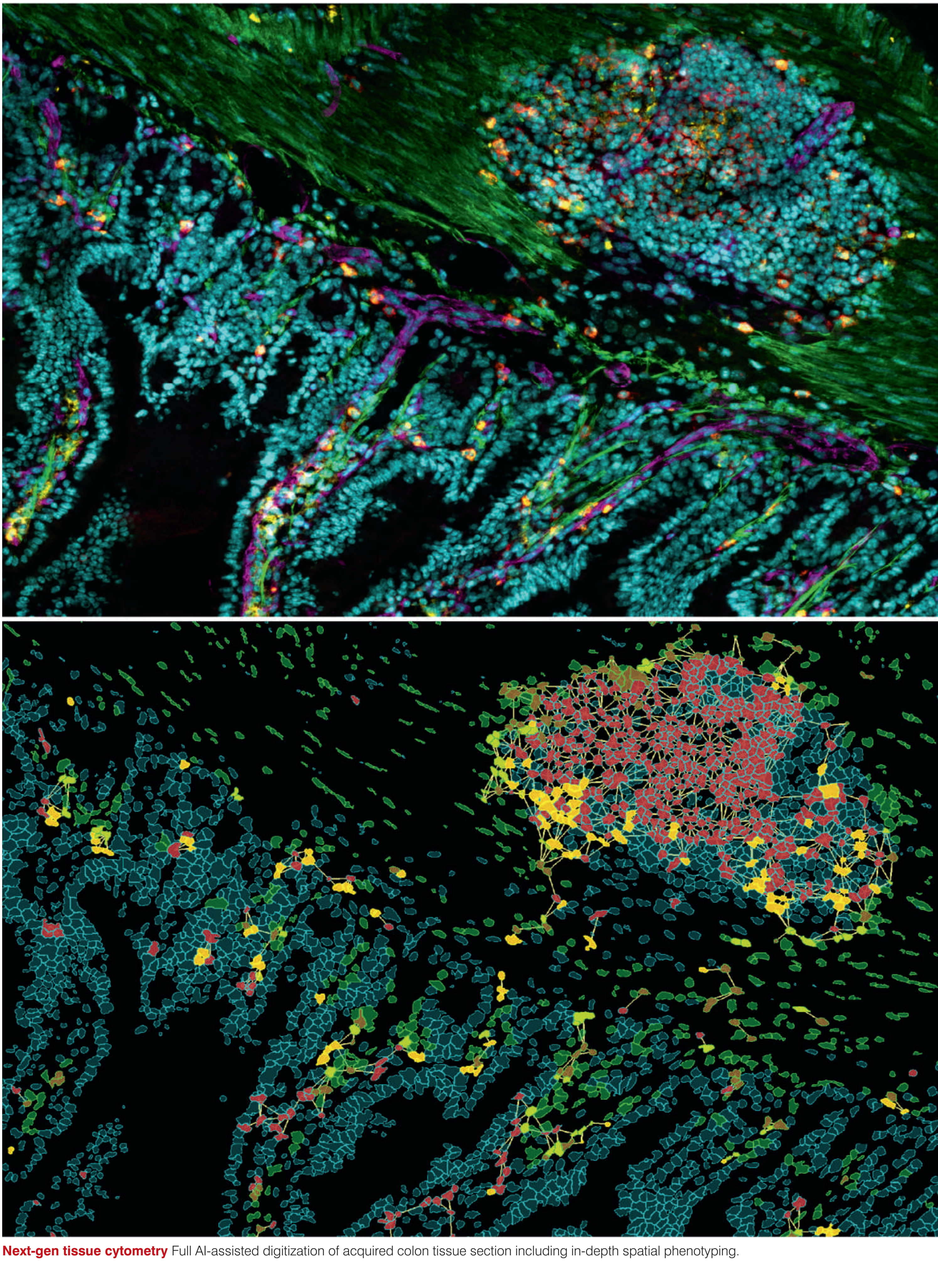
health economy

Artificial Intelligence in Biomedicine

A Global Outlook

Dossier
with the participation
of TissueGnostics and
other leading experts



Next-gen tissue cytometry Full AI-assisted digitization of acquired colon tissue section including in-depth spatial phenotyping.

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Oliver Jonke
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Editorial

Preparing the future

Dear Readers,
Artificial Intelligence (AI), Machine Learning, Deep Learning – these buzzwords can be found in almost every aspect of life these days. Many promises have been made, expectations fly high – maybe sometimes too high, successes inspire and failures are our constant companion. Some consider AI to be “the way into the future”, others perceive it as a temporary hype that will pass by like many other hypes have done before. The truth probably lies somewhere in between.

In this Dossier we address the question which role AI plays in today’s medicine and discuss with international experts the potential how AI may change medicine and global healthcare systems in the 21st century.

It was realized with the participation of leading experts in the field: First we asked Rupert Ecker (TissueGnostics GmbH Austria and Queensland University of Technology, Australia), who gave this document in order. Then we asked Stefan Barth (University of Cape Town), Jyotsna Batra (Queensland University of Technology), Kim RM Blenman (Yale University), Zodwa Dlamini (Pan African Cancer Research Institute PACRI, University of Pretoria), Georg Dorffner (Medical University Vienna), Isabella Ellinger (Medical University Vienna), Manuela Geiß (Software Competence Center Hagenberg), Yu-Chuan Jack Li (Taipeh Medical University) and Katia Ramos Moreira Leite (Faculdade de Medicina da Universidade de São Paulo) on their personal experience with AI and their personal opinion about the potential of AI in 21st century medicine, about the pros and cons of AI in biomedical research & clinical diagnostics, how AI will affect their field of work and how they envisage the development of AI in the next ten years and what will be the state of medicine in 2050 – will there be a “virtual doctor”.

I wish you an exciting read
Oliver Jonke

Dossier: Artificial Intelligence in Biomedicine

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The next-generation of biomedicine is on the horizon

Artificial Intelligence changes biomedicine from pre-clinical research over drug discovery to clinical diagnostics – views and contributions from TissueGnostics, an innovative SME with Austrian roots and global impact.

The source of TissueGnostics lies in a need – the need of scientists and diagnostic professionals to quantify molecular markers and single cells in tissue to better understand why and how certain diseases, like cancer or autoimmune disorders, form and progress. The human body has extensive self-control as well as defense mechanisms to protect itself against both, change of the genetic code through mutations as well as invaders from the environment (viruses, bacteria, parasites, toxins). Diseases occur – similar to most disasters – when several of these safety mechanisms fail at the same time. The common denominator in biomedical research around the globe is to understand the molecular and cellular mechanisms of homeostasis (the "inner biological stability" of an organism) and to find potential targets of therapeutic intervention.

History of pathology

It was around 1850 when the German doctor Rudolf Ludwig Carl Virchow recognized that cells are the source of diseases. Although the history of pathology dates back to the early 1700's, Virchow is referred to as the founder of cellular pathology and thus a pioneer of modern histopathology.

Following the groundbreaking work of Virchow and other pioneers, pathologists analyzed tissue by preparing ultra-thin sections of organs,by looking at them through microscopes and comparing patterns in tissue structures as well as by describing the morphology of cells.

