OMICS A Journal of Integrative Biology
Volume 28, Number 4, 2024

DOI: 10.1089/omi.2023.0278

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Blood-Based Multiomics-Guided Detection of a Precancerous Pancreatic Tumor

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Abstract

Over a decade ago, longitudinal multiomics analysis was pioneered for early disease detection and individually tailored precision health interventions. However, high sample processing costs, expansive multiomics measurements along with complex data analysis have made this approach to precision/personalized medicine impractical. Here we describe in a case report, a more practical approach that uses fewer measurements, annual sampling, and faster decision making. We also show how this approach offers promise to detect an exceedingly rare and potentially fatal condition before it fully manifests. Specifically, we describe in the present case report how longitudinal multiomics monitoring (LMOM) helped detect a precancerous pancreatic tumor and led to a successful surgical intervention. The patient, enrolled in an annual blood-based LMOM since 2018, had dramatic changes in the June 2021 and 2022 annual metabolomics and proteomics results that prompted further clinical diagnostic testing for pancreatic cancer. Using abdominal magnetic resonance imaging, a 2.6 cm lesion in the tail of the patient's pancreas was detected. The tumor fluid from an aspiration biopsy had 10,000 times that of normal carcinoembryonic antigen levels. After the tumor was surgically resected, histopathological findings confirmed it was a precancerous pancreatic tumor. Postoperative omics testing indicated that most metabolite and protein levels returned to patient's 2018 levels. This case report illustrates the potentials of blood LMOM for precision/personalized medicine, and new ways of thinking medical innovation for a potentially life-saving early diagnosis of pancreatic cancer. Blood LMOM warrants future programmatic translational research with the goals of precision medicine, and individually tailored cancer diagnoses and treatments.

Keywords: precision oncology, personalized medicine, longitudinal monitoring, multiomics, pancreatic cancer, diagnosis

Introduction

Recent progress in multiomics technologies has ushered in a new era in the field of precision medicine. Multiomics technologies are particularly useful for measuring a wide range of interconnected molecular, microbial, and physiological changes. As shown by several landmark studies (Babu and Snyder, 2023; Chen et al., 2012; Price et al., 2017), the use of longitudinal multiomics measurements allows both timely detection and precise treatment of diseases such as

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type 2 diabetes (T2D) and hemachromatosis. Indeed, these multiomics-based diagnostic methods have allowed the detection of medical conditions at sufficiently early stages. Moreover, significantly improved health outcomes could be achieved by adopting modest lifestyle modifications or medical interventions in response to multiomics diagnostics (Chen et al., 2012; Flores et al., 2013). These integrated, multiomics approaches to precision medicine have been called P4 (Predictive, Preventative, Personalized, and Participatory) medicine (Flores et al., 2013; Weston and Hood, 2004) or integrative personal omics profiling (iPOP) (Chen et al., 2012).

While the results of both iPOP and P4 medicine are impressive and have attracted considerable attention, they do have their shortcomings. The need for nearly daily monitoring (especially with the iPOP approach), and the requirement for extensive genomic, metagenomic, epigenomic, metabolomic, and proteomic measurements (for both iPOP and P4), combined with the challenging data analysis and data integration burden have made both iPOP and P4 far too expensive and time-consuming to become mainstream medical methods (Flores et al., 2013). Likewise, the diseases or conditions identified through these very sophisticated multiomics techniques, for example, T2D, hemochromatosis, various vitamin deficiencies, could have been detected with much simpler, lower cost, conventional clinical tests (Chen et al., 2012; Ponikowski et al., 2016). To address these limitations regarding patient commitment or burden, assay cost diagnostic speed, and medical impact, we have spent a number of years developing a faster, simpler, and cheaper approach called Longitudinal Multiomics Monitoring (LMOM) (Anwar et al., 2020). We have also focused the development of LMOM to detect less obvious or harder-to-diagnose medical conditions or early-stage diseases.

In creating LMOM, we chose to adopt only absolutely quantitative multiomics methods to facilitate rapid data comparison and integration. This required that we reduce the number of required omics measurements to just two: proteomics and metabolomics. It also meant that we had to develop and extensively test two assays: an in-house quantitative metabolomics assay that can accurately measure 143 high-value metabolites in serum and an in-house quantitative proteomics assay that can measure 140 high-value proteins in plasma. To reduce both patient burden and cost, we limited the number of sampling periods to once per year and harnessed the power of machine learning (ML) to accelerate the diagnostic methods. ML and text mining can be used to extract multiomic biomarker data from both published literature data and experimentally collected multiomics data (Arjmand et al., 2022; Feldner-Busztin et al., 2023).

Specifically, we used ML-based literature mining tools and techniques to assemble a large, in-house proprietary database of metabolite and protein biomarkers corresponding to the molecules measured by our quantitative proteomics and metabolomics assays at the Molecular You Corporation (MYCo) (Liu et al., 2015). Furthermore, by iteratively training a second ML method on large repositories of molecular profiles that were coupled to clinical outcomes, we were able to develop an algorithm that could automatically and accurately detect disease susceptibilities, identify disease-associated mechanisms, and diagnose specific early-stage diseases (Anwar et al., 2019; Keser et al., 2021).

Thanks to the reduced multiomic costs and a lowered data analytic burden, we have been able to deploy LMOM to track hundreds of individuals over multiple years. Throughout that time, the LMOM system has successfully detected and diagnosed cases of early-stage cardiovascular disease (Anwar et al., 2019) and early-stage T2D (Keser et al., 2021). Many other individuals have also used the data from LMOM at the MYCo, and molecularly guided diet/lifestyle interventions, with an eye to improve their cardiovascular, hormone, nutritional, and gut health (Marabita et al., 2022; Schüssler-Fiorenza Rose et al., 2019; Shen et al., 2023). We have also used the LMOM system to elucidate disease mechanisms and identify early-stage biomarkers for other conditions, including autism, Alzheimer's disease, chronic kidney disease (CKD), and polycystic ovary syndrome (articles in preparation).

