9)	98	13.5 (19.2)		5.6 %	-8.90 [-13.10, -4.70]
Protheroe 2007	69	23.4 (14.3)	69	40.5 (18.3)		4.8 %	-17.10 [-22.58, -11.62]
Shorten 2005	99	23.5 (12.5)	88	29.5 (18.25)		5.4 %	-6.00 [-10.54, -1.46]
Vandemheen 2009	70	11.6 (13.6)	79	20.4 (16.9)		5.2 %	-8.80 [-13.70, -3.90]
Vodermaier 2009	55	20.5 (14.75)	56	24.75 (15.5)		4.7 %	-4.25 [-9.88, 1.38]
Whelan 2004	94	10 (12)	107	15.5 (12.9)		6.1 %	-5.50 [-8.94, -2.06]
Subtotal (95% CI)	**1981**		**1979**			**100.0 %**	**-5.66 [-7.68, -3.64]**
Heterogeneity: $Tau^2 = 14.30$; $Chi^2 = 82.47$, df = 18 (P<0.00001); I^2 =78%							
Test for overall effect: Z = 5.49 (P < 0.00001)							

www.treatmentchoice.info

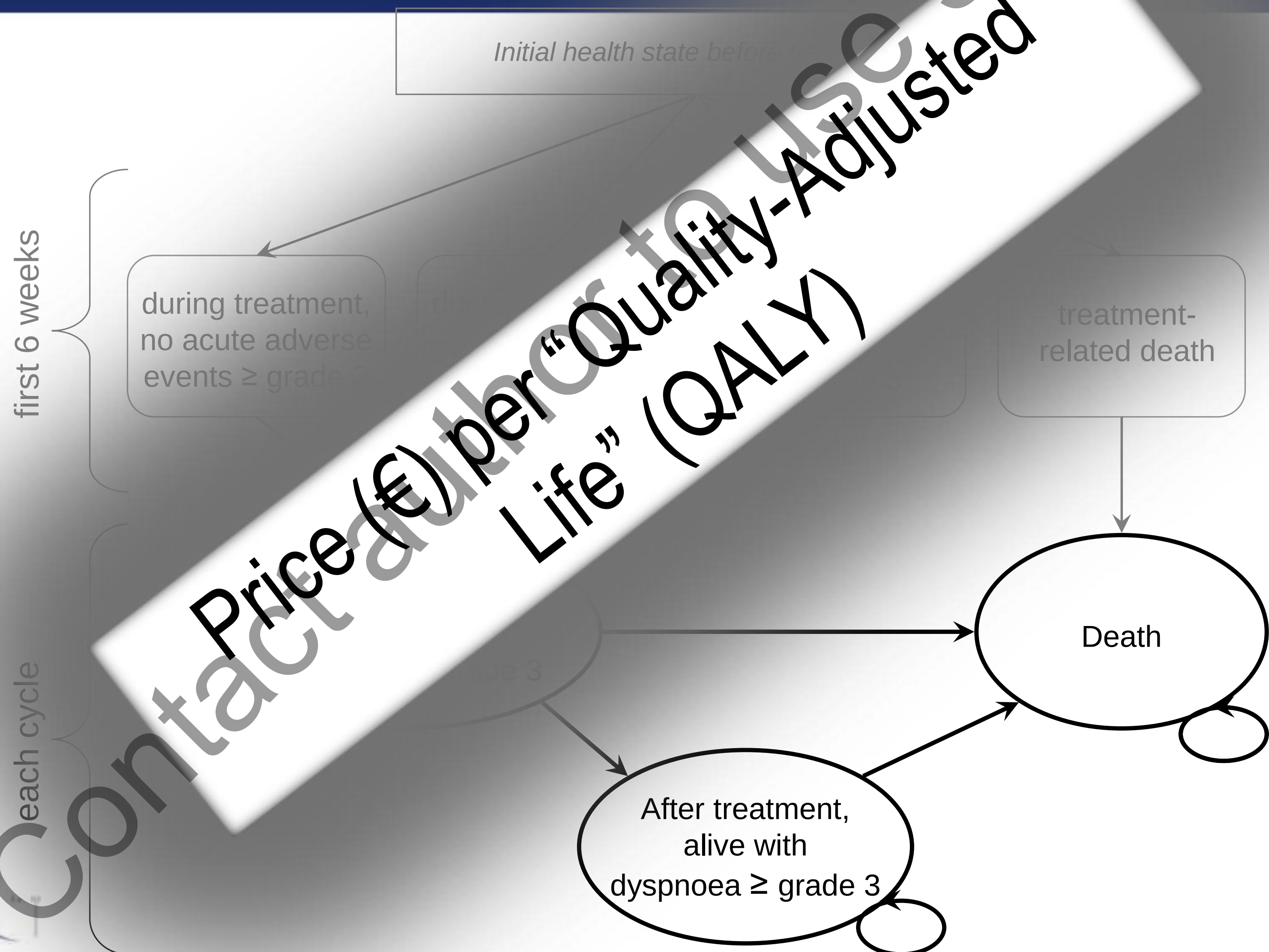


Will this approach increase

the cost of care?

