HSE·AG

Contact
Hombrechtikon Systems Engineering AG
Garstligweg 6
8634 Hombrechtikon
Switzerland
www.hseag.com
info@hseag.com

Engineering and biology thinking together - that sets us apart

A significant factor in HSE·AG's success is the mutual ambition of the company's engineers and scientists to understand each other's perspectives. Chairman Hans Noser and CEO Michael Collasius believe that this collaboration will become increasingly vital in the fields of modern oncology and personalized therapies.

Michael Collasius, CEO HSE·AG

Hans Noser, Chairman HSE·AG

How do you look back on 2024?
Michael Collasius: Our environment has experienced an extraordinary phase in recent months. For the first time in my memory, the global life sciences and diagnostics market has contracted for more than two years in total. Before that, an annual growth of around 4 % was the norm.

Hans Noser: Against this backdrop, I am very proud of what we have achieved. We were able to increase our sales by almost double digits, while the industry suffered a decline of over 2 %.

M. C.: Our longer-term development continues to be extremely positive. It seems that the dip following the "hypergrowth" in diagnostics triggered by the Covid-19 pandemic has now been overcome.

Is there a secret to success behind the above-average performance?
H. N.: We always think about device technology and biological processes together. It is crucial that the whole team thinks about both worlds. Our life sciences scientists want to understand technology and our engineers want to understand molecular biology. This enables us to work together much more effectively in teams. In many organizations, specialists remain confined to their own areas of expertise. When they then work together in a team, misunderstandings arise almost automatically.

M. C.: This shared thinking between biology and engineering is also evident when we ask our customers why they like to work with us. The answers are that they "feel understood," "can discuss things with us as equals" or that we "respond extremely flexibly and precisely to their needs." Added to this is the "tangible enthusiasm of our developers" and the fact that we "keep our promises."

What were the growth drivers last year?
H. N.: On the one hand, we are constantly acquiring new customers and can advance into new areas of application. This currently includes bioprocessing in connection with the automation of CAR T-cell therapies, for example. On the other hand, we are also increasingly being selected by existing customers for new projects. This shows us that we are on the right track with our focus on the automation of molecular biology laboratory processes and our aspiration to understand the applications just as well as the technologies.

> "Our customers feel understood by us and appreciate how flexibly we respond to their needs.

M. C.: We are currently developing an entire family of measurement modules based on our OEM component eviDense UV, an optical analysis module. They can be used to check the quality of samples directly in the analysis workflow. Depending on whether nucleic acids, proteins or cell samples are being assessed, a different measuring unit is simply used.

H. N.: The development of the evi family – the branding of the modules derived from the word evidence – is another example of our understanding of applications and laboratory practice. Over the years, our developers have noticed in many customer projects that there is a break in the analytical processes in the optical quality control of samples, which costs a lot of time and therefore money. We have therefore set ourselves the task of designing possible solutions. All device manufacturers can now benefit from the results of our development efforts.

Is the tight labor market slowing HSE·AG's growth?
H. N.: Fortunately, finding qualified employees has not been a problem for us so far. On the contrary, high-caliber developers approach us of their own accord.

M. C.: Our culture is a key factor for attracting top performers. Most individuals who join us have already gained experience in one or two jobs after completing their studies. Therefore, the decision to join HSE·AG is usually a well-considered one.

Our open communication and mutual understanding make us attractive to both young professionals and experienced specialists. Engineers quickly realize that they can develop much better solutions if they understand the molecular biology of the assay and the disease in oncology diagnostics, for example.

> "We have a very special corporate culture. Everyone takes responsibility.

Are there any projects that particularly stood out in 2024?
M. C.: One of our significant projects is in the field of bioprocessing for CAR T-cell therapies, where we are integrating ten tests into a single device. This integration not only makes the processes much more efficient compared to the manual analyses previously carried out but also greatly simplifies certification, as only the machine needs to be verified, not each individual manual step.
Other major projects include developing a complete liquid handler and a high-throughput diagnostics system.

A good corporate culture also includes responsible management
H. N.: That is very important to us. CSR (Corporate Social Responsibility) is an integral part of our corporate culture. Respect for each other and for society and the environment is two sides of the same coin.

