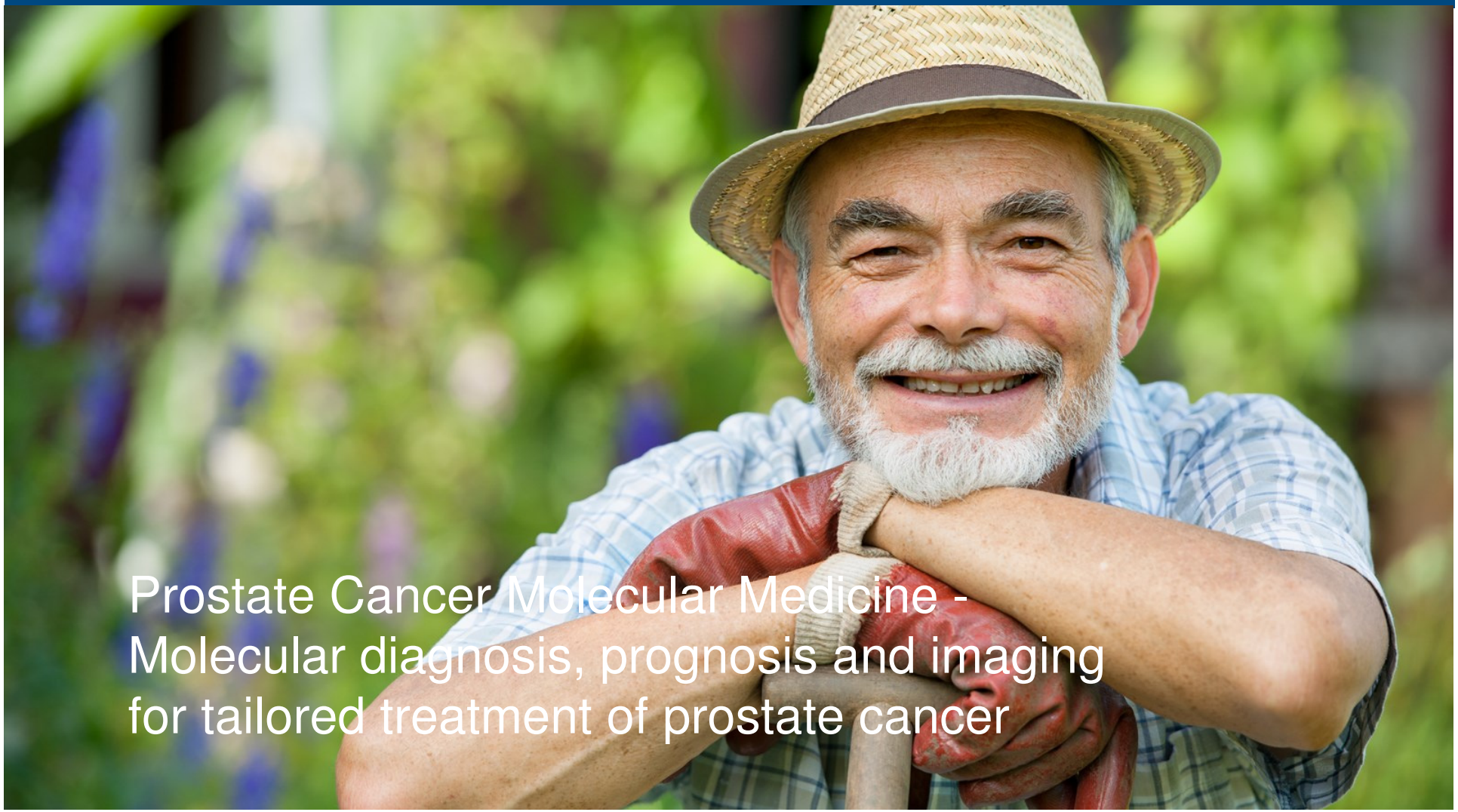
pcmm
a ctmm project

Center for Translational
Molecular Medicine

Translating science into better healthcare



Prostate Cancer Molecular Medicine - Molecular diagnosis, prognosis and imaging for tailored treatment of prostate cancer

Executive Summary

Prof. Dr. C. Bangma (EMC)

Principal Investigator of the PCMM consortium

PCMM has shown that an integrated approach by experts of various background leads to improvements in the clinical pathway of men at risk for, or having prostate cancer. The proper understanding between academia and industry is pivotal to make this progress now, and in the years to come.

Prostate cancer is a major cause of death of men in the Western world. It can be treated by radiotherapy or surgical removal of the prostate, but a substantial number of patients suffer relapse due to metastatic tumours for which only palliative therapy is available. The Prostate Cancer Molecular Medicine (PCMM) project has addressed two major clinical needs through a multi-disciplinary consortium composed of academic hospitals, biomarker and imaging research groups, and diagnostics, technological and pharmaceutical companies. The first need is the reduction of overdiagnosis and overtreatment of prostate cancer due to today's less than ideal diagnostic tests. The second need concerns better therapy monitoring tools for advanced disease. For this purpose, PCMM has developed novel diagnostic and prognostic biomarkers and targeted imaging tools.

The **PCMM Biomarker Programme** has delivered the following novel biomarkers:

- Quattro/*Select* MDx, a gene panel for diagnosis of prostate cancer in patient urine
- PDE4D7, a cAMP degrading phosphodiesterases gene for the prognosis of prostate cancer
- A set of tissue markers to discriminate between non-aggressive and aggressive tumours.

Besides these markers, Next Generation Sequencing (NGS) has resulted in the identification of novel recurrent and rare genomic features for which future research will define their true potential in clinical care of prostate cancer.

The **PCMM Imaging Programme** has delivered the following novel tools with preclinical proof-of-concept for therapy monitoring:

- Stabilized peptide based bombesine analogues using multimerization
- An antibody-based tool for PSMA-targeted imaging, outperforming current clinical standards in preclinical models
- Novel nanobodies for antigen-targeted imaging with proof of concept for PSMA
- 18F-labelled enzalutamide for androgen receptor targeted imaging

Next to these tools, PCMM will provide clinical proof-of-concept for androgen receptor targeted imaging as an early therapy response marker in patients with castration-resistant prostate cancer treated with enzalutamide through the recently initiated FuTuRe patient trial.

As a **supporting infrastructure** for its research programmes, PCMM has created a Dutch prostate cancer biobank composed of biomaterials from over 400 men with various stages of prostate cancer. This biobank is coupled to a database containing clinical, imaging, pathology and experimental data. For the integration of data, PCMM has closely collaborated with the CTMM TraIT project.

Through the delivery of novel diagnostic, prognostic and therapy monitoring tools, PCMM contributes to the worldwide need to improve the quality of life for a growing number of men diagnosed with prostate cancer and to develop tailored treatment for these patients. Furthermore, the PCMM biobank will be of great value for the future validation of novel biomarkers for prostate cancer, the continuous optimisation of methods for clinical imaging analysis, as well as the integration of biomarkers and imaging data into a future clinical decision support system to enhance prostate cancer care.

Translational Concept

PCMM has addressed the major clinical needs in prostate cancer through the development and validation of novel diagnostic and prognostic biomarkers, and of targeted molecular imaging for the guidance of tailored treatment in the hormone-refractory phase of the disease.

PCMM Biomarker Programme

Candidate genomic, proteomic and metabolomic markers found by profiling or already identified promising candidates were evaluated for their diagnostic or prognostic value in blood, urine or tissue. The most promising markers were selected for the development of a marker assay to be used for marker validation in clinical cohorts from the PCMM biobank and other biorepositories.

PCMM Imaging Programme

Molecular probes were constructed for molecular imaging by PET, SPECT and bio-optical imaging using innovative immunological techniques including pre-targeting antibodies, antibody fragments, nanobodies and small molecules as well as chemical techniques. The novel imaging tools have been validated for their use in improving the detection and characterisation of local and/or distant metastases and in therapy response monitoring in castration-resistant disease.

