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REVIEW

From pancreas and islet resources to diabetes insights

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Abstract

Pancreatic islets of Langerhans are central to the pathogenesis of all major forms of diabetes. The ability to study human islets ex vivo has advanced our understanding of diabetes and aided in the development of novel therapeutics. However, for decades, very few laboratories had access to this critical resource and experiments on human islets were typically underpowered. More recently, multiple consortia around the world have started to enable islet biology at scale, enriching our understanding of the intra-individual variability of islet function and disease mechanisms. This article reviews and compares existing large-scale human islet tissue and data resources, offering suggestions for their improvement and for developing new resources.

Keywords Biobanking · Data repositories · Diabetes · Islets of Langerhans · Knowledge bases · Multi-omics · Open science · Review · Standardisation · Tissue phenotyping

Abbreviations

ADI	Alberta Diabetes Institute
AI	Artificial intelligence
EADB	Exeter Archival Diabetes Biobank
EGA	European Genome–phenome Archive
eQTL	Expression quantitative trait locus
FFPE	Formalin-fixed paraffin-embedded
HANDEL-P	Human Atlas of Neonatal Development and Early Life Pancreas
HIPP	Human Islet Phenotyping Program
HPAP	Human Pancreas Analysis Program
IIDP	Integrated Islet Distribution Program
nPOD	Network for Pancreatic Organ Donors with Diabetes
RRID	Research Resource Identifier

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Introduction

Early histopathology [1], small-scale tissue isolation [2, 3], advances in semi-automated pancreas processing [4, 5] and storage [6–8] and improvements in the collection of high-quality research tissues from organ donors [9, 10] have all contributed to the evolution of pancreas and islet tissue repositories that are now available to diabetes researchers. This has also been enabled by improvements in clinical islet isolation and transplantation [9, 11], live tissue slice preparation [12, 13], donor screening [14], cryopreservation [8, 15] and profiling methods, which have yielded increasingly complex datasets. Advances in data collection and analysis have expanded the number of resources available to islet and diabetes researchers. As a result, the pancreas and islet resource landscape has become very complex, with challenges that include limited uptake of tracking tools such as Research Resource Identifiers (RRIDs) [16], non-standardised reporting, variable accessibility and prohibitive costs. As islets are critical to the pathogenesis of diabetes and related conditions, it is essential to improve access to and the usability of these resources.

In this review, we aim to provide an overview of the current landscape of human pancreatic tissue resources, coordinated phenotyping efforts and data platforms that are advancing our understanding of diabetes pathogenesis. We highlight major biobanking and islet distribution programmes that focus on archived or live tissue and explore the evolution of efforts from simple tissue repositories to sophisticated phenotyping initiatives. We discuss how new information is conveyed via an expanding ecosystem of data repositories and knowledgebases, from genomics-centric platforms to integrative tools that support multi-omics and functional data analysis. Finally, we consider future perspectives, advocating for improved accessibility, usability and donor diversity, while underscoring the need for global collaboration and open science to fully realise the translational potential of human pancreas research.

Human pancreas/islet biobanking and distribution programmes

Our understanding of human diabetes has benefited tremendously from efforts in pancreas tissue banking and islet isolation (Table 1). These efforts have focused primarily on either banked samples or the provision of live tissue, although the lines are blurring as some traditional banking programmes begin to offer live tissue and vice versa.

Primarily fixed tissue repositories The Exeter Archival Diabetes Biobank (EADB) is a post-mortem pancreas biobank established in Glasgow in the 1980s to meet the need for tissue from young, recently diagnosed individuals with type 1 diabetes [17]. Formalin-fixed paraffin-embedded (FFPE) blocks or slides were reviewed and collated from 171 donors with type 1 diabetes, 178 without diabetes, 24 with type 2 diabetes and 23 with other pancreatic diseases. This biobank was transferred to the University of Exeter in 2016 [18]. Its unique enrichment in young-onset, short-duration donors (119 donors with a diabetes duration of <1 year) has been used to address key questions in the field [19] relating to the profiles of insulitis and impacts of age at diagnosis [20], viral aetiology [21], interferon responses, immunogenicity of beta cells [22] and selective loss of small endocrine objects in type 1 diabetes [23].

In the past 20 years, large-scale projects on islet pathophysiology have been supported by the European Union, the European Federation of Pharmaceutical Industries and Associations (EFPIA), Breakthrough T1D, and the Leona M. and Harry B. Helmsley Charitable Trust [24]. These include the Innovative Medicines Initiative for Diabetes (IMIDIA), T2DSystems, the Innovative Medicines Initiative RHAPSODY (www.imi-rhapsody.eu) and INNODIA (www.innodia.eu). The majority of the pancreases handled within these broad projects were derived from brain-dead multi-organ donors [25] and processed in a single centre under standardised procedures at the University Hospital of Pisa, where a collection of pancreatic samples from 772 donors (144 with type 2 diabetes) is available on request for collaborative initiatives [26–28].

The UK Quality in Organ Donation whole pancreas tissue bank (QUOD-PANC) was established in 2017 with Medical Research Council funding as an expansion of the UK QUOD biobank (https://quod.org.uk), which collects clinical data, blood samples and tissue biopsies from organ donors (>135,000 samples in total). Pancreases are dissected into eight anatomical regions with multimodal biopsies from each region. The QUOD-PANC Core performs standardised histology on blocks from each region, and collates data in an Atlas portal that is available with registration (https://quod.org.uk/tag/panc/). This resource has contributed insights into the pancreas in cystic fibrosis [29, 30]. The QUOD-PANC tissue bank currently comprises >140 donors (age range 6–81 years), including a majority of donors without known diabetes (HbA_{1c} during terminal admission <42 mmol/mol [6.0%]), >50 with type 2 diabetes, and ten with type 1 diabetes. Expansion of this resource will include pancreatic resection tissue from donors with chronic pancreatitis and pancreatic neoplasia.

The Network for Pancreatic Organ Donors with Diabetes (nPOD; https://npod.org), located in Gainesville, USA, was created in 2007 with the goal of obtaining pancreases,

Table 1 Fixed and live tissue biobanks focusing on the pancreas and pancreatic islets

Programme	Diabetes status[a]	Live human islets	Live pancreas slices	Banked islets[b]	Banked pancreases[b]	Other fresh tissues[c]	Other banked tissues[c]	Donor metadata[d]	Access[e]
Exeter Archival Diabetes Biobank (EADB)	ND, T1D, Aab+, T2D	No	No	No	FFPE	No	No	O (limited)	On request
Quality in Organ Donation (QUOD)	ND, T1D, T2D, T3c	No	No	No	F, FFPE, RNA, EM	No	Bl, Sp, Ur, Li, Ki, He	R	https://quod.org.uk
Network for Pancreatic Organ Donors with Diabetes (nPOD)	ND, T1D, Aab+, T2D	Pilot programme	Yes	No	F, FFPE, OCT, RNA	No	Pln, nPln, Sp, Du, Th, Ad, Pl, Se	R	https://npod.org
European network of Pancreas Organ Donors (EUnPOD)	ND, T1D	No	No	No	F, FFPE, OCT, RNA	No	Unknown	Pu	On request
Integrated Islet Distribution Program (IIDP)	ND, T2D	Yes	No	F	FFPE	Duc, Pl, Se, Sp, Pln, Ac, Du	No	R	https://iidp.coh.org
Alberta Diabetes Institute (ADI) IsletCore	ND, T1D, T2D	Yes	Pilot programme	F, C, FFPE	FFPE	Bl, Ad, Ac, Sp, Du, Pln	No	O	www.isletcore.ca
Alberta Islet Distribution Program (AIDP)	ND	Yes	No	No	No	No	No	Pu	https://sites.google.com/a/ualberta.ca/alberta-islet-distribution-program/
Pisa University Hospital collection	ND, T2D	No	No	F	FFPE, OCT	No	Ad	R, Pu	On request
Diabetes Virus Detection (DiViD)	T1D	No	No	No	FFPE	No	No	Pu	On request
LiveOnNY	ND	No	No	No	FFPE	No	Du, Sp, Pln, Se, Pbmc	Pu	https://www.liveonny.org