Since the 1970's more advanced molecular methods have become available, which allowed to go beyond anatomical and morphological descriptions and to also look at subcellular structures and specific molecules (by a technique known as "immunohistochemistry") as well as to investigate the genetic background (by various methods referred to as "in-situ hybridization") of diseased cells. Such functional analyses of single cells are referred to as "cytometry" and are opposed to "anatomy" and "morphometry", which describe the morphology of cells and tissue structures but ignore the functional aspects.

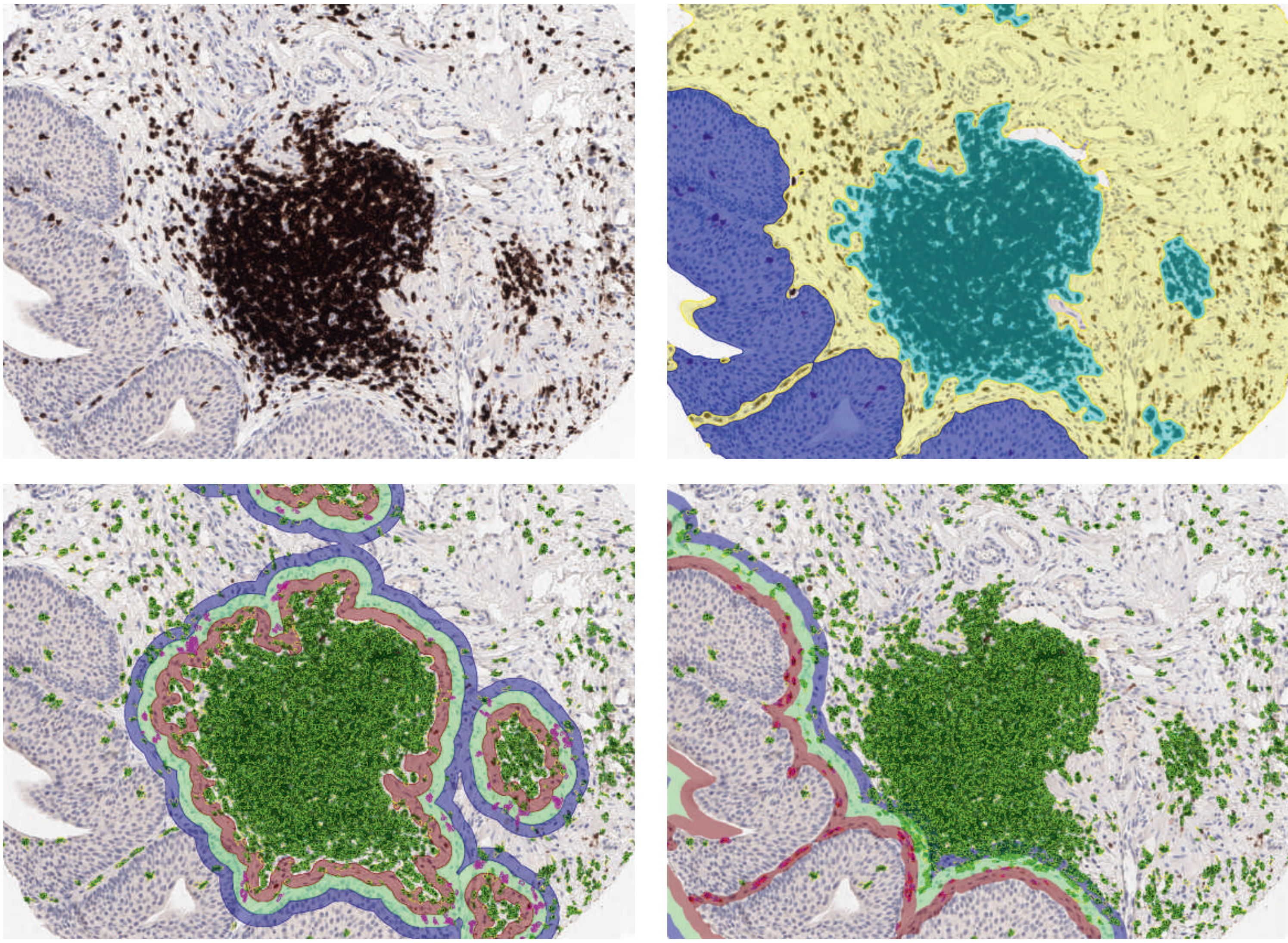
The computer and internet revolution, having taken place during our lifetimes, "naturally" include the area of medicine and diagnostics. In the late 1980's the idea of "telepathology" spread out, which referred to visual analysis of tissue samples over a video signal. This idea was expanded in the late 1990's and early 2000's in that the images were captured and archived in digital form, a technology referred to as "digital pathology" – with the analysis / diagnosis still being performed visually by a human expert.

Recent developments in Next-gen digital pathology

Over the last two decades, however, academia and industry worldwide have put major efforts into developing solutions for digital diagnosis. Automation of laboratory research and clinical routine has been a major topic, with reduction of cost of labor being a relevant but not the only topic. Other drivers of development are at least equally important: (i) the improvement in data quality and diagnostic precision and (ii) making quality data available to patients living in resource-limited settings – thinking of the globally increasing lack of pathologists and limited access to health services in rural areas and/or developmental countries.

Understanding the causes of diseases and finding therapies requires integration of data and knowledge on multiple levels – genetic, protein chemistry, enzyme and hormone interac-

Dr. Rupert Ecker
The CEO and co-founder of TissueGnostics GmbH, and Adjunct Professor in the Faculty of Health, School of Biomedical Sciences, Queensland University of Technology describes his perspective on the future of AI in medicine and the role of TissueGnostics in this expanding market.



Deciphering inflammatory immune responses
Immune status in-situ analysis including automated tissue classification and proximity measurements: detection of tertiary lymphoid structures (indicative of onsite immune response) and CD8+ cytotoxic T cells in bladder tissue using TissueGnostics' award winning analysis software StrataQuest.

tions, immune responses, toxicological and pharmacological aspects, as well as cultural, social and environmental influences.

Correlating multi-parametric entities and deriving effective knowledge in a holistic approach, however, quickly turns into a complex endeavor. While the cognitive capacity of the human brain and its ability to handle "fuzzy data" and to interpolate in all kinds of most different situations (i.e. to ability to find solutions to only partially understood or in their causality even unknown problems, in other words to find a "work around") are undoubtedly admirable, handling complexity and recognizing multiparametric interrelationships is not the strength of our neuronal control center. Handling and correlating huge and complex data sets, however, is exactly the strength of AI systems.

The combination of modern biochemistry and genetic methods with latest software tools and computer power allows to move to what is referred to as "next-generation histopathology". While classical "digital pathology" refers to digitizing slides (but analysis is still visual), that new approach focuses on digital analysis. With their instruments and software for tissue cytometry (i.e. automated and quantitative analysis of molecular markers on the single-cell level in whole tissue sections) the Austrian company TissueGnostics, founded in 2003, is a pioneer in this field and has become a globally active trend-setter, with subsidiaries and offices on all continents.

