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Rapid Learning Systems to improve patient outcomes & control health costs

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Innovations Center
Siemens Health Services

*This information about these product is preliminary. The product is under development and not commercially available for sale in the U.S. and its future availability cannot be ensured.

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Outline

- The Healthcare Problem
- Knowledge Solutions
- Rapid Learning Systems: Healthcare
- Focus on patient privacy
- Conclusions

The Healthcare Problem

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DATA OVERLOAD

- *Vast amounts of digital patient data available*
- Images, Labs, Text, Demographics, Patient risk factors, …
- Genomics, Proteomics will worsen data overload

1. **Healthcare costs growing explosively**
2. **Without matching improvement in the quality of care & patient outcomes**

KNOWLEDGE OVERLOAD

- *Explosion in the amount of medical knowledge*
- Estimated to double every 18-36 months

- *Many promising therapies.*
- 1000s of drugs with genetic indications in FDA pipeline
- Hard to implement @ poc

THERAPY OVERLOAD

One Size does not fit all

Solution: *Individualize Care to each patient*

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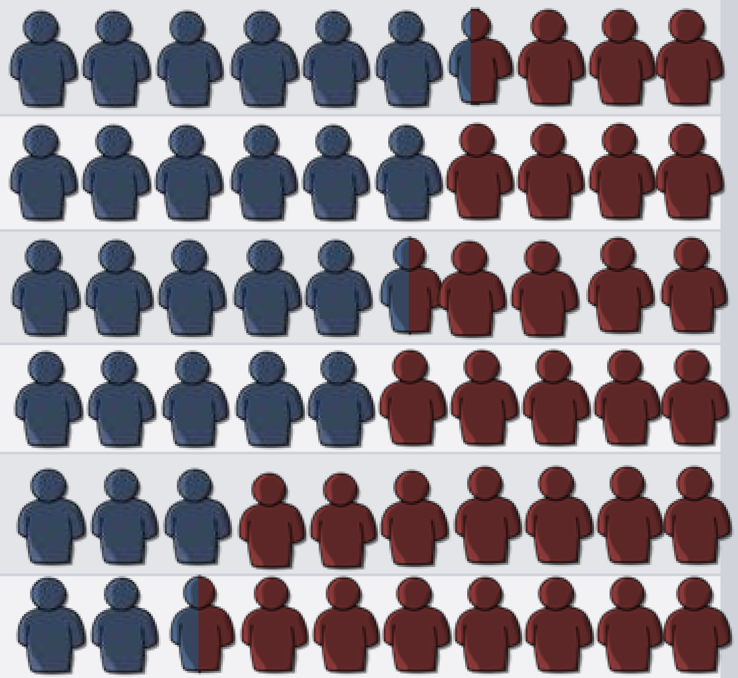
Patients can respond differently to the same medicine	
Anti-Depressives (SSRI´s)	62%
Asthma Drugs	60%
Diabetes Drugs	57%
Arthritis Drugs	50%
Alzheimer´s Drugs	30%
Cancer Drugs	25%



Percentage of the patient population for which
a particular drug in a class is effective on average

Individualizing care to every patient will:

Reduce Costs

- Cost of side effects
- Continued care costs
- Cost of ineffective treatment

Improve Quality

- Reduce side effects
- Select the best therapy for each patient

Source: Brian B. Spear, Margo Heath-Chiozzi, Jeffrey Huff, „Clinical Trends in Molecular Medicine – Volume 7, Issue 5, 1st May 2001; Pages 201-204

A Healthcare Solution: Knowledge-based Medicine

Key role for data mining

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DATA

- *Vast amounts of digital patient data available*
- Images, Labs, Text, Demographics, Patient risk factors, …
- Genomics, Proteomics will worsen data overload

KNOWLEDGE

- *Explosion in the amount of medical knowledge*
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- **Knowledge Utilization**
- **Knowledge Discovery**

THERAPY

- *Many promising therapies.*
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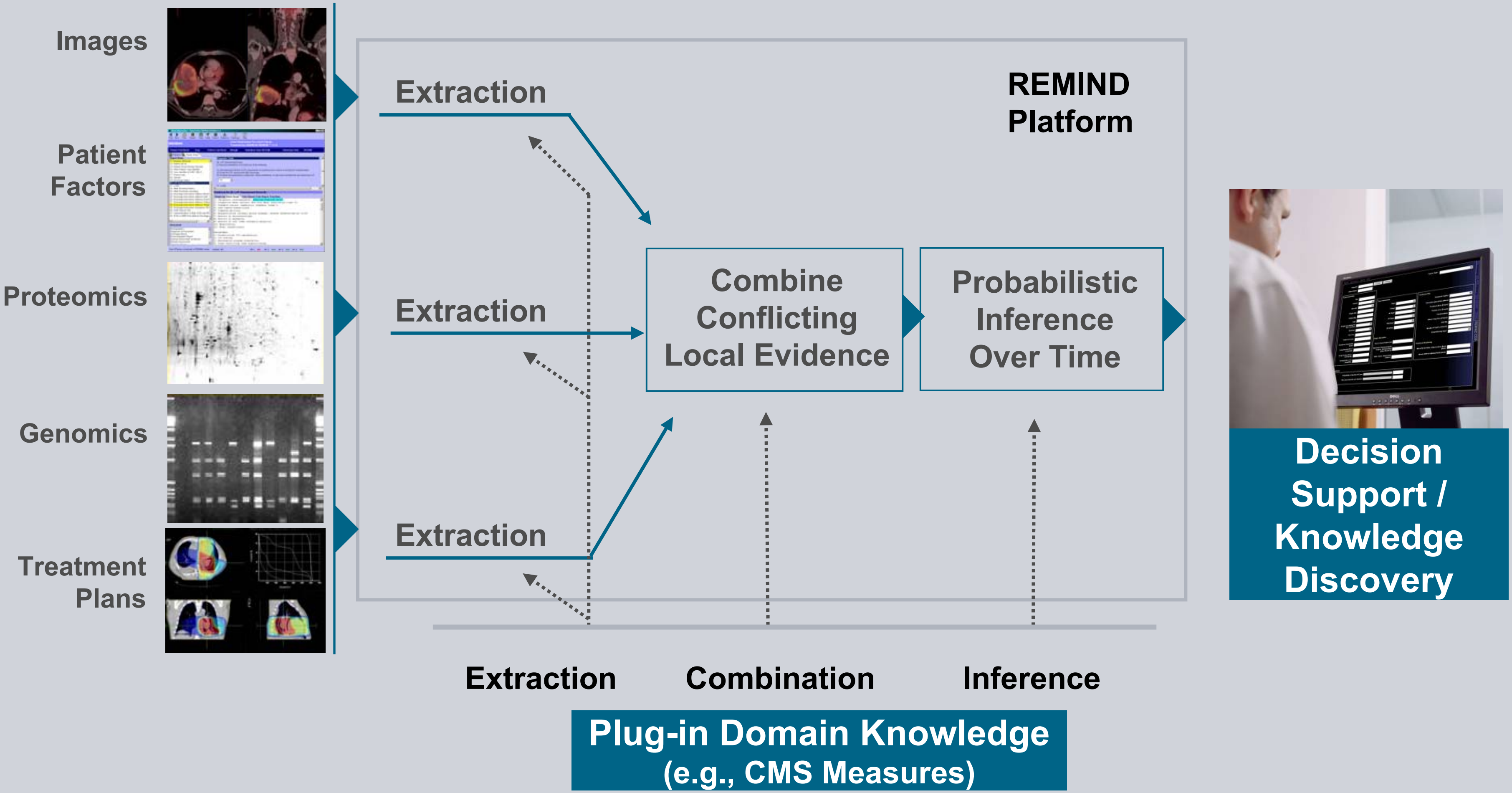
Two aspects of Data Mining to drive *Knowledge-Based Medicine*

- Knowledge Utilization
  - Knowledge-driven decision support
  - Data aggregation from disparate sources
  - Inject knowledge (e.g., guidelines, mined models) via Probabilistic inference
  - Present conclusive findings
- Knowledge Discovery
  - Combine clinical, lab, pharma, text, imaging & genetic information
  - Discover predictive models
  - ... from multi-institution data
  - Enable increasing personalization of care

REMIND Knowledge Platform*: Architecture

Reliable Extraction & Meaningful Inference from Nonstructured Data



*Not considered a Medical device.

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Outline

- The Healthcare Problem
- Knowledge Solutions
  - Computer Aided Diagnosis
  - Automated Quality Measurement
  - **Individualized Medicine**
- Rapid Learning Systems: Healthcare
- Focus on patient privacy
- Conclusions

Knowledge Solutions @ Siemens Healthcare

What are the different product lines?

DETECT

- **Computer Aided Diagnosis**:
- Task: *Analyze medical Images to identify abnormalities*
  - **Products**: Classifier solutions for detection of cancers (lung, colon, breast), and cardiac abnormalities (PE, wall motion) deployed on multiple imaging modalities (X-Ray, CT, MR, ultrasound) at thousands of hospitals worldwide
  - Clinical approval (including FDA trial for LungCAD) in US & worldwide

MEASURE / IMPROVE

- **Quality Measurement & Improvement**
- **Task:** *Automatically measure adherence to quality guidelines and reduce cycle time for Quality Improvement*
  - Products / Cloud Services: Semi- automated EMR mining solution sold to ~300 US hospitals. Helps them qualify for ARRA meaningful use incentives.

PREDICT

- **Individualized Medicine** (Personalized Medicine)
- Task: *Mine all available patient data for risk prediction, therapy selection and patient prognosis*
  - Many research projects to develop predictive models, infrastructure.
  - **Example: 5-nation Euro-US *rapid learning* network to share data and learn personalized therapy selection models for lung cancer**

RB Rao, J Bi, G Fung, M Salganicoff, N Obuchowski, D Naidich. ""LungCAD: a clinically approved, machine learning system for lung cancer detection" KDD-2007: 1033-1037

Knowledge Solutions @ Siemens Healthcare

Research Challenges?