[a]Aab+, autoantibody positive; ND, no diabetes; T1D, type 1 diabetes; T2D, type 2 diabetes

[b]C, cryopreserved; EM, glutaraldehyde fixed; F, flash frozen; FFPE, formalin-fixed paraffin-embedded; OCT, optimal cutting temperature compound; RNA, RNAlater vials

[c]Ac, acinar; Ad, adipose; Bl, blood; Du, duodenum; Duc, ductal; He, heart; Ki, kidney; Li, liver; (n)Pln, (non)pancreatic lymph nodes; Pbmc, peripheral blood mononuclear cells; Pl, plasma; Se, serum; Sp, spleen; Th, thymus; Ur, urine

[d]O, open access; Pu, on publication; R, registered users (may require approval)

[e]Contact details are available on the BioPanc 'Biobanks Summaries' tab (https://clekka.shinyapps.io/biopanc_donor_atlas/)

spleen, non-pancreatic lymph nodes from the mesenteric or inguinal areas, pancreatic lymph nodes, duodenum, peripheral blood, thymus and bone marrow from donors with type 1 diabetes or islet autoantibodies (Aab+) [10, 31, 32]. It was an early pioneer in this area, with many believing that such a programme was not only unfeasible but also of limited interest and would perhaps merely replicate existing knowledge gleaned from animal models. nPOD obtains transplant-grade pancreases from across the USA and has collated samples from 56 organ procurement organisations and >700 donors, making it the field's largest biobank. nPOD also has tissue from donors with monogenic diabetes, cystic fibrosis-related diabetes, type 2 diabetes and gestational diabetes and from non-diabetic autoantibody-negative (Aab–) individuals across a range of ages [33]. Recently, nPOD added >80 donors from the Human Atlas of Neonatal Development and Early Life Pancreas (HANDEL-P). nPOD also provides live pancreas slices [12], enabling in situ study of islet/pancreas function and immune interactions [34, 35]. nPOD West at City of Hope (Los Angeles, USA) processes pancreases for simultaneous islet isolation and tissue slices. nPOD research has been recently restructured around specific 'key questions': (1) possible differences between type 1 diabetes in children and adults; (2) prohormone processing defects in type 1 diabetes; (3) the exocrine pancreas in type 1 diabetes development; (4) translational studies to advance type 1 diabetes therapies; (5) beta- and/or islet-specific targets; and (6) the heterogeneity of type 1 diabetes. nPOD has made an immense contribution to our understanding of the pathogenesis of type 1 diabetes [36], including key insights into the role of viruses in type 1 diabetes by the nPOD-Virus group [37–41].

The LiveOnNY organ procurement organisation (https://www.liveonny.org) maintains a biobank of pancreases from ~300 donors (and growing) with a broad age range (0–87 years) in FFPE blocks from the organ head, body and tail. Samples of adjacent spleen, pancreatic lymph nodes, immune cell suspensions and plasma are also available for a subset of donors, making this resource potentially valuable for immunology-focused studies.

Finally, it is important to note that other smaller biobanks have been, and remain, important sources of pancreas tissue and insights. This is particularly notable given the rarity of some of the samples they house. The Diabetes Virus Detection (DiViD) resource includes pancreas tail biopsies from six adults within 3–9 weeks of diagnosis and is maintained at the University of Oslo, Norway [42]. The European network of Pancreatic Organ Donors with Diabetes (EUnPOD), part of INNODIA, collected samples from eight donors according to nPOD protocols, including two with type 1 diabetes; this resource is housed at the University of Siena, Italy.

Despite the growing importance and size of these biobanks worldwide, finding and understanding what is available in these resources can be challenging. In this regard, the BioPanc Donor Atlas (https://clekka.shinyapps.io/biopanc_donor_atlas/) outlines the availability of banked samples from >2200 donors across eight tissue banks and enables users to explore across different biobanks, filtering by donor characteristics and disease status (Fig. 1). This analysis of combined data from global collections indicates that certain donor demographics are well represented, such as type 1 diabetes donors diagnosed between ages 10 and 30 years. However, other donors are comparatively scarce, notably donors diagnosed with type 1 diabetes aged <10 years, those with a short disease duration and, especially, those diagnosed at age >30 years. Type 1 diabetes diagnosed in young children is increasingly being recognised as having distinct clinical, pathological and progression features, making it crucial that this demographic is not understudied in the field. There are currently only 15 samples from donors diagnosed with type 1 diabetes after the age of 30 years; this may be because some cases are misdiagnosed as type 2 diabetes [43].

Primarily live islet and pancreas resources A review of global contributors to human research islet distribution was published in 2019 [44], although it is difficult to determine the current activity of some programmes. Here, we do not discuss all individual programmes but instead describe the evolution of larger human islet isolation and distribution programmes in North America and Europe (Table 1), while recognising the potential for growth in islet distribution networks in China [45], India [46], South America [47], the Middle East [48, 49] and Australasia [50], and the unmet need for growth in Africa [51].

The Integrated Islet Distribution Program (IIDP; https://iidp.coh.org), which originated as the Islet Cell Resource in 2001 [9, 52], stems from early efforts in transplantation [53] and the refinement of human islet isolation [54], particularly via development of the Ricordi chamber [5, 55]. These advances broadened the use of human islets in research through the 1990s and 2000s, fuelled in part by an expansion of clinical islet transplant initiatives following the publication of the Edmonton Protocol [56]. The history of the IIDP and its pioneering coordination of research islet distribution is recounted elsewhere [57]. This programme has contributed greatly to the development and assessment of algorithms [58, 59] and the standardisation [60, 61] of the distribution of islets from >2500 donors across a user network. The IIDP has also enriched our understanding of variability in islet isolation outcomes across centres [62, 63]. The IIDP coordinates the distribution of human islets from donors without diabetes and with type 2 diabetes for research from ten centres across the USA and also provides other tissues, including spleen, pancreatic lymph nodes, duodenum, blood (serum and plasma), ductal and acinar