PCMM Clinical Support and Assessment

A Dutch multicentre prospective biobank has been established that contains blood, urine, tissue and integrated clinical, imaging and experimental data from patients with various stages of prostate cancer. This unique infrastructure allows for the validation of the novel biomarker and imaging tools developed within PCMM. Medical Technology Assessment experts provide support to decide on the selection of the most promising biomarkers and molecular imaging techniques for clinical introduction.

Clinical Need

- Reduction of overdiagnosis due to suboptimal current clinical standards
- Reduction of overtreatment due to the lack of tools to discriminate accurately between non-aggressive and aggressive tumours
- Improved treatment monitoring to assess therapy response and to support drug development

Tools

- Genomic, proteomic and metabolomic profiling in blood, urine and tissue to identify biomarkers
- Targeted validation of pre-selected biomarker candidates
- Gastrin-Releasing Peptide Receptor targeted imaging
- Tagged antibody-based imaging using an anti-PSMA monoclonal antibody
- Targeted imaging using nanobodies against prostate cancer-selective cell surface antigens
- Androgen receptor (AR)-targeted imaging
- Multicentre prostate cancer biobank with biomaterials and clinical, imaging and experimental data

Public-Private Partnership

GENERATE KNOWLEDGE…

…TRANSLATE INTO APPLICATIONS

…NEW CURE/CARE SOLUTIONS

SCIENCE

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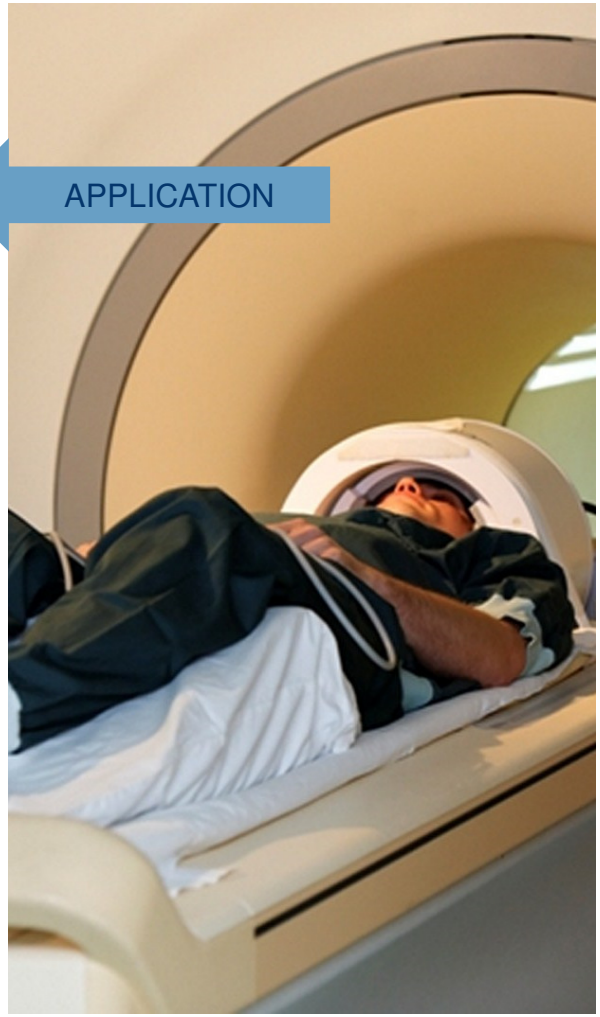
APPLICATION

PATIENT

New biomarker and imaging tools to improve diagnosis, prognosis of primary prostate cancer, and therapy response prediction of metastatic, hormone-refractory prostate cancer



Academic partners

Supporting Foundations

Industrial partners

Organization and Partners

ADVICE

Advisory board
ISAC CTMM

DECISIONS

SteeringCie
Partner Representatives
CTMM

Project Team
PI Prof. C. Bangma (EMC)
Dr. E. Schenk (EMC)
WP leaders (various)
Industrial partners (various)
Dr. E. Caldenhoven (CTMM)

OPERATIONS

CTMM

Partners
Coordination
Finance
Publications

Workpackage leaders

WP1: Prof. G. Jenster (EMC)
WP2: Prof. I-J. de Jong (UMCG)
WP3: Dr. H. Obbink (Philips),
Dr. T. Hulsen (Philips)

Budget: CTMM manages the flow of funds

Funding:
- 25% Academia
- 25% Industrial
- 50% Government Subsidy

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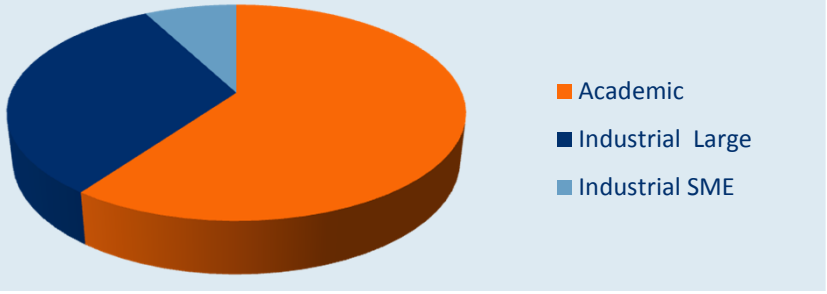
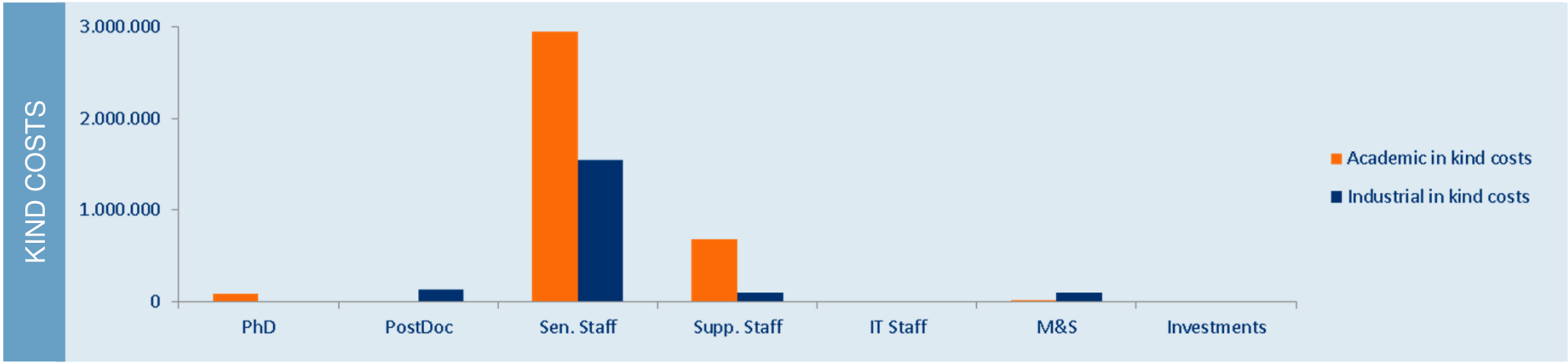
Project costs:
- Personnel
- Materials
- Use of existing equipment
- Investments
- Third parties
- Management (5%)

Facts & Figures

Budget	**14,1M €**
Start	**2008**
End	**2015**
Partners	**11**

Distribution of the PCMM consortium budgets to perform the R&D activities





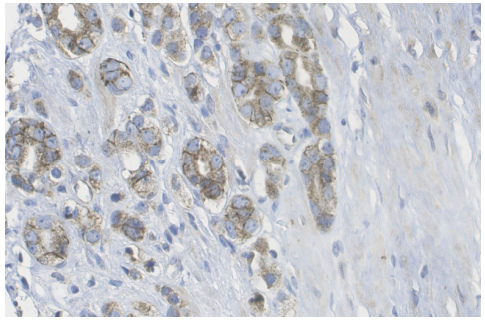
Facts & Figures

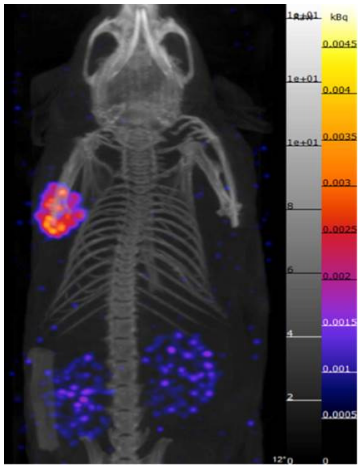
Budget	**14,1 M €**
Start	**2008**
End	**2015**
Partners	**11**
Persons	**68**
FTE	**82 (5 years period)**