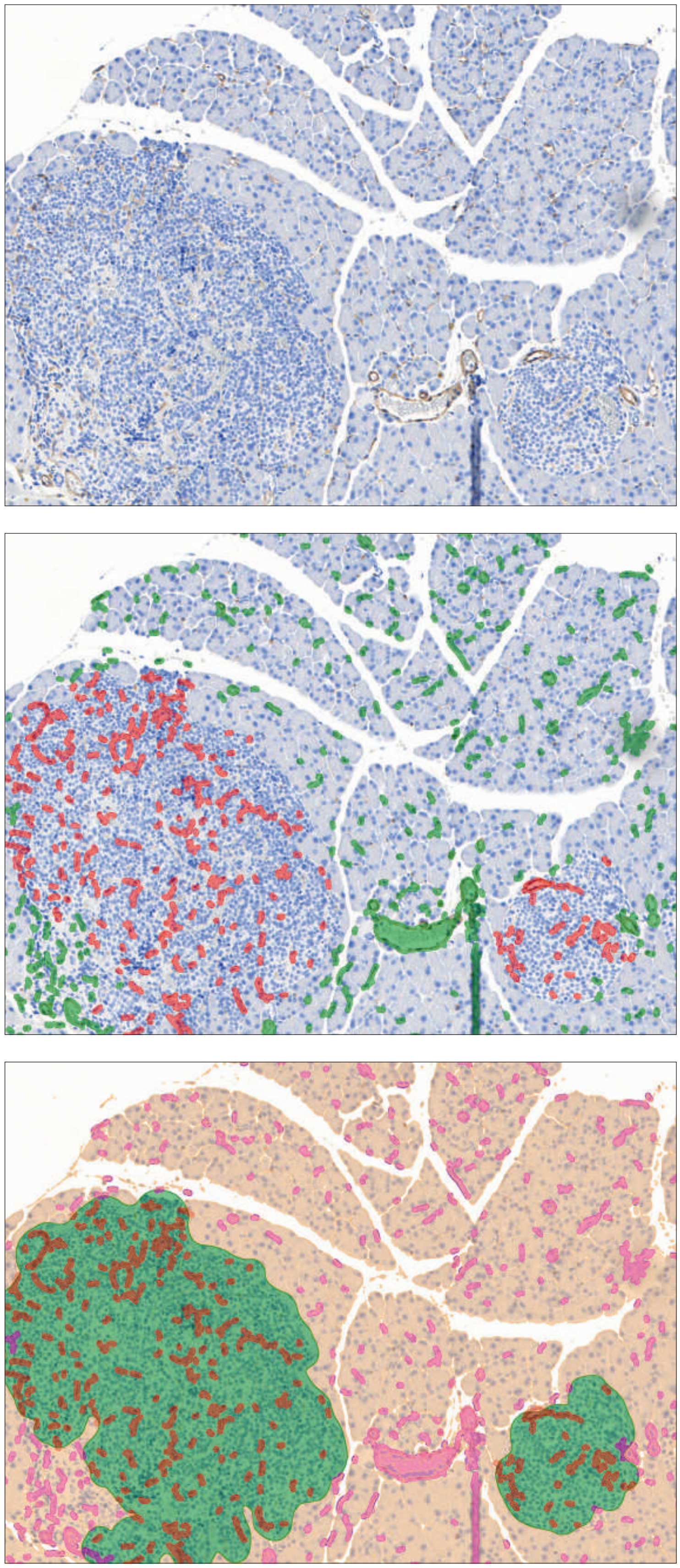
As medical diagnosis is a regulated business and all systems (instruments as well as software-only solutions) must comply with strict legal and quality requirements, there is an "artificial limit" to the usage of artificial intelligence in medicine. Not only that companies developing such solutions have to be certified in accordance to ISO 13485, In-Vitro Diagnostics Regulation (IVDR), Medical Device Regulation (MDR) and/or similar regulatory frameworks, but over the foreseeable future liability issues will largely refrain companies from offering real digital diagnosis, independent of what will be technologically possible. Instead, computer assisted diagnosis systems, be they AI-based or not, are used as technical means to assist human experts as "decision support systems".

Currently, we continue to face technical challenges as AI in medicine is still a new and growing field. Additionally we must face the perception of our legislators – who most likely represent the vast majority of patients – that diagnostic decisions must to be taken by human experts rather than computers. These human experts have to be and are liable for their decisions, albeit to a different extent depending upon the region in which they practice.

TissueGnostics' contribution

To join forces with academia TissueGnostics has been involved in numerous collaborative research projects with research institutions across Europe – among those are five EU-funded Marie Skłodowska Curie Innovative Training Networks such as HELICAL, a project focusing on machine learning-based health informatics, headed by a research group at Trinity College in Dublin (https://helical-itn.eu/about-us/). Other research partners are the Institute of Artificial Intelligence and Decision Support at Medical University of Vienna and the Software Competence Centre Hagenberg (SCCH) in Upper Austria, with a project focusing on security and safety for shared artificial intelligence systems (S3AI project – https://www.s3ai.at/home.html).

At present, TG acts in a global environment of highly dynamic technologies and a vibrant Life Science market, with new players, big investments and major achievements. For the first time in history in September 2021 the US Food and Drug Administration (FDA) approved an AI-based decision support system for diagnosis of prostate cancer.



A variety of applications in research and clinics

Next generation histopathology displaying a tissue classification and vascularization analysis in pancreas tissue. Such analysis are not only relevant for a better understanding of diabetes, but also Alzheimers disease, Multiple Sclerosis, or Covid-19 associated disorders.

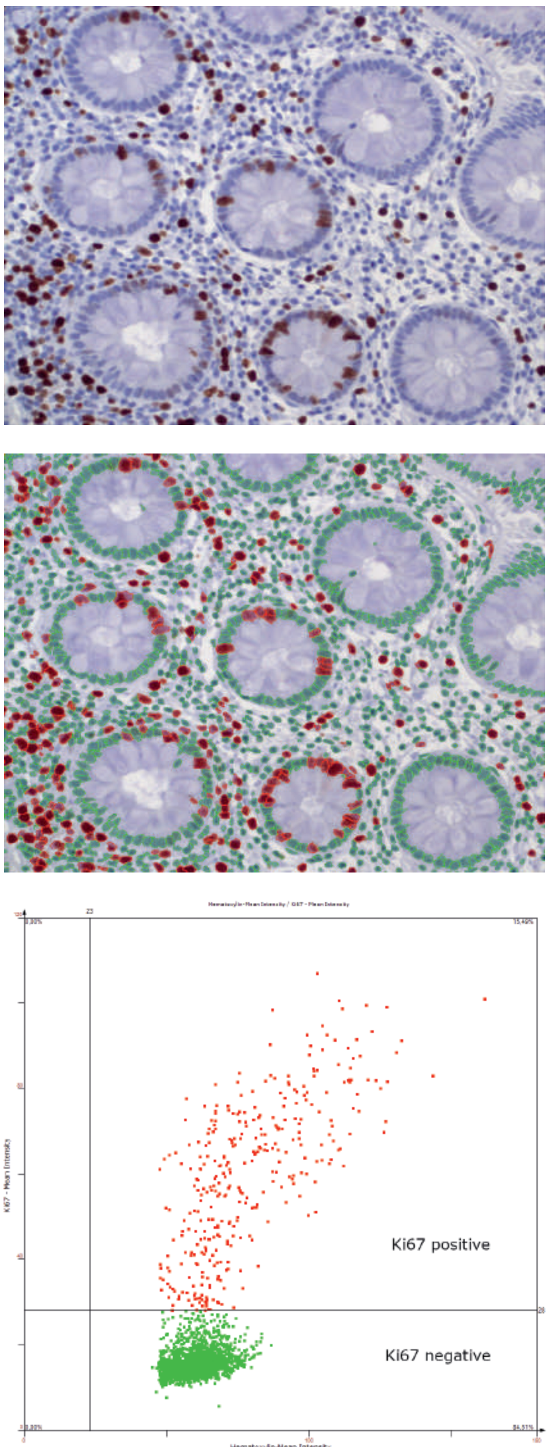
This was a landmark event representing an acceleration of the global development trend towards AI-based precision medicine and will be used as reference for future applications.