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DETECT

- **Computer Aided Diagnosis**:
  1. The breakdown of assumptions
  2. Highly unbalanced data
  3. Feature computation cost
  4. Incorporating domain knowledge
  5. No objective ground truth

MEASURE / IMPROVE

- **Quality Measurement & Improvement**
  1. Access data from multi-source, multi-vendor systems without standards
  2. Combine structured and unstructured (text, images) data
  3. Integrate knowledge (guidelines) into machine learning
  4. Knowledge Maintenance (Handle changes in guidelines)

PREDICT

- **Individualized Medicine**
  1. **All the above plus**
  2. **Discover new knowledge (comparative effectiveness)**
  3. **Variation of data capture / tests available / preparation / guidelines across institutions**
  4. **Incorporate genomic information***
  5. **Patient privacy (across institutions / across nations)**

R Seigneuric, MHW Starmans, G Fung, B Krishnapuram, DSA Nuyten, A van Erk, MG Magagnin, KM Rouschop, S Krishnan, RB Rao, CTA Evelo, AC Begg, BG Wouters, P Lambin. "Impact of supervised gene signatures of early hypoxia on patient survival," Radiotherapy and Oncology 83 (3), 374-382

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Outline

- The Healthcare Problem
- Knowledge Solutions
- Rapid Learning Systems: Healthcare
  - The promise of individualized medicine
  - Infrastructure
  - Machine learning
- Focus on patient privacy
- Conclusions

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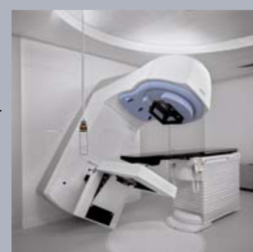
Example: Standard of Care Workflow for Rectum Cancer

- Today: Chemo-Radiotherapy (CRT) regimen followed by Rectal Surgery
- Rectal surgery is painful, with many side-effects
  - Morbidity: Colostomy, impotence, incontinence, plus surgery side-effects
  - Mortality

Diagnosis of Rectal Cancer

Pre-CRT Imaging + biomarkers



CRT: Chemo-Radio therapy

Rectal Surgery

2-year survival

Unfortunately, pCR is often hard to predict from pre-CRT data alone or detected pre-surgery via an imaging scan.

Pathologic Complete Response (pCR)
Upon resection after surgery, a significant number of tumors have a pCR, indicating that surgery may not have been needed.

Individualized Therapy workflow for Rectal Cancer*

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Combine pre- and post-CRT to personalize therapy

Identify the sub-population of patients for whom alternate therapy should be considered

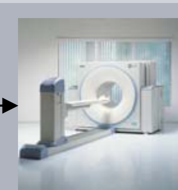
Diagnosis of Rectal Cancer

Pre-CRT Imaging + biomarkers

CRT: Chemo-Radio therapy

Surgery Decision Support

Prob (pCR) = high



Imaging follow-up / Alternate therapy

else

Rectal Surgery

2-year survival

Personalized Predictive model

Accurate Prediction of Survival & Side-effects (& Costs) helpful for rational decision-making

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C Dehing-Oberije, DD Ruysscher, A Baardwijk, S Yu, B Rao, P Lambin. "The importance of patient characteristics for the prediction of radiation induced lung toxicity," Radiotherapy and Oncology 91 (3), 421-426

How well do doctors predict outcomes?

Predict survival / sideeffects for NSCLC patients

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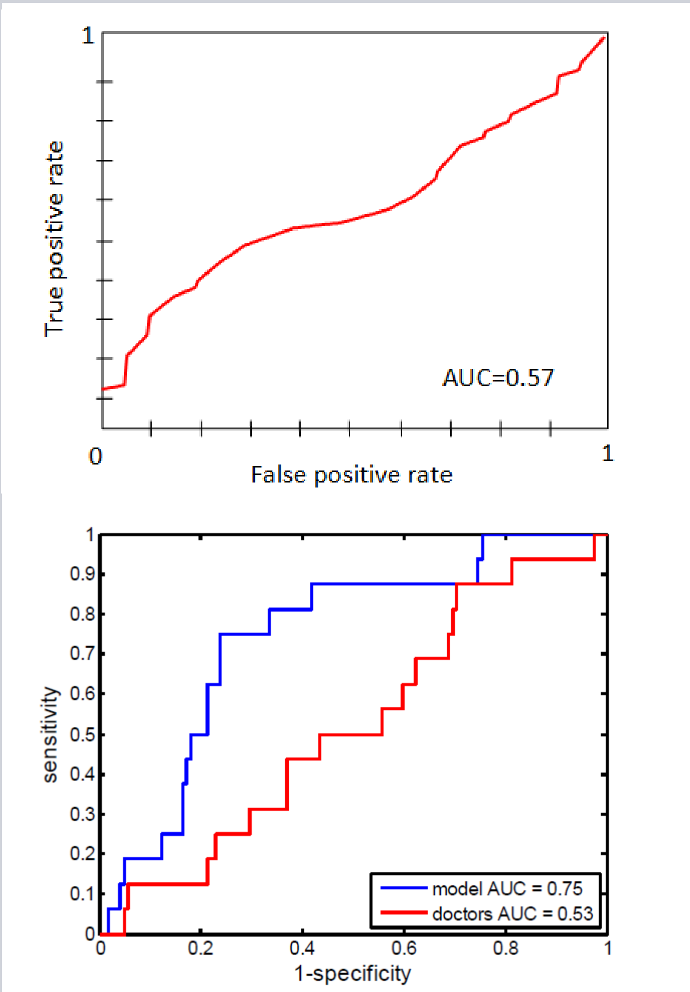


Non Small Cell Lung Cancer

Survival

- *2 year survival*
- 30 patients
- 8 MDs
- Retrospective
- **AUC: 0.57**

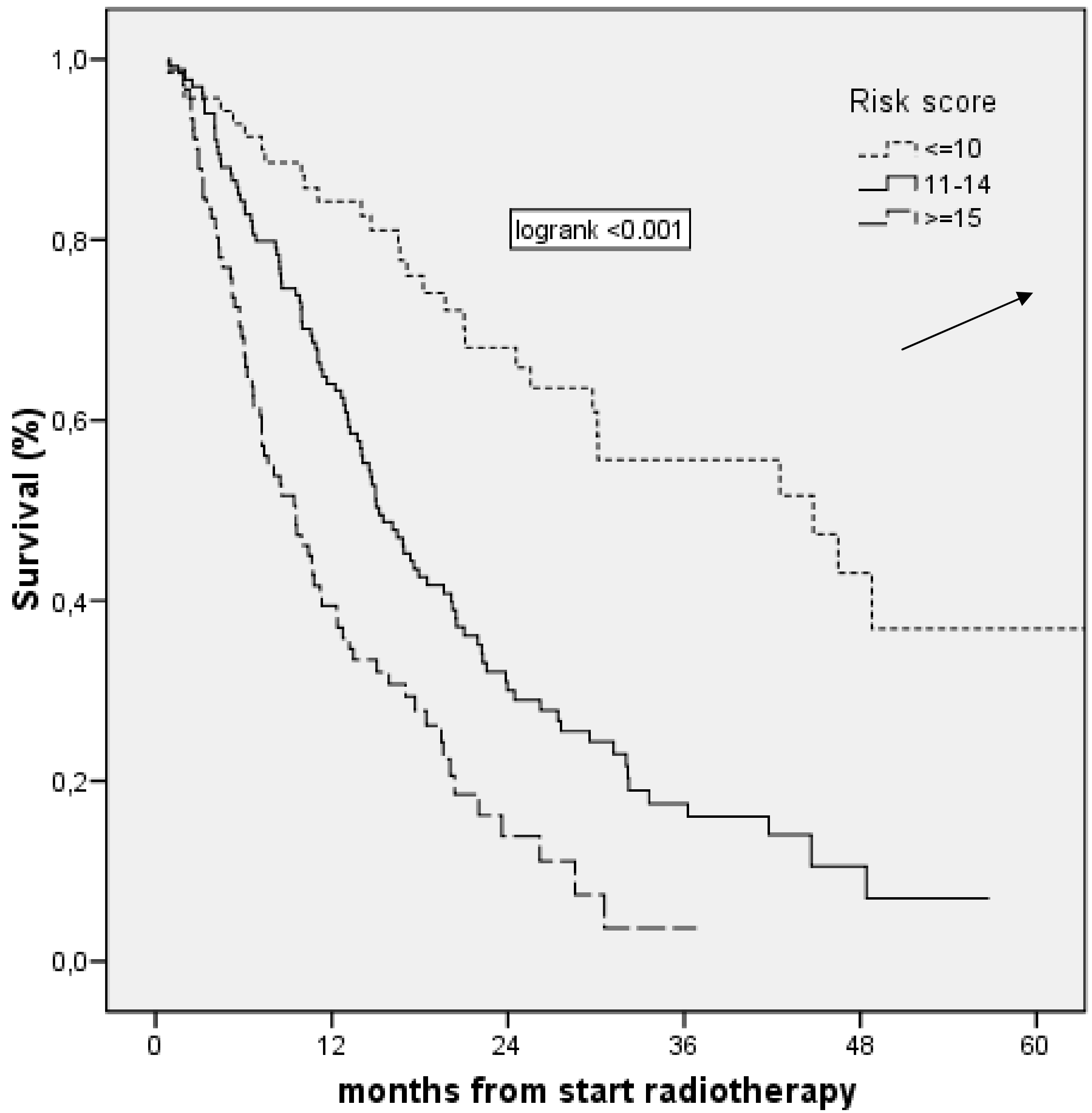
Side Effects

- *Esophagitis*
- 138 patients
- Prospective
- **AUC 0.53**

H. Steck, C. Dehing, H. van der Weide, S. Wanders, L. Boersma, D. de Ruysscher, B. Nijsten, P. Lambin, S. Krishnan, B. Rao. “Models Combining Clinical Data with Medical Knowledge are more Accurate than Doctors in Predicting Survival for NSCLC Patients,” ESTRO 2006.

