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FULL PAPER

T1 mapping for the diagnosis of early chronic pancreatitis: correlation with Cambridge classification system

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Objective: This study aims to determine if T1 relaxation time of the pancreas can detect parenchymal changes in early chronic pancreatitis (CP).

Methods: This study retrospectively analyzed 42 patients grouped as no CP (Cambridge 0; *n* = 21), equivocal (Cambridge 1; *n* = 12) or mild CP (Cambridge 2; *n* = 9) based on magnetic resonance cholangiopancreatography findings using the Cambridge classification as the reference standard. Unenhanced T1 maps were acquired using a three-dimensional dual flip-angle gradient-echo technique on the same 1.5 T scanner with the same imaging parameters.

Results: There was no significant difference between the T1 relaxation times of Cambridge 0 and 1 group (p = 0.58). There was a significant difference (p = 0.0003) in the mean T1 relaxation times of the pancreas between the combined Cambridge 0 and 1 (mean = 639 msec, 95% CI: 617, 660) and Cambridge 2 groups (mean = 726 msec, 95% CI: 692, 759). There was significant difference (p = 0.0009) in the mean T1 relaxation times of the pancreas between the Cambridge 0 (mean = 636 msec, 95% CI: 606, 666) and Cambridge 2 groups (mean = 726 msec, 95% CI: 692,759) as well as between Cambridge 1 (mean = 643 msec, 95% CI: 608, 679) and Cambridge 2 groups (mean = 726 msec, 95% CI: 692,759) (p = 0.0017). Bland–Altman analysis showed measurements of one reader to be marginally higher than the other by 15.7 msec (2.4%, p = 0.04).

Conclusion: T1 mapping is a practical method capable of quantitatively reflecting morphologic changes even in the early stages of chronic pancreatitis, and demonstrates promise for future implementation in routine clinical imaging protocols.

Advances in knowledge: T1 mapping can distinguish subtle parenchymal changes seen in early stage CP, and demonstrates promise for implementation in routine imaging protocols for the diagnosis of CP.

INTRODUCTION

Chronic pancreatitis (CP) is characterized by progressive inflammation, impairment of endocrine and exocrine function, and irreversible morphological changes leading to fibrosis and scarring.[1,2] Early stage CP is characterized by unevenly distributed fibrosis, while advanced CP involves diffuse fibrosis across the entire gland. These morphological changes often elude conventional radiologic and endoscopic imaging,[3] while the high risk of complications associated with pancreatic biopsy precludes a routine histological approach to diagnosing CP. Diagnosis of CP, therefore, currently relies on a combination of costly invasive endoscopic and radiologic imaging studies, alongside laboratory testing.[3–5] Conventional imaging studies, however, are often unable to capture the morphological features of early stage CP, creating a need for higher sensitivity imaging techniques to detect these cases.[3]

The Cambridge classification was developed in 1984 for the diagnosis of CP based on morphological changes in the pancreatic ducts using endoscopic retrograde cholangiopancreatography (ERCP).[6] Recent guidelines by the American Pancreatic Association have recommended the translational use of the Cambridge classification for CT and MRI or magnetic resonance cholangiopancreatography (MRCP) interpretation (Table 1).[4] The Cambridge classification, however, is based solely on ductal changes and does not adequately capture the role of parenchymal changes in CP.[7–9] With technical advances in minimally invasive imaging techniques that continue to enhance image contrast and resolution in CT, MRI, and MRCP, it has become possible to evaluate both parenchymal and ductal changes with greater sensitivity than ERCP.[10,11] MRI and MRCP sequences are capable of providing information

about both ductal and parenchymal features of CP—including T1 signal changes, diffusion restriction, increased extracellular volume fraction, gland atrophy, and irregular contours of the pancreatic duct.[12] These clinically significant parenchymal findings are noticeably absent from the Cambridge classification and are not featured in any other widely accepted classification system. However, a multi-institutional prospective study is funded by the National Institute of Diabetes and Digestive and Kidney Diseases and currently in progress to achieve this goal.[7,13,14]