Current challenges

Two current fields of research within AI, which are essential for the future expansion of AI in medicine, refer to (i) how computers can learn from each other as well as (ii) understanding why a certain AI technology creates a specific output.

A major difference between biological and virtual intelligence is that humans learn throughout their lifetimes and new knowledge is built upon existing knowledge, even when such knowledge belongs to very different domains, while teaching an existing AI-based system knowledge from a different domain typically means a start from scratch. Applying an existing machine learning algorithm to another problem means, the training phase ("learning") starts from the beginning – akin to sending humans back to kindergarten when ever they are confronted with a new problem. Biological intelligence does not work this way, but currently artificial intelligence does.

The second major topic pending, in particular from a regulatory standpoint, relates to the fact that most AI technologies like Machine Learning and Deep Learning are kind of "black boxes" – human operators define the input and observe the output but do not really understand why the system delivers a certain output. That is at least a challenge for development, a problem for regulatory bodies, and to some extent unsettling for patients.



Single cell analysis
Including Ki67-positive cell detection in IHC-stained colon tissue using StrataQuest.

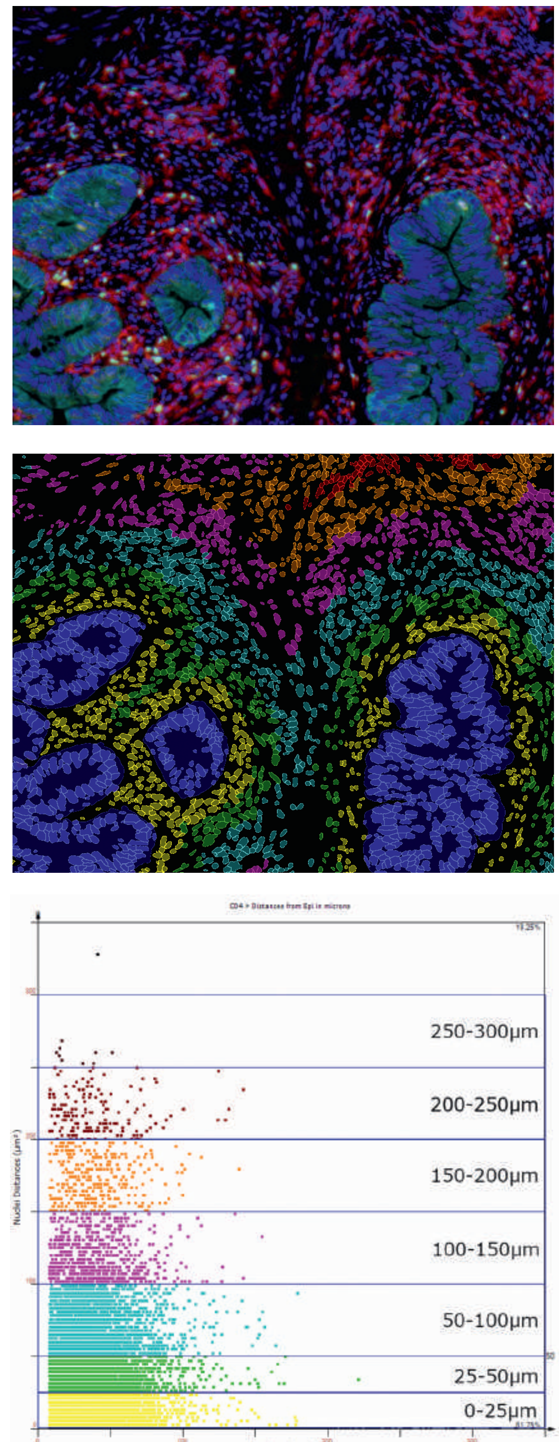
Before we build our entire life, including personal safety and health-related decisions, on artificial intelligence – shouldn't we at least understand how AI works? While most of us would intuitively answer "yes of course," alternatively some might argue that throughout human history we built and relied on biological intelligence and still don't even completely understand how that works.

In view of the status quo in all aspects with regards to available technologies, legal and regulatory frameworks, patient safety, social acceptance and the given differences between biological versus artificial intelligence – at least for the time being, a combination of computer power and human brain power appears to be the most advantageous and literally congenial approach.

Future of digital pathology

The line of development, from Virchow's insight that cells are the source of disease to AI-based decision support systems, however, will not come to an end or enter a "final stage of maturation" with our generation. What we eyewitness these days is without doubt exciting, but not more than a snapshot in history.

At some point – maybe in the late 21st century – we might have virtual doctors, but it is still a very long way to go! The topic is not only a technological one, even more so it has strong psychological, cultural and social aspects. The question is not "Will computers ever be able to diagnose patients?", we shall expect that the answer is Yes – the first question is "Will patients want/accept to be diagnosed by a computer?"



Tumor immune microenvironment (TIME) analysis
Including in-depth phenotyping and proximity measurements of IF stained colon cancer tissue (StrataQuest IF Immune Status in Situ App).

Current computer technology would be sufficient to fly a passenger aircraft without pilots – still, in every aircraft there sit two human pilots. We see a general increase in acceptance of computers controlling our life – in some cities (eg. Singapore) subway trains are fully computer controlled – there is no train driver any more, but in other parts of the world this idea is less accepted and realization lags behind.

It will probably take several decades until we will fly in aircrafts without human pilots. Until AI systems reach the technical maturity, regulatory clearance, but also the social acceptance that we can download a virtual GP on our mobile phone, or whatever means of communication we will have by then, it might take close to or even more than a century. Most likely, however, none of our current expectations will come true as disruptive technologies shall be expected to emerge in future, which we are not yet aware of! These technologies, however, will accelerate and/or change the direction of development in ways unpredictable as of today.

As the human mind is the creator of AI, from a philosophical standpoint, we should also reflect on the question whether artificial intelligence is a "natural phenomenon" – at least the human mind is.