How good is Survival prediction in NSCLC?

Standard staging vs. Rapid Learning System

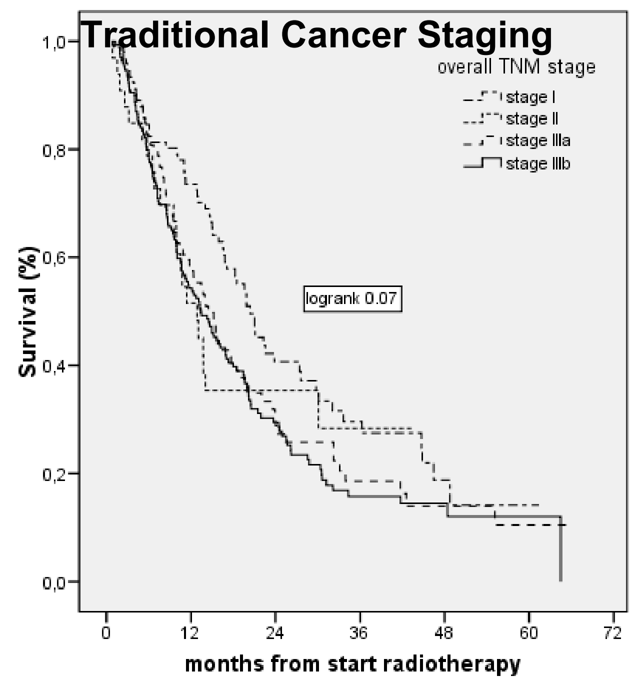


AUC 0.75

Stage IIIA 10 (14%)

Stage IIIB 13 (19%)

T4 12 (17%)



C Dehing-Oberije, S Yu, D De Ruysscher, S Meersschout, K Van Beek, Y Lievens, J Van Meerbeeck, W De Neve, B Rao, H van der Weide, P Lambin, "Development and external validation of prognostic model for 2-year survival of non-small-cell lung cancer patients treated with

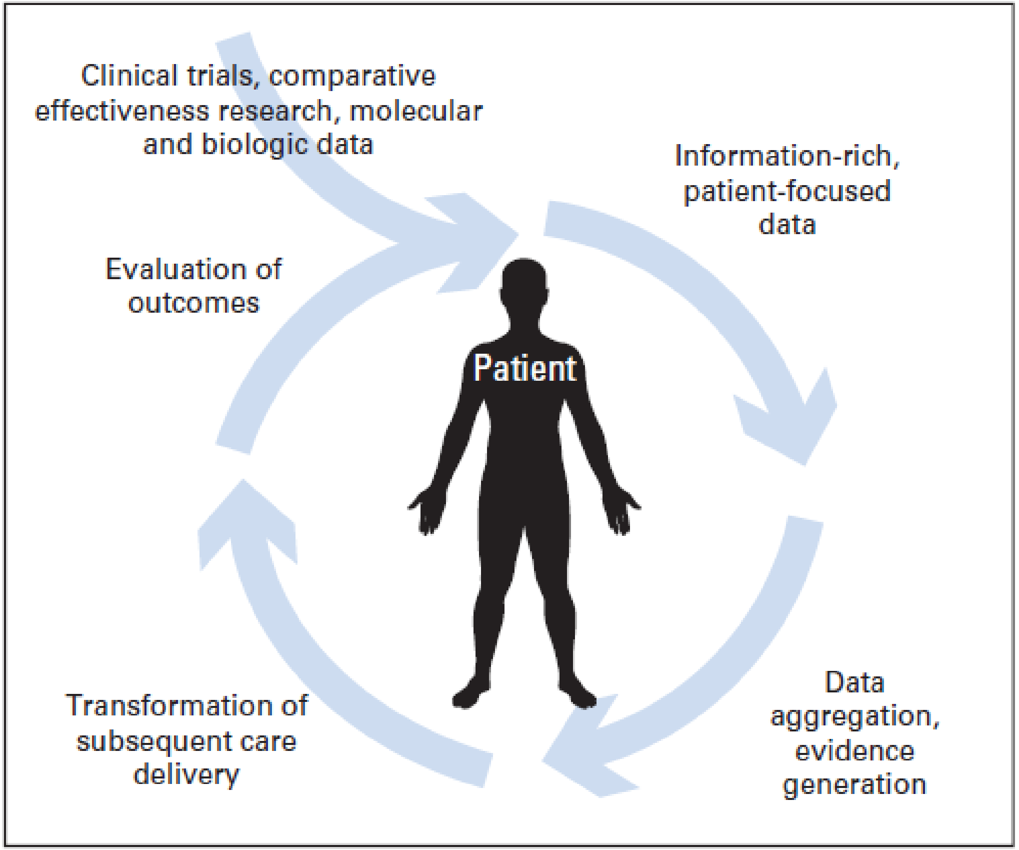
Rapid Learning System in Healthcare

Radical Notion

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

J Clin Oncol 2010;28:4268

- Traditionally, medicine advances via clinical studies: **evidence-based medicine**
- In the future, medicine could advance via rapid learning systems that learn from EMRs: **evidence-generated medicine**



EuroCAT: *A Rapid Learning System for Personalizing cancer care for NSCLC*

- Objectives: Clinical data sharing to facilitate
  - development of models that can predict patient survival and side effects as a function of all patient data and therapy.
  - Clinical trials for validation of model based personalized therapy selection
- Research collaboration with 5 hospitals across Netherlands, Belgium and Germany.
- Funded by grant from the InterReg region of EU
- More sites expected to join in the future.
- Siemens provides software to facilitate data capture & sharing across network

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Two aspects for this Rapid Learning System

- Theme 1: Build data sharing infrastructures
  - Integrated: euroCAT / duCAT / transCAT / Rome / EURECA
  - Imaging: Radiomics /QIN / caBIG/ TraIT
  - Genomics
  - **Preserve Patient Privacy**
- Theme 2: Machine learning for prediction modeling
  - **Privacy Preserving Data Mining**

Network 01/2012

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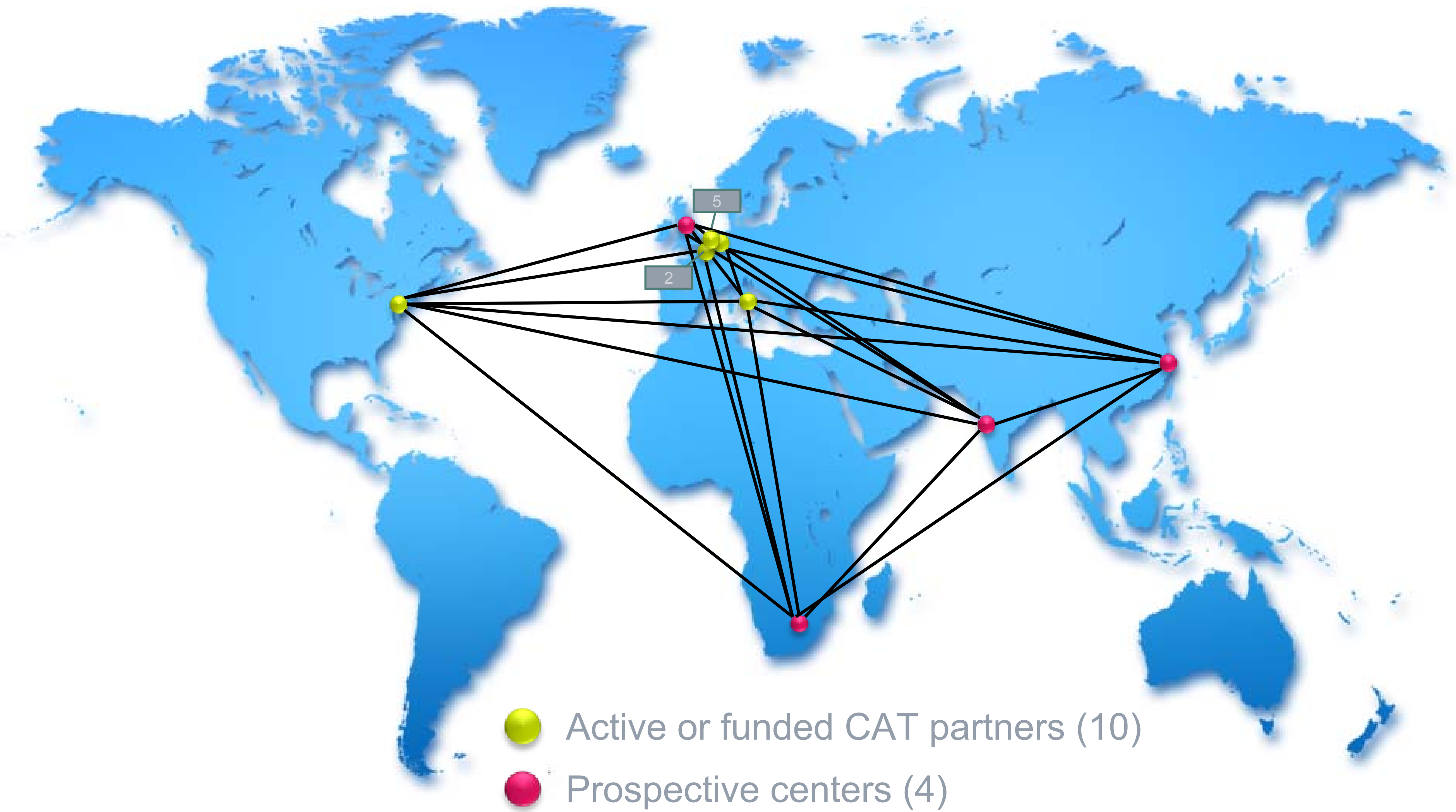

