BIOMEDICAL IMAGING: REINVENTED WITH AI

HORST HAHN, FRAUNHOFER MEVIS & JACOBS UNIVERSITY, BREMEN
8 OCTOBER 2019, 4TH FRAUNHOFER SYMPOSIUM, IMPERIAL HOTEL TOKYO, JAPAN

Fraunhofer MEVIS
„Werkstatt der Digitalen Medizin“
Building completion 2020

OUTLINE

WORLD MEDICAL INNOVATION FORUM, BOSTON

DEEP LEARNING AS DISRUPTIVE INNOVATION

PATHS TOWARDS THE NEW MEDICINE

NEW HUMAN-COMPUTER TEAMS

2016 Disruptive Dozen | CANCER

Below is our Disruptive Dozen for 2016, guided through the nomination and selection-ranking process by our committee, each earning scores along the way.

We present them to you in order of their rank after the final voting was completed.

The medical professionals listed below, experts in oncology, were each paired with a specific disruptive innovation.

At the Forum presentation, each expert explained its potential impact on cancer in the decade ahead.

1 | **Cellular Immunotherapy**
Marcela Maus, MD, PhD
Director of Cellular Immunotherapy, MGH, Assistant Professor, Harvard Medical School

2 | **Immune Modulators (Checkpoint Inhibitors) and Vaccines**
Antonio Chiocca, MD, PhD
Chairman, Neurosurgery, BWH, Professor of Surgery, Harvard Medical School

3 | **Liquid Biopsy for Oncology**
Shyamala Maheswaran, PhD
Associate in Molecular Biology, Surgery, MGH, Associate Professor, Surgery, Harvard Medical School

4 | **Machine Learning and Computational Biology to Transform Cancer Care**
James Brink, MD
Radiologist-in-Chief, MGH, Juan M. Taveras Professor of Radiology, Harvard Medical School

5 | **Epigenetics and Cancer Treatment**
Johnathan Whetstine, PhD
Tepper Family MGH Research Scholar, Associate Professor of Medicine, Harvard Medical School

6 | **The Microbiome and Cancer**
Lynn Bry, MD, PhD
Associate Professor of Pathology, Director, Massachusetts Host-Microbiome Center and Crimson Core, Dept. Pathology, BWH

7 | **CRISPR: Genome Editing and Cancer**
Keith Joung, MD, PhD
Associate Pathologist, Associate Chief for Research, The Jim and Ann Orr MGH Research Scholar, MGH, Professor of Pathology, Harvard Medical School

8 | **Single-Cell Molecular Profiling**
Carl Novina, MD, PhD
Cancer Immunology, DFCI, Associate Professor, Microbiology and Immunobiology, Harvard Medical School

9 | **mHealth and Cancer Care**
Ann Partridge, MD
Director, Adult Survivorship Program, Program for Young Women with Breast Cancer, DFCI, Associate Professor of Medicine, Harvard Medical School

10 | **Patient-Specific Research to Enable Efficient Drug Development**
Jeffrey Engelman, MD, PhD
Director, Center for Thoracic Cancers, MGH Cancer Center, Associate Professor of Medicine, Harvard Medical School

11 | **Redefining Value in Cancer Care**
Tim Ferris, MD
Senior Vice President of Population Health Management, PHS

12 | **Nanotechnology and Cancer Treatment**
Omid Farokhzad, MD
Physician–scientist, Anesthesiology, BWH
Associate Professor,
Harvard Medical School

WORLD MEDICAL
INNOVATION
FORUM

Machine Learning and Computational Biology to Transform Cancer Care

The accelerating field of precision medicine includes all of those diagnostics and treatments targeted to the needs of individual patients on the basis of their genetic, biomarker or physical characteristics that distinguish one patient from another with similar clinical presentations.

In recent years, great progress has been made in recording an individual's state of health, right down to the molecular level of gene activity. However, the ultimate goal of using this information for precision medicine has remained largely unfulfilled when it comes to cancer care.

With all of the reams of data available from a patient's full genome sequencing, the thousands of pages of critically important background information from medical journals and with the doubling of overall medical information every five years, most cancer researchers and clinicians can't keep up with this avalanche of information and derive maximum value from it. Unfortunately, it's the patient with cancer who ultimately misses out on crucial information that may be pertinent to their care and, many times, has to then settle for a one-size-fits-all cancer treatment and hope for the best.

This is where computational biology, which involves the development and using of tools to analyze and model biological data and systems, along with machine learning, which is the ability of computers to learn without being explicitly programmed, can revolutionize personalized medicine and make cancer diagnoses more accurate.

To understand the cause of cancer and to develop more effective methods of prevention, detection and treatment, clinicians and researchers need access to rich molecular and clinical data sets. The good news is that over the next few years, technology will be revolutionizing the understanding and treatment of diseases, especially cancer. By gathering the latest information from the patient's biology, and combining that with trillions of data points from tens of thousands of other cancer patients, individualized patient-specific cancer treatment options can then be created in days, and sometimes in just a matter of minutes.

Thanks to the latest machine learning algorithms and bioscience advancements, future advances in cancer diagnosis and treatment will be based on DNA mutations, not simply the location of the cancer in a person's body. Using supercomputers, researchers will be able to quickly examine specific genes in pathology samples, note the type and location of the cancer, the grade and size of the tumor, review all of the proteins, metabolites, and lipids, and then compare them all, taking into account demographics, age and gender. After subjecting this to a mathematic algorithm that uses machine learning to compare the many associations and correlations, a more precise and targeted treatment plan can then be developed.

In just a few years, experts envision that these targeted cancer treatment plans will be available within the span of 24 hours. This, of course, will represent the true value of machine learning and computational biology. Human intelligence and medical experience is not being replaced by the gathering and distillation of this statistical data, but rather it's being augmented and enhanced by it, which allows researchers and clinicians to be better at what they do.

Leading U.S. and European research institutes in machine learning and statistical genetics are now working together to develop techniques for robust biomarker discovery and elucidation of the causal mechanisms governing cancer and its progression. Ultimately, this treasure trove of information will be added to data banks and help cancer researchers from across the world mine and glean insights from the gigantic amounts of data in order to truly progress in the fight against cancer.

