

START PAGE

MARIE SKŁODOWSKA-CURIE ACTIONS

Individual Fellowships (IF)
Call: H2020-MSCA-IF-2015

PART B

“ProDeepCAD”

This proposal is to be evaluated as:

Standard GF

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0 LIST OF PARTICIPANTS

Participants	Legal Entity Short Name	Academic	Non-academic	Country	Dept. / Division / Laboratory	Supervisor	Role of Partner Organisation
<u>Beneficiary</u>							
- NAME							
<u>Partner Organisation</u>							
- NAME							

Data for non-academic beneficiaries

Name	Location of research premises (city / country)	Type of R&D activities	No. of fulltime employees	No. of employees in R&D	Website	Annual turnover (approx. in Euro)	Enterprise status (Yes/No)	SME status (Yes/No)

Note that:

- Any inter-relationship between different participating institutions or individuals (e.g. family ties, shared premises or facilities, joint ownership, financial interest, overlapping staff or directors, etc.) must be declared and justified in this part of the proposal;
- The information in the table for non-academic beneficiaries must be based on current data, not projections;
- The data provided relating to the capacity of the participating institutions will be subject to verification during the Grant Agreement preparation phase.

1 SUMMARY

That will be the abstract of the proposal

2 EXCELLENCE

2.1 Quality, innovative aspects and credibility of the research

2.1.1 Introduction

In Europe, prostate cancer is reported to be the most frequently diagnosed cancer of men and thus one of the leading cause of death of cancer¹. Currently, addressing this issue is a major public debate, in which the implementation of appropriate screening methods and subsequent treatments is key.

In this regard, the European Randomised Study of Screening for Prostate Cancer (ERSPC) is conducted to investigate the potential benefits of a population-based screening². The screening consists of a Prostate-Specific Antigen (PSA) test and depending of the PSA level measured, an additional “blind” biopsy is carried out. Despite the fact of a significant reduction of the prostate cancer mortality, the screening strategy employed suffers of a high rate of over-diagnosis and over-treatment³, due to the fact that prostate cancer growth is characterized by two main types of evolution: slow and fast. The slow-growing tumours account for up to 85 % of all cancers and stay confined to the prostate gland, while the fast-growing tumours rapidly develop and metastasise to other organs, significantly affecting the morbidity and mortality rate. Furthermore, prostate cancer is more likely to develop in specific regions of the prostate: around 70-80 % of prostate cancers originate in the Peripheral Zone, whereas 10-20 % in the Central Gland (CG), but appear to be more aggressive and more likely to invade other organs. **Thus, additionally to cancer detection, the screening methods need to provide an estimate of the cancer aggressiveness to allow clinicians to act accordingly.**

In addition, the investigators of the ERSPC have come to the conclusion that the use of “*multi-parametric Magnetic Resonance Imaging (MRI) and the development of new markers are the hope for the future*”. That is why, Computer-Aided Diagnosis (CAD) systems revolved around mono- and multi-parametric MRI are currently developed by the medical imaging community, and were recently reviewed by Lemaître *et al.*⁴. The CAD systems developed are designed under the same architecture as depicted in Fig. 1. The available MRI modalities during prostate exam are T₂-Weighted (T₂-W)-MRI, Diffusion Weighted (DW)-MRI, Dynamic Contrast-Enhanced (DCE)-MRI, and Magnetic Resonance Spectroscopy Imaging (MRSI). Additionally, Apparent Diffusion Coefficient map is based on the computation of a coefficient derived from multiple DW-MRI. **Currently, no CAD system has been developed using all the available modalities and thus discarding their potential discriminating power to diagnose prostate cancer.**

The closest attempts used three of these modalities (i.e., T₂-W-MRI, DW-MRI, DCE-MRI) and discarded MRSI^{5,6}. This latter, however, has been shown to be extremely helpful to grade cancer aggressiveness particularly in the CG⁷, which is the most challenging zone in terms of cancer detection. **Furthermore, the current researches solely focus on the delineation of prostate cancers rather than on the cancer aggressiveness assessment.**