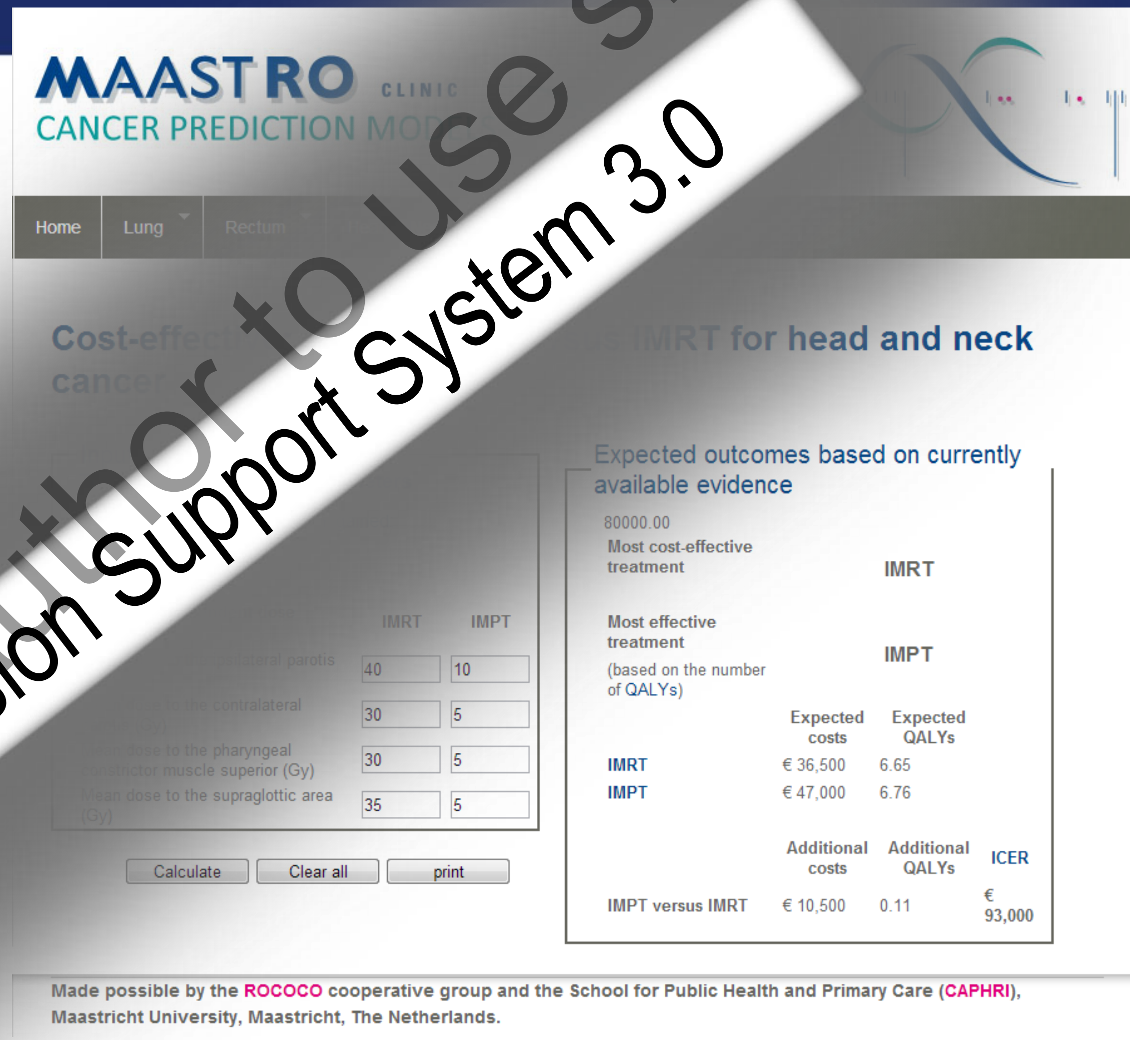
No, it could even decrease them if you look at the cost of the *whole care cycle.*