2017 DISRUPTIVE DOZEN
OVERVIEW

2017 Disruptive Dozen
CARDIOVASCULAR

Below is our Disruptive Dozen for 2017, which was guided through the nomination and selection-ranking process by our committee, each earning scores along the way.

We present these disruptors to you in order of their rank after the final committee voting was completed.

The medical professionals listed below, experts in cardiovascular and cardiometabolic disease, were each paired with a specific disruptive innovation.

At the Forum presentation, each expert explained its potential impact on cardiovascular and cardiometabolic disease in the decade ahead.

1 | **Quantitative Molecular Imaging for Cardiovascular Phenotypes**
Marcelo DiCarli, MD
Brigham and Women's Hospital

2 | **Harnessing Big Data and Deep Learning for Clinical Decision Support**
Christian Ruff, MD
Brigham and Women's Hospital

3 | **Targeting Inflammation in Cardiovascular Disease**
Matthias Nahrendorf, MD, PhD
Massachusetts General Hospital

4 | **Adopting the Orphans of Heart Disease**
David Milan, MD
Massachusetts General Hospital

5 | **Power Play: The Future of Implantable Cardiac Devices**
Christine Albert, MD
Brigham and Women's Hospital

6 | **Understanding Why Exercise Works for Just About Everything**
Gregory Lewis, MD
Massachusetts General Hospital

7 | **Less is More: Minimalist Mitral Valve Repair**
Prem Shekar, MD
Brigham and Women's Hospital

8 | **Finding Cancer Therapies without Cardiotoxicity**
Anju Nohria, MD
Brigham and Women's Hospital

9 | **Expanding the Pool of Organs for Transplant**
Joren Madsen, MD, DPhil
Massachusetts General Hospital

10 | **Breaking the Code: Diagnostic and Therapeutic Potential of RNA**
Saumya Das, MD, PhD
Massachusetts General Hospital

11 | **Nanotechnologies for Cardiac Diagnosis and Treatment**
Natalie Artzi, PhD
Brigham and Women's Hospital

12 | **Aging and Heart Disease: Can We Reverse the Process?**
Jason Roh, MD
Massachusetts General Hospital

WORLD MEDICAL INNOVATION FORUM

2017 DISRUPTIVE DOZEN
NUMBER TWO

2

Harnessing Big Data and Deep Learning for Clinical Decision Support

A single patient can generate considerable meaningful pieces of data based on information gleaned from the 20,000 to 30,000 genes in the human genome. Multiplying so much data by tens of thousands of patients with heart disease and other ailments results in "big data." Big data implies large volume and complexity, such that advanced mathematics and high-performance computers are needed to make sense of it.

With all of the reams of electronic health data now available from patients, the thousands of pages of critically important background information from medical journals, and with the doubling of overall medical information every five years, most heart researchers and clinicians can't keep up with this avalanche of information and derive maximum value from it.

This is where computational biology, which involves the development and use of tools to analyze and model biological data and systems, along with deep learning, which is the ability of computers to learn without being explicitly programmed, can revolutionize personalized medicine and, over the course of the next decade, make heart diagnoses more accurate.

Computational biology offers the promise of finding novel associations in the vast sea of data that underlie important mechanisms of disease and can help uncover potential targets for treatment that would remain hidden to even the most expert investigator.

Doctors can't manage what they can't measure, which is why to better understand the cause of heart disease and develop more effective methods of prevention, detection, and treatment, clinicians and researchers are being provided access to rich molecular and clinical data sets. The use of electronic information is changing rapidly and over the next few years technology will be revolutionizing the understanding and treatment of diseases, especially heart disease. By gathering the latest information from the patient's biology, and combining that with trillions of data points from tens of thousands of other heart patients, individualized patient-specific treatment options can then be created in days, and oftentimes in just a matter of minutes.

Over the next decade, the use of big data from the oceans of electronic medical health records that has been sorted, reviewed, analyzed, and stored will help researchers and doctors better understand the root causes of heart disease.

The potential for big data analytics to improve cardiovascular quality of care and patient outcomes is enormous, thanks especially to two ongoing studies. A $75 million five-year study launched by Boston investigators and a team of international collaborators has begun gathering extensive health information from volunteers whose contributions will potentially provide new insights as to what marks the transition from a healthy heart to one on the road to serious disease.

While much has been learned in the past two decades about coronary disease—lesion formation, inflammation, plaque rupture, thrombosis, and heart attack—very little is known about the initial stages of the disease, where it may initiate in the body, and how it progresses. This novel study promises to provide those answers.

Another heart study, this an ambitious one spearheaded by investigators in San Francisco, is expected to enroll up to one million participants worldwide who will be using smartphones, mobile health apps, and other technology to relay information about their heart health.

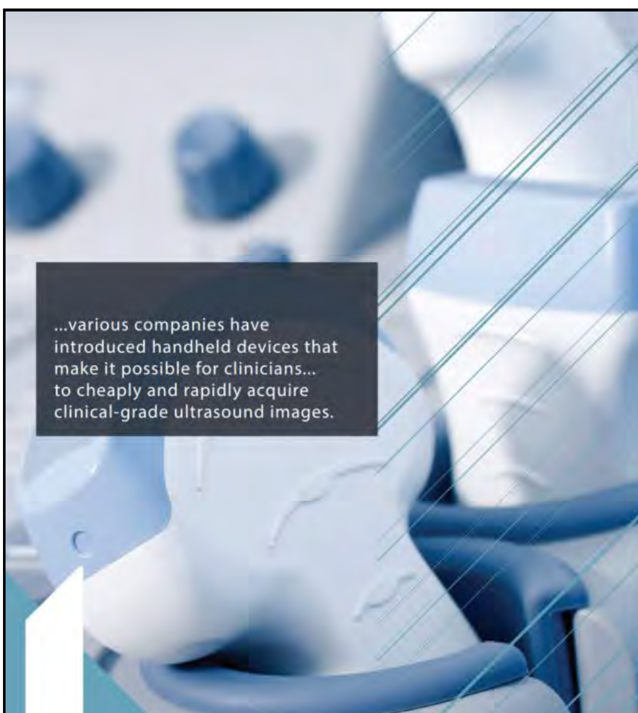
After sorting through this big data and analyzing the wealth of information, the Boston and San Francisco researchers hope to be able to reduce deaths due to heart disease by using the accumulated data to create better ways to predict the occurrence and progression of heart disease.

