University of Glasgow

College of Medical, Veterinary & Life Sciences

GLASGOW MOLECULAR PATHOLOGY NODE

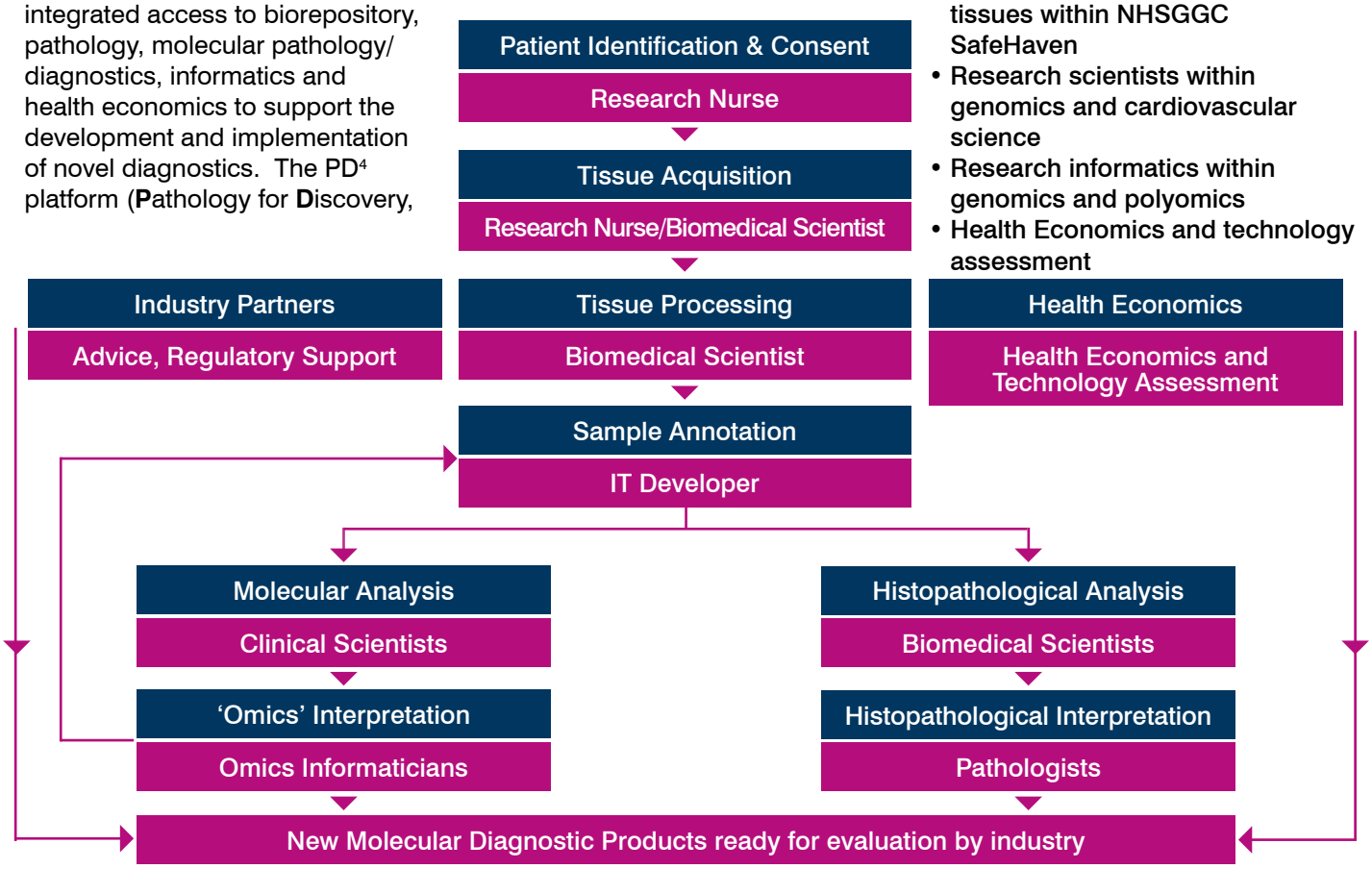
Enabling Development and Implementation of

