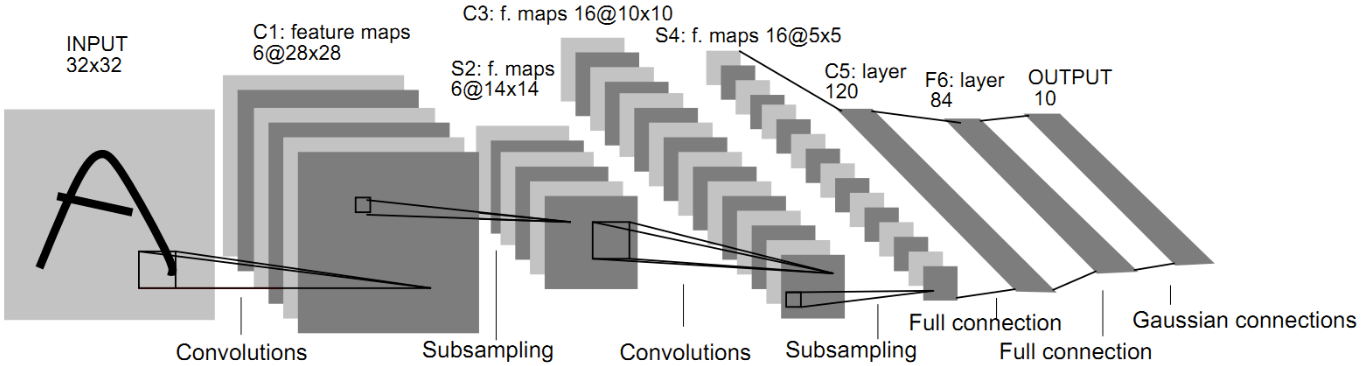
Cost-Effective Deep Learning in Medical Image Analysis

Zongwei Zhou

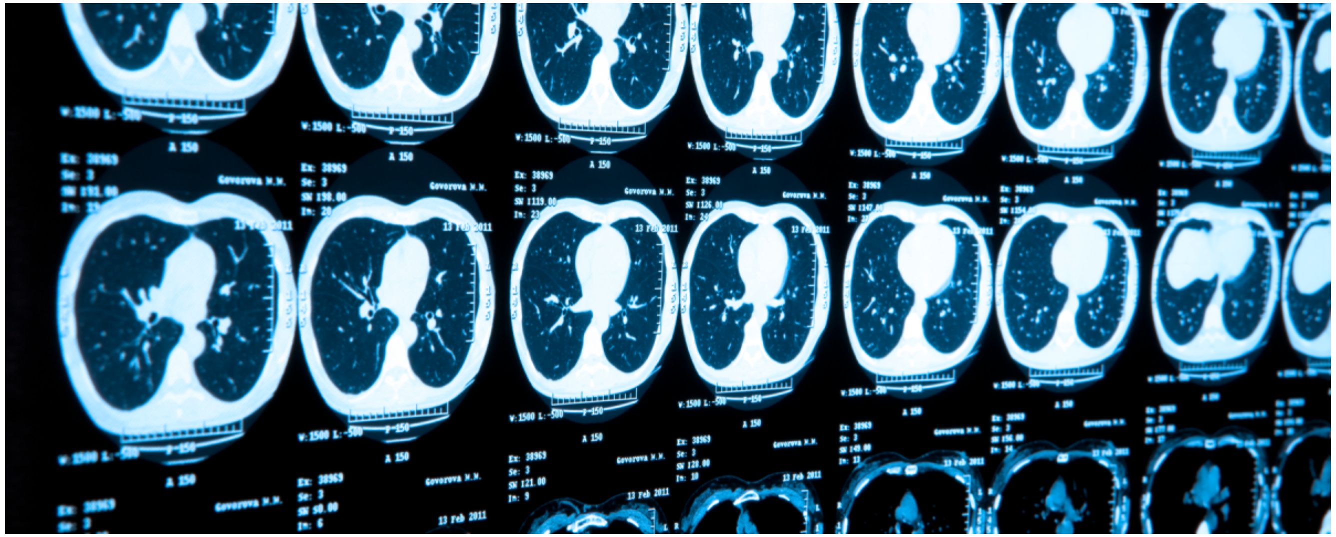
Ph.D. Candidate, Biomedical Informatics
College of Health Solutions, Arizona State University
P: 1-(480)738-2575 | E: zongweiz@asu.edu

Sep 4, 2020 @ BMI Seminar

Deep Learning propels us into the so-called artificial intelligence (AI) era



Imaging data account for about 90% of all healthcare data



1. LeCun, Yann, Yoshua Bengio, and Geoffrey Hinton. "Deep learning." nature 521.7553 (2015): 436-444
2. "The Digital Universe Driving Data Growth in Healthcare." published by EMC with research and analysis from IDC (12/13)

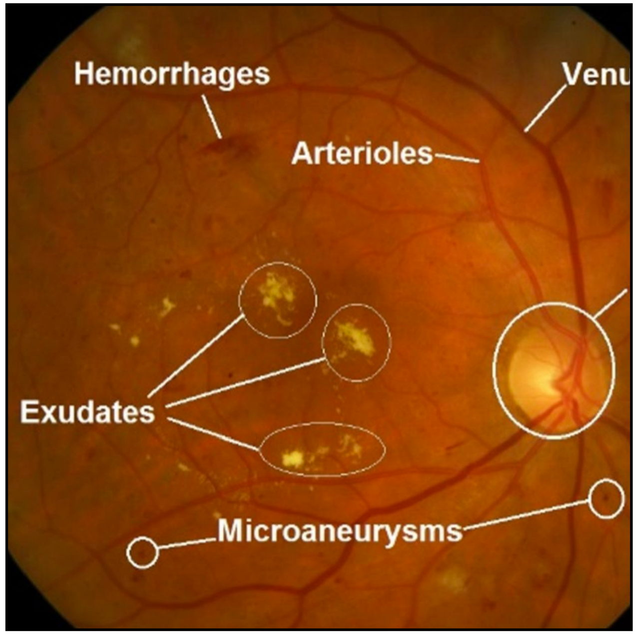
ARIZONA STATE UNIVERSITY · 1885 ·

Introduction
Objective
Aim #1
Aim #2
Aim #3
Summary

Deep Learning works well in medical imaging, but it demands massive annotation costs.

To match human diagnostic precision, deep learning algorithms require

- **42,290** radiologist-labeled CT images for lung cancer diagnosis
- **128,175** ophthalmologist-labeled retinal images for diabetic retinopathy detection
- **129,450** dermatologist-labeled images for skin cancer classification



1. Ardila, Diego, et al. "End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography." Nature medicine 25.6 (2019): 954-961.
2. Gulshan, Varun, et al. "Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs." Jama 316.22 (2016): 2402-2410.
3. Esteva, Andre, et al. "Dermatologist-level classification of skin cancer with deep neural networks." nature 542.7639 (2017): 115-118.

Deep Learning works well in medical imaging, but it demands massive annotation costs.

To match human diagnostic precision, deep learning algorithms require

- **42,290** radiologist-labeled CT images for lung cancer diagnosis[1]
- **128,175** ophthalmologist-labeled retinal images for diabetic retinopathy detection[2]
- **129,450** dermatologist-labeled images for skin cancer classification[3]

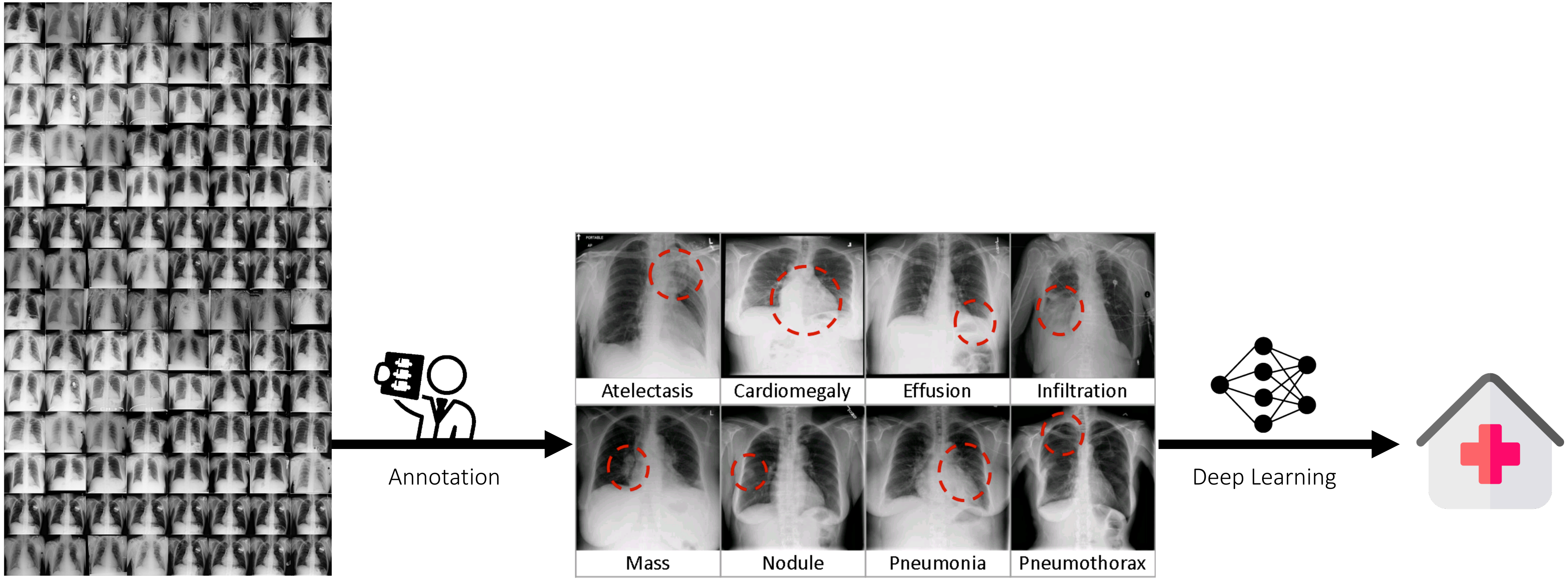
How to develop cost-effective deep learning algorithms for those diseases that have no such labeled big data?

Consider the scenarios as follows:

- A flood of patients are pending during an outbreak
- Doctors do not have time to annotate every case
- Not many doctors have expertise for novel diseases

1. Ardila, Diego, et al. "End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography." Nature medicine 25.6 (2019): 954-961.
2. Gulshan, Varun, et al. "Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs." Jama 316.22 (2016): 2402-2410.
3. Esteva, Andre, et al. "Dermatologist-level classification of skin cancer with deep neural networks." nature 542.7639 (2017): 115-118.

Research goal: Exploit novel methods to minimize the manual labeling efforts for a rapid, precise computer-aided diagnosis system

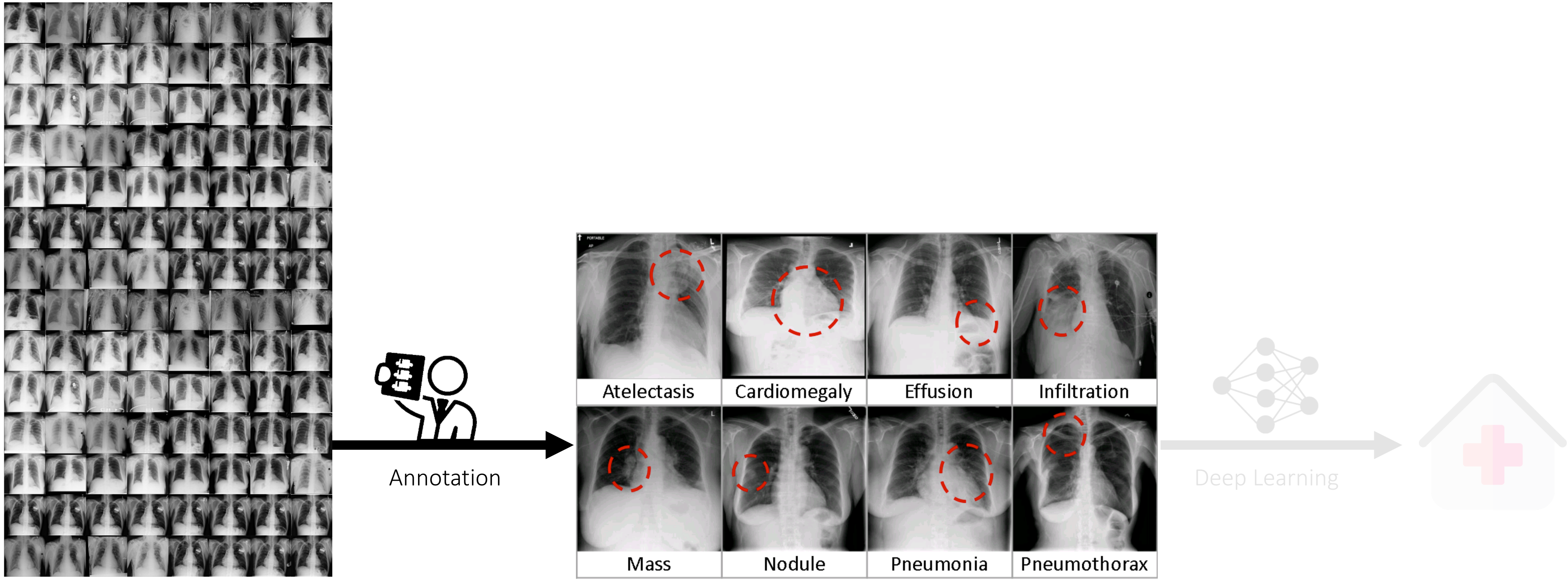


$1,000,000 annotation cost ☹

$1,000 annotation cost ☺

Research goal: Exploit novel methods to minimize the manual labeling efforts for a rapid, precise computer-aided diagnosis system

Aim #1: Select necessary patients/samples for annotation



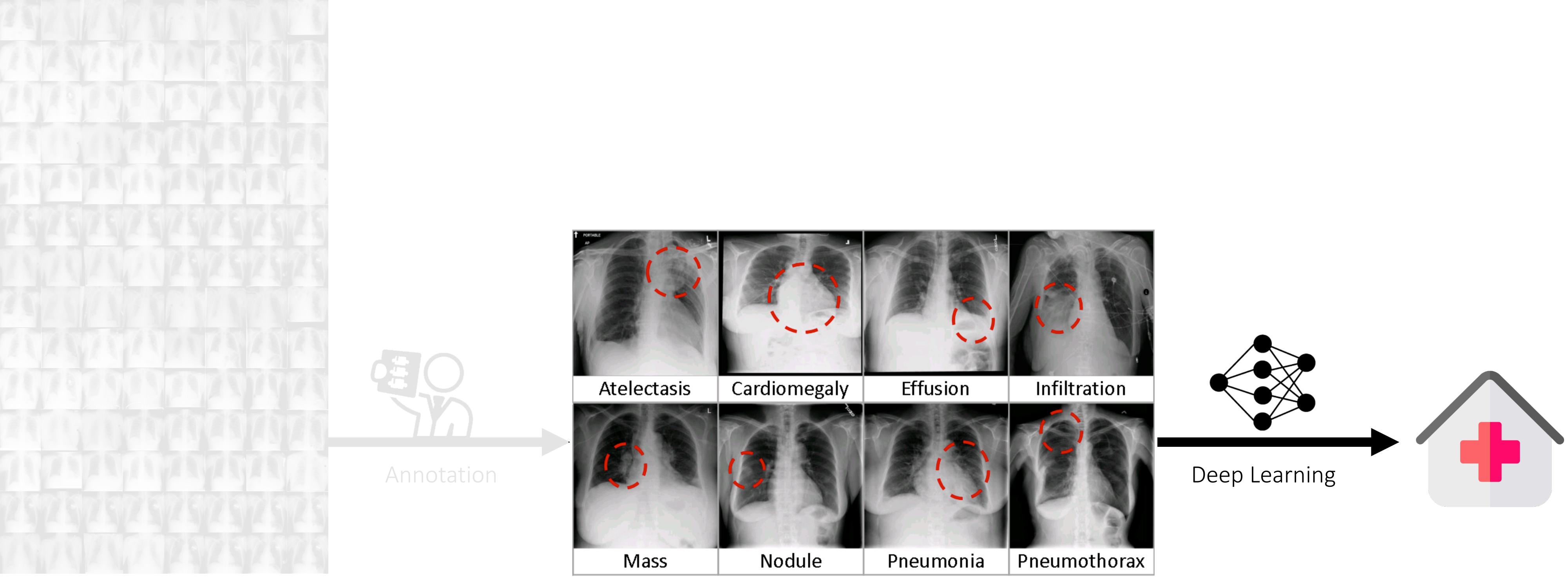
$1,000,000 annotation cost ☹

$1,000 annotation cost ☺

Research goal: Exploit novel methods to minimize the manual labeling efforts for a rapid, precise computer-aided diagnosis system

Aim #1: Select necessary patients/samples for annotation

Aim #2: Develop advanced architectures with existing annotation



$1,000,000 annotation cost ☹

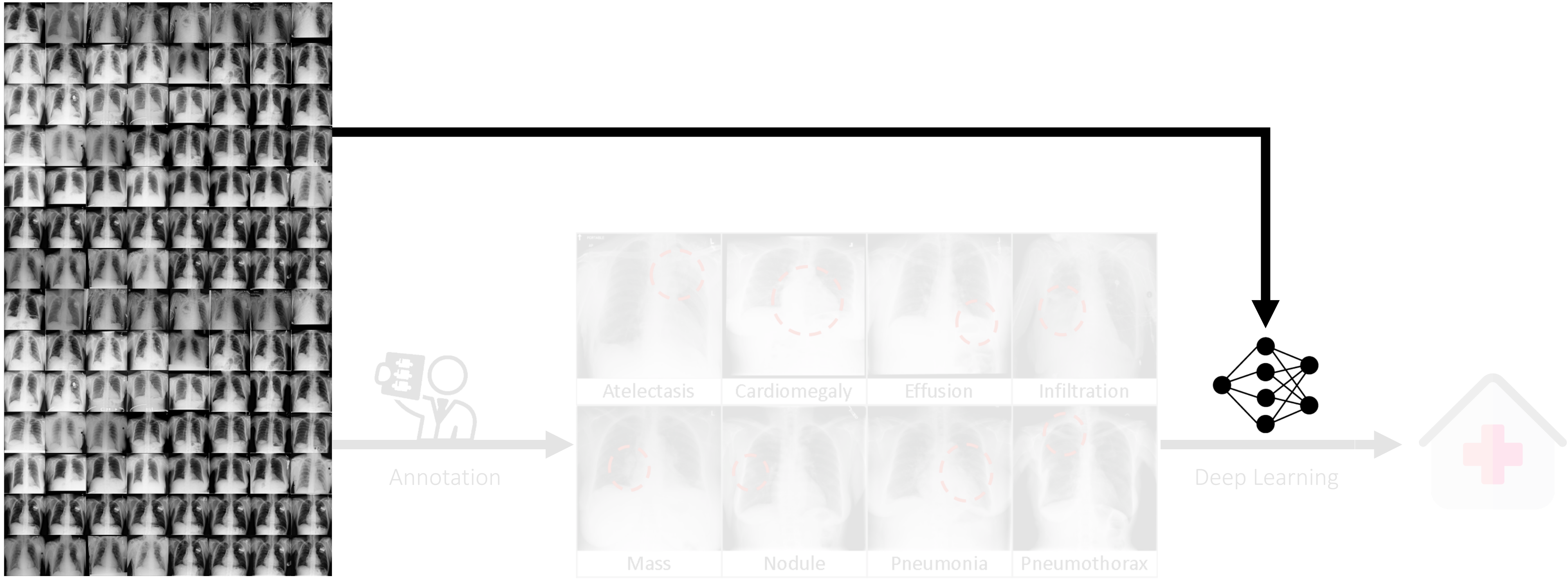
$1,000 annotation cost ☺

Research goal: Exploit novel methods to minimize the manual labeling efforts for a rapid, precise computer-aided diagnosis system

Aim #1: Select necessary patients/samples for annotation

Aim #2: Develop advanced architectures with existing annotation

Aim #3: Extract generic knowledge directly from unannotated images

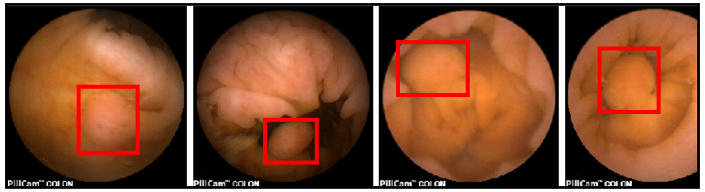


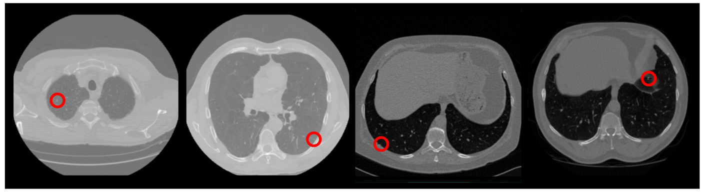
Research goal: Exploit novel methods to minimize the manual labeling efforts for a rapid, precise computer-aided diagnosis system