MRCP is capable of assessing and grading ductal changes under the Cambridge classification and also detecting subtle parenchymal abnormalities in early stage CP, which often precede ductal abnormalities.[15,16] The soft tissue contrast of MRI is derived from differences in the intrinsic relaxation properties of T1 and T2; quantitative assessment of T1 and T2 relaxation times, also known as MR relaxometry, can provide information about evolving tissue characteristics.[5] Specifically, T1 mapping quantitatively measures the T1 relaxation time of the target organ, and has been successfully implemented across various cardiac models including myocardial fibrosis and deposition diseases.[10,17] While the conventional T_1 weighted MRI technique was dependent on imaging parameters and has been previously hindered by the long imaging times required to produce traditional spin echo images, it is now possible to perform rapid acquisition T1 mapping with single breath-hold imaging, making it an efficient and cost-effective procedure.[18] Importantly, T1 relaxation time is a tissue-specific property independent of imaging parameters, and has shown promise in recent studies in the diagnosis of CP by detecting pancreatic fibrosis.[17] T_1 weighted signaling has also been correlated with pancreatic exocrine function; decreased T1 signal intensity in pancreatic tissue is associated with loss of protein-rich acinar cells and fibrotic replacement, as T1 relaxation times increase.[5,19]

The utility of T1 mapping in the diagnosis of early stage suspected CP has not been thoroughly investigated. The ability to identify early stage CP through parenchymal abnormalities that precede ductal changes may help guide clinical decision-making and preventative care, reducing rates of progression and risks of complications. The purpose of this study, therefore, is to determine if the T1 relaxation time of the pancreas can detect parenchymal changes in early stages of CP, including equivocal cases of CP.

METHODS AND MATERIALS

Patients

This retrospective study analyzed 42 patients with and without CP who underwent MRI between 2016 and 2019 at the Indiana University Heallth University Hospital, Indianapolis, USA. The study has been approved by the institutional review board (IRB) by Indiana University School of Medicine. Through retrospective review of medical records (Cerner, North Kansas City, MO), approximately 250 patients were screened for selection for the study according to clinical history and laboratory findings. Case selection was consecutive among those with available T1 mapping, while those whose MR scans did not have T1 maps were excluded. The Cambridge classification was used as the reference standard.[20]

Image analysis

T1 maps were acquired using a standardized 3D dual flip-angle gradient-echo sequence. All patients were imaged using the same 1.5 T MR scanner (MAGNETOM Avanto Fit, Siemens Healthcare GmbH Erlangen, Germany) using VFA VIBE (Volumetric Interpolated Breath-hold Examination, Siemens Healthcare),[21] using the same uniform imaging parameters. Image reconstruction was performed at the scanner using MapIt software (Siemens Healthcare GmbH), using two flip angles on each case. Typical imaging parameters were 48 axial slices of 4 mm thickness acquired within an 18 sec breath-hold, acquisition matrix of 320 × 168, parallel imaging (Siemens GRAPPA) factor of 2 and field of view of 300 x 400 mm (adjusted according to patient size). A vendor-supplied B_1 mapping acquisition of 10 sec was applied prior to VFA acquisition and used for B_1 correction in the reconstruction.[22] All data were diagnostic.

The largest diameter of the main pancreatic duct and the number of ectatic branch ducts were recorded to obtain Cambridge grade, and measured by a fellowship trained body imager with 19 years of experience (TT). Circular regions of interest (ROIs) of 1.5 cm^2 were drawn by two authors (MC and AP) in a homogenous

Table 1. Cambridge Classification for diagnosis and grading of chronic pancreatitis

Cambridge classification	Main PD	Abnormal side branches
Grade 0 (Normal)	Normal	None
Grade 1 (Equivocal)	Normal	Fewer than 3
Grade 2 (Mild CP)	Normal	Three or more
Grade 3 (Moderate CP)	Abnormal	More than 3
Grade 4 (Severe CP)	Abnormal	All of the above with at least one additional following feature: large cavity (>10 mm); obstruction (stricture); intraductal filling defect (calculi); severe dilation or gross irregularity

CP, chronic pancreatitis;PD, pancreatic duct
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region of the parenchyma while avoiding volume averaging from retroperitoneal fat, vessels, and pancreatic duct. Smaller ROIs were used in areas that demonstrated severe atrophy.