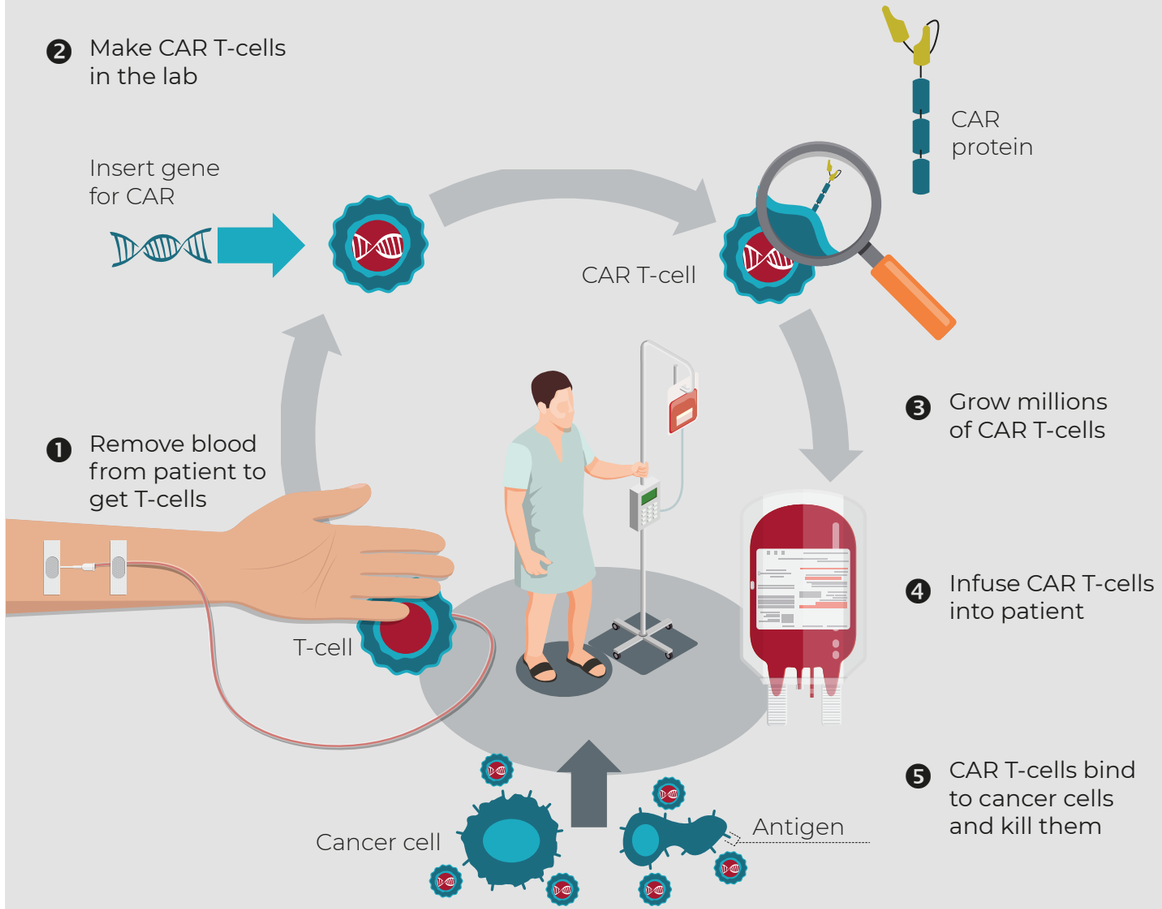
After having our sustainability assessed by EcoVadis specialists for the first time in 2023, we drew up a binding Code of Conduct in 2024 and introduced it throughout the company. It uses specific examples to ensure that all HSE·AG employees, partners, customers and other stakeholders always meet high ethical standards. It is based on our six fundamental corporate values: enjoyment, usefulness, ambition, sense of reality, search for the best solution, fairness and respect.

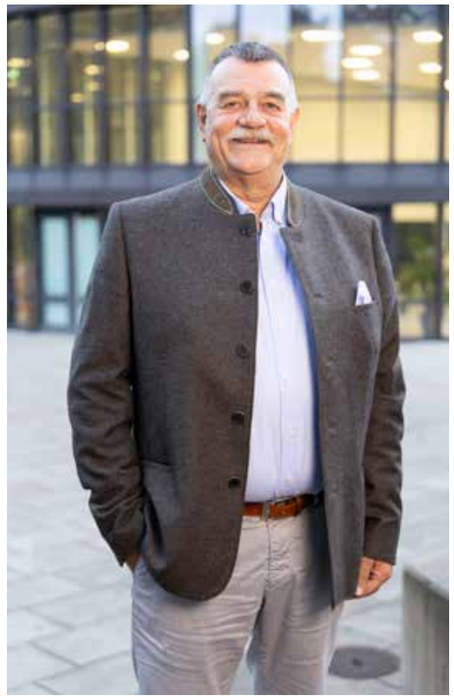
The Code of Conduct includes a whistleblower app, which can be used to report any irregularities anonymously.

What are your expectations for 2025?
M. C.: I expect our growth to increase again to up to 15 %. We will launch product innovations and products from our evi module family for checking sample quality. We will also continue to expand our range of services in line with sales. Our headcount is therefore likely to increase in line with sales growth.

H. N.: The silver lining on the horizon of the global diagnostics market is getting wider and wider. The industry is returning to its long-term growth path.

How modified T-cell cancer therapy works





What trends are emerging in diagnostics? Is this the reason for this year's focus on oncology in the annual report?

H. N.: The future pace of technology will largely depend on which forms of medical therapy become dominant. In this annual report, we focus on oncology. Pavel Pisa, with extensive experience in academic research and as former Head of Translational Medicine at Roche Pharmaceuticals, highlights that advances in diagnostics are crucial to reducing the fear associated with cancer. For instance, Next-Generation Sequencing (NGS) has paved the way for personalized therapies. One of the current challenges is to automate new, targeted treatments like CAR T-cell therapies to transition them from the experimental stage to widespread application.

M. C.: Diagnostics, and especially their automation, are very effective means of reducing costs in the healthcare sector. The calculation is simple: the earlier a disease is detected, the more effective and less expensive the treatment is.

> "Now it's time to automate new, targeted treatment forms such as CAR T-cell.

M. C.: Ann Costello, former Head of the Roche Group's Diagnostics Solutions division, explains that developing a successful diagnostic device requires mutual understanding between engineers and scientists. We present various examples from our current projects where we assist our customers in the field of oncology.

The last few years have shown, especially in oncology, how quickly new technology and therapy trends can emerge and then lose importance again. However, these rapid changes do not worry us. We have an insight into a large number of market segments and can therefore sense early on when a diagnostics train is picking up speed or falling off the rails. Our broad and in-depth market knowledge is an additional added value from which our customers benefit.