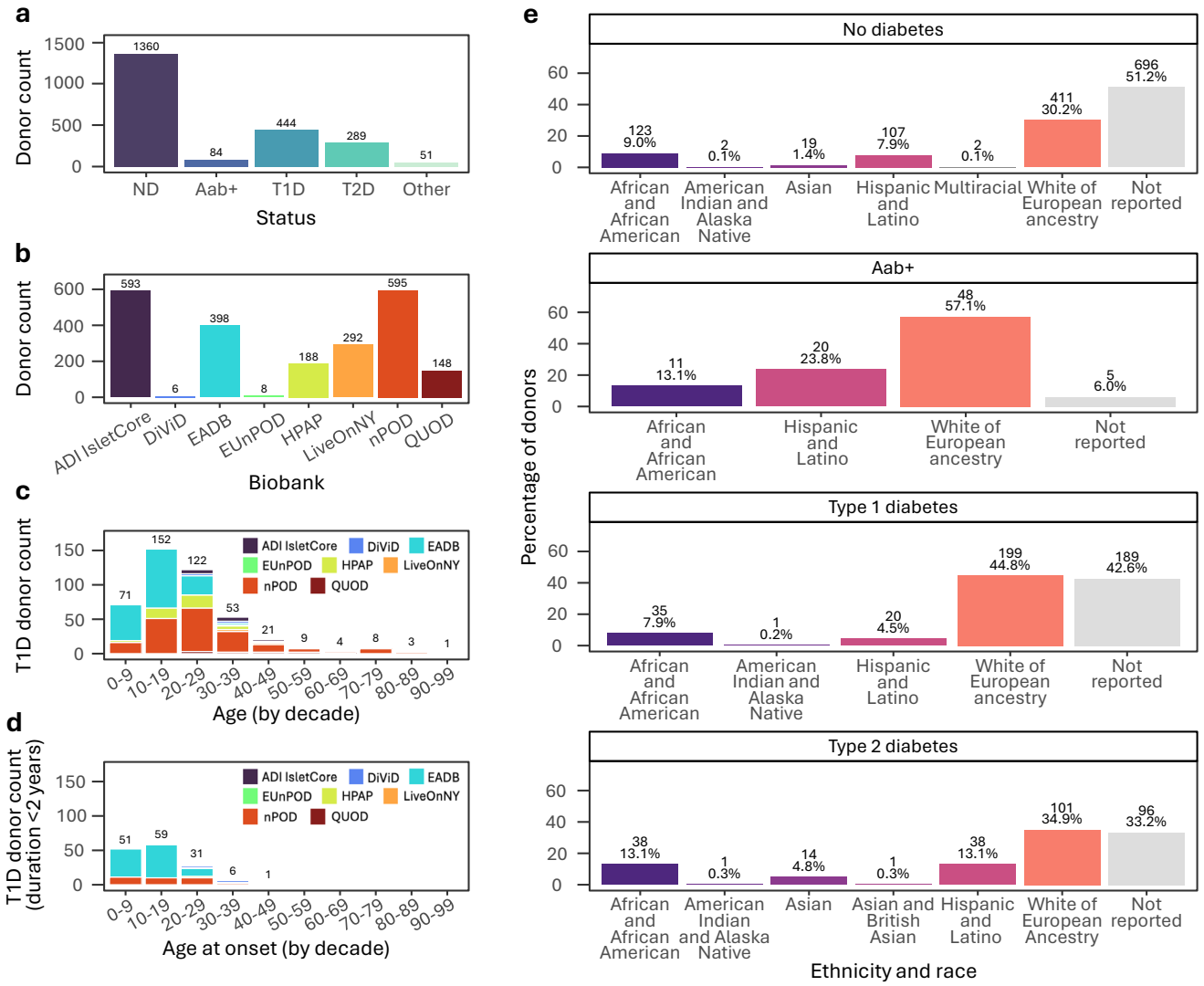

Fig. 1 Summary of human pancreas biobanks included in the Bio-Panc Donor Atlas (https://clekka.shinyapps.io/biopanc_donor_atlas/). (**a**) Total donor count by diabetes status, including donors without diabetes and those with related conditions. (**b**) Total donor count per pancreas biobank. (**c**) Total type 1 diabetes donor count by age (decade) and pancreas biobank. (**d**) Total type 1 diabetes donor count by age at onset (decade) among those with diabetes of <2 years' duration. (**e**) Percentages of donors by diabetes status and race and ethnicity. Aab+, autoantibody positive; ADI, Alberta Diabetes Institute; HPAP, Human Pancreas Analysis Program; ND, no diabetes; T1D, type 1 diabetes; T2D, type 2 diabetes. This figure is available as part of a downloadable slideset

samples. One of these centres, Prodo Laboratories (www.prodolabs.com), also serves as a key commercial source for human research islets and supplies other industry vendors, such as InSphero (www.insphero.com), which generates and distributes human pseudoislet products. The IIDP is notable in its strong online resources detailing both its support of the research community (>300 million islet equivalents and >1.6 million snap-frozen islets distributed since inception) and the resulting scientific publications. The IIDP has also made significant strides in islet phenotyping and data accessibility, which are described below.

Studies in Europe with live human islets started in the early 1980s [64, 65], and European Union-supported programmes have enabled prolific collaborations between several centres [66–70]. The standardisation of procedures and data analyses have been facilitated by several regional collaborations between clinical islet transplant centres, such as those in the European Collaborative Islet Transplant Registry (www.citregistry.org), the GRAGIL network [71], the Nordic Network for Islet Transplantation (https://nordicislets.medscinet.com) and the European Pancreas and Islet Transplantation Registry (EPITR; esot.org/epitr/). These networks may also provide islets for research; for example, the Nordic Network for Islet Transplantation distributes islets and other tissues from Uppsala throughout the Nordic countries [72]. Other centres also contribute to collaborative

research activities beyond transplantation, with different degrees of involvement, sometimes under specific human tissue transfer agreements [66, 73–75].

In recent years, emerging regulatory differences among European nations have renewed interest in the use of surgical samples derived from pancreatectomised individuals [76–78]. While isolating whole islets from such samples remains elusive, they have been used to study insulin release from tissue slices and the molecular features of islet cells isolated by laser capture microdissection [79–81]. Surgical samples have the benefit of minimal cold ischaemia time and enable in vivo assessment of insulin secretion and insulin sensitivity before and, in some cases, after the procedure. Limitations include the possible presence of impaired glucose tolerance or diabetes due to the underlying exocrine pancreas disorder (type 3c diabetes, which may be misclassified as type 2 diabetes), and the potential influence of tumours on neighbouring cells. An inventory of European centres applying these approaches, and any associated repositories, is currently missing.

From the 1980s, efforts in Edmonton, Canada, focused on advancing human islet isolation and cryopreservation [6, 82–84] to optimise transplantation [85–88]. This culminated in the successful Edmonton Protocol for islet transplants in type 1 diabetes [11, 56, 89]. An important offshoot has been the Alberta Islet Distribution Program (AIDP; sites.google.com/a/ualberta.ca/alberta-islet-distribution-program/). This programme has performed >2500 human islet isolations (likely to be the most in the world by a single isolation centre) at the Clinical Islet Laboratory of the University of Alberta and has supported foundational science since 2007 [90, 91]. In 2010, the parallel Alberta Diabetes Institute (ADI) IsletCore (www.isletcore.ca) was established at the ADI, which, from its conception, has uniquely focused on processing research-consented donor pancreases that are not accepted for clinical whole pancreas or islet transplantation [92]. This programme, like the IIDP, makes all standard operating procedures and protocols publicly available online. In addition to freshly isolated islets from donors with and without diabetes, ADI IsletCore provides acinar, pancreatic lymph node, spleen, intestine, adipose and blood tissues, along with banked FFPE biopsies, cryopreserved islets and snap-frozen islets from >615 donors.