ROI measurements are a practical and commonly used method for analyzing imaged pancreatic parenchyma, and superior to whole volume measurements which significantly increase the labor cost of data collection. ROIs up to 1.0 or 1.5 cm^2 are commonly used for the pancreas due to the small diameter of this organ, in order to avoid volume averaging from surrounding fat and vessels. One ROI was drawn in each pancreatic head, body, and tail. Mean T1 relaxation time used in the analysis was obtained from the measurements of the pancreatic head, body, and tail for each patient.

Statistical analysis

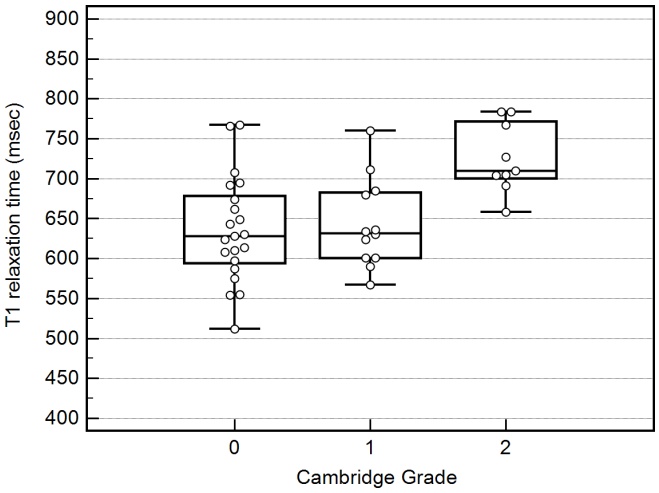
A two-tailed probability *t*-test was used to determine differences between two groups; Cambridge 2 (mild CP) compared to Cambridge 0 (no CP) and 1 (equivocal). One-way analysis of variance (ANOVA) test was used to differentiate the T1 times among the three groups and also the head, body and tail. Statistical analysis was performed using MedCalc v. 19.1 (MedCalc Software, Mariakerke, Belgium). Normality of data was verified prior to applying parametric statistic testing. The Bland–Altman analysis was used to assess interobserver variability.[23,24] Bland and Altman introduced the Bland–Altman plot to describe agreement between two quantitative measurements.[23] They established a method to quantify agreement between two quantitative measurements by constructing limits of agreement. These statistical limits are calculated by using the mean and the standard deviation (SD) of the differences between two measurements. To check the assumptions of normality of differences and other characteristics, they used a graphical approach. The resulting graph is a scatter plot XY, in which the Y axis shows the difference between the two paired measurements (A-B) and the X axis represents the average of these measures ((*A* + B)/2). The Bland–Altman plot method recommended that 95% of the data points should lie within ±2 SD of the mean difference.

RESULTS

Eligible patients ($n = 42$) were grouped as: (a) no CP (Cambridge 0; $n = 21$), (b) equivocal (Cambridge 1; $n = 12$) or (c) mild (Cambridge 2; $n = 9$) CP on the basis of MRCP findings using the Cambridge classification as the reference standard.[20] Patients with normal ductal findings on ERCP/EUS, normal serum amylase and lipase levels, and without history of acute or chronic pancreatitis were placed in the Cambridge 0 group ($n = 21$). Cambridge 1 and 2 groups were selected from patients who had abdominal pain suspected of CP or had known acute pancreatitis episode(s) in the past. The final diagnosis of no CP ($n = 21$), equivocal CP ($n = 12$) and mild CP ($n = 9$) in these patient groups were determined by ductal findings (or lack thereof) on MRCP, using the Cambridge classification as the diagnostic standard (Table 1).

The average age of the patients was 42.9 (range: 19–71) and female to male ratio was 32:10. The T1 relaxation times measured in the head, body, and tail of the pancreas were similar in the Cambridge 0 ($p = 0.72$), Cambridge 1 ($p = 0.85$), and Cambridge 2 groups ($p = 0.75$); therefore, average values were used in the analysis. The distribution of signal intensities in Cambridge 0, 1 and 2 groups are shown in a box-and-whisker plot (Figure 1).

Figure 1. Comparison of T1 relaxation times in three patient cohorts. This box-and-whisker chart illustrates that there was a significant difference ($p = 0.0009$) in the mean T1 relaxation times of the pancreas between the Cambridge 0 (normal) and Cambridge = 2 (mild CP) groups. Similarly, there was a significant difference ($p = 0.0017$) in the mean T1 relaxation times of the pancreas between the Cambridge 1 (equivocal) and Cambridge 2 (mild CP) groups. CP, chronic pancreatitis.



