Melbourne Urological Research Alliance: Turning patient tumours into tools for studying prostate cancer

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INTRODUCTION

- Prostate cancer is one of the most common diagnosed cancers worldwide.
- Despite this, there are few preclinical models of prostate cancer available that represent the heterogeneity of disease.
- Effective, preclinical research relies on robust and accurate models of prostate cancer.
- A Patient Derived Xenograft (PDX) is a human tumour sample grown in mice that allows for preclinical studies on prostate cancers, similar to those seen in clinical practice.
- PDXs from hormone naïve and resistant tumours need to be created to accurately test new therapeutic options to treat prostate cancer.
- The Melbourne Urological Research Alliance (MURAL) was established to facilitate the collection of urological tumours from patients, with the plan to create new PDX models of prostate cancer.
- MURAL was founded in 2017 by Professor Risbridger and Professor Taylor, alongside renowned clinicians from Cabrini Health.

Aims:
1) To establish a comprehensive repository of PDX models that span all stages of prostate cancer.
2) Use these samples to create serially-transplantable PDX models that can be grown over many years.
3) Share the PDX models with academic and commercial research partners nationally and internationally.

Figure 1: MURAL is a collaboration between research scientists and clinicians from different disciplines.

METHODS

SAMPLE COLLECTION

- Suitable participants, including patients from Cabrini Malvern, were identified by the treating clinicians and consented to the study by the clinical coordinators.
- At time of routine procedure related to their prostate cancer, samples were collected in theatre and transported to pathology where cancer tissue was confirmed and provided for research.
- Samples have been collected from participants at various stages of disease and from different procedures including radical prostatectomy, transurethral resection of the prostate, metastatic biopsy and surgical excision and after death biopsy.
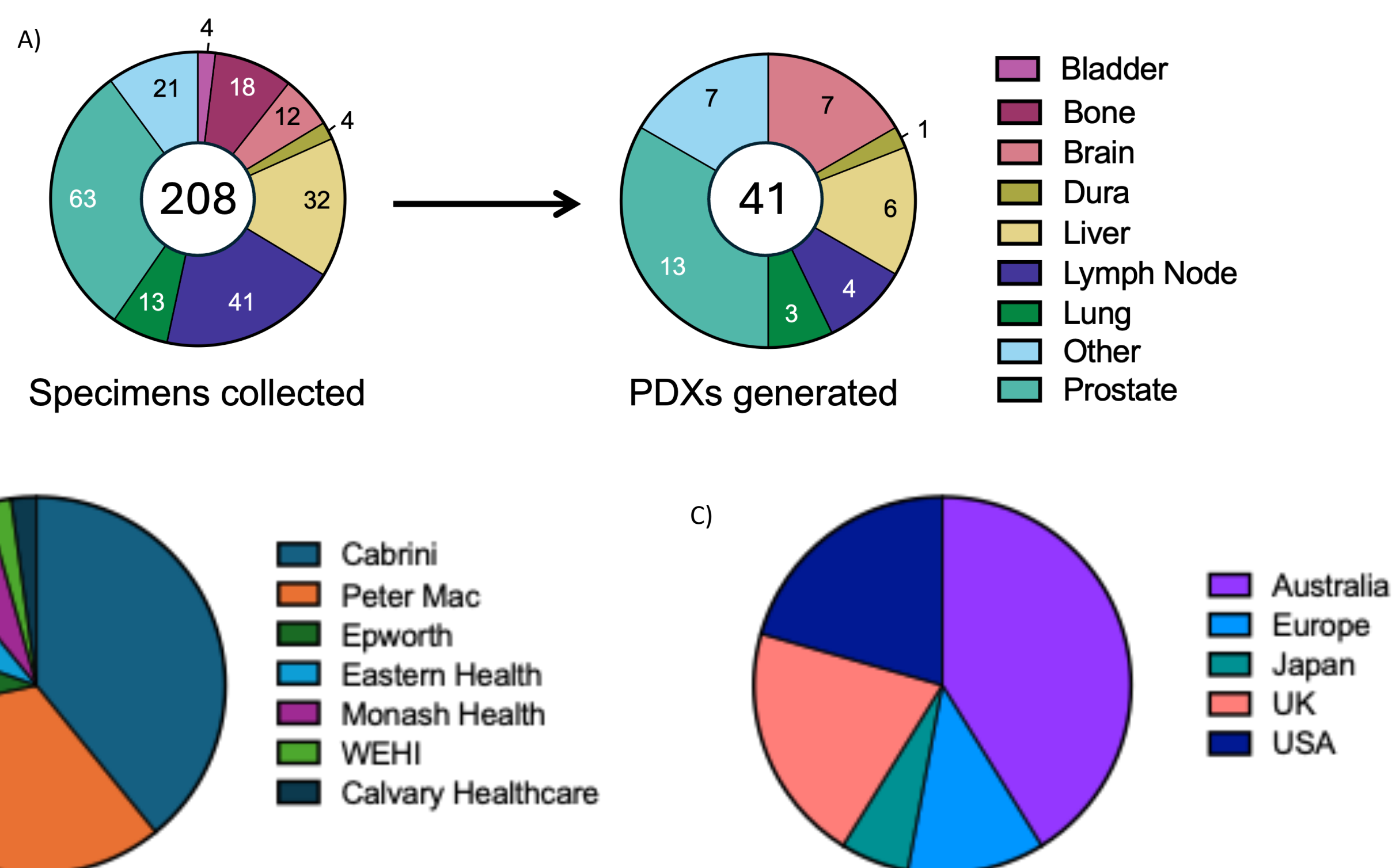

