How the biology of pancreatic cancer-related diabetes informs early detection biomarkers and vice versa.

Eithne Costello

CANCER RESEARCH UK

UK EDI UK Early Detection Initiative for Pancreatic Cancer

Pancreatic CANCER UK

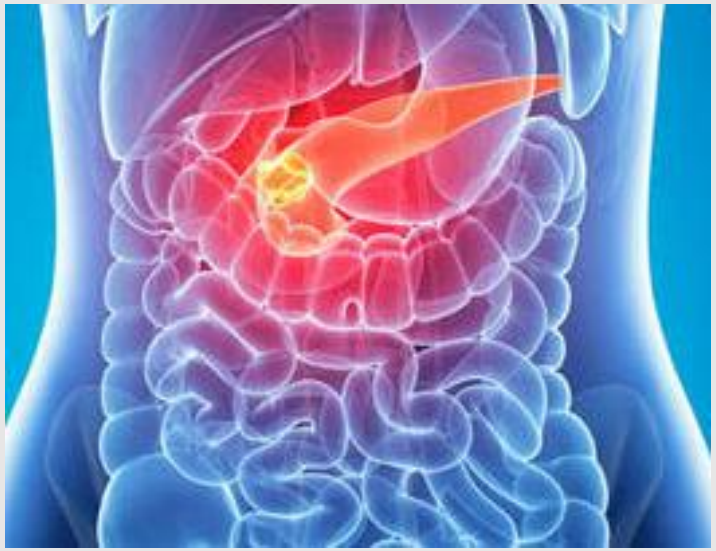
UNIVERSITY OF LIVERPOOL

NHS National Institute for Health Research

ecmc Liverpool

Early Detection of Pancreatic cancer (PDAC) – The unmet need

Pancreatic Cancer (Pancreatic Ductal Adenocarcinoma-PDAC)

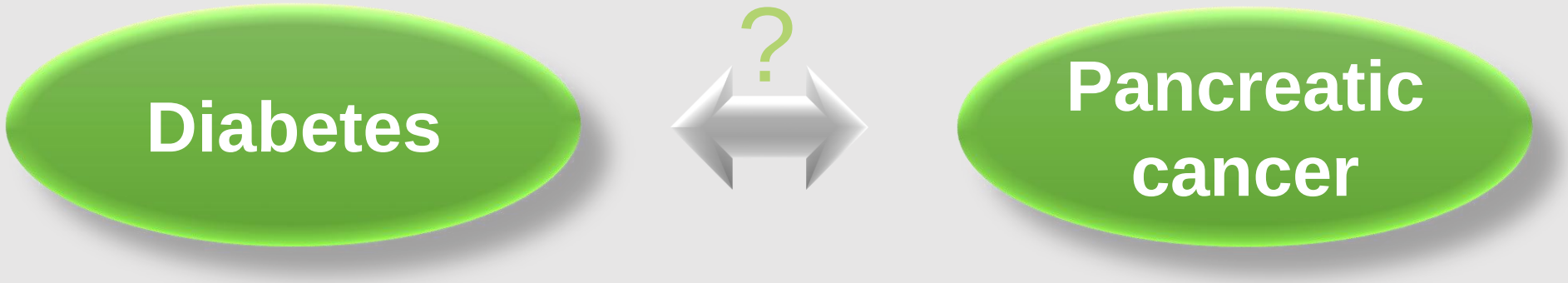


- The **deadliest** of the common cancers
- Incidence rates **increasing**
- Overall five-year survival is ~**9-10%**

Percentage of patients	Tumour	5-year survival
10-20%	Operable	37%
30-40%	Spread locally	12%
>50%	Spread to distant organs	3%

- In 10% of cases there is a family history of pancreatic cancer – screening programs are available.
- **There is no test/screen that allows earlier detection for the remaining 90% of cases (sporadic pancreatic cancer).**

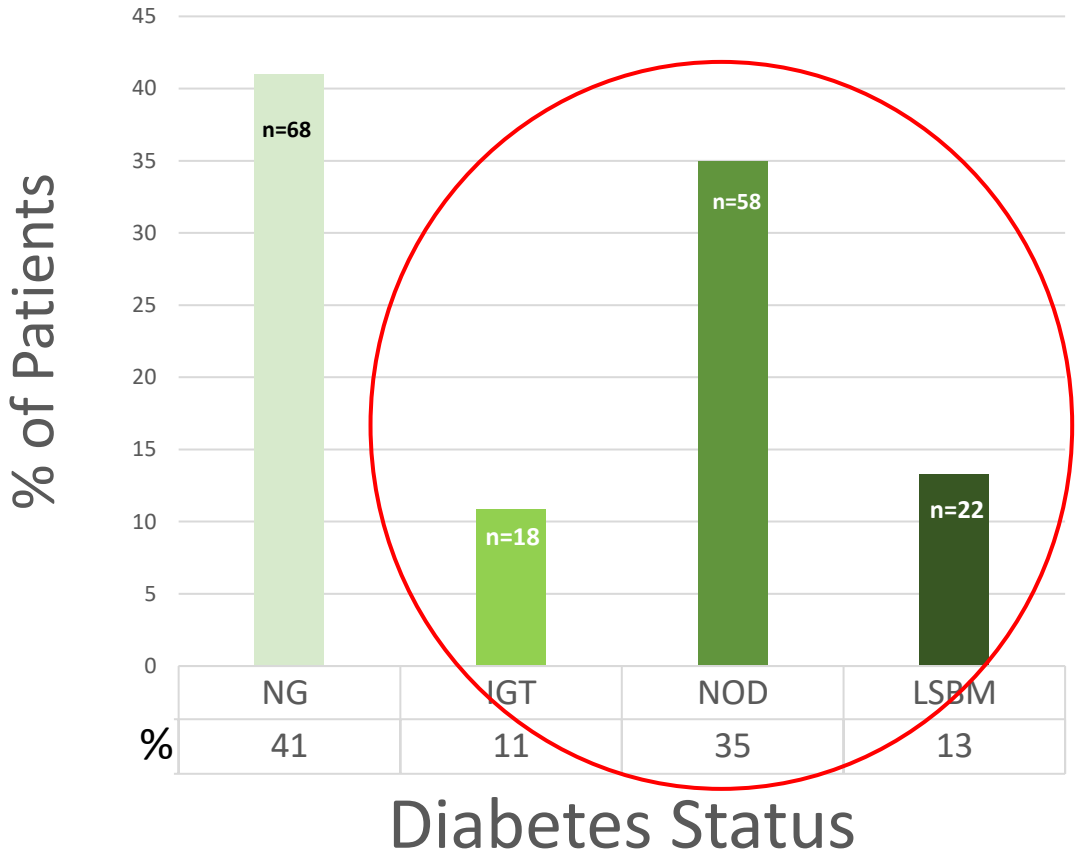
Relationship between pancreatic cancer and diabetes



Diabetes and pancreatic cancer

- **Between 2016-2020, 483 patients underwent pancreas surgery at the Royal Liverpool University Hospital**
- **185 patients had PDAC**
- **For 19 of these the diabetes status was unknown**
- **166 patients where diabetes status was known**

59% of 166 patients operated on for PDAC at LUHFT had disrupted glucose regulation