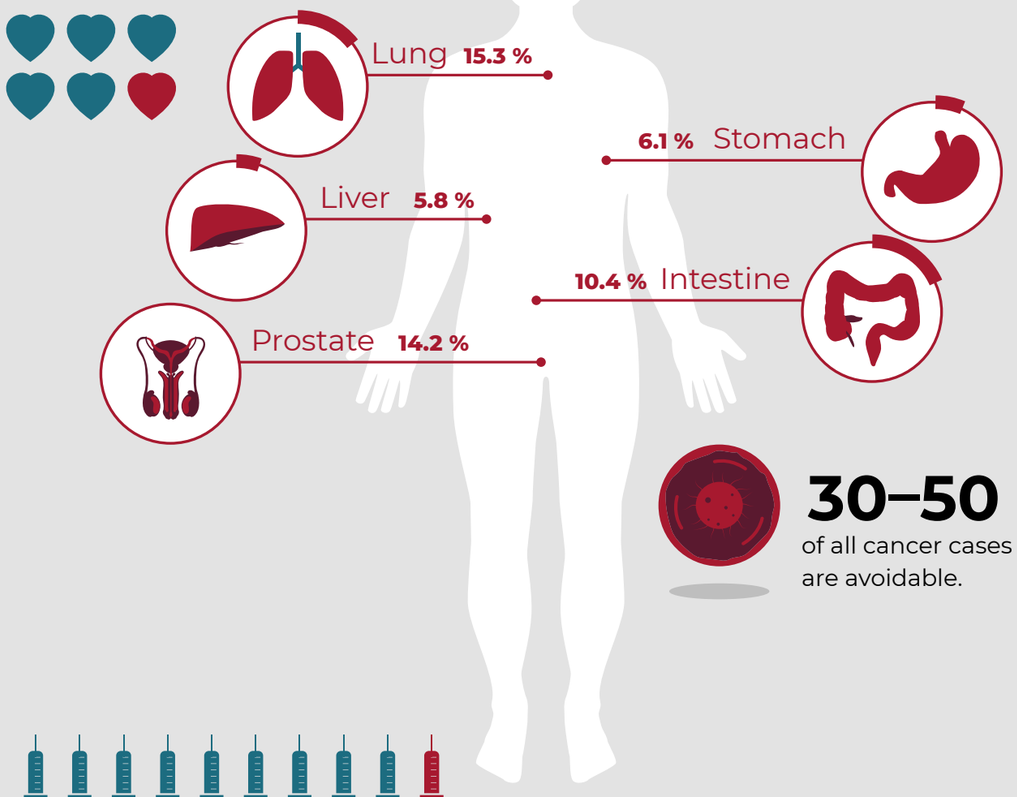
Facts and figures on cancer*

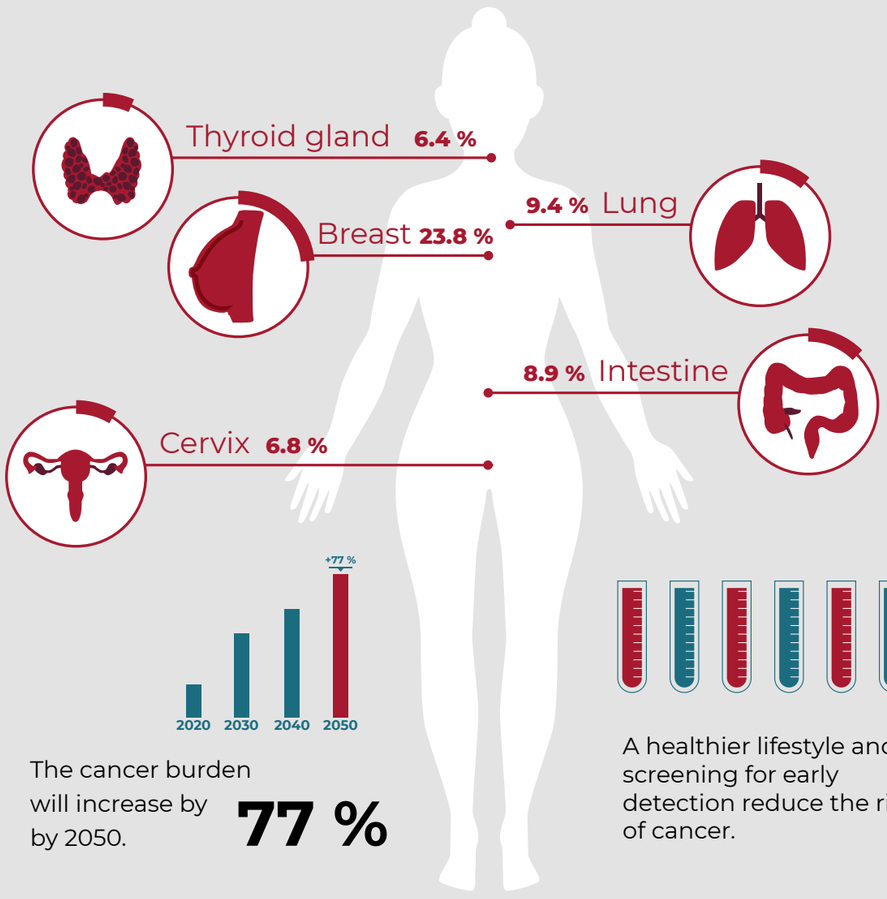
GLOBAL CANCER OBSERVATORY

40 % of all cancer diagnoses are due to obesity.

According to the WHO, cancer is one of the main causes of mortality worldwide, causing around one in six deaths and affecting almost every household.

Today there are **43.8 million** people who were diagnosed with cancer in the last five years and who are still alive.





30–50 %
of all cancer cases are avoidable.