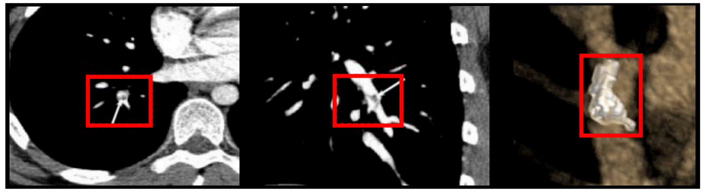
Aim #1: Select necessary patients/samples for annotation

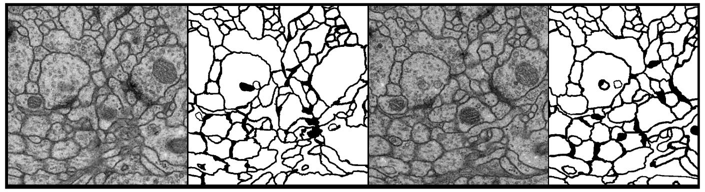
Aim #2: Develop advanced architectures with existing annotation

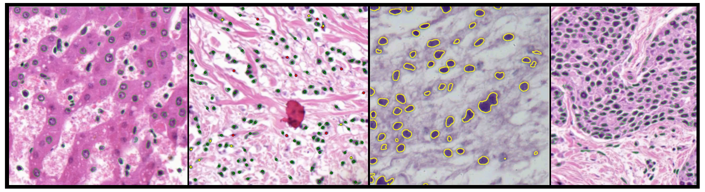
Aim #3: Extract generic knowledge directly from unannotated images


Polyp detection

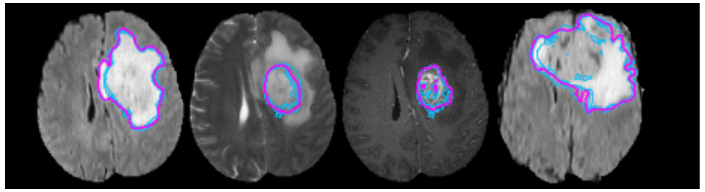

Lung nodule detection

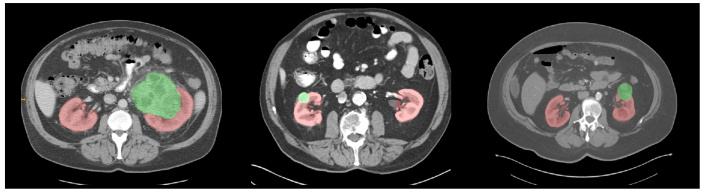

Pulmonary embolism detection

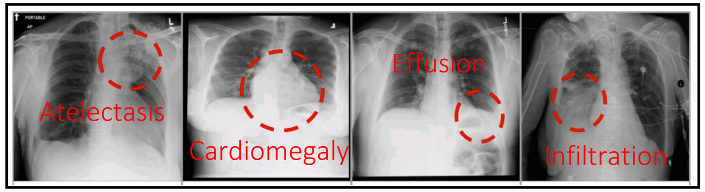

Neuronal structure segmentation


Cell/nuclei segmentation


Liver/lesion segmentation


Brain/tumor segmentation

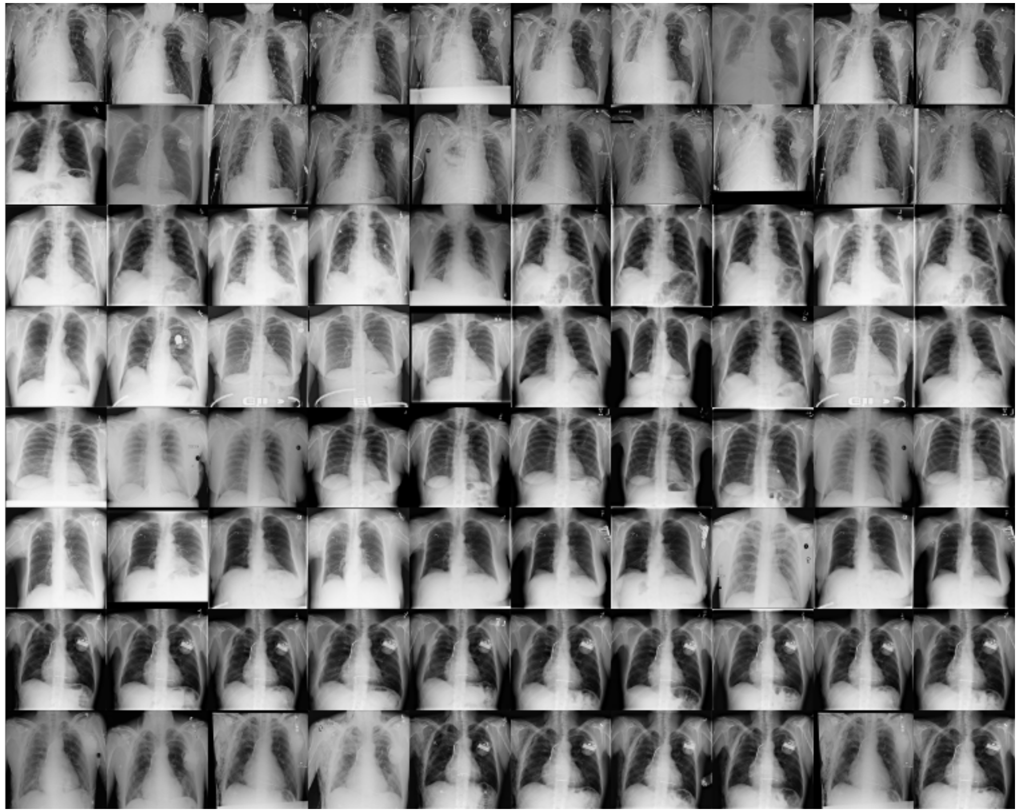

Kidney/lesion segmentation



Pulmonary diseases classification

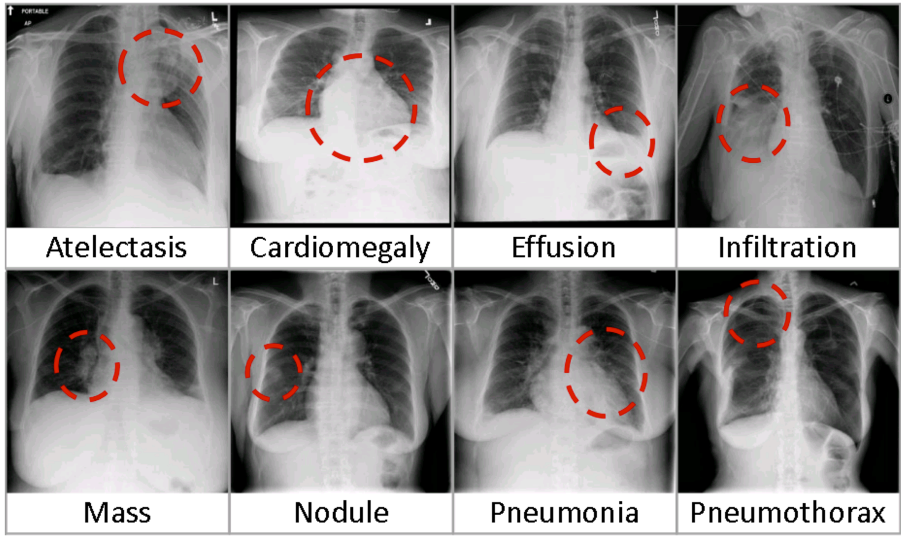
Aim #1: Select necessary patients/samples for annotation

Problem: Find the most important 1,000 images from 1,000,000 images



$ 1,000,000 annotation cost ☹

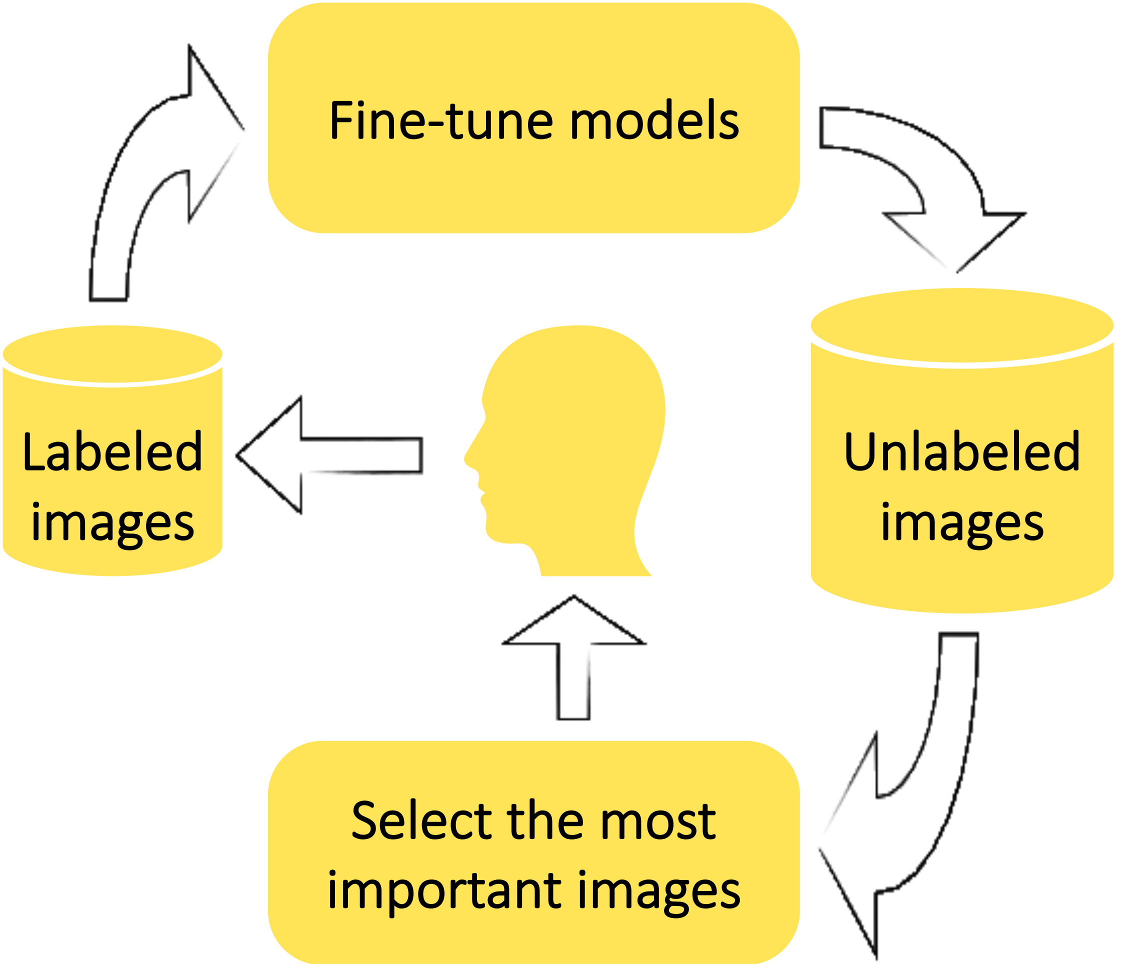
`$1 per subject`



$ 1,000 annotation budget ☺

Aim #1: Select necessary patients/samples for annotation

Approach: "Human-in-the-loop" active learning procedure



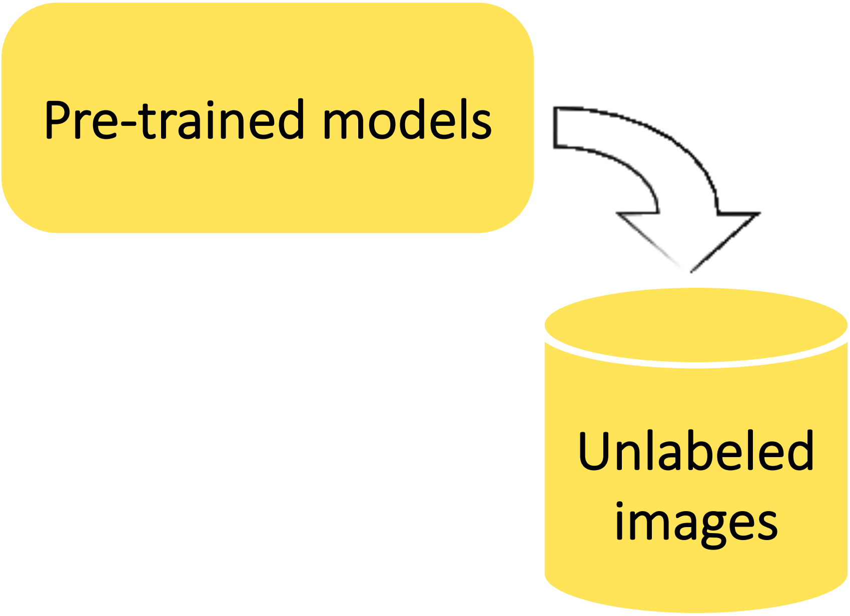
Aim #1: Select necessary patients/samples for annotation

Approach: “Human-in-the-loop” active learning procedure

Pre-trained models

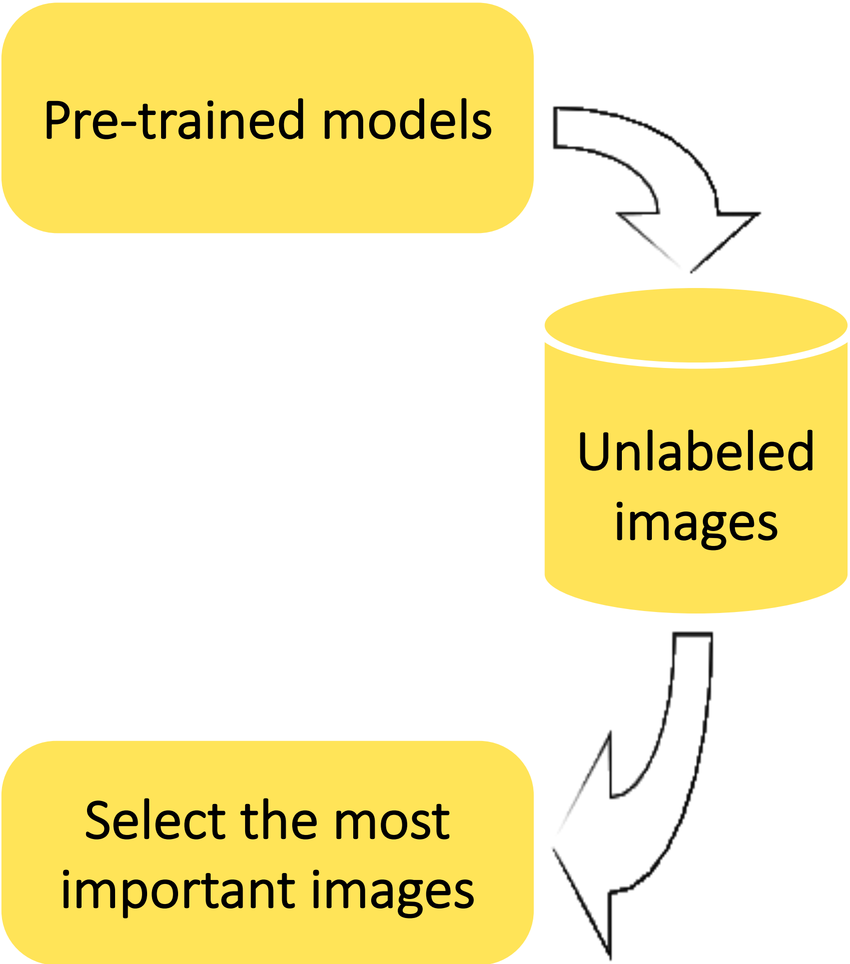
Aim #1: Select necessary patients/samples for annotation

