

Risk-stratified treatment by biomarkers?

Launch of the PROCABIO project: tailored treatment of prostate cancer



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In Europe and other developed countries, prostate cancer is now the most commonly diagnosed cancer in men due to the widespread use of the PSA-based screening tool. A major disadvantage of screening for prostate cancer is the detection of asymptomatic, non-aggressive tumours that have a very low risk of progression. Current clinical practice subjects a high proportion of patients with these indolent tumours to treatment involving radiotherapy or surgery. In turn, this is associated with side effects that severely impair the quality of life of a proportion of patients.

Thus, screening and its role in the unnecessary detection of indolent cancers is intrinsically linked to overtreatment. Recent results from the European Randomized Study of Screening for Prostate Cancer have shown that in a screening setting in the general population, about 50 % of diagnosed cases have indolent prostate cancers [1]. These patients may better be managed by active surveillance of their disease instead of standard curative therapy, so avoiding the side effects of overtreatment.

The need for tailored treatment of prostate cancer - stratifying between patients who need active curative therapy and patients who are better off with active surveillance - is therefore growing. Tailored treatment not only reduces cancer-related anxiety and improves quality of life for the patient. It will also have a positive impact on health care costs by redirecting health care resources towards those that need it most. Results from observational studies on active surveillance are promising, and show that active surveillance is a safe and efficient alternative for men thought to have indolent disease [2].

The value of active surveillance is currently being tested in a prospective programme entitled Prostate Cancer Research International: Active Surveillance (PRIAS, www.prias-project.org) initiated in Rotterdam, The Netherlands [3]. A prerequisite for the clinical acceptability of active surveillance will be proper risk stratification of eligible patients, which depends on the availability of good predictors. Current models developed for the selection of men thought to have indolent prostate cancer are based on PSA, prostate volume, clinical stage and biopsy pathology features [4], and can be used for the outcome of active surveillance. The predictive power of these models that are strongly dependent on biopsy pathology needs to be increased. This can be done primarily by the development of markers that address the early genetic changes of aggressive cancers, and overcome sampling limitations of the biopsy procedure. Biomarkers that can identify indolent prostate cancer in body fluid, or be used as an indication of progressive disease during active surveillance, are of pivotal importance to improve the selection criteria, as well as the efficacy and the clinical applicability of this new form of disease management.

The PROCABIO project

There are several genomic, proteomic and molecular pathology biomarkers for prostate cancer in development in commercial and in academic research laboratories that may have the potential to improve identification of indolent prostate cancer. Importantly, they may also be indicators of disease progression during active surveillance. New technological developments allow for the analysis of a considerable number of biomarkers simultaneously in a standard set of clinically relevant biomaterials. The PROCABIO (Tailored treatment of PROstate CAncer by BIOmarkers) project provides the unique opportunity to translate a broad range of the most promising biomarkers for prostate cancer that are currently looked upon by the industry as well as the academic institutes being of interest. Over a period of three

years, the following objectives will be addressed by the PROCABIO consortium:

1. Integration of biomarkers in an updated and improved model for the prediction of indolent prostate cancer.
2. Integration of biomarkers in the development of guidelines for efficient strategies for active surveillance as a treatment for indolent prostate cancer.
3. Delivery of validated biomarker tools that are easily applicable for high throughput use in clinical and screening settings.
4. Establishment of the overall acceptance of active surveillance as a treatment modality for indolent prostate cancer by informing all stakeholders, including patients, clinicians, scientists and policy makers.

The PROCABIO consortium is composed of 11 clinical and academic partners, five commercial partners and two advisory partners (table 1). The project was officially launched at the recent 2008 Congress of the European Association of Urology in Milan.

Table 1: The PROCABIO consortium

Academic partners

Clinical centers for active surveillance and biomarker research centers

- Erasmus MC, Department of Urology, Rotterdam, The Netherlands
- Lund University, Malmö University Hospital, Department of Urology, Malmö, Sweden
- University of Münster, Department of Urology, Münster, Germany
- University of Sheffield, Department of Urology, Sheffield, United Kingdom

Clinical centers for active surveillance

- Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy
- Institute of Cancer Research, Academic Unit of Radiotherapy & Oncology, London, United Kingdom