This is where deep learning will turn this vision into reality by using patient data for improved and robust biomarker discovery, enhanced disease diagnosis, prognosis, and prediction of therapy outcomes. This form of artificial intelligence uses computer algorithms to identify patterns in large data sets, and can continuously improve with additional data.

The use of electronic health information is changing rapidly, and over the next decade it's clear that big data and deep learning will play an ever increasingly important role in the care of the heart, particularly when quality data is available for individual patient.

2

content



1

Reimagining Medical Imaging

Medical imaging technologies including ultrasound and X-ray have been in clinical use for decades. While these methods are widely used — X-ray forms the basis of mammography, which is used to screen millions of women each year for breast cancer — they are imperfect. Now, bolstered by AI-enabled approaches, research teams across the world are working to enhance these fundamental technologies, making them smarter, more sensitive, and more accessible.

Globally, breast cancer is a leading cause of death in women. In the U.S. alone, some 40,000 women die each year from the disease. Mammograms play an important role in early detection. However, mammograms can detect lesions that appear suspicious but are actually not cancerous, causing anxiety and leading to overtreatment and unnecessary costs.

Now, researchers are using AI-based approaches to increase the power of mammography, transforming it from a one-size-fits-all method to a more targeted tool for assessing breast cancer risk. For example, a team in Massachusetts is leveraging machine learning in multiple ways to improve breast cancer screening. The researchers developed an AI-based method, now in clinical use at a large hospital for just over a year, which can automatically determine breast density using mammograms. Dense breast tissue obscures tumors on mammography and can also independently raise a woman's risk of developing breast cancer. Moreover, radiologists' assessments of breast density are subjective and can vary widely from one reader to another.

The new AI tool was used to screen over 10,000 patients in routine clinical practice; its density assessments were accepted by experienced radiologists in 94% of cases. Based on these results, the researchers believe their system could help standardize and automate breast density measurements. Now, the team is enhancing their AI-based system, incorporating both clinical and breast imaging data, to give individualized assessments of breast cancer risk that can automatically flag patients for follow-up tests, such as ultrasound or MRI. Over the next few years, they hope to make mammograms more like Pap smears — which are now read by automated systems in many parts of the world to screen women for cervical cancer.

AI is also making a big splash in ultrasound. In the last few years, various companies have introduced handheld devices that make it possible for clinicians — and, in some cases, patients themselves — to cheaply and rapidly acquire clinical-grade ultrasound images. Those innovations are now spurring new ways of harnessing ultrasound images. For example, a Massachusetts-based team is applying AI to enable a rapid, ultrasound-based method to automatically localize large veins, like the femoral and jugular veins. These blood vessels form the primary portals for rapid infusion of fluid during emergency resuscitation — a life-saving procedure that often must be performed in stressful, sometimes chaotic circumstances. In these situations, time is of the essence with little room for errors. The team's goal is to package their AI-powered software into a handheld device that will enable first responders to readily identify large veins and guide them on proper needle placement.

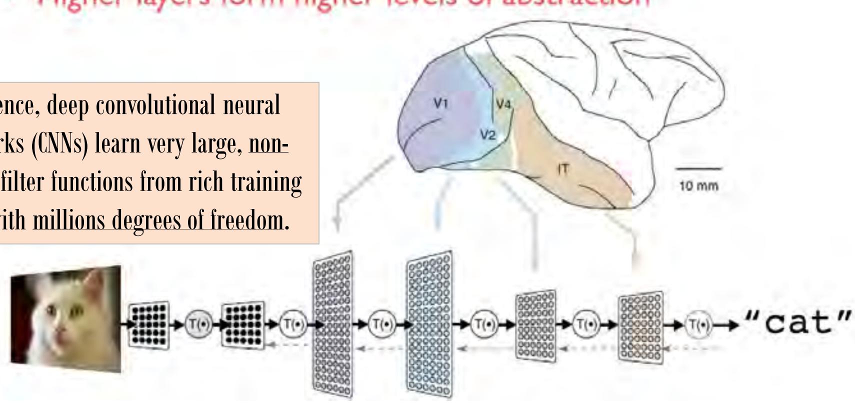
Researchers are also developing ultrasound-based methods to improve the detection and diagnosis of liver disease. Nonalcoholic fatty liver disease (NAFLD) is increasingly common across the world, especially in Western countries. In the United States, it is a major cause of chronic liver disease, affecting roughly 80 to 100 million people. Unfortunately, NAFLD often goes unnoticed in its earliest stages; if not adequately diagnosed and treated, it can lead to liver cirrhosis, cancer, and even death.

As its name suggests, NAFLD stems from the abnormal accumulation of fat in the liver for reasons unrelated to alcohol consumption; it is more prevalent in people who are obese or have type 2 diabetes. The standard approach for detecting fat in the liver is a biopsy. Although noninvasive methods exist (mainly MRI), they are costly and therefore impractical for screening millions of people.

What is Deep Learning?

- Loosely inspired by what (little) we know about the biological brain.
- Higher layers form higher levels of abstraction

In essence, deep convolutional neural networks (CNNs) learn very large, non-linear filter functions from rich training data with millions degrees of freedom.