Figure 2: A) Number of prostate tumour samples collected and established as PDX lines; B) Hospital sites where participants were consented and specimens collected; C) Distribution of PDX models worldwide.

ESTABLISHING PDX MODELS

- Patient tissues were grafted into immunocompromised male NSG mice with testosterone implants.
- Samples were grafted under the renal capsule to maximise engraftment rates.
- Grafts are monitored for up to 12 months to assess *in vivo* tumour growth.
- Actively growing tumours can be regrafted into additional mice to establish serially-transplantable PDXs and will add to the MURAL collection.
- When applicable, tumours are regrafted into the subcutaneous site of a new host mouse to allow for pre-clinical testing.
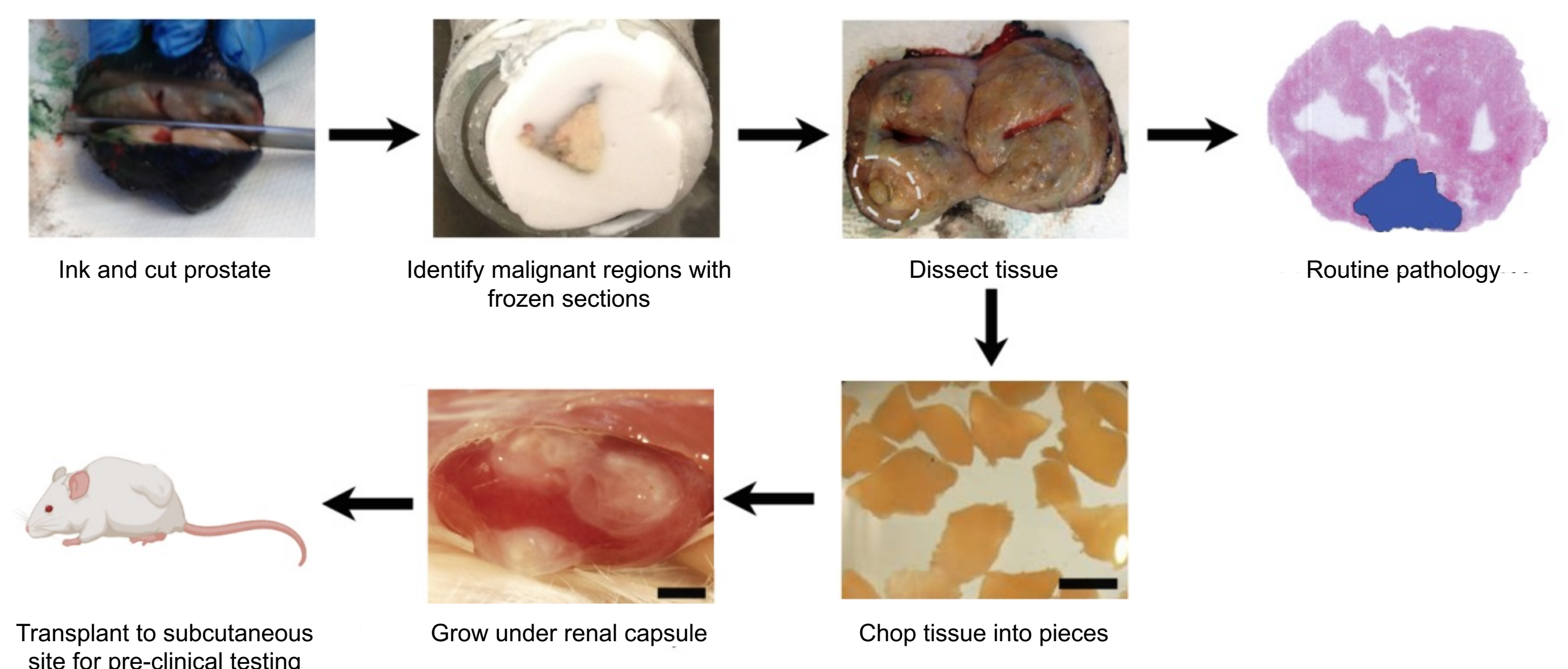