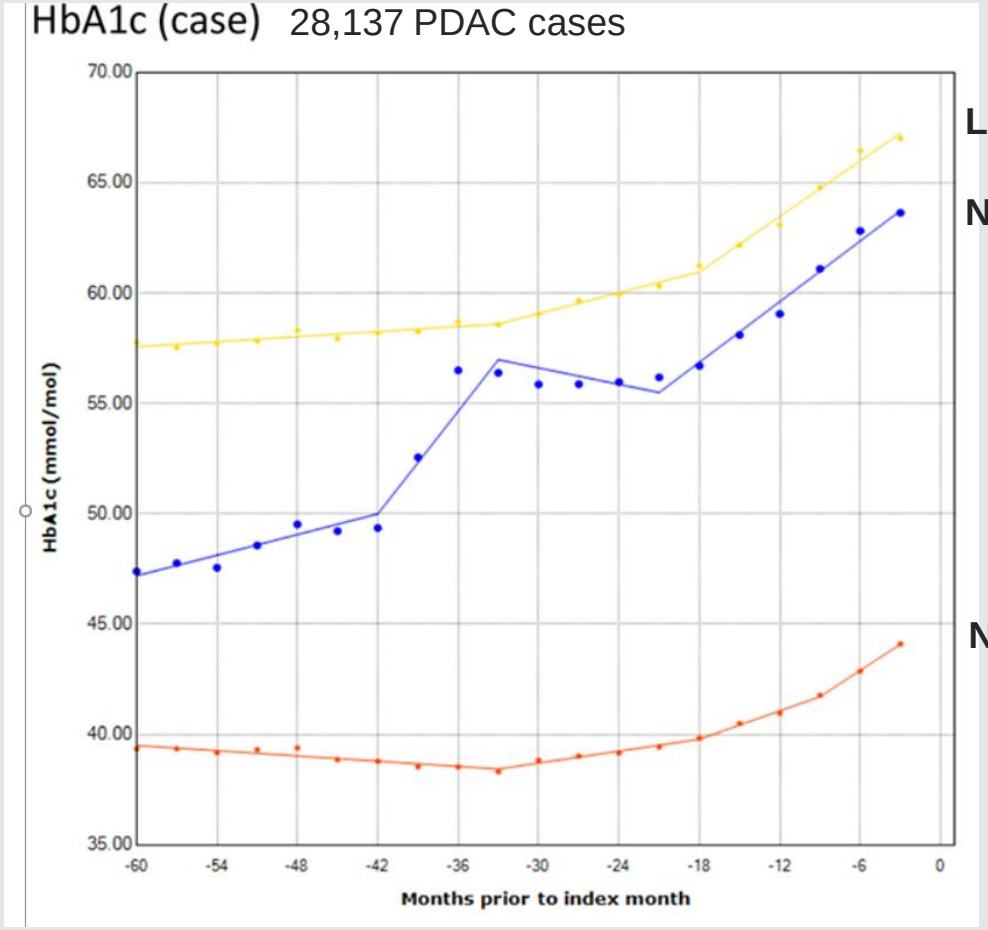


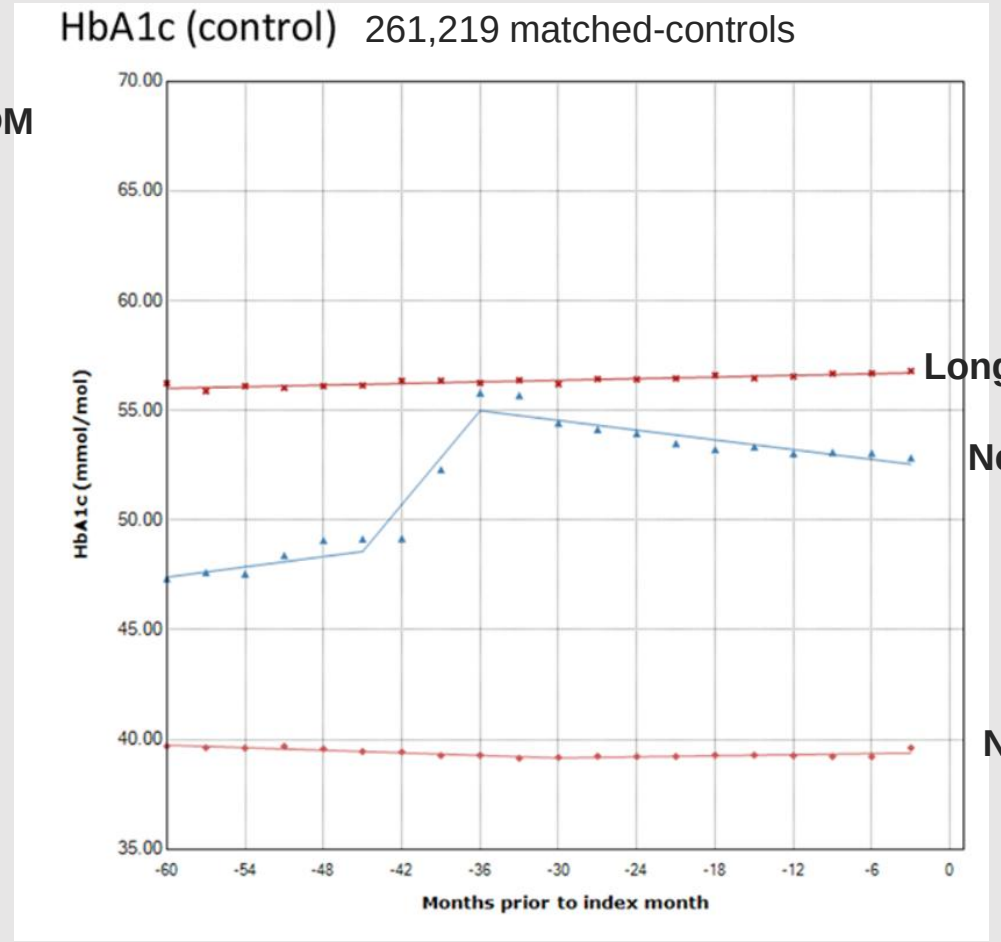
NG: Normoglycemic *(HbA1c below 42 mmol/mol (6.0%);*
IGR: *Impaired Glucose Regulation (HbA1c: 42 -47 mmol/mol (6.0–6.4%));*
DM: *Diabetes (HbA1c ≥ 48 mmol/mol, (6.5%))*
LSDM: *long-standing diabetes mellitus (DM diagnosed >3yr);*
NOD: *new-onset diabetes mellitus within 3yr*

Under revision

Differences between pancreatic cancer-related diabetes and T2DM

Population-based nested case–control study of 28,137 PDAC cases and 261,219 matched-controls in England





Tan PS, Garriga C, Clift A, Liao W, Patone M, Coupland C, Bashford-Rogers R, Sivakumar S, Hippisley-Cox J. Temporality of body mass index, blood tests, comorbidities and medication use as early markers for pancreatic ductal adenocarcinoma (PDAC): a nested case-control study. Gut. 2023 Mar;72(3):512-521. doi: 10.1136/gutjnl-2021-326522. Epub 2022 Jun 27. PMID: 35760494; PMCID: PMC9933161.

Differences between pancreatic cancer-related diabetes and T2DM

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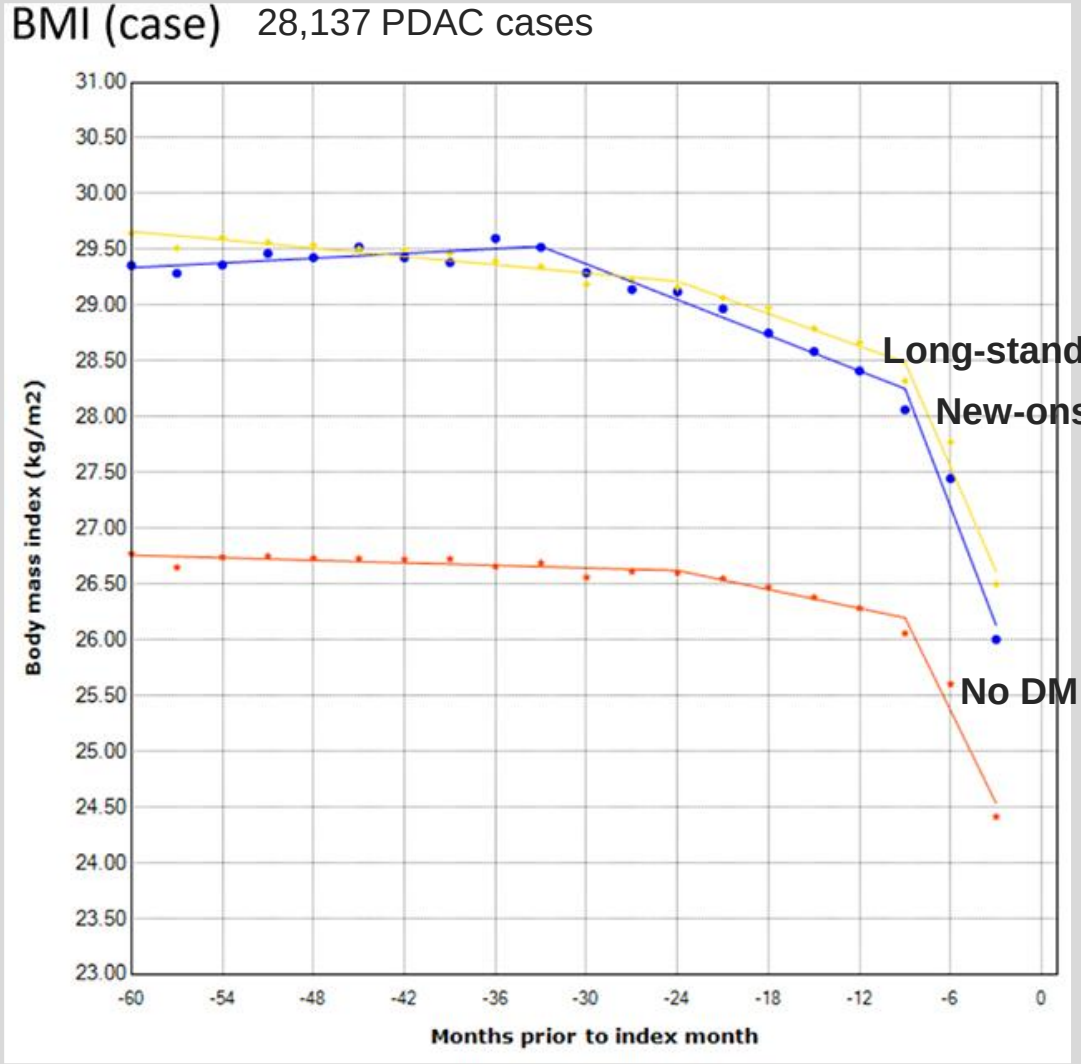