What we can take as granted is that development will continue to occur as it has always done throughout the history of humankind. Artificial Intelligence is inevitable – and unstoppable.

Dr. Rupert Ecker is co-founder and CEO of the Austrian medtech company TissueGnostics GmbH and Adjunct Professor in the Faculty of Health, School of Biomedical Sciences, at the Queensland University of Technology.

Dr. Rupert Ecker explains that the analytical solutions of TissueGnostics permit to quantify multiple markers in tissue on the single cell-level and thereby constitute an essential tool for Precision Medicine. Therefore TissueGnostics is actively involved in academic collaborations and conducts R&D projects both, on national as well as international levels, in order to provide solutions at the frontiers of science and biomedical technology.

TissueFAXS cytometers
Highly flexible imaging and analysis platforms for IF/IHC processed samples.

Intelligence in only a very narrow sense

••• *By Georg Dorffner*

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I have been working with neural networks as machine learning technique since the mid-1980s. Back then they were not considered Artificial Intelligence, but nowadays AI is almost synonymous with them. Thus I feel like being at the very heart of AI. The potential of neural networks, especially in the context of deep learning, is large when it comes to recognizing and detecting complex patterns, but one must consider the inherent limits of data-based approaches, i.e. the systems can only be as good as the data they use.

Definitely, AI can contribute to improved diagnosis, treatment and monitoring of diseases as a valuable tool supporting medical personnel. It can also help spread diagnostic or monitoring expertise to areas that are understaffed by experts. However, AI systems should not be used to replace medical personnel, even in seemingly simple cases, since the human component in medical care is so essential that it must be maintained. Medicine is much more than pattern recognition.

My field of work has been AI in Medicine for my whole career, so it cannot affect it more than it has already. AI will continue to play a large role as a tool in Medicine.

Some of what is currently happening in AI must be considered a hype, due to the overestimation of what data-based approaches can achieve. This hype will go away over the coming years, leaving AI applications where they are most useful. Medicine in 2050 will largely be characterized by semi-automated diagnostic and monitoring procedures, hopefully providing safe and beneficial data storage and processes for every patient, but it will still rely on human skills for communication, empathy and creativity to keep up a high-level health system.

ao. Univ.Prof. Georg Dorffner, PhD is Associate Professor at the Institute of Artificial Intelligence, Center for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna, Austria.

Challenging, exciting, supportive and accurate

••• *By Katia Ramos Moreira Leite*

With the number of pathologists reducing worldwide and an increasingly complex workload, there is a necessity to develop novel technologies in surgical pathology. The use of AI is inevitable and will be soon part of the daily lab routine.

At the moment we are involved in a study using AI algorithms to diagnose and grade prostate cancer based on H&E samples, and by working with AI algorithms, we have the opportunity to witness the difficulties and pitfalls in teaching the system to evaluate the lesions properly. One challenge is that AI algorithms should always be trained by specialists in each area of knowledge. This refers to subspecialists, because there are a milieu of aspects that need to be considered in order to make a correct diagnosis in a specific disease. Further an appropriate number of images must be selected, annotated, and presented to the system to teach based on which patterns the diseases must be identified by.

The potential long-term goal for such an AI-based algorithms is to help pathologists with their routine work. AI has the potential to be applied on screening as well as suggesting diagnosis to support pathologists in terms of handling patients with more complex diseases. This would also include utilizing the power of AI algorithms to analyze morphological, immunohistochemical and molecular data to classify neoplasms.

AI is considered to be a future necessity, and it will be part of our job. We already use AI for the screening of cytology of samples but AI-assisted technologies will be more affordable and available and will become an essential part of our laboratories.

photo courtesy of the author

Katia Ramos Moreira Leite is Assistant Professor at the Faculdade de Medicina da Universidade de São Paulo, Brazil.

AI-enhanced medicare

••• *By Zodwa Dlamini*

AI enhances precision oncology and is applicable to low and middle income countries (LMICs), it universally improves early diagnosis, prevention and therapeutic approaches to improve health outcomes and promotes the reduction of cancer health inequalities. AI is conducive to healthcare systems because it can analyze more health data than before and improves current diagnostic techniques. it can perform sophisticated calculations and determine the outcome with minimal or even without human interference.

AI will improve cancer drug discovery and promises a more powerful and efficient way to work with the great amount of data produced by the modern drug discovery approaches. It will improve cancer point of care diagnostics, prevention and treatment. AI will enhance automation of healthcare systems in resource deprived LMICs and mitigate shortage of well-trained health care workers and specialists which is a major concern in developing nations and finally enable early, precise and quicker diagnosis.

At the Pan African Cancer Research Institute (PACRI) we aim to conduct world-class research to understand, prevent and cure cancer in the African region and the world. PACRI promotes pioneering interdisciplinary research using a collaborative model, to translate new knowledge into product development and provides effective and compassionate clinical care that improves the lives of patients with cancer. PACRI is about pushing the boundaries of precision oncology, cancer prevention and bringing new approaches for early diagnosis and novel therapeutic agents to improve health outcomes, reduce health inequalities, strengthen health systems in underserved and socio-economically disadvantaged communities in South Africa and the African region.

photo courtesy of the author

Professor Zodwa Dlamini is Founding Director of PACRI and Professor of Molecular Oncology at PACRI, University of Pretoria, South Africa.

Deep learning promotes knowledge acquisition and health care

••• *By Isabella Ellinger*

As a cell biologist, I am interested in understanding the cell biological basis for human diseases. The quantitative analysis of microscopic images of cells and tissues is important not only for research applications to promote the understanding of the biological mechanisms of the disease process, but also for clinical applications such as the detection, diagnosis and prognosis of diseases. Currently, I am part of an interdisciplinary project team applying deep learning, one of the most promising branches of AI, to histological (pathological) images to improve the detection, classification and segmentation of nuclei as a prerequisite for the detection and classification of cells. The big benefit I see is that deep learning methods like convolutional neural networks (CNNs) can recognize and efficiently extract complex features that humans may not be able to grasp.

Pros: AI can not only enable a deeper understanding of (large-scale) microscopic images, but also find links between different types of data, including images, data derived from *omics* technologies, or even electronic health records. This is important to advance our vision of precision medicine.

Cons: AI-based (bio)medical tools should not aim to replace healthcare professionals or researchers.

In recent years, new model systems such as three-dimensional multicellular spheroids have been developed, which can be used as preclinical *in vitro* models for e.g. cancer research. The combination of such near-physiological model systems with imaging technologies and deep learning / AI promises to accelerate discoveries in our understanding of diseases from basic research to clinical applications. However, this type of research clearly depends on working in interdisciplinary teams. Working in and leading multidisciplinary teams must become essential research skills that universities should include in the training of students.

The combination of microscopes and AI for answering (bio) medical questions has great potential. Aside from research applications small but intelligent devices are being developed to aid the work of doctors, pathologists, and other healthcare professionals. These include, for example, light microscopes that enable simultaneous AI-based image analysis with real-time presentation of results for the diagnosis of tissue biopsies, or AI systems working on mobile devices for point-of-care-testing.