DEEP LEARNING (DL):
Deep neural networks exploit the property that many natural signals are compositional hierarchies, in which higher-level features are obtained by composing lower-level ones

Jeff Dean, Google

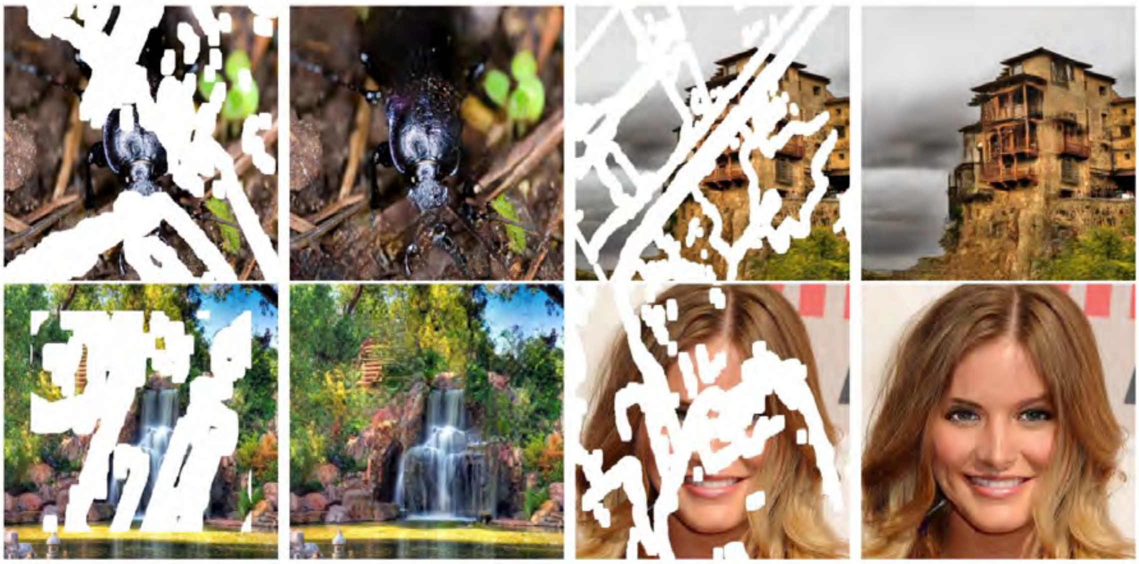
Medical Knowledge Through Research

ami automation in medical imaging Radboudumc Fraunhofer MEVIS

Image Inpainting for Irregular Holes Using Partial Convolutions

Guilin Liu Fitsum A. Reda Kevin J. Shih Ting-Chun Wang Andrew Tao Bryan Catanzaro
NVIDIA Corporation

arXiv:1804.07723v2 [cs.CV] 15 Dec 2018



Deep learning for undersampled MRI reconstruction

Chang Min Hyun*, Hwa Pyung Kim*, Sung Min Lee*, Sungchul Lee† and Jin Keun Seo*
* Department of Computational Science and Engineering, Yonsei University, Seoul, 03722, South Korea
† Department of Mathematics, Yonsei University, Seoul, 03722, South Korea

arXiv:1709.02576v2 [stat.ML] 11 Sep 2017

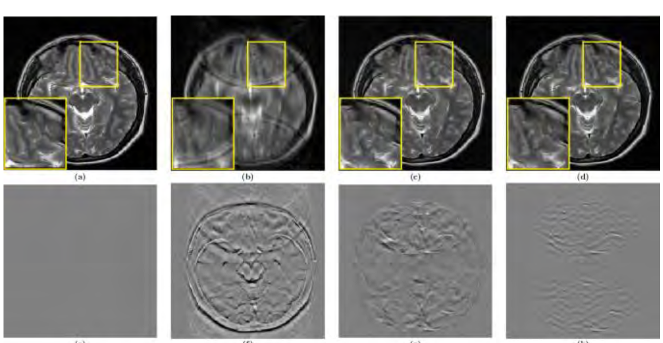
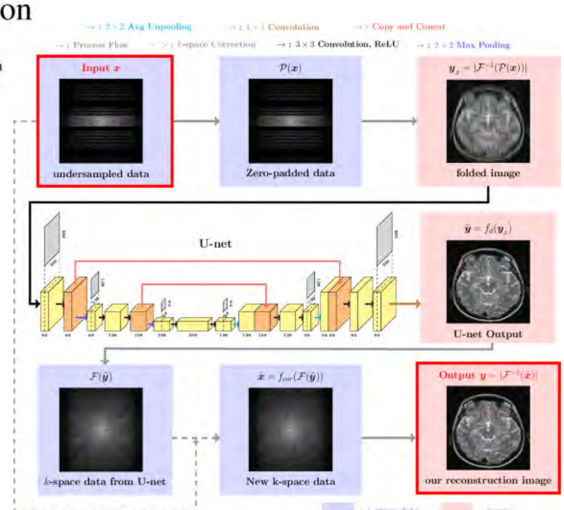


TABLE I
QUANTITATIVE EVALUATION RESULTS IN TERMS OF MSE AND SSIM USING THE TEST SET OF 400 IMAGES.

	Aliased	U-net	Proposed
MSE	0.0043 ± 0.0016	0.0012 ± 0.0006	0.0004 ± 0.0002
SSIM	0.6516 ± 0.0815	0.8782 ± 0.0411	0.9039 ± 0.0431



Reduction of the acquired data to 29% (speed x3.4)

Deep learning acts as intelligent interpolator
learning dictionaries of plausible image patches.

DL creates **totally new portrait photos**, starting from existing ones, even mixing them.
(Kerras, Laine, Aila, Mar 2019)
see also: „thispersondoesnotexist“

Example: Precision Medicine for Prostate Care Relies on Imaging at Numerous Stages

Early Detection → Diagnosis & Staging → Therapy → Follow-Up

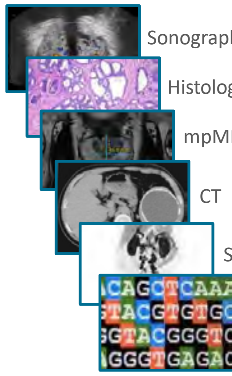
Early Detection

Anamnesis and DRE

PSA

... and imaging

Diagnosis & Staging



Sonography

Histology

mpMRI

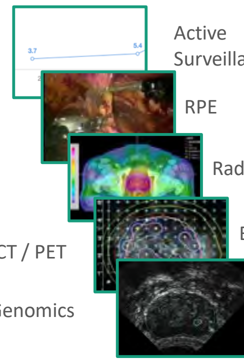
CT

SPECT / PET

Genomics

...