Approach: “Human-in-the-loop” active learning procedure



Aim #1: Select necessary patients/samples for annotation

Approach: “Human-in-the-loop” active learning procedure



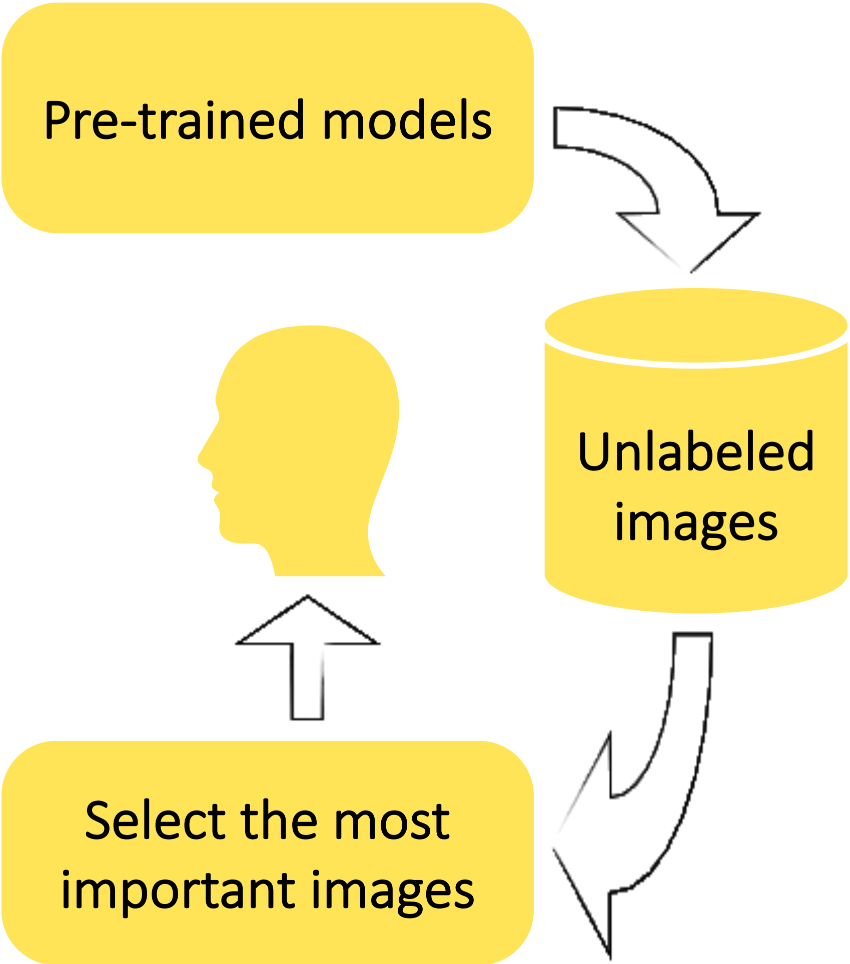
Pre-trained models

Unlabeled images

Select the most important images

Aim #1: Select necessary patients/samples for annotation

Approach: "Human-in-the-loop" active learning procedure



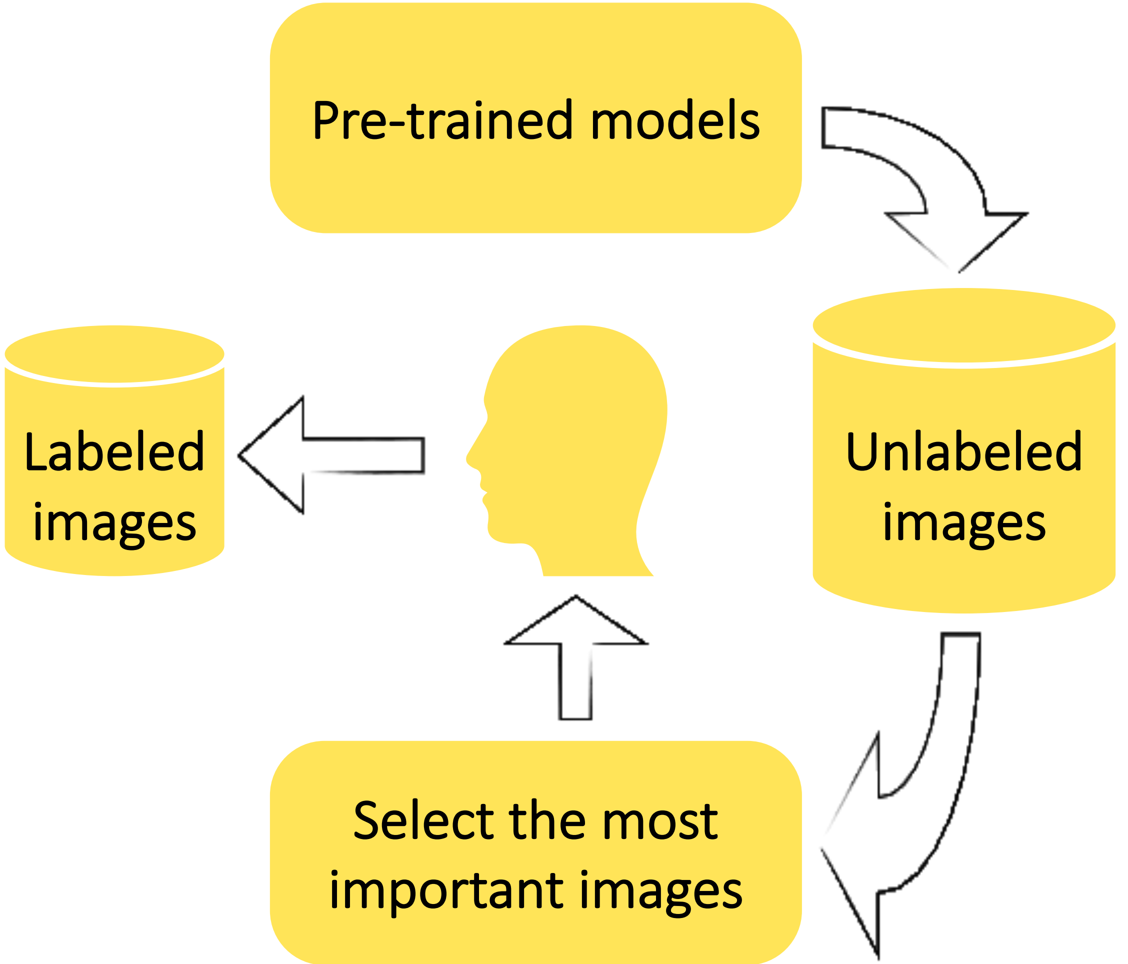
Pre-trained models

Unlabeled images

Select the most important images

Aim #1: Select necessary patients/samples for annotation

Approach: “Human-in-the-loop” active learning procedure



Pre-trained models

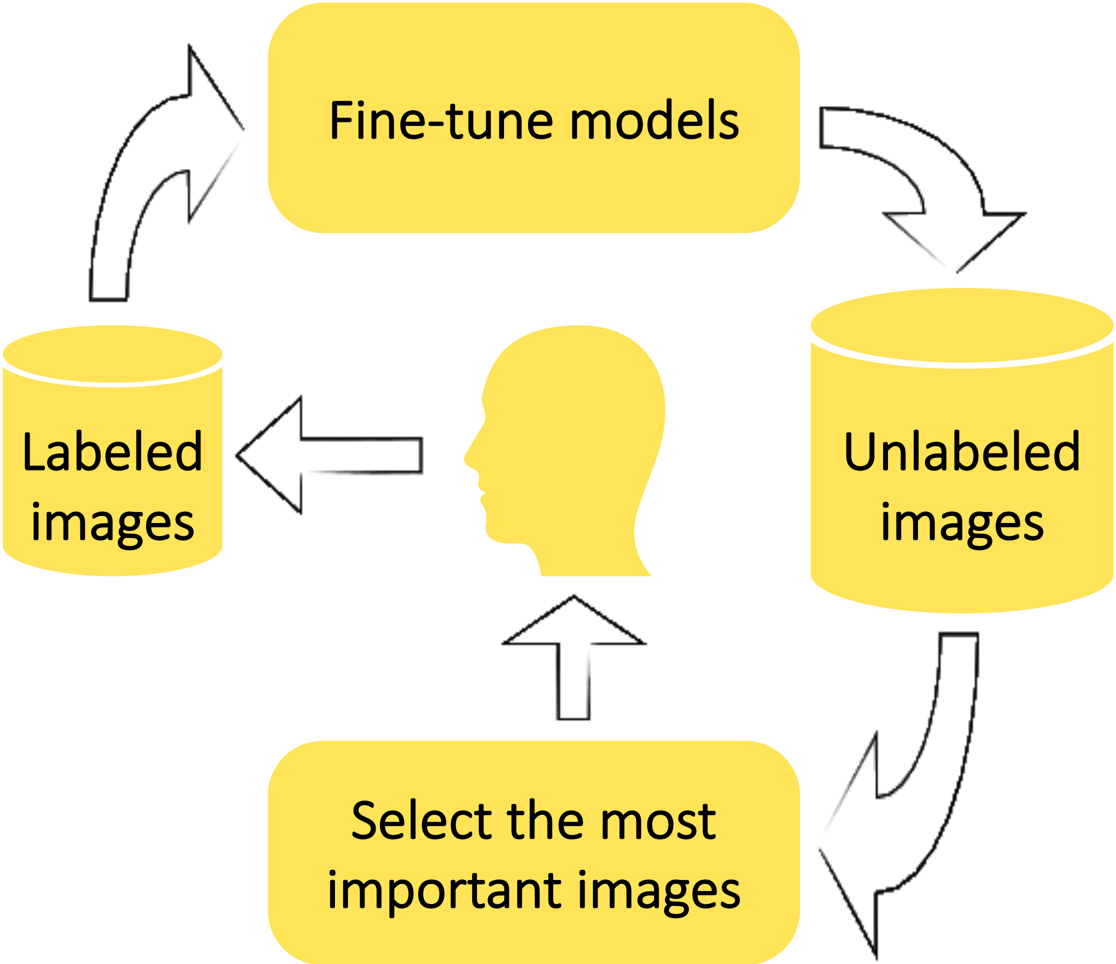
Unlabeled images

Select the most important images

Labeled images

Aim #1: Select necessary patients/samples for annotation

Approach: “Human-in-the-loop” active learning procedure



Fine-tune models

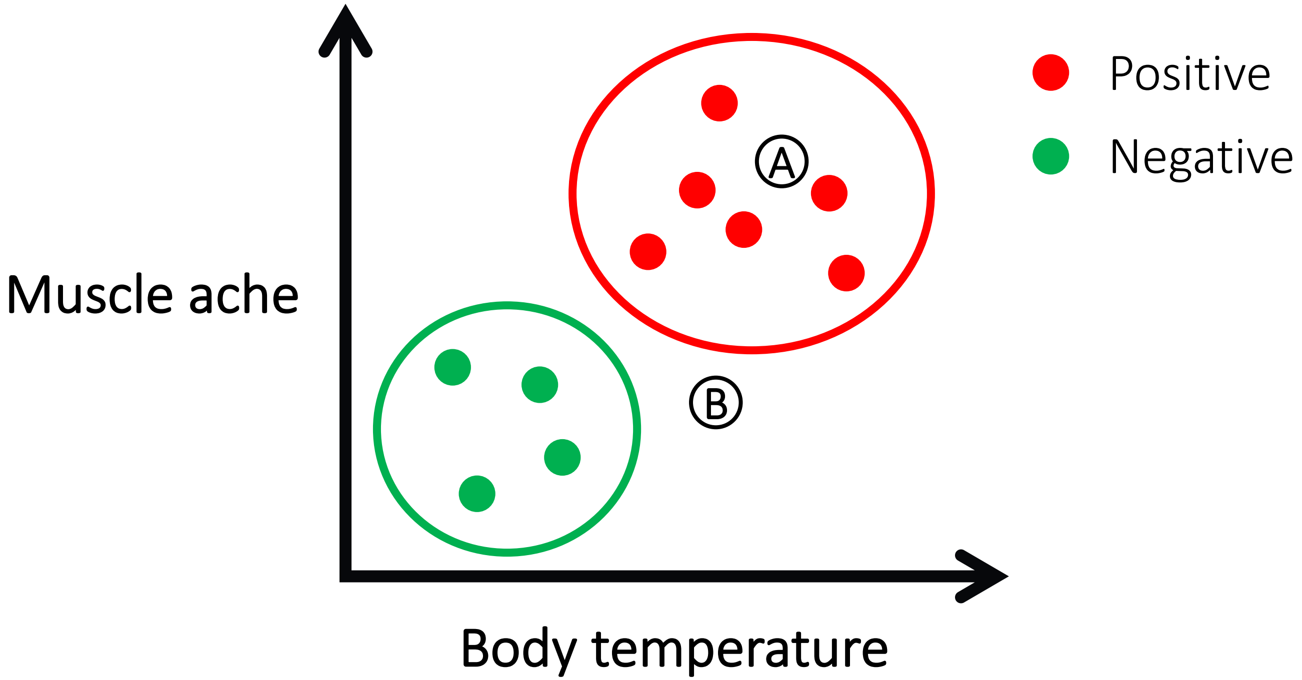
Unlabeled images

Select the most important images

Labeled images

Aim #1: Select necessary patients/samples for annotation

Approach: “Human-in-the-loop” active learning procedure

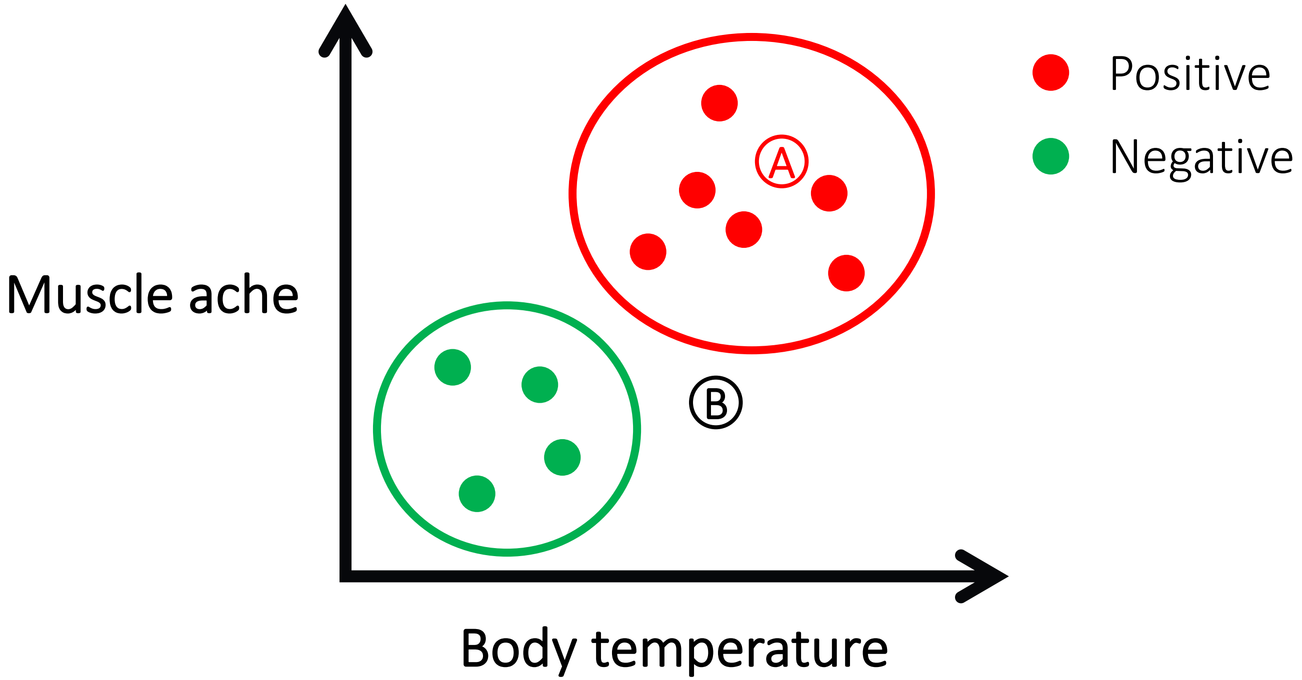


Select the most important samples

Given one dollar, which patient would you annotate, A or B?

Aim #1: Select necessary patients/samples for annotation

Approach: "Human-in-the-loop" active learning procedure

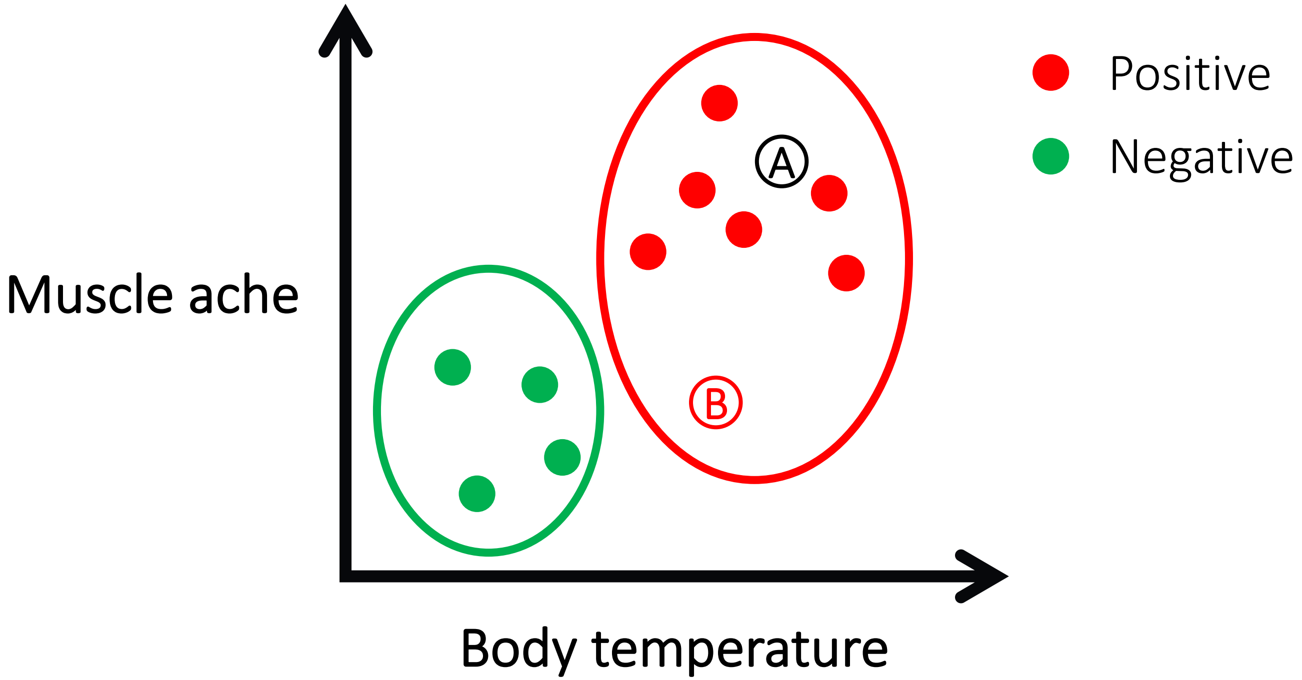


Select the most important samples

Given one dollar, which patient would you annotate, A or B?

Aim #1: Select necessary patients/samples for annotation

Approach: “Human-in-the-loop” active learning procedure



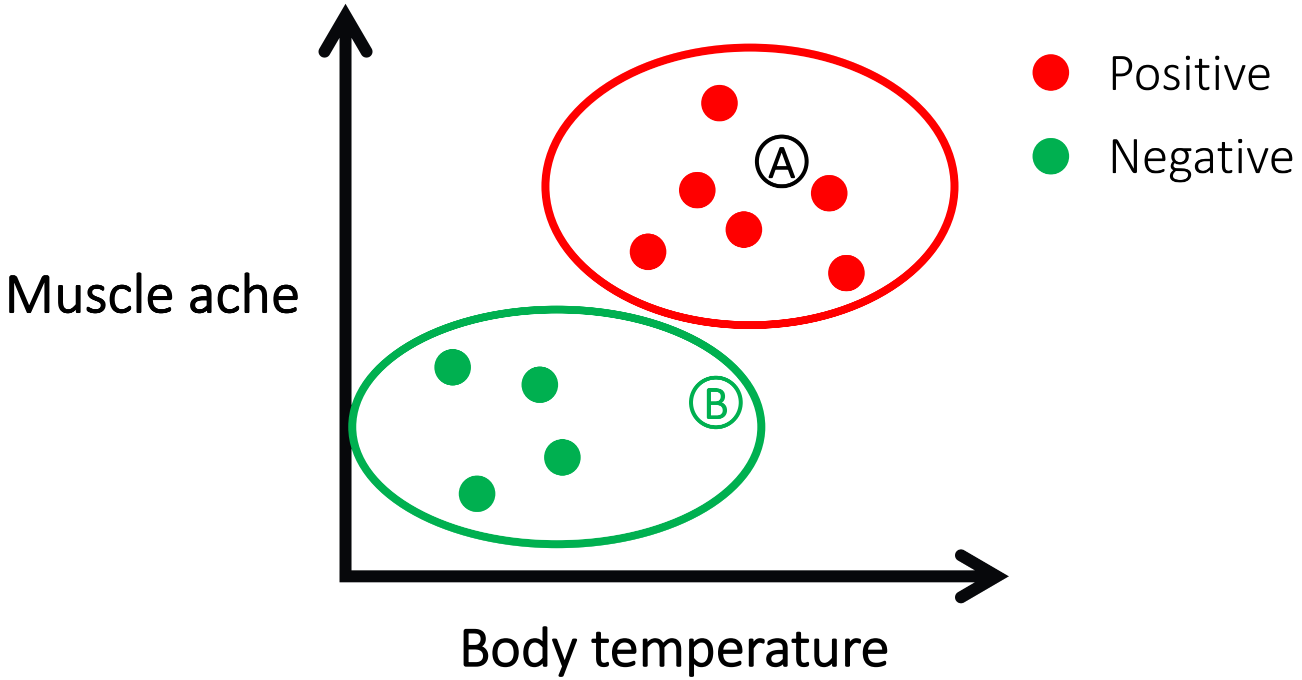
Select the most important samples

Given one dollar, which patient would you annotate, A or B?

Introduction
Objective
Aim #1
Aim #2
Aim #3
Summary

Aim #1: Select necessary patients/samples for annotation

Approach: “Human-in-the-loop” active learning procedure

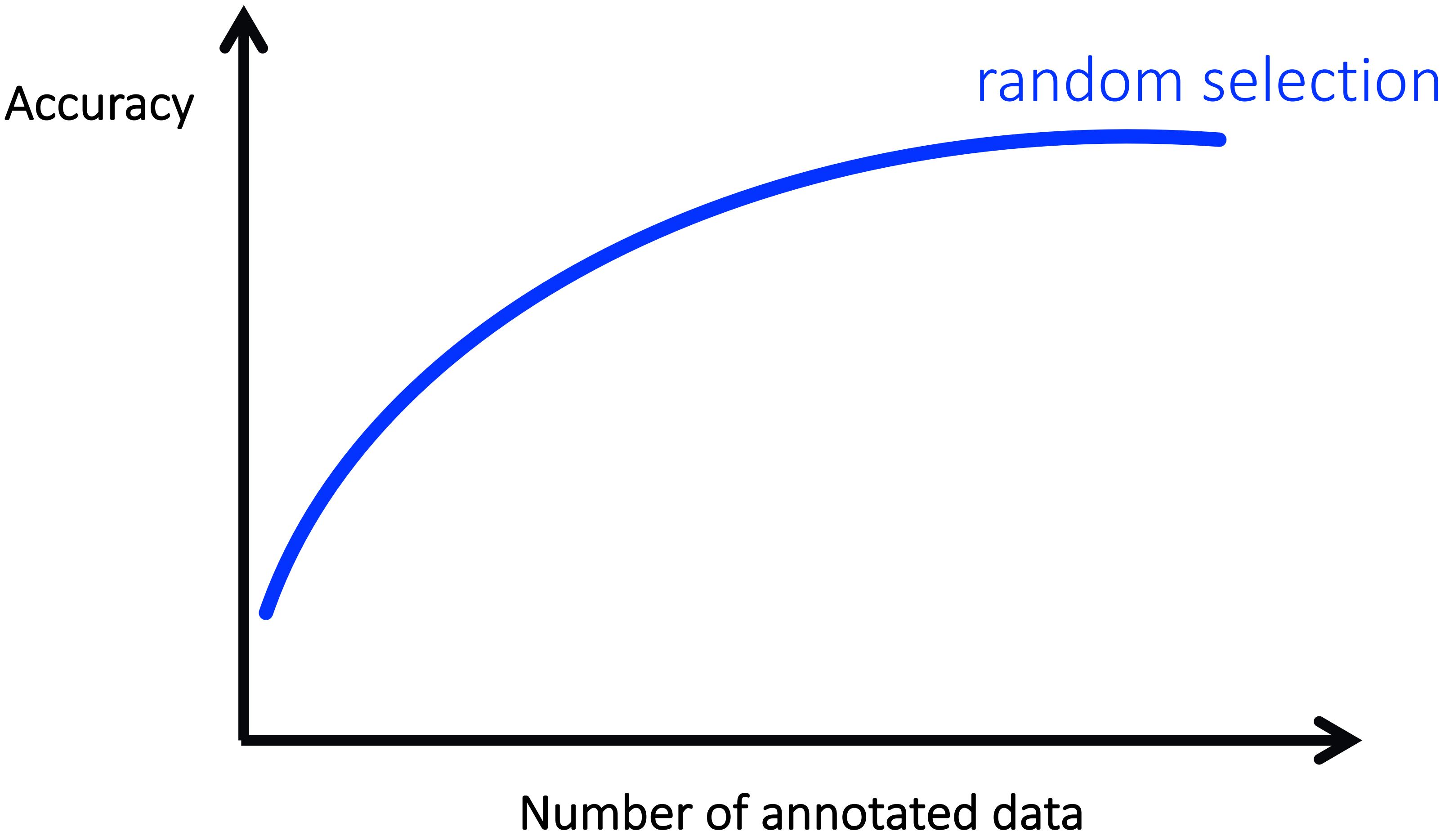


Select the most important samples

Given one dollar, which patient would you annotate, A or B?