In this case report, we describe the use of multiyear LMOM in helping detect early-stage pancreatic cancer in a postmenopausal female. We believe this example of a successful LMOM diagnosis is particularly compelling because pancreatic cancer is a nonobvious, hard-to-diagnose condition that has life-threatening implications.

Pancreatic cancer is one of the deadliest of all malignancies, with a 5-year survival rate of less than 9% (American Cancer Society, n.d.; Siegel et al., 2019). Pancreatic cancer accounts for $\sim$3% of all cancers diagnosed in the United States and each year, more than 60,000 new cases of pancreatic cancer are expected to be diagnosed (Park et al., 2021). While pancreatic cancer only accounts for a small percentage of all cancer diagnoses, its lack of symptoms and insidious onset usually means it is diagnosed at a late stage and often after the pancreatic tumor has become unresectable or metastatic (Mizrahi et al., 2020). Therefore, the development of newer methods to enable precision medicine and the early diagnosis of pancreatic cancer or precancerous pancreatic tumors is desperately needed.

We present a case report wherein LMOM guided the diagnostic trajectory and helped detect early-stage pancreatic cancer. We also cover the patient's case history, paying special attention to the sequence of events, dates, key medical/molecular findings, diagnosis, treatment, and outcome. We conclude with a discussion of the implications that LMOM may have for precision/personalized medicine and how it is poised to ultimately empower patients to have a more proactive role in the governance of their health.

Materials and Methods

Ethics considerations

This is a case report involving one patient only and does not constitute research. Case reports of three or fewer patients ''do not meet the U.S. Department of Health and Human Services (DHHS) definition of ''research''', as noted in an academic source, for example, John Hopkins Medicine (www.hopkinsmedicine.org/institutional-review-board/guidelines-policies/guidelines/case-report), and the University of Alberta, where the corresponding author is based, which states ''Writing a report on a unique or interesting clinical case would not fall within the definition of research requiring Research Ethics Board (REB) review per the second edition of

the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2)'' (www.ualberta.ca/research/services/research-ethics/human-research-ethics/personal-data-privacy/health-information.html).

Additionally, the ethics considerations in the present case report are in alignment with the ''Terms and Conditions'' document set forth by MYCo to all patients and participants in its LMOM program. This report adheres to the ethical standards and principles specified in the MYCo Privacy Policy, MYCo Consent and Authorization Form. The collection and analysis of health data, including molecular marker information, were conducted in accordance with applicable laws and regulations, including the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The patient's privacy and confidentiality are safeguarded, and all personal identifiers are appropriately managed, ensuring compliance with the standards set forth in the HIPAA Privacy Regulations.

The patient in this case report has provided informed consent through the MYCo Consent Document, acknowledging willingness to participate and understanding the nature of the present case report. The case report's procedures, including the collection of biological samples and the generation of Health Data reports, adhere to the protocols established by MYCo and relevant regulatory authorities.

Sample collection

Blood samples (5 mL) were collected by a phlebotomist over a course of 5 years from 2018 to 2023 inclusive, with the annual sampling dates noted in the Results section. Immediately after collection, the blood samples were centrifuged, separated into two aliquots, and plasma and serum were prepared using established standard protocols (Anwar et al., 2019). The plasma and serum samples were frozen shortly thereafter and submitted for metabolomics and proteomics analysis. Two fully standardized, absolutely quantitative omics assays were conducted: a metabolomics assay on the serum samples and a proteomics assay on the plasma samples.

Quantitative metabolomics

The metabolomic assays were conducted at The Metabolomics Innovation Center (TMIC, Edmonton, Alberta, Canada). TMIC is a Canadian ''nationally-funded core facility supported by the Canada Foundation for Innovation (CFI) Major Science Initiatives (MSI) program, Genome Canada (GC), and other funding agencies'' (https://metabolomicscentre.ca/). These assays use a combination of direct injection mass spectrometry (DI-MS) and reverse-phase LC–tandem mass spectrometry (LC-MS/MS) to identify and determine the concentration of 143 different endogenous metabolites. Isotope-labeled internal standards (ISTDs) along with isotope-labeled chemical derivatization reagents were used for accurate metabolite quantification. Methods describing sample preparation, LC-MS/MS conditions, and the quantification analysis were described previously (Foroutan et al., 2020; Foroutan et al., 2019; Fraser et al., 2020; Zhang et al., 2020) and are available in the Supplementary Information.

Quantitative proteomics

The proteomic assays were conducted at MRM Proteomics, Inc. (Montreal, Quebec, Canada). A panel of 140 proteins was used for targeted quantitation by peptide-based analysis using LC-MRM mass spectrometry. These peptides had been previously validated for their use in LC-MRM experiments following the CPTAC guidelines for assay development (https://assays.cancer.gov/). Tryptic peptides were selected to serve as molecular surrogates for the 140 target proteins according to a series of peptide selection rules and previous detectability in plasma samples (Kuzyk et al., 2013). To compensate for matrix-induced suppression or variability in LC-MS performance, $^{13}C/^{15}N$ -labeled peptides (SIS peptides) were used as internal standards. Methods detailing sample preparation, LC-MRM/MS conditions, and the quantification analysis were described previously and are available in the Supplementary Information.