Therefore, the aim of this project is to design a CAD system able to both detect and assess prostate cancers using all currently available multi-parametric MRI modalities. The architecture of our CAD system will imply the following investigations:

1. Pre-processing to enhance the quality of MRI images (bias field correction, denoising, and normalisation),
2. Segmentation of prostate zones using multi-parametric MRI and deep-learning,

¹J. Ferlay et al. “Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012”. In: *European Journal of Cancer* 49.6 (2013), pp. 1374 –1403.

²F. H. Schroder et al. “Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up”. In: *The Lancet* 384.9959 (2015), pp. 2027 –2035.

³C. Delpierre et al. “Life expectancy estimates as a key factor in over-treatment: the case of prostate cancer”. In: *Cancer Epidemiol* 37.4 (2013), pp. 462–468; Schroder et al., “Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up”.

⁴G. Lemaître et al. “Computer-Aided Detection and Diagnosis for Prostate Cancer based on mono and multi-parametric MRI: A review”. In: *Computers in Biology and Medicine* 60 (2015), pp. 8 –31.

⁵G. Litjens et al. “Computer-aided detection of prostate cancer in MRI”. in: *Medical Imaging, IEEE Transactions on* 33.5 (2014), pp. 1083–1092. ISSN: 0278-0062.

⁶S. Viswanath et al. “Enhanced multi-protocol analysis via intelligent supervised embedding (EMPrAvISE): detecting prostate cancer on multi-parametric MRI”. in: *Proc. SPIE 7963, Medical Imaging 2011: Computer-Aided Diagnosis*. 2011.

⁷E. K. Vos et al. “Multiparametric Magnetic Resonance Imaging for Discriminating Low-Grade From High-Grade Prostate Cancer.” In: *Investigative Radiology* (2015).

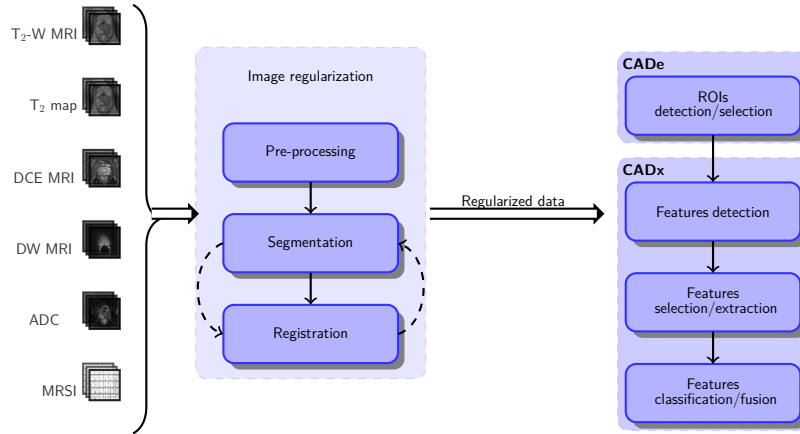


Figure 1: Common CAD framework based on MRI images used to detect prostate cancer.

3. Registration of multi-parametric MRI using spline-based non-linear diffeomorphism,
4. Detection and assessment of prostate cancers using using multi-parametric MRI and deep-learning,
5. Identification of markers by inspection of the neural-network and transfer to classical machine learning approach.

These methodologies will be extensively presented and argued in Sect. 2.1.2.

2.1.2 Research methodologies

Pre-processing MRI images are corrupted by different phenomena: (i) bias field, (ii) noise, and (iii) inter-patient variations. In this regard, particular attention to correct each of these drawbacks will be addressed.