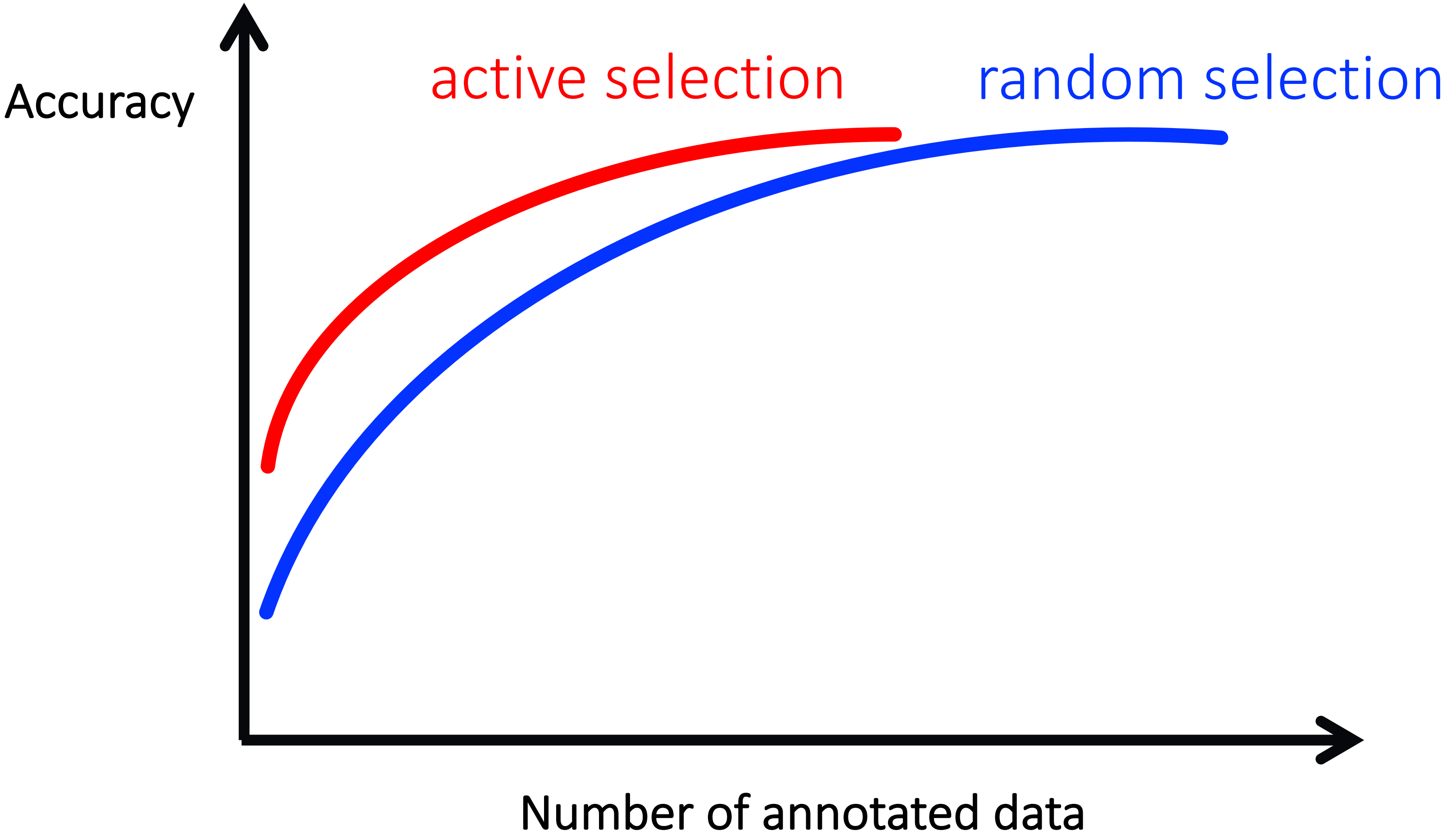
Aim #1: Select necessary patients/samples for annotation

Hypothesis: Wisely selecting important samples can reduce annotation cost



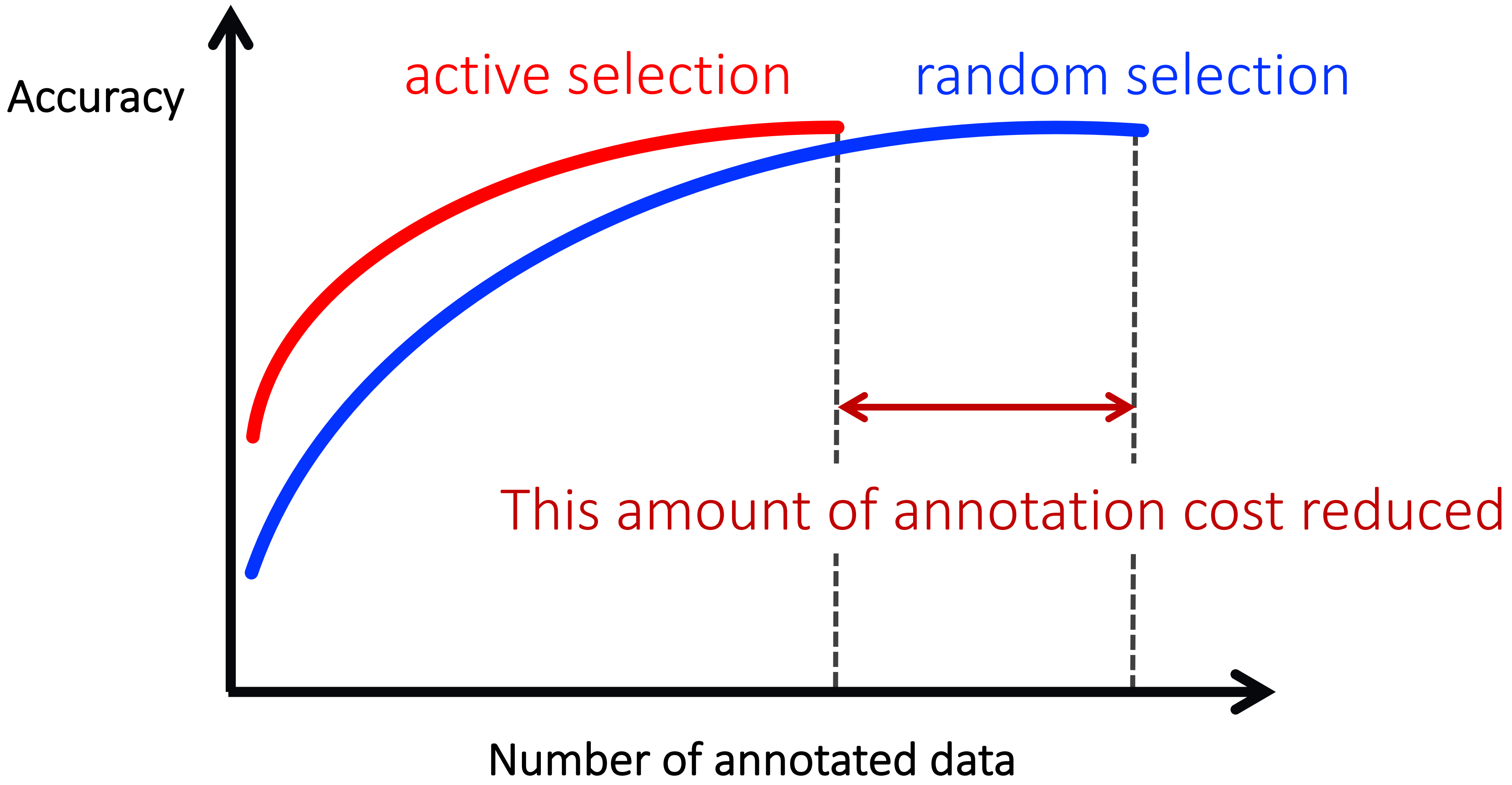
Aim #1: Select necessary patients/samples for annotation

Hypothesis: Wisely selecting important samples can reduce annotation cost



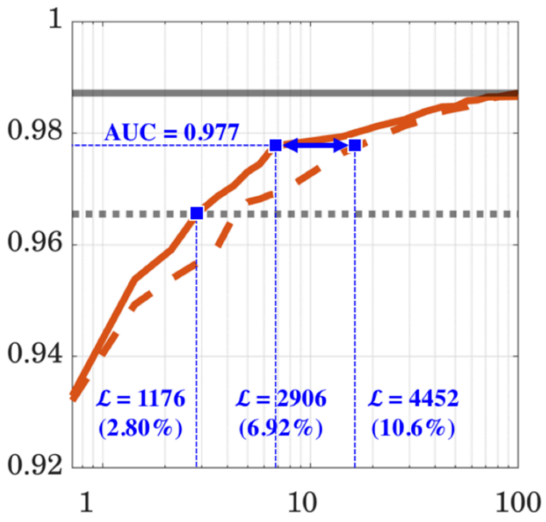
Aim #1: Select necessary patients/samples for annotation

Hypothesis: Wisely selecting important samples can reduce annotation cost

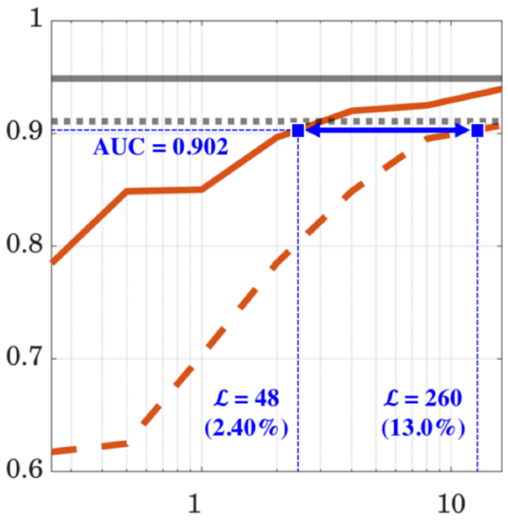


Aim #1: Select necessary patients/samples for annotation

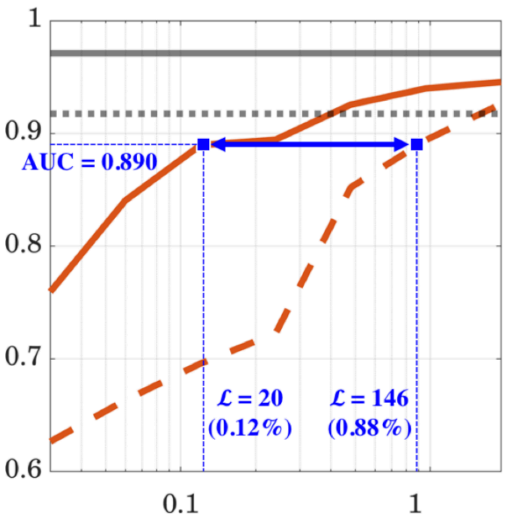
Contribution: Reduce annotation cost by >60% compared to random selection



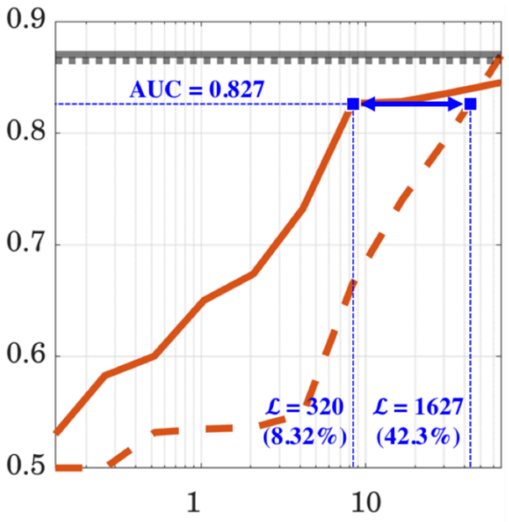
Places: Scene Classification



Colonoscopy Frame Classification



Polyp Detection

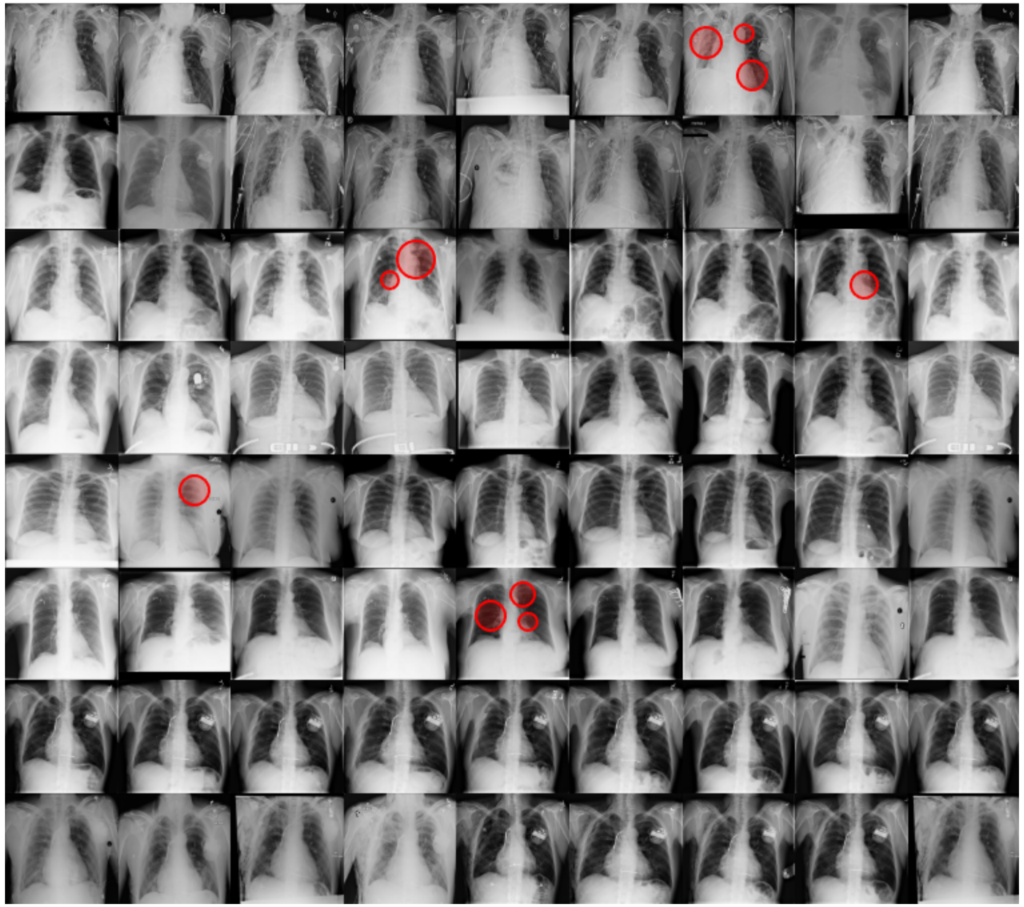


Pulmonary Embolism Detection

1. Zhou, Zongwei, et al. "Integrating active learning and transfer learning for carotid intima-media thickness video interpretation." Journal of digital imaging 32.2 (2019): 290-299.
2. Zhou, Zongwei, et al. "Active, Continual Fine Tuning of Convolutional Neural Networks for Reducing Annotation Efforts." arXiv preprint arXiv:1802.00912 (2018).
3. Zhou, Zongwei, et al. "Fine-tuning convolutional neural networks for biomedical image analysis: actively and incrementally." Proceedings of the IEEE conference on computer vision and pattern recognition. 2017.

Aim #1: Select necessary patients/samples for annotation

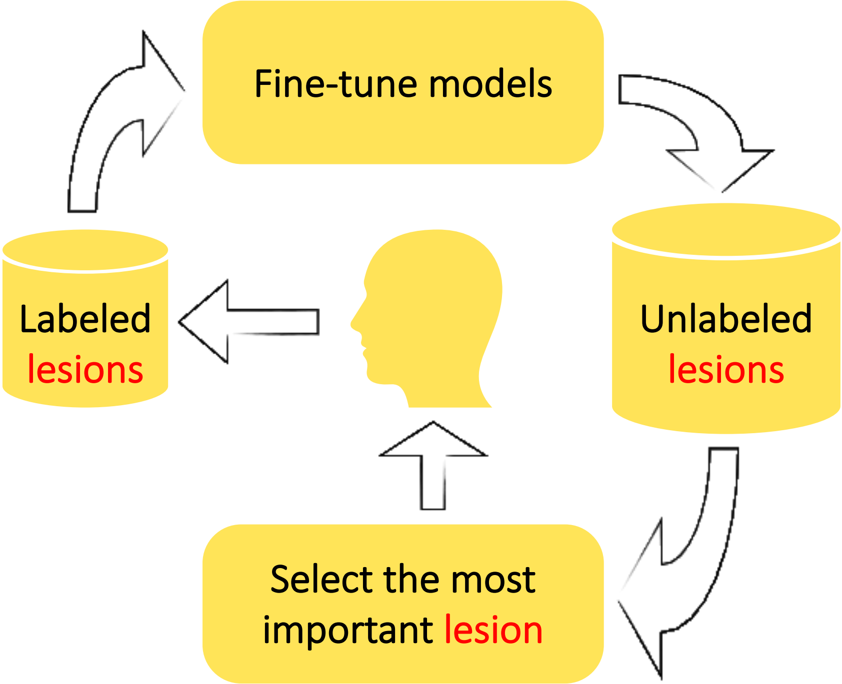
Proposal: Iteratively suggest important samples at the patient-level



Lesion-level annotation

Drawbacks:

- Experts must annotate the same patient multiple times



Fine-tune models

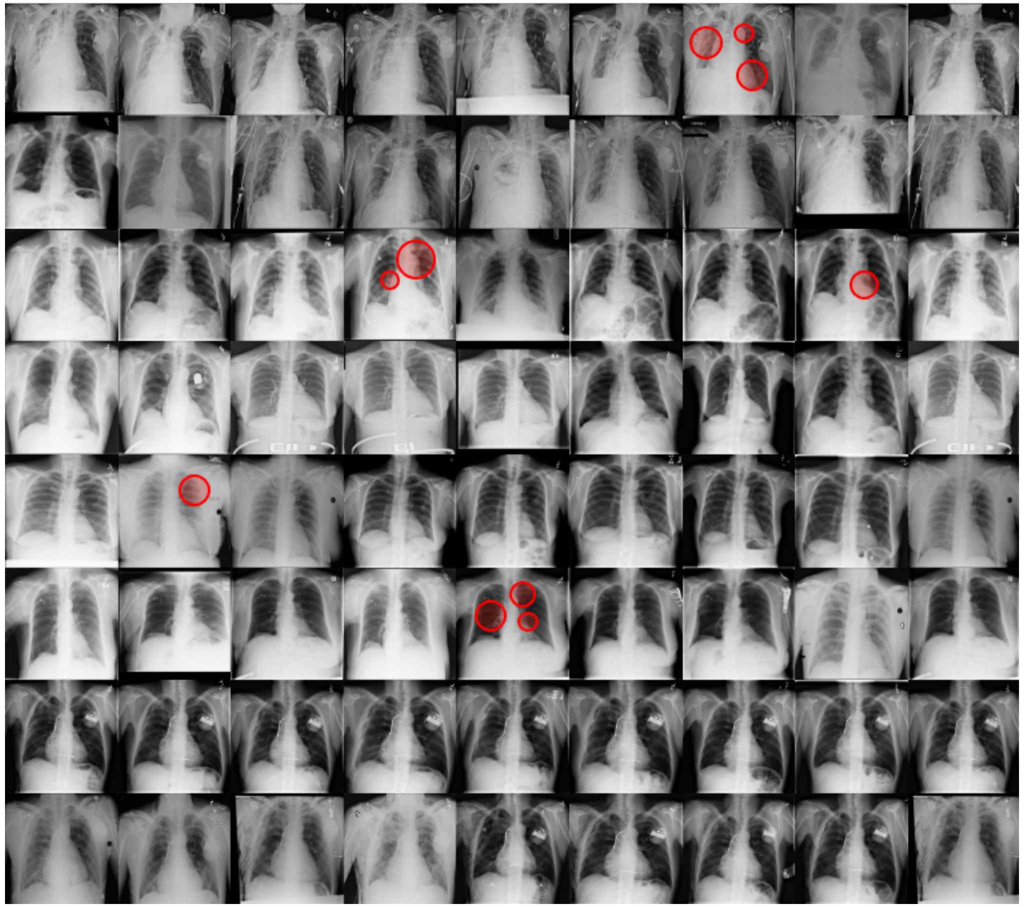
Unlabeled lesions

Select the most important lesion

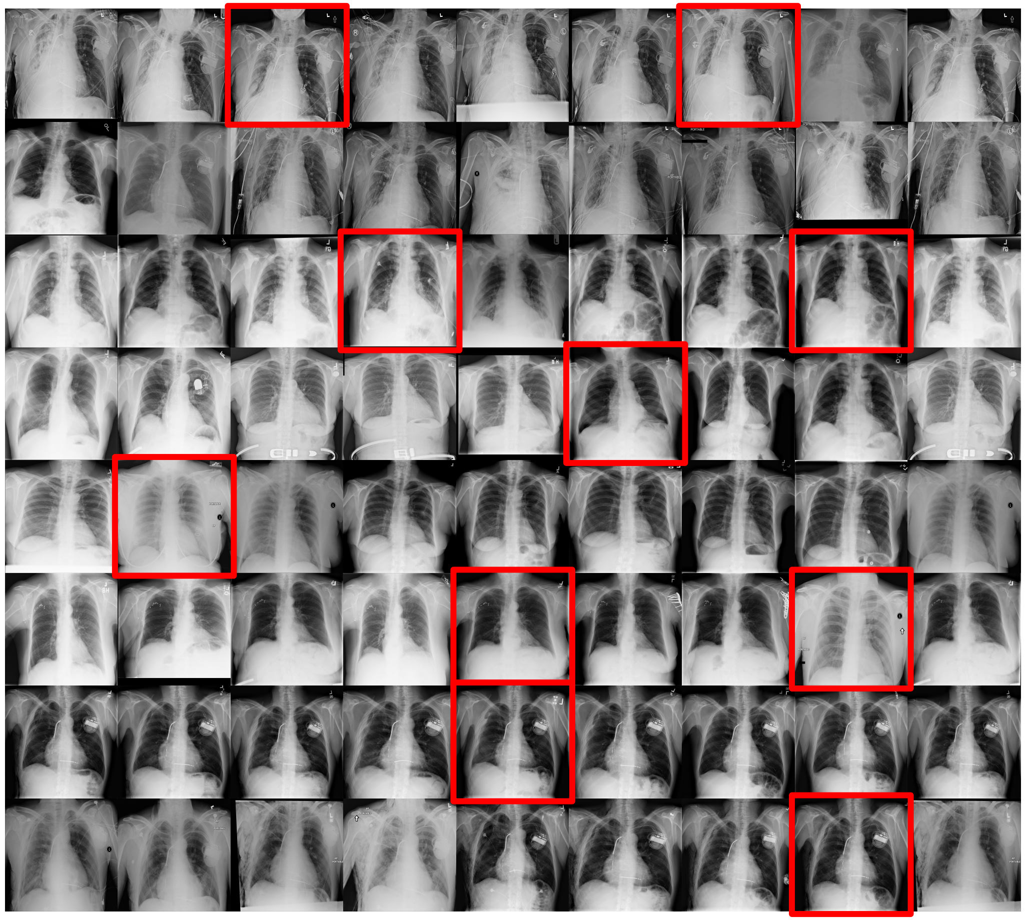
Labeled lesions

Aim #1: Select necessary patients/samples for annotation

Proposal: Iteratively suggest important samples at the patient-level



Lesion-level annotation

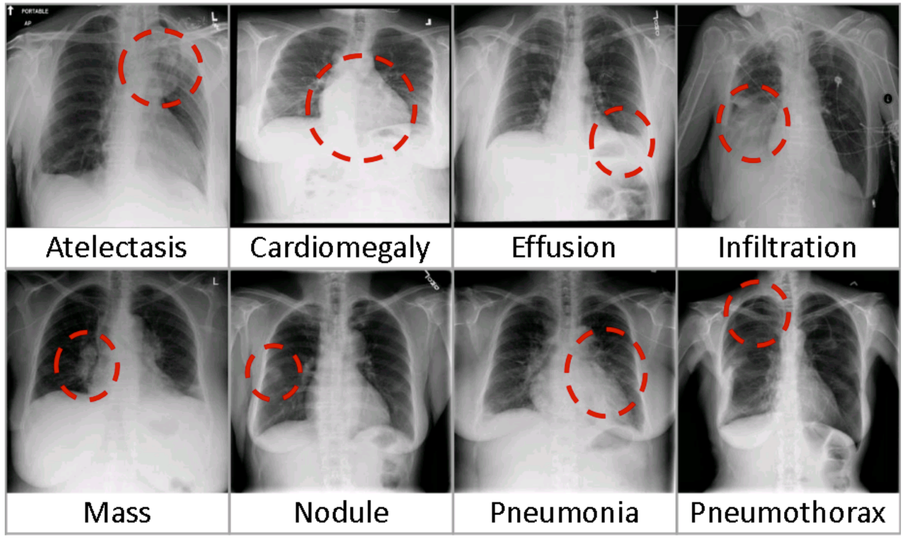


Patient-level annotation

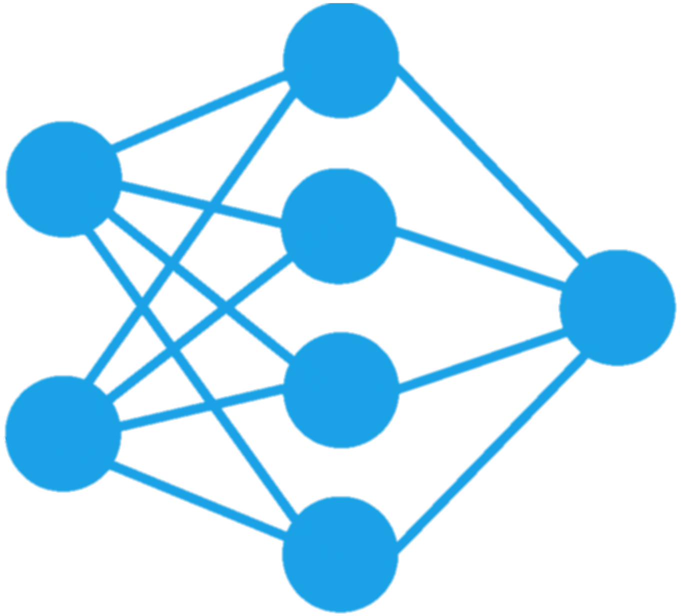
Not All Data Is Created Equal

Aim #2: Develop advanced architectures with existing annotation

Problem: Enhance the architecture for modeling 1,000 annotated images

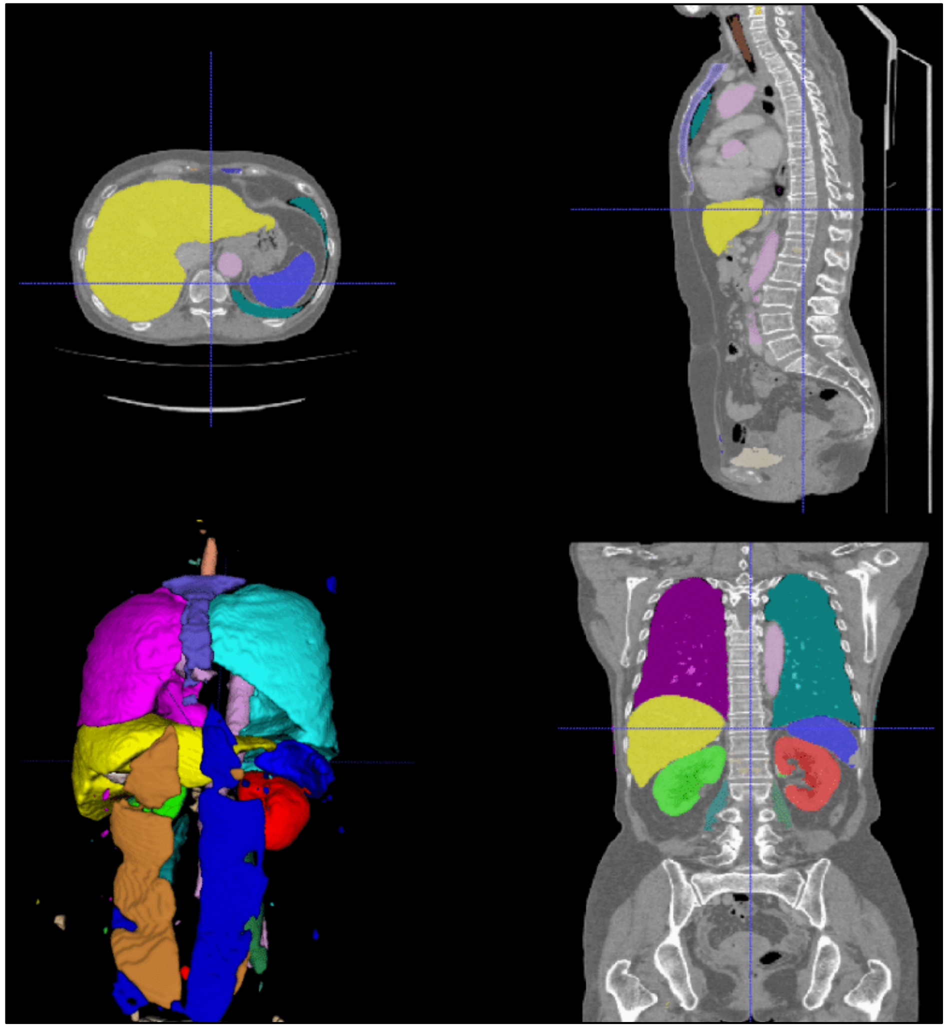


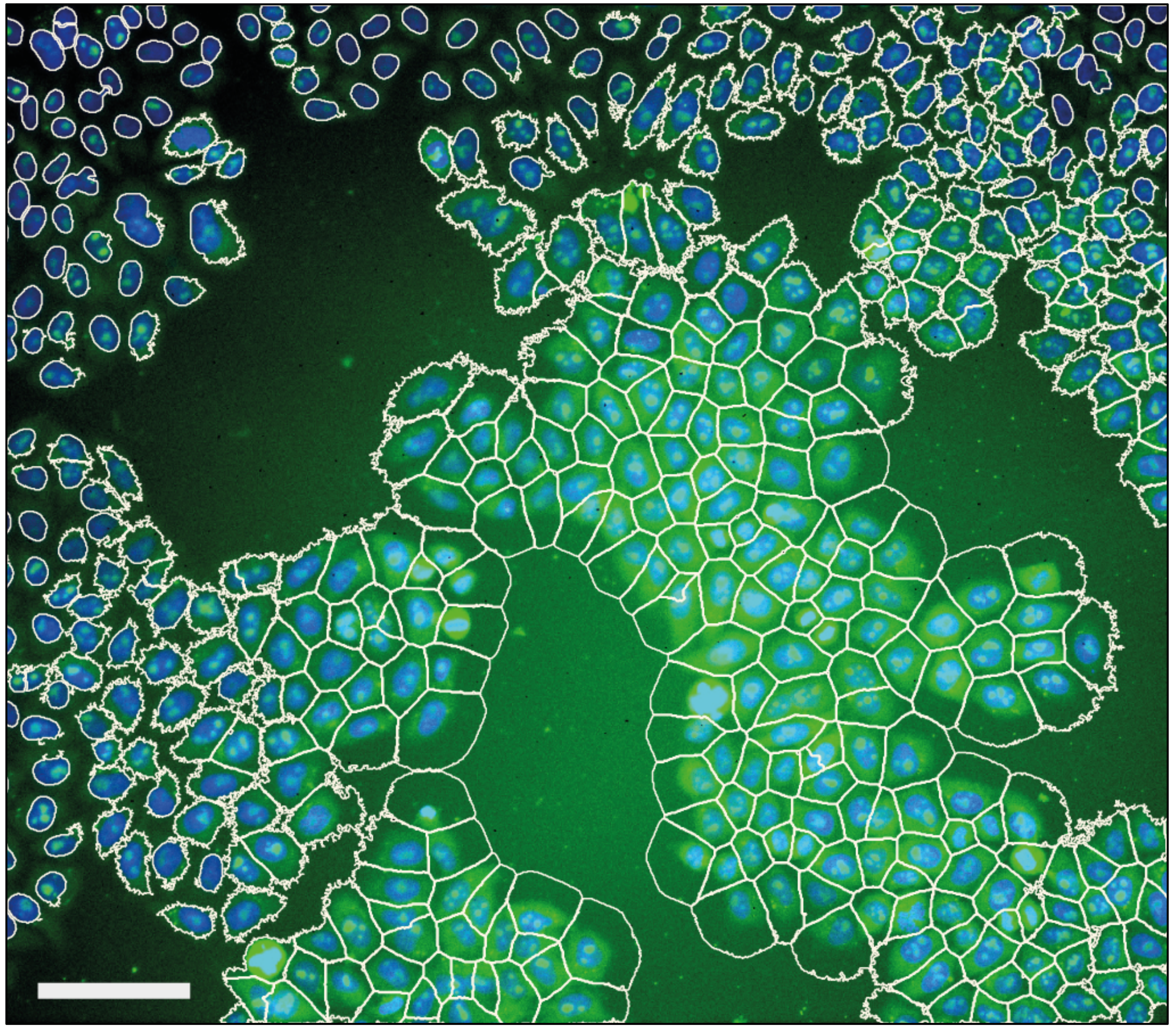
$ 1,000 annotation budget ☺



Aim #2: Develop advanced architectures with existing annotation

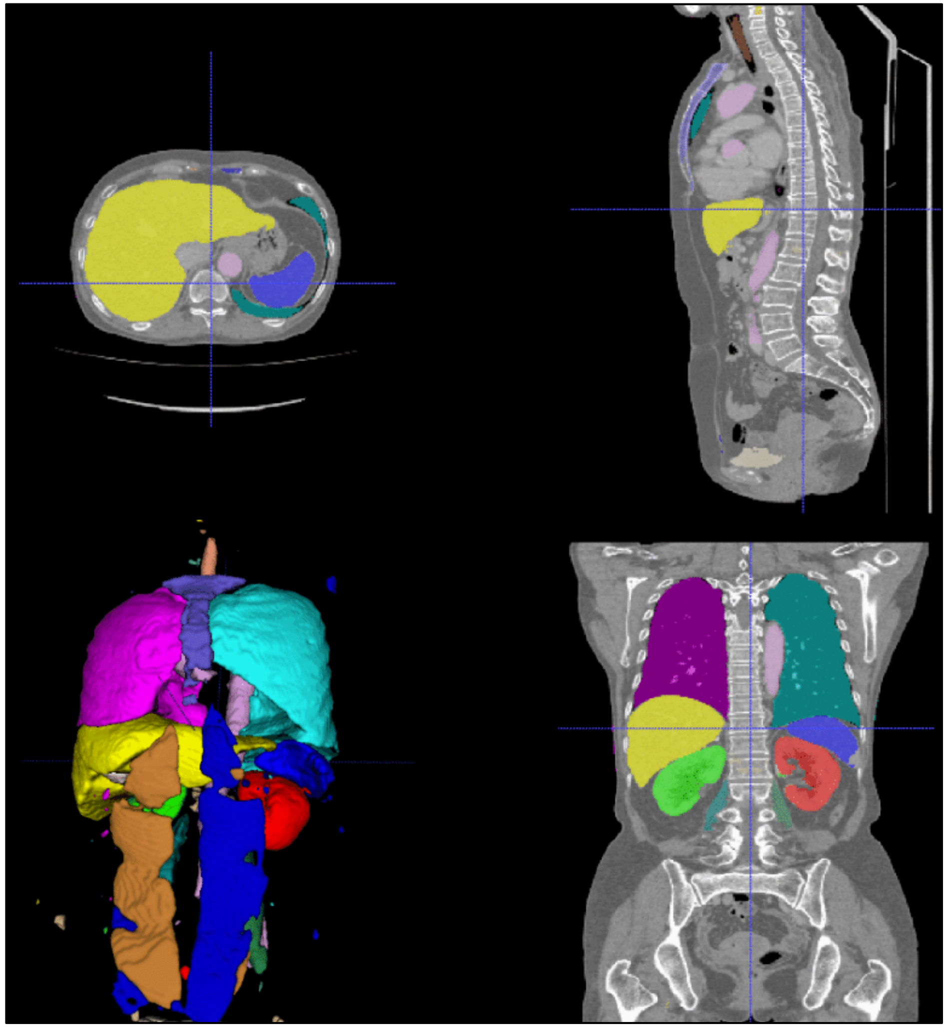
Segmentation: Partition an image into multiple segments to ease the analysis