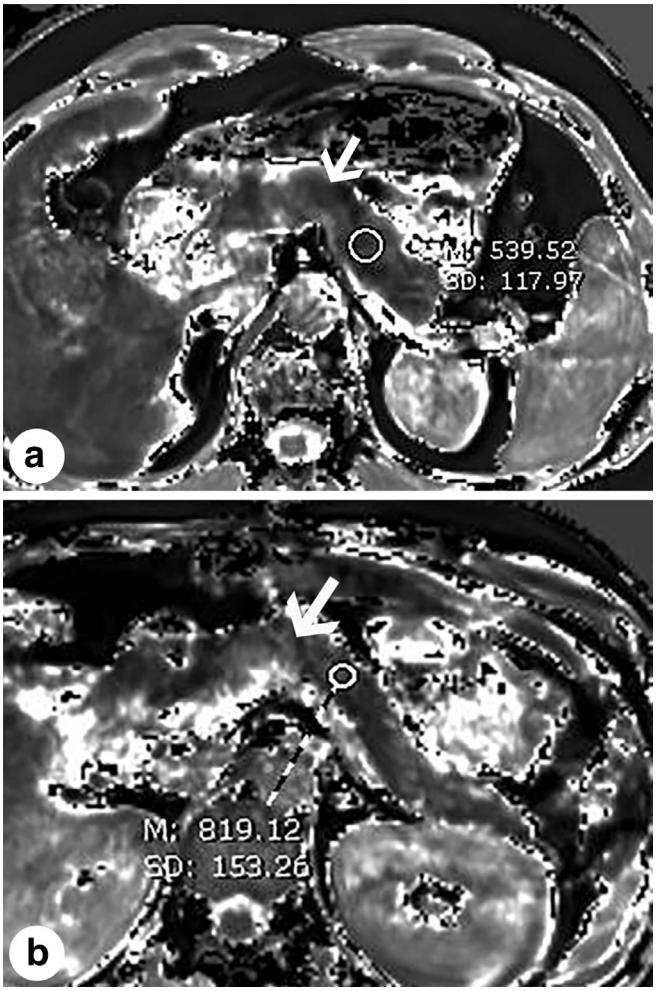
All three groups showed difference in T1 relaxation times when ANOVA test was used ($p = 0.04$). However, the *t*-test showed no significant difference between the T1 relaxation times of Cambridge 0 and 1 groups ($p = 0.58$). There was a significant difference ($p = 0.0003$) in the mean T1 relaxation times of the pancreas between the combined Cambridge 0 and 1 (mean = 639 msec, 95% CI: 617, 660) groups and the Cambridge 2 group (mean = 726 msec, 95% CI: 692, 759) (Figure 2). When Cambridge 0 and 1 groups individually compared to Cambridge 2, there was also a significant difference ($p = 0.0009$) in the mean T1 relaxation times of the pancreas between Cambridge 0 ($p = 0.0009$, mean = 636 msec, 95% CI: 606, 666) and Cambridge 2 (mean = 726 msec, 95% CI: 692,759), and Cambridge 1 ($p = 0.0017$, mean = 643 msec, 95% CI: 608, 679) compared to Cambridge 2 (mean = 726 msec, 95% CI: 692,759).

The Bland–Altman plot showed one reader scored marginally higher than the other by 15.7 msec (2.4%, $p = 0.04$) (Figure 3).