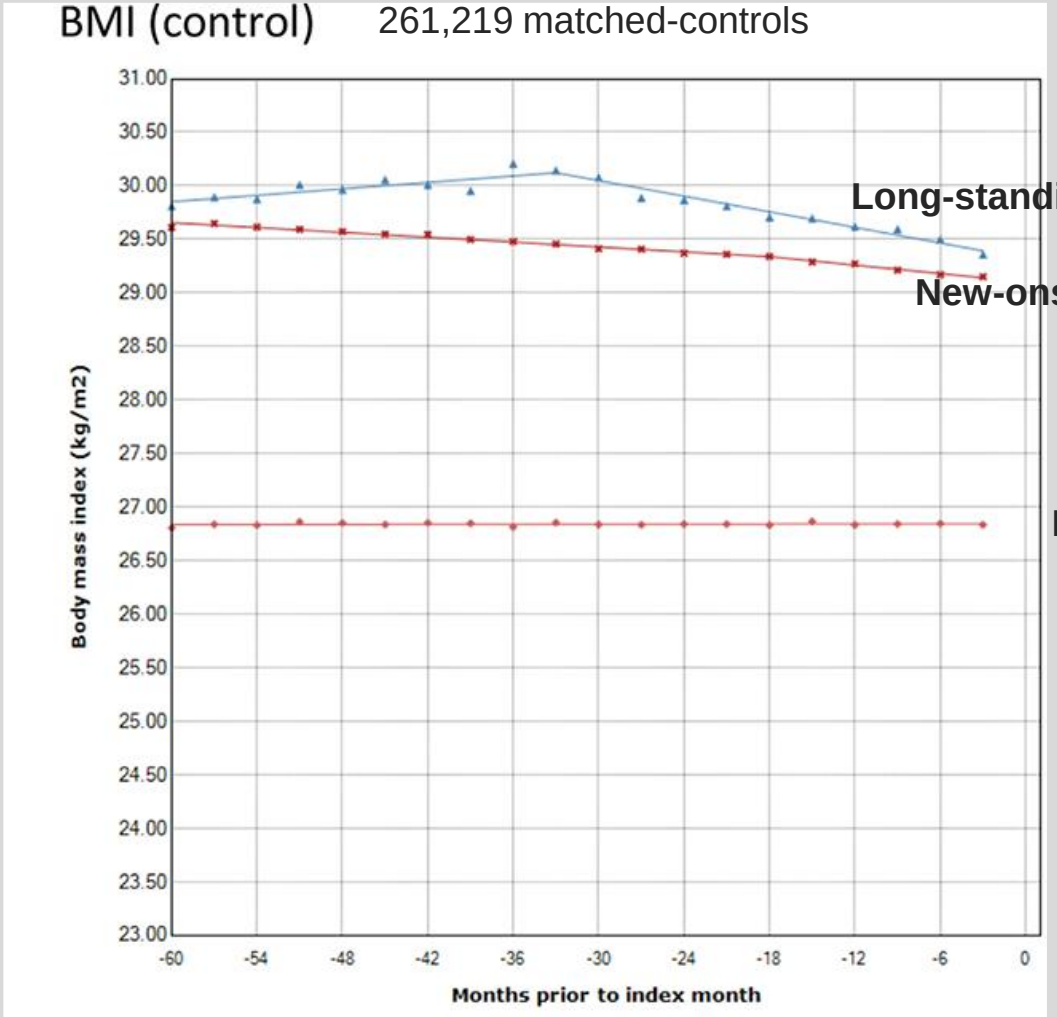

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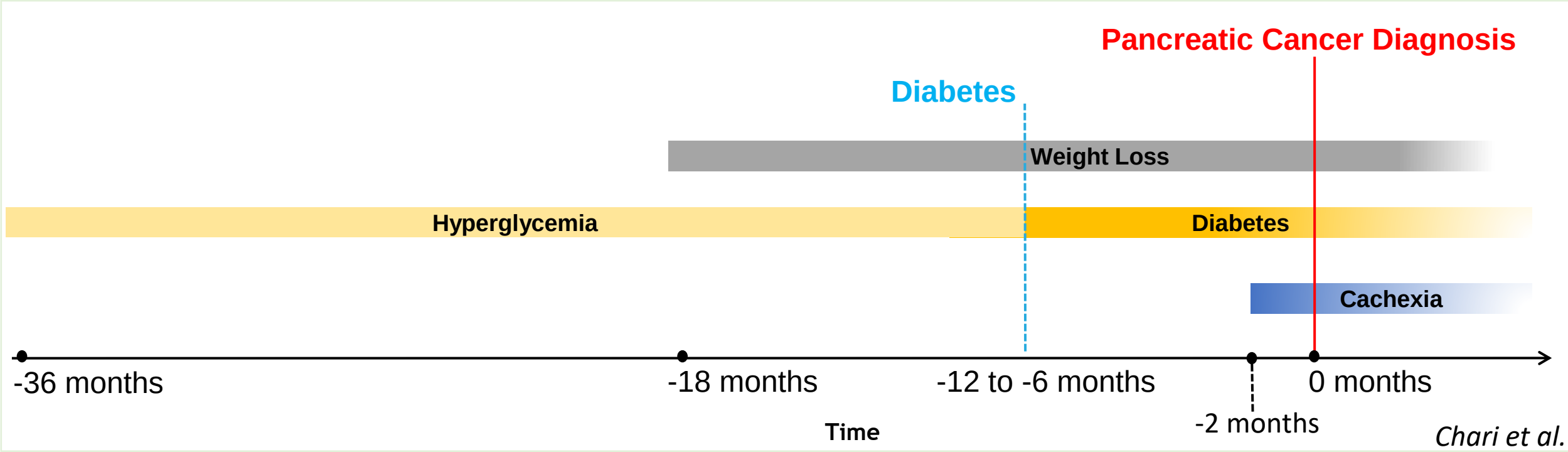
New-onset diabetes mellitus precedes pancreatic cancer diagnosis



~48% of pancreatic cancer patients have diabetes; of which >60% is new-onset diabetes

- **Largest high-risk group for pancreatic cancer**

New-onset diabetes is common with >250,000 new cases/year in the UK

Proposed pathways for early PDAC detection

New-Onset Diabetes is a High-risk group for pancreatic cancer

Type 2 Diabetes

Type 3c Diabetes

PDAC-related Diabetes

UK Early Detection Initiative for Pancreatic Cancer

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It is not feasible with current modalities to screen all individuals with NOD for pancreatic cancer

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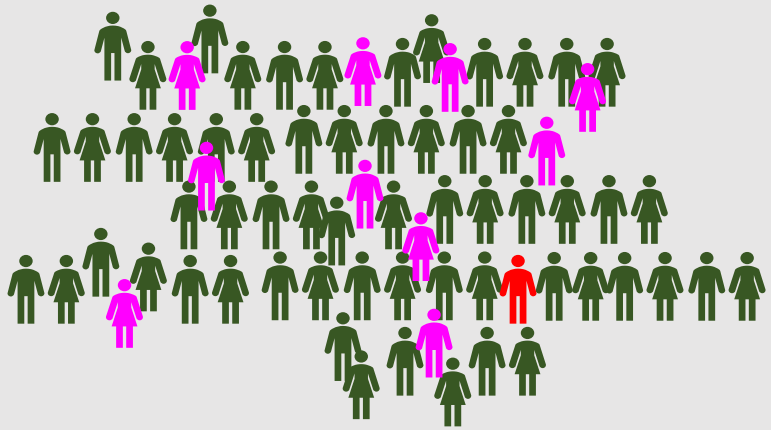

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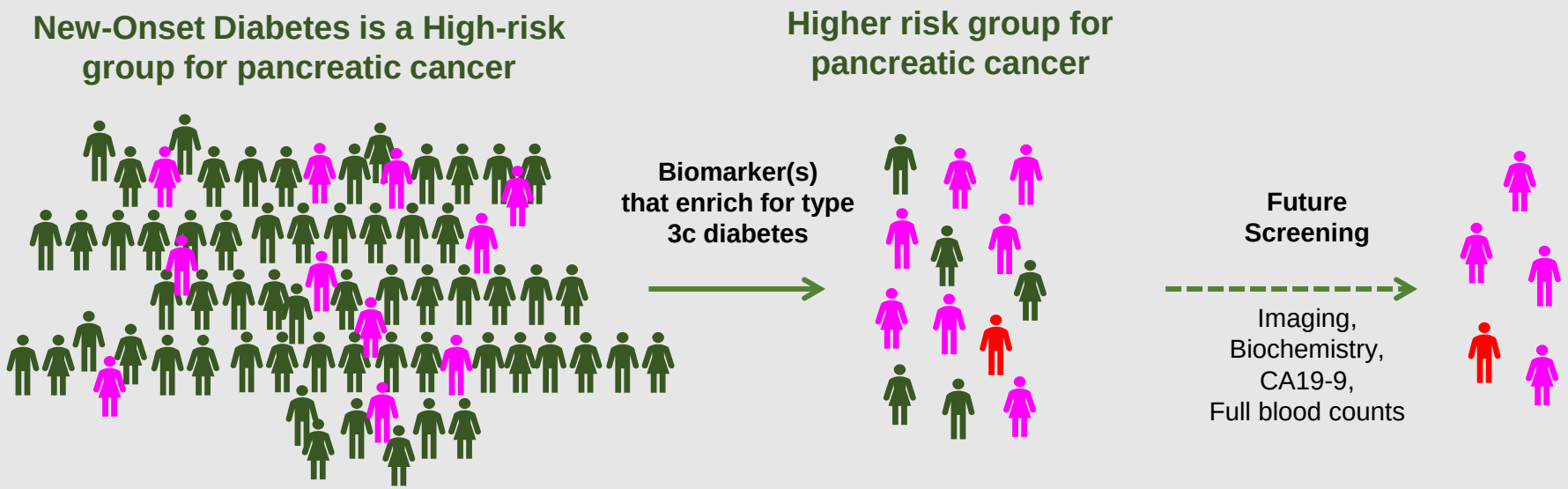


Type 2 Diabetes

Type 3c Diabetes

PDAC-related Diabetes

UK EDI UK Early Detection Initiative for Pancreatic Cancer

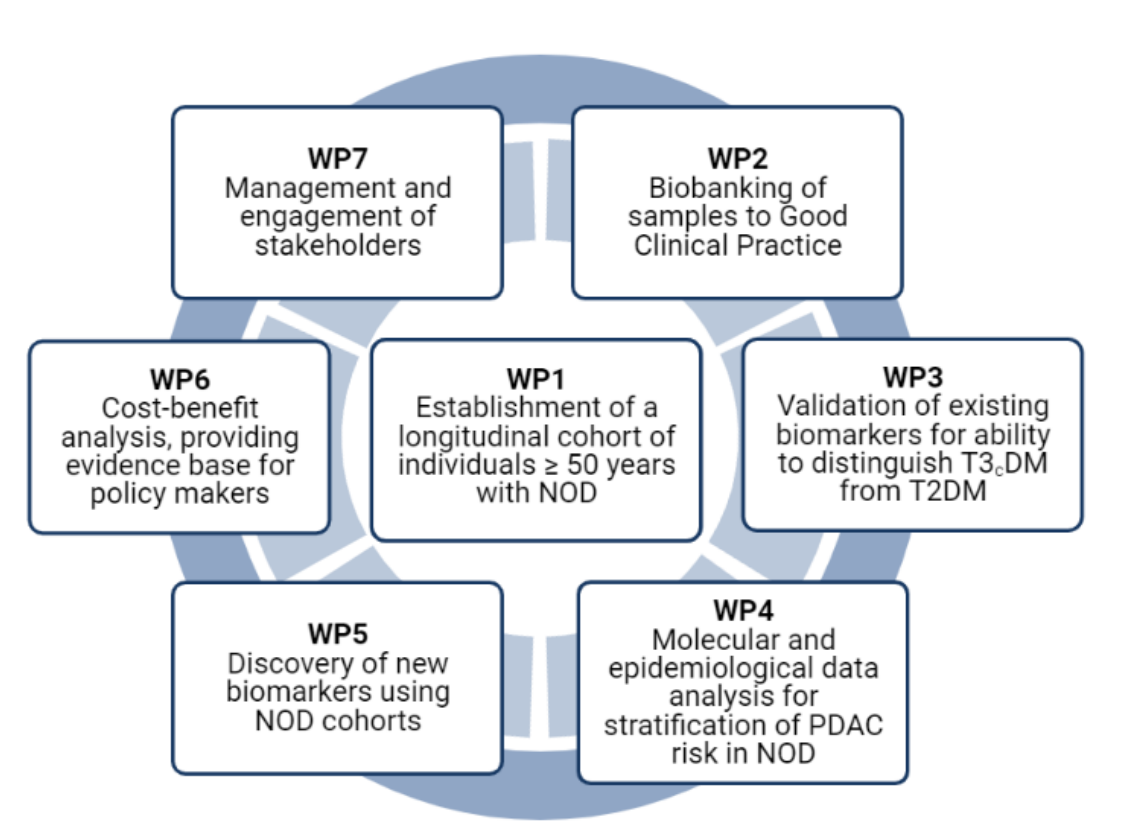
Validation required in pre-diagnostic samples