Map from cgadvertising.com

Outline

- The Healthcare Problem
- Knowledge Solutions
- Rapid Learning Systems: Healthcare
- Focus on patient privacy
  - Privacy preserving via random projections
  - Dealing with different data in each institution
  - Distributed learning
- Conclusions

Focus: 3 aspects of research

1. **Privacy preserving via random projections**
2. Dealing with different data in each institution
3. Distributed learning

A real scenario: Description of the Patient data

- Patients form three institutions:
  - 455 inoperable NSCLC patients, stage I-IIIB referred to MAASTRO clinic (Netherlands) to be treated with curative intent.
  - 112 Patients from Gent hospital (Belgium)
  - 40 patients from Leuven hospital (Belgium), were also collected for this study.
- Data collected Between May 2002 and January 2007
- Same set of clinical variables for all patients in all centers were measured:
  - Gender
  - WHO performance status
  - lung function prior to treatment (forced expiratory volume)
  - number of positive lymph node stations
  - GTV
  - dose corrected by time.

How do we use data from different institutions while preserving patient privacy?

Example: Cox Regression for Survival Analysis

- Cox regression, or the Cox propositional-hazards model, is one of the most popular algorithms for survival analysis
  - Defines a semi-parametric model to directly relate the predictive variables with the real outcome (i.e. the survival time)
  - Assumes a linear model for the log-hazard:

$$\lambda(t|\mathbf{x}_i) = \lambda_0(t)\exp[\mathbf{w}^\top \mathbf{x}_i]$$

- We propose privacy-preserving Cox regression (PPCox) which is based on random projection
  - Provides accurate classification
  - Does not reveal private information

$$\lambda_{\text{HPPCox}}(t|\mathbf{x}_i) = \lambda_0(t)\exp[\mathbf{w}^\top \mathbf{B}^\top \mathbf{x}_i]$$

How does this differ from commonly used random projection approach?

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- **Relative distance preservation**: Finds a projection that is optimal at preserving the properties of the data that are important for the specific (learning) problem at hand.
- **Lower dimensionality in the projected space**: Produces an sparse mapping to generate a PP mapping that projects the data to a lower dimensional
- **Lower dimensionality in the input space**: Provides explicit feature selection as it also depends on a smaller subset of the original features

S Yu, G Fung, R Rosales, S Krishnan, RB Rao, C Dehing-Oberije, P Lambin "**Privacy-Preserving Cox Regression for Survival Analysis**," KDD 2008 Pages 1034-1042.

Privacy Preserving Cox Regression

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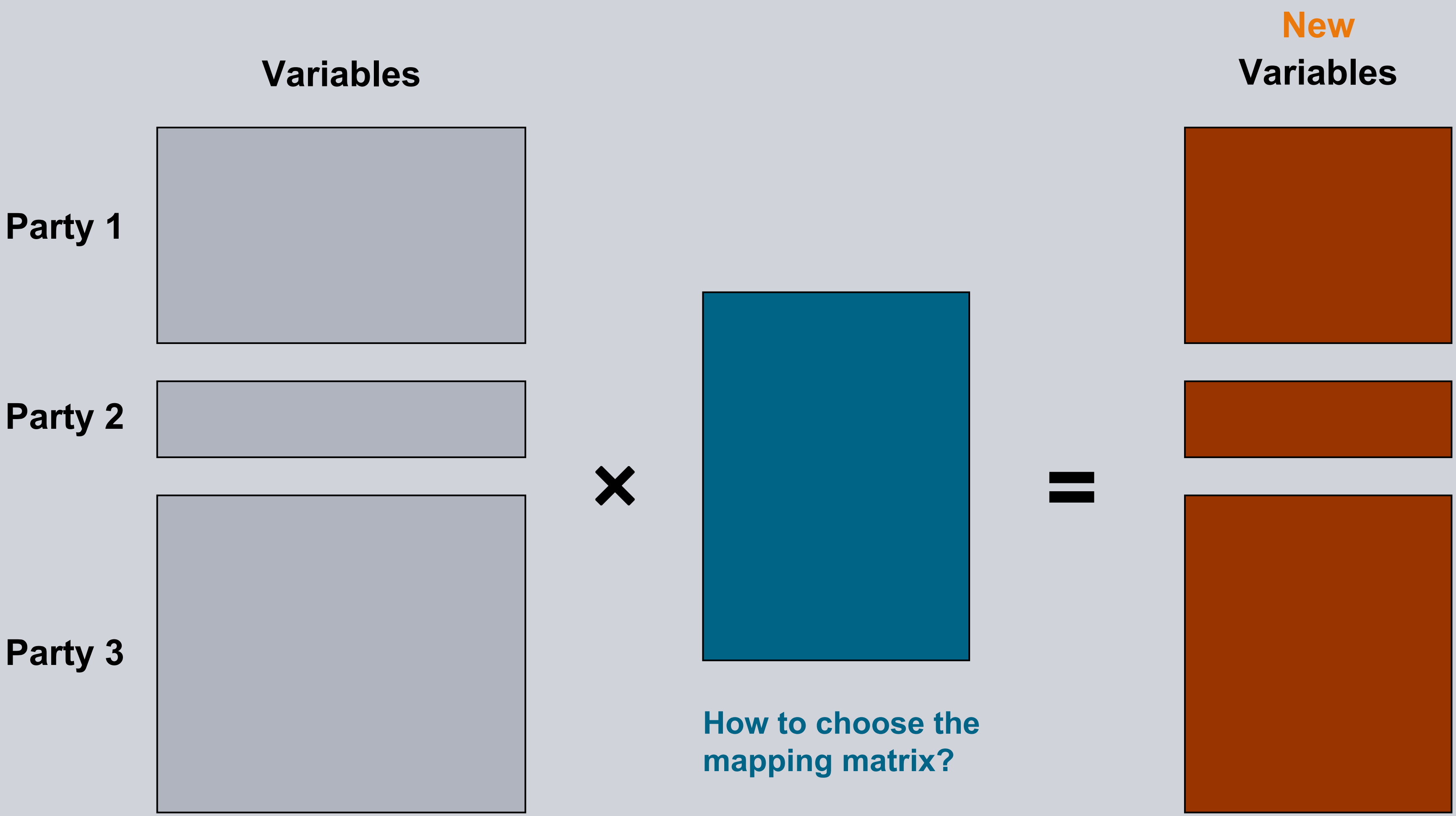
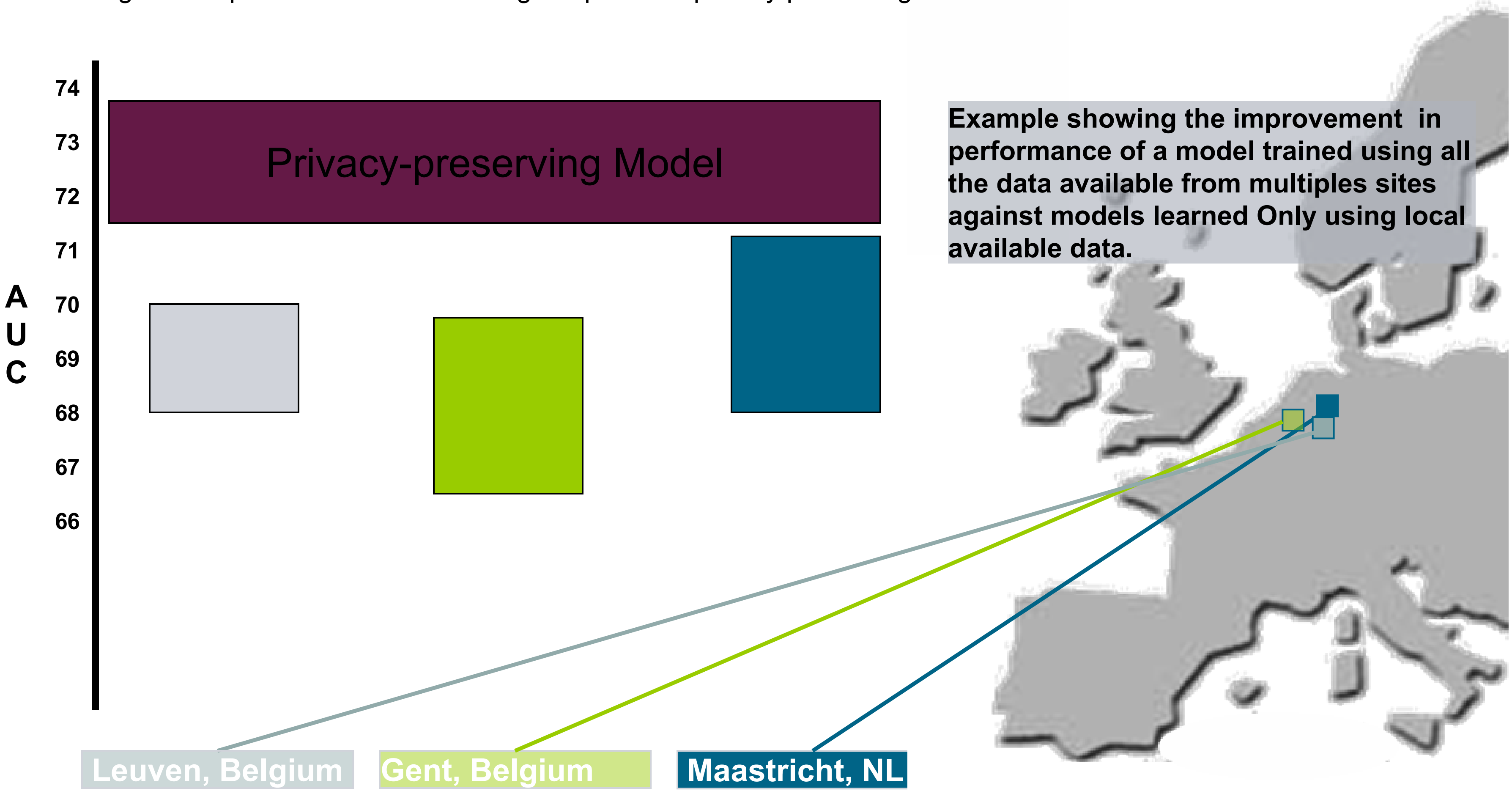


How to choose the mapping matrix?