Biomarker database assembly and bioinformatic analysis

The Molecular You Knowledge Database (MYND) is an in-house proprietary comprehensive database containing both automatically and manually curated data on metabolites, proteins, and their associations with diseases. It also contains extensive dietary and lifestyle recommendations to normalize these values. When an individual's blood sample undergoes metabolomics and proteomics analysis, the measured concentrations are submitted to the MYND for disease risk assessment. While the patient's data were submitted to the MYND to ascertain changes in health risks, because the MYND is an in-house proprietary database at MYCo and thus not publicly accessible, these data are not presented as part of the case report. We present in this case report the within-patient changes over time in the actual LMOM data from 2018 to 2023 that provided the initial clinical impetus that triggered the pancreatic cancer-related clinical diagnostic work-up for the patient. We also offer in the present article the broader context of LMOM-guided clinical decision making that guided the patient's diagnostic journey and trajectory from LMOM to the clinical diagnosis of pancreatic cancer.

Data availability

All data that support the present case report and its conclusions, temporal changes within patient multiomics data, are provided in Figures 1–3 and in Supplementary Table S1.

Results

Case history

The patient described in this case report is a 62-year-old female living in Canada. Her medical history includes a total hysterectomy and bilateral oophorectomy in 2003 due to endometriosis. The patient was known to have other mild medical conditions, including osteoporosis, thyroid nodules, demyelination of cerebral white matter, migraine, diverticulosis, hemorrhoids, and gallbladder polyps. She is a non-smoker and drinks alcohol rarely. She had a sibling who was diagnosed with breast cancer and later died of ovarian cancer. The patient enrolled in MYCo's LMOM program in 2018 and has been monitored annually from 2018 to 2023. In the patient's first MYCo multiomic report in 2018, some modest health risks were detected and she modified her lifestyle based on diet and exercise recommendations in the report.

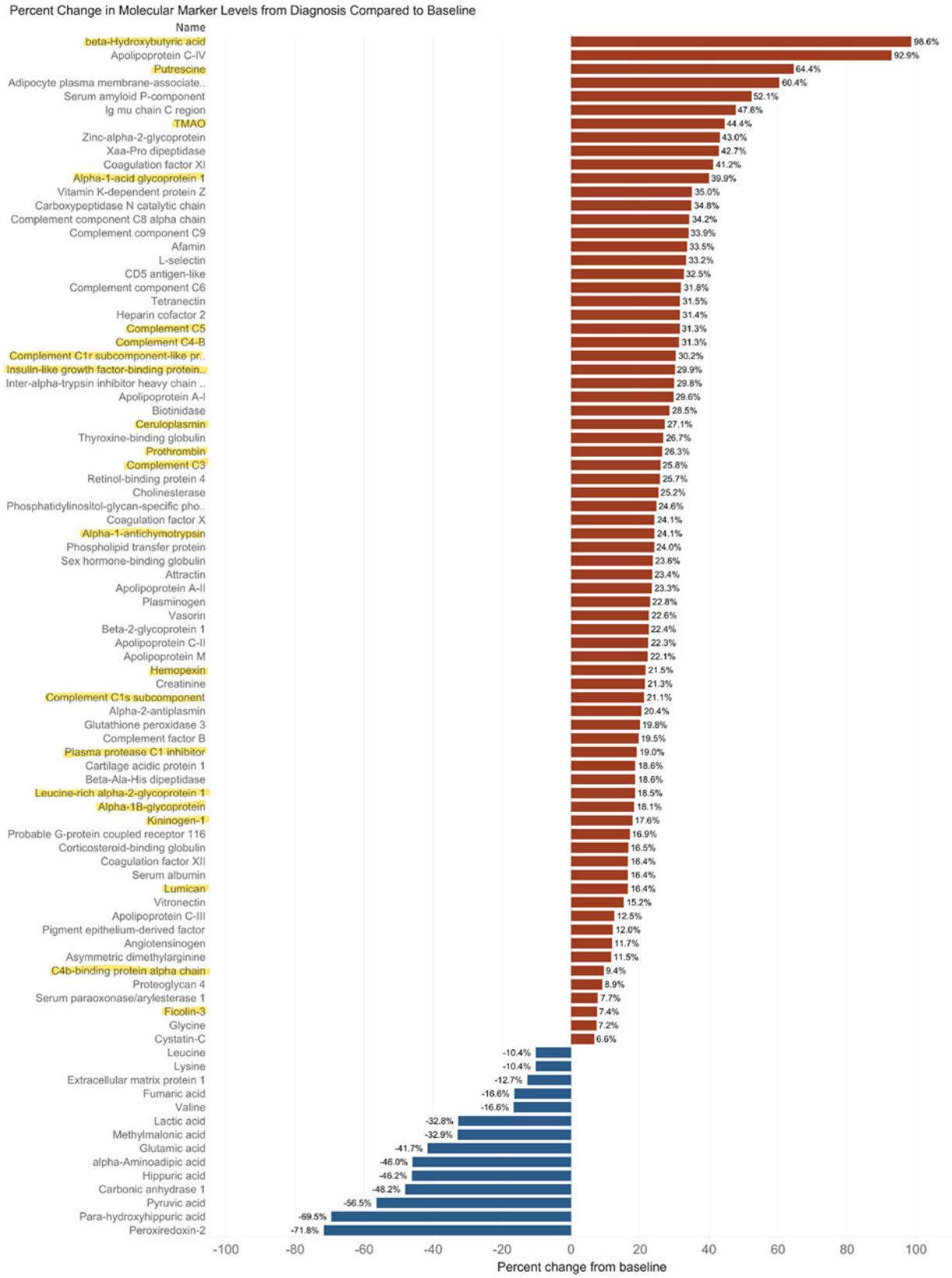

FIG. 1. Percent change in molecular marker levels in the patient's 2022 report compared with patient baseline levels. The concentration levels of molecular markers from the patient's MYND 2022 report with the stage I pancreatic cancer diagnosis was compared with the patient's baseline molecular marker levels, computed by calculating the median marker levels in the previous three tests before pancreatic cancer diagnosis. Positive values (in *red*) indicate the percentage increase of designated markers in the patient's 2022 report compared with baseline and negative values (in *blue*) indicate the percentage decrease of designated markers in the patient's 2022 report compared with baseline. The molecular markers associated with early pancreatic cancer detection, as defined in our results and discussed in the report, are highlighted in *yellow*. MYND, Molecular You Knowledge Database.