MRI images are affected by the inhomogeneity of the MRI field called bias field, resulting in a smooth variation of the intensities. Although bias correction methods are commonly used to enhance brain MRI images⁸, only one CAD system for prostate has reported to use such pre-processing⁹. The same authors performed an empirical evaluation of the state-of-the-art methods¹⁰ concluding that N3 algorithm¹¹ yields to better classification results than other methods^{12,13}. Recently, Lin *et al.*¹⁴ proposed a method combining the N3 algorithm with the FCM algorithm¹⁵ which outperforms the original methods in terms of breast segmentation. **Therefore, we will perform an empirical comparison of these state-of-the-art methods^{16,17,18,19}, by ensuring the benefits of the method of Lin *et al.* for our specific application.**

Apart of the bias field, MRI images are also degraded due to a Rician noise. Similarly to bias correction, only two CAD systems for prostate denoised images using wavelet-based techniques^{20,21}, offering a proper theoretical baseline for Rician corruption²². Non-Local Means-based denoising techniques have never been used for MRI

⁸U. Vovk, F. Pernus, and B. Likar. "A review of methods for correction of intensity inhomogeneity in MRI". in: *Medical Imaging, IEEE Transactions on* 26.3 (2007), pp. 405–421. ISSN: 0278-0062.

⁹S. Viswanath et al. "Integrating structural and functional imaging for computer assisted detection of prostate cancer on multi-protocol in vivo 3 Tesla MRI". in: *Society of Photo-Optical Instrumentation Engineers (SPIE) Conference Series*. Vol. 7260. Society of Photo-Optical Instrumentation Engineers (SPIE) Conference Series. Feb. 2009.

¹⁰S. Viswanath et al. "Empirical evaluation of bias field correction algorithms for computer-aided detection of prostate cancer on T2w MRI". in: *SPIE Medical Imaging*. International Society for Optics and Photonics. 2011, pp. 79630V–79630V.

¹¹J. G. Sled, A. P. Zijdenbos, and A. C. Evans. "A nonparametric method for automatic correction of intensity nonuniformity in MRI data". In: *IEEE Trans Med Imaging* 17.1 (1998), pp. 87–97.

¹²M. Styner et al. "Parametric estimate of intensity inhomogeneities applied to MRI". in: *Medical Imaging, IEEE Transactions on* 19.3 (2000), pp. 153–165. ISSN: 0278-0062.

¹³M. S. Cohen, R. M. DuBois, and M. M. Zeineh. "Rapid and effective correction of RF inhomogeneity for high field magnetic resonance imaging". In: *Human brain mapping* 10.4 (2000), pp. 204–211.

¹⁴M. Lin et al. "A new bias field correction method combining N3 and FCM for improved segmentation of breast density on MRIa)". In: *Medical physics* 38.1 (2011), pp. 5–14.

¹⁵M. N. Ahmed et al. "A modified fuzzy c-means algorithm for bias field estimation and segmentation of MRI data". In: *Medical Imaging, IEEE Transactions on* 21.3 (2002), pp. 193–199.

¹⁶Sled, Zijdenbos, and Evans. "A nonparametric method for automatic correction of intensity nonuniformity in MRI data".

¹⁷Styner et al., "Parametric estimate of intensity inhomogeneities applied to MRI".

¹⁸Cohen, DuBois, and Zeineh, "Rapid and effective correction of RF inhomogeneity for high field magnetic resonance imaging".

¹⁹Lin et al., "A new bias field correction method combining N3 and FCM for improved segmentation of breast density on MRIa)".

²⁰S. Mallat. *A wavelet tour of signal processing, Third Edition: The sparse way*. 3rd. Academic Press, 2008. ISBN: 0123743702, 9780123743701.

²¹A. Pizurica et al. "A versatile wavelet domain noise filtration technique for medical imaging". In: *IEEE Trans Med Imaging* 22.3 (2003), pp. 323–331.