[Yu et al, 2008]

Developing Privacy Preserving (PP) models for Survival

- We are using real data from several institutions across Europe to build models for survival prediction for non-small-cell lung cancer patients while addressing the potential privacy preserving issues



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Focus: 3 aspects of research

1. Privacy preserving via random projections
2. **Dealing with different data in each institution**
3. Distributed learning

C Dehing-Oberije, S Yu, D De Ruysscher, S Meersschout, K Van Beek, Y Lievens, J Van Meerbeeck, W De Neve, B Rao, H van der Weide, P Lambin, "Development and external validation of prognostic model for 2-year survival of non-small-cell lung cancer patients treated with chemoradiotherapy," International Journal of Radiation Oncology* Biology* Physics 74 (2), 355-362

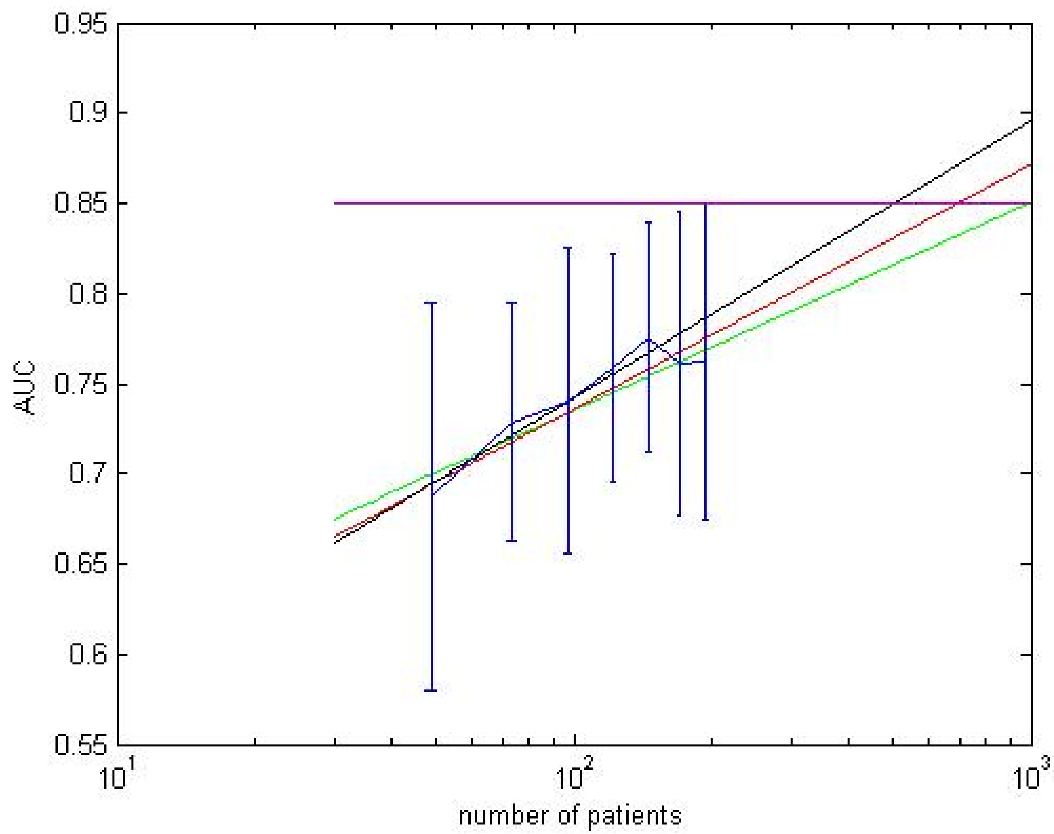
S Yu, C Dehing-Oberije, D De Ruysscher, K Van Beek, Y Lievens, J Van Meerbeeck, W De Neve, G Fung, B Rao, P Lambin "Development, external validation and further improvement of a prediction model for survival of non-small cell lung cancer patients treated with (Chemo) radiotherapy," International Journal of Radiation Oncology* Biology* Physics 72 (1), S60-S60

How to learn better?

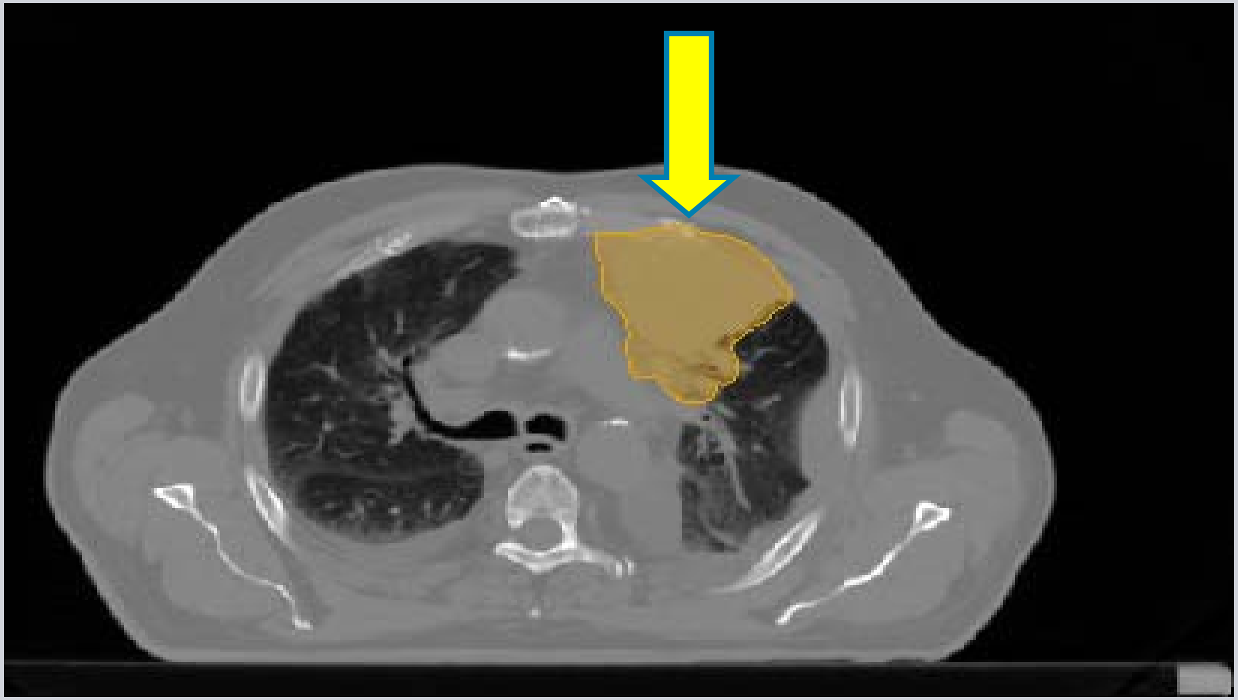
- AUC of 0.85 is minimal
- Survival model AUC 0.75

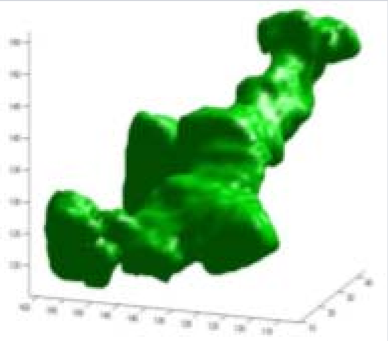
- More patients
- More variables
- Diversity

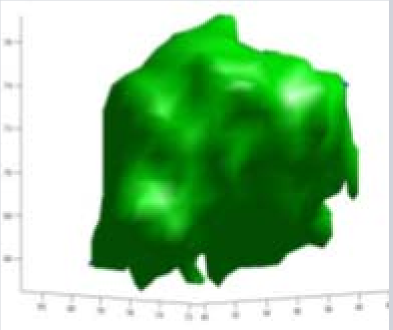
But….
As we increase the # of variables the variation of data stored at hospitals grows non-linearly