Costs of the whole care cycle: Markov Model

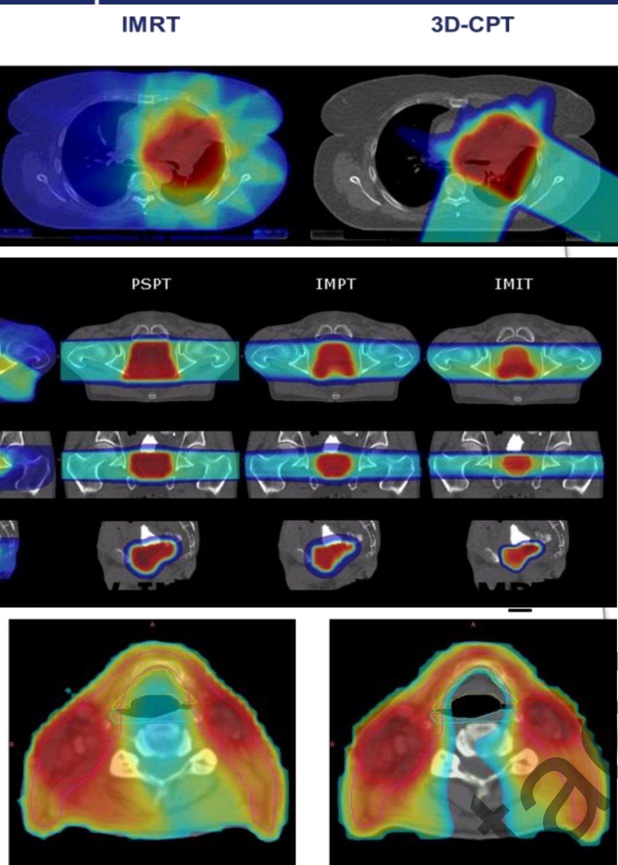


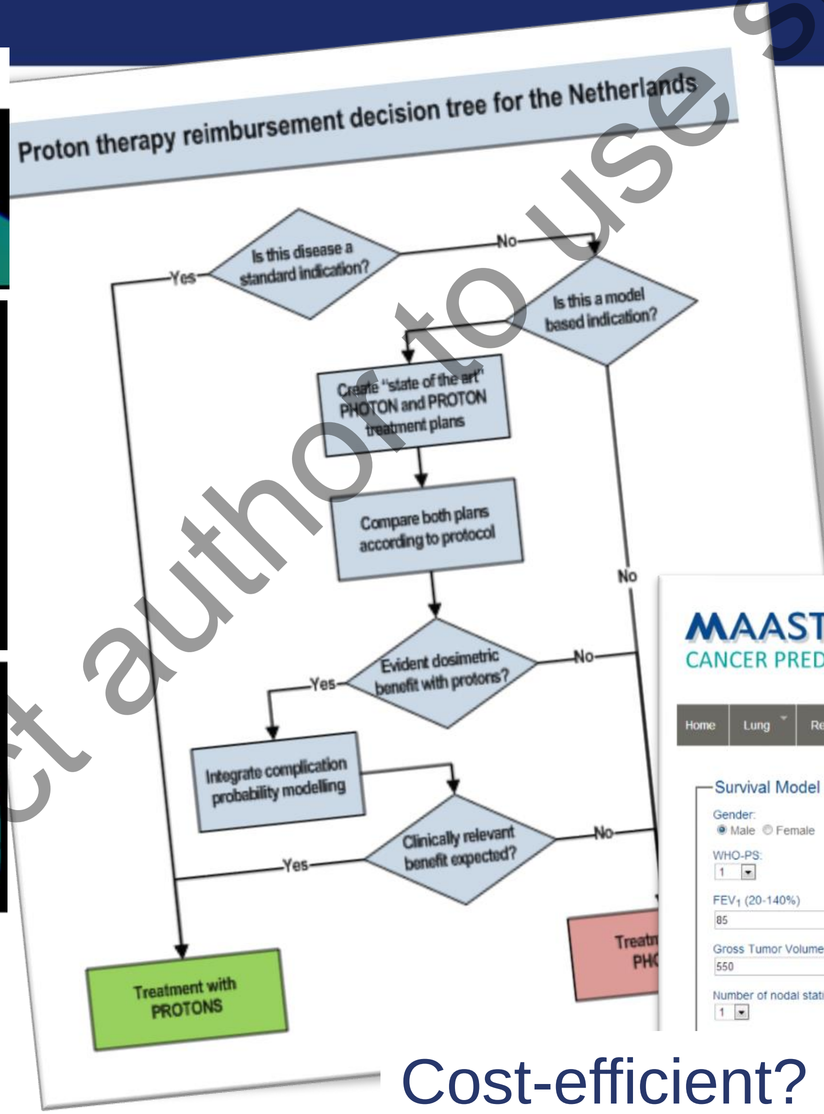
Price (€) per "Quality-Adjusted Life" (QALY)