I believe that such intelligent devices, when their diagnostic reliability has been validated against extensive data sets, have the potential to improve access to medical care, support disease prevention and relieve the burden on the health system. Generating the necessary comprehensive data sets and validated algorithms will require concerted and global efforts.

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Assoc. Prof. Isabella Ellinger is a cell biologist and head of the research group 'Pathophysiology of the human placenta' in the Institute of Pathophysiology and Allergy Research, at the Medical University of Vienna, Austria.

A major future contributor for rational development of next generation targeted therapeutics

••• *By Stefan Barth*

We have used and are using high performance computing simulations of dynamic protein interactions in tight collaboration with the Institute for Advanced Simulation at the Forschungszentrum Jülich (Germany) to rationally improve the recombinant immunotherapeutics we are developing. We recently started a collaboration with the Computational Biology Group at the University of Cape Town aiming at mining, and integrating data from multiple public resources by applying statistical methods, machine learning and predictive modeling to identify best suited targets for immunotherapy.

Obvious pros are the use of such computer based platforms to (1) reduce the number of biological assays for proof of concept analyses, and (2) access large data collection to derive consolidated interpretation on differentially expressed antigens confirmed by appropriate quality control tools. Immediate cons are in both cases the needs to confirm these data by the appropriate biological references.

AI will strongly influence the rational development of next generation targeted therapeutics based on increasing knowledge on pathophysiological changes leading to diseases as well as the design of next generation drugs decorated with favorable features.

Further exploitation of AI in the area of medical biotechnology will provide significant contributions to generate better targeted therapeutics with higher performance and less off target effects as well as to the identification of patients best benefitting from such targeted therapies leading to strong reductions in treatment failures and resulting reduction in overall costs of treatment.

photo courtesy of the author

Prof. Dr. Dr. Stefan Barth is South African Research Chair in Cancer Biotechnology at University of Cape Town, South Africa.

AI is the key for future medicine

••• *By Yu-Chuan Jack Li*

I have devoted myself to evolving the next generation of AI in patient safety and prevention ("Earlier Medicine") in Taiwan and currently serve as president of the International Medical Informatics Association (IMIA).

My opinion of AI is that it could help us to manage all knowledge that we are trying to memorize with our limited brain capacity. AI is able to figure out the complexity of disease and provide clinical doctors with suitable therapeutic methods.

People have to feed huge datasets to train AI & neural networks. If we input data with bias, the outcomes will be biased. So one of the cons is how to get high-quality and multi-dimensional big data. In other words, it is how to standardize the data format among hospitals, institutes even at the worldwide level. The Second is the privacy issue. For example, although we could apply de-identification on medical data, your personal genome data also represent a portion of your family. What if some of your family members don't want to reveal it?

photo courtesy of the author

Cons: First, AI can improve early diagnosis and help to achieve Preventive Medicine. I have done some AI modules with local and high-quality datasets and verified it works and is valuable to patients. Second, AI can accelerate new drug development. For example, it could find out the candidate drugs and structures from thousands of compounds which possibly shortens the process to 1 year, rather than 10 years.

As a dermatologist, I have developed an AI-based software called MoleMe to screen the risk of moles on the human body. It has also been published in the *British Journal of Dermatology.* Doctors hope patients come to the clinic at the right time, neither too early nor too late. MoleMe helps to screen the risk of skin moles which will save both doctors' and patients' time.

I think we could standardize the format of medical datasets within 10 years to facilitate usage of high quality, multi-dimensional big data to train AI and get valuable output.

In 2050, I expect we could achieve "Earlier Medicine", including early detection, early diagnosis, and, if necessary apply therapies in early stages of disease formation. In such an "AI-optimized and preventive world", people will enjoy a healthier life because almost all diseases could be detected at onset and are thus curable at low cost, at least when compared to the major investments required for targeted therapies at late-stage diseases. The costs of AI are at a comparatively low price and are more efficient at early stage of disease detection an diagnosis, allowing patients to live a longer and healthier life.

Yu-Chuan Jack Li MD. PhD. is Distinguished Professor at Graduate Institute of Biomedical Informatics, Taipei Medical University.

AI as a driving force for new technologies in complex systems

••• *By Manuela Geiß*

I am currently working on projects about (i) object detection through incremental and fast learning with few data, (ii) explainability (understanding why an AI system does what it does) and (iii) Al on embedded devices. I see great potential of Al, especially in the context of biology and medicine due to the massive and fast growing amount of data that is often poorly understood due to high dimensionality, noise, and hidden relationships. However, one should always keep in mind that Al is not the one and only solution for everything but there are tasks for which traditional deterministic algorithms are better suited.

Pros & Cons

+ Handling large amounts of data, uncovering patterns in data that would otherwise remain hidden from human eyes.
+ Support for doctors, not in terms of replacing but supporting them in repetitive tasks. Well integrated into workflows, Al can speed up the doctor's work and leave him/her with more time for his/her patients.
+ Performance of Al algorithms often comparable to humans, but algorithms never get tired or lose concentration.
– Privacy-preserving will be an important topic, errors here can cause big issues with sensitive patient data.
– Medical data are often biased (e.g. gender, more data from Western countries, etc.). Some biases might remain undetected and therefore the resulting models are not suitable for all applications (e.g. drugs developed based on patient data from Western countries might not be working or be harmful in African populations).

Al will provide new insights into biological questions that have been challenging for years (one prominent example in biology is Deepmind's deep learning algorithm "Alphafold 2" for protein 3D structure prediction). In particular, explainability methods are urgently needed. Without explainability and reliability of Al methods, trust and acceptance in these methods will largely limit their application in many areas, in particular in medical applications.

The development of Al within the next 10 years will be driven by the integration of Al in industrial processes and medical fields, which includes topics such as explainability, privacy-preserving and "Al on the edge" (intelligent devices connecting users to data networks) but also questions about ethical regulations and legal rules. I believe that in 2050, medicine will be largely intertwined with Al in terms of e.g. doctors supported by Al (diagnosis and treatment, tele-medicine, administration workflows, etc.), smart hospitals, and self-monitoring of the physiological body state by edge devices. In particular, Al will significantly improve the healthcare situation of poor regions and provide a broader access to medical treatment allover the world.

photo courtesy of the author

Dr. Manuela Geiß is Senior Data Scientist and Researcher at the Software Competence Center Hagenberg GmbH, Austria.

Greater benefits for patients

photo courtesy of the author

••• *By Kim Blenman*

We have used AI in pathology for well over a decade to help to identify and isolate single cells, cell populations, structures, and tissue architecture. We have combined these components to better understand disease mechanisms and therapeutic responses in the context that they occur naturally, *in situ.*

AI has changed the way that we view pathology and has high potential to have a meaningful impact in patient care.

For pathology, AI has the potential to augment the great work that pathologists already perform as part of their routine practice. As human beings we have limited ability to see patterns in large volumes of high-complexity data. AI tools can potentially isolate those patterns and present them in a context that is digestible by the human brain.