UK Early Detection Initiative (UK-EDI) for Pancreatic Cancer

Aim: To gather and interrogate key data to advance earlier detection of pancreatic cancer in individuals with new-onset diabetes

UK Early Detection Initiative (UK-EDI) for Pancreatic Cancer

UK-EDI Programme outline



- Centred around the establishment of the UK-NOD cohort
- **UK-EDI is creating a bio-resource for future early detection research**
- Socio-economic impacts and cost-effectiveness of earlier detection of pancreatic cancer in the high-risk new-onset diabetes group evaluated

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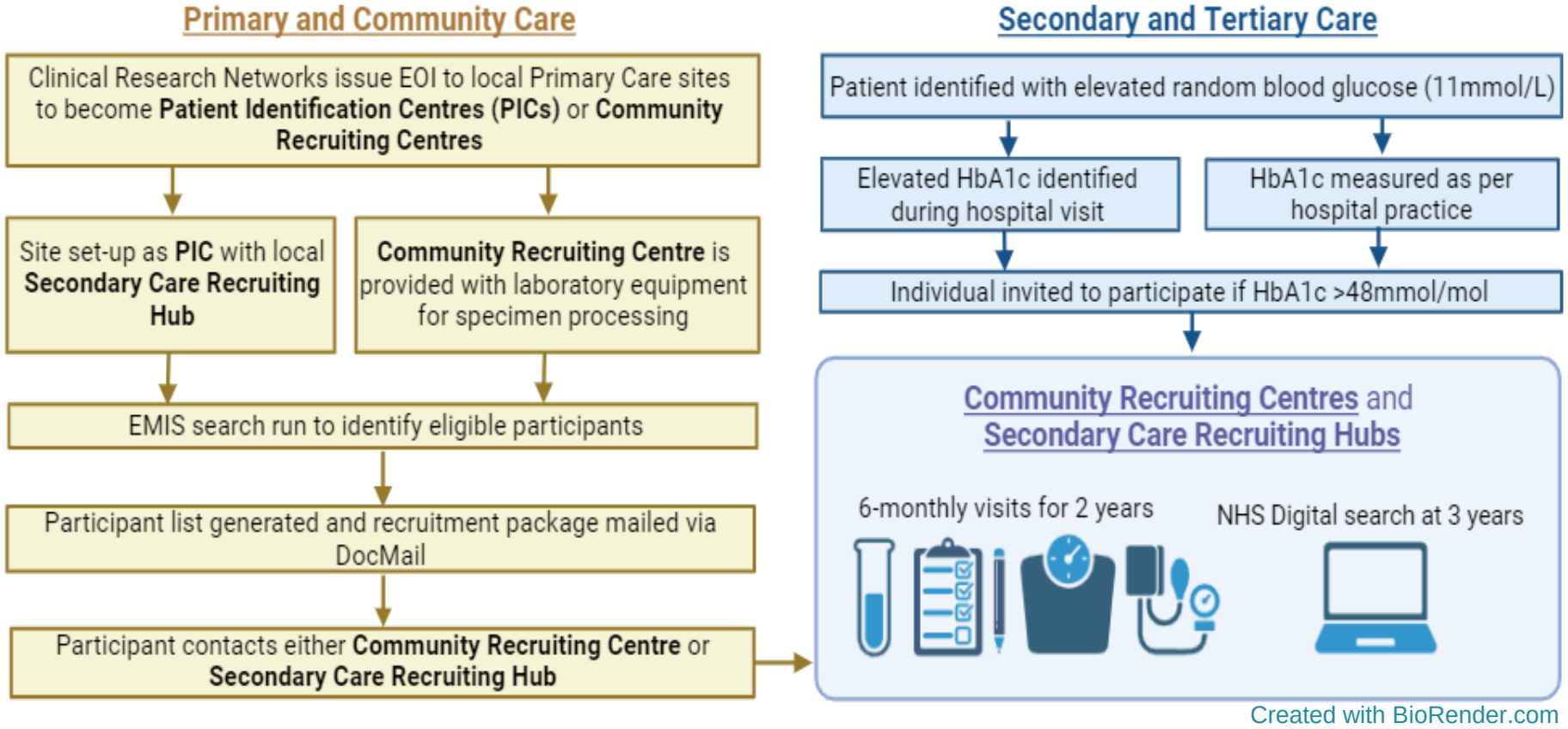
UK EDI UK Early Detection Initiative for Pancreatic Cancer

Oldfield, Stott et al., The United Kingdom Early Detection Initiative (UK-EDI): Protocol for establishing a national multi-centre cohort of individuals with new-onset diabetes for early detection of pancreatic cancer. BMJ Open, Accepted Sept 2022

UKEDI WPs 1 & 2: Establishment of the UKEDI cohort

UK-EDI participant recruitment and follow-up



- **Recruiting individuals >50 yr with NOD (<6 months post-diagnosis), with follow-up every 6 months, over a 3-year period**
- **Pancreatic Referral Centres, Diabetic Specialist Centres, Primary care/community based, associated participant identification centres**

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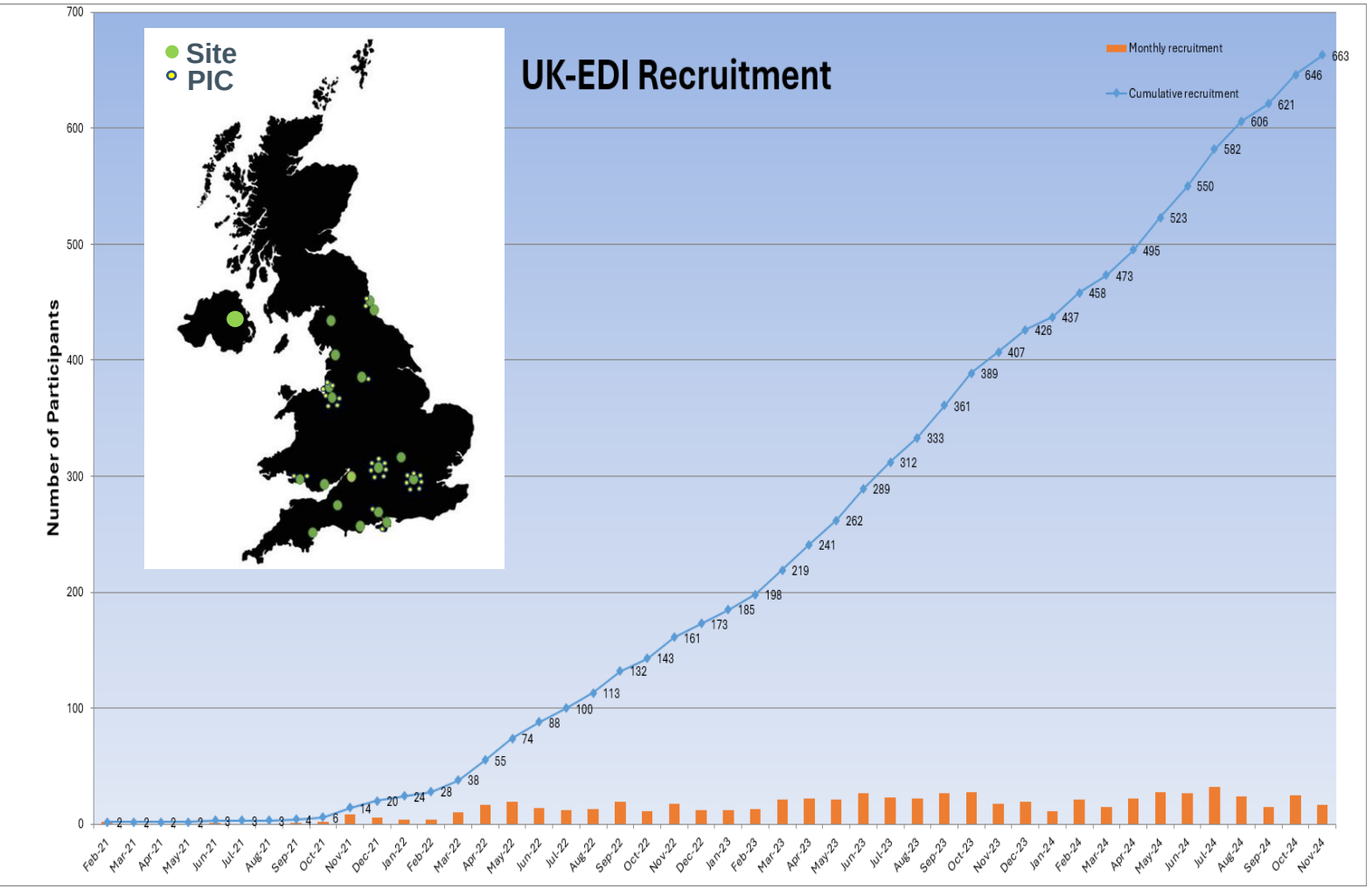


- 32 Sites
- > 60 Affiliated Participant Identification Centres
  - Pancreatic Referral Centres
  - Diabetes Specialist Centres
  - Primary Care / Community-Based
- >690 participants recruited (Dec 2024)
  - Base-line + 6 monthly samples and CRF and questionnaire over 3-year period
  - 58% of samples are currently centrally biobanked in Liverpool (base-line + follow-up):
    - 9597 Serum; 10155 Plasma
    - 5000 Cell pellet

Ashworth M, Small B, Oldfield L, Evans A, Greenhalf W, Halloran C, Costello E. ***The holding temperature of blood during a delay to processing can affect serum and plasma protein measurements.*** *Sci Rep. 2021 Mar 22;11(1):6487. doi: 10.1038/s41598-021-85052-5. PMID: 33753773; PMCID: PMC7985364.*

UK-Early Detection Initiative For Pancreatic Cancer

UK-EDI Outreach and Collaborations

Recruitment pathways / screening

- NHS Digi Trials
- CIPHA
- NHS Clinical Research Networks
- Viatris
- National Diabetes Audit (UK)
- New Dawn
- DESMOND
- Liverpool Diabetes Partnership