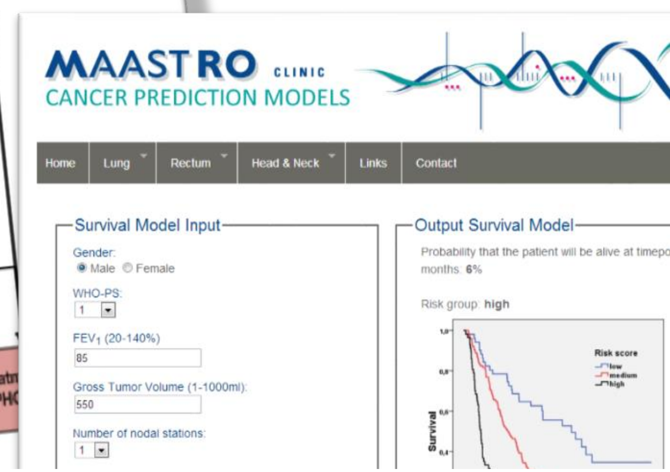
Cost effectiveness: www.predictcancer.org



PRODECIS: Clinical grade decision support system fo protontherapy with three modules

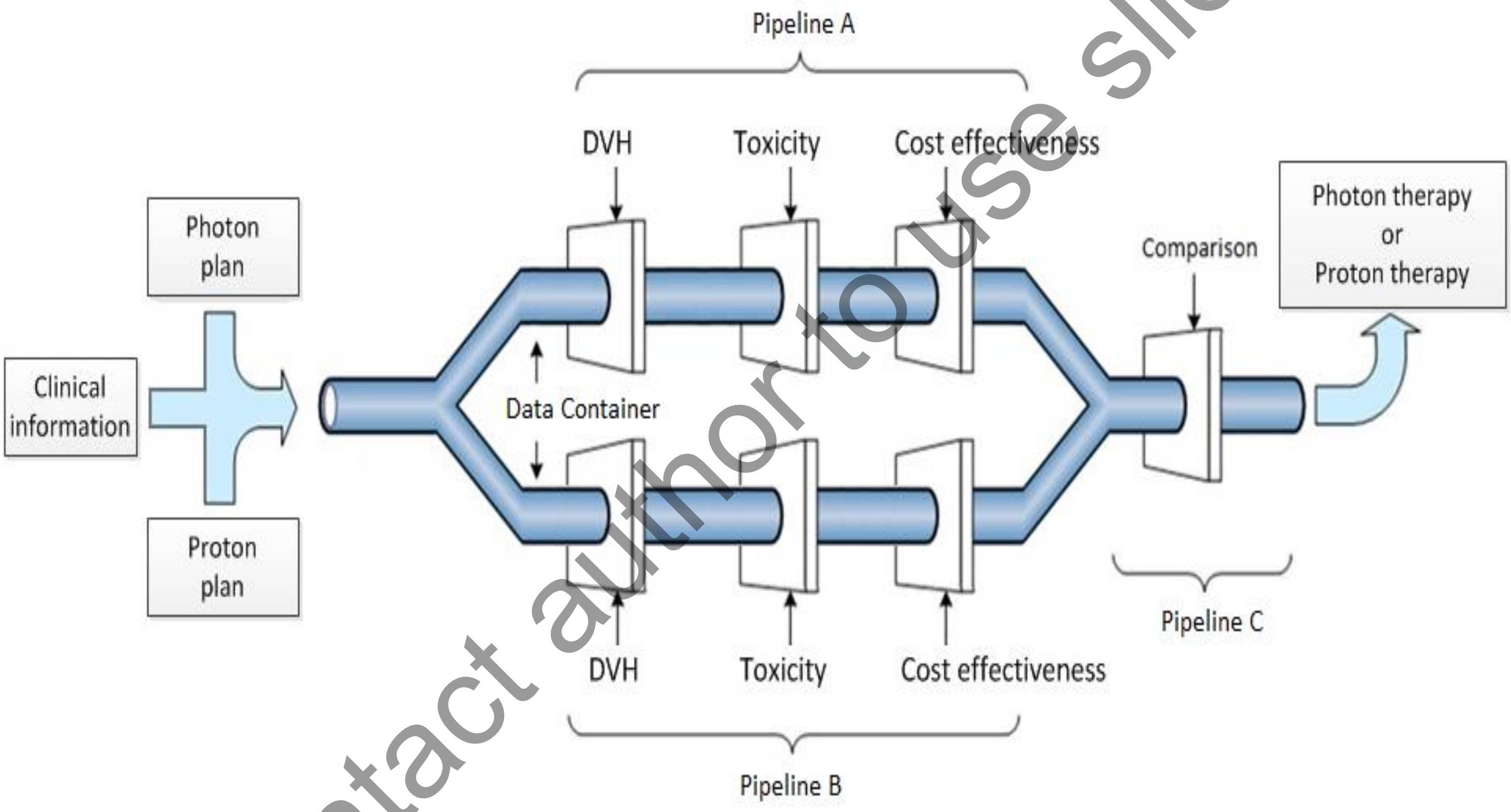






Cost-efficient? Price per QALY?

PRODECIS: working for head & neck cancer



Cheng Q, Roelofs E, Lambin P et al. Submitted

Take home message

1. We need Decision Support Systems (DSS = a "meta TPS") to manage the large quantity of data and implement Personalized medicine in radiotherapy in particular for protontherapy due to its costs.

2. Two complementary approaches: conventional clinical trials (+ data reuse) + Rapid Learning Health Care