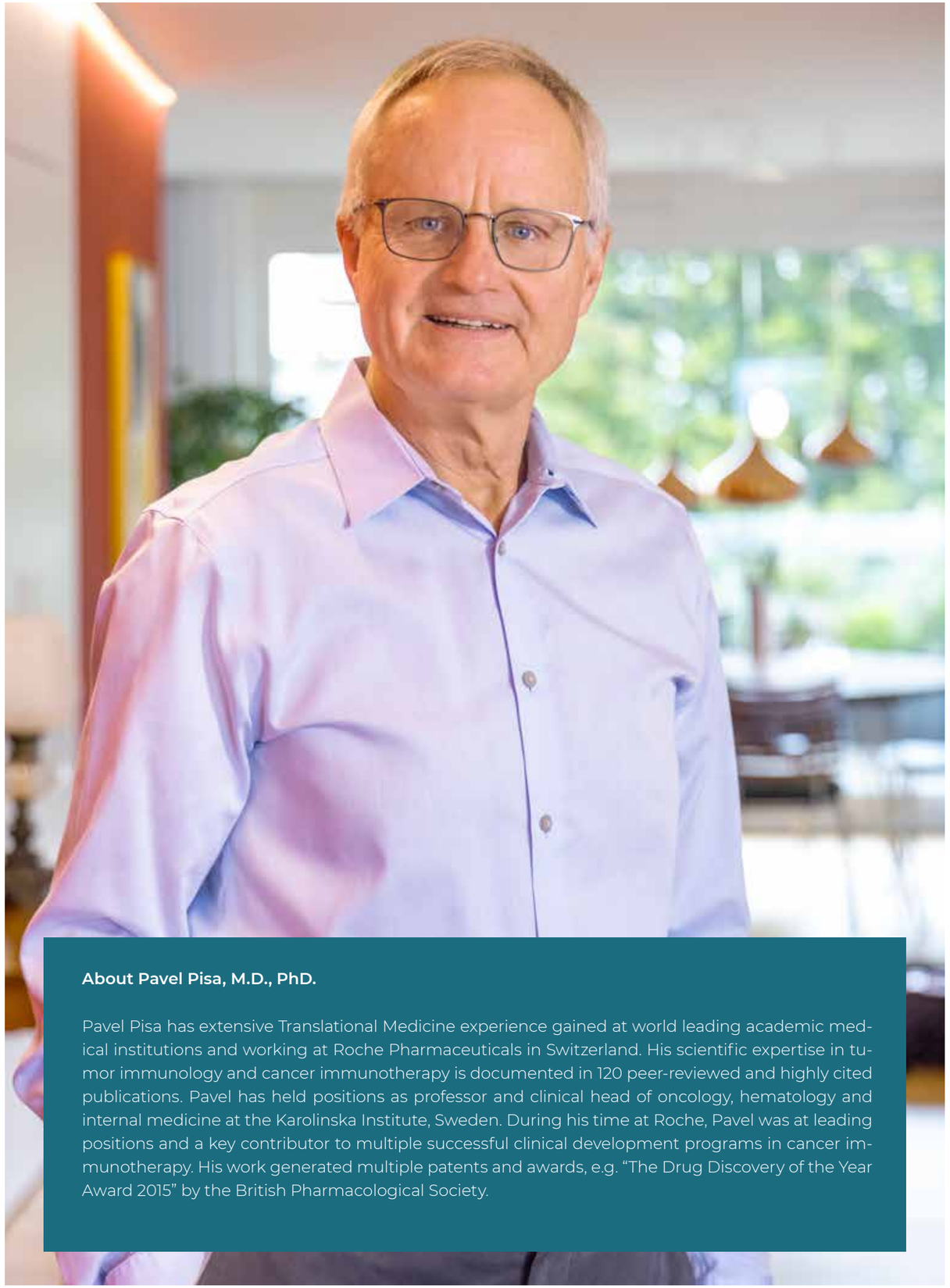
The cancer burden will increase by by 2050. **77 %**

A healthier lifestyle and screening for early detection reduce the risk of cancer.

70 %
of cases of cervical cancer can be prevented with HPV vaccines currently available.

The total global economic cost of cancer is estimated at
1.16 trillion USD

*Status 2022



About Pavel Pisa, M.D., PhD.

Pavel Pisa has extensive Translational Medicine experience gained at world leading academic medical institutions and working at Roche Pharmaceuticals in Switzerland. His scientific expertise in tumor immunology and cancer immunotherapy is documented in 120 peer-reviewed and highly cited publications. Pavel has held positions as professor and clinical head of oncology, hematology and internal medicine at the Karolinska Institute, Sweden. During his time at Roche, Pavel was at leading positions and a key contributor to multiple successful clinical development programs in cancer immunotherapy. His work generated multiple patents and awards, e.g. “The Drug Discovery of the Year Award 2015” by the British Pharmacological Society.

Cancer is losing its scare: thanks in part to diagnostics

The chances of surviving a cancer diagnosis have increased significantly in recent years. In addition to new, more targeted forms of treatment, advances in diagnostics are the main reason for this. Experienced oncologist Pavel Pisa is convinced that their importance will continue to grow. Diagnostics are essential for personalized diagnosis, but also for monitoring treatment and detecting resistance.

Cancer is the second leading cause of death worldwide, after cardiovascular disease. According to the World Health Organization (WHO), around 9 million people die each year from malignant tumors. But recent developments are encouraging. Mortality rates have fallen significantly over the past 20 years. In the US, for example, it has decreased by around 25 %.