Phenotyping, data repositories and knowledge bases

Making use of tissue resources: phenotyping A goal of our field is to understand islets well enough to (1) design treatments that correct defects in diabetes; (2) devise ways to protect islets from stresses associated with diabetes and transplantation; and (3) produce surrogates for diabetes cell therapy. For decades, most experiments involving human islets had low statistical power and often simply sought to confirm results from cell lines or rodent models. However, a hallmark feature of human islets is their variability in responsiveness [93]. This means that much of the previous work using human islets cannot stand on its own. Phenotyping efforts aim to address this by generating extensive datasets that capture and leverage the significant variability in human islet functional and molecular profiles (Table 2).

Crucially, teams with diverse and complementary technical abilities can compile well-powered datasets on hormone secretion, cellular metabolism, stress resilience, cell survival and proliferative capacity that together dictate functional beta cell mass. These ‘hard biological endpoints’ can be complemented by omics data, which are relatively abundant but often lack physiological context. Novel insights can be achieved when omics data are obtained from deeply phenotyped islets linked with key donor characteristics. For example, by combining proteomics, transcriptomics and careful phenotyping of dynamic insulin responses to nutrients, hundreds of high-confidence protein hits associated with insulin secretion and type 2 diabetes were identified [93]. In another study, systematic and standardised testing of type 2 diabetes donor islet function and ex vivo recovery led to the unexpected finding of beta cell functional plasticity and associated transcriptome signatures [66].

Data repositories Data repositories serve as access points for the scientific community. Generic repositories include the NCBI Gene Expression Omnibus [94] and the European Genome–phenome Archive (EGA) [95] for genomics, and ProteomeXchange [96] for proteomics. Datasets can be integrated in specialised resources using standardised and open workflows. The first islet- or pancreas-focused repositories provided access to transcriptomic and genomic datasets and included EPConDB [97], T1DBase [98] and GeneSpeed Beta Cell [99]. The focus on these types of data was influenced by the early adoption of open data principles and the establishment of minimum information guidelines in the DNA array and sequencing communities, as well as methodological developments that made the technologies fast, cheap and scalable. Most contemporary genomics resources (Fig. 2), such as the Type 2 Diabetes Knowledge Portal [100], maintain a focus on these technologies but are increasingly expanding by integrating genome-wide association study (GWAS) data and islet and donor phenotyping data. The Human Islet Research Network (HIRN) Resource Browser (https://resourcebrowser.hirnetwork.org) provides links to more than 400 human islet datasets, including omics and imaging data. The National Institute of Diabetes and Digestive

Table 2 Large-scale human pancreas and islet phenotyping programmes

Programme	Islet source	Tissue level(s)	Breadth	Depth of data	Data access[a]	Strengths	Website	Key publication(s)
Human Pancreas Analysis Program (HPAP)	University of Pennsylvania and Vanderbilt University, screened by nPOD	Pancreas, islets, single cell	~200 donors	Comprehensive	Or	Deepest data, freely available	https://hpap.pmacs.upenn.edu	[108, 109]
Human Islet Phenotyping Program (HIPP)	IIDP	Islets	~660 donors	Baseline	A	Strong user interface Extensive donor data Data on islets distributed to users	https://iidp.coh.org	[57]
HumanIslets consortium	ADI IsletCore	Islets, single cell	~620 donors	Intermediate	O	Simple data access and analysis tools for all experience levels	www.humanislets.com	[111]
Islet Gene View	Nordic Network for Islet Transplantation	Islets	<200 donors	Baseline	C	Easy to use, includes analysis tools	https://mae.crc.med.lu.se/IsletGeneView/	[72]

[a]A, approval required; C, closed; O, Open; Or, open with registration. Note that data access may vary depending on data type. For example, even the open access programmes may indirectly link some data to closed repositories, for example in the case of genetic data

and Kidney Diseases dkNET platform (https://dknet.org) serves as a centralised hub of material, computational and data resources [101] that include 'high value data sets' related to diabetes, including many described in the present review. Of note, the important contributions of dkNET have included promoting the use of RRIDs for resource identification.

The Islet Regulome Browser (www.isletregulome.com) allows exploration of islet-specific epigenome and transcriptome data, providing access to a wealth of information on different classes of regulatory elements, enhancer clusters, transcription factor binding sites and GWAS variants in adult human islets and pancreatic progenitors [102]. The browser can be searched for gene names or genome coordinates, together with a selection of specific chromatin maps, and the interactive interface displays virtual 4C maps, loci of type 2 diabetes SNPs, and different types of regulatory elements and transcription factor binding sites.

Pancreatlas (pancreatlas.org) was developed to share histological and immunostaining data [103]. Collections include cystic fibrosis-related diabetes samples [104], Human Pancreas Analysis Program (HPAP) samples, neonatal development and early life samples (HANDEL-P), the IIDP Human Islet Phenotyping Program (HIPP) samples, and images from the EADB [18]. Images, numbering more than 4300, can be opened directly in PathViewer (v.3.11.0, Glencoe Software, www.glencoesoftware.com) to enable visualisation, marker comparison and annotation of regions of interest. Detailed image analysis, however, requires the images to be downloaded and analysed using a specialised workflow. Raw images are not available, and users must rely on PathViewer exports, thus limiting this repository's utility. Pancreatlas currently includes some single-cell datasets, which may position this resource well to handle and analyse future spatial omics datasets.

Histological data are also available online via the nPOD Data Portal (https://portal.jdrfnpod.org/), following an application for access. This site provides histopathology assessments based on whole slide scans from H&E-stained sections; sections stained for insulin, glucagon, somatostatin and pancreatic polypeptide to visualise endocrine cells; and sections stained with Ki67 and CD3 for quantification of cell proliferation and immune cell infiltration. These data are accessible via the Aperio eSlide Manager (https://aperioeslide.ahc.ufl.edu/), which offers similar utility and limitations to Pancreatlas. An advantage of nPOD, however, is its primary role as a tissue repository, allowing online histopathology to be used as a screening tool for selecting donors and samples for further analysis. The nPOD Data Portal also hosts donor