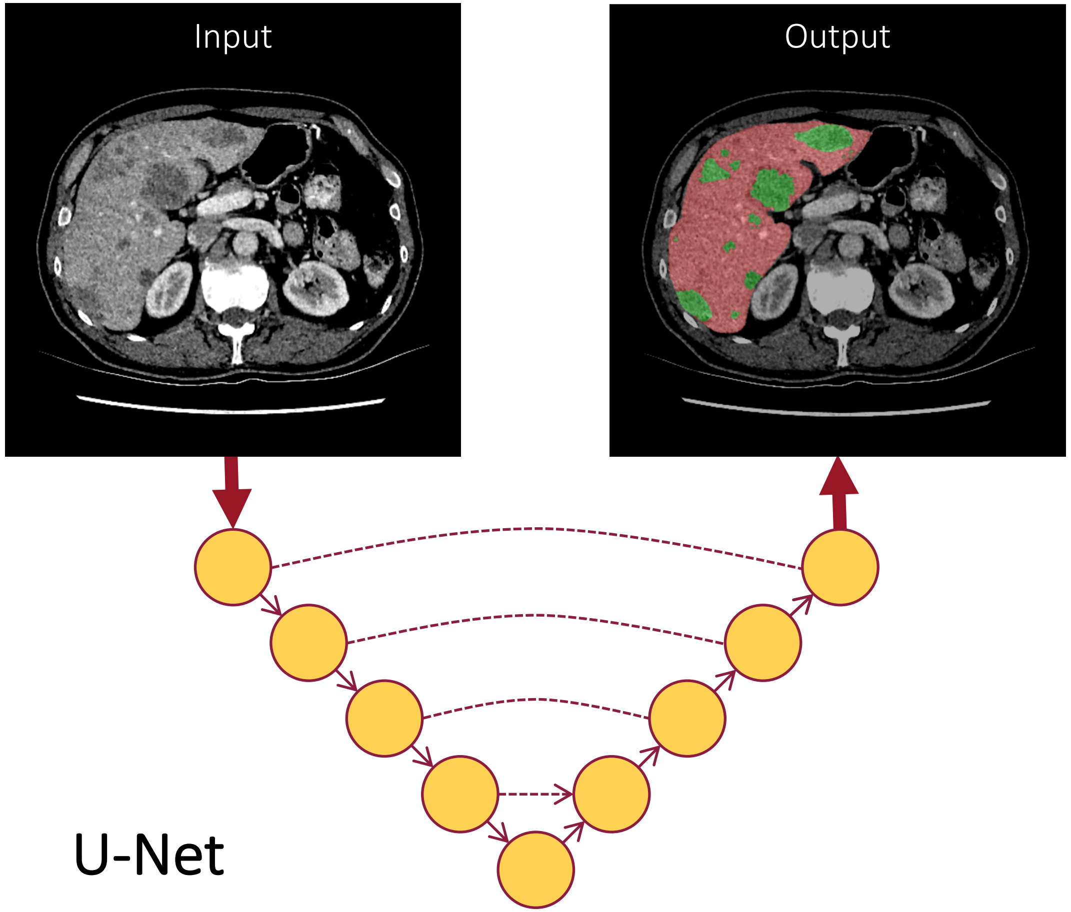


Aim #2: Develop advanced architectures with existing annotation

Segmentation: Partition an image into multiple segments to ease the analysis

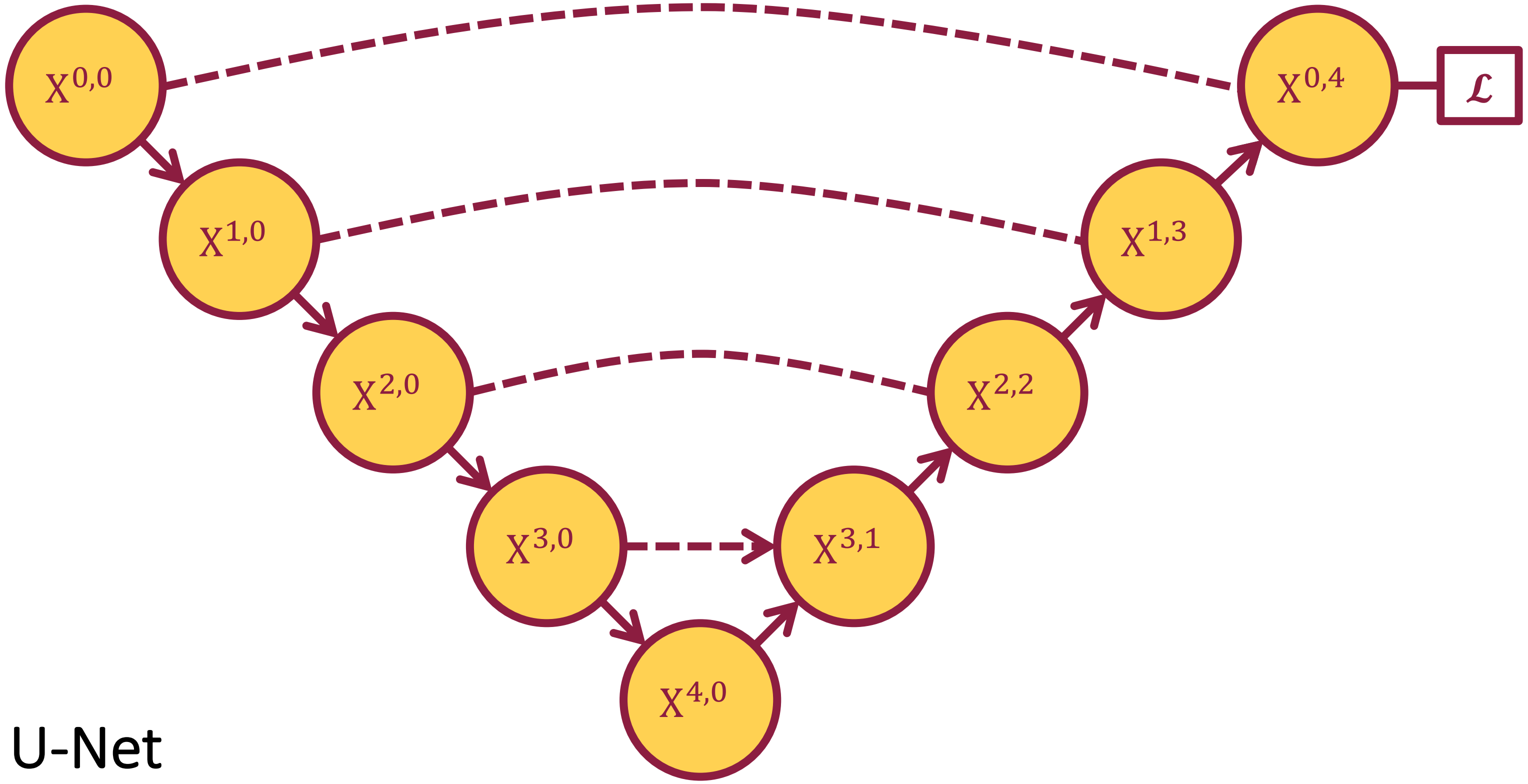


e.g., liver & lesion segmentation



Aim #2: Develop advanced architectures with existing annotation

Hypothesis: Multi-scale feature aggregation leads to powerful models

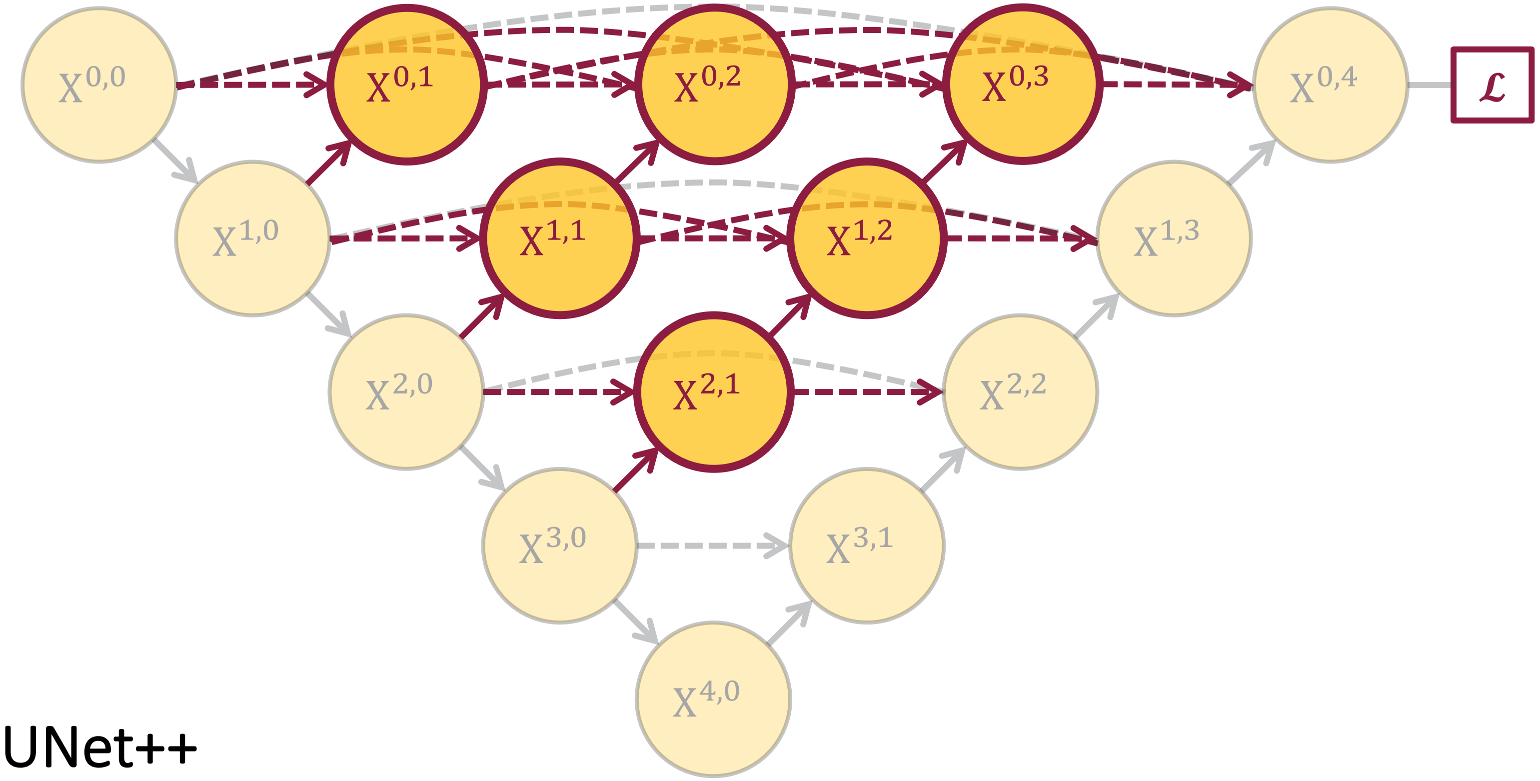


U-Net

1. Ronneberger, Olaf, Philipp Fischer, and Thomas Brox. "U-net: Convolutional networks for biomedical image segmentation." International Conference on Medical image computing and computer-assisted intervention. Springer, Cham, 2015.

Aim #2: Develop advanced architectures with existing annotation

Approach: Redesigned skip connections aggregate multi-scale features

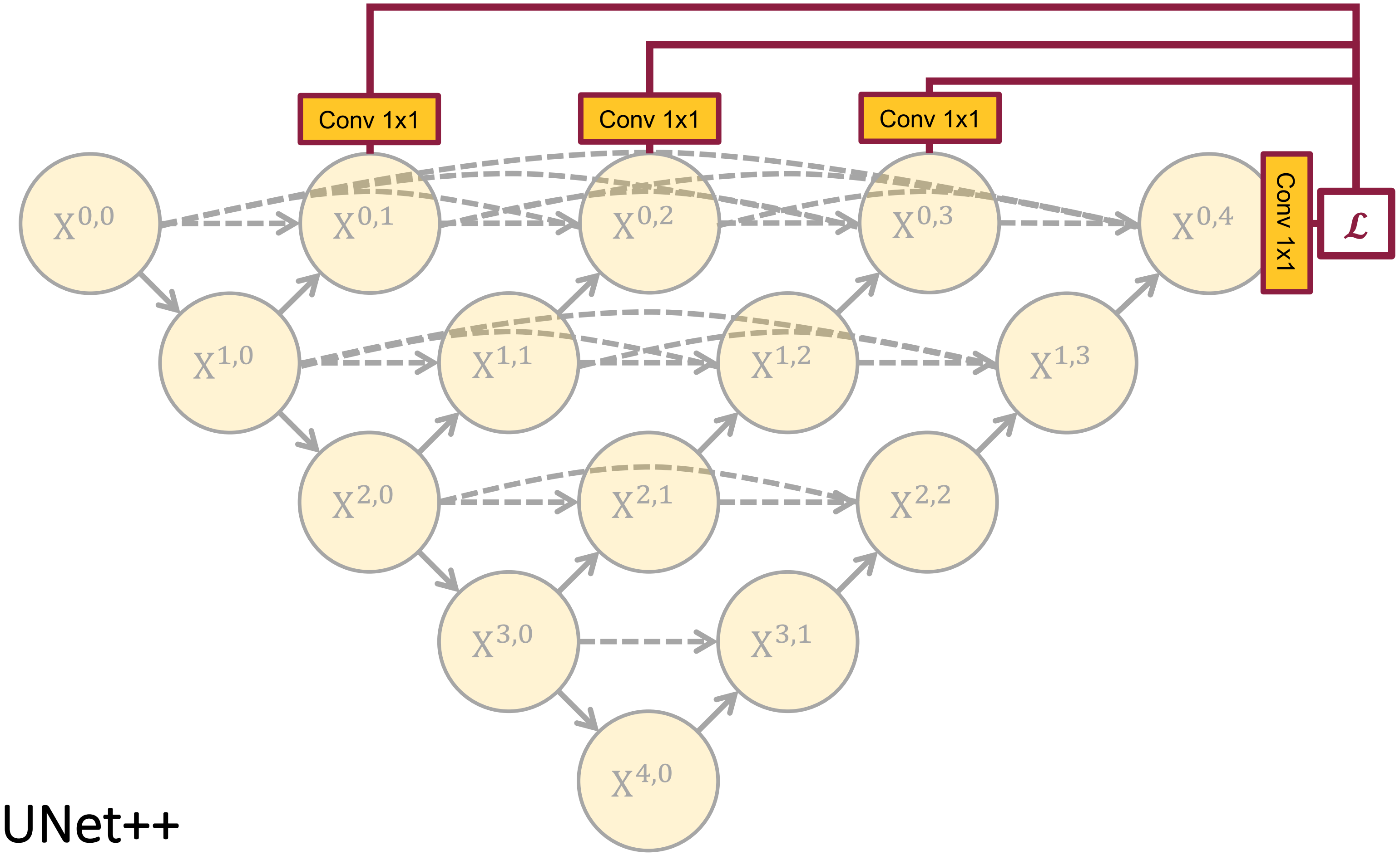


UNet++

1. Zhou, Zongwei, et al. "Unet++: A nested u-net architecture for medical image segmentation." Deep Learning in Medical Image Analysis and Multimodal Learning for Clinical Decision Support. Springer, Cham, 2018. 3-11.

Aim #2: Develop advanced architectures with existing annotation

Approach: Deep supervision enables a higher segmentation accuracy

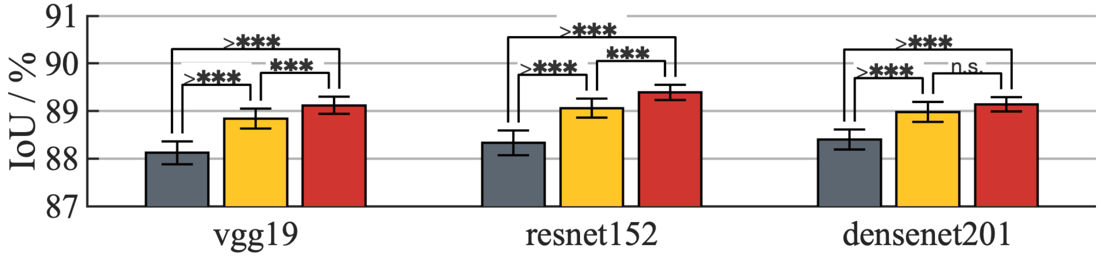


UNet++

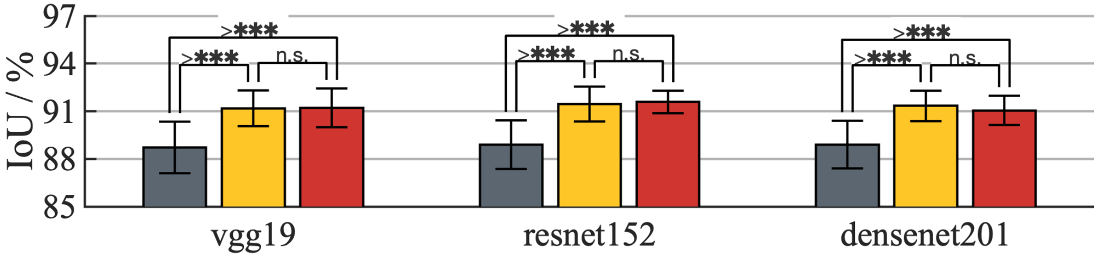
1. Zhou, Zongwei, et al. "Unet++: A nested u-net architecture for medical image segmentation." Deep Learning in Medical Image Analysis and Multimodal Learning for Clinical Decision Support. Springer, Cham, 2018. 3-11.

Aim #2: Develop advanced architectures with existing annotation

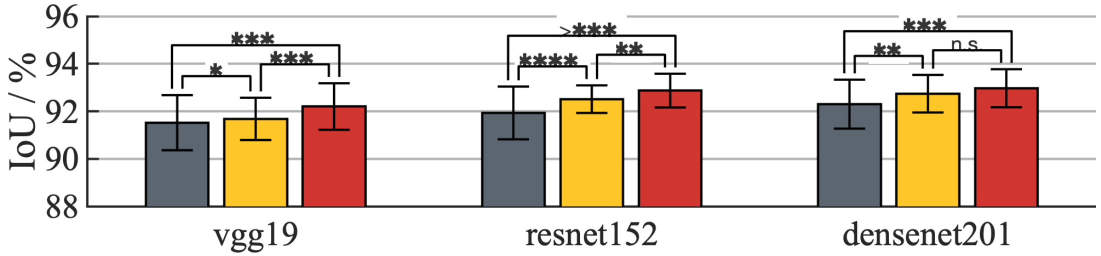
Contribution: UNet++ significantly improves disease/organ segmentation



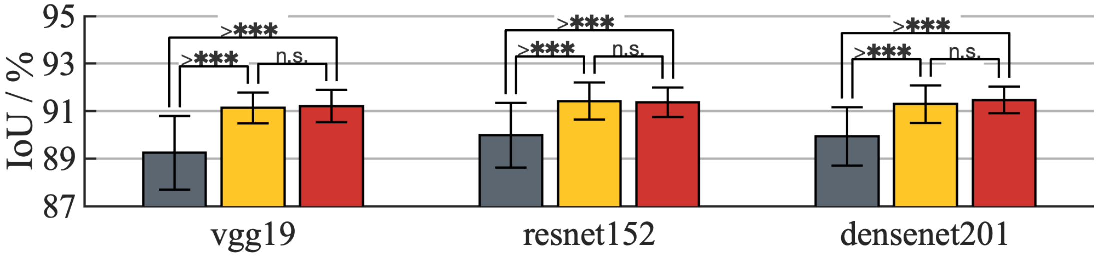
(a) Neuronal structure segmentation



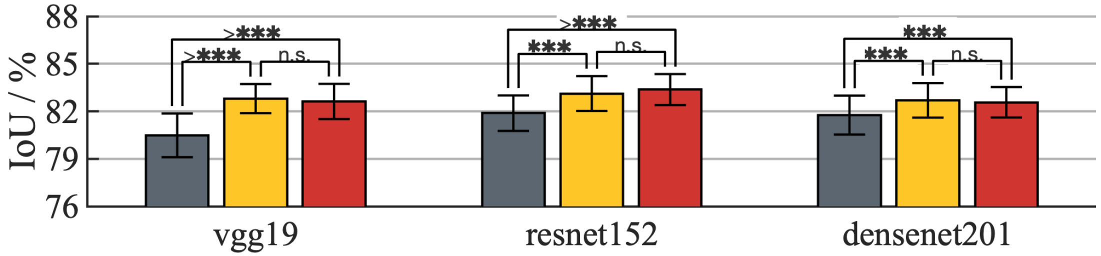
(b) Cell segmentation



(c) Nuclei segmentation



(d) Brain tumor segmentation



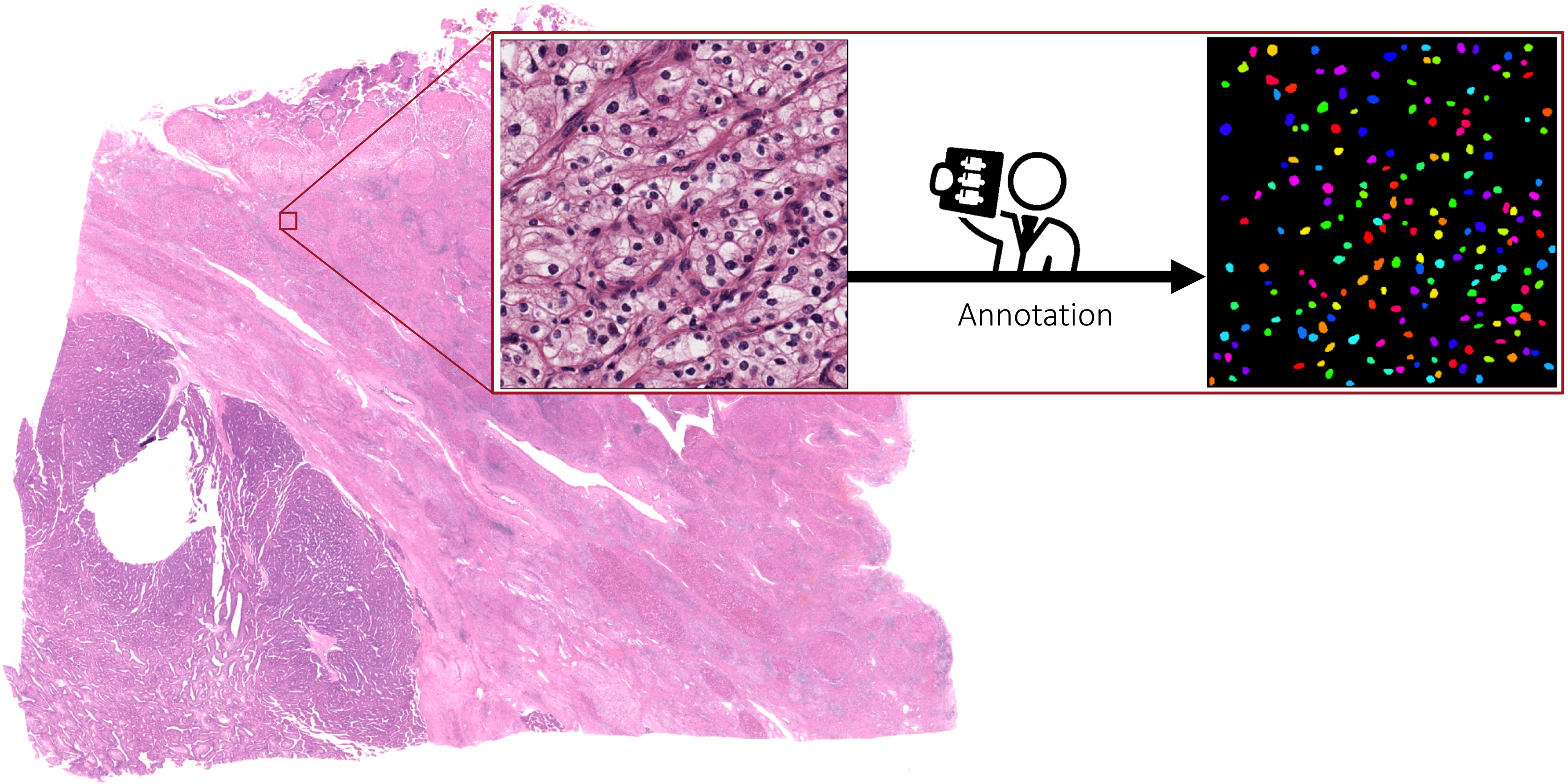
(e) Liver segmentation

⬛ U-Net 🟨 UNet+ 🟥 UNet++

1. Zhou, Zongwei, et al. "Unet++: A nested u-net architecture for medical image segmentation." Deep Learning in Medical Image Analysis and Multimodal Learning for Clinical Decision Support. Springer, Cham, 2018. 3-11.
2. Zhou, Zongwei, et al. "Unet++: Redesigning skip connections to exploit multiscale features in image segmentation." IEEE transactions on medical imaging 39.6 (2019): 1856-1867.