Output	No	
Papers	37	5 papers in submission - mean impact factor all published PCMM papers: 5,0
Theses	8	5 planned for 2016
Personal grants	2	The Urinome Project: RNAseq of urine to identify diseases of the urogenital tract (Jenster (EMC), 85 keuro by SUWO), extension of the investigator-initiated trial FuTuRe (de Jong (UMCG), 200 keuro by Astellas)
Patent fillings	0	
Spin-off Companies	1	Acquisition of NovioGendix by MDxHealth (2015)
Raising Capital	5	NGS-ProToCol (Valorization Grant CTMM, 890 keuro), ProCaMolMed (Transition Grant CTMM, 750 keuro), Movember Global Action Plan 3 (Movember Foundation, 1,664 keuro), Eurostars 'EffiBody' (2,713 keuro) en KWF-Alpe dHuzes 'IMMPROVE' (2,015 keuro).
Awards	1	Movember Foundation Award Prof. Baillie (75 keuro)
Public Media	3	Press release 2010, article in Urograaf 2010, BBC News interview Prof. Baillie 2015

Scientific Value Creation - Breakthroughs

- 2011: CRISP-3 and beta-microseminoprotein in biopsies do not predict outcome after surgery, and ERG expression in surgery specimens is not associated with tumour behaviour (EMC).
- 2012: Multimerization improves targeting of peptide radio-pharmaceuticals (UMCG).
- 2012: A novel promising bombesin-based radiotracer allows for *in vivo* nuclear imaging of GRPR expressing prostate tumours (UMCG).
- 2013: Alpha6-integrin expression is a predictor for non-aggressive prostate cancer (EMC).
- 2013: The new anti-PSMA monoclonal antibody D2B allows for *in vivo* imaging of prostate cancer (RUNMC, UMCG, UNIVR)
- 2014: PDE4D7 is differentially expressed during prostate cancer progression (Philips, UGLA).
- 2014: NGS identifies novel recurrent and rare fusion events in prostate cancer (EMC, Philips).
- 2014: Arachidonic acid pathway is associated with prostate cancer progression (EMC).
- 2014: Novel serum and urine biomarkers add to the predictive ability of risk prediction models for prostate cancer (EMC).
- 2014: Dual-modality imaging with an anti-PSMA monoclonal antibody enables image-guided surgery (RUNMC, UMCG).
- 2015: The urinary three-gene panel HOXC6, TDRD1 and DLX1 improves PSA-based diagnosis of aggressive prostate cancer (RUNMC, NovioGendix/MDxHealth).
- 2015: PDE4D7 expression is increased in tumours with TMPRSS2-ERG (EMC, Philips, UGLA).
- 2015: Radiosynthesis procedure of a high affinity AR ligand 18F-Enzalutamide and preclinical evaluation (UMCG, Astellas).

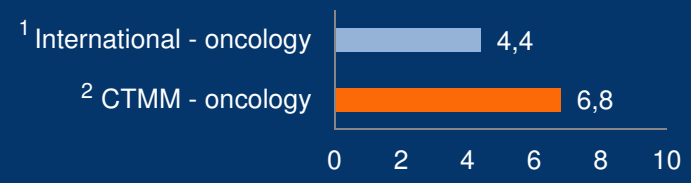




Highest Impact Papers – mean 11,6

1. Riley RD et al, PLoS Med. 2013;10(2):e1001380
2. Leening MJD et al, Ann Intern Med. 2014 Jan 21;160(2):122-31
3. Carlsson S et al, Eur Urol. 2013 Nov;64(5):693-9
4. Vedder MM et al, Eur Urol. 2014 Dec;66(6):1109-15
5. Lütje S et al, Cancer Res. 2014 Nov 1;74(21):6216-23

Mean Impact Factor



1 - Panaxea 2013. Steute et al Impact Analysis CTMM (internal report, paper in preparation).

2 - Mean impact factor based on 200 papers from the CTMM oncology first call projects.

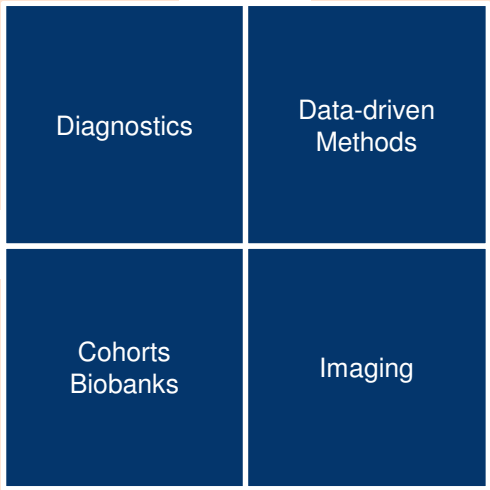
Scientific Value Creation - Theses

Thesis	Partner	Year
Giuseppe Carlucci	UMCG	2014
Hildo Ananias	UMCG	2014
Susanne Lütje	RUNMC	2014
Zilin Yu	UMCG	2014
Inês Teles Siefers Alves	EMC	2015
Marije Hoogland	EMC	2015
Maxim Rybalov	UMCG	2015
Moniek Vedder	EMC	2015
Hilde Hoving	UMCG	2016
Katja van Rij	RUNMC	2016
Kristell Chatallic	EMC	2016
Giovanny Rodriguez-Blanco	EMC	2016
René Böttcher	EMC	2016
R.J. Dost	UMCG	2016

Scientific Value Creation - Infrastructure

- Real time quantitative PCR for the analysis of the three gene panel Quattro/*Select* MDx in urine (RUNMC, NovioGendix/MDxHealth)
- Quantitative PCR for the analysis of the PDE4D7 gene marker PDE4D7 in urine and tissue from biopsies (Philips)
- Immunohistochemistry methods for the analysis of α6-integrin, EZH2, HELLS and ZIC5 in biopsies (EMC)
- NGS dataset for novel genomic features associated with prostate cancer (EMC, Philips)

- Bioinformatics for analysis of NGS data (EMC, Philips in collaboration with Technical University of Applied Sciences Wildau)
- Validation of method for prostate MRI reporting and annotation (Philips)
- Net Reclassification Risk graph for analysis of marker performance (EMC)
- Adapted MISCAN-Prostate microsimulation-model for analysis cost-effectiveness of addition of novel marker to PSA testing for prostate cancer screening (EMC)



- PCMM biobank, a Dutch multi-center collection of blood, urine and tissue from over 400 patients suspected of having prostate cancer, treated by surgery for localised disease or with castration-resistant hormone-refractory prostate cancer (EMC, NKI, RUNMC, UMCG)
- PCMM database with clinical, imaging (contrast-enhanced ultrasound and MRI), pathology, biobanking and experimental data from the patients in the PCMM biobank (EMC, NKI, RUNMC, UMCG, Philips)

- Stabilized peptide-based bombesine analogues (UMCG)
- GMP production process of18F-DHT radioligand for targeted AR imaging with clinical proof-of-concept (UMCG)
- Anti-PSMA monoclonal antibody D2B for dual modality imaging with preclinical proof-of-concept (RUNMC, UMCG, UNIVR)
- Anti-PSMA nanobody for targeted imaging of prostate cancer with preclinical proof-of-concept (EMC)
- Nanobody library for selection of human prostate cancer-selective cell surface binders for targeted imaging (EMC)
- 18F-enzalutamide radioligand radiosynthesis and preclinical evaluation (UMCG, Astellas)