²²R.D. Nowak. "Wavelet-based Rician noise removal for magnetic resonance imaging". In: *Image Processing, IEEE Transactions on* 8.10 (1999), pp. 1408–1419. ISSN: 1057-7149.

prostate images, but extensively and successfully for other MRI applications²³. **Thus, we will perform an empirical evaluation of the Non-Local Means-based techniques^{24,25} and wavelet-based technique²⁶ to select the appropriate method to our application.**

CAD systems are based on machine learning classifiers which are trained to differentiate cancerous from healthy tissue. The classification performance of these classifiers highly relies on the consistency of the dataset. Subsequently, one can emphasize the desire to reduce the inter-patient variability of the MRI dataset. In this regard, each patient dataset needs to be standardised/normalised to common basis, modality by modality. Only two methods have been used in CAD for prostate: the first method consists in normalising the images via the z -score, while the second technique is based on a linear normalisation by parts²⁷. Lemaître *et al.*²⁸ developed a normalisation technique using the Rician properties of the MRI signal, which outperforms the previous methods for T₂-W-MRI images. **Thus, we will extend this work to the other modalities DCE-MRI and DW-MRI.**

MRSI is a modality related to one dimensional signal, thus enhancing techniques differs from the one used in MRI. The MRSI spectra have to be corrected for several phenomena: phase correction, water and lipid residuals filtering, baseline correction, frequency alignment, and normalisation. This set of enhancement techniques already have been investigated by Lemaître *et al.*²⁹, in a study focusing solely on the MRSI modality for prostate cancer detection; **this knowledge will be the basis of MRSI enhancement.**

Segmentation Litjens used t2w and adc to segment the prostate using multi-atlas method. Viswanath used an active shape model

From the survey of Soumya, probabilistic atlas bring robustness and ASM accuracy. We can do an hybrid with machine learning and an ASM to refine

Registration In multi-parametric MRI, the data are collected in a sequential manner, involving a possible misalignment between the different modalities. Mitra *et al.*³⁰ developed an automatic multi-modal non-rigid registration method, which has been shown to outperform the state-of-the-art methods. This method was initially used for registration between T₂-W-MRI and Ultra-Sound prostate images, **therefore, we will extend this method to align our multi-parametric MRI dataset.**

Detection and assessment

2.2 Clarity and quality of transfer of knowledge/training for the development of the researcher in light of the research objectives

2.3 Quality of the supervision and the hosting arrangements

Qualifications and experience of the supervisor(s)

Career development

2.4 Capacity of the researcher to reach and re-enforce a position of professional maturity in research

3 IMPACT

3.1 Enhancing research- and innovation-related human resources, skills, and working conditions to realise the potential of individuals and to provide new career perspectives

In this section, please explain the impact of the research and training on the Experienced Researcher's career. The fellowship, including any secondments in Europe should maximise the impact on the researcher's activity on European society, including the science base and/or the economy, in a manner appropriate to the research field.

²³ J. V. Manjon et al. "MRI denoising using non-local means". In: *Med Image Anal* 12.4 (2008), pp. 514–523.

²⁴ J. V. Manjon et al. "New methods for MRI denoising based on sparseness and self-similarity." In: *Medical Image Analysis* 16.1 (Jan. 2012), pp. 18–27.

²⁵ P. Coupé et al. "Adaptive Multiresolution Non-Local Means Filter for 3D MR Image Denoising". In: *IET Image Processing* (Nov. 2011), accepted.

²⁶ Pizurica et al., "A versatile wavelet domain noise filtration technique for medical imaging".

²⁷ A. Madabhushi and J. K. Udupa. "New methods of MR image intensity standardization via generalized scale". In: *Med Phys* 33.9 (2006), pp. 3426–3434.

²⁸ This work is submitted for publication.

²⁹ G. Lemaître. "Absolute quantification at 3 T". MA thesis. Université de Bourgogne, Heriot-Watt University, Universitat de Girona, 2011.

³⁰ J. Mitra et al. "A spline-based non-linear diffeomorphism for multimodal prostate registration". In: *Med Image Anal* 16.6 (2012), pp. 1259–1279.