Huge progress in the last 20 years

Especially in countries with a well-developed healthcare system, the diagnosis of cancer is becoming less frightening, confirms Pavel Pisa. A former professor of experimental clinical oncology at the Karolinska Institute in Sweden and head of translational medicine at Basel-based pharmaceutical giant Roche, Pisa has more than 40 years’ experience in cancer research. “When I started as oncologist, my daily life was filled with frustration: patients first appeared with advanced stage disease, the available ’one fits all’ therapies were excessively harming the healthy tissues, and relapse, which always happened, was a death sentence,” he says.

Thanks to groundbreaking advancements in early detection, personalized therapies, and continuous monitoring, cancer is now becoming less of a feared diagnosis. Pisa is optimistic: “There are still many challenges, but compared to the 1990s, the situation today is very different. Curing cancer is no longer a pipe dream. ’It is not even the beginning of the end. But it is, perhaps, the end of the beginning,’ to quote Winston Churchill.”

Genomic diagnostics pave the way for personalized medicine

According to Pisa, the main reason for the great progress made in recent years lies in diagnostic techniques. On the one hand, they make it possible to detect tumors at an increasingly early stage and thus combat them more effectively. On the other hand, NGS has made it possible to pinpoint the genetic changes in cells and gradually understand them better.

The findings of NGS are changing the face of oncology, as Pisa points out: “Just imagine that with a lung X-ray you can see lumps of

the size of 2–4 cm and with a CT scan you can focus down to 1 cm. That area corresponds to 100 million tumor cells. With molecular diagnostics we can detect circulating tumor DNA at concentrations below 0.1 % of all cell-free DNA found in blood samples. It is not only the sensitivity we see, but also the information we obtain nowadays that is mind-boggling. We have so many subgroups of a tumor type that we previously called by just one name: 'lung or breast cancer'! Now, we do not speak about 'targeted' but 'personalized' therapies, tailored to the genetic make-up of an individual tumor in the patient."

For pharmaceutical companies, the personalization of therapies also means moving away from blockbuster drugs. For the diagnostic industry it creates greater volumes and workload, increased through-put and higher speed. For the clinical oncologist it requires managing and correctly interpreting such information and constantly following new advances in the field. For the patient, as the statistics prove, it means not only "life extension" but also higher chances of combating cancer death with maintained quality of life.

Successful drug- and cell-based immunotherapies

Targeted immunotherapies are among the treatments that have been successfully personalized in recent years. These include drugs such as checkpoint inhibitors, which block specific receptors that a tumor uses to downregulate the immune system, or tumor-specific antibodies produced in the laboratory.

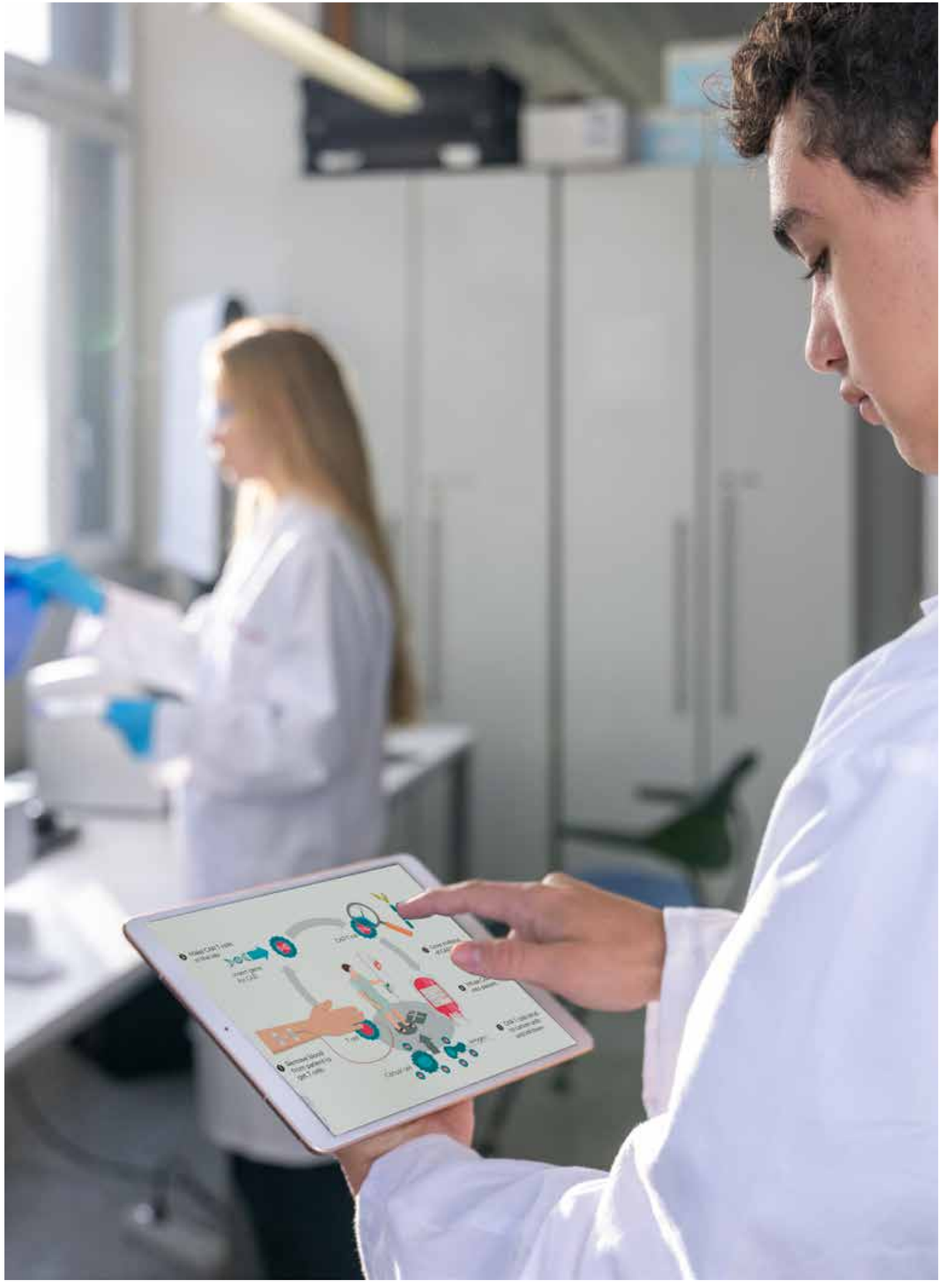
The latest patient-specific immunotherapy, which can now be used to fight metastases throughout the body, is chimeric antigen receptor (CAR) T-cell therapy. T lymphocytes, which are part of the patient's white blood cells, are manipulated in the laboratory to act as "drug cells" and attack a specific surface antigen on the individual tumor. In many patients, this not only significantly reduces the tumor burden throughout the body. In some cases, it is even possible to clear the body of malignant cancer cells completely.

