Risk Prediction of Pancreatic Ductal Adenocarcinoma using AI Analysis of Abdominal CT Scans

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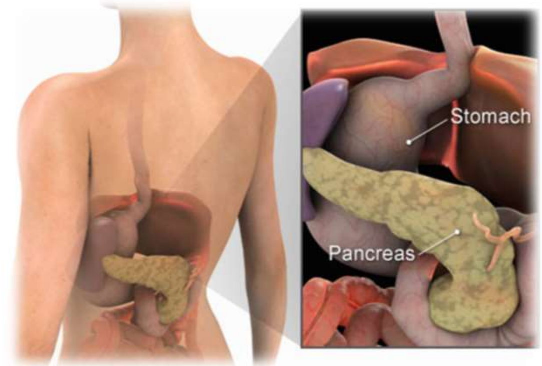
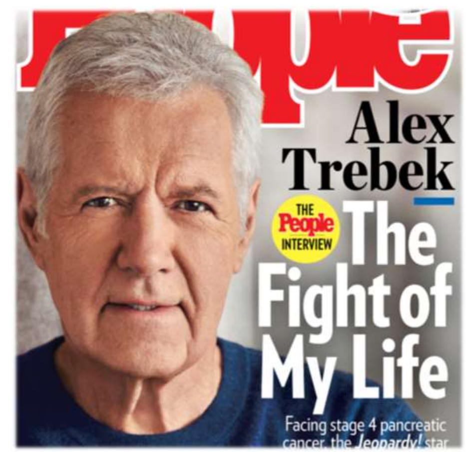
Pancreatic Cancer

- The Pancreas has two main jobs
  - Make digestive enzymes that help the intestines break down food
  - Regulate body's use of Sugars and starches
- Pancreatic Cancer, also known at the "Silent Killer", has been diagnosed in many prominent figures





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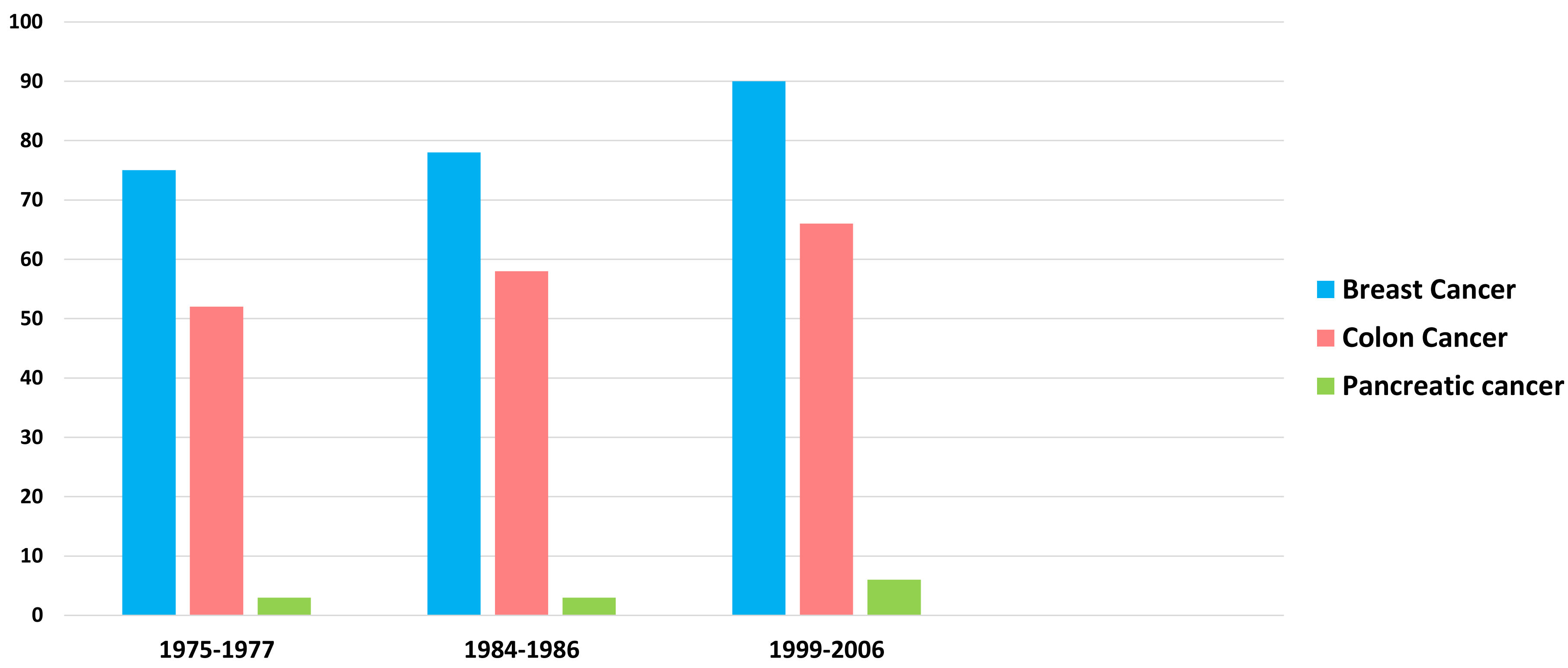
Pancreatic Ductal Adenocarcinoma (PDAC)

- Accounts for **3**% of all cancers and is **4th** leading cause of all cancer deaths
- Expectedly becoming the **2**nd most by 2030.
- ~**60,430** new cases and **48,220** deaths are expected this year.
- ~**80**% of diagnosis occurs at late stage of cancer.
- The 5-year survival rate is **11**% but can be as high as **50**% with early-stage diagnosis.
- Early-stage diagnosis of PDAC is challenging:
  - Lack of specific symptoms (e.g., abdominal pain)
- **Prediction (risk stratification) can assist improving early diagnosis**!