DISCUSSION

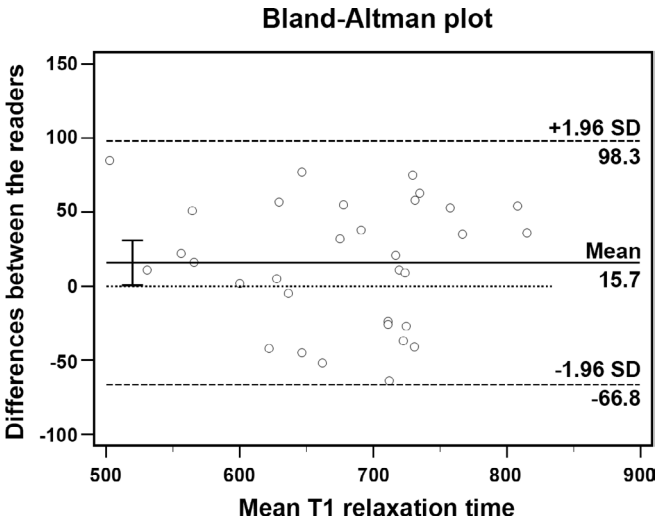
MRCP is capable of not only grading ductal changes under the Cambridge classification, but also detecting subtle parenchymal abnormalities in early stage CP, which often precede ductal dilatation. In this study, analyzing MRCP with T1 mapping in patients evaluated for pancreatic disease, there was a significant difference in mean T1 relaxation times between the combined Cambridge 0 (normal) and 1 (equivocal) groups and the Cambridge 2 (mild CP) group. As expected, there was no significant difference

Figure 2. T1 mapping of pancreas. (A) shows an axial T1 map in a 33-year-old female with a history of alcoholic hepatitis and hepatic fibrosis being screened for hepatocellular carcinoma. Region of interest measurements reveals the mean T1 relaxation time in the pancreatic body to be 539 msec. Cambridge score was 0 (normal). (B) is an axial T1 map in a 38-year-old female with a history of non-specific colitis who was evaluated for epigastric pain suspected of pancreatic origin. Pancreatic parenchyma is grossly unremarkable however the Cambridge score was 2 (mild CP). Region of interest measurements reveals the T1 relaxation time in the pancreatic body to be 819 msec. CP, chronic pancreatitis.



between the T1 relaxation times of Cambridge 0 and Cambridge 1 groups, which is consistent with the knowledge that these groups are difficult to distinguish both clinically and radiographically. Our data indicate that T1 mapping is capable of distinguishing the ductal and subtle parenchymal changes seen in early CP as determined by the Cambridge classification system. T1 relaxation times between Cambridge 0 to Cambridge 2 groups ranged from 305 to 953 msec, therefore providing a much wider spectrum of quantitative data for assessing early stage CP. This wide range of scale may be more useful in practice and clinical trials as a biomarker of the disease severity particularly in the early stages of CP (Figure 2a and b).

Figure 3. Bland–Altman plot displays the scatter diagram of the differences plotted against the average measurements of two independent readers. There was borderline normal distribution (p = 0.0429) and line of normality (dashed line at 0) is within the 95% CI of the arithmetic mean (bias) of 15.7 therefore, the limits of agreement (two dashed lines) are defined as the mean difference ±1.96 SD of differences. All of the measurement differences between the two readers were within the ±1.96 SD lines. Arithmetic mean (bias): 15.7187 (95% CI: 0.5362 to 30.9013) (p = 0.0429). Lower limit: −66.8181 (95% CI: −93.0393 to −40.5969). Upper limit: 98.2556 (95% CI:72.0344 to 124.4768).



The current study's findings of quantitative T1 mapping demonstrates the ability to identify the morphologic features of early stage CP. In correlation with clinical findings, T1 mapping shows promise as an important adjunct that provides patients with an earlier diagnosis of chronic pancreatitis, which may further guide clinical management. Nonetheless, larger studies are necessary to confirm these findings prior to routine clinical implementation, and this study's findings strengthen the need for future and ongoing multi-institutional studies.[14]

T1 mapping was previously precluded from practical routine clinical applications due to the long imaging times required to produce traditional spin echo images while minimizing respiratory motion artifacts. The rise of commercially available T1 mapping techniques have made it possible to limit imaging time to a single breath-hold, and since then, T1 mapping has demonstrated its feasibility for evaluating diseases ranging from myocardial fibrosis to liver fibrosis. A variety of T1 relaxometry techniques are in clinical use, such as the Look-Locker T1 mapping sequence, but each have distinct drawbacks and few are available for abdominal MR imaging.[5] The conventional T_1 weighted MRI technique was reliant on the imaging parameters and sequences specific to each scanner, which required the use of signal intensity ratios—the ratio of the pancreas to another organ such as the spleen or kidney. The T1 mapping technique used in this study serves as a more accurate and reliable measurement by utilizing the Siemens MapIt software to produce a quantitative

metric that is independent of imaging parameters.[11] This 3D T1 mapping acquisition takes 20 sec and has the potential to be practically implemented across routine clinical settings for the diagnosis of CP without additional time or cost.