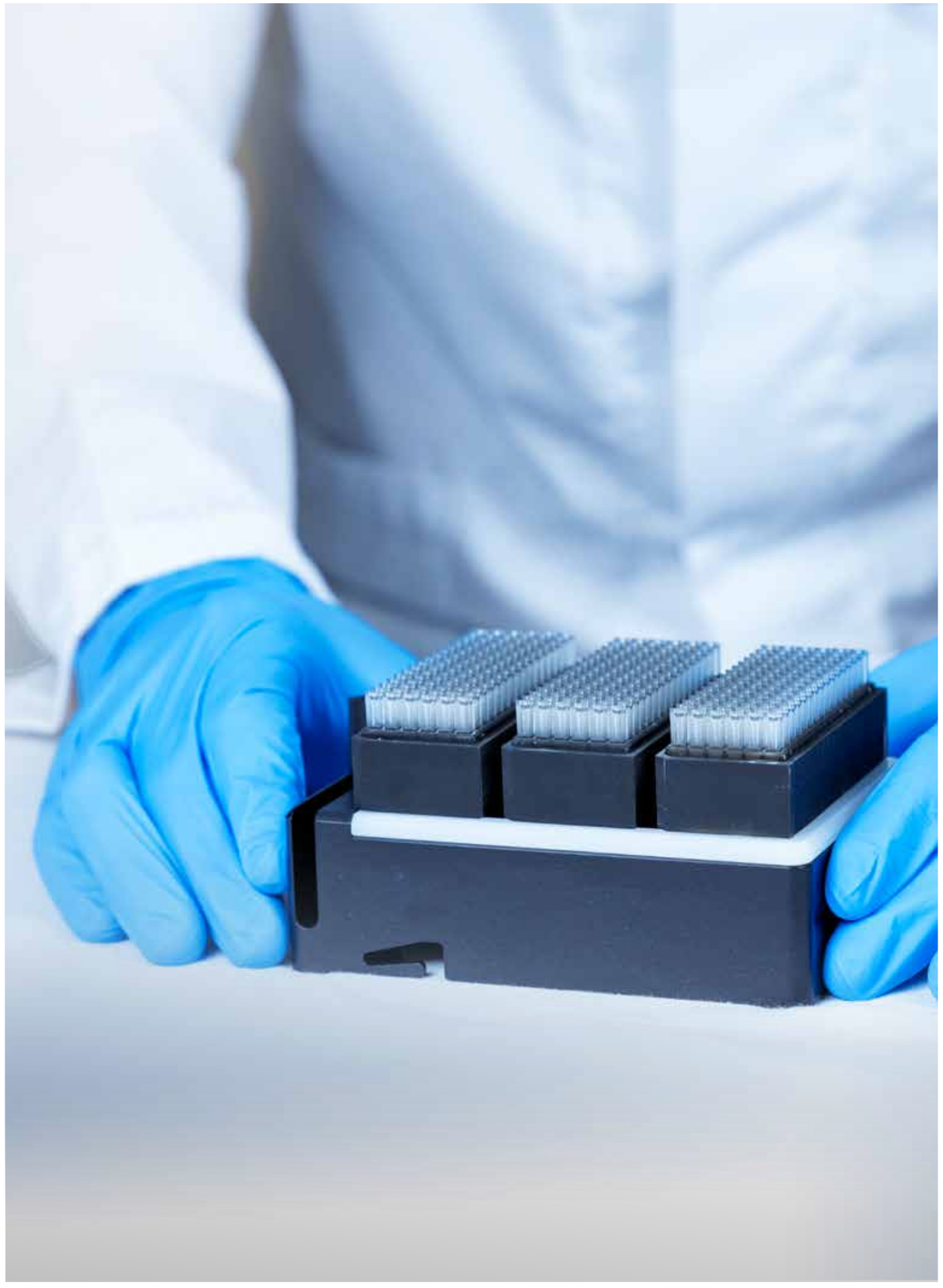
Mandatory automation requires understanding of the application

As successful as CAR T-cell therapy has been in clinical practice, the cost barriers to its widespread use are just as great. The production of individual T-cells alone costs more than CHF 100,000. Today, it is still largely based on manual work that has to be carried out by specialists in sophisticated "germ-free" facilities under difficult labor conditions. A lot of resources could be saved by automating the processes and thus making it more accessible to a wider patient population.

However, automating such specific medical therapies is extremely challenging, as Pisa knows from experience: "It requires engineers who not only know the technological side of the device. They also need to understand the biology and the laboratory reality of the application. This is the only way they can discuss with manufacturers on an equal footing and find a solution that can effectively reduce costs and improve the real-life manufacturing conditions. It needs to be a joint effort, not the world's best solution to an issue that doesn't exist. Conversely, sometime the biologists don't even know about technical solutions to mitigate their workload."