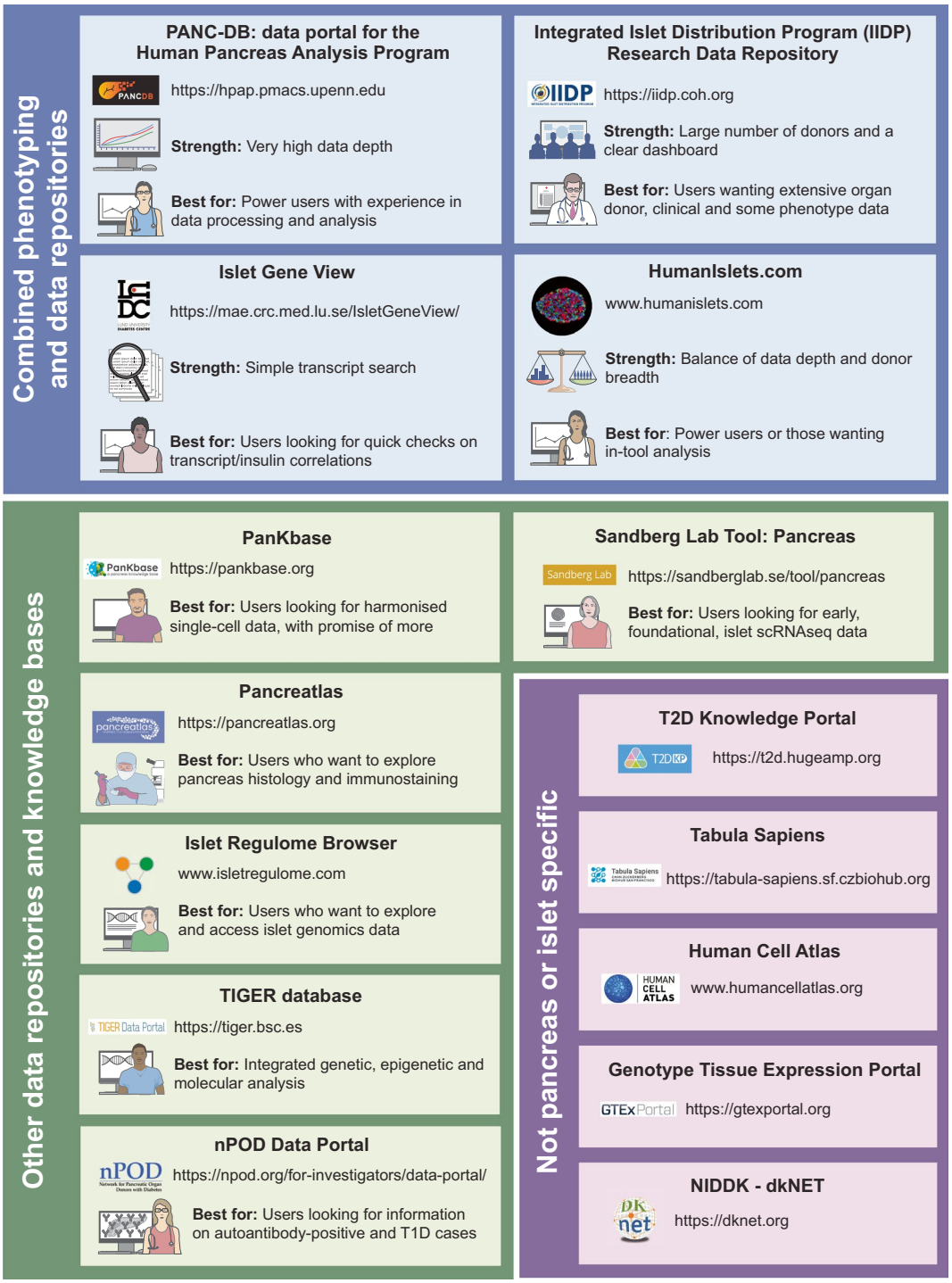

Fig. 2 Summary of key data resources and knowledge bases. The data resources shown are linked directly to large-scale phenotyping programmes (blue), are project-based or based on data aggregation (i.e. 'standalone', green), or include pancreas and islet data within a larger context (purple). Key strengths and use cases are highlighted but are non-exhaustive. NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; scRNAseq, single-cell RNAseq; T1D, type 1 diabetes; T2D, type 2 diabetes. This figure is available as part of a downloadable slideset

and diabetes-related information (similar to the IIDP), along with published and unpublished datasets. These include high-resolution four-digit HLA genotypes, immune phenotyping, some functional data on live pancreas slices, custom SNP microarray donor genotyping, and a standardised whole-exome sequencing (WES) pipeline [105].

Integrated phenotyping and data repositories Some resources directly connect pancreas and islet phenotyping efforts to data access and/or analysis tools (Table 2). Islet Gene View (https://mae.crc.med.lu.se/IsletGeneView/) leverages phenotyping and omics output for added insight [72]. This programme from the Nordic Network for Islet Transplantation and the Human Tissue Laboratory at the Lund University Diabetes Centre (LUDC) integrates donor phenotypes, bulk RNAseq data and insulin secretion data (stimulation index) from 188 donors, along with tissue expression and islet expression quantitative trait loci (eQTL) data. The web tool allows easy searching of transcript-level correlations (e.g. correlating an islet transcript with donor phenotype), co-expression analysis, and tissue and cell type specificity (although the last uses an older, relatively small, single-cell RNAseq dataset [106]). However, while the open web tool provides easily interpretable outputs, the underlying data are not accessible, and results (or visualisations) are not downloadable.

The IIDP has made significant strides in collecting and presenting phenotyping data, enhancing the accessibility of donor information through the IIDP HIPP and the Human Islet Genotyping Initiative (HIGI), and securing an agreement to access United Network for Organ Sharing (UNOS) data. These data from >1700 human islet isolations are accessed via the IIDP Research Data Repository (https://iidp.coh.org/). Access requires an application and provides more donor-level data than other resources. Beyond age, sex and BMI, the details available include donor social and clinical history, prior treatments and medications, and information on organ processing. Available phenotyping data (~660 isolations) include measures of insulin and glucagon secretion (as stimulation index or AUC), insulin content, cell composition and cell viability. Data also include >1400 images from FFPE samples, with H&E and immunohistochemical staining for insulin and glucagon and unstained slides available on request. Approximately 360 of these donors have also been genotyped and, while genotyping data are subject to restricted access through the EGA, the web tool provides polygenic risk scores for both type 1 and type 2 diabetes for these donors along with genetic ancestry [107]. Strengths of the IIDP Research Data Repository include an easy-to-use web dashboard, extensive pancreas/islet donor information, which increasingly includes genetic risk assessment, and islet phenotyping data from a relatively large number of donors. The available data are integrated across isolation, donor, phenotype and genotype results; however, the resource provides no tools for data analysis.

The HPAP seeks to phenotype pancreases from Aab+ organ donors, donors with early type 1 diabetes and donors with type 2 diabetes, compared with reasonably matched control individuals [108, 109]. It is worth noting that many adult donors who are positive for a single autoantibody may not progress to type 1 diabetes. Processing pancreases from donors identified through a collaboration with nPOD, this programme undertakes what can be considered the most comprehensive pancreas and islet phenotyping currently available. To date, the HPAP has profiled pancreas samples from 193 donors (22 Aab+, 45 with type 1 diabetes, 52 with type 2 diabetes), although these are used for extensive in-house profiling and are not distributed directly to the research community. In addition to standard donor characteristics data, the associated PANC-DB data portal (https://hpap.pmacs.upenn.edu) provides bulk islet and single-cell genomics, whole-genome sequencing, dynamic hormone secretion and oxygen consumption data, and spatial data (standard histology, CODEX/PhenoCycler, imaging mass cytometry). A strength of the HPAP and the PANC-DB data portal is the depth of phenotyping data that is freely and quickly available via a simple, free registration. However, the ability to analyse this data can require specialised expertise, and some datasets (e.g. Ca^{2+} imaging) may therefore be underused. A more user-friendly web tool has been developed to enable gene expression analysis in single islet cells from HPAP donors, allowing subsets of donors with specific demographic (age, sex, ethnicity) or clinical characteristics (Aab+, type 1 diabetes, type 2 diabetes, no diabetes, disease duration, HbA_{1c}, BMI) to be selected [110].