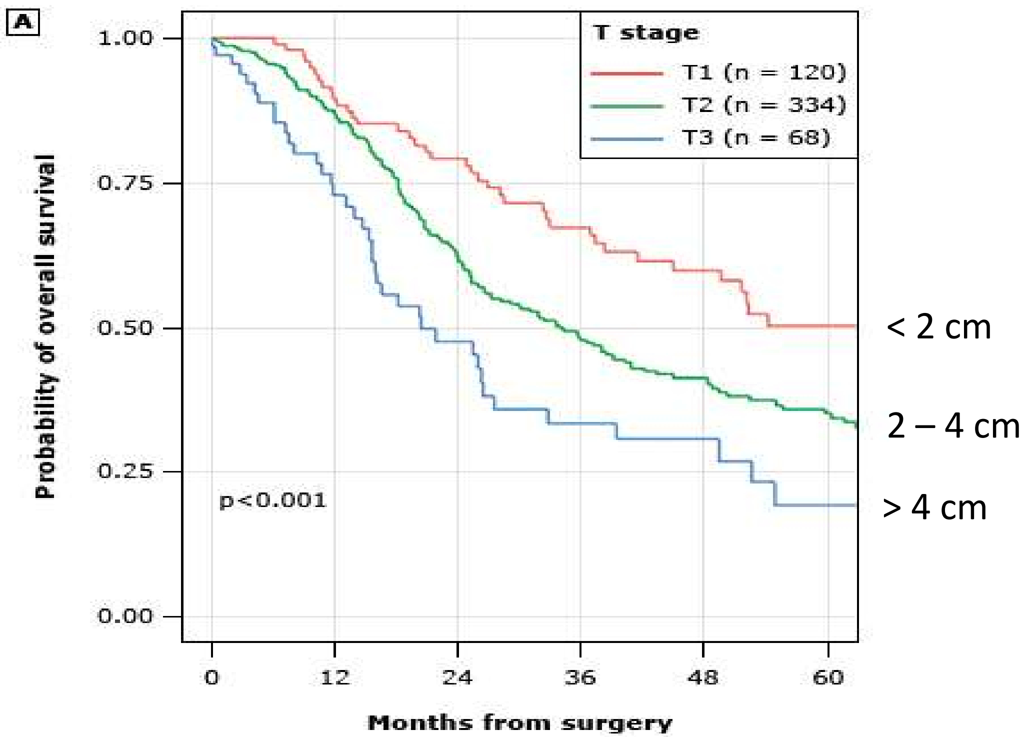
- Key Statistics for Pancreatic Cancer, American Cancer Society,
- A. Adamska, et al"Pancreatic Ductal Adenocarcinoma: Current and Evolving Therapies", *Int J Mol Sci*. 2017;18(7).
- W. Muhammad, et al, "Pancreatic Cancer Prediction Through an Artificial Neural Network", *Front Artif Intell*. 2019;2.
- R. Pannala et al, "New-onset Diabetes: A Potential Clue to the Early Diagnosis of Pancreatic Cancer", *Lancet Oncol*. 2009;10(1):88-95.

5-Year Relative Survival Rates %



Connor O'Malley

Can Early Detection Improve Pancreatic Cancer?

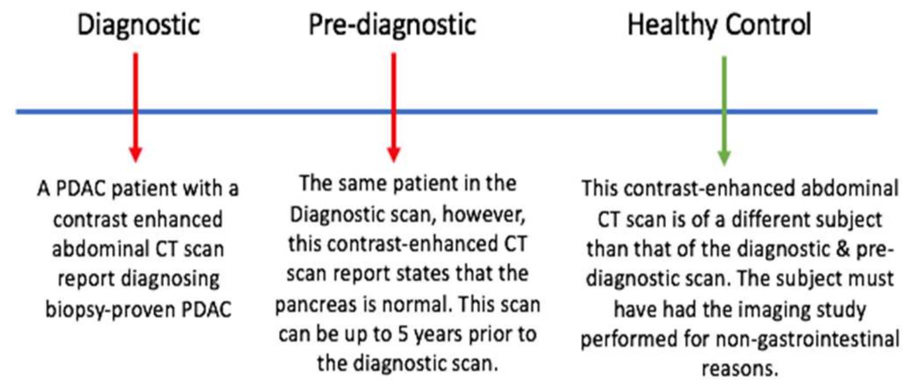


Rationale, Objective, and Hypotheses

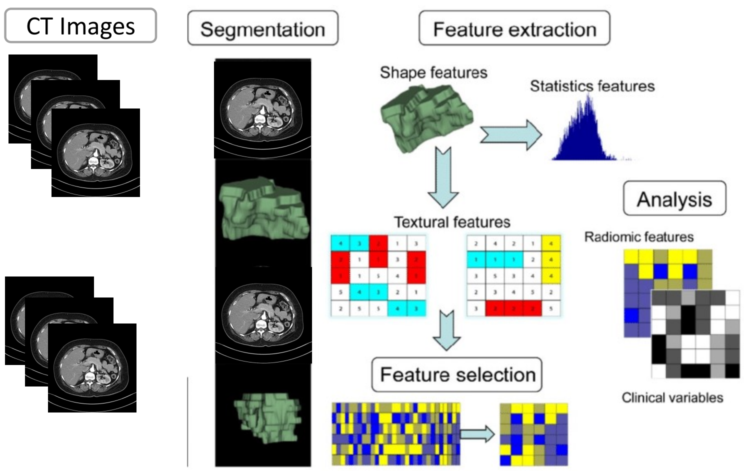
- **Motivation**:
  - Seven million ER visits per year due to abdominal reasons in the USA, where abdominal Computed Tomography (CT) scan is usually performed.
  - Pre-diagnostic CT scans may provide critical morphological information associated with pre-cancer or early cancer biological changes to predict PDAC risk.
- **Objective:**
  - To develop an artificial intelligence (AI) model to predict PDAC risks in 3 years using a combination of pre-diagnostic CT image features and non-imaging factors.
- **Hypotheses**
  - AI allows extraction of unique image features in pre-diagnostic CT images associated with pre-cancer or early cancer biological changes that are invisible to naked eyes.
  - The combination of pre-diagnostic image features and non-imaging factors improves the accuracy of PDAC risk stratification and prediction over that using conventional non-imaging factors alone.

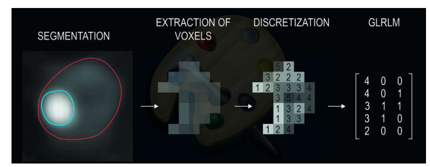
Data Design

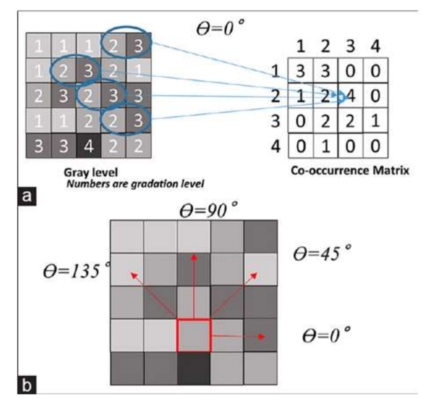
- **Diagnostic**:
  - Contrast-enhanced abdominal CT scan
  - Histopathologically established PDAC (visible tumor)
- **Pre-diagnostic**:
  - Contrast-enhanced abdominal CT scan
  - same patient as in the diagnostic scan,
  - acquired **up to 3 years** prior to the PDAC diagnosis
- **Healthy control**:
  - Contrast-enhanced abdominal CT scan
  - Different subject with pancreas is declared healthy on the imaging and non-imaging clinical reports.
  - Non-gastrointestinal disorders or accidents.
  - This group didn't develop PDAC in the following 3 years.
  - Gender, age, and CT scan time are matched with pre-diagnostic imaging.