Table 2: Biomarkers in PROCABIO

Biomarker	Description	Partners involved
Biomarkers in blood or urine		
BPSA, proPSA, total PSA, free/total PSA	PSA variants associated with PCa or benign prostate	University of Münster Beckman-Coulter
fPSA, nicked free PSA	Free forms of PSA associated with PCa	Lund University University of Turku
hCGb	Protein associated with poor prognosis in cancer	University of Helsinki
hK2, hK4	Serine proteases associated with PCa	Lund University University of Turku
mRNA from various genes	Expression analysis of candidate genes associated with PCa	University of Turku Abacus Diagnostica
OPG	Bone turnover protein associated with PCa	University of Sheffield
PCA3	Prostate-specific non-coding mRNA overexpressed in PCa	University of Nijmegen Gen-Probe Incorporated
TATI	Protease inhibitor associated with PCa	University of Helsinki Orion Diagnostica
TMPRSS2-ERG	Fusion transcript overexpressed in PCa	University of Nijmegen Gen-Probe Incorporated
Biomarkers in tissue		
CRISP-3	Overexpression in PCa tissue	Lund University
EZH2, p27, p53, Ki67	Tissue markers overexpressed in PCa	Erasmus MC
HERPUD1	Androgen-regulated gene associated with PCa metastases	Erasmus MC
mRNA from various genes	Expression analysis of candidate genes associated with PCa	University of Turku Abacus Diagnostica
MSP	Prostate-specific protein associated with PCa	Lund University
PITX2	DNA methylation marker associated with PCa	Erasmus MC Epigenomics

Abbreviations: BPSA = benign PSA, CRISP-3 = cysteine-rich secretory protein 3, hCGb = beta subunit of human chorionic gonadotropin, hK2 = human kallikrein 2, hK4 = human kallikrein 4, MSP = beta-microseminoprotein, OPG = osteoprotegerin, Pca = prostate cancer, TATI = tumor-associated trypsin inhibitor.

- L'Hôpital Saint-Louis, Department of Urology, Paris, France
- University of Tampere, Department of Urology, Tampere, Finland

Biomarker research centers

- Radboud University Nijmegen Medical Centre, Department of Experimental Urology, Nijmegen, The Netherlands
- University of Helsinki, Department of Clinical Chemistry, Helsinki, Finland
- University of Turku, Department of Biotechnology, Turku, Finland

Commercial partners

- Beckman-Coulter, France
- Epigenomics AG, Germany
- Gen-Probe Incorporated, USA
- Abacus Diagnostica Oy, Finland
- Orion Diagnostica Oy, Finland

Advisory partners

- Europa Uomo, Belgium
- EORTC, Belgium

PROCABIO biomarkers

Within PROCABIO, extensive academic and commercial biomarker expertise is joined. The candidate proteomic and genomic biomarkers to be evaluated for their use in active surveillance are listed in table 2. A part of these biomarkers arise from the P-Mark project (www.p-mark.org) funded by the European Commission Sixth Framework Programme [5].

Three year plan of PROCABIO

The eight clinical PROCABIO partners will recruit about 300 patients in total for active surveillance according to the PRIAS protocol [3], using a web-based tool for patient inclusion and monitoring. The translation of the PROCABIO Patient Information Form and Consent Form in national languages is managed by Europa Uomo, a European coalition of patients'

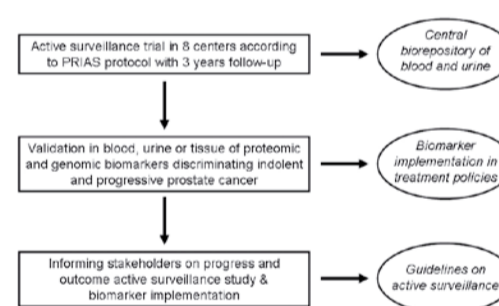


(ECAM members are: Chris Bangma, Anders Bjartell, Zoran Culig, Freddie Hamdy, Norman Maitland, Jack Schalken and George Thalmann)

supporting groups for prostate diseases in general and prostate cancer in particular. For a period of three years, blood and urine will be obtained at inclusion and subsequently annually from the recruited patients according to a standardized protocol.

Centralised storage of blood and urine specimens is foreseen at the Sheffield Biorepository Facility in the United Kingdom. Prostate biopsy materials will be collected at t = 0 and 12 months, and onwards if indicated by the protocol. The academic and commercial partners will use the biospecimens to test the potential application of their biomarkers (see table 2) in active surveillance. Statistical analysis linking the results from the biomarker analyses with clinical data will demonstrate if biomarkers can improve the prediction of indolent prostate cancer at diagnosis as well as the monitoring during active surveillance, and if implementation of biomarkers in an algorithm will lead to a more refined selection of patients for active surveillance. With the support and advice from Europa Uomo and EORTC, stakeholders in Europe will be informed on the outcome of PROCABIO. The ultimate milestone will be the implementation of PROCABIO results in updated guidelines on active surveillance. An overview of the three year plan of PROCABIO is presented in figure 1.

Figure 1: Three year plan of PROCABIO



PROCABIO is an international initiative that will be one of the first to study if biomarkers are useful for risk-stratified treatment selection for prostate cancer and if biomarkers can be used for treatment-response monitoring or to detect progression during active surveillance. Patient inclusion for PROCABIO will be started in due time.

For further information on PROCABIO, please contact Dr. Ellen Schenk (PROCABIO project manager) at e.schenk-braat@erasmusmc.nl.

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