In order to use AI in biomedical research and medicine, we must have trusted validated algorithms that consistently produce accurate, reliable, and reproducible results. We must develop best practices that at minimum include processes, mechanisms, and templates/checklist to harmonize the study designs, training, validation, statistical analysis, minimal metadata, and other outputs that are critical for use of AI tools.

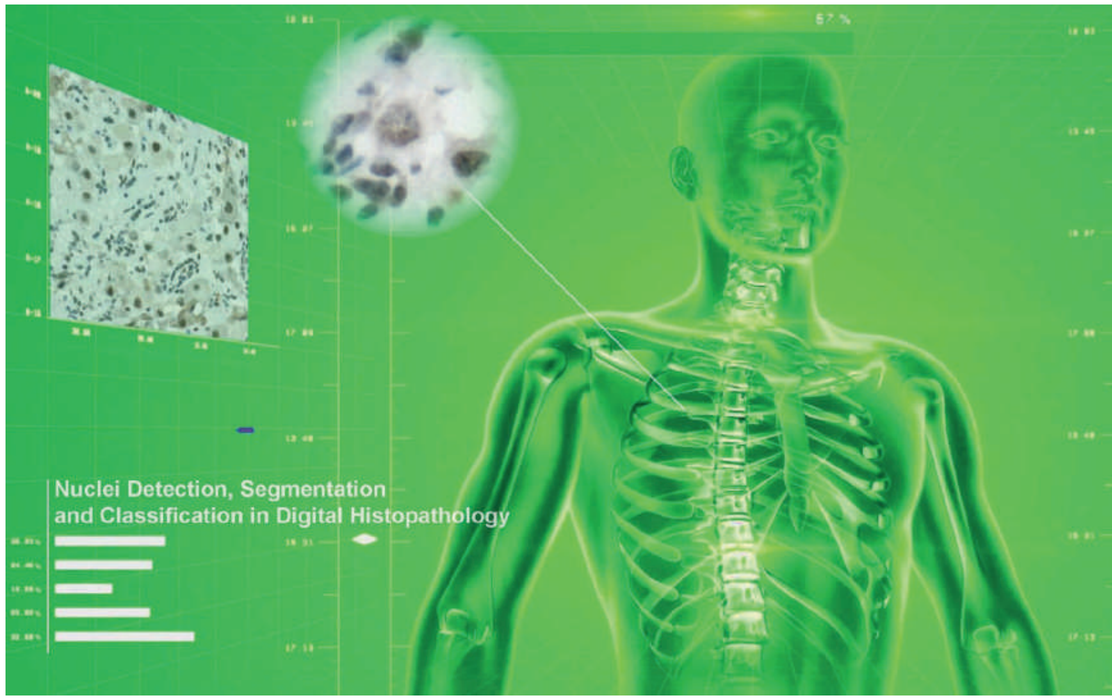
We use a limited amount of information that we collect from our patients. AI could potentially allow us to do more, to dig deeper, to collect more, to analyze more, and potentially lead to greater benefit for patients.

We and others are integrating AI into all of our work at some level. However, currently AI for pathology is still relatively in its infancy. A few of the bottlenecks for AI tools in pathology today is that they tend to be slow (limited high throughput), bulky (large files), and have limited high statistical performance measures (accuracy, precision, recall/sensitivity, specificity, etc.). In the next 10 years, this is expected change as we find better ways create and run our algorithms, write and store our data, and test our outputs. In 2050, all aspects of medicine will have at least one AI component within its workflow.

Dr. Kim Blenman is Assistant Professor of Medicine (Medical Oncology) and Assistant Professor of Computer Science at the Yale School of Medicine, USA.

AI-enabled personalized medicine

••• *By Lukas Fischer, Manuela Geiß and Bernhard A. Moser*



Personalized medicine from a Data Science and AI perspective. The ongoing digitization and AI have the potential to transform our healthcare system through an increased patient stratification based on the patient's individual biomedical profile and life condition. While established medicine often has no choice but to take a "trial-and-error"[1] approach for disease treatment due to lack of information, personalized medicine will facilitate a more principled approach by taking advantage of the clues contained in data. In this way, the envisioned personalized medicine will reduce mistreatment and thus prevent or mitigate drug toxicity, severe side effects, reactive treatment, and misdiagnosis. Tailored diagnostic and therapeutic strategies induced by data analysis will have an impact not only on treatment, but also on prevention and pro-active treatment regimens, resulting in reduced costs and quality of life enhancement.

In this context, digitization and AI will have a profound impact on the entire chain of information processing across the pyramid of refinement layers from raw data up to high level knowledge gain, in particular

- from data acquisition (e.g., single-cell omics providing genomic, epigenomic, and proteomic data; microscopy cell images; x-ray images etc.),
- to data fusion across different scales (molecular, microscopy) and modes (due to different sensing techniques, e.g. fluorescence below visual resolution versus dark-field microscopy),
- to their analysis (e.g. cell nucleus segmentation),
- up to the establishment of a final medical assessment (e.g. malignant tumor probability).

In this way, personalized medicine is primarily a matter of data science, aiming not at establishing new medication for patients but at structuring individuals into subpopulations that differ in their characteristics, e.g. with respect to their response to a therapeutic for their specific disease, or with respect to a phenotypic manifestation.

Challenges & future research

Each stage in this information processing chain presents specific challenges in terms of facilitating data analysis through machine learning and reasoning models to synthesize higher-level knowledge gain from lower-level input.

While model synthesis at higher levels is more related to the human way of thinking, the challenges become more apparent as we climb higher in the information processing pyramid. In this context, we face the need to enhance what is called Narrow Machine Learning (ML) towards **Relational ML**[2,3]. While Narrow ML is restricted to building models from statistically independently and identically distributed (i.i.d.) samples, Relational ML aims at taking also contextual data in terms of linked data and relations into account.

At the level of data collection, that is at the bottom of the pyramid, we above all face problems related to data provenance such as the phenomenon of data shift e.g. due to different life or genomic conditions, imbalance of the different subpopulations, imbalance of data quality or availability of meta-data e.g. due to costs arising from time-consuming annotation. The greater amount of data therefore can have a paradoxical effect if the data sampling violates the assumption of independent and identically distributed data. A data set shift can cause misleading parameter tuning when performing test strategies such as cross-validation. Therefore, engineering machine learning systems largely relies on the skill of the data scientist to examine and resolve such problems. The ML subfield of **transfer learning** tackles such problems by exploiting knowledge in the source domain to improve the performance of an algorithm on a related target (presumably shifted) domain.

At SCCH we focus on the whole life cycle of software and AI system engineering by addressing in particular (i) sustainability monitoring, (ii) AI modeling, (iii) system evolution, and (iv) audit and certification. Currently, its interdisciplinary team of mathematicians, data and software scientists consists of about 100 researchers.

A specific focus is on privacy preserving transferable as well as explainable machine and deep learning.

SCCH, www.scch.at, was founded in 1999 by the Johannes Kepler University Linz (JKU) as Austrian non-university RTO, participating in the Austrian FFG COMET program (https://www.ffg.at/comet).