3. Building cancer informatics tools to enable analysis, exploration, and rapid evaluation of novel therapies or stratification e.g. Distributed learning,

4. DSS facilitate Share Decision Making and cost effective Health care (the 4th & 5th "P"). One key example could be protontherapy.

Lambin et al. Aug 28, Radiother Oncol 2013 (Review)

Thank you for your attention

More :

www.predictcancer.org

www.eurocat.info

www.cancerdata.org

www.mistir.info

www.predictcancer.org

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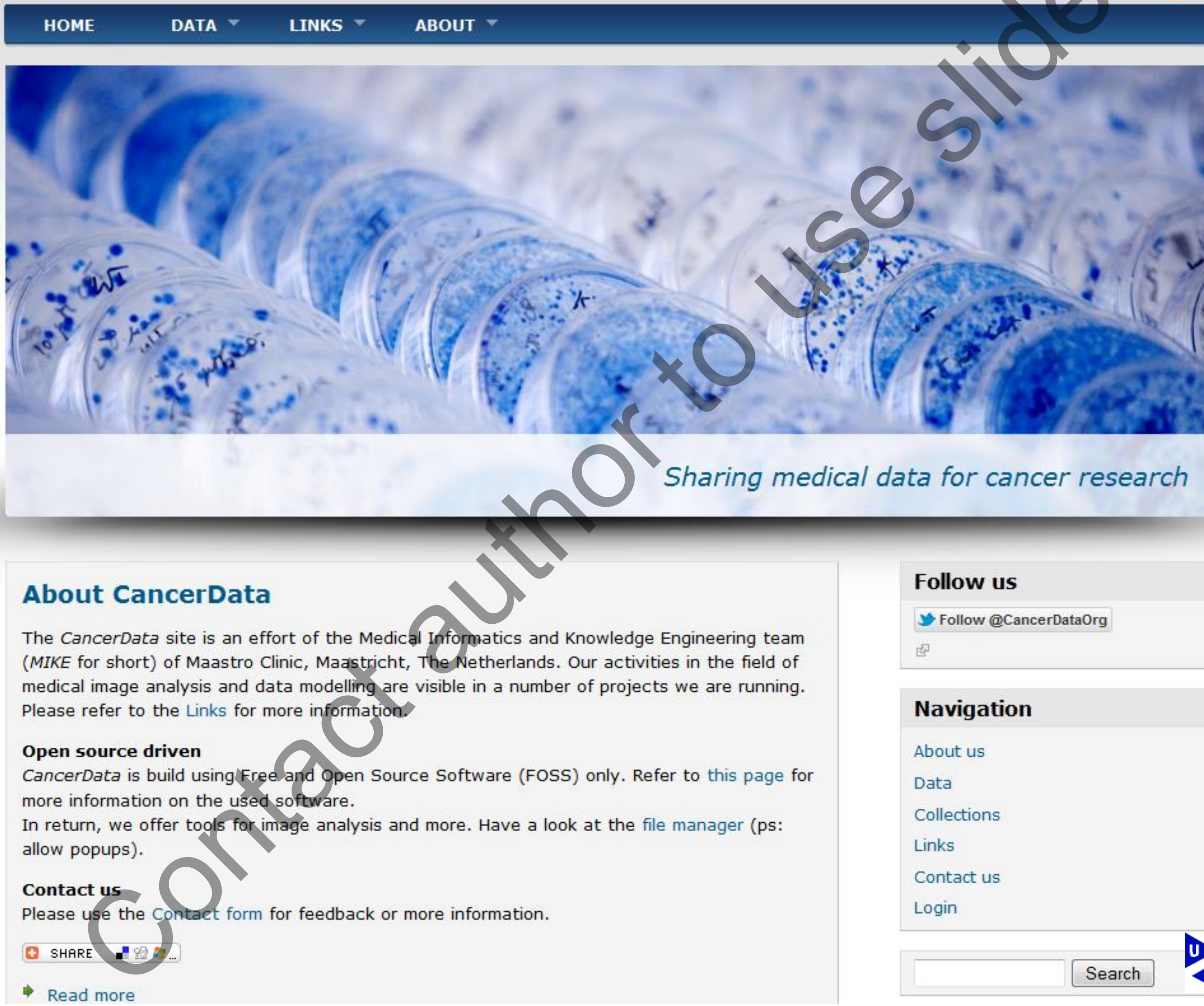
Take home message: Questions?