Therapy



Active Surveillance

RPE

Radation

Brachytherapy

HIFU

...

Follow-Up

PSA Control

Detection of Recurrence

... by imaging

Medical Knowledge Through Research

Images Courtesy by Uni Heidelberg, University Nijmegen, MedicalNewsToday, IBA Molecular, AUA

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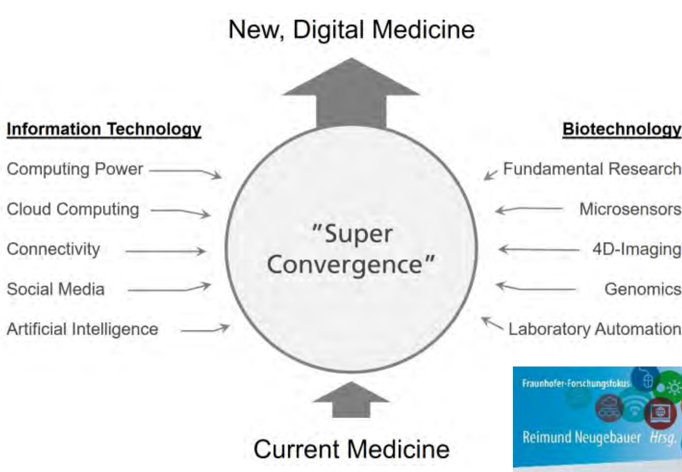
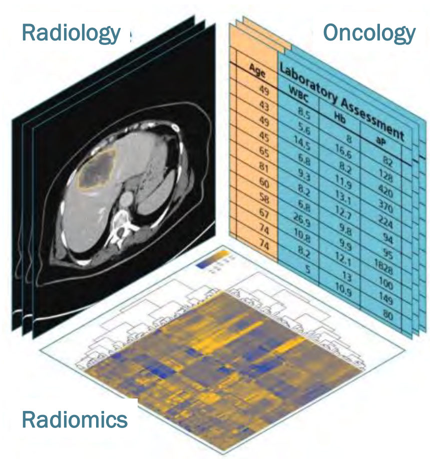
Large Steps Towards the New Medicine





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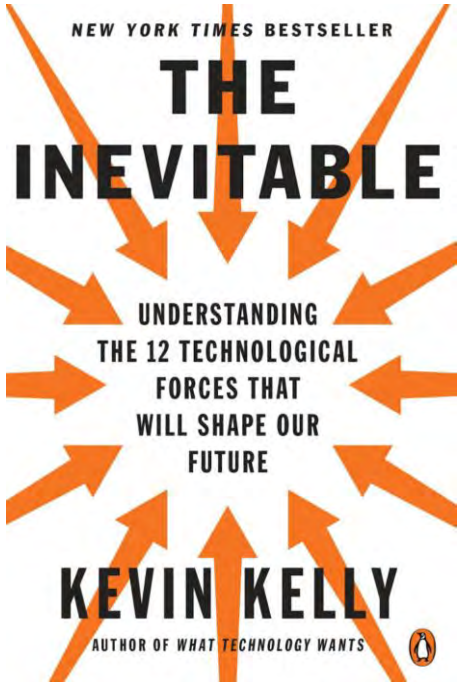

"We are morphing so fast that our ability to invent new things outpaces the rate we can civilize them."

The Inevitable, Kevin Kelly, 2016

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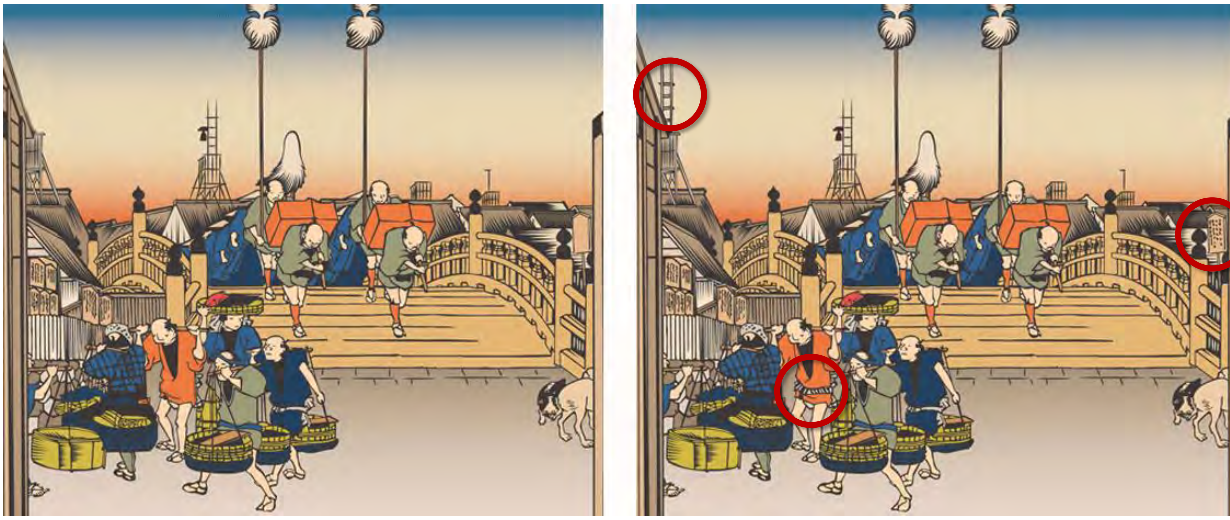
„Screening“ = Find the N relevant differences (N: unknown)

(doctors must find any relevant difference in very complex medical images. For illustration, here a non-medical search task is shown)



Why do we like such search games?
...because we humans are not particularly good at it.
(most people take 1-3 minutes to find the 3 differences.)