"I have seen many promising innovations from scientists that have not been turned into a marketable product. And often the reason was that the development partner did not properly understand the biology behind the process and the specific market conditions in the life sciences," says Pisa.





Small molecules with a big future
According to Pisa, medicine has by no means reached the end of the road with targeted immunotherapies such as CAR T-cell: “Currently, so-called antibody-drug conjugates, in which tumor-specific antibodies are combined with cell-destroying agents, are on their way into clinical practice. For example, chemotherapeutic agents or radioactive isotopes can be targeted to the tumor cells. By targeting the tumor instead of the entire body, they are much more effective and have far fewer side effects.”

Pisa also sees a great future for targeted small-molecule drugs. They are designed to bind specifically to certain tumor proteins and block the division of cancer cells. They could also be used instead of antibodies for the targeted transport of cell-destroying substances.

Diagnostics crucial during and after treatment
Regardless of which form of therapy is most successful in curing cancer in the future, diagnostics will play an increasingly important role in all of them. As Pisa explains, diagnostics are no longer just crucial for the precise identification of tumors before personalized therapy: “Cancer is not a disease that can be detected and then cured forever with a single treatment. Tumors evolve. With each cell division, new mutations occur and, over time, resistance to an initially successful therapy can develop.”

But today we can also respond much better to these changes in the tumor, states Pisa: “Formerly we had only one line of treatment to offer to a patient and the majority of our patients were too sick to receive any treatments when the cancer came back. Now there are three to four treatment lines that patients are fit to receive later, depending on how their cancer changes.”

As the correct treatment choice depends on diagnostics, pharmaceutical companies today often develop diagnostic tools in parallel with a new therapy submission. With systematic monitoring, relapses can be detected early and new targets for the treatment of the mutated cancer can be systematically identified.

Science, clinics, pharmaceuticals and engineering together
Pisa’s many years of experience have shown that the key to translating new scientific findings into successful therapies is the best possible interaction between all the players involved: from scientific research at universities, through translation into pharmaceutical therapeutics by industry and clinical practice in university hospitals, to the engineering of automation solutions that enable widespread and reliable application.

According to Pisa, Switzerland is particularly well positioned in this respect. It has world-class companies and research organizations in all key areas, concentrated in a very small geographical area. “In Switzerland, I can find first-class specialists in practically every field of expertise, and they can even meet in person quickly and easily if necessary. This makes interdisciplinary collaboration even easier.”

Sources:
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Spatial Biology helping to shape the revolution

Spatial Biology technologies enable us to track the development of tumors and the effects of drugs at the molecular level, down to individual cells. Andreas Geipel, who previously served as technology manager at spatial pioneer Resolve Biosciences, has recognized the unique qualities of HSE·AG through their development partnership. Today, as a principal system engineer, he is one of the biologists who make HSE·AG stand out from other engineering companies.

The precise spatial visualization of the transcription of up to several hundred mRNAs in the cells of tissue sections is revolutionizing our understanding not only of the development of tissues and organs, but also of diseases and especially of cancer. Since June of last year, Nature Communications Biology has dedicated a curated collection of articles to the spatial biology of cancer.

From Spatial Chief Developer to Senior Systems Engineer

One person who knows exactly what is possible with spatial technologies is Andreas Geipel. The Principal System Engineer at HSE·AG was previously Head of Technology at Resolve Biosciences and thus primarily responsible for the development of the Molecular Cartography platform, one of the most advanced spatial technologies ever.

"Spatial technologies can be used to track exactly which genes are active in which area of the cell and in which order. In this way, the development of a tumor can be tracked in just as much detail as the effect of drugs and immunotherapies," explains Geipel.

Many process steps require highest precision

The reliability of the method is crucial for the technology, as it allows for the individual identification of up to several hundred different mRNA molecules through differentiated staining. "An analysis takes more than a day," Geipel points out. Instead of creating just one image per color, around 1,000 image regions are captured dozens of times. To obtain a meaningful result, hundreds of individual steps must be successfully carried out. Because a code system is used to