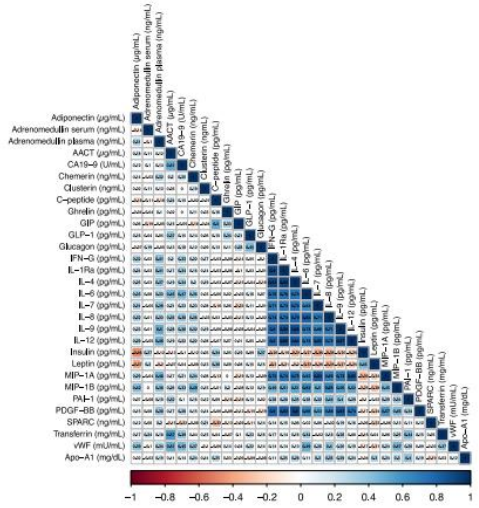
Research / knowledge exchange

- United States NIH Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer **(CPDPC)**
- **US-NOD** – Suresh Chari, MD Anderson
- **DETECT** – Phil Hart, Ohio State
- **VAPOR** – George Hanna, Imperial
- **NODMED** – Zaed Hamady / Bluestar Genomics
- **Galleri Trial** – Harpal Kumar, GRAIL
- **SHARE / GODARTS** – NHS Tayside
- **DARE** – Exeter

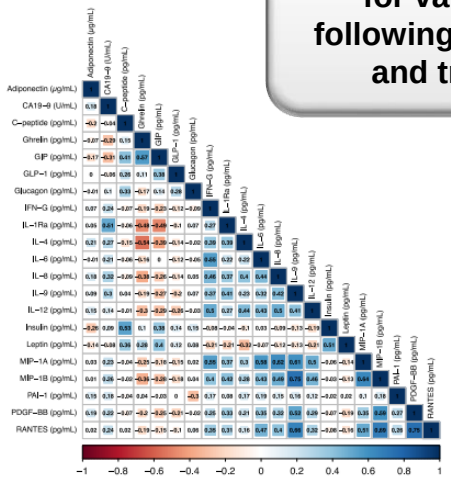
UKEDI WP 3: Advancing existing markers of early detection of PDAC in NOD

Multi-stage biomarker development

- MS-based discovery (PDAC/HC/CP) **(Set 1)**
- Luminex and literature-based discovery (PDAC/HC/CP)
- IPA selected proteins with an association to DM; (PDAC v HC)
- Targeted training for diabetes-associated proteins (PDAC/HC/CP/LSDM) **(Set 2)**
- Protein markers identified for validation
- Validation for type 3c diabetes-associated proteins (PDAC/HC/CP/LSDM/NOD) **(Set 3)** and/or pre-diagnostic detection (pre-diagnostic PDAC/HC) **(Set 4)**

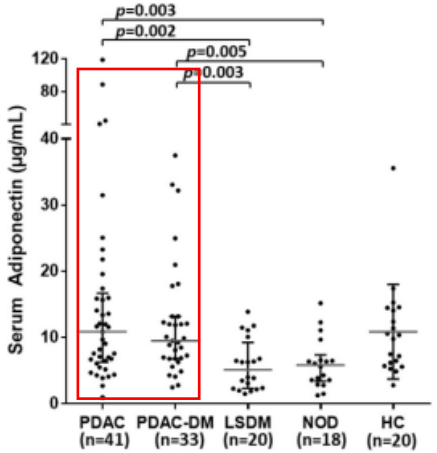


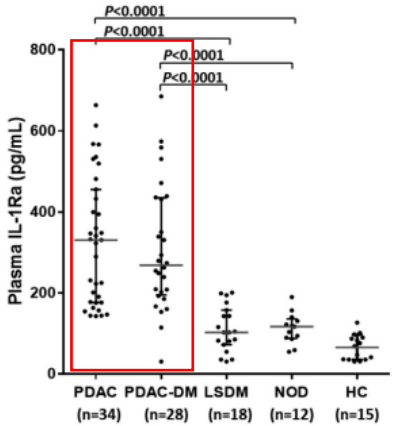
12 candidate selected for validation following discovery and training

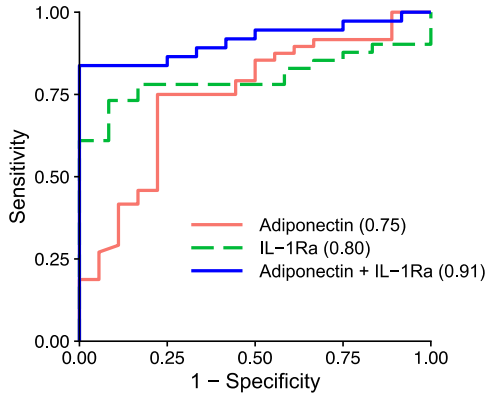


Pathway	P value	Genes coding for identified proteins
Glucose metabolism disorder	1.19×10^{-13}	ADIPOQ,AGT,AHSG,ALB,AMBP,APOB,APOC3,APOD, APOE,APOM,C3,C4A/C4B,C5,CFB,CFD,CLEC3B,CLU, CRP,F10,F2,FCGR3A/FCGR3B,GPLD1,HBB,HP,LBP, PON1,PPIA,RBP4,SERPINC1,SERPIND1,SERPINF1, SHBG,TF,THBS1,TNXB
Metabolism of protein	1.11×10^{-12}	AFM,AGT,AHSG,ALB,APCS,APOA2,APOA4,APOB, APOE,C1S,C3,C4A/C4B,C4BPA,CLU,CP,CST3,F2,F5, FGA,GPLD1,GSN,IGFALS,IGFBP3,ITIH2,KLKB1,KNG1, PROC,SAA1,SERPINA1,SERPINA10,SERPINC1, SERPIND1,TF,THBS1
Diabetes mellitus	7.59×10^{-12}	ADIPOQ,AGT,AHSG,ALB,AMBP,APOB,APOC3,APOD, APOE,APOM,C3,C4A/C4B,C5,CFB,CLEC3B,CLU, CRP,F10,FCGR3A/FCGR3B,GPLD1,HBB,HP,PON1,PPIA, RBP4,SERPINC1,SERPIND1,SERPINF1,SHBG,TF,TNXB

Blood levels of adiponectin + IL-1 Ra distinguish type 3c- from new-onset type 2 diabetes (AUC 0.91)







Oldfield L, et al., EBioMedicine. 2022 Jan;75:103802. doi: 10.1016/j.ebiom.2021.103802. Epub 2022 Jan 3. PMID: 34990893; PMCID: PMC8741427. *Patent* WO2020169511A1

Advancing existing markers of early detection of PDAC in new-onset diabetes

Blood levels of adiponectin and IL-1Ra distinguish type 3c from type 2 diabetes: Implications for earlier pancreatic cancer detection in new-onset diabetes

Lucy Oldfield,[a] Anthony Evans,[a] Rohith Gopala Rao,[a] Claire Jenkinson,[a] Tejpal Purewal,[b] Eftychia E. Psarelli,[a] Usha Menon,[c] John F. Timms,[d] Stephen P. Pereira,[e] Paula Ghaneh,[a] William Greenhalf,[a] Christopher Halloran,[a] and Eithne Costello[a,*]

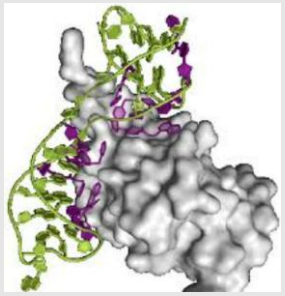
- Adiponectin and IL-1Ra scheduled for independent validation in plasma from the DETECT study
- With the support of Dr. Phil Hart, Ohio State Wexner Medical Centre

DETECT study samples			
PANCREATIC DISEASE STATE	DIABETES STATUS		
	New-onset	Long-standing	Nondiabetic
No disease	37+37^	10*	10†
Chronic pancreatitis	37	10	10
Pancreatic cancer	37	14	20

- In collaboration with the **United states NIH Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer** (CPDPC)
  - MTA in place
  - Samples undergoing analysis (blinded) in Liverpool now
  - Data will be available to UoL and CPDPC

Oldfield L, et al., EBioMedicine. 2022 Jan;75:103802. doi: 10.1016/j.ebiom.2021.103802. Epub 2022 Jan 3. PMID: 34990893; PMCID: PMC8741427.

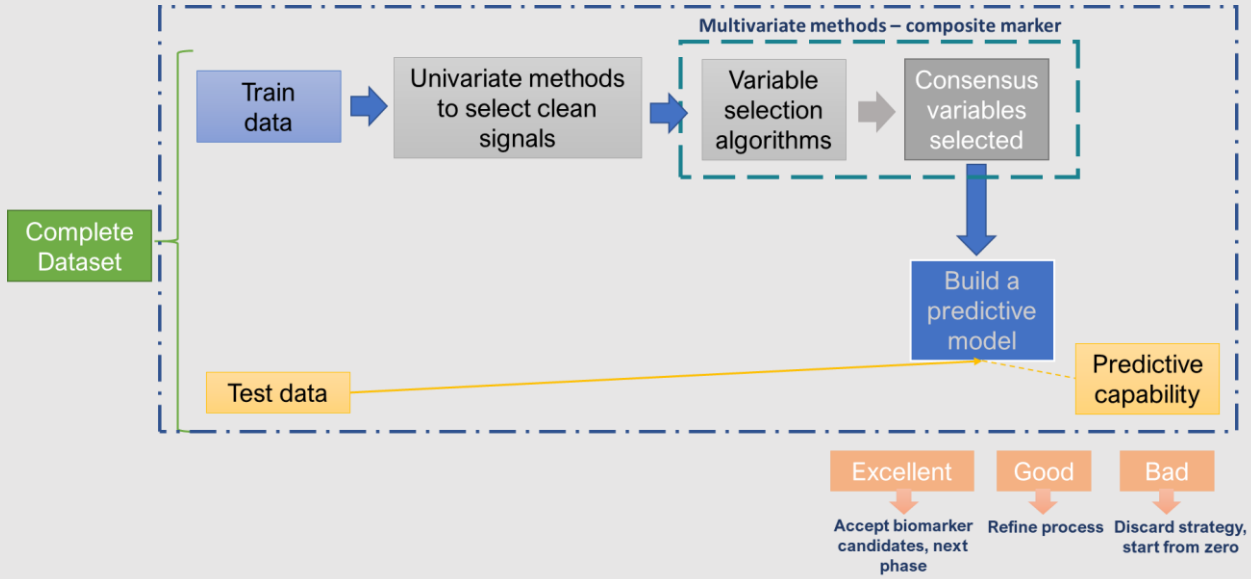
WP5: Discovering new markers for early PDAC detection in new-onset diabetes: deep proteomics approach