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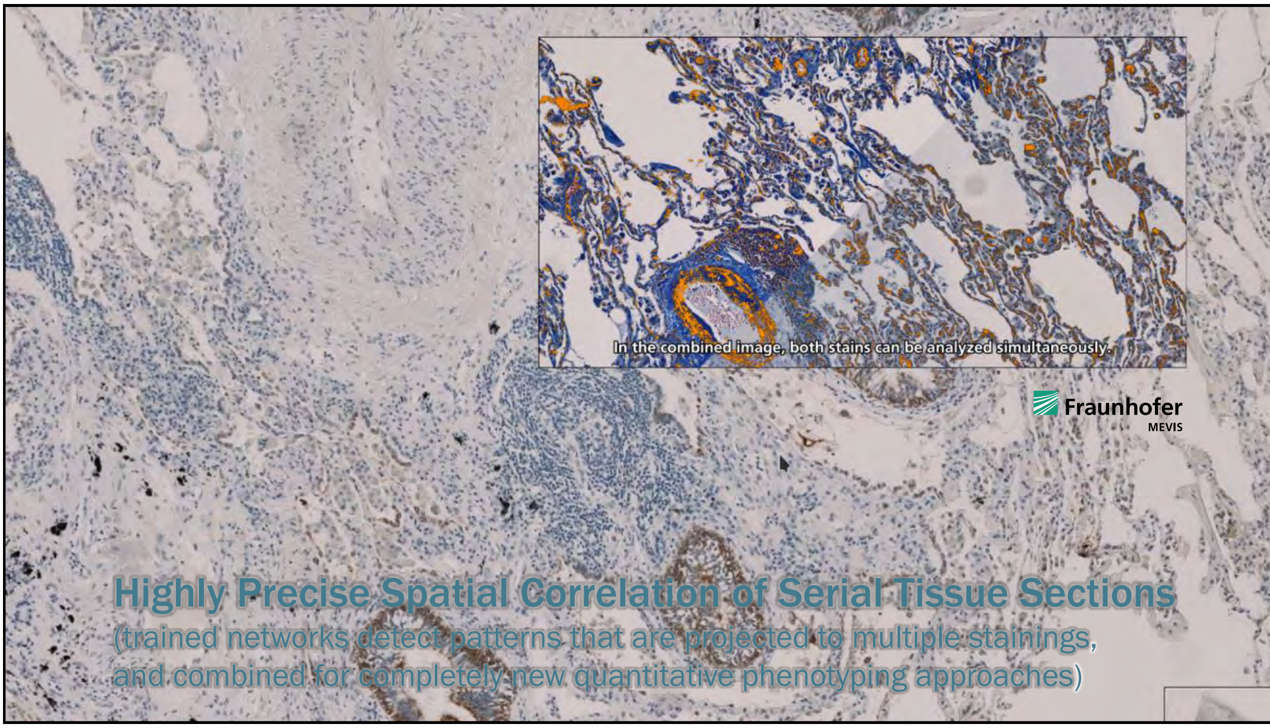
Information Integration Across Scales

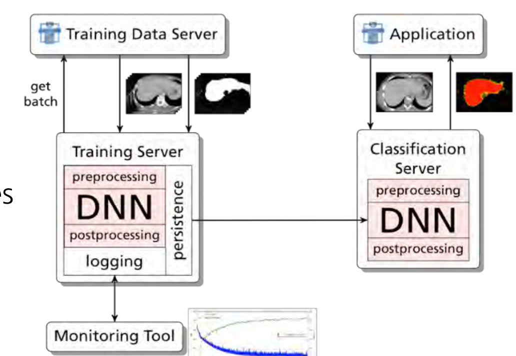


Research and Development Platform for **Reproducible Deep Learning**

Deep learning (DL) for pattern recognition in 3 stages

- Automatic segmentation of annotated structures
- Prediction of clinical categories and parameters from image data
- Prediction of clinical categories and parameters from image data with corresponding clinical data

Comparison of DL results and Radiomics features with framework for algorithm validation *ChallengR*