1. We need Decision Support Systems (DSS = a “meta TPS”) to manage the large quantity of data and implement Personalized medicine

2. Two complementary approaches: conventional clinical trials (+ data reuse) + Rapid Learning Health Care

3. Building cancer informatics tools to enable analysis, exploration, and rapid evaluation of novel therapies or stratification e.g. Distributed learning, Radiomics...

Open source data of publications: www.cancerdata.org


HOME DATA LINKS ABOUT

Sharing medical data for cancer research

About CancerData

The *CancerData* site is an effort of the Medical Informatics and Knowledge Engineering team (*MIKE* for short) of Maastro Clinic, Maastricht, The Netherlands. Our activities in the field of medical image analysis and data modelling are visible in a number of projects we are running. Please refer to the Links for more information.

Open source driven
CancerData is build using Free and Open Source Software (FOSS) only. Refer to this page for more information on the used software.
In return, we offer tools for image analysis and more. Have a look at the file manager (ps: allow popups).

Contact us
Please use the Contact form for feedback or more information.

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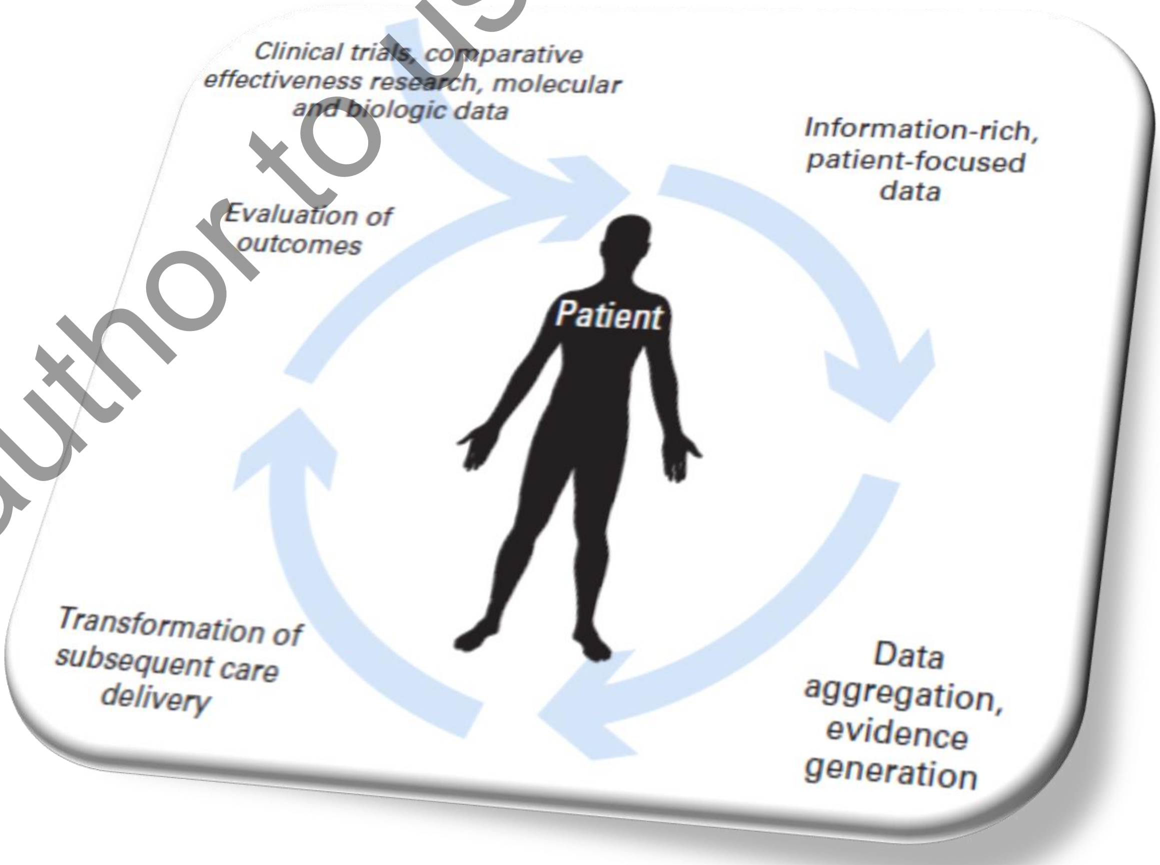
Rapid Learning