Clinical and Economic Value Creation of PCMM

New 'products' for clinical care

Main Product Pipelines

	Discovery biomarkers	Selection of promising markers	Clinical & Experimental Verification	Final measurement platform/protocol	Clinical Validation platform
Genomic markers	Affimetrix platfom	40 biomarkers with RT-qPCR	4 gene panel selection in urine sediments. Kit validation and CE-registration	Validation in two multicentre cohorts	QUATTRO assay was LDT/CE-IVD tested
		PDE4D7 gene	multiplex PCR assay to run PDE4D7 and its reference gene in a single assay was developed (the PDE4D7 assay).	Clinical validation n=1500	*Prospective study financed by CTMM-ProCaMolMed*
	NGS (DNA and RNA)	*in collaboration with CTMM-NGS-ProToCol and TraIT*	*Not financed within CTMM*		
Protein markers	TMA platfom	Selection of 4 tissue markers	*Not financed within CTMM*		
Imaging markers		Gastrin releasing peptide receptor (GRPR)	PET tracers - Bombesin analogues	*Not financed within CTMM*	
		Pre-clinical validation anti-PSMA nanobodies	*Not financed within CTMM*		
	Androgen Receptor	IMPD	GMP	Clinical evaluation of AR targeted imaging in metastatic hormone naive and in mCRPC patients for early treatment respons and drug delivery.	

Select MDx - a urine test for the diagnosis of clinically significant prostate cancer

PRODUCT

Background: There is an urgent need for a test to detect clinically significant prostate cancer (PCa) to reduce overdiagnosis and overtreatment. Quattro, now known as Select MDx for prostate cancer, is an in vitro qPCR based test in which the mRNA expression levels of DLX1, HOXC6 and KLK3 are determined in male urine specimens obtained after Digital Rectal Examination (DRE). The results are used in a model which can predict the presence of clinically significant PCa.

Leading: NovioGendix/MDxHealth

Current Diagnostics: For more than two decades, serum PSA (sPSA) has been the marker for diagnosis of PCa. However, due to its low specificity, men with false-positive sPSA results undergo unnecessary biopsies. sPSA testing also leads to the identification of patients with clinically indolent disease, resulting in overtreatment. Current decision-making about potential PCa status and whether to biopsy or re-biopsy is not standardized, but depends on a variety of clinical factors (e.g., age, family history, race). A test with enhanced diagnostic specificity has the potential to reduce the uncertainty that is associated with this decision-making process.

SelectMDx

PARTNERSHIP

Progress obtained in translational pipeline

➢Biomarker discovery: GeneChip exon 1.0ST microarray platform (Affymetrix) and 100 frozen tissues (normal prostate and PCa) were used to select a panel of 48 differentially expressed genes. Validation studies using the qPCR based TLDA analysis and inclusion of urinary sediments reduced the biomarker panel to 13.

➢Assay development: RT-qPCR assays were developed for the 13 biomarkers and the expression levels were determined in 400 urinary sediments.

➢Lead markers selection: A 4 gene panel with enhanced diagnostic specificity for detection of clinically significant PCa was selected by binary logistic regression analysis.

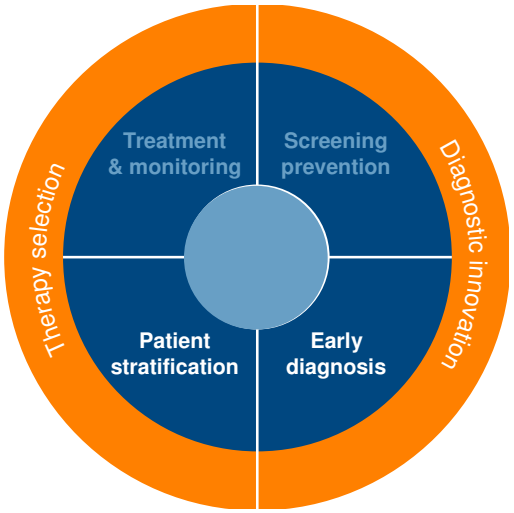
➢Model development and clinical validation: In two prospective multicenter studies urine was collected after DRE. In the first study (n=492), a predictive model was developed based on the mRNA levels of the genes DLX1, HOXC6 and KLK3. This model was validated in the second study (n=371).

➢Technical validation, kit design and CE-registration: This was performed in close collaboration with DDL/LBP (Rijswijk) and partly financed Innovatie Krediet.

Future Outlook

Launch of the product in Europe November 2015; http://mdxhealth.com/press-release/mdxhealth-launches-selectmdx-liquid-biopsy-test-europe

PATIENT



Number of patients: EU&US ~1,000,000 p.a.

Quality of Life:
Select MDx is a non-invasive test with a higher specificity for clinically significant PCa than currently used sPSA. It reduces the number of false positives (reduces anxiety for the patient) and (invasive) unnecessary biopsies (risk of co-morbidity), and in this way reduces overtreatment. Overall, *Select* MDx results in improved patient management and QoL.

Accessibility:
Select MDx can be used on several quantitative RT-PCR systems, integrated in most clinical laboratories.

Affordability:
The pricing of the *Select* MDx test will be competitive to currently available tests for the diagnosis of PCa.

Prognostic Prostate Cancer, the PDE4D7 assay

PRODUCT

Background: Prostate Cancer is the most common tumor in men with globally 900,000 novel cases and >150,000 deaths each year. The societal impact of this disease is enormous – in the US alone at least US$ 12 billion are spent annually for disease management. Nevertheless, Prostate Cancer care is very ineffective still and particularly the lack of accurate *diagnostic* tools leads to serious over-diagnosis and over-treatment in the early stages of disease management, whereas in later stages patients would benefit from earlier and better targeted therapy if *prognostic* tests would allow for appropriate therapy stratification.

Phosphodiesterases are a family of genes coding for more than 80 different gene variants. We have identified PDE4D7 as a relevant diagnostic and prognostic biomarker for prostate cancer.

Device: The PDE4D7 assay is based on qPCR or RNA seq based molecular assay of PDE4D7 and a reference gene

Leading Company: Philips Electronics B.V.

Current Diagnostics: at this moment for molecular diagnostics there is only one diagnostic marker regulatory approved, namely PCA3. However, performance is limited. There is currently prognostic biomarker for prostate cancer approved

PARTNERSHIP

Progress obtained in translational pipeline

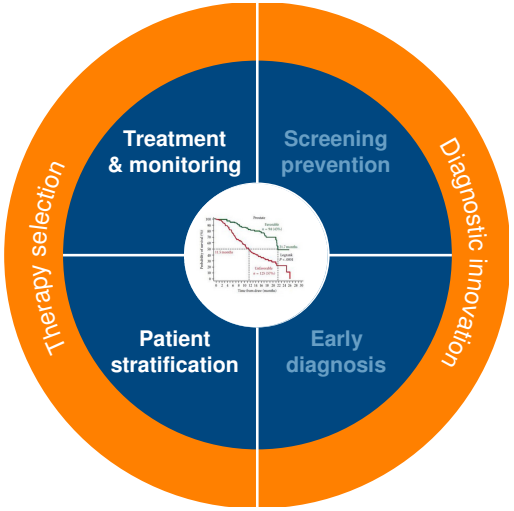
➢Biomarker development: The PDE4D7 gene and a reference gene qPCR assays were optimized for performance. Further, a multiplex assay to run PDE4D7 and its reference gene in a single assay was developed (the PDE4D7 assay). The clinical performance of the PDE4D7 was tested on >1,500 patients for diagnostic as well as prognostic applications including various platform technologies (qPCR, DNA microarray, NGS RNA sequencing). All tested platforms show comparable performance in discriminating relevant patient groups (non-cancer vs. cancer, non-aggressive vs. aggressive).