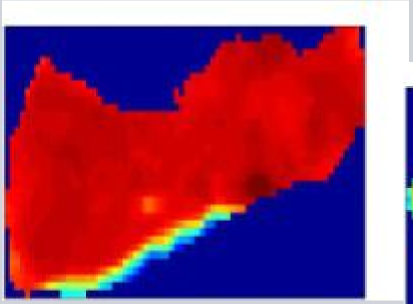


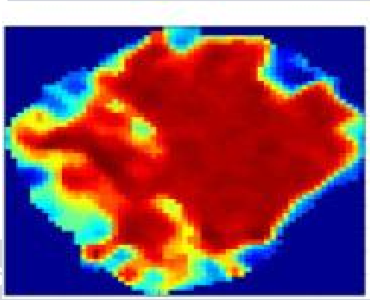
More variables from a simple CT





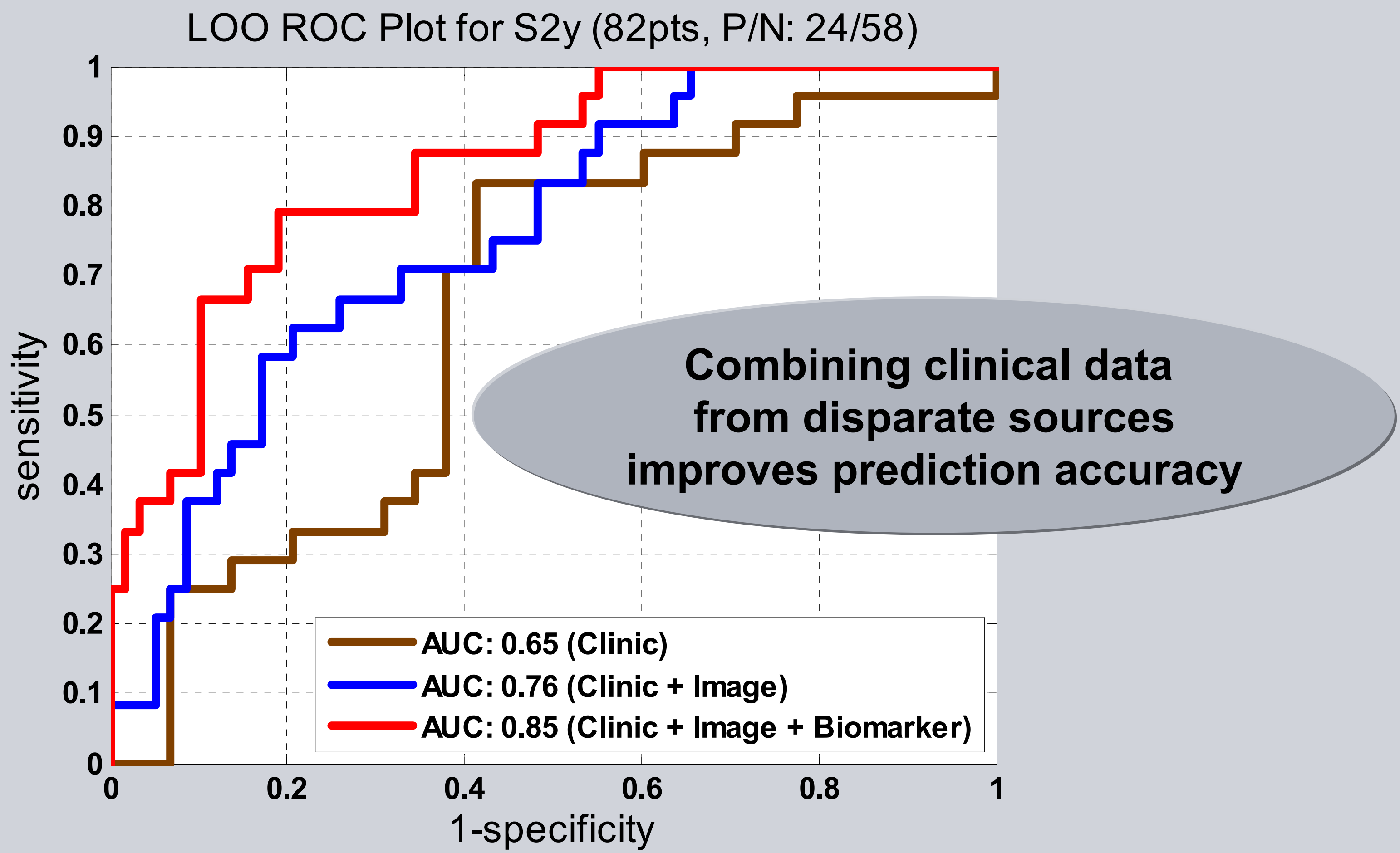






Knowledge Discovery: Learning Combined Diagnostics

Does incorporating more data help? (Collaboration with MAASTRO)



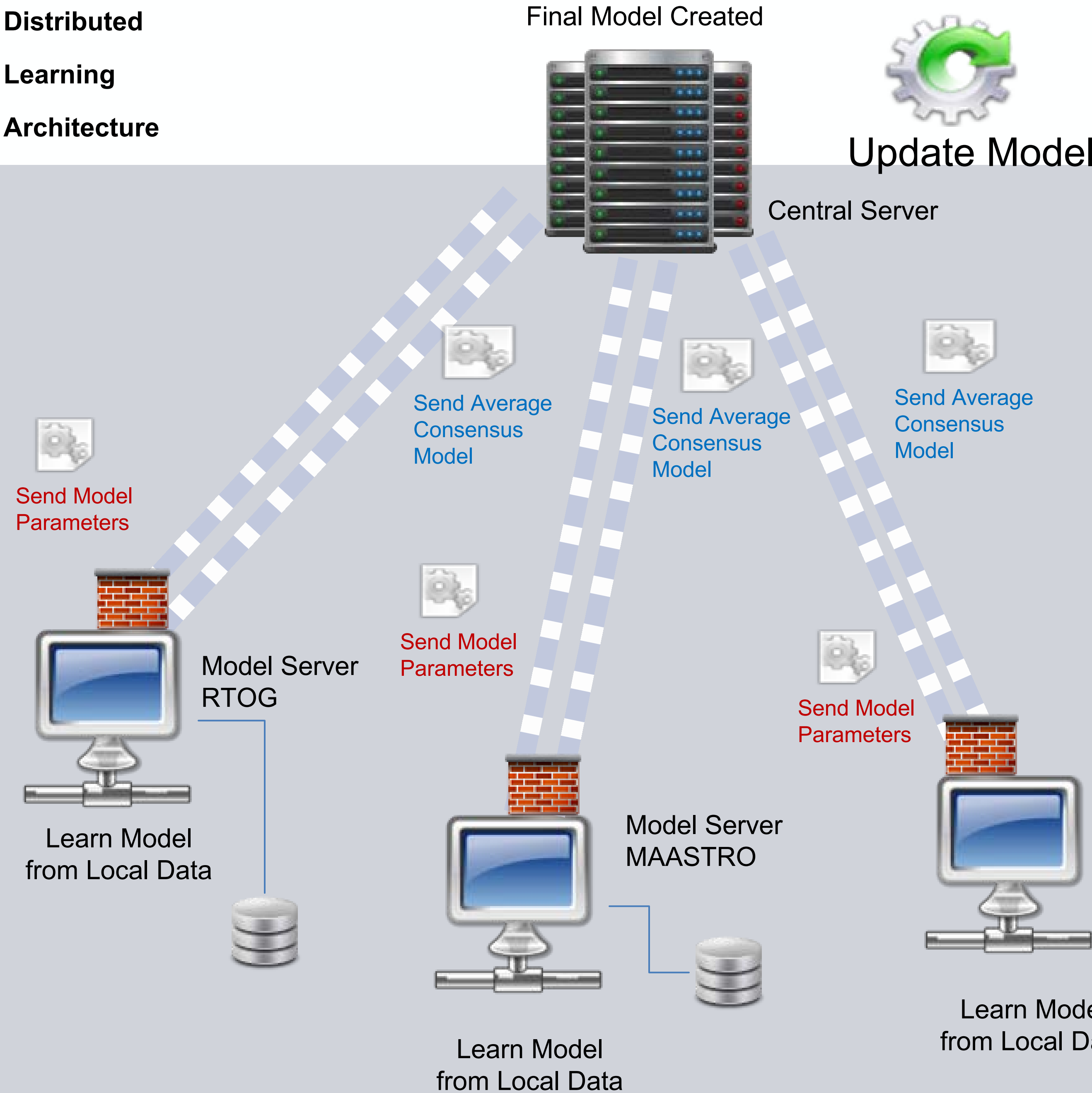
S. Yu, C. Dehing-Oberije, D. De Ruysscher, K. van Beek, Y. Lievens, J. Van Meerbeeck, W. De Neve, G. Fung, B. Rao, P. Lambin, "Development, External Validation and further Improvement of a Prediction Model for Survival of Non-Small Cell Lung Cancer Patients treated with (Chemo) Radiotherapy,", ASTRO 2008

Focus: 3 aspects of research

1. Privacy preserving via random projections
2. Dealing with different data in each institution
3. **Distributed learning**

D. Gabay and B. Mercier, “A dual algorithm for the solution of nonlinear variational problems via finite element approximations,” *Computers and Mathematics with Applications*, vol. 2, pp. 17–40, 1976

Distributed Learning Architecture



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

Focus: 3 aspects of research

1. Privacy preserving via random projections
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3. Distributed learning

- **Putting it all together**

Example: Standard of Care Workflow for Rectum Cancer

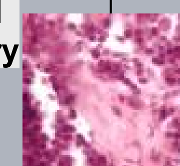
- Today: Chemo-Radiotherapy (CRT) regimen followed by Rectal Surgery
- Rectal surgery is painful, with many side-effects
  - Morbidity: Colostomy, impotence, incontinence, plus surgery side-effects
  - Mortality

Diagnosis of Rectal Cancer

Pre-CRT Imaging + biomarkers

CRT: Chemo-Radio therapy

Rectal Surgery



2-year survival

Pathologic Complete Response (pCR)
Upon resection after surgery, a significant number of tumors have a pCR, indicating that surgery may not have been needed.

Unfortunately, pCR is often hard to predict from pre-CRT data alone or detected pre-surgery via an imaging scan.