The HumanIslets consortium (www.humanislets.com) focuses on islets and pancreases processed by the ADI IsletCore [111], leveraging a broad islet distribution network and decentralised phenotyping linked back to the same donors. With data from 588 donors currently available on this platform, it is among the broadest of such resources. Although phenotyping is not as comprehensive as in the HPAP, several data types are unique, including whole-islet proteomics, electrophysiology, dynamic insulin responses to nutrients beyond glucose, and prohormone processing [93, 112, 113]. A strength of the HumanIslets consortium is its accessibility to biologists without specialised bioinformatics skills, enabling user-friendly analyses and gene/protein lookups directly on the website. The underlying data, metadata, analysis results and associated workflows can be downloaded to enable more flexible or customised analysis. For bulk RNAseq data, the HumanIslets consortium provides a highly accessible dataset, offering users raw counts, TPM (transcripts per kilobase million) and logCPM (log-transformed counts per million) data following batch correction in a spreadsheet format with clear documentation. Advanced bioinformatics experts seeking to work with the raw data can follow links to the relevant repositories.

Aggregating data for power and insight The open access Translational human pancreatic Islet Genotype tissue-Expression Resource (TIGER) portal compiled data on >500 human islet preparations (including 30 from type 2

diabetes donors) from five cohorts. Bulk RNAseq and array-based genotypes underwent stringent quality control, and genotype imputation using four different reference panels improved coverage of low-frequency and rare variants that may have larger effect sizes on gene expression and diabetes risk [68]. Genetic variation was associated with gene expression by eQTL studies in four islet cohorts and subsequently meta-analysed, resulting in >1 million eQTLs. The user-friendly TIGER browser enables users to look up gene expression, (epi)genomic regions, eQTL and allele-specific expression, with gene- or genetic variant-centric queries, and provides links to external resources (i.e. UCSC Genome Browser, Gene Ontology [GO] terms, Ensembl and UniProtKB/Swiss-Prot). Colocalisation of GWAS and eQTL SNPs permits risk variants for glycaemic traits, type 1 diabetes and type 2 diabetes to be linked with islet gene expression [68, 114]. TIGER thereby provides insight into the molecular underpinnings of islet pathophysiology and the genetics of diabetes.

The Pancreas Knowledge Base (PanKbase; pankbase.org), started in 2024, is a centralised resource for human islet and pancreas data. Its goal is to aggregate datasets and curate knowledge from multiple sources to generate robust, standardised and computationally ready omics data, analytic libraries and pipelines, and metadata. Available resources currently include single-cell RNAseq and single-nucleus ATAC-seq data from islets obtained through the HPAP and IIDP programmes, as well as a commercial source (Prodo Laboratories). This is the largest single-cell map to date, processed through a harmonised pipeline. The data can be downloaded, explored and examined using an integrated cell browser. Tools for principal component analysis (PCA) and cell-specific pseudo-bulk differential expression analysis are also available. A particularly novel component of PanKbase is the pancreas knowledge graph (PanKgraph), a prompt-based artificial intelligence (AI)-guided knowledge repository that enables the exploration of links between transcript expression and SNPs, with a primary focus on type 1 diabetes. PanKbase is a relatively new resource and is currently under active development. With a stated commitment to the Findable, Accessible, Interoperable, and Reusable (FAIR) principles of data curation (www.go-fair.org), this promises to be a key resource for curating and accessing datasets from disparate sources.

Challenges and gaps

In contrast to studies on inbred rodents, human islet data are shaped by more complex factors that can influence molecular and functional phenotypes. Donor metadata such as age, BMI, HbA_{1c} and sex associate with islet cell composition [115, 116], insulin content [92, 117] and insulin secretion [92, 117–119]. Nearly 10 years ago, this field was encouraged to improve transparency in the description of human islets used in research [120]. In response, several journals, including *Diabetologia*, called for the reporting of (limited) donor characteristics [121]. While a welcome advance, the availability of donor characteristics remains a common limitation, with factors such as genetic ancestry, menopause status and diabetes duration potentially influencing molecular and functional outcomes. This gap may be bridged through studies of islets from live donors [69], although existing gaps in representation across ages and ethnicities (Fig. 1) may continue. In addition, metadata may be incorrect; the reported donor sex was incorrect in 3.7% of TIGER samples based on Y chromosome gene expression. Metadata reporting may be improved through the greater uptake of RRIDs, although these are not the ultimate solution, as the parameters reported at best explain only a minor proportion of the variation in islet isolation [63, 122]. In addition to clinical data, technical parameters such as purity, cold ischaemia time and islet culture duration also affect islet insulin content and secretory function [92, 117]. Understanding the technical and biological factors that drive heterogeneity in islet isolation outcomes and islet function remains an important question.

Variability and standardisation Islet phenotyping consortia developed organically and independently of each other, typically around major islet isolation centres. As a result, experimental conditions are not standardised, making it challenging to pool data across centres, despite recent efforts (e.g. many centres use and recommend Prodo media, although the composition of the different types of media is not disclosed). A consistent feature of human islet data is significant variation among donors [93], which can limit our ability to resolve key biological differences. Stimulation indices measured during dynamic insulin secretion assays show coefficients of variance of ~95% (calculated from data at HumanIslets.com and PANC-DB). This means that detecting a 20% difference between two groups at 80% power and α=0.05 requires a sample size of ~370. Such sample sizes are currently not achievable with a single data source, precluding comparison of minority donor subgroups, such as female donors (40–46% of total donors), donors with diabetes (3–23% type 1 diabetes, 11–27% type 2 diabetes), donors of specific age brackets (12–46% aged <40 years) and donors from minority ancestry groups (<24%), donors with BMI <25 kg/m^2 (~35%), or donors with multiple such characteristics. One solution is to combine data from several sources, which has been accomplished with RNAseq [123–126]. However, other data types are frequently obtained using site-specific protocols, making their combination challenging, if not impossible. Publicly available data on