PANDIA Cohort						
PDAC		Chronic pancreatitis		Type-2 diabetes		Non-cancer, non-diabetes
+DM	-DM	+DM	-DM	Long-standing	New-onset	Healthy

- Analysis of 210 plasma samples
  - **SWATH-mass spectrometry** (data independent acquisition mode)
  - **Aptamer-based platform** (Somalogic's SomaScan platform)
- >7500 proteins quantified per sample
- Linear models created to identify proteins differentially expressed between:
  1) Type 3c DM and NOD
  2) PDAC and NOD

Strategy for biomarker discovery

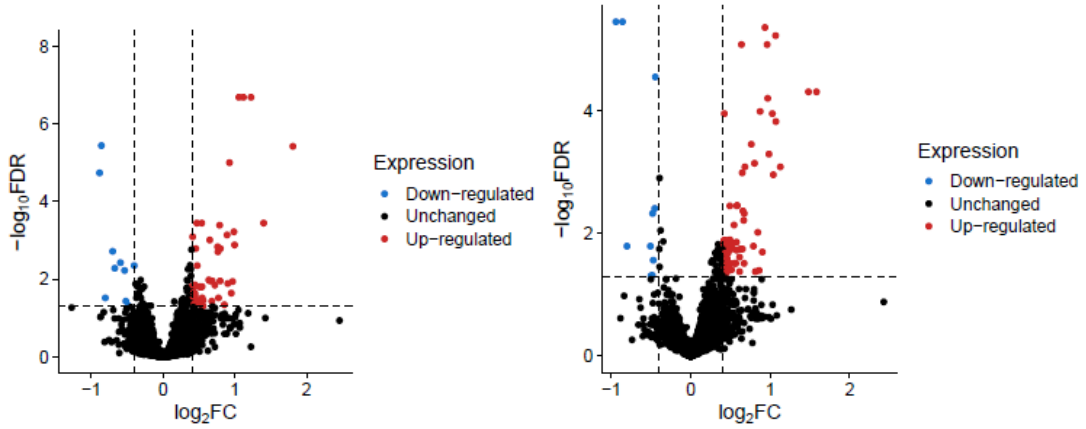


Univariate analysis of aptamer-based data

We incorporated fold change and minimum abundance thresholds (strongest signals carried forward)

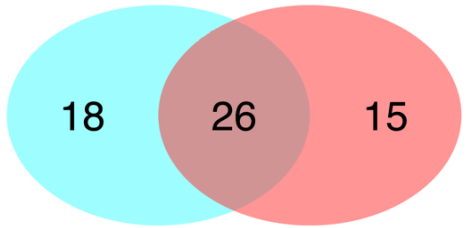
Selection of protein signals

T3cDM vs NOD **PDAC vs NOD**

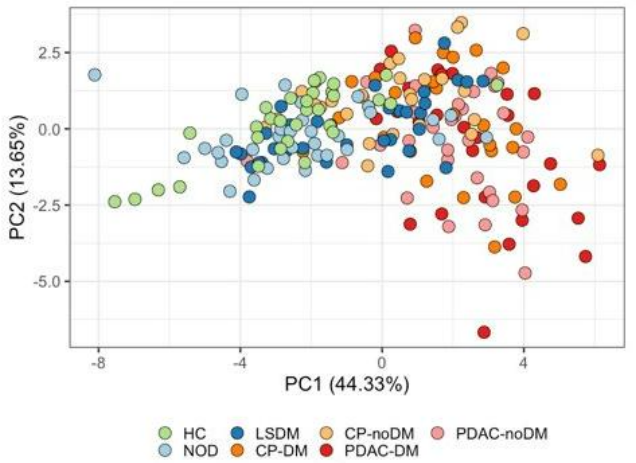


Aptamer		
	T3cDM vs NOD	PDAC vs NOD
Down-regulated	24	41
Up-regulated	18	103

T3cDM vs NOD **PDAC vs NOD**



Proteins common to each comparison selected for multivariate



Disease-specific structure observed in PCA

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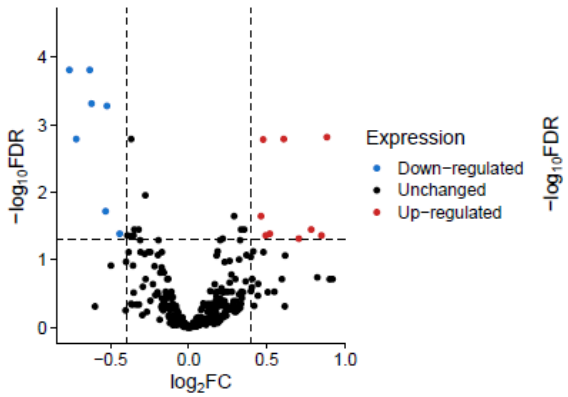
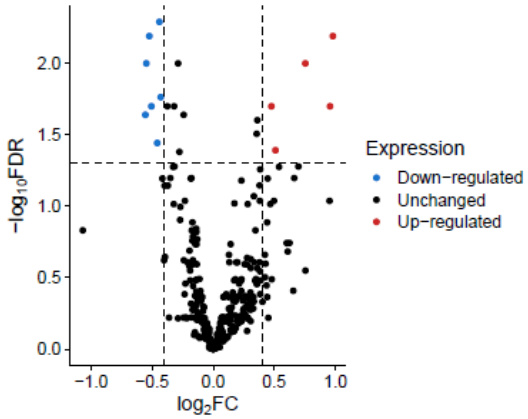
Univariate analysis of SWATH-based data

Selection of protein signals

T3cDM vs NOD

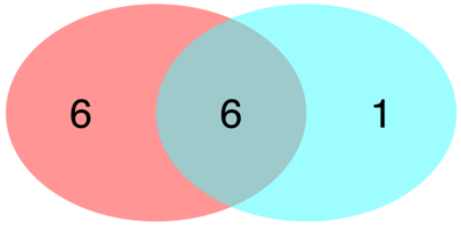


PDAC vs NOD



SWATH		
	T3cDM vs NOD	PDAC vs NOD
Down-regulated	5	15
Up-regulated	4	8

T3cDM vs NOD **PDAC vs NOD**



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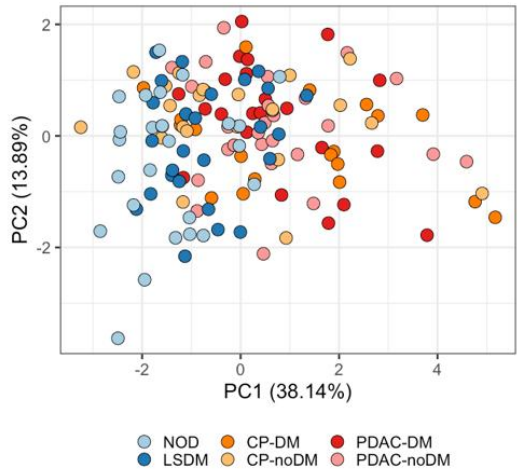

Disease-specific structure observed in PCA

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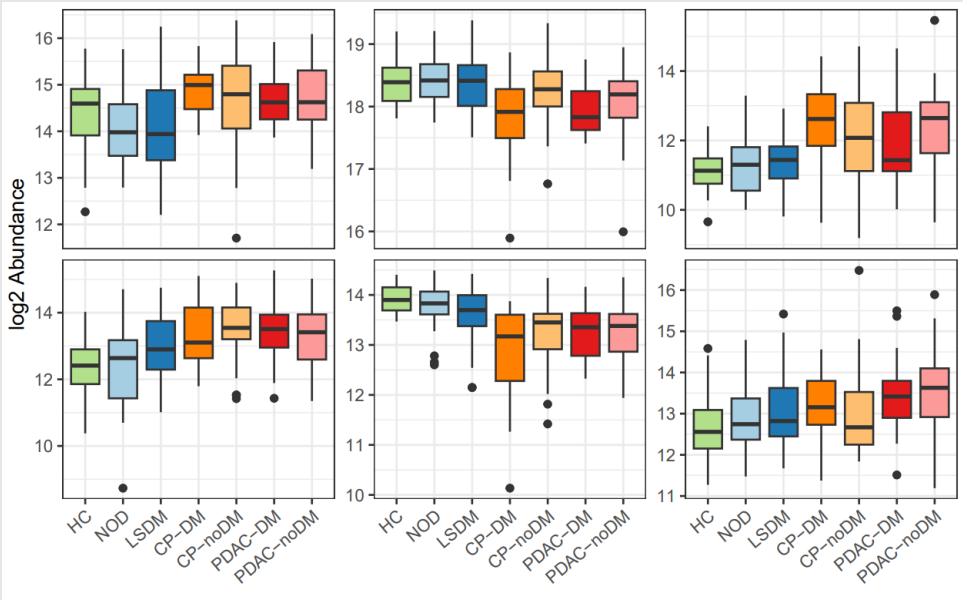
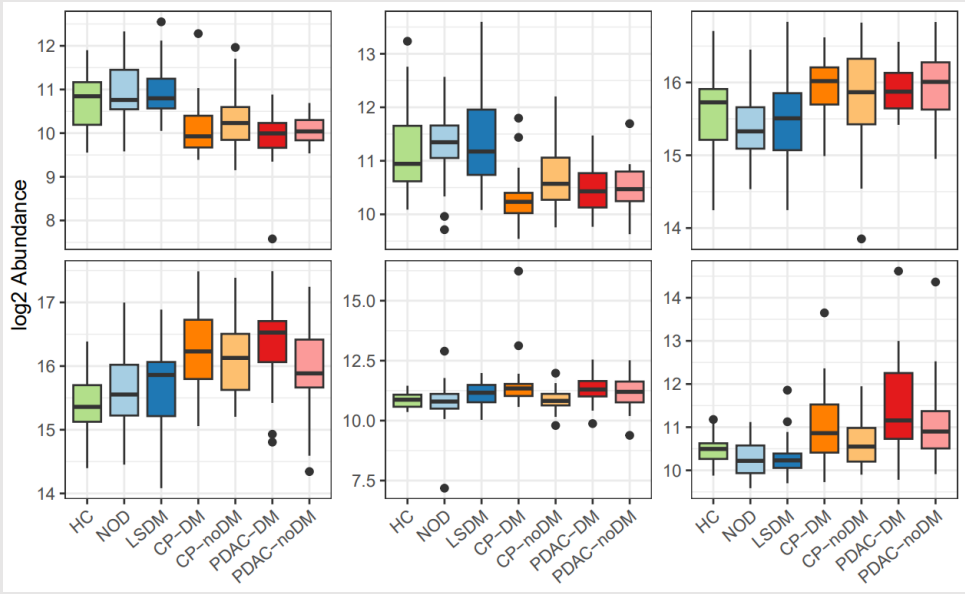
Performance of markers in the distinction of T3cDM from NOD