➢Next development: Currently, a clinical study including >500 patients with longitudinal follow-up and outcome data is performed to test the power of PDE4D7 to predict post-surgical outcome (biochemical and clinical disease recurrence) within 5/10 years after primary treatment on a tumor biopsy sample

Future Outlook

- prospective, multi-center clinical trials
- CE marking of the PDE4D7 assay

PATIENT



Number patients:
EU&US: ~350-400,000 p.a.

Quality of Life: The improved risk stratification of patients before primary treatment will increase the use of active surveillance schemas in men with primary, localized disease. This will save a significant number of men from unnecessary treatment and its consequent adverse effects.

Accessibility: The test accessibility will be delivered through a service lab model

Associated Costs: The PDE4D7 pricing will be competitive to currently marketed prognostic cancer tests (e.g., Oncotype Dx)

Prostate Cancer NGS

PRODUCT

Background: Next-Generation Sequencing (NGS) of tumor DNA and RNA is one of the most promising technologies for the diagnosis, prognosis and monitoring of cancer. Genomic aberrations were identified using whole genome DNA sequencing and RNA sequencing to identify and validate cancer-associated differential expression, mutations and fusion events. The identification and clinical implementation of these novel genomic and transcriptomic features are essential for improved patient stratification in the coming years.

Device: NGS using Complete Genomics whole genome DNA sequencing and Illumina RNA sequencing.

Leading: Erasmus MC and Philips Electronics B.V.

Current Diagnostics: Standard practice for risk assessment of the presence of prostate cancer is still reliant on blood PSA and rectal examination. The power of genomic diagnostics is poorly exploited and very few relevant diagnostic DNA and RNA markers are clinically available. Also prognostic, predictive and monitoring markers are unavailable, inadequate or not yet used. Importantly, many DNA and RNA markers are ready to fulfill their promise using urine and blood-based NGS technologies.

PARTNERSHIP

Progress obtained in translational pipeline

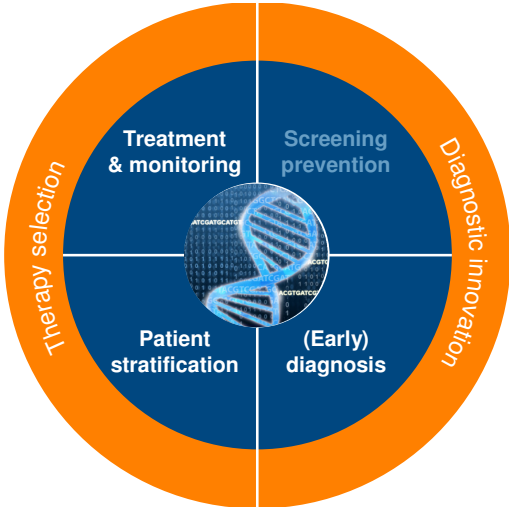
➢Biomarker discovery: Next-generation sequencing was performed on a surgical resection of men undergoing radical prostatectomy between 2000-2004. The goal of this study is to identify novel genomic and transcriptomic features for improved patient stratification.
- A selection of samples was whole genome DNA sequenced for the identification of breaks and gene fusion events. Using SNP array data, novel frequent rearrangements were identified.
- A large collection was RNA sequenced by NGS. The RNAseq data was analyzed for known and novel genomics features like gene expression changes, genetic mutations, gene fusions and splice variants.

➢Next development: Currently, relevant genomic features have been filtered from the NGS RNAseq data and are correlated to various relevant clinical endpoints like pathology or disease progression after primary treatment. In collaboration with NGS-ProToCol and TraIT, the genomic aberrations are validated in an additional independent set of clinical samples.

Future Outlook

Verification and clinical validation of novel genomic and transcriptomic features

PATIENT



Number patients:
EU&US: ~350-400,000 p.a.

Quality of Life:
- The (early) more accurate differential diagnosis of prostate cancer vs. benign prostate diseases will lead to a significant reduction in unnecessary biopsies.
- The improved risk stratification of patients before primary treatment will increase the use of active surveillance schemas in men with primary, localized disease. This will save a significant number of men from unnecessary treatment and its consequent adverse effects.
- The identification of novel genomic and transcriptomic features may lead to new treatment regimes for prostate cancer.

Tissue markers in clinical prostate cancer

PRODUCT

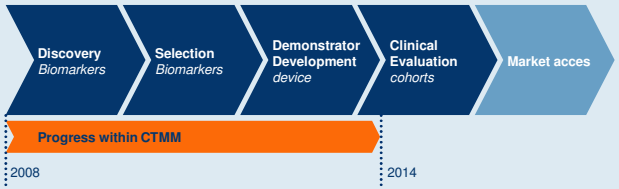
Background: Prostate cancer (PCa) is diagnosed by microscopic analysis of prostate biopsies. While microscopic growth features of PCa are related to disease behavior, there is a need for additional tumor markers to objectively support clinical decision-making. Our objectives were to create a robust platform for high-throughput tissue marker testing in clinical PCa samples, to discover and test potential markers for their predictive value for PCa behavior.

Leading: Erasmus MC

Results:
1) We have created a tissue micro-array (TMA) platform of 481 well-characterized clinical PCa samples with long-term follow-up for robust tissue marker testing.
2) Through TMA analysis has revealed that α6-integrin and EZH2 proteins are related to relatively indolent and aggressive PCa, respectively.
3) Using laser capture micro-dissection (LCM) and RNA sequencing, we identified HELLS and ZIC5 as novel tissue markers for aggressive PCa.

PARTNERSHIP

Progress obtained in translational pipeline



Platform facility: Our TMA platform supported various partners within and outside PCMM in their biomarker validation analyses.

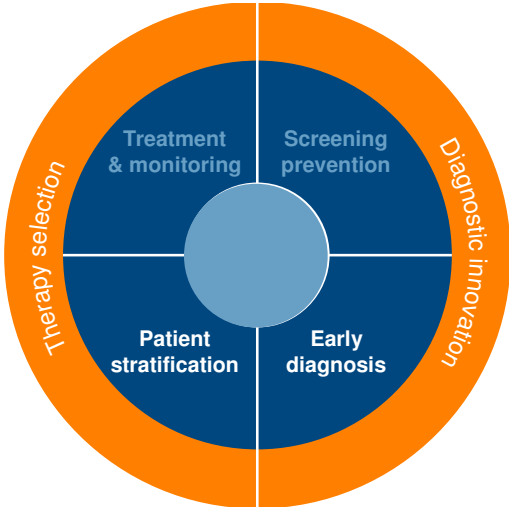
Supporting imaging: Ultrasound and MRI imaging guide optimal optimal biopsy procedures. By thorough microscopic analysis of 70 Pca operation specimen and provision of their comprehensive schematic representations, we enabled ultrasound and MRI imaging to be optimized for detection of significant Pca.

Sharing expertise: We supported PCMM partners with marker testing, study design and interpretation by sharing our expertise of urogenital pathology.

Future Outlook

- Clinical implementation of novel tissue biomarkers identified in PCMM

PATIENT



Prospective: We are currently testing a set of promising and newly detected tissue markers α6-integrin, EZH2, HELLS and ZIC5 on diagnostic prostate biopsies of PCa patients to support clinical decision-making in either to treat or not to treat their disease.

GRPR Medical-imaging - a non-invasive imaging test for prostate cancer

PRODUCT

Background: Gastrin releasing peptide receptor (GRPR) may be a valid target for nuclear imaging of prostate cancer. GRPR is highly expressed in several human cancer cell lines (breast cancer, colon cancer, prostate cancer) and could be used as a potential target for cancer detection. Radiolabeled bombesin analogues could be potential probes for GRPR targeted nuclear imaging.

Leading: UMC Groningen

Current Diagnostics: A series of rapid tests can be helpful for the diagnosis, such as the prostate specific antigen (PSA) blood test and the digital rectal examination (DRE). PSA discovery certainly improved the early detection of PCa over the last decades and became indispensable for diagnosis and follow-up of PCa patients, but also increased overdiagnosis and overtreatment of PCa by generating false positives. In addition, PSA performs poor in restaging of recurrent prostate cancer after local treatment or in metastatic disease. Especially for prediction of response in bone metastases a non-invasive specific imaging tool is urgently needed. Positron emission tomography (PET) and single photon computed tomography (SPECT) with high sensitivity, specificity and resolution may help to investigating the staging and restaging of prostate cancer and obtaining molecular tumour information.