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Artificial intelligence is changing the facade of clinical genomics

Guest Commentary

••• *By Jyotsna Batra*

photo courtesy of the author

Analysis of an individual's complete genetic information (genomics) has become a constitutive component of biomedicine and pharmacology. Applications of genomics in the field of disease diagnostics and therapeutic targeting have skyrocketed within the last decade. The world-famous case of Angelina Jolie vastly popularized genetic testing of the BRCA gene for breast cancer. While we have been highly successful at the single gene mutation front, integration and interpretation of gigantic data sets generated through current world-wide sequencing/genotyping projects makes analysis error-prone when addressed with standard statistical approaches and impractical to perform using human intelligence. Advances have been made in AI-based computer vision approaches and have gained FDA clearance for a variety of clinical diagnostics, especially imaging-based diagnostics. However, a molecular diagnosis from a combination of genomic and phenotypic data using AI is still in its infancy, but with enormous potential. Several AI-based tools have been proposed to support identification of genetic variants from latest next-generation sequencing data, as well as genome annotation and variant classification with respect to their pathogenicity, in order to potentially implement targeted therapies for certain diseases.

For example, AI algorithms have been successfully trained on variants of known pathogenicity with data augmentation using cross-species information. Similarly, deep-learning-based approaches have substantially improved our ability to detect DNA-DNA and DNA-protein interactions, as well as annotation of regulatory elements and allow to predict the influence of genetic variation on those elements including that in non-coding RNAs. Nevertheless, cautious approaches towards the selection of methods and consideration of regulatory and ethical challenges around the sourcing and privacy of the data used to train the algorithms are required for the comprehensive implementation of AI in clinical genomics in high risk settings.

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Glossary

Artificial Intelligence
The theory and development of computer systems able to perform tasks normally requiring human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages.

Deep Learning
A type of machine learning based on artificial neural networks in which multiple layers of processing are used to extract progressively higher level features from data.

Digital Pathology
Digital pathology, also known as whole slide imaging (WSI) or virtual pathology can be defined as a digital acquisition of stained large-scale tissue sections for a digital visualization.

Histology
The study of the microscopic structure of tissues.

Immune Phenotyping
A process that uses antibodies to identify cells based on the types of antigens or markers on the surface of the cells.

Machine Learning
The use and development of computer systems that are able to learn and adapt without following explicit instructions, by using algorithms and statistical models to analyse and draw inferences from patterns in data.

Precision Medicine
Medical care designed to optimize efficiency or therapeutic benefit for particular groups of patients, especially by using genetic or molecular profiling.

Tissue Cytometry = Next generation digital pathology
Tissue Cytometry can be defined as the in-situ identification and quantification of molecular marker expression, cellular phenotypes, mRNA, multicellular tissue entities, etc. within the native tissue environment. Tissue cytometry is equivalent to flow cytometry in terms of phenotypical and functional analysis, with the advantage of retaining tissue integrity.

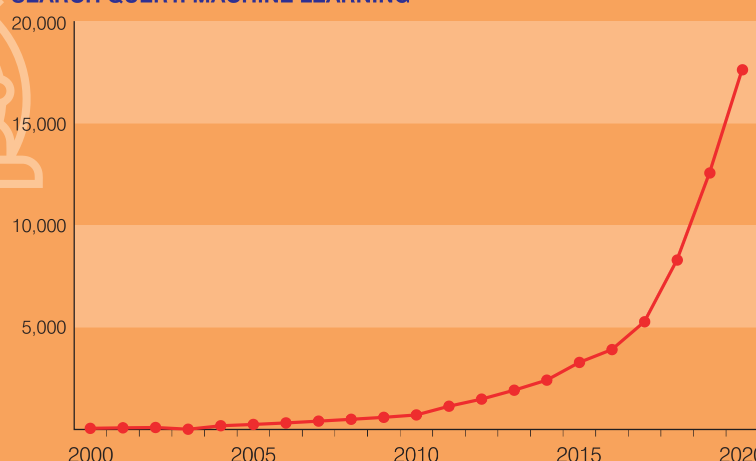
Facts & figures

Artificial Intelligence (AI) in the context of healthcare or biomedicine can be characterized as machine learning/deep learning models, i.e. algorithms specializing in pattern recognition. Over the last decades these tools have continuously evolved to become more robust.

$ 2 bn.

The United States alone is predicted to invest over quadruple the amount spent in 2019 on AI associated medical research ($2 billion) over the next 5 years.

SEARCH QUERY: MACHINE LEARNING



98%

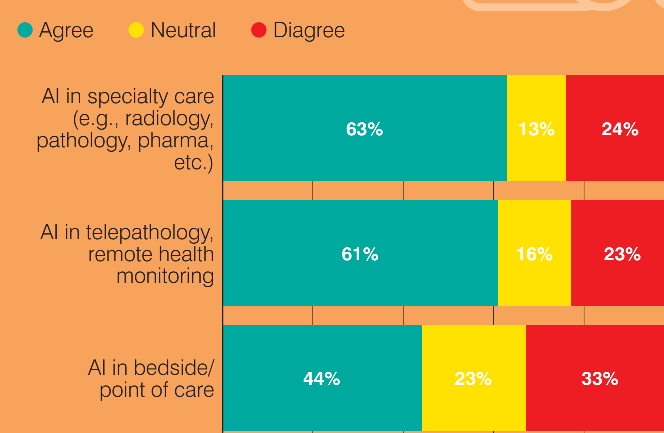
Sensivity

The University of Pittsburgh developed an AI algorithm in 2020 which was shown to detect prostate cancer with a 98% sensitivity and 97% specificity.

10%

The significance of AI in radiology has been steadily increasing as shown by the number of references in scientific publications. Between 2015 and 2018 we have seen an increase from 0 to 10% of all radiology associated publications mentioning the use AI.

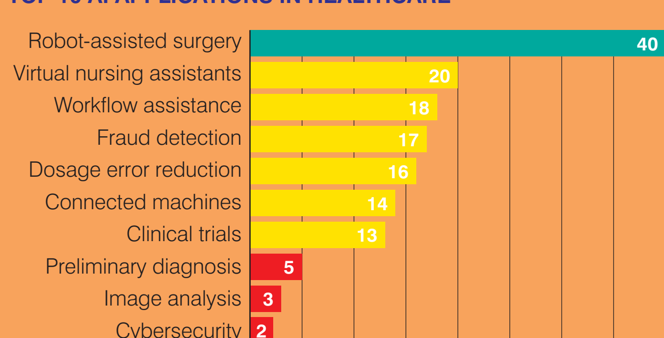
WHERE IS AI ALREADY DELIVERING VALUE TODAY?



$ 150 bn.

The consulting agency Accenture forecasts the AI medical industry will expand to at least $6.6 billion with a massive compound annual growth rate of 40%. This will likely lead to an uptake of artificial intelligence technologies, resulting in an estimated $150 billion in yearly savings.

TOP 10 AI APPLICATIONS IN HEALTHCARE



Top 10 healthcare AI applications and the value they will produce by 2026 in billion $

CHRONIC HEALTH CONDITIONS EXPECTED TO BENEFIT MOST FROM AI