Soft tissue contrast of MRI in traditional T_2- and T_2 weighted sequences is relative and not comparable across platforms. MR relaxometry, on the other hand, offers quantitative assessment of T1 and T2 relaxation times by extracting differences in intrinsic relaxation in order to provide a more objective measure of evolving tissue characteristics. T1 mapping may be combined with imaging techniques such as MR elastography-based stiffness or extracellular volume fraction to further inform the diagnosis of CP and detection of pancreatic fibrosis.[5,10] Notably, the present study focuses on T1 mapping within the broader context of other more extensive multi-institutional research.[14]

The importance of identifying key diagnostic features of CP is underscored by the various recent multidisciplinary efforts to establish a new consensus approach to guide CP diagnosis, staging, and management.[7] For example, the Consortium for the Study of the Chronic Pancreatitis, Diabetes and Pancreatic Cancer (https://cpdpc.mdanderson.org) launched a large longitudinal cohort study in 2017 entitled the Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies, in order to accurately define the progression of CP for clinical trials and disease management, based on Cambridge classification criteria and clinical findings.[7] CT and MRI/MRCP are ubiquitous and have become first-line investigations to diagnose CP and to assess for alternative diagnoses. A newer severity scoring system specifically designed to incorporate the capabilities of CT and MRI is likely needed. The MINIMAP study (Magnetic Resonance Imaging as a Non-Invasive Method for the Assessment of Pancreatic Fibrosis) was designed to fulfill this clinical need and was funded in September 2018 by the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK116963).[14] This is a comprehensive quantitative MR imaging study which is being performed on well-phenotyped CP patient cohorts at seven US academic centers. The study is evaluating the role of T1 relaxometry, ECV, T_1 weighted gradient echo SIR, MR elastography (MRE), arteriovenous enhancement ratio, DWI, pancreas volume/atrophy, pancreatic fat fraction, ductal features and pancreatic exocrine output following secretin stimulation in the assessment of CP. Such a severity scoring system for CP can help in clinical management, prognosticate outcomes and have utility for continued research in CP. An improved radiographical severity scoring system could be used to objectively quantify the disease burden, which in turn helps to facilitate communication between radiologists and with clinicians in a standardized fashion, and to assess longitudinal changes of CP to predict prognosis.

The current study findings can contribute to improved radiologic characterization of quantitative and qualitative features in early stage CP, providing a standardized longitudinal metric for future clinical trials using MRI and MRCP. By validating the use of T1 mapping in diagnosing early stage suspected CP and mild CP, this study demonstrates the feasibility of a fast, affordable, and non-invasive MR technique that has the potential to be implemented across routine clinical practice to guide clinical decision-making on CP. In patients with mild or lower grade CP, currently available conventional imaging techniques are unable to distinguish the subtle morphologic features.[4] Our findings therefore make a valuable contribution by demonstrating that T1 is capable of distinguishing the early stages of suspected CP with equivocal features and mild CP. Given that the present study is retrospective with relatively small subject numbers, future studies would be valuable for further validation of the study findings in early stage CP. Moreover, due to sample size, the present study findings pertain to T1 relaxation times using a 1.5 T MRI, while recognizing the value of future studies that can compare measurements across varying magnet strengths to determine the most appropriate setting. There was also predominance of female patients; however, previous studies did not demonstrate a difference of T1 between the two genders.[13] Due to sample size limitations, Cohen's κ statistics for interobserver variability could not be performed, however, the Bland–Altman plot analysis was presented. One reader scored marginally higher than the other by 15.7 msec (2.4%, $p = 0.04$).

In conclusion, T1 mapping is an efficient and affordable quantitative MR imaging technique that is capable of quantitatively reflecting morphologic changes, even in the early stages of CP, and shows promise for implementation in routine clinical imaging protocols. By combining clinical presentation with the ductal information obtained from MRCP with parenchymal information obtained from T1 mapping, it may become possible to more accurately diagnose the disease in the early stages, allowing treating physicians to intervene in the disease process at an earlier point.

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INFORMED CONSENT

The Institutional Review Board (IRB) approved this study, and the requirement for informed consent for the patient data review was waived.

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