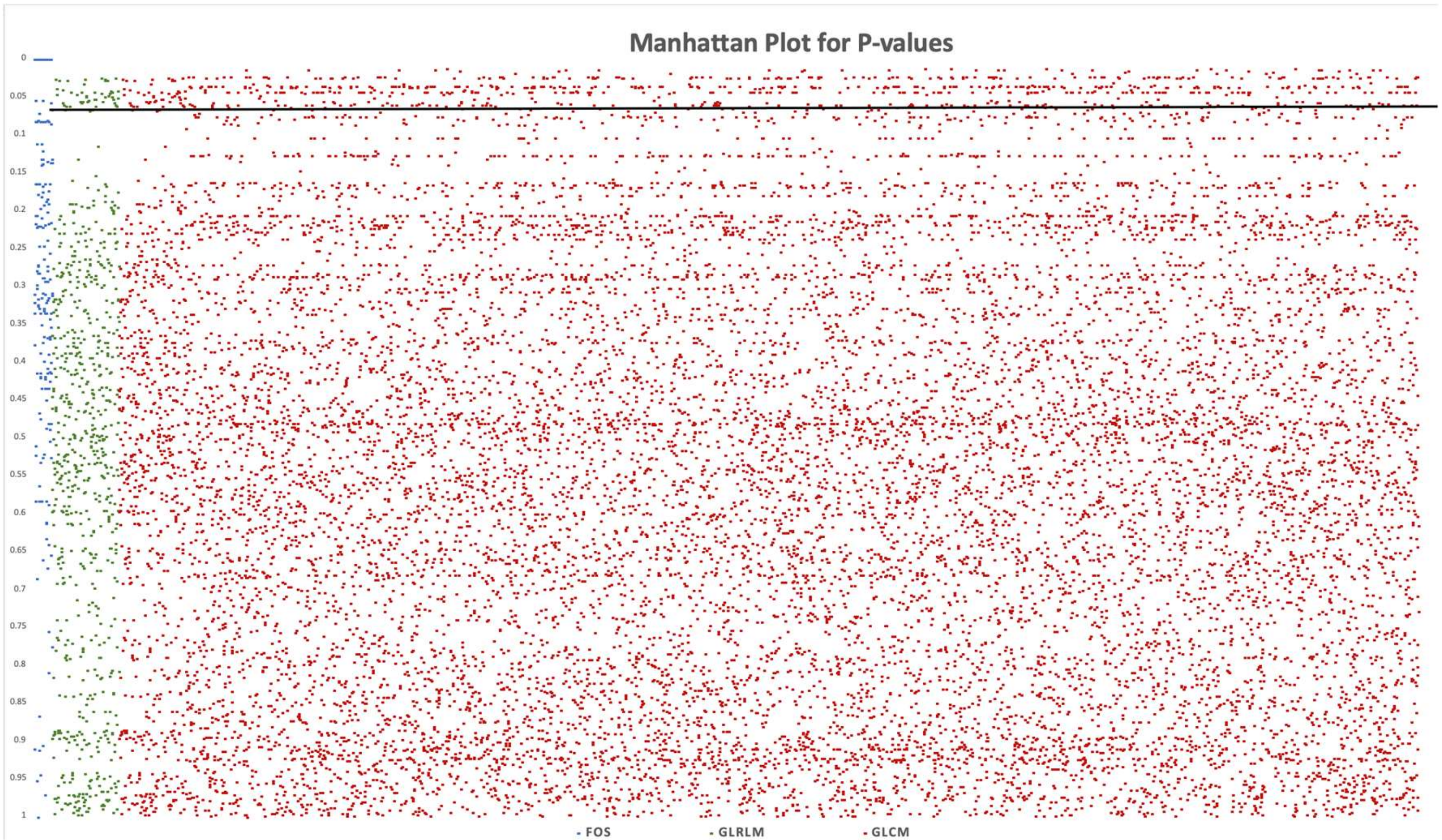
Radiomic Analysis





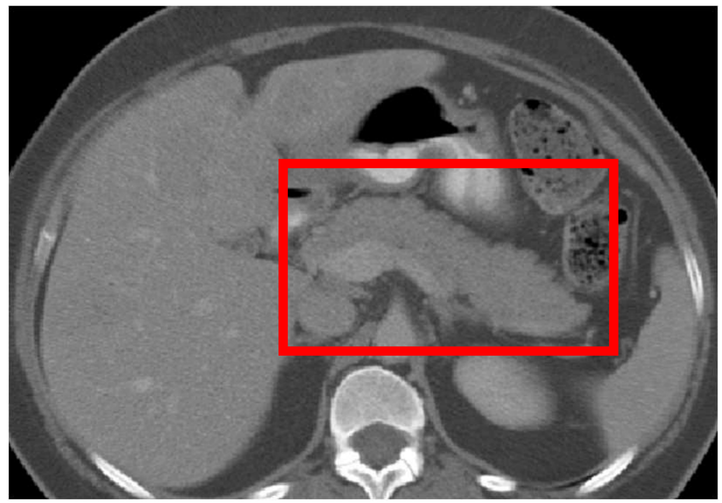


108 CT scans (36 from Healthy, Pre-Diagnostic, and Diagnostic)


Manhattan Plot for P-values
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
0.5
0.55
0.6
0.65
0.7
0.75
0.8
0.85
0.9
0.95
1
FOS
GLRLM
GLCM

Pilot analysis: Healthy vs Pre-diagnostic scans

Healthy



Pre-diagnostic

Healthy Control vs Pre-Diagnostic

Healthy

Pre-diagnostic

Identification of PDAC predictors

Intensity	Variations in tissue **intensity** of the whole pancreas and pancreatic subregions. For example, the affected region starts to become darker during the development of PDAC.
	Pancreatic calcifications may appear within the tissue or duct during PDAC development, resulting in variations in subregional **intensity**.
Texture	Changes in the cellular mechanism and vasculature cause **textural** changes, increasing tissue heterogeneity.
	Ductal complications, such as distal parenchymal atrophy, intraductal papillary mucinous neoplasms of the pancreas (IPMNs), and intraductal calculi (pancreatolithiasis) are often associated with PDAC. Such complications are demonstrated as **textural** changes in PD.
Size	Pancreatic inflammation is often associated with PDAC, which may cause changes in the **size** of the pancreas.
	Cancerous cells lining the PD distract the normal behavior of the duct during PDAC development. This can be observed as dilatation or increased **size** of the duct.
Shape	PD tends to turn tortuous during PDAC development (deformed **shape**).

- S. Tanaka et al., 2010. Slight dilatation of the main pancreatic duct and presence of pancreatic cysts as predictive signs of pancreatic cancer: a prospective study. *Radiology*, *254*(3), pp.965-972.
- Shadhu, K. and Xi, C., 2019. Inflammation and pancreatic cancer: An updated review. *Saudi journal of gastroenterology: official journal of the Saudi Gastroenterology Association*, *25*(1), p.3.
- K. Sandrasegaran, et al., 2019. CT texture analysis of pancreatic cancer. *European radiology*, *29*(3), pp.1067-1073.

Preliminary studies and results

- Bayesian Classification model
- Classification accuracy **85%** in predicting that a patient will develop PDAC within 3 years.
- Confusion matrix for classification of 28 CT scans of the external set consisting of 14 from each of Healthy control and Pre-diagnostic group. Numbers in the green blocks show true positives.