PARTNERSHIP

Progress obtained in translational pipeline

➢Bombesin tracers for SPECT

Several SPECT labelled bombesin analogs have been evaluated in a preclinical setting. After its succesful evaluation two pilot studies with a selected SPECT-tracer in patients have been performed. Despite the favourable preclinical results, no prostate cancer could be detected in patients with SPECT.

➢Bombesin tracers for PET

Several approaches to develop potent GRPR PET-tracers have been investigated. Since metabolic stability of the bombesins was shown to be a determinant factor for the succesful application in prostate cancer patients, PET-labelled bombesin-tracers with increased metabolic stability were developed and succesfully evaluated in animal models.

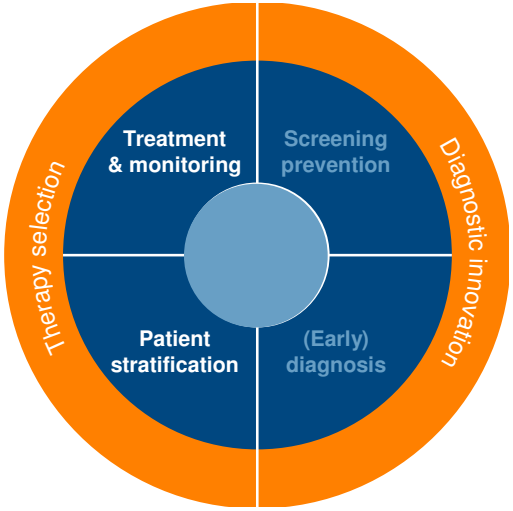
➢Next development:

PET-tracers are developed to move to the stage of patient studies, once toxicity studies have been carried out. Besides GRPR, PSMA has gained much attention and may be a better target for prostate cancer imaging

Future Outlook

- Investigation of multimers and GRPR tracers with improved metabolic stability
- Change from GRPR to PSMA PET-imaging

PATIENT



Number patients:
EU&US: ~1,000,000 p.a.

Quality of Life:

In the future, treatment approaches for metastatic PCa would lead to improve the prognosis of patients but costs and side effects should be balanced against increased life time and quality of life. Several studies are focused on discovering new treatment agents and approaches that can reduce side-effects and further improve quality of life in patients with prostate cancer on the basis of potent treatment efficacy. It is expected that a personalized approach will be needed given multiple drugs are already available. Selection of patients could be improved by adding knowledge of tumour biology into decision algorithms.

PSMA-targeted imaging for prostate cancer by a nanobody

PRODUCT

Goal: Due to the lack of specificity of conventional imaging techniques, there is no universal imaging method approved for detection of early prostate cancer (PCa). The goal was to establish highly PCa-specific tracers to be used in molecular imaging.

Nanobodies: Nanobodies represent the smallest binding fragment of a heavy chain antibody possessing full antigen binding capacity. Their high target specificity and fast clearance makes these nanobodies ideal for molecular imaging. Our objectives were to create a PCa-specific nanobody library and to select novel nanobodies for PCa-specific imaging.

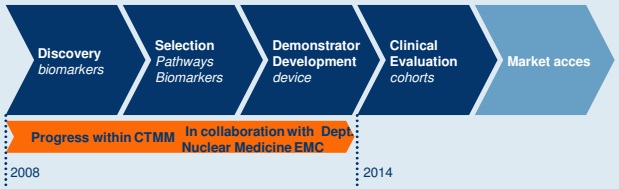
PSMA: Prostate-specific Membrane Antigen (PSMA) is overexpressed in PCa cells and is a relevant target for molecular imaging. We used PSMA as a target to validate our nanobody library.

Patient-derived xenografts (PDX): Unique patient-derived xenografts (PDXs) of PCa were used as preclinical model systems to validate selected anti-PSMA nanobodies.

Nuclear imaging: This work was done in close collaboration with CTMM partners and with the Dept. of Nuclear Medicine of the Erasmus MC

PARTNERSHIP

Progress obtained in translational pipeline



Main results in CTMM

PCa-targeted nanobody platform: A nanobody library was generated specific for PCa. We selected a novel nanobody targeted against PSMA, JVZ007.

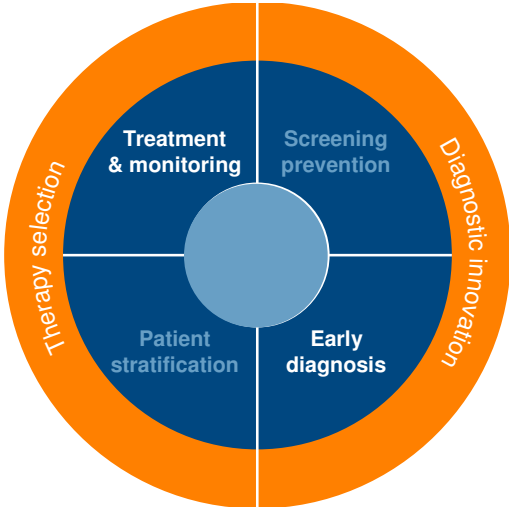
Preclinically validated imaging tool: The PSMA nanobody JVZ007 was conjugated and radiolabeled for imaging purposes. Ex vivo autoradiography on frozen tissue section confirmed its PCa specificity. SPECT and PET imaging revealed excellent and highly sensitive localisation of prostate tissue with high contrast at early time points and remarkably low kidney uptake.

Next development: We are currently comparing the PCa-specificity of JVZ007 to that of the PSMA-inhibitors that have been developed and are in clinical evaluation.

Future Outlook

JVZ007 may have a potential as a theranostic agent in metastatic PCa

PATIENT



Prospective: We are testing JVZ007 as a potential theranostic agent for imaging and radionuclide therapy for prostate cancer in preclinical models of PCa.

Androgen Receptor for Targeted bioimaging in metastatic prostate cancer

pcmm a ctmm project

PRODUCT

Background: During the course of treatment of metastatic prostate cancer the androgen receptor (AR) has shown maintain active. Mutation of the AR is one of the backgrounds for resistance to castrate-based treatment. Molecular imaging techniques measuring the AR in vivo in multiple lesions throughout the body could be of additional value for (re)staging and treatment evaluation. In addition this could allow for monitoring of drug delivery and individual dosing to improve response.

Leading: UMC Groningen, Astellas

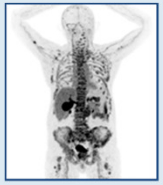
Current Diagnostics: At present there is no approved technique to evaluate response in the skeleton. So there is an urgent need to develop and validate an imaging technology to monitor bonemetastases. Especially in mCRPC the development of a treatment response technique would allow for patient-tailored decision making. Distinguishing responders from non-responders in the early phase of the treatment would allow for a tailored treatment thus minimizing toxicity, improving quality of life and health care management.
The ultimate goal is to develop, optimize and validate new targeted molecular imaging technology in metastatic hormone naïve PC and in mCRPC.

PARTNERSHIP

Progress obtained in translational pipeline

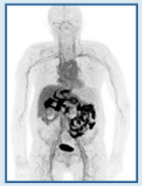
➢GMP production of [^{18}F]DHT (IMPD) for AR positive tumors

➢Clinical evaluation of AR targeted imaging in metastatic hormone naive and in mCRPC patients for early treatment respons and drug delivery.