Personalized Therapy workflow for Rectal Cancer*

Combine pre- and post-CRT to personalize therapy

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Identify the sub-population of patients for whom alternate therapy should be considered

Diagnosis of Rectal Cancer

Pre-CRT Imaging + biomarkers

CRT: Chemo-Radio therapy

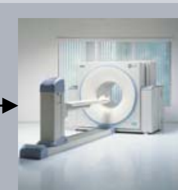
Post-CRT Imaging + biomarkers

Personalized Knowledge (IDS) for Decision Support
By comparing patient imaging / biomarkers pre-CRT with patient imaging / biomarkers post-CRT it is possible to predict pathologic complete response with high accuracy.

Personalized Companion Diagnositc IDS

Surgery Decision Support

Prob (pCR) = high



Imaging follow-up / Alternate therapy

else

Rectal Surgery

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Janssen MH, Ollers MC, Riedl RG, van den Bogaard J, Buijsen J, van Stiphout RG, Aerts HJ, Lambin P, Lammering G, "Accurate prediction of pathological rectal tumor response after two weeks of preoperative radiochemotherapy using (18)F-fluorodeoxyglucose-positron emission tomography-computed tomography imaging." Int J Radiat Oncol Biol Phys. 2010 Jun 1;77(2):392-9.

Network 01/2012

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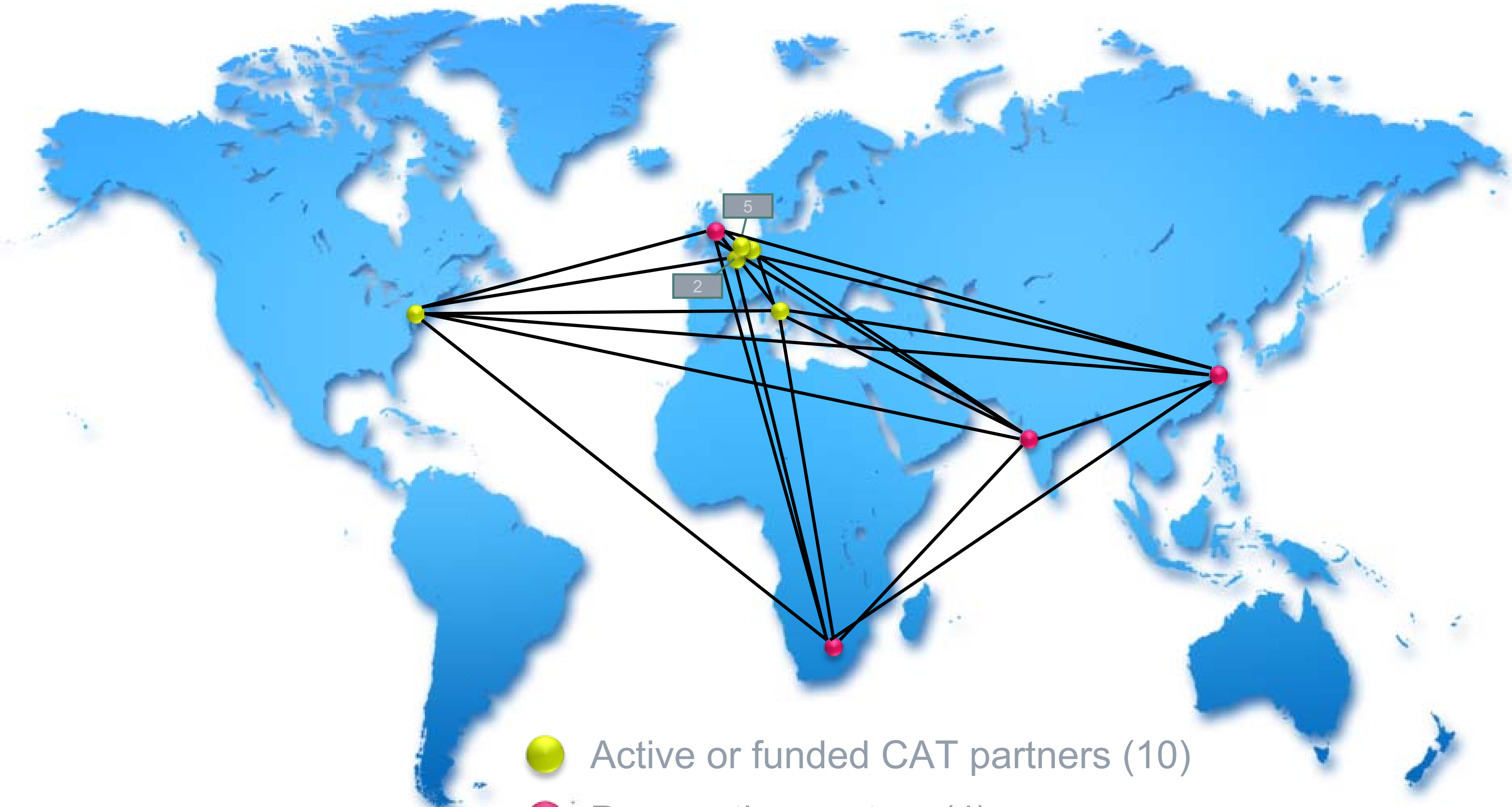


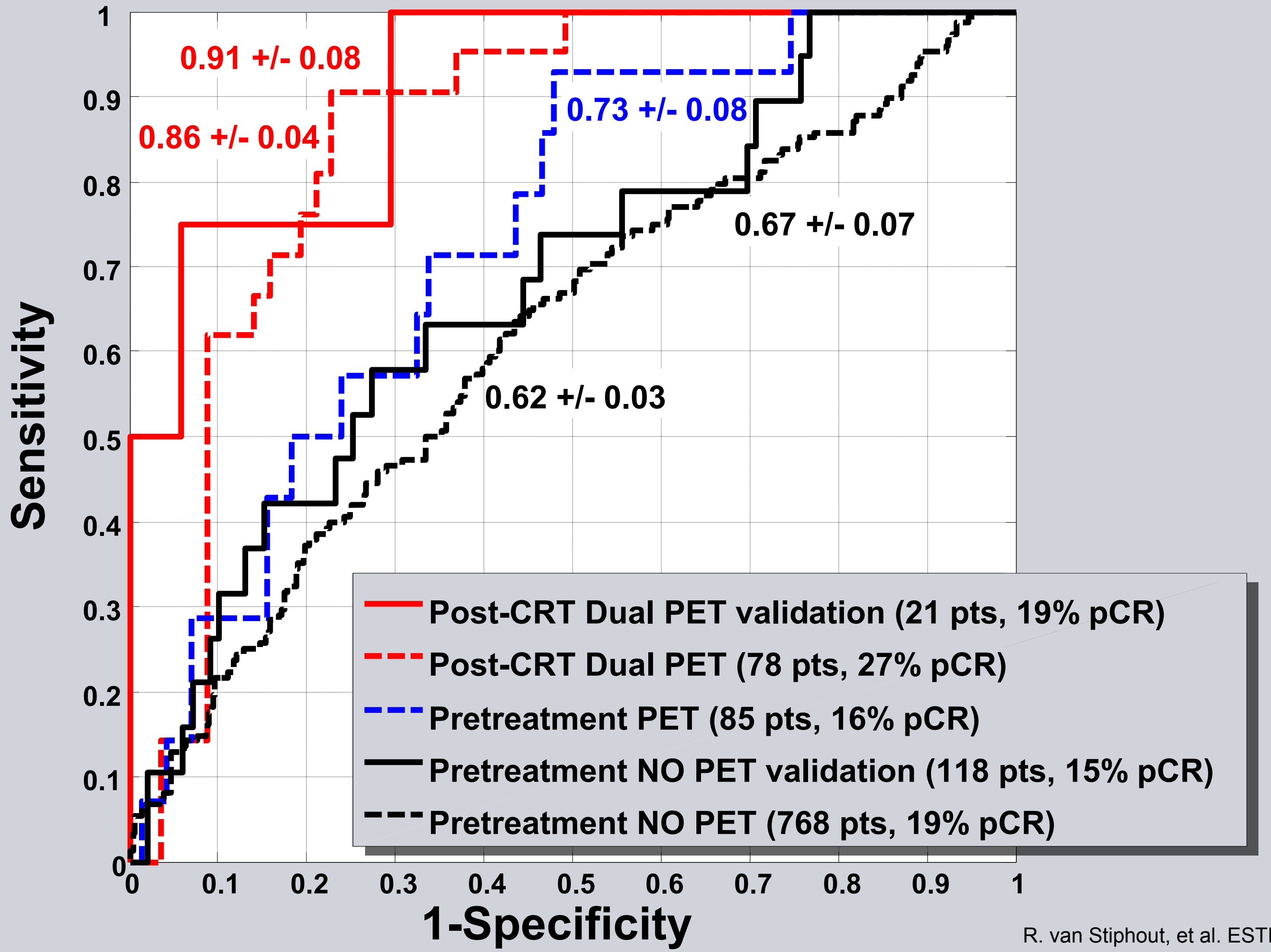
Active or funded CAT partners (10)

Prospective centers (4)

Map from cgadvertising.com

Experimental Results

Post-CRT Dual PET vs Pretreatment PET only



R. van Stiphout, et al. ESTRO 2008.

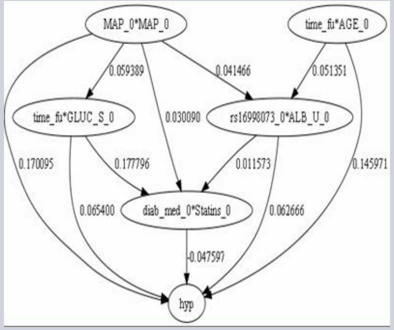
Creating Medical Knowledge

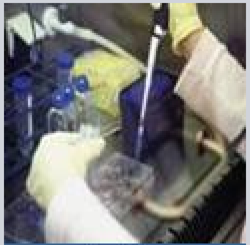
Mining large patient databases from multiple institutions