In [..] rapid-learning [..] data routinely generated through patient care and clinical research feed into an ever-growing [..] set of coordinated databases.

•*Abernethy, J Clin Oncol 2010;28:4268*

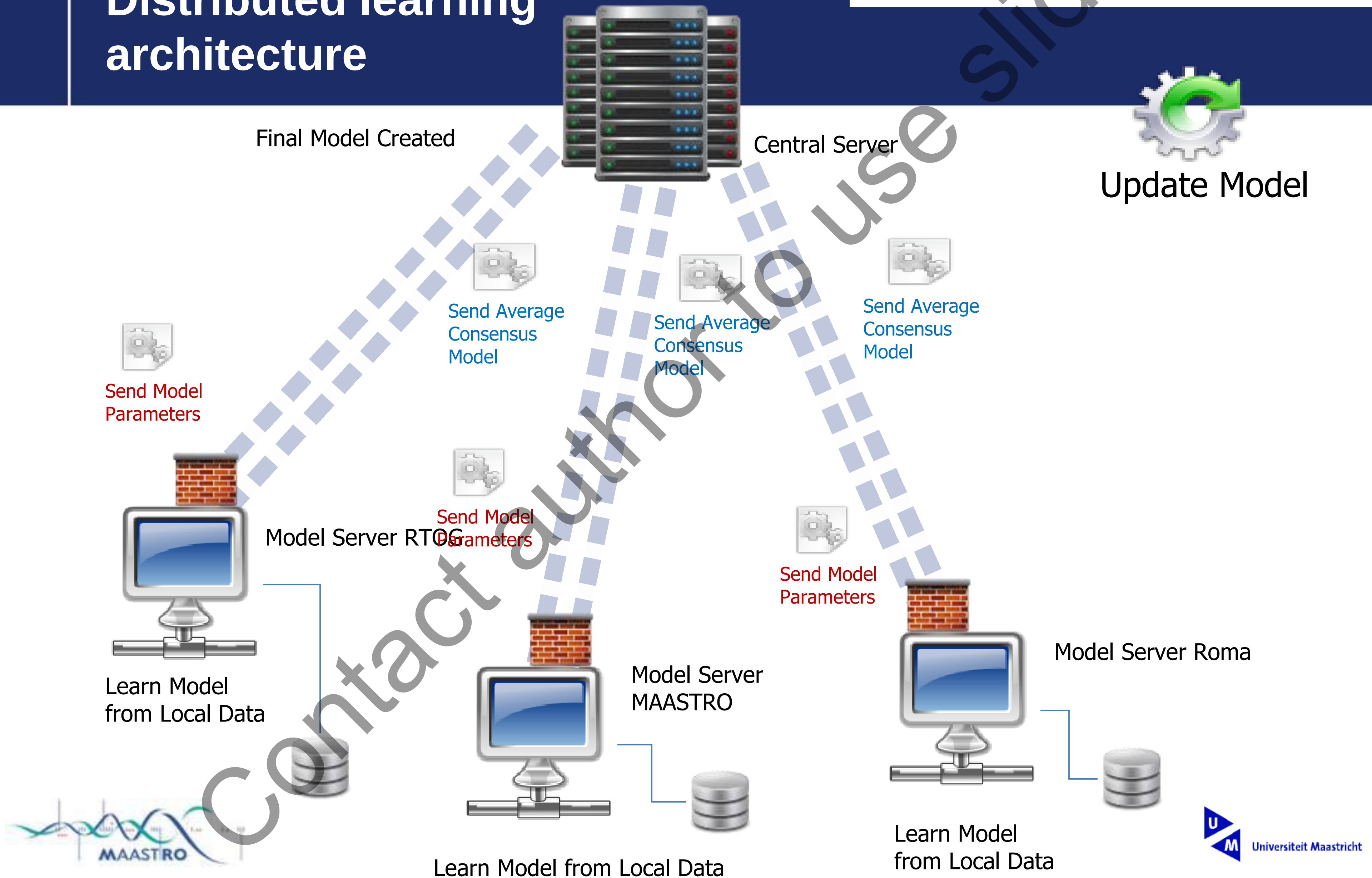
•[..] rapid learning [..] where we can learn from each patient to guide practice, is [..] crucial to guide rational health policy and to contain costs [..].