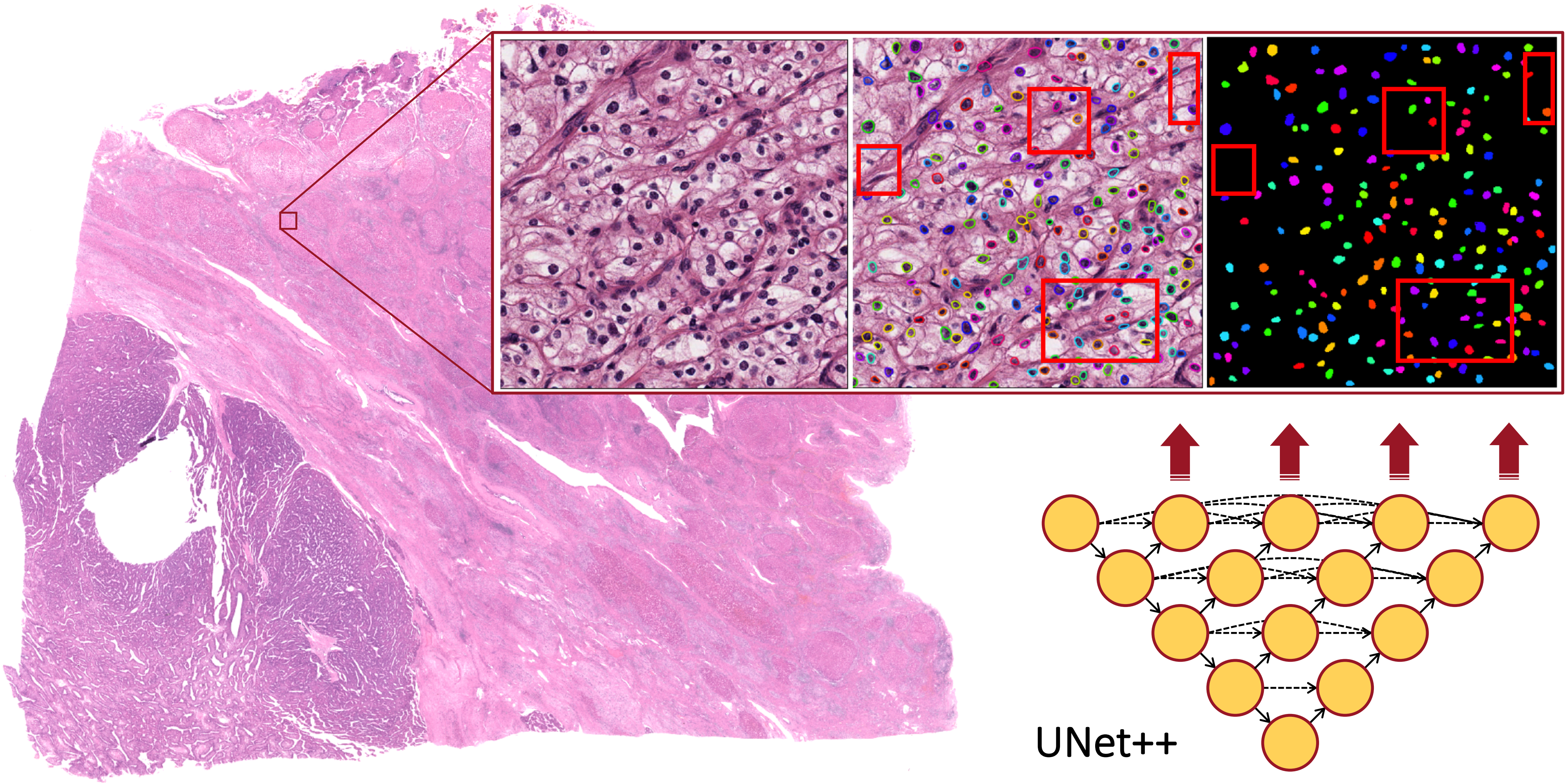
Aim #2: Develop advanced architectures with existing annotation

Proposal: Optimize active learning by leveraging unique architectural design



Aim #2: Develop advanced architectures with existing annotation

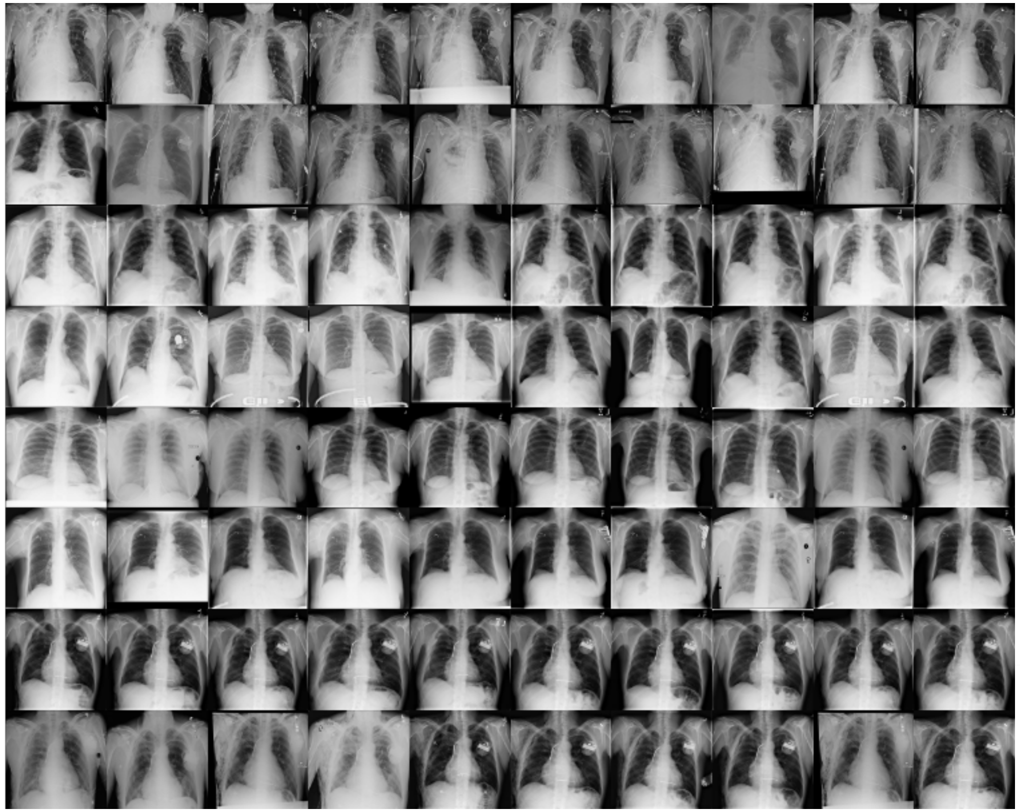
Proposal: Optimize active learning by leveraging unique architectural design



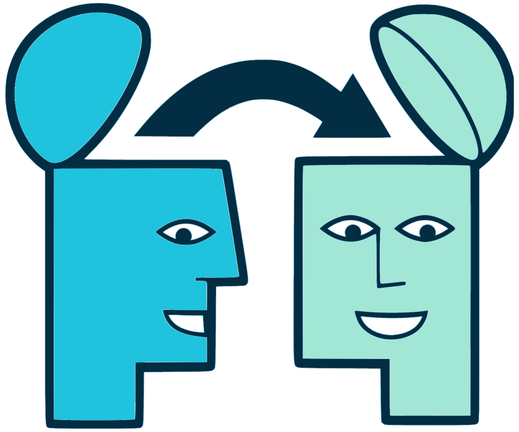
Intertwine the visual representation

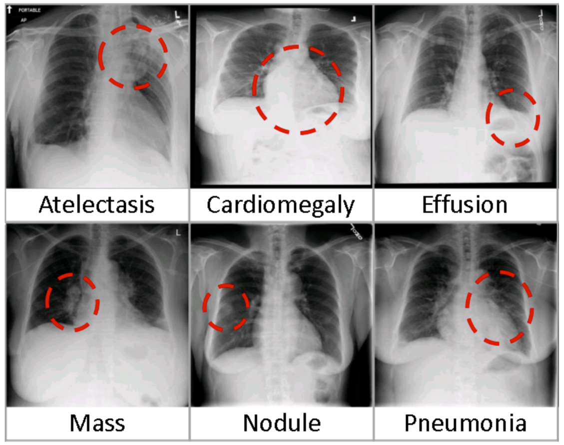
Aim #3: Extract generic knowledge directly from unannotated images

Problem: Utilize 1,000,000 images without systematic annotation



$ 1,000,000 annotation cost ☹



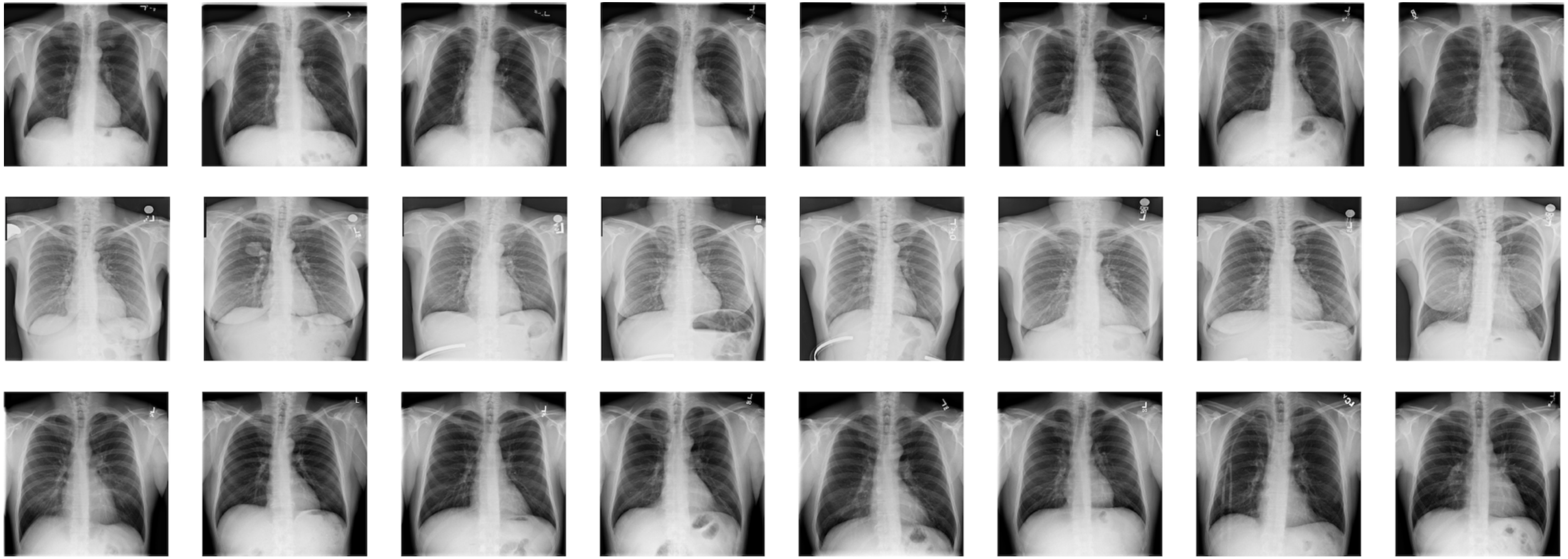


$ 100 annotation budget ☺

Introduction
Objective
Aim #1
Aim #2
Aim #3
Summary

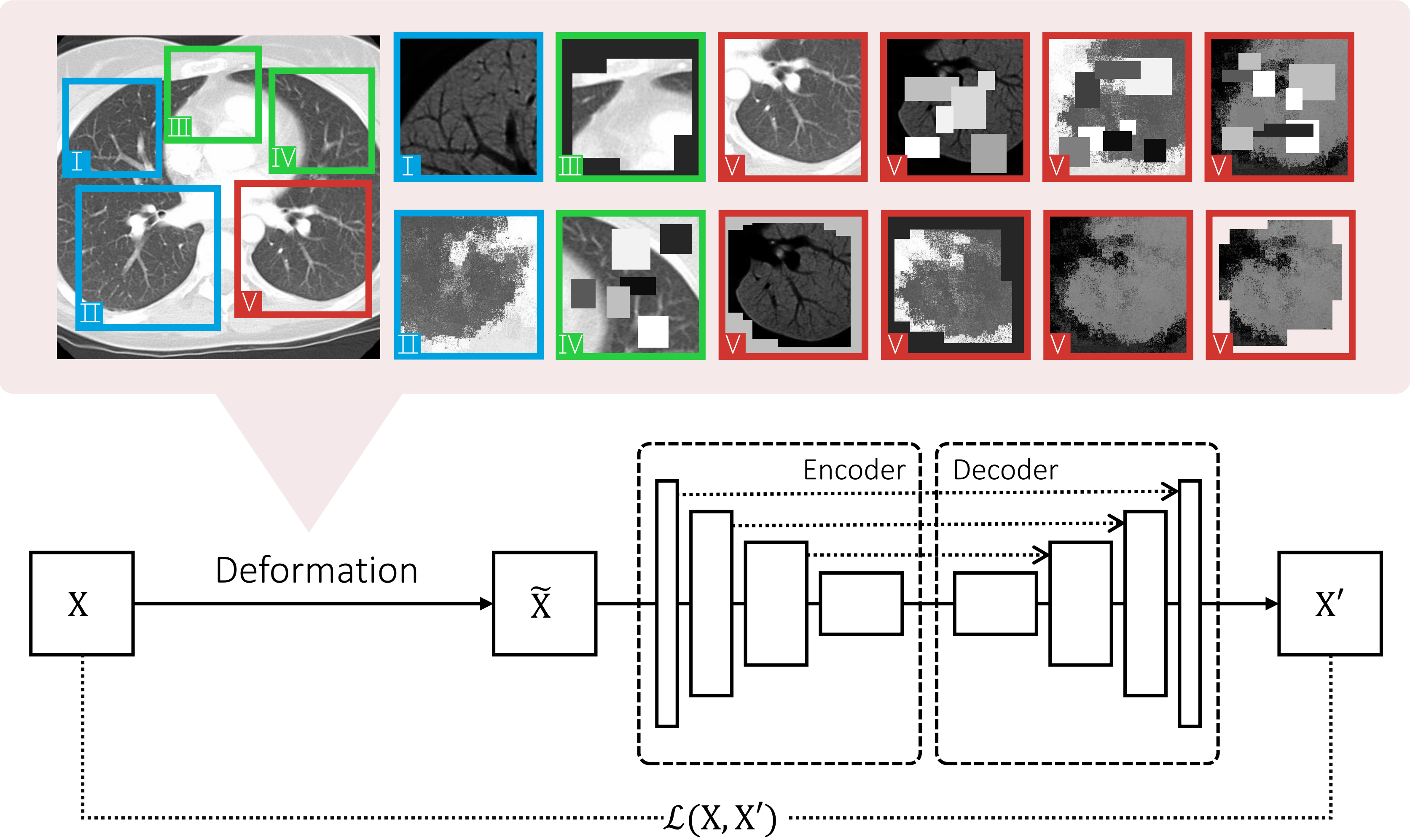
Aim #3: Extract generic knowledge directly from unannotated images

Hypothesis: Generic models can be built upon consistent, recurrent anatomy



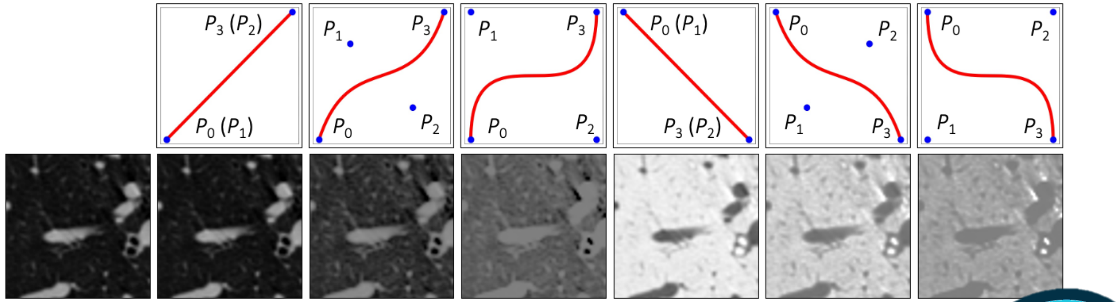
Aim #3: Extract generic knowledge directly from unannotated images

Approach: Image restoration task helps model learn image representation

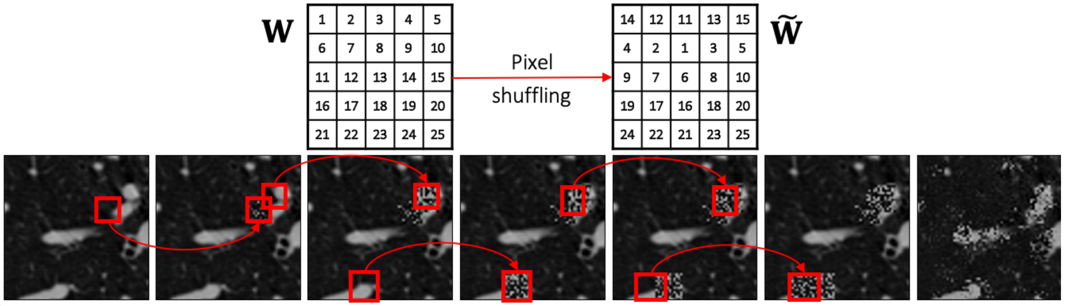


Aim #3: Extract generic knowledge directly from unannotated images

Approach: Learning from multiple perspectives leads to robust models



1. Learning organ appearance via **non-linear transformation**



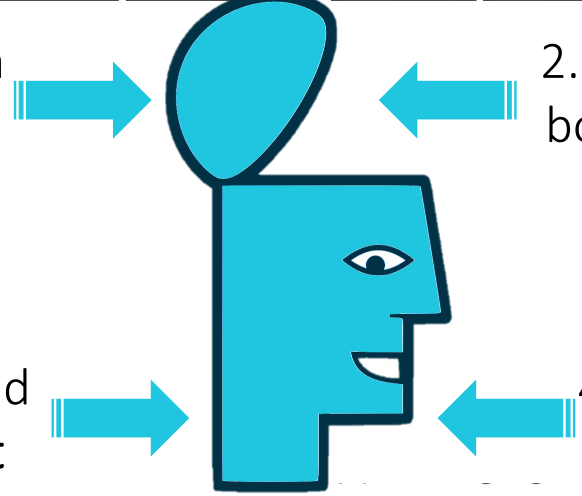
W

1	2	3	4	5
6	7	8	9	10
11	12	13	14	15
16	17	18	19	20
21	22	23	24	25

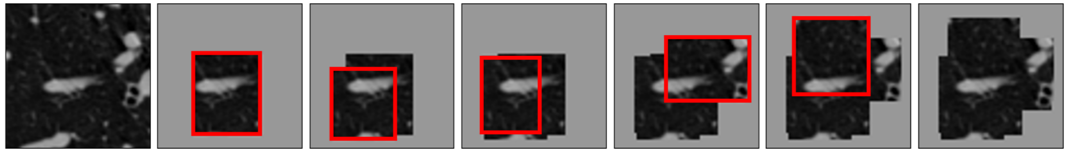
W̃

14	12	11	13	15
4	2	1	3	5
9	7	6	8	10
19	17	16	18	20
24	22	21	23	25

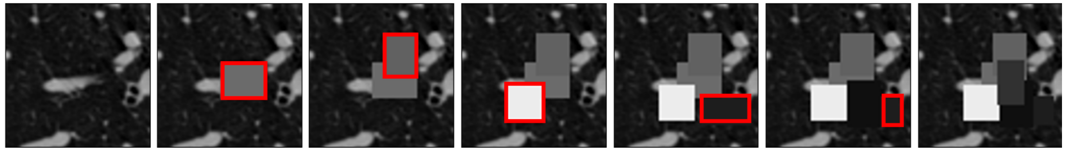
2. Learning organ texture and local boundaries via **local pixel shuffling**