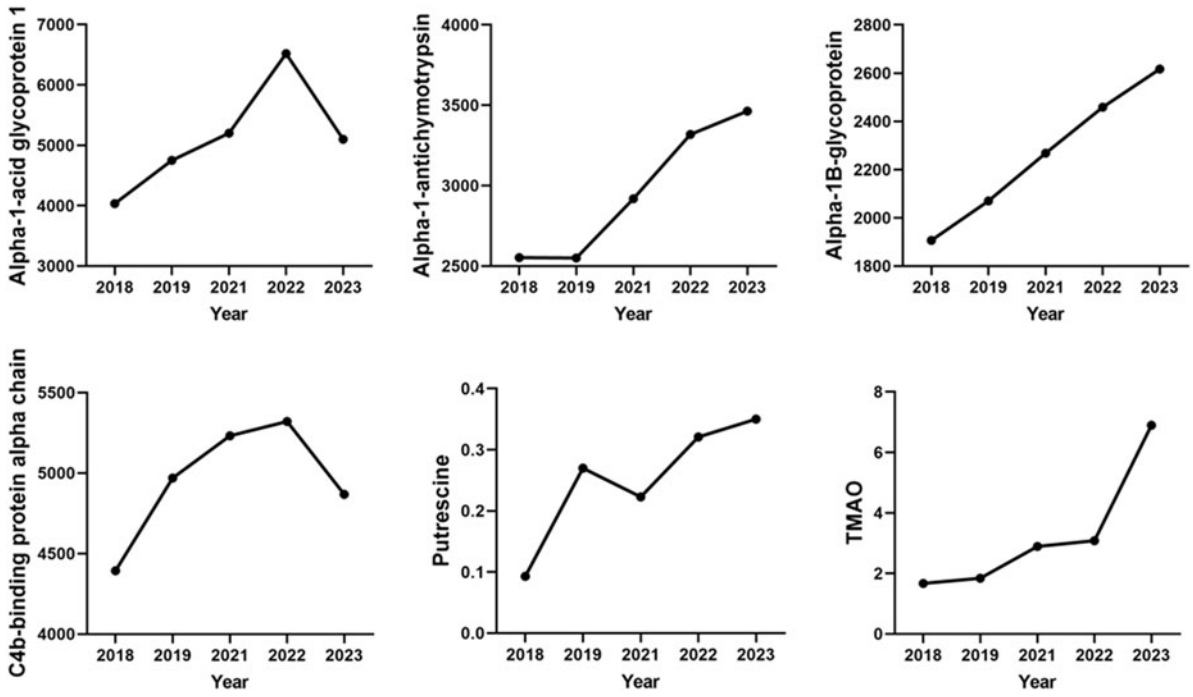

FIG. 2. Longitudinal concentrations of key molecular markers from the patient. Blood concentrations, plasma, and serum for proteins and metabolites, respectively, for key molecular markers associated with pancreatic MCNs, were plotted over 2018–2023 from the patient's MYND health reports. Most molecular markers showed a similar pattern of sudden and rapid increase and elevation in concentration in the patient's 2022 report (i.e., during diagnosis). Some markers also showed a decrease following surgical resection, while some markers did not return to baseline levels. All concentrations are in nM, except for putrescine, which is measured in μM. Please note: each molecular marker will have its own unique concentration values in the serum/plasma. Therefore, the Y-axes scales will vary for each molecular marker. TMAO- trimethylamine N-oxide; MCN, mucinous cystic neoplasms.

These modifications were specifically targeted to normalize certain molecular biomarkers that were outside of normal physiological ranges. In the patient's subsequent report in 2019, these health risks were decreased and many of her out-of-range metabolite and protein biomarkers had returned to baseline levels in 2018.

In May 2022, following a bout with COVID-19 in January/February 2022, the patient began suffering from persistent fatigue and night sweats. These symptoms persisted for about 2 months. She visited her family physician in July 2022 for further evaluations. At that time, she did not report any fever, abdominal pain or discomfort, jaundice, diarrhea, changes in appetite or bowel habits, or recent weight loss, all of which are typical signs of pancreatic cancer. Physical examinations conducted in July 2022 were unremarkable. Laboratory results performed on July 28, 2022, including complete blood count, C-reactive protein, liver function tests, thyroid enzymes, and blood glucose, were within normal ranges. During her July 2022 visit, the patient informed her family physician about her LMOM enrollment with MYCo. While earlier LMOM reports and tests from 2018 to 2021 did not reveal anything of significant concern based on the in-house MYCo database, the 2022 multiomics analyses conducted for the patient in June 2022 showed notable year-over-year temporal shifts in several metabolites and proteins. The LMOM report provided by MYCo identified the patient as exhibiting a cancer-like molecular profile consistent with pancreatic cancer. The molecular within-patient changes in multiomics data over time, reported in the present case report (Figs. 1–3), and though not detected in standard laboratory tests, were indicative of a tumor-promoting microenvironment.