	True Healthy	True Pre-diagnostic
Predicted Healthy	13	3
Predicted Pre-diagnostic	1	11

Progress

- **Patent** - LI/PANDOL/QURESHI/WU/GADDAM [PREDICTION OF PANCREATIC DUCTAL ADENOCARCINOMA USING COMPUTED TOMOGRAPHY IMAGES OF PANCREAS]; CSMC Ref. li001287; Our Ref.: 065472-000797WO00

- **Publication**: Touseef Ahmad Qureshi, Bechien Wu, Stephen Pandol, and Debiao Li. Predicting Pancreatic Ductal Adenocarcinoma Using Artificial Intelligence Analysis of Pre-diagnostic Computed Tomography Images. Journal of Cancer Biomarkers. In press

- **NIH Award:** NIH R01 CA260955, 09/01/21 - 08/31/26 "Predicting Pancreatic Ductal Adenocarcinoma (PDAC) Through Artificial Intelligence Analysis of Pre-Diagnostic CT Images"
  - 8 centers will collaborate
  - Large dataset (>3000 CT scans)
  - Extensive validation of the prediction model

PDAC Risk prediction model

- **Aim 1 (Technical Development)**:

  To develop automated segmentation techniques for the pancreas, pancreatic subregions, and pancreatic duct (PD) in abdominal CT scans.
- **Aim 2 (Analysis)**:

  To derive pre-diagnostic CT image features that are predictive of PDAC
- **Aim 3 (Prediction modelling)**:

  To develop and evaluate the PDAC prediction model using image features and non-imaging factors.

Target Enrollment

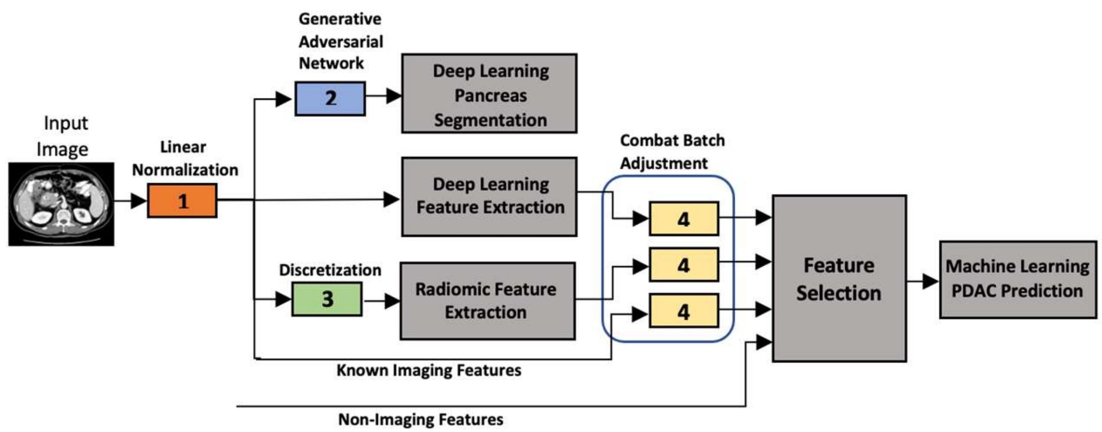
- **Target enrollment**: <2000 subjects (~3000 CT scans)
- **8 Centers will collaborate**
    1. Cedars-Sinai Medical Center (CSMC)
    2. Greater LA Veterans Affairs Healthcare System (GLA VA)
    3. University of Michigan (UM)
    4. Massachusetts General Hospital (MGH)
    5. Northwestern University (NU)
    6. University of Southern California (USC)
    7. University of California, Irvine (UCI)
    8. Rutgers University (RU)

Aim 1: Data harmonization

Target enrollment: > 2,000 subjects, 3000 scans

Challenge: variability in voxel size, contrast, etc.

1. Linear transformation
2. Generative adversarial network
3. Image discretization
4. ComBat correction



- Zhaoa, Z., Wang, Y., Liu, K., Yang, H., Sun, Q. and Qiao, H., 2021. Semantic Segmentation by Improved Generative Adversarial Networks. *arXiv preprint arXiv:2104.09917*.
- Kothari, S., Phan, J.H., Stokes, T.H., Osunkoya, A.O., Young, A.N. and Wang, M.D., 2013. Removing batch effects from histopathological images for enhanced cancer diagnosis. *IEEE journal of biomedical and health informatics*, *18*(3), pp.765-772.
- Duron, L., Balvay, D., Vande Perre, S., Bouchouicha, A., Savatovsky, J., Sadik, J.C., Thomassin-Naggara, I., Fournier, L. and Lecler, A., 2019. Gray-level discretization impacts reproducible MRI radiomics texture features. *PLoS One*, *14*(3), p.e0213459.

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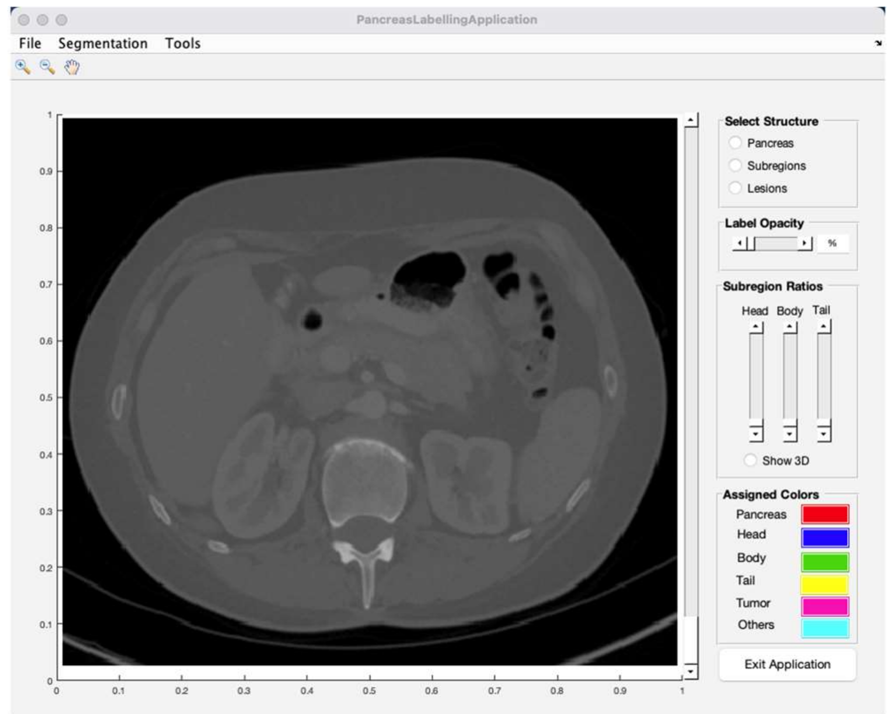
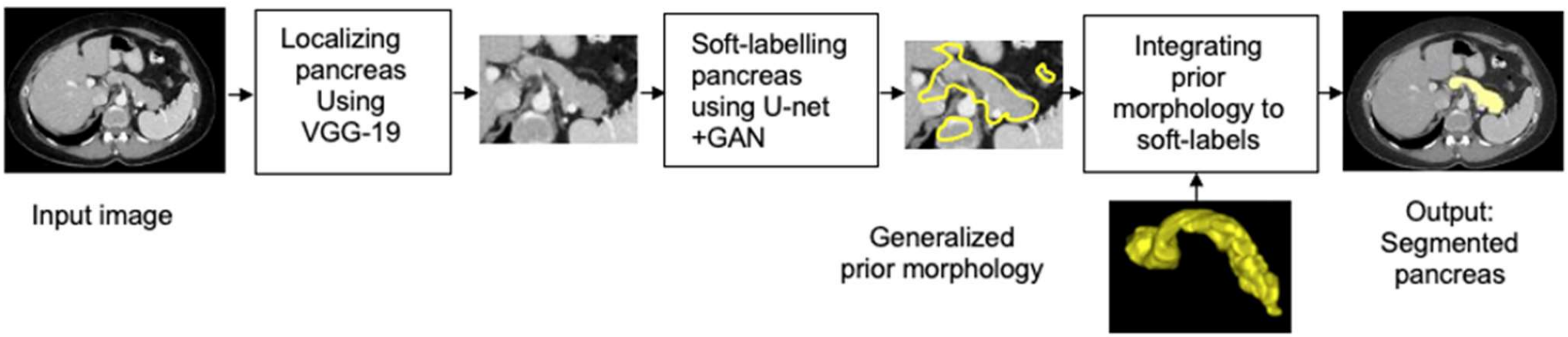
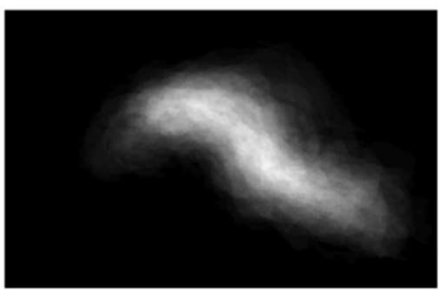
Aim 1: Data labelling application