Novel Diagnostics

The Glasgow Molecular Pathology Node was established to transform the management of cancer and chronic disease by accelerating biomedical research, high quality healthcare provision and economic growth. Central to this vision is the development of a platform that provides integrated access to biorepository, pathology, molecular pathology/ diagnostics, informatics and health economics to support the development and implementation of novel diagnostics. The PD⁴ platform (**P**athology for **D**iscovery, **D**evelopment and **D**elivery of **D**iagnostics) is embedded within the Laboratory Medicine Building at the Queen Elizabeth University Hospital enabling costs and cultures to be shared and development pipelines to be firmly rooted in clinical practice and widely translatable.

The PD⁴ platform enabled by the Glasgow Molecular Pathology Node includes:

- NHSGGC biorepository activities for tissue acquisition and handling
- Clinical and biomedical scientists and pathologist contributions
- Clinical informatics/developer including annotation of research tissues within NHSGGC SafeHaven
- Research scientists within genomics and cardiovascular science
- Research informatics within genomics and polyomics
- Health Economics and technology assessment



This platform can be accessed by researchers and industry that are at different stages in the development pathway including discovery, assay development, validation, evaluation and translation into clinical use. The PD⁴ platform provides opportunities for engagement for researchers and industry to facilitate molecular diagnostics development and associated technologies and software enabling a range of outcomes including: new molecular diagnostics for clinical trials and clinical practice; enhance of molecular diagnostic and pathology services; improved efficiency and cost savings and transfer of expertise and assays across the Node network.

From Patient to Panel to Patient –

The Precision-Panc Sample Pipeline

Pancreatic cancer has one of the highest mortality rates of any cancer type, with fewer than 6% of patients in the UK surviving longer than 5 years after diagnosis. Even if identified early, treatment options for the disease are limited in their efficacy: targeted surgery in conjunction with chemotherapy remains the only currently viable option to improve prognosis; for many patients who do not qualify for surgery, current chemotherapeutic techniques do little to improve survival. Precision-Panc offers an alternative to standard treatment strategies: using molecular phenotyping to find the right clinical drug trial for each patient.

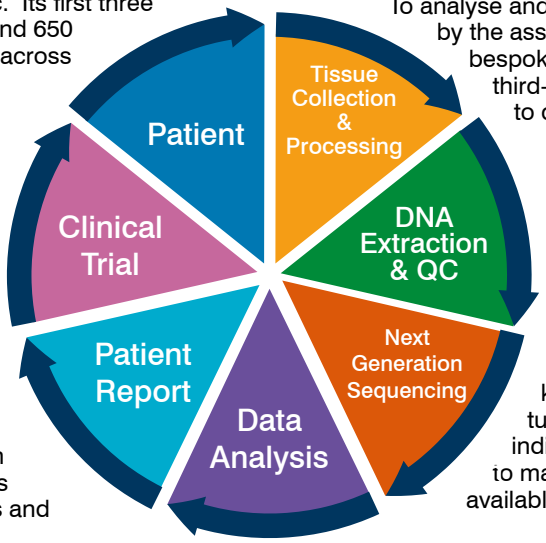
Overview: The Precision-Panc Approach

Precision-Panc is an ambitious program of discovery, pre-clinical and clinical work that aims to accelerate the evolution of pancreatic cancer treatment in the clinic. Its first three clinical trials launched in 2018 and around 650 patients will be recruited from hospitals across the UK.

Consented patients will have a tumour biopsy taken for analysis by Next Generation Sequencing (NGS). NGS will be carried out at the Wolfson Wohl Cancer Research Centre's (WWCRC) state-of-art sequencing facility, using a pancreatic-cancer specific assay that has been optimised for clinical use. The data obtained will be used to select the clinical trial best suited for that individual.

