Multimodal Prediction of Immunotherapy Treatment Outcomes for Renal Cell Carcinoma

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Abstract

Renal cell carcinoma is a type of kidney cancer that starts from the kidneys. It is the 8th most common cancer in the UK and an increase of new cases of 2% has been seen in the last twenty years. Immunotherapy is a type of cancer treatment that 'wakes up' the patient's own immune system so it can fight the cancer. New drugs which act in this way have worked well in patients with skin cancer (melanoma), lung cancer and in patients with kidney cancer that has spread outside the kidney. Nevertheless, most patients do not achieve meaningful benefit from immunotherapy, due to primary or acquired resistance, while immune-related adverse events can limit the use and effectiveness of Immune Checkpoint Inhibitors and negatively impact quality of life and survivorship. Biomarkers that can predict response, resistance and immune-related adverse events are an unmet clinical need with profound implications on health resources and therapeutic outcomes.

The PhD project will produce novel AI innovations in multimodal data integration and modelling that allows biomarker discovery, predicting treatment outcomes and toxicities for standard care and emerging immunotherapies using in depth patient profiles that include molecular profiling, immune profiling, spatial image profiling. The PhD research will aim to understand the role of each of these modalities for immunotherapy response and combine the modalities to discover biomarkers and predict treatment outcomes. The research will also validate and explain the results of the model using explainable AI techniques.

The PhD student will work closely with researchers and clinicians in the Manifest project, led by Francis Crick Institute, that includes 6 NHS trusts, 14 academic institutes and Universities, and several industry partners, including Roche-Sequencing, M:M Bio, IMU Biosciences. This collaboration will help generate clinical and industry impact.

Introduction

Harnessing the immune system to treat cancer has revolutionised survival outcomes for many patients. Immune checkpoint inhibitor therapies which unleash the brakes from immune cells to kill cancer cells, have become standard of care for many cancer subtypes. The success of existing, emerging and future immunotherapies and their routine use in the NHS is dependent on the appropriate tools, data and technology to rationalise their use and manage their side effects. Nevertheless, almost no biomarkers today can effectively distinguish responders from non-responders, predict toxicity, or guide treatment choices.

The goals of this PhD project aligns with the Manifest project, lead by Francis Crick Institute, that aims at multimodal data integration and modelling for multiple tumour types (melanoma, renal cell carcinoma, bladder cancer and triple negative breast cancer) to predict treatment outcomes and toxicities for immunotherapy. The PhD will use the existing multi-modal data on

Renal cell carcinoma, collected as part of the Manifest project – multi omics data, histopathology and clinical data -- to design predictive AI models for biomarker discovery, predicting treatment outcomes and toxicity.
The black-box nature of modern deep learning (DL) models makes it challenging to trust and understand the rationale behind their decisions, especially in high-stakes domains such as medical diagnostics. Explainable artificial intelligence (XAI) techniques aim to increase the trustworthiness and transparency of a DL model's decision-making process by providing accessible interpretations. The PhD student will design XAI techniques for the multi-modal predictive models to help validate and interpret the model decisions. The student will have the opportunity of working directly with clinicians with renal cancer and/or modality expertise to interpret these results. In addition to all the 'standard' explainability techniques this consortium also has the advantage of a spatial biology work package whose outputs will further explain and validate model outputs.

Research Challenge

The research challenges that will be addressed in this project are as follows,

1. **SOTA models for individual modalities:** Applying SOTA deep learning methods to individual modalities and reviewing the results across modalities (late fusion), enabling us to:
    a. Understand which modalities provide the best predictor of Immunotherapy response
    b. Understand the relationships between modalities
    c. Understand the optimal combination and ordering of a pipeline of models which could be mapped to clinical care (and collection of samples).
2. **Combining modalities:** Given a comprehensive dataset for renal cell carcinoma, the student will experiment with data integration methods to see where and how modalities can be combined to provide further insight (via intermediate fusion). In particular, where we have varying amounts of overlapping data across modalities, the student will need to be creative with the approaches we select. For example, similar modalities such as omics, might allow earlier integration and the opportunity to jointly learn representations. Whereas a distinct modality such as image data – with a very different distribution – might be integrated later, after representations have already been obtained. In this way, a hierarchy of integrations can be created to ensure fusion between modalities is effective at each level.
3. **Explainability:** Design novel XAI techniques targeting interpretation of AI models for individual modalities and AI models for combined modalities to help explain and validate the results. The student will work closely with clinicians and experts in the area to ensure the explanations are accessible to clinicians and take biological/clinical assumptions into account. Compare against state-of-the-art XAI techniques.
4. **Uncertainty quantification:** Develop uncertainty quantification metrics to associate model predictions with a degree of confidence, for clinical correlations. Explore Monte Carlo dropout and conformal analysis as a start
5. **Technical Robustness**: Assess robustness of the models with respect to incompleteness (eg. missing modalities in samples during testing), out-of-distribution test data from different device settings using techniques like knowledge distillation, weight space ensembling, adversarial testing.
6. **Evaluation:** Conduct an evaluation study with clinicians to evaluate the accuracy of the model outputs and explanations for treatment outcomes with clinicians. The student will also benchmark his/her methods on public data and public methods on Manifest data for renal cancer.

Data

The PhD will use data from the following Clinical trials

1. RAMPART – Sample size 551. The study looks at two new immunotherapy treatments. The aim was to find out whether taking one drug (durvalumab) or a combination of two drugs (durvalumab and tremelimumab) for one year can prevent or delay kidney cancer from coming back compared to the current standard of care (active monitoring after surgery).
2. PRISM [1] – Sample size 192. The aim of the PRISM study is to assess whether less frequent dosing of ipilimumab (12-weekly versus 3-weekly), in combination with nivolumab, is associated with a favourable toxicity profile without adversely impacting efficacy.
3. MITRE [2] – Sample size 81. The MITRE study explores and validates a microbiome signature in a larger scale prospective study across several different cancer types.

The student will also use public data from The Cancer Genome Atlas Program (TCGA)

Responsible AI/Ethical Considerations

The PhD student working on this project will complete ethics training and responsible AI training offered as part of the CDT and take the following course on Data Ethics, AI and Responsible Innovation from EFI – https://efi.ed.ac.uk/programmes/data-ethics-ai-and-responsible-innovation-free-short-online-course-from-the-university-of-edinburgh/

All members of the research team are required to follow Responsible AI and ethical practices. The PhD student and supervisors will also follow the data sharing agreements in place as part of the Manifest project for access to clinical data.

Expected Outcome & Impact

1. A suite of unimodal models to predict immunotherapy response and toxicities
2. Multimodal fusion for modular integration of unimodal immunotherapy response and understanding modalities with shared and disjoint information on immunotherapy response.
3. Explainability for establishing unimodal and multimodal biomarkers for immunotherapy response
4. Uncertainty quantification as a human oversight measure for confident predictions

The project has immense scope for impact in the clinic and industry through the large network of NHS and industry partners in the Manifest project.

References

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2. Thompson NA, Stewart GD, Welsh SJ, Doherty GJ, Robinson MJ, Neville BA, Vervier K, Harris SR, Adams DJ, Dalchau K, Bruce D, Demiris N, Lawley TD, Corrie PG. The MITRE trial

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