Figure 3: Fresh tissue dissection process for PDX models (Adapted from *Lawrence et al., Nat Protoc. 2013*)
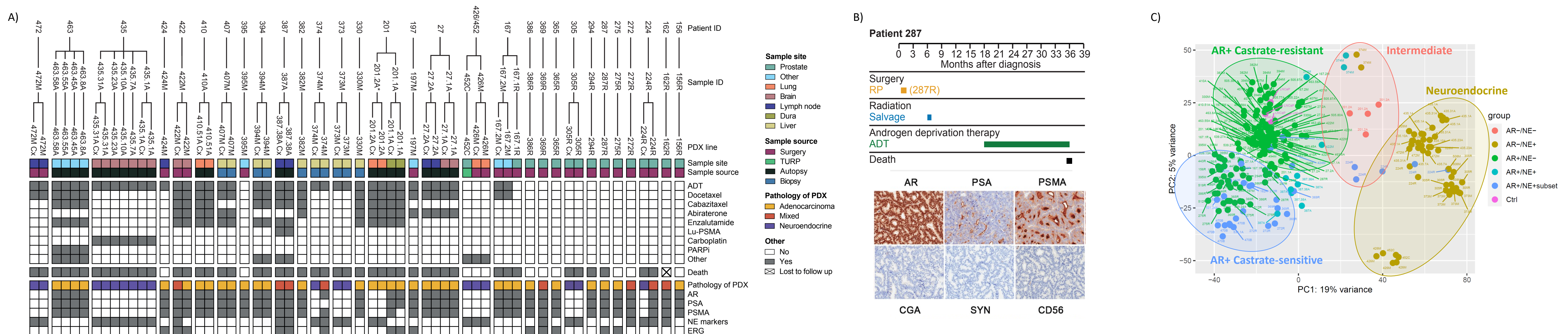
MURAL PDX MODELS

Figure 4: Heatmap summarising 59 prostate cancer PDXs established from 41 specimens obtained from 30 patients (*Risbridger et al., Nat Comms 2021*); B) Treatment timeline and IHC staining from diagnosis to death from a representative patient (287R) (*Risbridger et al., Nat Comms 2021*); C) Bulk RNAseq data showing how the MURAL PDX cohort represents diverse phenotypes of prostate cancer (*unpublished data*).

CONCLUSIONS & FUTURE DIRECTIONS

- The establishment and continual growth of MURAL is crucial for advancing our understanding of prostate cancer, improving patient outcomes, and driving innovation in treatment approaches.
- As the repository develops, it is vital to continually update it with new models that reflect recent findings in the field, ensuring that it remains a relevant and essential tool for researchers worldwide studying prostate cancer.