Noting her multiomics results provided by MYCo and her sibling's history of cancer, the patient advocated for further medical evaluation. An abdominal ultrasound was performed on July 31, 2022, which confirmed the presence of a complex lesion anterior to the pancreatic tail. The lesion, measuring $13 \times 12 \times 17$ mm, had a solid component. To follow up, a magnetic resonance imaging (MRI) of the abdomen (with and without enhancement) was conducted on September 18, 2022. The MRI identified that the lesion had grown to $14 \times 13 \times 26$ mm and was located at the junction of the body and tail of the pancreas. The lesion demonstrated lobulated contours and contained thin internal septations, predominantly peripheral. It was suggested that it might be connected to the main pancreatic duct. The MRI suggested a low-grade septal enhancement at the inferior aspect of the lesion with minimal nodularity medially. The MRI investigation concluded that the lesion was likely a side-branch intraductal papillary mucinous neoplasm and suggested that an endoscopic ultrasound (EUS) assessment be performed according to guidelines set out by Alberta Health Services, the provincial health care provider.

The EUS was conducted on October 28, 2022, accompanied by a fine needle aspiration biopsy of the tumor fluid. The carcinoembryonic antigen (CEA) level in the tumor fluid

specimen was 13,572 μg/L. This was $\sim$10,000$\times$above normal or expected levels. Additionally, an evaluation of routine laboratory tests from the first encounter with the family physician in July 2022 revealed an increase in the serum lipase level (from 53 IU to 223 IU) and an increase in platelets (from 140×10^9/L to 416×10^9/L) within just 3 months.

Diagnosis

Based on several characteristics (position, cyst fluid composition, age of patient), the lesion was tentatively identified as a pancreatic mucinous cystic neoplasm (MCN). MCNs are mucin-producing cystic tumors of the pancreas, which account for about 10% of pancreatic tumors. They occur almost exclusively in 40–60-year-old women and are mostly located in the body or tail of the pancreas (93–95%). Since pancreatic MCNs are considered to be precancerous tumors and can be precursors to aggressive pancreatic carcinomas, surgical resection of them is highly recommended (Babiker et al., 2023; Farrell, 2015; Moris and Wallace, 2017). Indeed, invasive pancreatic cancers can originate from MCNs (Zamboni et al., 2013). Like other forms of pancreatic cancers (Pereira et al., 2020), MCNs are difficult to detect in their early stages due to the absence or vagueness of physical symptoms. Typical physical symptoms are abdominal pain, weight loss, and fatigue (Babiker et al., 2023; Farrell, 2015; Moris and Wallace, 2017).

Treatment

In January 2023, the patient underwent a tumor resection surgical procedure, which involved a distal pancreatectomy and splenectomy. According to the surgical pathology report, there was a single unilocular tumor measuring nearly 8 cm^3 in the distal pancreatectomy sample. Histological examination indicated the tumor was made up of a single layer of epithelium with intracytoplasmic mucin (positive for mucin's ceramide). There was no significant atypia, dysplasia, or evidence of malignancy. The typical ovarian-type stroma characteristic of MCN was not visible. The spleen was within normal limits and multiple benign reactive lymph nodes were also identified. In agreement with the initial diagnosis, the tumor was categorized as a mucinous cystadenoma of the