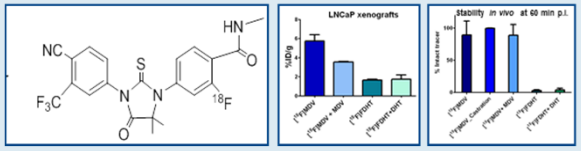
mCRPC [^{18}F]DHT PET/CT, Enzalutamide® pre docetaxel

Pre-treatment (left) and 4 wks post-treatment (right)



➢Radiosynthesis, pre-clinical evaluation of [^{18}F]Enzalutamide®

[^{18}F]Enzalutamide® uptake was significantly higher in LnCaP xenografts and highly stable *in vivo* versus [^{18}F]FDHT.

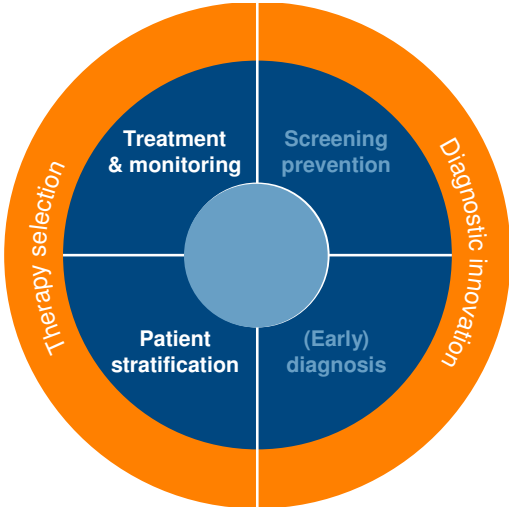


Future Outlook

➢ Evaluation clinical value of [^{18}F]DHT PET/CT in mPC/ mCRPC

➢ GMP production of [^{18}F] Enzalutamide®

PATIENT



Number patients:
EU&US: ~1,000,000 p.a.

Quality of Life:
In the future, treatment approaches for metastatic PCa would lead to improve the prognosis of patients but costs and side effects should be balanced against increased life time and quality of life. Several studies are focused on discovering new treatment agents and approaches that can reduce side-effects and further improve quality of life in patients with prostate cancer on the basis of potent treatment efficacy. It is expected that a personalized approach will be needed given multiple drugs are already available. Selection of patients could be improved by adding knowledge of tumour biology and drug delivery into decision and dosis algorithms.

PCMM biobank

PRODUCT

Background: a well annotated repository of urine, blood and tissue was created in five clinical centers from three patient groups:

- 1) 215 men undergoing prostate biopsies
- 2) 182 men with localised PCa undergoing radical prostatectomy
- 3) 20 men with castrate resistant PCa undergoing pre- and posttreatment DHT scanning and biopsies of metastatic sites.

Leading company: Philips

Product: a PCa instance of tranSMART, a software platform for the integration of patient related data: clinical, biomarkers, genomics, multimodality MRI, contrast ultrasonography, radiology and pathology data, ready for statistical analysis. tranSMART connects to other CTMM-TraIT tools were needed, such as OpenClinica, NBIA, Catalogue and Workflow (and a SharePoint for documents).

The data collected for the several groups consists of:

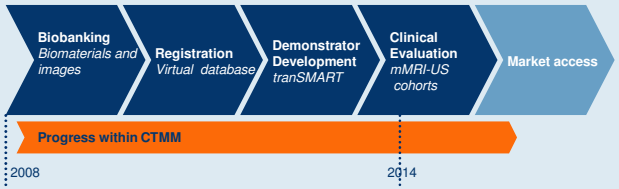
- Group 1: Clinical data (76 items), biobank data, pathology reports and radiology reports (for a subset)

- Group 2: Clinical data (182 items, under which a QoL questionnaire of 80 items), MRI and CEUS images, biobank data, pathology and radiology reports, and PI-RADS scores (for a subset)

- Group 3: Clinical data (14 CRFs) and biobank data

PARTNERSHIP

Progess obtained in translational pipeline



Main Results

- Decentralised biorepository
- Centralised databank
- Validated software tranSMART
- Consistency plan for biobanking (March 2016)

Next development

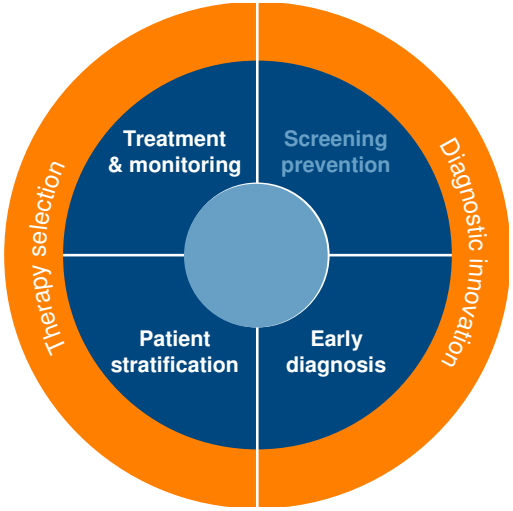
The tranSMART software will be connected to and integrated with clinician orientated decision technology (miProstate).

The biorepository is the basis of the retrospective analysis within the prefinal validation phase of various PCMM markers of the ProCaMolMed study (2015-2017).

Future outlook:

Accessible biobank for clinical and preclinical PCa research

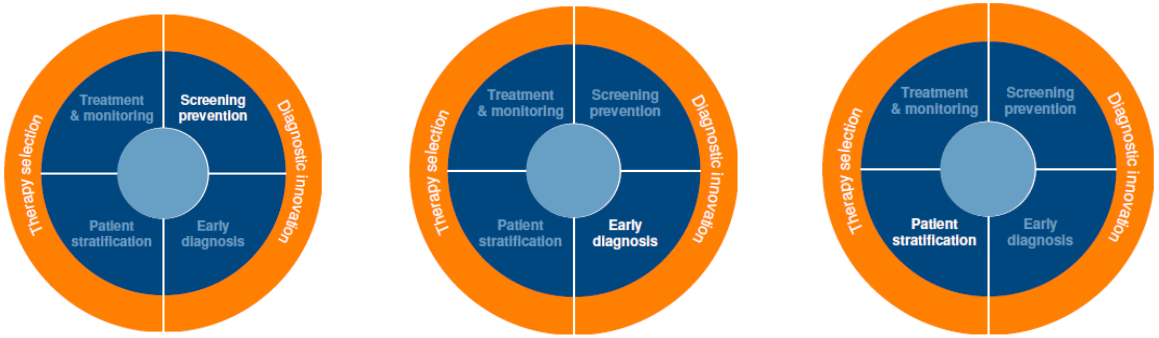
PATIENT



The PCMM biobank offers data and materials for national and international PCa research, allowing more scientists to participate in relevant research projects and consortia. Already, the database is used to analyze new diagnostic and prognostic parameters in contrast enhanced ultrasonography (Technical University of Eindhoven) and MRI (Technical University of Delft, Erasmus MC).

tranSMART software is used for the construction of a worldwide database of patients on Active Surveillance (Global Action Plan 3 of Movember)

Early HTA: Evaluating promising markers



Evaluation of markers

Statistical evaluation: performance measures for screening, diagnostic and prognostic markers
Prediction models are important to guide decision making on screening, diagnosis and prognosis. The serum level of Prostate Specific Antigen (PSA) is not accurate enough on its own to guide screening decisions, such as in which men to perform a biopsy to detect prostate cancer, or to identify the men in whom surgery should be done after diagnosing prostate cancer.
Prediction models may be improved by markers, but there is debate on which statistical summary measures quantifies performance best in the early HTA phase, where full cost-effectiveness analyses may not yet be performed. We compared various approaches and propose a framework for statistical and decision-analytic performance evaluation.

Prostate cancer screening: Head room analysis for new markers
Prostate cancer is in need of better markers to better target biopsy to those men who benefit from early detection of disease. A headroom analysis can estimate the societal value and commercial viability of the use of such new markers. The headroom analysis addresses the question of when a new marker would be cost-effective, considering both its quality as quantified by performance measures such as sensitivity and specificity, predictive value, and the financial costs. The analysis gives a price threshold (the maximum for the potential costs), given a cost-effectiveness threshold. If this price threshold is relatively low, complex marker technology may not be worthwhile to develop.