SWATH-generated composite marker



Accuracy	0.72
Sensitivity	0.82
Specificity	0.64

Aptamer-generated composite marker



Accuracy	0.84
Sensitivity	0.91
Specificity	0.79

Composite biomarkers show promising performance for the distinction of T3cDM from among type 2 NOD
Validation is now needed (especially in pre-diagnostic samples)

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WP5: Validation in pre-diagnostic samples

1997-

Liverpool Lung Project Population cohort

9000 subjects

Healthy cohort: at risk population, 50 – 80 yr

Longitudinal , Epidemiology

Lifestyle & Disease

(Oct2011 – Feb2013)

UKLS LDCT Lung Cancer Screening Trial

4055 subjects

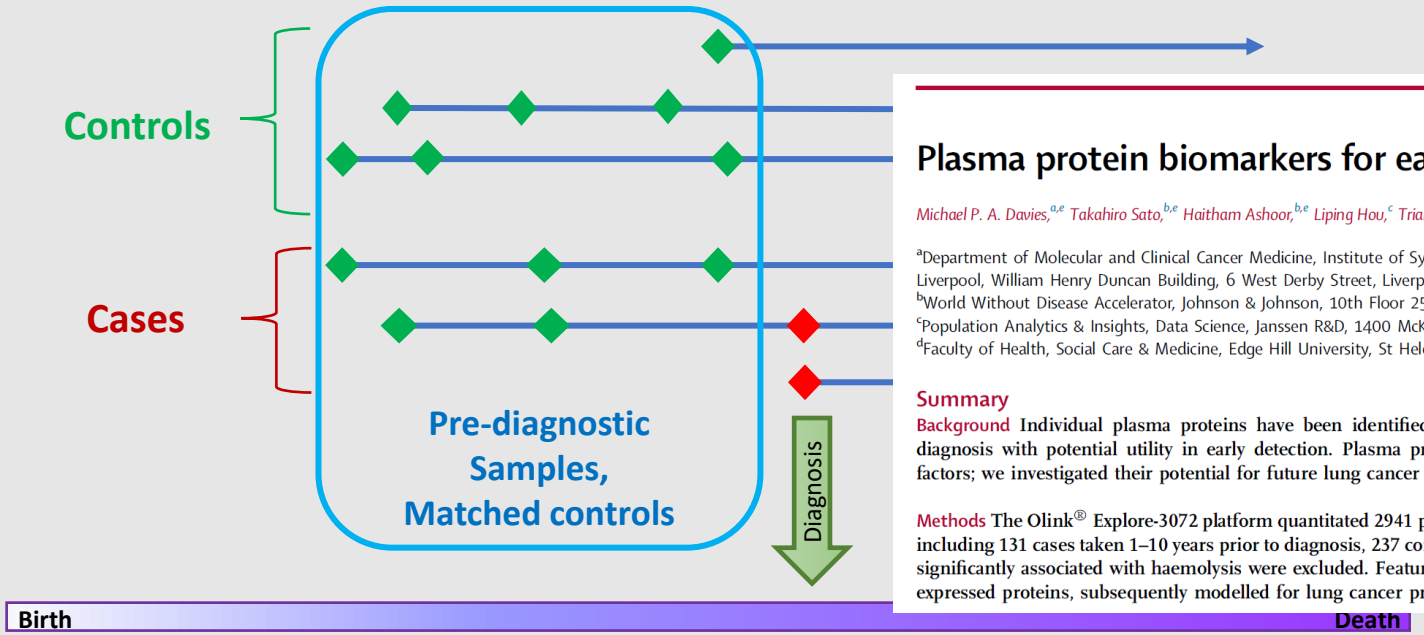
Randomised to LDCT or no LDCT, Plasma collected from **3658** to GCP standard

Healthy cohort: at risk population, 50 – 80 yr

Longitudinal , Epidemiology, Lifestyle & Disease

Medical Research Council

Impact Acceleration Accounts (IAAs) Award



Plasma protein biomarkers for early prediction of lung cancer

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Summary

Background Individual plasma proteins have been identified as minimally invasive biomarkers for lung cancer diagnosis with potential utility in early detection. Plasma proteomes provide insight into contributing biological factors; we investigated their potential for future lung cancer prediction.

Methods The Olink® Explore-3072 platform quantitated 2941 proteins in 496 Liverpool Lung Project plasma samples, including 131 cases taken 1–10 years prior to diagnosis, 237 controls, and 90 subjects at multiple times. 1112 proteins significantly associated with haemolysis were excluded. Feature selection with bootstrapping identified differentially expressed proteins, subsequently modelled for lung cancer prediction and validated in UK Biobank data.

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ROY CASTLE LUNG CANCER FOUNDATION

*A research-led **bio-resource, tissue and data repository** for use in **lung cancer** research, Part of the **Roy Castle Lung Cancer Research Programme** led by **John Field with Mike Davies***

Understanding the biology of pancreatic cancer-related diabetes

- How does pancreatic cancer cause diabetes?
- Why do some pancreatic cancer patients develop diabetes and others not?
- Are cancers that develop in the presence of glucose dysregulation different from those that do not?

Pancreatic
CANCER UK

Single-Cell RNA sequencing from PDAC tumours

Dataset Details:

- N=8 cases:
  - 4 cases with PDAC and DM
  - 4 cases with PDAC without DM

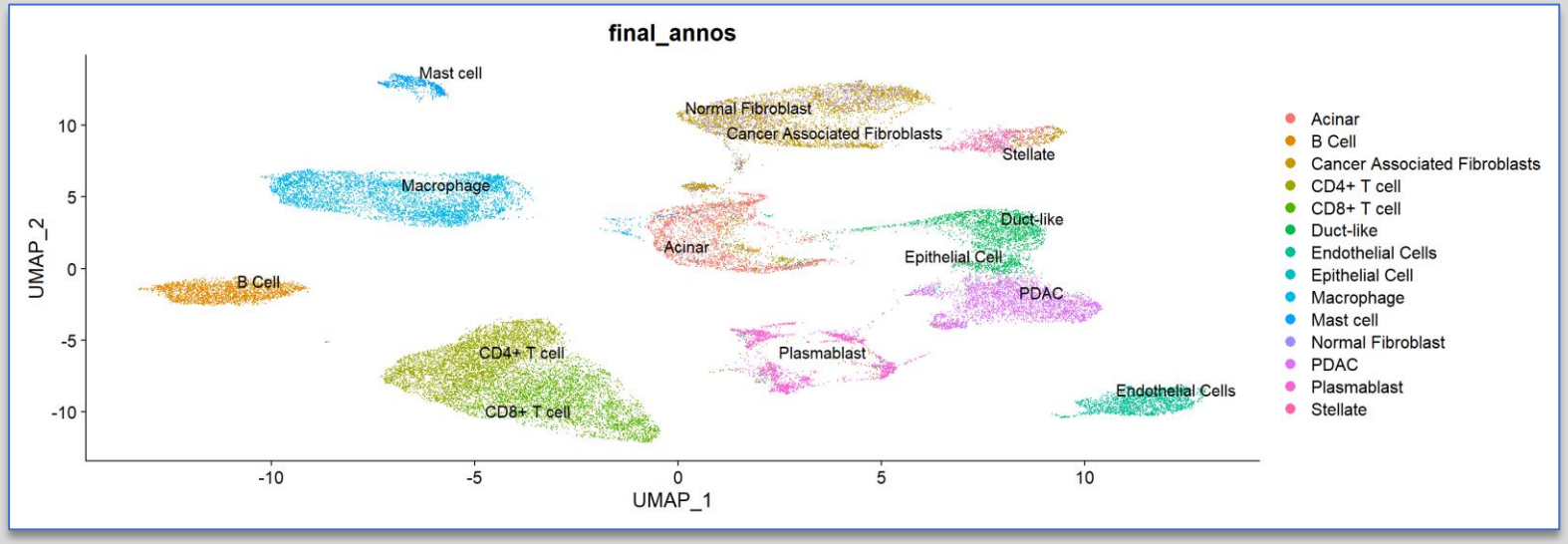
Derived from true cut biopsies of PDAC tumour tissue.

Preliminary Results from Differential Expression (DE) Analyses

Cell Types:

Significantly DE genes were observed in **11 out of 14** identified cell types.

The table to the right highlights the cell types with the highest number of DE genes and lists the three genes with the largest absolute fold change values for each cell type.



UMAP plot illustrating 14 distinct cell types identified through the analysis of single-cell sequencing data obtained from true-cut biopsies of PDAC tumour tissue (N=8). Each cluster represents a specific cell type, colour-coded as shown in the accompanying legend.