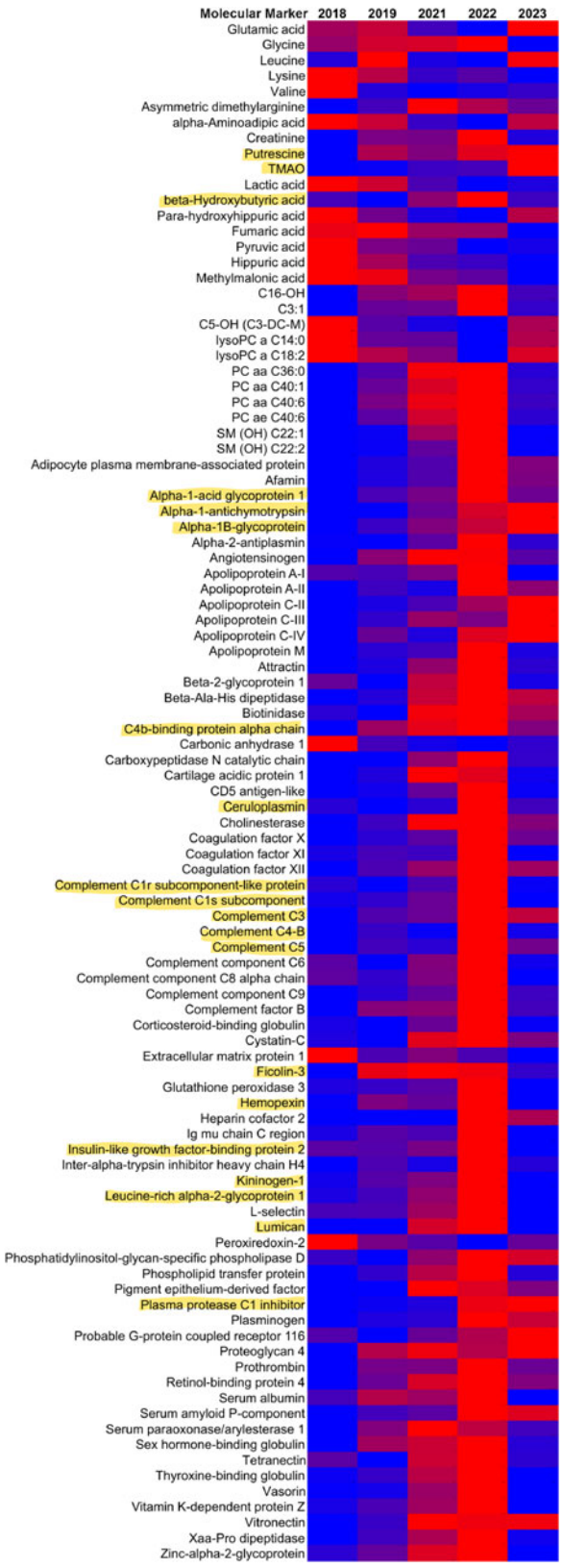

FIG. 3. Heatmap of all multiomics molecular markers from the patient's MYND reports from 2018 to 2023. Concentration levels of all significantly changed metabolites and proteins analyzed from patient MYND reports from 2018 to 2023 were plotted as a heatmap showing the large-scale changes in concentrations that occurred across the longitudinal tests. The heatmap was constructed by computing a mean concentration value from all the patient's reports for each molecular marker and then normalizing each molecular marker reported concentration to the mean by computing its z score, i.e. how many standard deviations the reported value deviates from the mean. *Blue* represents decreased concentration levels and *red* represents increased concentration levels compared with patient baseline concentrations. The molecular markers associated with early pancreatic cancer detection, as defined in our results and discussed in the report, are highlighted in *yellow*. lysoPC, lysophosphatidylcholine; PC, phosphatidylcholine; SM (OH), hydroxylated sphingomyelin.

pancreas (a subtype of MCN). As the pancreatic tumor was determined to be (mostly) precancerous and fully contained (i.e., a stage 1 tumor), adjuvant chemotherapy was not administered postoperatively, but the patient was prescribed pancreatin 25,000, three times daily. Total recovery time following surgical resection for the patient took ~4–6 weeks.

After recovery, the patient received a follow-up multiomics test (serum metabolomics and plasma proteomics) in June 2023 by MYCo. These postsurgical multiomics results revealed that the high cancer risk that was flagged in June 2022 by MYCo's in-house multiomics report was no longer indicated. In particular, the key biomarkers identified to have been associated with the patient's pancreatic cancer risk had returned to normal physiological ranges (Figs. 1 and 2). MYCo recommended to the patient to continue with her annual multiomics testing as pancreatic cancer has one of the highest recurrence rates of any cancer type and most recurrences happen within the first 18 months after surgery.

Discussion

Pancreatic cancer is a highly aggressive and malignant disease and early diagnosis can offer interventions highly valuable for patients and planetary health. Unfortunately, the absence of specific early symptoms often leads to late-stage diagnosis. Indeed, ~80% of diagnosed pancreatic cancer cases have already advanced to stage 3 or stage 4 at the time of initial assessment, missing the opportunity for potentially curative surgery. Surgical resection remains the main curative option for pancreatic cancer. Therefore, early diagnosis plays a crucial role, as it offers a significant advantage to patients by detecting localized, precancerous or nonmetastatic tumors, increasing the chances of successful treatment.

As this case report illustrates, the early diagnosis of a pancreatic tumor was possible with guidance from quantitative proteomic and metabolomic tests, which was later confirmed using imaging and histopathological findings.

MYCo's in-house, literature-derived database, MYND, identified several proteins and metabolites as being associated with high pancreatic cancer risk. In the patient discussed in this case report, these increased notably between 2021 and 2022, and as significant in the MYND report for the patient (Supplementary Table S1). These include alpha-1-acid glycoprotein 1 (AGP1), alpha1-antichymotrypsin, alpha-1B-glycoprotein, complement system proteins (C4b-binding protein α-chain, C1, C3, C4B, and C5), ceruloplasmin, ficolin-3, hemopexin, insulin-like growth factor-binding protein-2, kininogen-1, leucine-rich α2-glycoprotein-1, lumican, plasma protease C1 inhibitor, prothrombin, and three metabolites: putrescine, trimethylamine N-oxide (TMAO), and beta-hydroxybutyrate (BHB).

Specifically, we detected a substantial increase in plasma AGP1 levels from 2018 to the time of pancreatic tumor diagnosis with a subsequent decrease following the surgery. AGP1 is one of the major acute phase glycoproteins synthesized in the liver. It has been demonstrated to regulate immunity and play a role in proinflammatory and anti-inflammatory responses (Keser et al., 2021). It has been suggested to be involved in central signaling cascades related to pancreatic cancer cell proliferation, migration, and invasion. A recent study (Zhou et al., 2019) found that overexpression of AGP1 in pancreatic tumor tissue was an independent factor of poor prognosis in pancreatic cancer patients. In addition, these authors indicated that circulating AGP1 levels could be used to distinguish resectable pancreatic cancers from healthy controls. Similar findings on the role of increased AGP1 as a novel biomarker in the diagnosis and prognosis of pancreatic cancer has also been reported in other studies (Balmaña et al., 2016; Hashimoto et al., 2004). Other proteins, such as alpha1-antichymotrypsin (Koomen et al., 2005; Matsubara et al., 2010; Nie et al., 2014; Tian et al., 2008; Trichopoulos et al., 1990; Yu et al., 2005) and alpha-1B-glycoprotein (Tian et al., 2008) have been suggested as potential diagnostic or prognostic biomarkers for pancreatic cancer. Elevated levels of alpha1-antichymotrypsin and alpha-1B-glycoprotein were found in this patient.