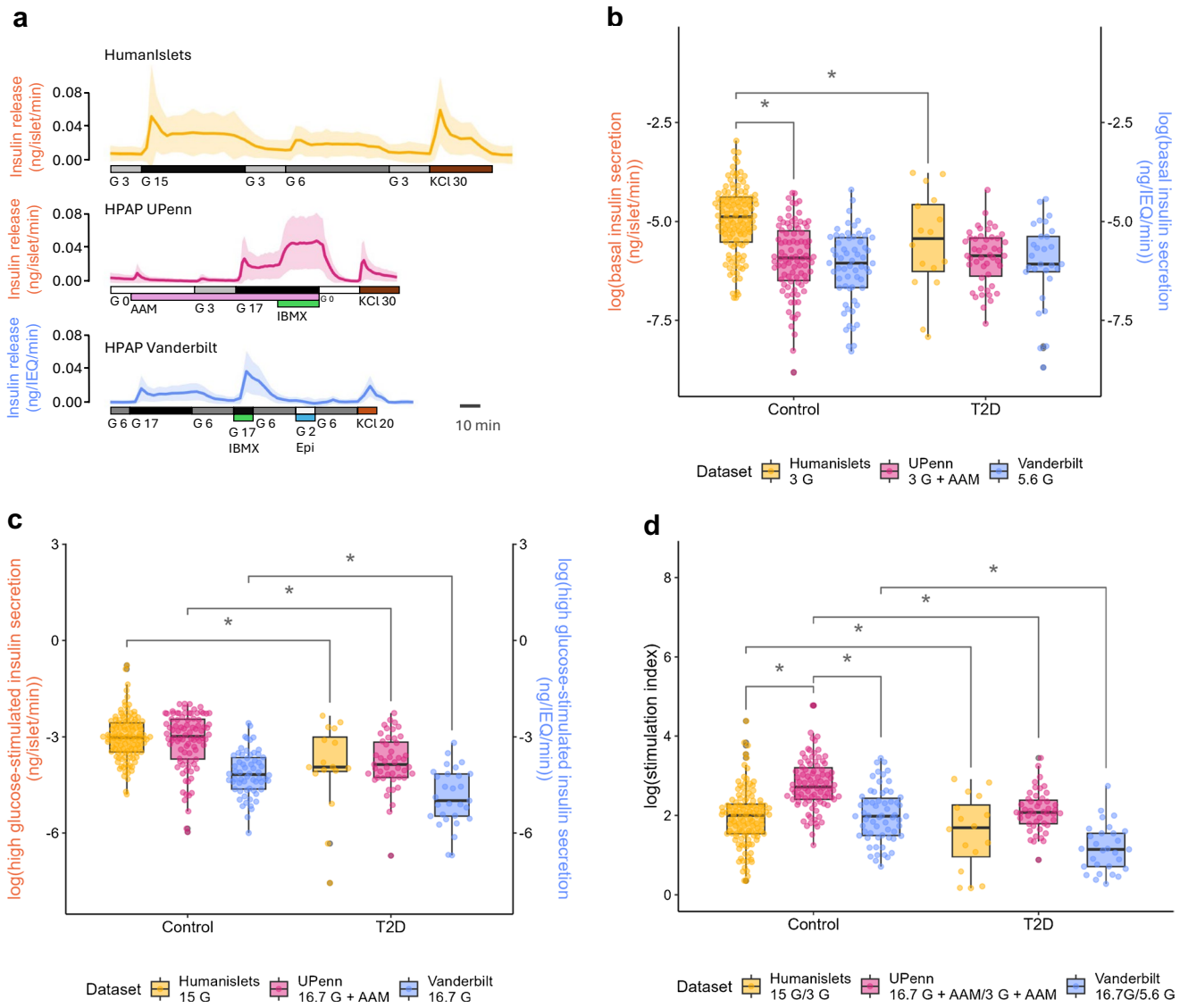

Fig. 3 Comparison of glucose-stimulated dynamic insulin secretion from different centres. (**a**) Dynamic insulin secretion measurements from HumanIslets.com, performed at the University of British Columbia, or from the HPAP, performed at the University of Pennsylvania (UPenn) or Vanderbilt University. Data from HumanIslets.com and UPenn are normalised per islet, while data from Vanderbilt are normalised per islet equivalent (IEQ). (**b**–**d**) Summary of mean basal insulin secretion (**b**), maximum high glucose-stimulated insulin secretion (**c**) and the simulation index, calculated as high glucose-stimulated insulin secretion over basal insulin secretion (**d**). Note the different conditions used at each centre. *p<0.05 by two-way ANOVA with Tukey's correction. For basal and high glucose-stimulated secretion, comparisons between the Vanderbilt University dataset and the other two datasets were not performed because of the different normalisation methods used. AAM, amino acid mix; Epi, adrenaline (epinephrine); G, glucose; IBMX, isobutylmethylxanthine; T2D, type 2 diabetes. This figure is available as part of a downloadable slideset

dynamic insulin secretion [57, 108, 111] are generated using different stimuli, timings, flow rates, normalisation modes (number of islets vs islet equivalents), lysis solutions for extracting insulin content, and assay kits. These differences are non-trivial (Fig. 3). Looking ahead to improving current programmes and establishing new centres, with the benefit of hindsight, it would be incredibly powerful to synchronise at least some experimental protocols for procuring functional data.

One of the largest sources of between-consortia variation may be the decision to hand-pick islets after shipment. While hand-picking islets removes damaged or fragmented islets and exocrine tissue from even high-purity preparations, potentially reducing exposure to enzymes that stress islets, this process may select for uniformity of islet size (ignoring small islets) that may not accurately reflect the in vivo situation. As a result, stimulation indices for static incubation and perifusion studies from groups that hand-pick can be

at least twofold greater than those from groups that do not [122]. Even within consortia, potential sources of variation persist that could benefit from standardisation. For example, circadian variation in gene expression [127] and metabolism [128] suggests important impacts that could be addressed by introducing synchronisation protocols or, at the very least, by recording the time of experiments.

Clear and methodical data and metadata reporting can improve accessibility and provide structure to support future standardisation across data sources. Ideally, a user should be able to download, understand and analyse a dataset without needing to contact the data manager for clarification. Ideal metadata reporting should be intuitive while conforming to local and regional laws governing patient privacy, with clear data headings. For example, the HPAP and IIDP provide detailed metadata files with logically ordered sheets, consistent use of RRIDs and, in the case of the IIDP, a clear distinction between ethnicity and race/ancestry. Data reporting should be accompanied by protocols that are sufficiently detailed for the user to interpret the data, including updates as needed, and easy to locate in the user interface. For example, HumanIslets.com has a dedicated documentation section that provides such details. This is particularly critical when only raw data files are provided and methodological details are required for proper data processing.

Gaps in geographical and donor diversity Genetic ancestry has important influences on diabetes risk and presentation, including islet characteristics. First, we note that different resources assess and define ancestry, race and ethnicity in different ways, whether through genetic testing or self-reporting. Here, we use terminology as recommended in guidelines from *JAMA* [129]. Isolated islet perifusion data from the HPAP show a greater type 2 diabetes-associated decrease in insulin secretion among donors of Black/African American ethnicity than among White donors of European ancestry [130], and substantial variation in insulin secretion across genetic ancestry groups [119]. A recent study found that a distinct type 1 diabetes subtype in which autoantibodies are absent is common among sub-Saharan African individuals, a finding also observed among Black participants in the US SEARCH cohort [131]. Overlooking the effects of ancestry and geography on diabetes risk and progression may limit the efficacy of treatment and management strategies. While current islets datasets provide some insight, these remain heavily weighted towards individuals of European ancestry.