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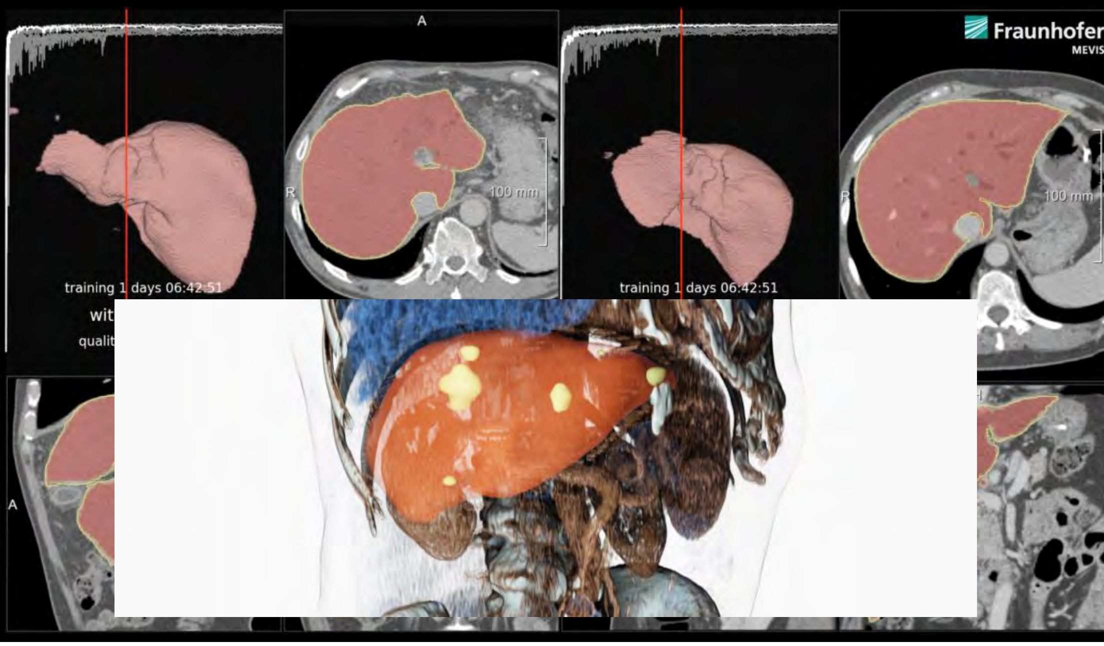
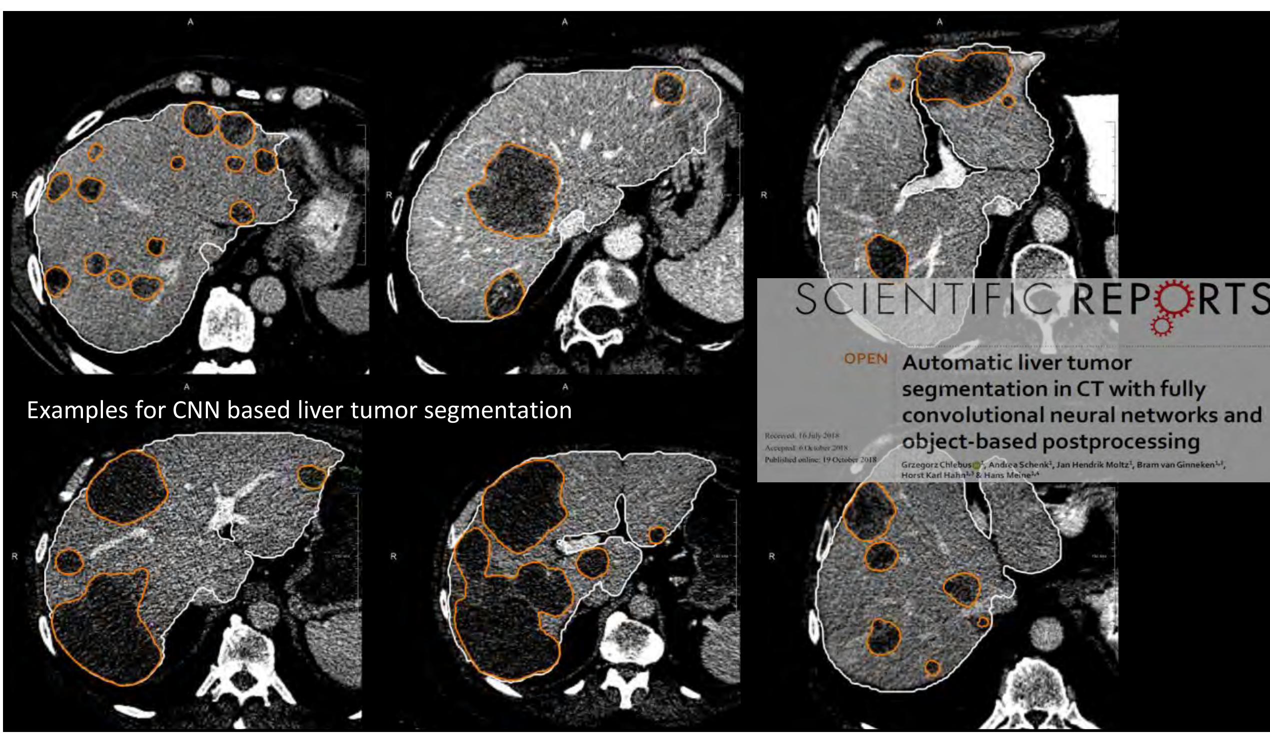
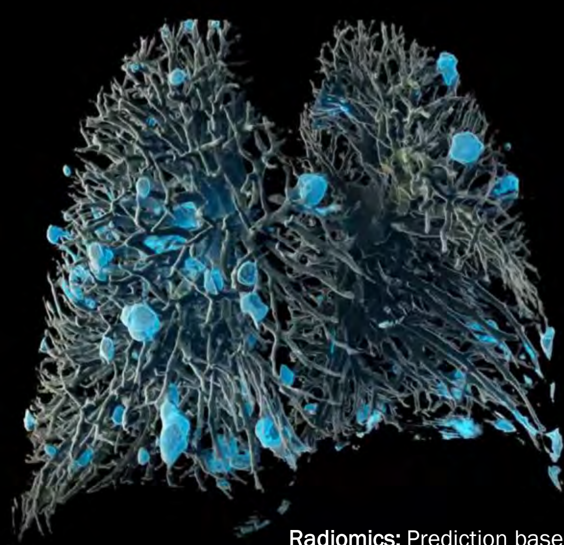
Watching the Learning of a CNN: Automatic Liver Analysis

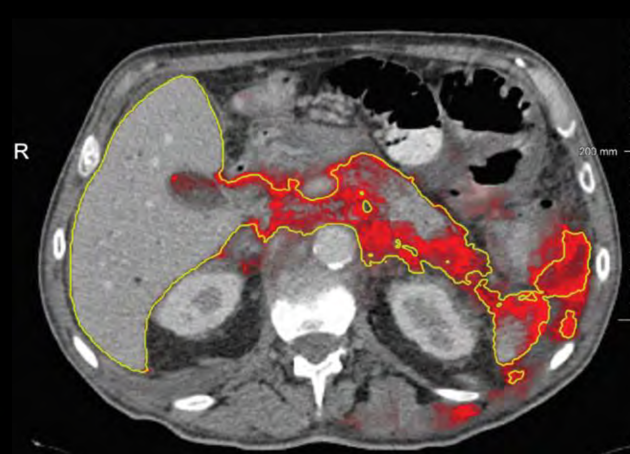
Grzegorz Chlebus, Hans Meine, et al.





Visualization of Temporal Changes in a Lung CT (left) & Uncertainty of a Premature Segmentation Network (right)





Radiomics: Prediction based on features beyond size and shape.
Hot Research Topic: **Explainable Artificial Intelligence (XAI)**