3.2 Effectiveness of the proposed measures for communication and results dissemination

Required sub-headings:

Communication and public engagement strategy of the action

Dissemination of the research results

Exploitation of results and intellectual property

Concrete plans for the above must be included in the Gantt Chart. The new knowledge generated by the action should be used wherever possible to enhance the career of the researcher, to advance research, to foster innovation, and to promote the research profession to the public. The following sections of the European Charter for Researchers refer specifically to public engagement and dissemination:

Public engagement Researchers should ensure that their research activities are made known to society at large in such a way that they can be understood by non-specialists, thereby improving the public's understanding of science. Direct engagement with the public will help researchers to better understand public interest in priorities for science and technology and also the public's concerns.

Dissemination, exploitation of results All researchers should ensure, in compliance with their contractual arrangements, that the results of their research are disseminated and exploited, e.g. communicated, transferred into other research settings or, if appropriate, commercialised. Senior researchers, in particular, are expected to take a lead in ensuring that research is fruitful and that results are either exploited commercially or made accessible to the public (or both) whenever the opportunity arises.

4 IMPLEMENTATION

4.1 Overall coherence and effectiveness of the work plan

The proposal should be designed in the optimal way to achieve the desired impact. A Gantt Chart should be included in the text where the following should be listed:

- Work Packages description;
- List of major deliverables;
- List of major milestones;
- Secondments if applicable.

The schedule should be in terms of number of months elapsed from the start of the project.

4.2 Appropriateness of the management structure and procedures, including quality management and risk management

Develop your proposal according to the following lines:

- Project organisation and management structure, including the financial management strategy, as well as the progress monitoring mechanisms put in place;
- Risks that might endanger reaching project objectives and the contingency plans to be put in place should risk occur.

The following could be also included in the Gantt Chart:

- Progress monitoring;
- Risk management;
- Intellectual Property Rights (IPR).