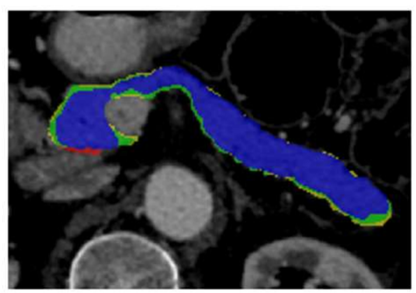
- **Key features of the application**:
  - **Interactive predefined procedure to outline subregions**
    - Baseline segmentation are defined already (using regional ratios)
    - None-to-slight change might be required
  - **Relatively simpler than commercial applications**
    - Color schemes predefined
    - File formatting predefined
    - Less complex interface
  - **Reduced time and workload**
    - Saves ~60-70% of subregion labelling efforts and time.



Aim 1: Segmentation of Pancreas





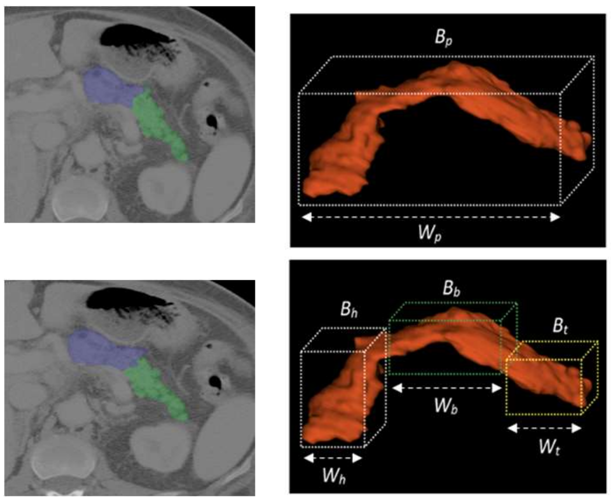


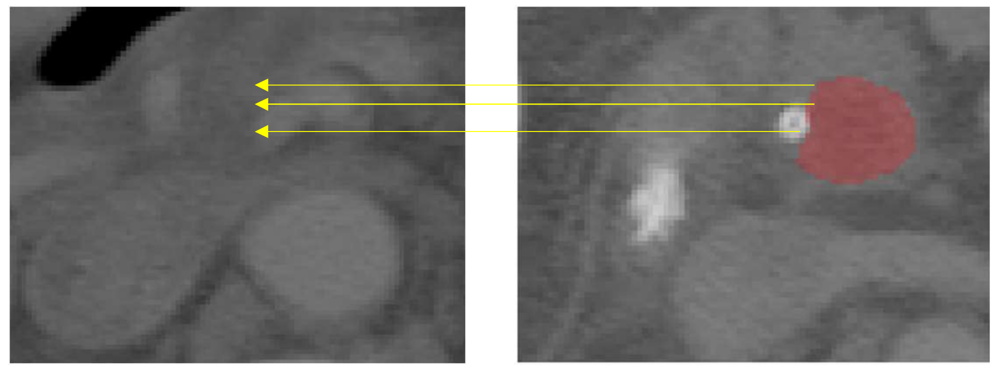
- Preliminary segmentation results
- NIH public data (n=83)
- Compared with manual labelling as ground truth
- Sørensen–Dice coefficient (DSC) score > 89%
- Manuscript under review by Journal of Medical Imaging

Aim 1: Segmentation of pancreatic subregions

Reference Labels

Automated Segmentation





Pre-diagnostic scan

Diagnostic scan

- D. J. Birnbaum, et al. 2019. Head and body/tail pancreatic carcinomas are not the same tumors. *Cancers*, *11*(4), p.497.
- G. Tomasello, et al. "Outcome of head compared to body and tail pancreatic cancer: a systematic review and meta-analysis of 93 studies." *Journal of gastrointestinal oncology* 10, no. 2 (2019): 259.