A notable increase in several complement system proteins was mentioned in the patient's 2022 MYND report. Among them is the C4b-binding protein (α-chain). The MYND database indicated that elevated levels of C4b-binding protein (α-chain) in serum, displayed in Figure 2, could distinguish pancreatic ductal adenocarcinoma from healthy controls, chronic pancreatitis, and major gastroenterological cancers, including biliary tract cancers (see also Sogawa et al., 2016). The potential role of other components of the complement system such as complement factor B, complement C1, C3, C4B, and C5 in diagnosing pancreatic cancer or prognosing its outcomes has been reported in several previous studies (Chen et al., 2013; Lee et al., 2021; Lee et al., 2014; Tonack et al., 2013) and accordingly, are included in the MYND resource.

Ceruloplasmin, a serum ferroxidase and an acute-phase reactant responsible for copper transport in the blood, was also greatly increased in the patient's 2022 report (Supplementary Table S1). The MYND-generated report for the patient noted that elevated ceruloplasmin levels in the blood and in cancerous tissues have been associated with pancreatic cancer through different oncogenic-related mechanisms, including angiogenesis and neovascularization (Balmaña et al., 2015; Brandi et al., 2016; Hanas et al., 2008; Sha et al., 2022).

The MYND report of the patient noted a number of other pancreatic cancer-related molecular markers as being elevated in this patient. These were consistent with and noted in previously published studies included in the MYND resource. Among these markers are ficolin-3 (Palchetti et al., 2019), hemopexin (Fiorito and Tolosano, 2022), insulin-like growth factor-binding protein-2 (Dahlem et al., 2019), kininogen-1 (Zhao et al., 2007), leucine-rich α2-glycoprotein-1 (Furukawa et al., 2015), lumican (Pan et al., 2012), plasma protease C1 inhibitor (Peng et al., 2020), and prothrombin (Saraswat et al., 2017).

In addition to the observed protein changes, several metabolites were particularly elevated over levels noted as normal in the literature, including putrescine, BHB, and TMAO. Putrescine is a polyamine metabolite and polyamines play an important role in cell growth, proliferation, differentiation, migration, gene regulation, and several other cellular functions. Increased intracellular polyamine concentrations are associated with cell proliferation and tumorigenesis in different ways, including their interactions with oncogenes (e.g., MYC, p53; Li et al., 2020). The MYND report cited several other published studies in the literature

that demonstrate the role of polyamines in pancreatic cancers (Gitto et al., 2018; Nakkina et al., 2021).

Another metabolite that notably increased from the patient's baseline multiomics data in 2018, especially during the 2021 to 2022 reports, was the well-known ketone body, BHB. According to the patient's MYND report, when elevated over normal levels, BHB is a strong indicator of diabetic ketoacidosis or insulin deficiency (Depczynski et al., 2019). As our patient was not known to be diabetic or on a ketogenic diet, this marker indicated that something was affecting pancreatic function. There is additional evidence from a recent study suggesting that BHB may play a role in pancreatic cancer, and that BHB promotes pancreatic cancer progression (Gouirand et al., 2022). As seen in Figures 1 and 3, BHB became greatly elevated in the patient's 2022 report and then decreased following surgical treatment. The markedly increased levels of BHB at the patient's precursor stage in 2022 suggested not only pancreatic dysfunction but the development of a ketogenic state that may aid pancreatic tumor progression.

Another metabolite that was elevated was TMAO. This waste product metabolite is generated from dietary choline, betaine, and carnitine by gut microbial/liver cometabolism. In the body, TMAO acts as a nonspecific proinflammatory mediator by decreasing anti-inflammatory regulators and has been associated with several chronic diseases, including type 2 diabetes and metabolic syndrome (Constantino-Jonapa et al., 2023), cardiovascular diseases (Constantino-Jonapa et al., 2023), CKD (Tang et al., 2014), nonalcoholic fatty liver disease (NAFLD; Constantino-Jonapa et al., 2023; Flores-Guerrero et al., 2021), and some cancers (Chan et al., 2019; Liu et al., 2018; Tacconi et al., 2023). Increased TMAO levels in cystic fluid and plasma samples of patients with precancerous and cancerous cystic lesions of pancreas have been previously noted (Morgell et al., 2021).

Interestingly, both the putrescine and TMAO levels in our patient continued to rise after the pancreatic tumor was removed (Fig. 2). Therefore, we have suggested further monitoring of these metabolites for future assessments to monitor postoperative changes, including recurrence of the disease. Pancreatic cancer has an extremely high rate of recurrence even after seemingly successful surgical resection. The use of regular multiomics testing combined with appropriate multiomics risk scoring may potentially enable improved monitoring for indicators of recurrence risk in pancreatic cancer survivors.

The surgical pathology results in our patient strongly suggested the presence of a pancreatic tumor or MCN, which, as noted earlier, can be a precursor to aggressive pancreatic cancer. The extraordinarily high CEA levels in the tumor fluid (10,000× above normal) and the rapid growth of the tumor (nearly 2.5 cm^3 in July, and nearly 8 cm^3 by October, 2022) combined with the markedly altered protein and metabolite markers (all highly characteristic of pancreatic cancer) lead us to hypothesize that the precancerous tumor was in the process of transitioning to a more malignant pancreatic carcinoma. Indeed, the operating surgeon remarked that it appeared to be caught just before it ''blossomed'' into a full-fledged carcinoma. All the medical professionals involved in this work indicated that this was the first time that they had encountered such an early-stage pancreatic tumor.