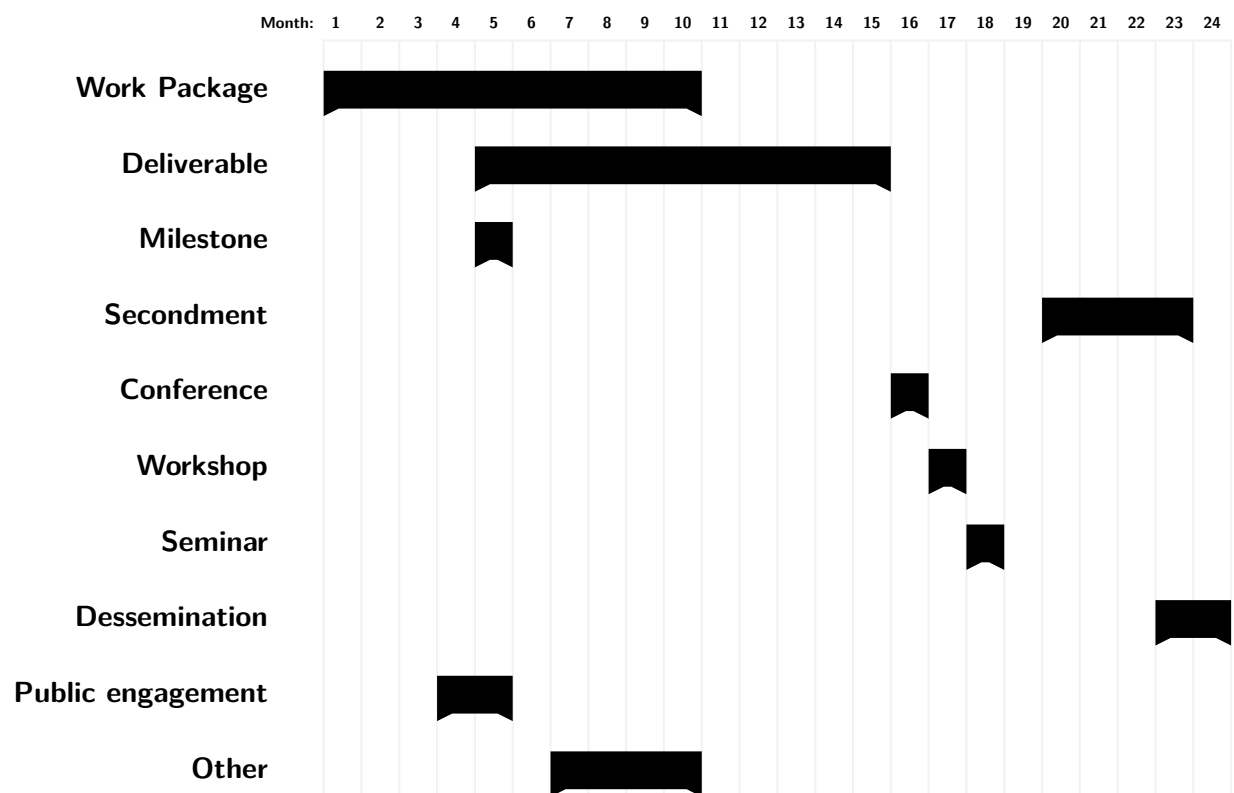


Figure 2: Example Gantt Chart

4.3 Appropriateness of the institutional environment (infrastructure)

Give a description of the legal entity/ies and its main tasks (per participant). Explain why the fellowship has the maximum chance of a successful outcome.

NB: Each participant is described in Section 6. This specific information should not be repeated here.

4.4 Competences, experience and complementarity of the participating organisations and institutional commitment

Here describe how the fellowship will be beneficial for both the Experienced Researcher and host organisation(s).

- Commitment of beneficiary and partner organisations to the programme (for partner organisations, please see also section 6)

Partner organisations: The role of Partner organisations in MS/AC for secondments and their active contribution to the research and training activities should be described.

5 CV OF THE EXPERIENCED RESEARCHER

This section should be limited to maximum 5 pages and should include the standard academic and research record. Any research career gaps and/or unconventional paths should be clearly explained so that this can be fairly assessed by the independent evaluators. The Experienced Researchers must provide a list of achievements reflecting their track, and this may include, if applicable:

1. Publications in major international peer-reviewed multi-disciplinary scientific journals and/or in the leading international peer-reviewed journals, peer-reviewed conference proceedings and/or monographs of their respective research fields, indicating also the number of citations (excluding self-citations) they have attracted.
2. Granted patent(s).
3. Research monographs, chapters in collective volumes and any translations thereof.
4. Invited presentations to peer-reviewed, internationally established conferences and/or international advanced schools.
5. Research expeditions that the Experienced Researcher has led.
6. Organisation of International conferences in the field of the applicant (membership in the steering and/or programme committee).
7. Examples of leadership in industrial innovation.
8. Prizes and Awards.

6 CAPACITIES OF THE PARTICIPATING ORGANISATIONS

All organisations (whether beneficiary or partner organisation) must complete the appropriate table below. Complete one table of maximum one page for the beneficiary and half a page per partner organisation (min font size: 9). The experts will be instructed to disregard content above this limit.

Beneficiary X

General Description	
Role and Commitment of key persons (supervisor)	(Including names, title, qualifications of the supervisor)
Key Research Facilities, Infrastructure and Equipment	(Demonstrate that the team has sufficient facilities and infrastructure to host and/or offer a suitable environment for training and transfer of knowledge to recruited Experienced Researcher)
Independent research premises?	
Previous Involvement in Research and Training Programmes	
Current involvement in Research and Training Programmes	(Detail the EU and/or national research and training actions in which the partner is currently participating)
Relevant Publications and/or research/innovation products	(Max 5)

Partner Organisation Y

General Description	
Key Persons and Expertise (supervisor)	
Key Research facilities, infrastructure and equipment	
Previous and Current Involvement in Research and Training Programmes	
Relevant Publications and/or research/innovation product	(Max 3)

ENDPAGE

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