Key findings early HTA in PCMM

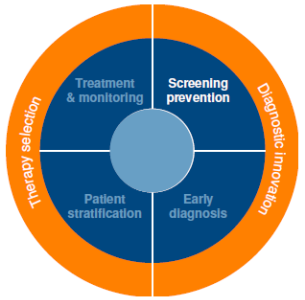
There is a need for methodologically rigorous evaluation of markers to improve decision making for screening, diagnosis, and stratification for therapy in prostate cancer.

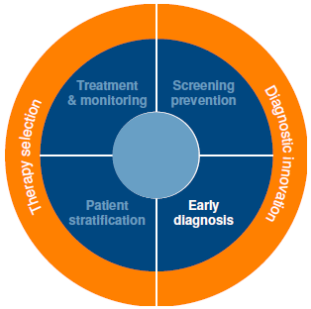
The statistical evaluation of markers is complex. We first focused on the pros and cons of alternative performance measures when a marker is evaluated for its incremental value in a statistical prediction model. We reviewed various recently proposed summary measures that focus on reclassification of subjects from low to high or from high to low risk. We found that some measures were potentially misleading while graphical approaches were informative, supporting decision-analytic summary measures such as the Net Benefit.

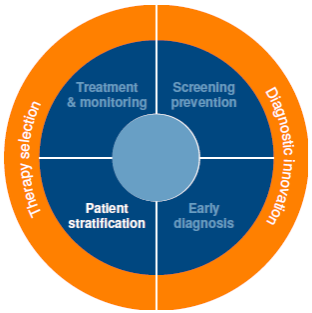
A headroom analysis for markers to improve screening found that PSA combined with a novel marker will only be a cost-effective alternative to screening with PSA alone if costs are very low (<€50), or the marker is selectively used in those with high PSA (<€300). These analyses assumed the novel marker had perfect performance characteristics (sensitivity and specificity 100%), while no marker will achieve this.

Early reports on markers are usually optimistic, which indicates a need for further validation of promising markers to inform cost-effectiveness analyses.

Early HTA: Evaluating promising markers





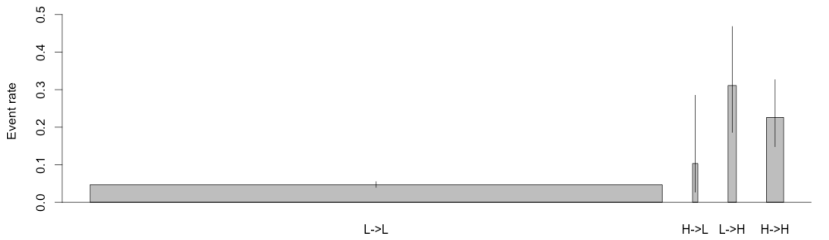


Statistical evaluation: performance measures for screening, diagnostic and prognostic markers

New markers may improve prediction of diagnostic and prognostic outcomes. We reviewed various options for graphical display and summary measures to assess the predictive value of markers over standard, readily available predictors. We found that important initial assessments should consider statistical significance, distributions of predicted risks, and receiver operating characteristic curves (with the area under the curve (AUC) as a well-accepted summary measure). Reclassification of participants with and without an event is well visualized in a reclassification graph, with the continuous Net Reclassification Improvement (NRI) as a summary measure [1].

When we focus on one particular decision threshold, the changes in sensitivity and specificity are central. We propose a Net Reclassification Risk graph, which allows us to focus on the number of reclassified persons and their event rates. Summary measures include the binary AUC, the two-category NRI, and decision analytic variants such as the Net Benefit (NB).[2]

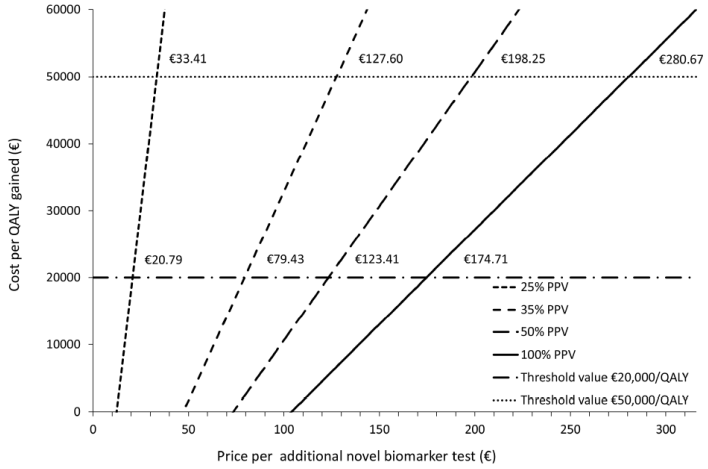
Net Reclassification Risk graph for adding a marker to risk predictions [2]



Prostate cancer screening:
Head room analysis for new markers

We investigated under what conditions adding a novel biomarker to Prostate Specific Antigen (PSA) testing is cost-effective for prostate cancer (PC) screening. We hereto adapted the MISCAN-Prostate microsimulation-model, which includes data from the European Randomised study of Screening for Prostate Cancer (ERSPC) trial to estimate costs and Quality Adjusted Life Years (QALYs) for different PC screening strategies. At a threshold of €20,000/QALY, annual screening with PSA combined with a novel biomarker was cost-effective at Positive Predictive Values of 35% and 100%, if the costs of the novel biomarker were very low (€6 and €13, respectively). For testing with 100% PPV after initial PSA >3.0ng/ml, the threshold was substantially higher, at €280 for annual screening and a threshold of €50.000/QALY.
These price thresholds are uncertain due to various assumptions, such as that no additional burden was caused by the biomarker measurement.[3,4]

Price threshold analysis for an additional marker after PSA > 3.0 ng/ml [3]



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2. Graphical assessment of incremental value of novel markers in prediction models: From statistical to decision analytical perspectives. *Biom J. 2015 Jul;57(4):556-70*
3. Cost-effectiveness of prostate cancer screening using a PSA test combined with a novel biomarker. *Submitted.*
4. Evaluation of biomarkers: application in urological cancers. *Thesis M Vedder, Erasmus University, Jan 13, 2016.*

Partners

Erasmus University Medical Center (EMC)	Rotterdam
Netherlands Cancer Institute (NKI)	Amsterdam
Radboud university medical center (Radboudumc)	Nijmegen
University Medical Center Groningen (UMCG)	Groningen
University of Glasgow	Glasgow (Scotland)
University of Verona	Verona (Italy)
Astellas Pharma Europe BV	Leiden
Dionex Benelux BV	Amsterdam
IQ Therapeutics BV	Groningen
NovioGendix Research BV / MDxHealth	Nijmegen
Royal Philips	Eindhoven

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Abbreviations

AR	Androgen Receptor
cAMP	cyclic Adenosine Monophosphate
CE	Conformité Européenne Markering
CRISP	Clustered regularly-interspaced short palindromic repeats
CT	Computed tomography
DRE	Digital Rectal Examination
GMP	Good Manufacturing Practices
GRPR	Gastrin-Releasing Peptide Receptor
HTA	Health Technology Assessment
IMPD	Investigational Medicinal Product Dossier
mCRPC	metastatic Castration- Resistant Prostate Cancer
MISCAN	Microsimulation Screening Analysis
MRI	Magnetic Resonance Imaging
MTA	Medical technology Assessment
mRNA	Messenger RNA
NGS	Next Generations Sequencing
PCa	Prostate Cancer
PCR	Polymerase Chain Reaction
PDX	Patient-Derived Xenografts
PET	Positron Emission Tomography
PSA	Prostate Specific Antigen
PSMA	Prostate-Specific Membrane Antigen
QoL	Quality of Life
QALYs	Quality Adjusted Life Years
RT-PCR	Real-Time PCR
SNP	Single Nucleotide Polymorphism
SPECT	Single-Photon Emission Computed Tomography
TLDA	TaqMan® Low Density Array
TMA	Tissue Micro Array

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