In Glasgow, this precision oncology approach relies on close collaboration between academia, industry and a team of multi-disciplinary healthcare providers including surgeons, oncologists, nurses and scientists.

The Glasgow Molecular Pathology Node supports staff members working on Precision-Panc at the WWCRC, Glasgow Clinical Trials Unit and the NHSGGC Safe Haven.



STEP 1 Tissue Collection & Processing

Samples are collected from patients at the Glasgow Royal Infirmary and transferred to the Molecular Diagnostics team at the Queen Elizabeth University Hospital (QEUH) for DNA extraction and then on to the sequencing team at the WWCRC.

Close cooperation between the teams at each site allows the rapid processing of samples that is needed to get patients on to trials in a clinically relevant timeframe.

Tissue samples undergo standard formalin fixation and paraffin-embedding to produce blocks that can be used for routine clinical processes, such as pathology workflows and long-term archiving, or used for DNA extraction for the molecular pathology that underpins Precision-Panc.

STEP 2 DNA Extraction & QC

Tissue "curls" cut from FFPE blocks undergo DNA extraction in QEUH's Molecular Diagnostics laboratory. Once DNA has been extracted it undergoes quality control (QC) tests take place to ensure its integrity and suitability for further analysis. "Minimal sample information", a de-identified set of data supplying crucial details about each sample, along with the QC results and the sample itself, will be passed to the WWCRC Genomics Lab for molecular analysis.

STEP 3 Next Generation Sequencing

A "target capture" sequencing approach is used: molecular probes known as "capture baits" attach to and extract pre-determined DNA sequences of interest from the sample. This approach facilitates analysis of only the clinically relevant areas of the tumour genome, making it faster, cheaper and more powerful than whole genome analysis.

The sequences that we capture for Precision-Panc are based on extensive literature curation and integrated data analysis of whole genome data from the International Cancer Genome Consortium (ICGC), The Cancer Genome Atlas (TCGA) and other large databases of genomic data.

STEP 4 Data Analysis

The target capture panel is a multiplex assay designed to capture a broad range of pancreatic cancer-specific genomic features and all events that are potentially clinically actionable/relevant, including those linked to immunotherapy response and drug resistance.

To analyse and interpret the complex data generated by the assay we are developing HOLMES, a bespoke pipeline combining best-of-breed third-party software with custom algorithms, to deliver the required analytics.

STEP 5 Patient Report

HOLMES outputs a single-page PDF report for each patient. Reports will be reviewed at a multi-disciplinary team meeting and signed off for return to treating physicians.

The report presents physicians with the key genomic features of the patient's tumours and any corresponding clinical indications, allowing them and their patient to make an informed decision based on available options.

STEP 6 Clinical Trial

Precision-Panc is a platform for the **PRIMUS** trials **(Pancreatic canceR Individualised Multi-arm Umbrella Study)**. Different trials recruit patients at different disease stages, with the ultimate aim of Precision-Panc being to expand the portfolio of clinical trials such that the right trial can be found for every pancreatic cancer patient.

In addition to the drug/therapeutic combination being tested, each trial also collects data for translational research, allowing the next wave of trials to be developed in parallel. This ensures rapid progress in Glasgow, this precision oncology approach relies on close collaboration between academia, industry and a team of multi-disciplinary healthcare providers including surgeons, oncologists, nurses and scientists.

Precision-Panc aims to revolutionise treatment of pancreatic cancer by offering new, patient-specific approaches to both surgical and non-surgical therapy of the disease. The programme will first be available to patients across Scotland before expanding throughout the rest of the UK, facilitated by ground-breaking partnerships spanning research, industry and the clinic. Patient samples will be sequenced and analysed via a custom approach; this will produce a report on that patient's tumour profile in a timescale which will enable further treatment. The report will indicate which available clinical trials will offer the best chance to improve prognosis: how that patient responds to this therapeutic approach will help shape the development of future trials and the clinical approach to pancreatic cancer overall.