REMIND Platform

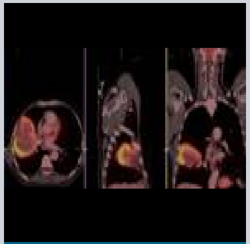
Data

Predictive Models



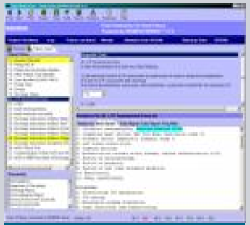


Labs



Images

Medication



Patient Factors

Genomics

Knowledge

Existing guidelines
for cancer therapy

Learned knowledge
- Predictive models discovered from patient data

www.predictcancer.org

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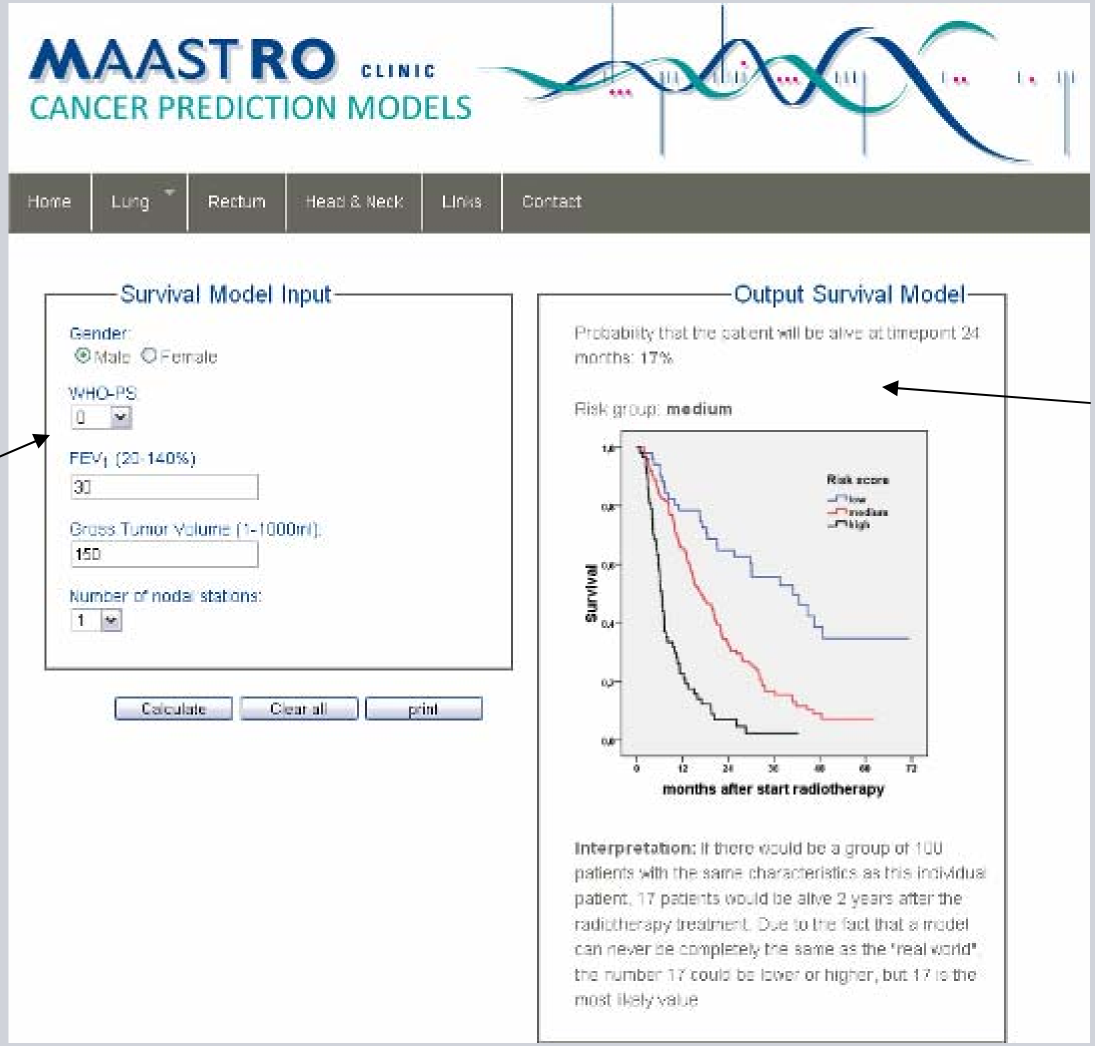
Available:
All published MAASTRO models (Lung, rectum, H&N)



Online input of patient data

Online calculation of probability of outcome and risk group stratification

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Challenges for Data Mining (Rapid Learning Systems) in Healthcare

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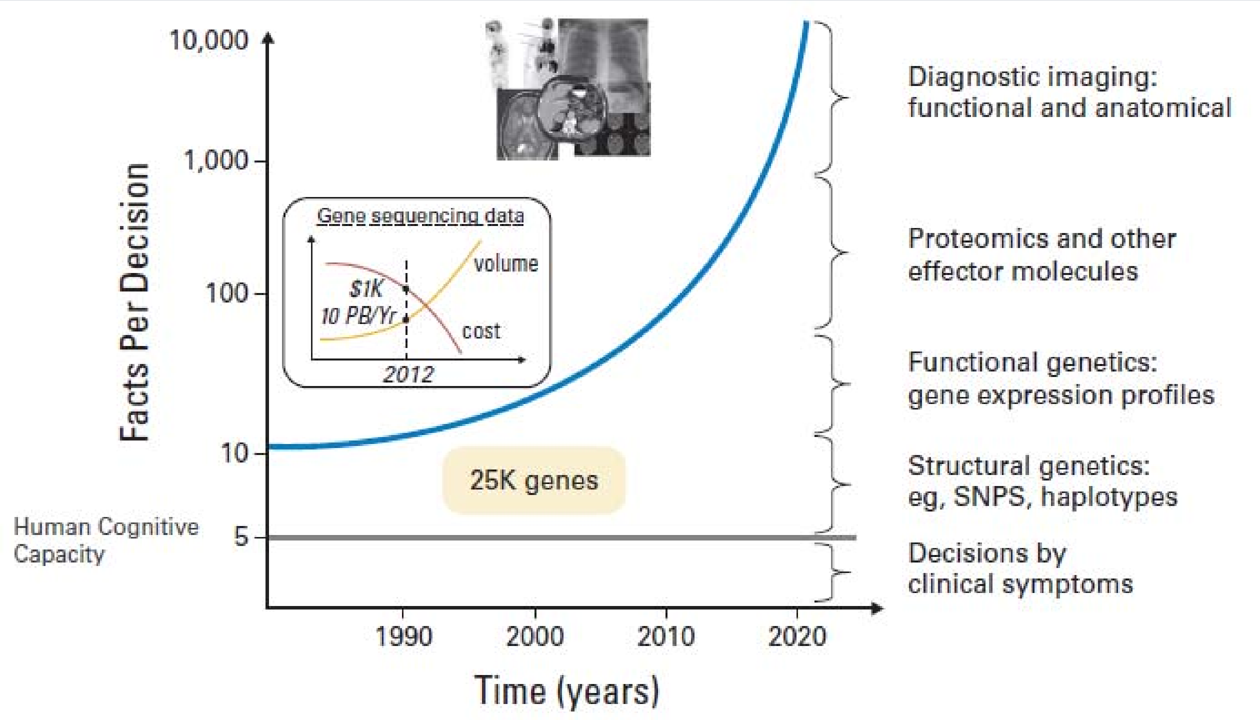
[..] the problem is not really technical […]. Rather, the problems are ethical, political, and administrative. Lancet Oncol 2011;12:933

1. Administrative (time)
2. Political (value, authorship)
3. Ethical (privacy)

4. Technical

Why is this so critical now?
Overload of data



- Explosion of data
- Explosion of decisions
- Explosion of 'evidence'*

*2010: 1574 & 1354 articles on lung cancer & radiotherapy = 7.5 per day

A Healthcare Solution: Knowledge-based Medicine

Key role for data mining

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DATA

- *Vast amounts of digital patient data available*
- Images, Labs, Text, Demographics, Patient risk factors, …
- Genomics, Proteomics will worsen data overload

KNOWLEDGE

- *Explosion in the amount of medical knowledge*
- Estimated to double every 18-36 months

- **Knowledge Utilization**
- **Knowledge Discovery**

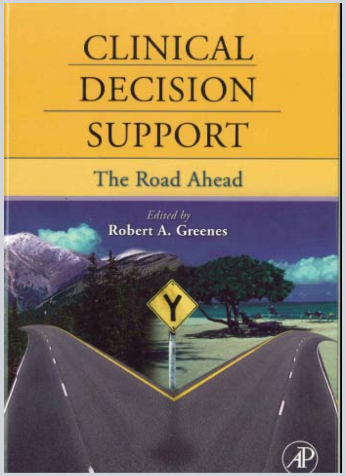
- *Many promising therapies.*
- 1000s of drugs with genetic indications in FDA pipeline
- Hard to implement @ poc

THERAPY

Personal Opinion

It will become *unethical* to ask Doctors to make, on their own, complex decisions.

We need a validated "decision support system"



…based *on all* the available data

P, Lambin et al, "The ESTRO Breur Lecture 2009" Radiotherapy & Oncology Volume 96, Issue 2 , Pages 145-152, August 2010

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More info on: www.predictcancer.org www.cancerdata.org www.eurocat.info www.mistir.info

To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and cure of disease—these are our ambitions.

Sir William Osler, 1849–1919

Father of Modern Medicine