3. Learning organ spatial layout and global geometry via **outer-cutout**

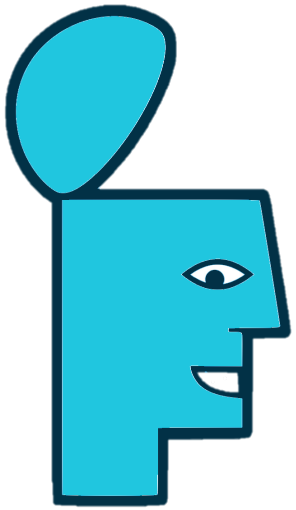


4. Learning local continuities of organs via **inner-cutout**

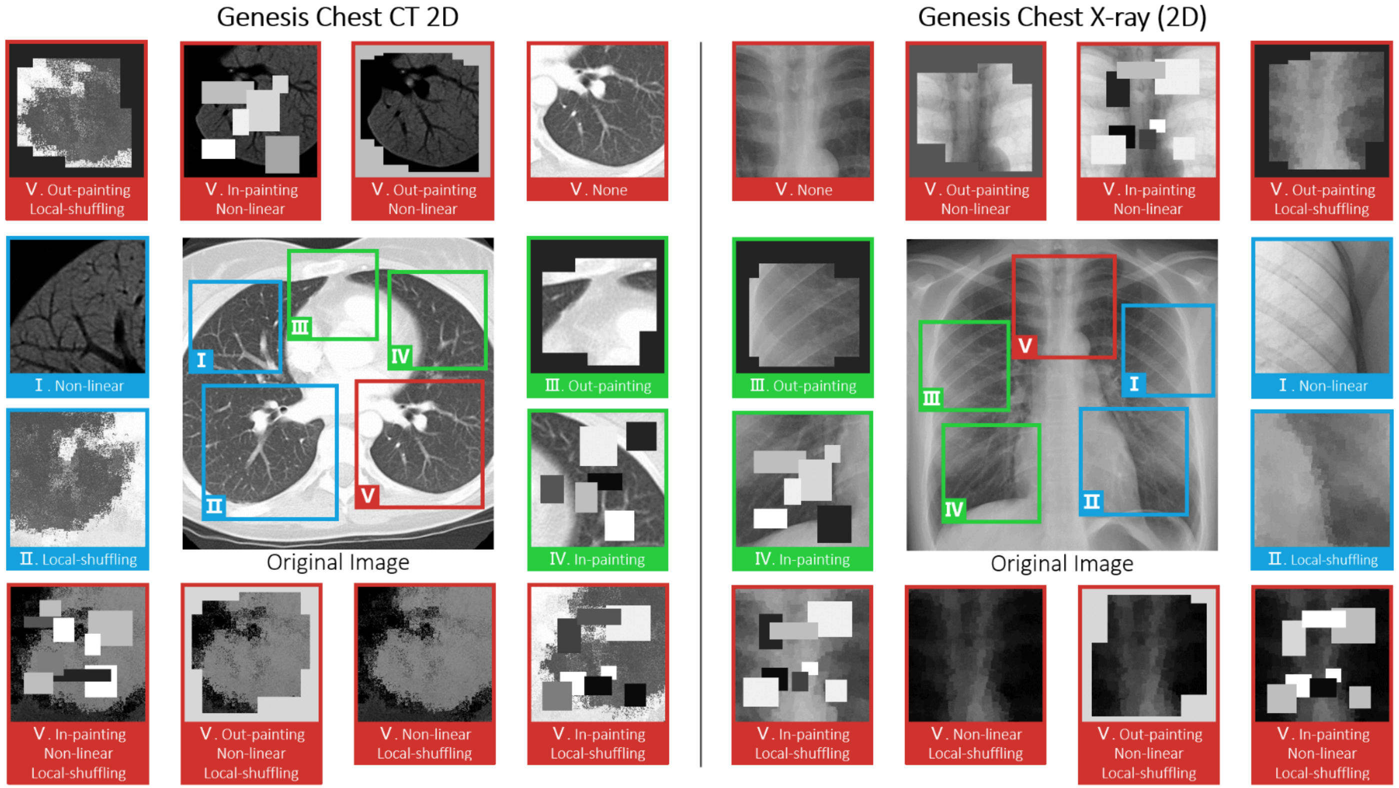


Aim #3: Extract generic knowledge directly from unannotated images

Contribution: Build generic pre-trained 3D models, named "Models Genesis"



Models Genesis



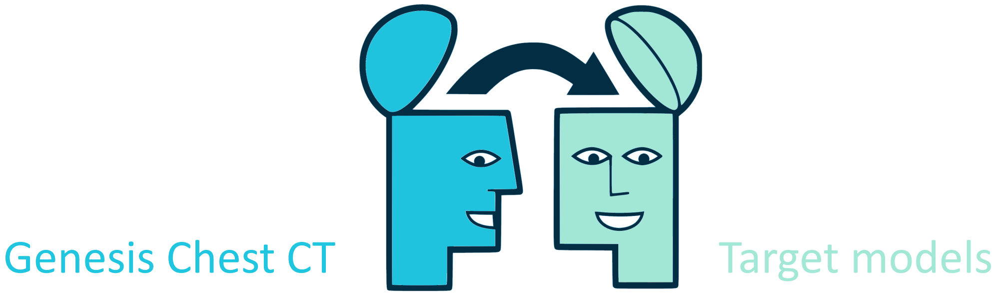
1. Zhou, Zongwei, et al. "Models genesis: Generic autodidactic models for 3d medical image analysis." International Conference on Medical Image Computing and Computer-Assisted Intervention. Springer, Cham, 2019.
2. Zhou, Zongwei, et al. "Models Genesis." arXiv preprint arXiv:2004.07882 (2020).

Aim #3: Extract generic knowledge directly from unannotated images

Contribution: Models Genesis exceed publicly available pre-trained 3D models

Approach	Target tasks				
	NCC^1 (%)	NCS^2 (%)	ECC^3 (%)	LCS^4 (%)	BMS^5 (%)
Random with Uniform Init	94.74±1.97	75.48±0.43	80.36±3.58	78.68±4.23	60.79±1.60
Random with Xavier Init (Glorot and Bengio, 2010)	94.25±5.07	74.05±1.97	79.99±8.06	77.82±3.87	58.52±2.61
Random with MSRA Init (He et al., 2015)	96.03±1.82	76.44±0.45	78.24±3.60	79.76±5.43	63.00±1.73
I3D (Carreira and Zisserman, 2017)	98.26±0.27	71.58±0.55	80.55±1.11	70.65±4.26	67.83±0.75
NiftyNet (Gibson et al., 2018b)	94.14±4.57	52.98±2.05	77.33±8.05	83.23±1.05	60.78±1.60
MedicalNet (Chen et al., 2019b)	95.80±0.49	75.68±0.32	86.43±1.44	**85.52±0.58**†	66.09±1.35
De-noising (revised in 3D) (Vincent et al., 2010)	95.92±1.83	73.99±0.62	85.14±3.02	84.36±0.96	57.83±1.57
Patch shuffling (revised in 3D) (Chen et al., 2019a)	91.93±2.32	75.74±0.51	82.15±3.30	82.82±2.35	52.95±6.92
Rubik's Cube (revised) (Zhuang et al., 2019)	96.24±1.27	72.87±0.16	80.49±4.64	75.59±0.20	62.75±1.93
Genesis Chest CT (ours)	**98.34±0.44**	**77.62±0.64**	**87.20±2.87**	85.10±2.15	**67.96±1.29**

^{1}NCC	Lung nodule false positive reduction in CT images
^{2}NCS	Lung nodule segmentation in CT images
^{3}ECC	Pulmonary embolism false positive reduction in CT images
^{4}LCS	Liver segmentation in CT images
^{5}BMS	Brain tumor segmentation in MR images

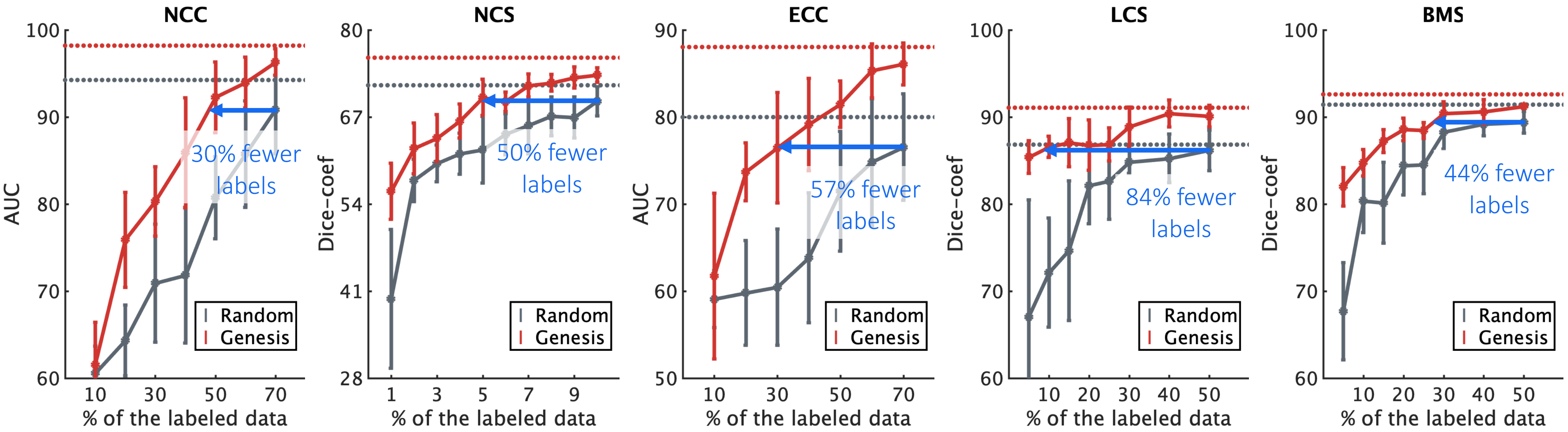


1. Zhou, Zongwei, et al. "Models genesis: Generic autodidactic models for 3d medical image analysis." International Conference on Medical Image Computing and Computer-Assisted Intervention. Springer, Cham, 2019.
2. Zhou, Zongwei, et al. "Models Genesis." arXiv preprint arXiv:2004.07882 (2020).

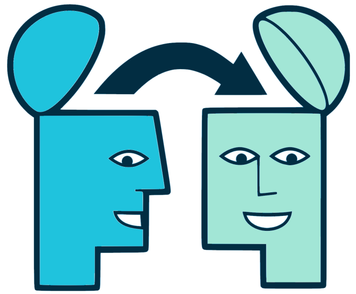
Introduction
Objective
Aim #1
Aim #2
Aim #3
Summary

Aim #3: Extract generic knowledge directly from unannotated images

Contribution: Models Genesis reduce annotation efforts by at least 30%



[1]NCC	Lung nodule false positive reduction in CT images
[2]NCS	Lung nodule segmentation in CT images
[3]ECC	Pulmonary embolism false positive reduction in CT images
[4]LCS	Liver segmentation in CT images
[5]BMS	Brain tumor segmentation in MR images

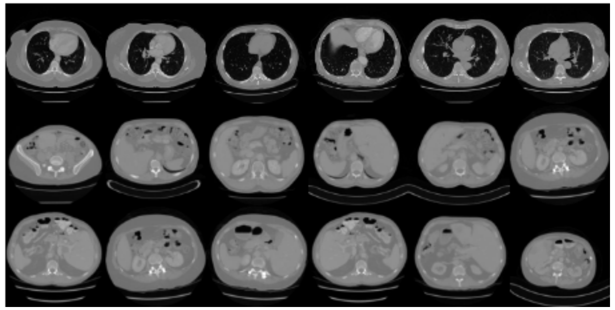


1. Zhou, Zongwei, et al. "Models genesis: Generic autodidactic models for 3d medical image analysis." International Conference on Medical Image Computing and Computer-Assisted Intervention. Springer, Cham, 2019.
2. Zhou, Zongwei, et al. "Models Genesis." arXiv preprint arXiv:2004.07882 (2020).

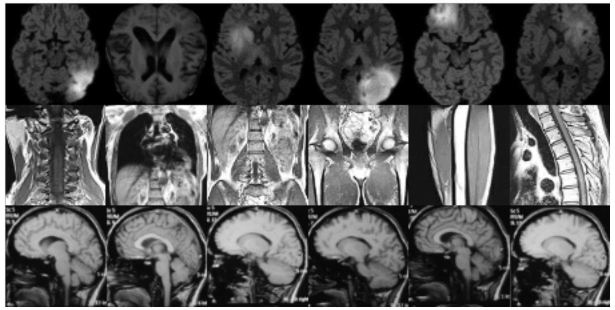
Aim #3: Extract generic knowledge directly from unannotated images

Proposal: Extend to modality-oriented and organ-oriented models

Genesis X-ray



Genesis CT

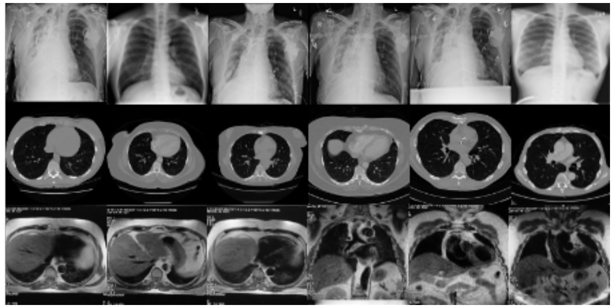


Genesis MRI

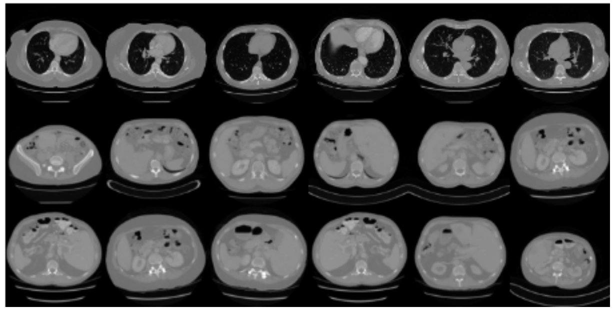
Aim #3: Extract generic knowledge directly from unannotated images

Proposal: Extend to modality-oriented and organ-oriented models

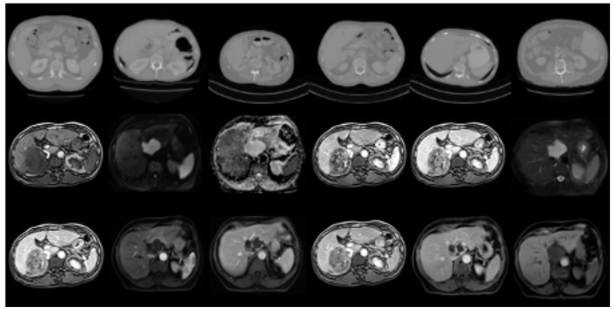
Genesis X-ray



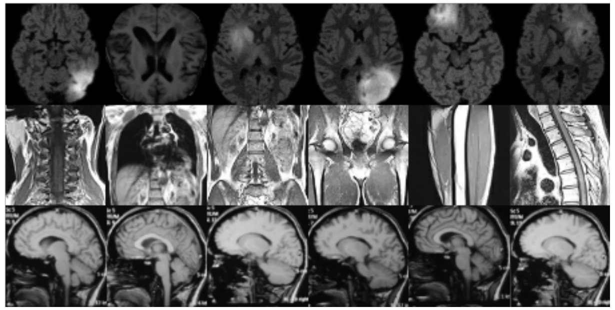
Genesis Lung



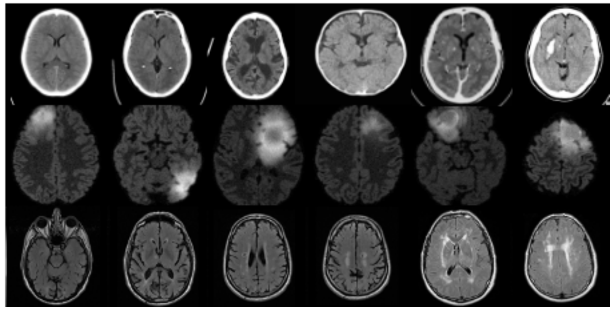
Genesis CT



Genesis Liver



Genesis MRI



Genesis Brain

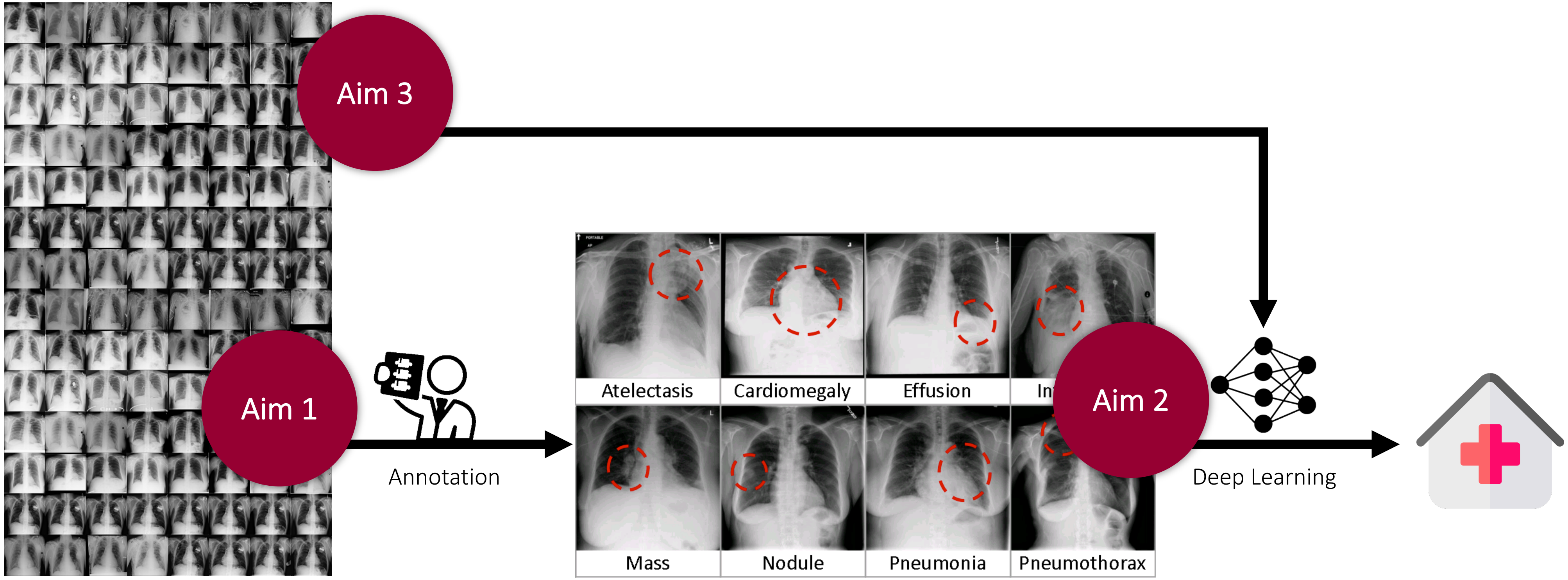
Holy Grail: effective across diseases, organs, and modalities.

Research goal: Exploit novel methods to minimize the manual labeling efforts for a rapid, precise computer-aided diagnosis system

Aim #1: Select necessary patients/samples for annotation

Aim #2: Develop advanced architectures with existing annotation

Aim #3: Extract generic knowledge directly from unannotated images



Acknowledgements

- Jianming Liang, Ph.D.
- Edward H. Shortliffe, M.D., Ph.D.
- Murthy Devarakonda, Ph.D.
- Michael B. Gotway, M.D.

Funding for research program supported by

- NIH R01 (R01HL128785)
- ASU-Mayo Grant
- Mayo Innovation Grant

Cost-Effective Deep Learning in Medical Image Analysis

Zongwei Zhou

Ph.D. Candidate, Biomedical Informatics
College of Health Solutions, Arizona State University
P: 1-(480)738-2575 | E: zongweiz@asu.edu

Sep 4, 2020 @ BMI Seminar