Pancreatic CANCER UK

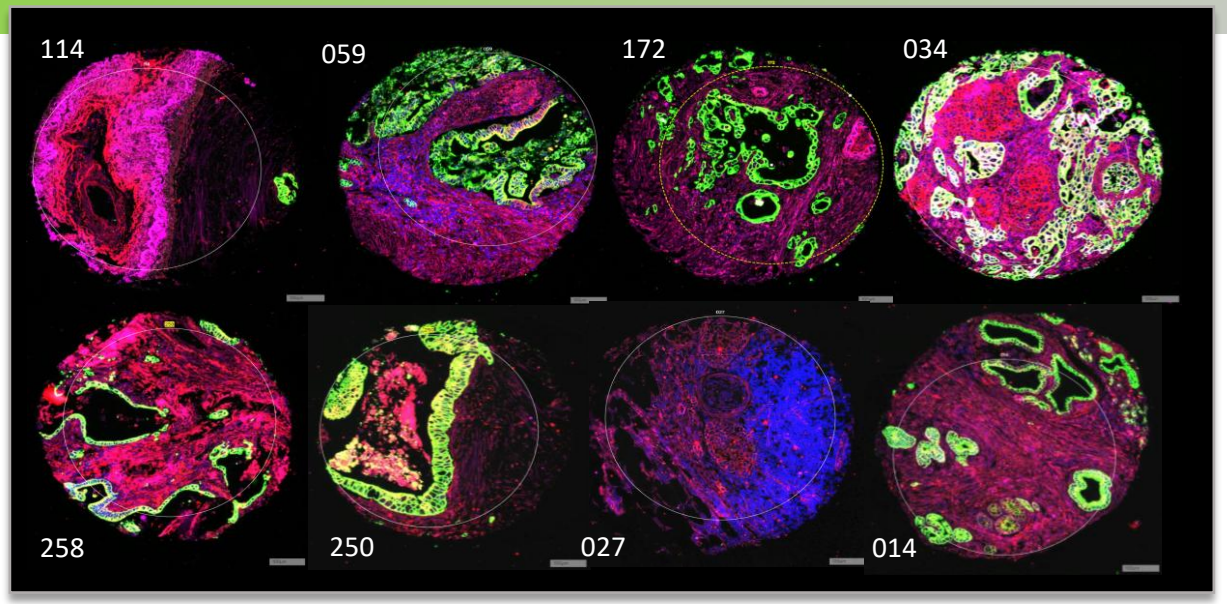
GeoMx Spatial Transcriptions Work

- **Study Design:** Multistage analysis of 59 pancreatic cancer patients with known diabetes status
- **Tissue Microarray:** Created from patient tissue samples
- **GeoMx Transcriptomic Profiling:** Focused on islets, tumour, and tumour microenvironment
- **Samples:**
- Tumour Cores: 3 per patient (total of 171 cores)
- Islet Cores: 3 per patient (total of 171 cores)
- **Overall Total: 342 cores available for GeoMx analysis**

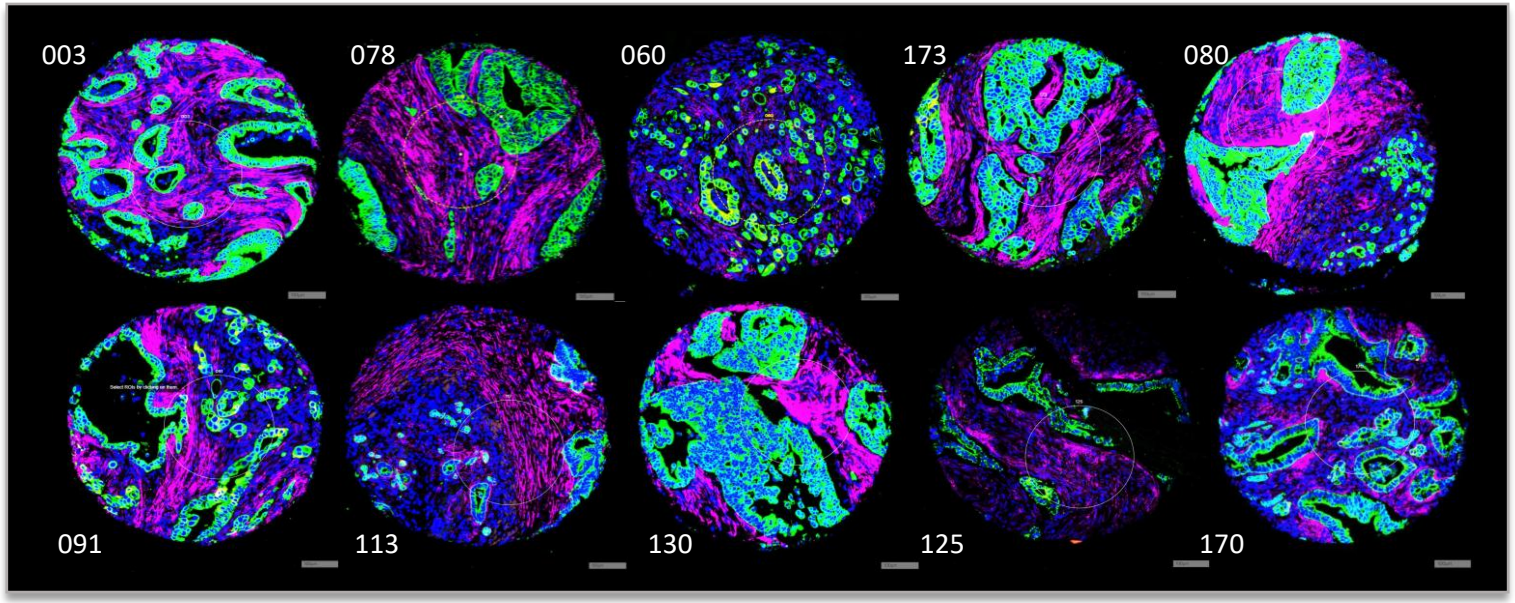
1) Staining Performed for Islet Scan
- DNA (blue) – Nuclei of cells
- PanCK (green) – Tumour tissue
- Insulin (red) – Beta cells
- Glucagon (magenta) – Alpha cells

2) Staining Performed for PDAC Scan
- DNA (blue) – Nuclei of cells
- PanCK (green) – Tumour tissue
- CD45 (red) – Tumour microenvironment
- αSMA (magenta) – Fibrogenic cells

1) Islet Scan and Cores



2) PDAC Scan and Cores

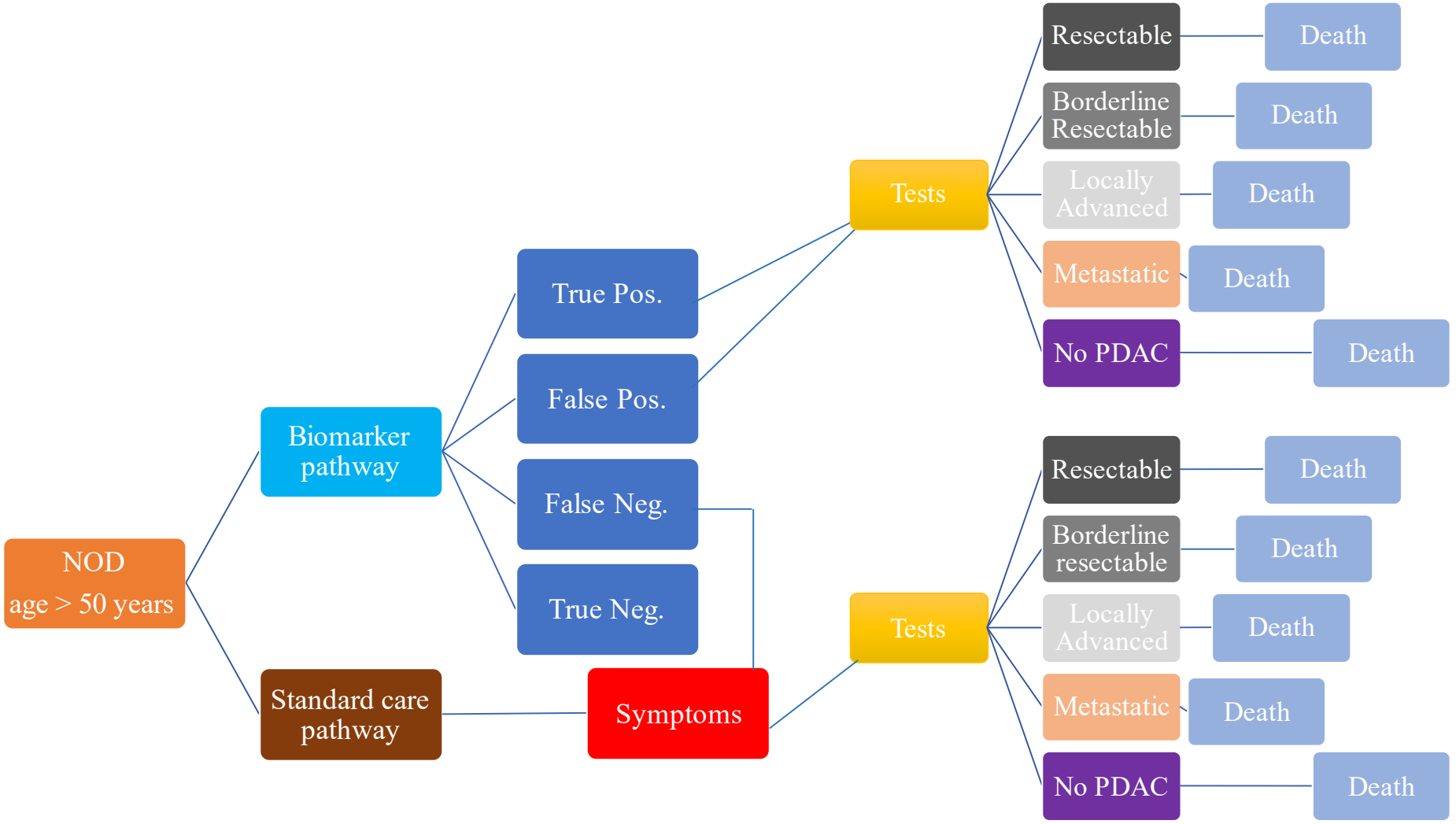


UKEDI WP6: Cost-benefit analysis

Aim: To identify and analyse **key criteria and conditions** to aid decision making regarding an **economically viable screening solution** for the high-risk group of individuals ≥ 50 years, with new-onset diabetes.

Robert Van Der Meer, Nathan Thompson, University of Strathclyde

Markov State-Transition Model



Methods – Model Inputs

- Calculation of:
  - Incremental cost-effectiveness ratios (difference in costs divided by the difference in outcomes)
  - Net benefits
  - Willingness-to-pay threshold (what a health consumer is prepared to pay for a health benefit) per Quality-Adjusted Life Year (QALY) of £30,000.

- One-way and multi-way sensitivity analysis, to allow for parameter uncertainty and determine critical factors for cost effectiveness.

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Partnerships

CPDPC

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