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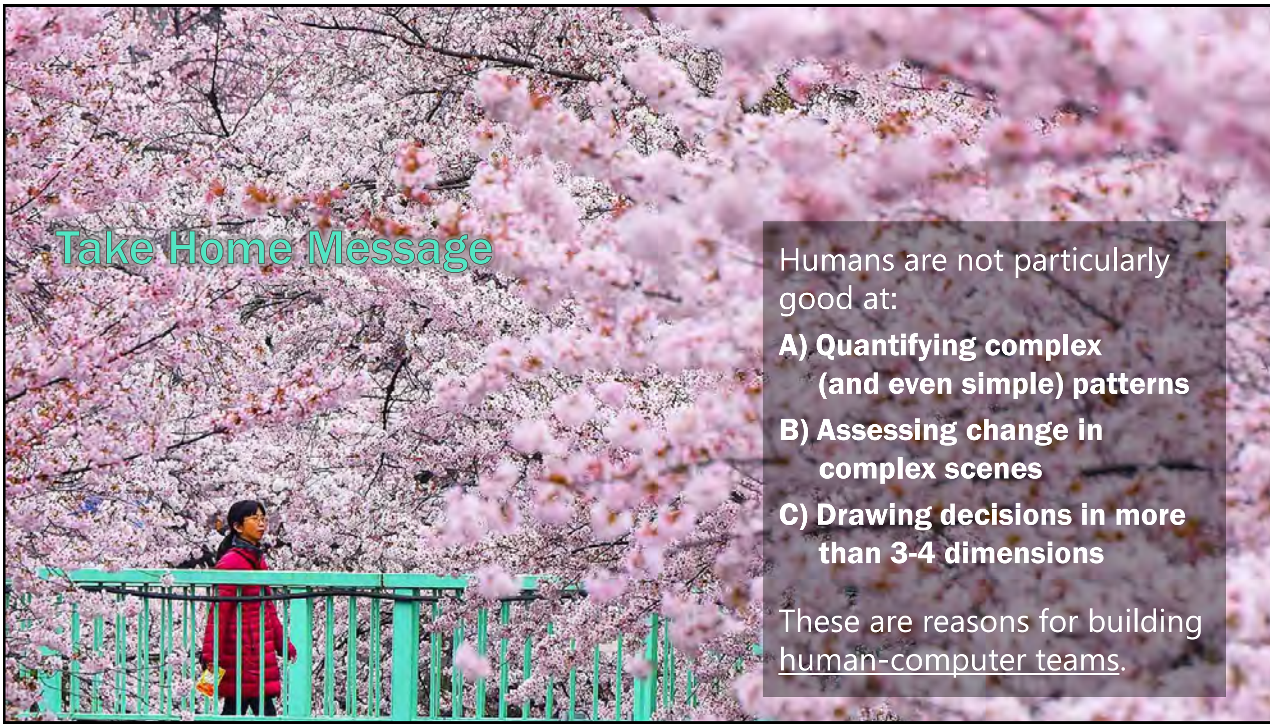


Take Home Message

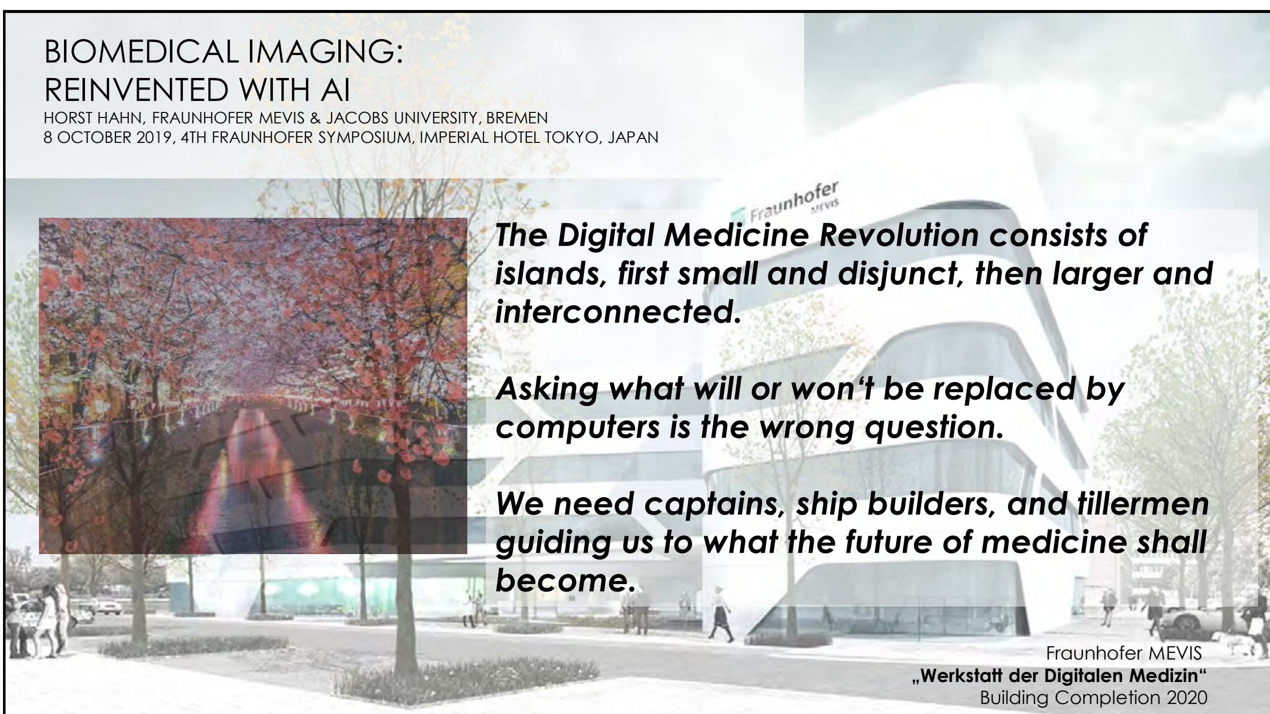
Humans are not particularly good at:

A) Quantifying complex (and even simple) patterns

B) Assessing change in complex scenes

C) Drawing decisions in more than 3-4 dimensions

These are reasons for building human-computer teams.



BIOMEDICAL IMAGING:
REINVENTED WITH AI

HORST HAHN, FRAUNHOFER MEVIS & JACOBS UNIVERSITY, BREMEN
8 OCTOBER 2019, 4TH FRAUNHOFER SYMPOSIUM, IMPERIAL HOTEL TOKYO, JAPAN

The Digital Medicine Revolution consists of islands, first small and disjunct, then larger and interconnected.

Asking what will or won't be replaced by computers is the wrong question.

We need captains, ship builders, and tillermen guiding us to what the future of medicine shall become.

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Building Completion 2020