•*Lancet Oncol 2011;12:933*

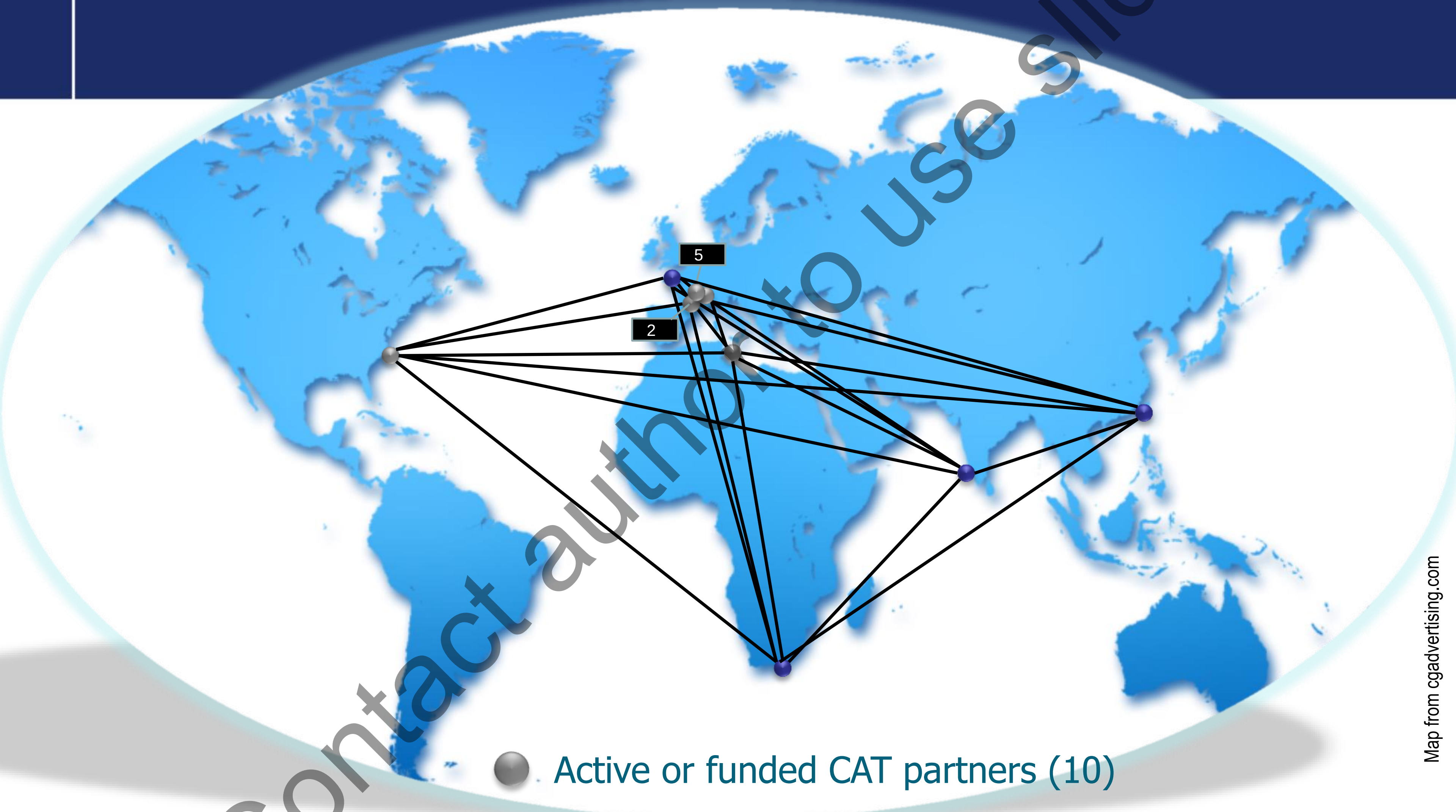


Distributed learning architecture

Only aggregate data is exchanged between the Central Server and the local Servers



Network euroCAT+ in 9/2013



Active or funded CAT partners (10)

Prospective centers (4)