Significance of subregional analysis

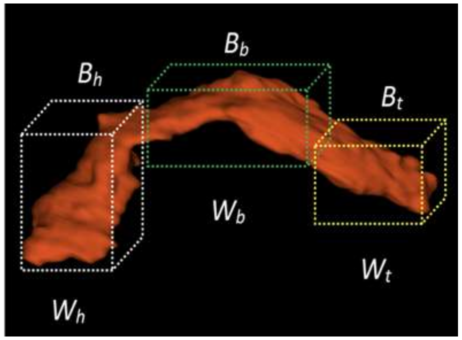
Discrepancies among pancreatic subregions

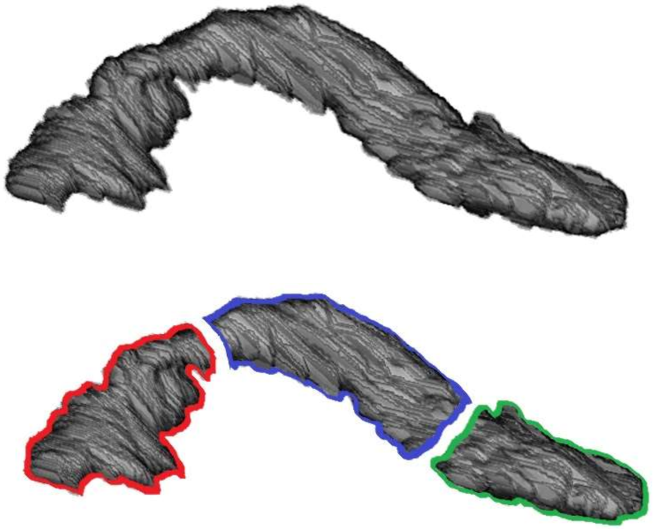
	Head	Body	Tail	Application
Tumor Structure	**Histology**: Non- Squamous tumors **Genetics**: Less Aggressive Low Grade, Well differentiated	**Histology**: Squamous tumors **Genetics**: More Aggressive, High Grade, Poorly or undifferentiated		Variable tumor biology among sub regions leads to tumor heterogeneity across subregions
Symptoms	Jaundice, Dark urine, Light stool, and Weight loss	Back and upper abdominal pain	Lower abdominal pain	Helps corelating unique clinical factors to specific subregions
Drug Response	More sensitive to Gemcitabine-based regimen	More sensitive to Fluorouracil-based regimen		Better treatment plan and prediction of treatment response
Metastasis	Low (42%)	Moderate (68%)	Extreme (84%)	Helps identifying high risk organs
Incidence Rate	High (71%)	Low (13%)	Low (16%)	
Survival Rate	44%	27%	27%	
Resection Rate	17%	4%	7%	

- Lee, Mirang, et al. "The Role of Location of Tumor in the Prognosis of the Pancreatic Cancer." *Cancers* 12, no. 8 (2020): 2036.
- Yin, Lingdi, et al. "Comparative bioinformatical analysis of pancreatic head cancer and pancreatic body/tail cancer." *Medical Oncology* 37, no. 5 (2020)
- Birnbaum, et al. "Head and body/tail pancreatic carcinomas are not the same tumors." *Cancers* 11, no. 4 (2019): 497

Segmentation of Pancreatic subregions

- Developed Anatomy-guided deep learning model
  - Incorporating Structural constraints
    - Width ratio, shape analysis
  - Convolution Neural Network
- 2D segmentation
  - NIH 82 CT images
  - 82% Dice score
- 3D segmentation
  - In process

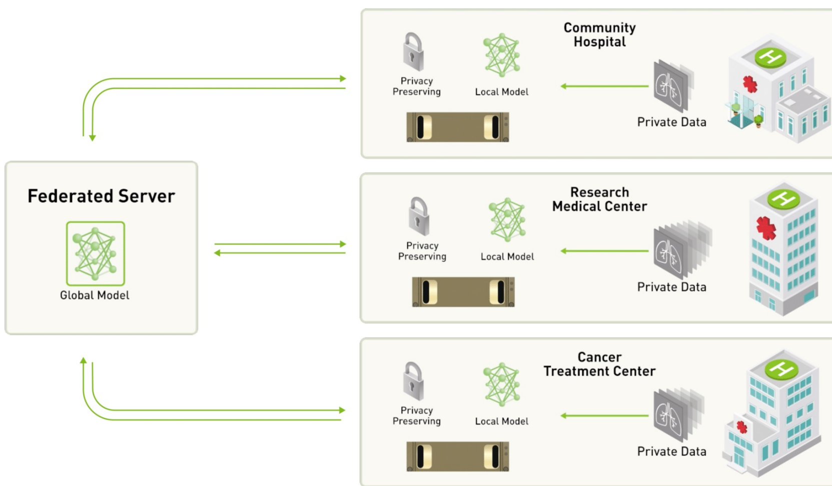




Aim 1: Federated Learning

Privacy preserved decentralized training without data sharing !

- EDRN, MD Anderson [Collaboration]
- Address critical issues:
  - Data privacy
  - Data security
  - Data access rights
- Eliminate data transfer
  - Only model updates are shared
  - Different ways to updates
- Utilize large amount of unused data from centers

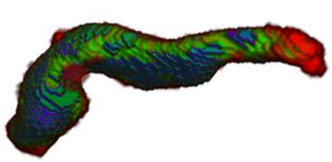


- Chandiramani, K., Garg, D. and Maheswari, N., 2019. Performance analysis of distributed and federated learning models on private data. *Procedia Computer Science*, *165*, pp.349-355.
- Yang, Q., Liu, Y., Chen, T. and Tong, Y., 2019. Federated machine learning: Concept and applications. *ACM Transactions on Intelligent Systems and Technology (TIST)*, *10*(2), pp.1-19.

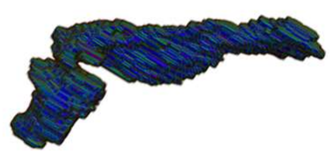
Aim 1: Federated Learning pancreas segmentation

- Three datasets
  - Medical Segmentation Decathlon
  - NIH 82 Pancreas CT
  - Beyond the Cranial Vault(BTCV) Abdomen dataset
- Existing methods only average updates based on training size
- Our goal: Automatically adapted aggregation scheme based on history of loss and aggregation weight
- Better and stable performance across multiple datasets

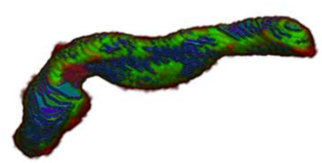
— Overlap
— Ground Truth
— Prediction



FedAvg



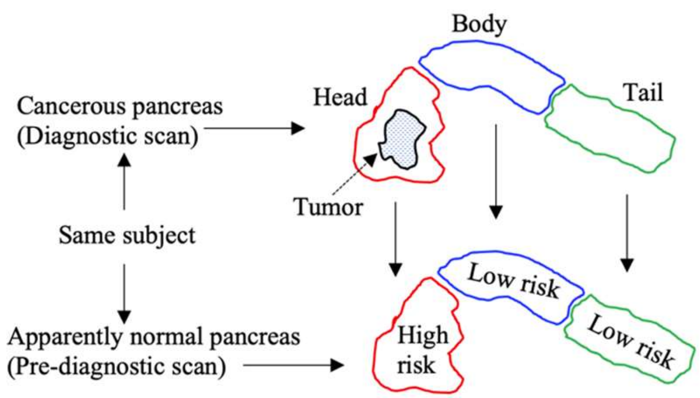
DWA

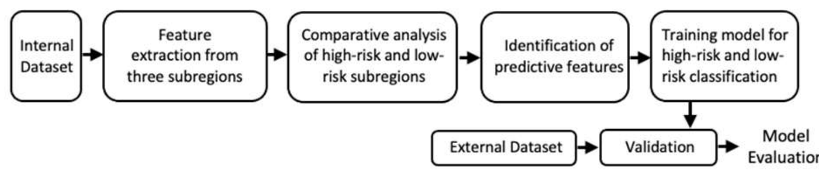


RNN Aggr(Ours)

Test dataset / Training method	Case-wise Avg (130 cases)	Site-wise Avg (3 sites)
Local-Decathlon	76.80%	76.11%
Local-NIH-82	64.04%	66.39%
Local-BTCV	31.40%	38.30%
DWA	76.60%	77.35%
FedAvg	77.32%	75.94%
RNN-Aggr(ours)	**78.74%**	**78.90%**

Risk prediction based on subregional analysis





Javed, S., Qureshi, T.A., Gaddam, S., Wang, L., Azab, L., Wachsman, A.M., Chen, W., Asadpour, V., Jeon, C.Y., Wu, B. and Xie, Y., 2022. Risk prediction of pancreatic cancer using AI analysis of pancreatic subregions in computed tomography images. *Frontiers in Oncology*, *12*.