Globally, human islet cores are concentrated in Europe and North America, with a handful in South America, Australia, East Asia and Singapore [44]. Even in countries such as the USA and disregarding the crude classification of heterogeneous ethnic groups [132, 133], the donor pool shows under-representation of diverse racial and ethnic groups, among whom diabetes onset, progression and complications vary [134, 135]. Indeed, when excluding samples from donors where ancestry is not reported, most of the tissue in biobanks derives from White donors of European ancestry (61.9%). Among type 1 diabetes donors, this proportion is higher (78.0%), while it is lower among type 2 diabetes donors (52.3%) (Fig. 1e). Consideration of genetic ancestry in islet phenotyping efforts remains an important challenge.

Assembling tissues across the life course is also important. Initiatives such as HANDEL-P and the Human Developmental Biology Resource are facilitating studies in young donors, providing insights into the early stages of pancreatic development. In summary, the remarkable work of organ procurement organisations, biobanks and global researchers is significantly expanding our understanding of the human pancreas. However, given limited donor representation, we must exercise caution before generalising findings.

Barriers to data access While the resources mentioned above include abundant data, accessibility remains an area for improvement. Cross-cutting issues include experimental protocols with limited or outdated information, unclear (or absent) data preprocessing, and data downloads that are either unavailable or pose unnecessary barriers for laboratories without a strong computational focus. The rapid expansion of multi-omics and phenotyping technologies has created a huge volume of complex, high-dimensional datasets, but post hoc analyses remain limited by inconsistencies in cell type annotations and the availability of processed count data [136]. To extract meaningful insights, standardised reporting, principled methods of access and dedicated analytical pipelines are essential to fully capitalise on the substantial investments in human islet research.

It is, however, important to exercise care when performing post hoc analyses of already processed data, given the potential confounding factors discussed above in 'Variability and standardisation'. Indeed, naive integration may obscure disease-specific differences that are later brought to light via improvements in dataset integration [137, 138]. Thus, inconsistent systematic and programmatic data availability remains a major bottleneck. In particular, access to raw data and standardised metadata is important as it enables future reanalysis using improved analytical pipelines and facilitates improved integrative analyses that are not confounded by differences in upstream data processing. Metadata standards for reporting islet characteristics exist [120, 121], but they require additional specification and definition using controlled ontologies and increased adaptation in the field. For example, which units are HbA_{1c} reported in? Which clinical definition was used to diagnose diabetes? It is essential for the community to establish and maintain reporting standards that incorporate information about treatments. In addition to incoherent metadata reporting, the datasets themselves

are scattered across multiple public and private databases with inconsistent structures and metadata requirements, making data collection and curation cumbersome and time consuming. A solution to this problem is to create secondary databases that collect and curate data from a diverse set of primary databases and share it in accordance with FAIR principles. Efforts such as Type 2 Diabetes Knowledge Portal and PanKbase are working to bring resources together, but often provide access only to processed data summaries. Data protection and privacy regulations create barriers to sharing genotypes and raw sequencing data. While these safeguards are necessary, they slow/hinder data access, partly due to differences in the interpretation and implementation of the General Data Protection Regulation (GDPR) across the European Union [139]. Solutions, inspired by experiences from large international consortia, such as the Human Cell Atlas (https://humancellatlas.org), include defining a code of conduct for data sharing that details a standardised privacy-compliant data use agreement, donor consent templates, and data sharing standards that assess identifiability while maintaining FAIR and open data standards.

Data usability and analytics Data usability is an important bottleneck when analyses require bioinformatics skills or proprietary software. Lowering the barriers to accessing, analysing and exploring data through point-and-click interfaces can accelerate discovery. Resources such as Human Islets.com and PanKbase integrate analytical tools by co-locating data and analytics. These initial initiatives are currently restricted to basic analyses with limited flexibility. As data collection evolves to include more omics and imaging modalities, simply providing data access will be insufficient. Future data repositories should integrate data analytics to maximise data reuse.

Multi-omics integration methods fall into two main categories: knowledge driven and data driven. In knowledge-driven approaches, researchers first analyse each individual omics dataset to identify their molecular signatures, which are then mapped onto a pre-existing knowledge base of molecular relationships, such as gene regulatory networks, protein–protein interaction networks or metabolic pathways. Researchers visualise and interpret how different omics layers interact to reveal underlying biological processes [140]. Data-driven approaches integrate multiple omics datasets using statistical or machine learning techniques such as multivariate correlation analysis or dimensionality reduction to identify shared patterns across omics layers [141]. These approaches can be used together [141]. A significant limitation of current multi-omics integration is the insufficient support for complex metadata. While some tools allow researchers to visualise how different experimental factors affect the results, most do not formally incorporate this metadata into the analytical model.

Multimodal analysis, integrating spatiotemporal maps of molecules such as genes, proteins and metabolites, allows researchers to link gene expression, protein abundance and other molecular data to their exact locations within a tissue [142]. This enables detailed reconstruction and dynamic monitoring of complex biological microenvironments, such as the islet. By overlaying molecular data onto high-resolution histology or immunostaining images, researchers can visually select regions of interest, then perform targeted analyses on these regions to identify key molecules and biological functions. The development of efficient and intuitive data analysis and visualisation tools will be critical.

AI is increasingly vital for data analysis and interpretation, particularly in complex fields such as biology. While deep learning models are powerful for tasks such as multi-omics integration and image recognition, they often act as a 'black box', making their decisions difficult to interpret compared with traditional methods. The rise of generative AI, such as large language models and knowledge graphs, offers a promising solution. Integrating these technologies into current knowledge bases and computational workflows will help make AI-driven insights more interpretable and greatly democratise data analysis to accelerate knowledge, discovery and translation.

Looking forward

We require deep sampling across data modalities and donor diversity for system-level insights into islets in health and disease. Demographic imbalances limit the generalisability of current resources. Organ donor data typically provide a single snapshot of disease, often at end-stage or after years of progression, but do not capture longitudinal trajectories. Thus, it is important to continue methodological developments to enable scalable data generation for dense sampling across demographic groups and disease stages. We envision that new insights will be driven not only by the integration of additional datasets and modalities into knowledge bases, but also by technological advancements in information retrieval and analysis. An interesting avenue to explore will be the creation of scientific reasoning engines using an appropriately tuned large language model that has access to the knowledge bases enhanced with biologically informed knowledge graphs, which, through graph-based retrieval-augmented generation, can aid researchers in discovering new associations by linking disparate pieces of information through multi-hop retrieval across biologically plausible associations.

The experience and expertise gathered by established phenotyping programmes should be leveraged to support the development of similar islet distribution centres and phenotyping programmes in regions that lack such resources,

building a global foundation for islet research that includes researchers, clinicians, donors and their families, and beneficiaries of all backgrounds. A key opportunity lies with human islet isolation programmes in regions that are not connected to broader phenotyping initiatives but that may be ideally poised to collaborate with existing programmes. Such collaborations will critically address the diversity and ancestry gaps in our understanding of human islet variability, enable consolidation of protocols and the development of clear, standardised reporting mechanisms to support powerful phenotyping data generation, and support extraction of the most useful possible data from precious donor samples.

Supplementary Information The online version contains a slide-set of the figures for download available at https://doi.org/10.1007/s00125-026-06731-4.

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