Early detection and early intervention are key for the successful treatment and resolution of pancreatic cancer. Generally, pancreatic cancer is known for its poor prognosis, with a 5-year survival rate of only 9% (McGuigan et al., 2018; Rawla et al., 2019). However, early diagnosis can increase the potential 5-year survival rate to 30–40% (Gheorghe et al., 2020). Furthermore, as seen in this example, early detection and early intervention while the tumor is still contained requires relatively minimal surgery, no chemotherapy, and relatively little follow-up. As importantly, our patient resumed full-time work within 6 weeks of surgery and continues to lead an active life. On the other hand, late detection and the required highly specialized treatment significantly increase both the economic and social burden of the disease (Cipora et al., 2023).

While the present case report is not intended for a formal cost or cost-effectiveness analysis, the potential economic context of the LMOM-guided diagnostic and therapeutic interventions are noteworthy. Studies have indicated that the cost of treating (late-stage) pancreatic cancer is high, with the direct costs of treatment ranging from $49,000 to $135,000, with most outcomes, unfortunately, leading to death (O'Neill et al., 2012). Furthermore, the indirect costs of the disease, such as lost productivity, reduced quality of life, and lost years of life, are also significant and contribute even more to the economic burden of this disease (Cipora et al., 2023).

Most early cancer detection methods employ widespread screening or regular surveillance (especially prostate and breast cancer). A systematic review of the cost-effectiveness of pancreatic cancer surveillance in high-risk individuals found that surveillance was more cost effective compared with no surveillance (Cipora et al., 2023). The latter study projected the economic burden of pancreatic cancer in Sweden in 2030 and based on those calculations, determined that early detection and treatment could reduce the economic burden of the disease in Sweden, by $10 to $70 million USD per year (Cipora et al., 2023). Unfortunately, screening for pancreatic cancer is currently not well established nor is screening currently recommended for the general population according to the U.S. Preventive Services Task Force (USPSTF; Owens et al., 2019). However, as shown by the present case report, LMOM appears to offer a potentially lower cost, effective, and noninvasive route for detecting early-stage pancreatic cancer. More widespread use of LMOM or other approaches that are poised to reduce the costs of screening approaches so as to implement low-cost pancreatic cancer screening or facilitate the identification of high-risk individuals for pancreatic cancer, would be timely.

Conclusions and Outlook

This case report illustrates the potentials of blood LMOM for precision/personalized medicine and rethinking medical diagnostic innovation for a potentially life-saving early diagnosis of pancreatic cancer. Noninvasive, quantitative LMOM combined with digital technologies aimed at computer-enabled molecular marker analysis can usefully inform clinical decisions and help detect early biochemical changes associated with pancreatic cancer, even when standard clinical tests and imaging are relatively unrevealing. In this patient, early detection likely enabled a surgical cure, eliminated symptoms, and removed the need for follow-up chemotherapy. LMOM may potentially allow early identification and intervention in

cases that could otherwise progress to late-stage incurable disease. Blood LMOM warrants future programmatic translational research with the goals of precision medicine, and individually tailored cancer diagnoses and treatments.

Acknowledgments

The authors wish to thank the patient for participating, and Dr. Marcia LeVatte for administrative help in article preparation.

Authors' Contribution

M.A.A.: Formal analysis, Investigation, Validation, Visualization, Writing—original draft, and Writing—review & editing. A.H.K.: Formal analysis, Writing—original draft, and Writing—review & editing. H.Y.: Data curation, Formal analysis, and Project administration. W.W.: Data curation, Formal analysis, and Project administration. X.L.: Data curation, Formal analysis, and Project administration. H.M.M.: Project administration, and Resources. P.R.C.: Validation, and Writing—review & editing. R.F.: Validation, and Writing—review & editing. C.H.B.: Investigation, Methodology, Resources, Data curation, Funding acquisition, and Writing—review & editing. D.S.W.: Investigation, Methodology, Resources, Data curation, Funding acquisition, and Writing—review & editing. All authors made a significant intellectual contribution, read, and approved the final article.

Author Disclosure Statement

M.A.A., C.H.B., P.C., R.F., and D.S.W. are cofounders of MYCo. C.H.B. is the CSO of MRM Proteomics, Inc., and the VP of Proteomics at MYCo. The other authors are employees of MYCo.

Funding Information

This work was partially supported by funding to CHB from Genome Canada's Genomics Technology Platform (264PRO) and by funding to The Metabolomics Innovation Center (TMIC) through the Genomics Technology Platform from Genome Canada for operations and technology development (265MET). CHB is also grateful for support from the Segal McGill Chair in Molecular Oncology at McGill University (Montreal, Quebec, Canada), for support from the Terry Fox Research Institute, the Warren Y. Soper Charitable Trust, and the Alvin Segal Family Foundation to the Jewish General Hospital (Montreal, Quebec, Canada).

This work was done under the auspices of a Memorandum of Understanding between McGill and the U.S. National Cancer Institute's International Cancer Proteogenome Consortium (ICPC). ICPC encourages international cooperation among institutions and nations in proteogenomic cancer research in which proteogenomic datasets are made available to the public. This work was also done in collaboration with the U.S. National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium (CPTAC).

Supplementary Material

Supplementary Information and Supplementary Table S1

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Abbreviations Used

AGP1 = alpha-1-acid glycoprotein 1
BHB = beta-hydroxybutyrate
CEA = carcinoembryonic antigen
CKD = chronic kidney disease
EUS = endoscopic ultrasound
iPOP = integrative personal omics profiling
LMOM = longitudinal multiomics monitoring
MCN = mucinous cystic neoplasm
ML = machine learning
MRI = magnetic resonance imaging
MYCo = molecular you corporation
MYND = molecular you knowledge database
T2D = type 2 diabetes
TMAO = trimethylamine N-oxide