Aim 2: Identification of PDAC predictors

Category	Factors
Demographic	Age at imaging, sex, race/ethnicity
Epidemiologic risk factors	Smoking history
Anthropometry	Weight, weight change, height, BMI
Clinical comorbidities	pancreatitis, liver disease, alcoholism, chronic obstructive pulmonary disease
Laboratory tests	Creatinine, hemoglobin A1c, cholesterol, bilirubin

Intensity	Variations in tissue **intensity** of the whole pancreas and pancreatic subregions. For example, the affected region starts to become darker during the development of PDAC.
	Pancreatic calcifications may appear within the tissue or duct during PDAC development, resulting in variations in subregional **intensity**.
Texture	Changes in the cellular mechanism and vasculature cause **textural** changes, increasing tissue heterogeneity.
	Ductal complications, such as distal parenchymal atrophy, intraductal papillary mucinous neoplasms of the pancreas (IPMNs), and intraductal calculi (pancreatolithiasis) are often associated with PDAC. Such complications are demonstrated as **textural** changes in PD.
Size	Pancreatic inflammation is often associated with PDAC, which may cause changes in the **size** of the pancreas.
	Cancerous cells lining the PD distract the normal behavior of the duct during PDAC development. This can be observed as dilatation or increased **size** of the duct.
Shape	PD tends to turn tortuous during PDAC development (deformed **shape**).

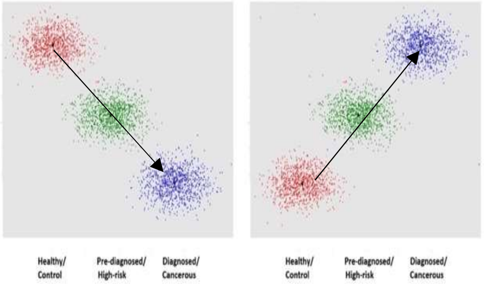
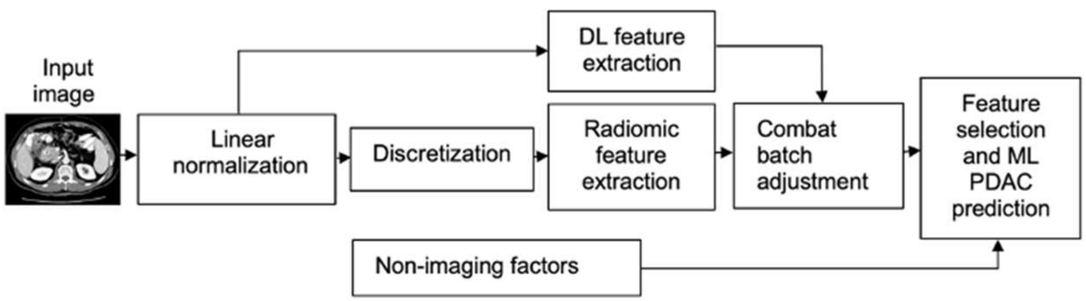


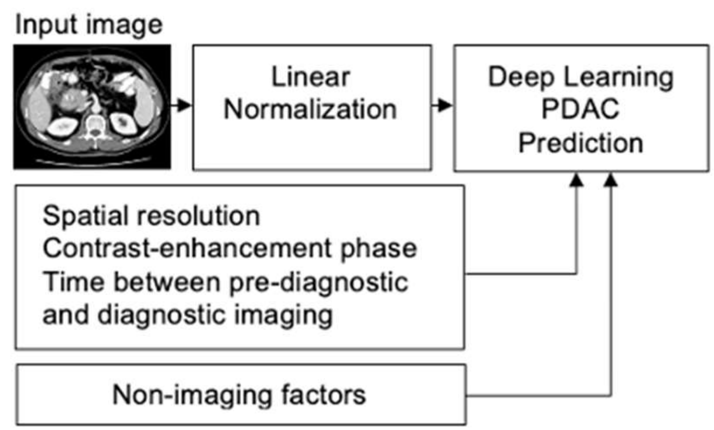
Fig. Criteria for including features in F^2

Significance test
Information gain ranking
Trend identification

Aim 3: Prediction model development



Integrated machine learning for risk prediction
Combining radiomics, Deep learning and clinical features



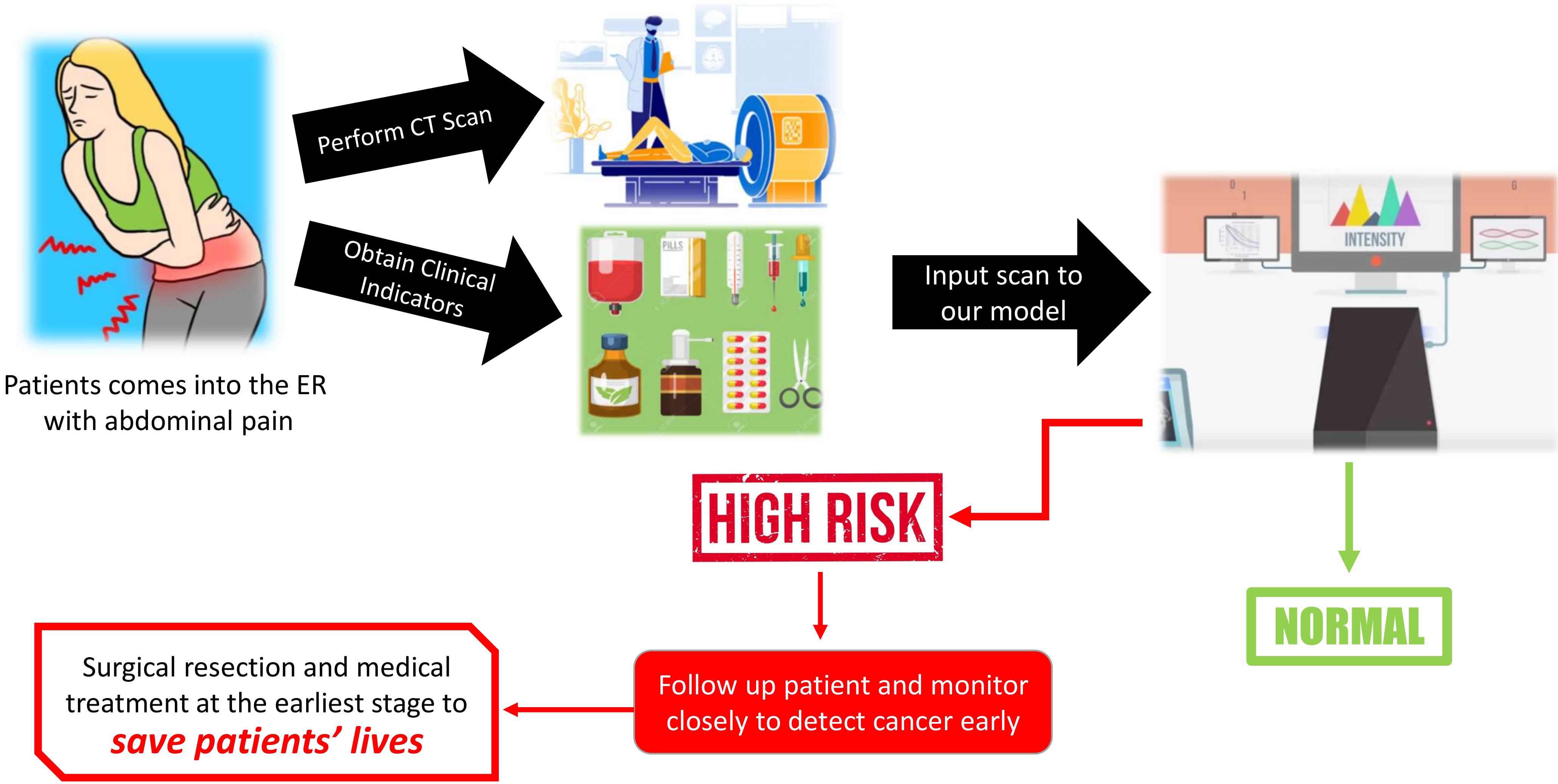
End-to-End risk prediction model
Integrating deep learning and clinical features

Training
Validation

Progress summary

- **Collaboration with partners**
  - IRBs approved from most centers, Data agreements documents are prepared
  - Schemes for data mining and data collection are being designed
  - 500 cases are obtained, analysis is undergoing.
- **Technical Development**
  - Labelling application
  - Pancreas segmentation model
  - Pancreatic subregional segmentation model
  - Federated learning framework
  - Distributed system for efficient processing
- **Publications**
  - Touseef Ahmad Qureshi, Bechien Wu, Stephen Pandol, and Debiao Li. Predicting Pancreatic Ductal Adenocarcinoma Using Artificial Intelligence Analysis of Pre-diagnostic Computed Tomography Images. Journal of Cancer Biomarkers. Accepted: December 2021.
  - Touseef Ahmad Qureshi, Sehrish Javed, Tabasom Sarmadi, Stephen Pandol, Debiao Li. "Artificial intelligence and imaging for risk prediction of pancreatic cancer: a narrative review", Journal on Chinese Clinical Oncology (CCO). Accepted: Jan. 2022.
  - Touseef Ahmad Qureshi, Cody Lynch, Linda Azab, Yibin Xie, Srinavas Gaddam, Stepehen Jacob Pandol, Debiao Li, Morphology-guided deep learning framework for segmentation of pancreas in Computed Tomography images, Journal of Medical Imaging. Under review.

Five Year Plan (prospective study and implementation)



Major Novelties of This Project

- Data structure – pre-diagnostic time point never explored before due to data pool limitation
- Product software will significantly improve prognosis and decrease treatment cost
- Prediction of PDAC will save patients' lives and early detection will allow for effective medical intervention with ability to cure the disease
- AI massive population screening tool will allow for large data collection which will enable researchers to explore many questions about this disease not previously possible due to data limitation

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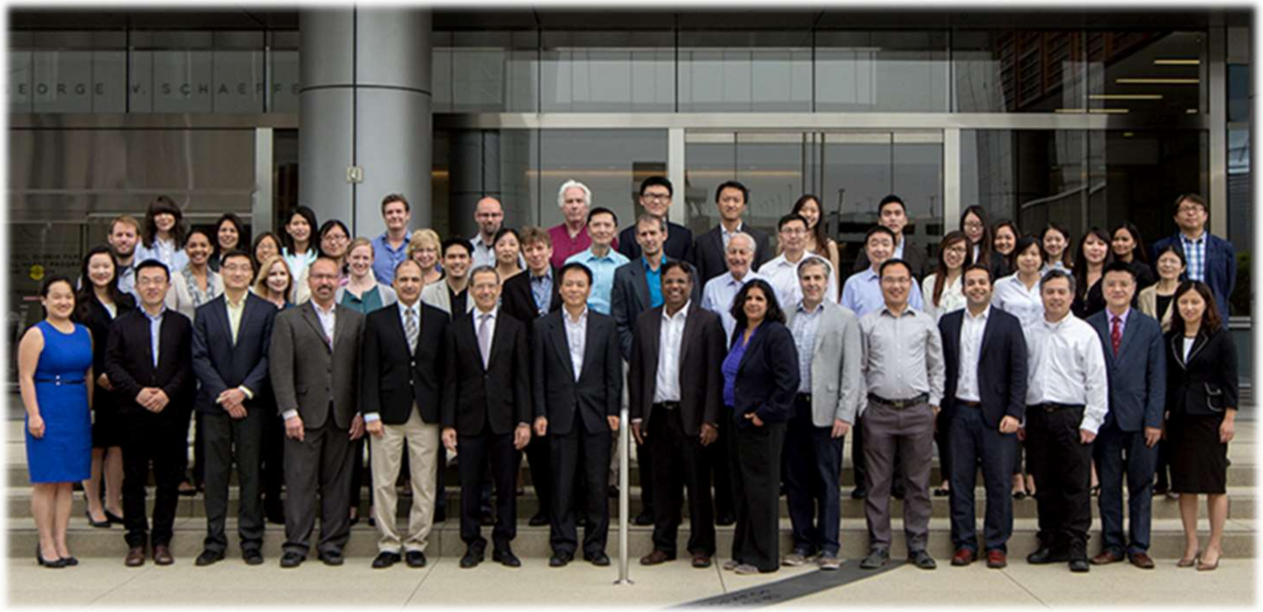
Future direction and other projects

- Including liver organ as part of analysis for early changes.
- Replicating model on liver cancer, bladder cancer, etc.
- Predicting PDAC treatment response.

Biomedical Imaging Research Institute at Cedars-Sinai Medical Center



One of the most comprehensive imaging research center in the world

25
Faculty Members

40
Research Scientists

20
Supporting Staff and Management

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Areas of Research

- Pancreatic Cancer Imaging
- Breast Cancer Imaging
- Cardiovascular Imaging
- Quantitative Image Analysis
- Neuroimaging
- Oncologic Radiation Therapy Imaging
- Abdominal Computerized Tomography