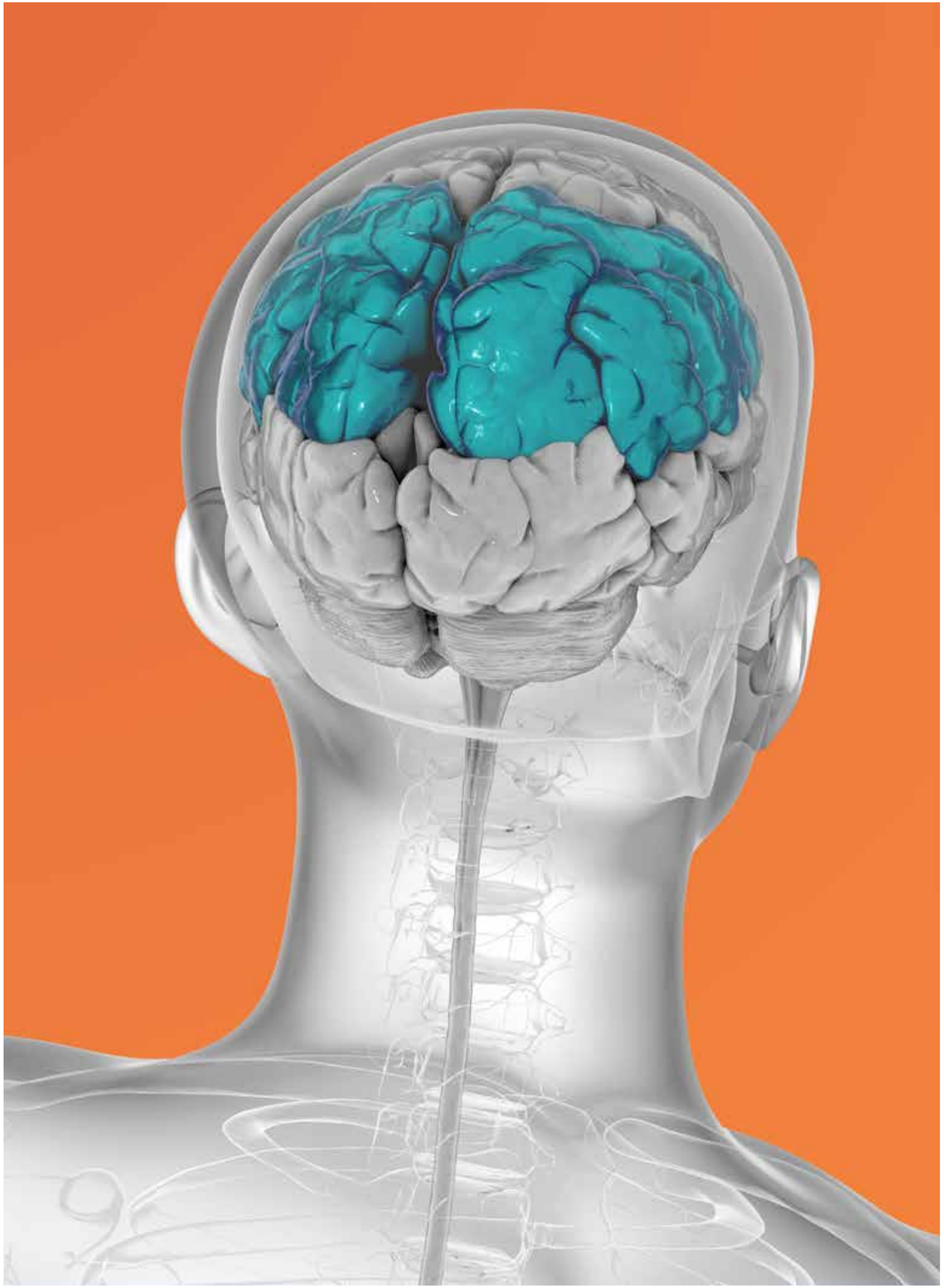
distinguish hundreds of mRNAs with several colors, the result of the entire image region can be lost if just one staining in this area does not work correctly.

This is compounded by the long exposure times that are necessary because, despite amplification mechanisms, there is only a small amount of fluorophore per mRNA molecule. Geipel emphasizes: "To ensure that the individual signal points can be reliably identified in all stains, the work must be extremely precise."

Understanding applications precisely thanks to biology knowledge

As the person responsible for development at Resolve Biosciences, Geipel quickly realized that HSE·AG as a partner understands more than just device engineering: "Many biologists also work at HSE·AG. This means that all employees can understand the biological-chemical processes that take place during the analysis very precisely and can therefore find extremely precise engineering answers to any challenges that arise.

Through collaboration, Geipel was able to successfully automate his groundbreaking spatial technology. The biologist also discovered a new field of activity in device development that personally fascinates him. Today, as Principal System Engineer, he is part of HSE·AG and is jointly responsible for ensuring that the company stands out from its competitors with its understanding of diagnostic applications in their laboratory environment.



Personalized therapies must become more economical

Automating the production of personalized cancer therapies is crucial. This approach not only reduces costs but also minimizes the need for highly qualified personnel, making widespread use feasible. Additionally, the complex quality controls for each therapeutic agent must become significantly more efficient.

The future of oncology is personalized, with therapies tailored precisely to each individual's cancer. A fundamental aspect of this approach is an exact genetic diagnosis of the individual tumor and its development throughout the entire treatment period, including aftercare. This ensures optimal treatment at all times.

Making production faster and more cost-effective

Production of individual therapies must also be automated, emphasizes Felix Westhoff, Head of Projects and Quality Management at HSE·AG: "Without automation, it will not be possible to make personalized methods such as CAR T-cell or mRNA cancer vaccination – however successful they may be – available to as many cancer patients as possible. The current costs of up to several 100,000 dollars per treatment are still far too high for this and the production rates of existing methods are also far too low for widespread use."

What's more, automation is also unavoidable due to the need for skilled labor. "With intuitive operation, a device not only makes a lot of manual work superfluous. It also reduces the training requirements for operating personnel," says Westhoff.

One device each for mRNA vaccines and CAR T-cell activation

In the field of mRNA cancer vaccines, for example, automation means that the synthesis of the mRNA sequences, whose protein products specifically immunize the organism against the patient's cancer cells, and the production of the lipid envelopes, which mediate the transfer of the mRNA into body cells, are integrated into a single device wherever possible. In the same way, the entire process of producing a CAR T-cell therapeutic must be brought together in a continuous system, starting with the selection of T-cells from the patient's serum and the vector-induced activation of the T-cells on the patient-specific tumor through to the selection and isolation of the activated cells, for example using magnetic beads.

Quality controls must also be automated

In addition, there is another area in all personalized therapies where efficiency must be increased: the quality controls required for approval. Up to now, they have required practically as much effort as the production of the individual therapeutics, emphasizes Westhoff: "Automating the verification assays can save as much time as automating the production. And the need for qualified personnel can also be reduced to a similar extent."

Diagnostics in oncology

Screening, prevention

Therapy development

Therapy production

Diagnosis therapy decision

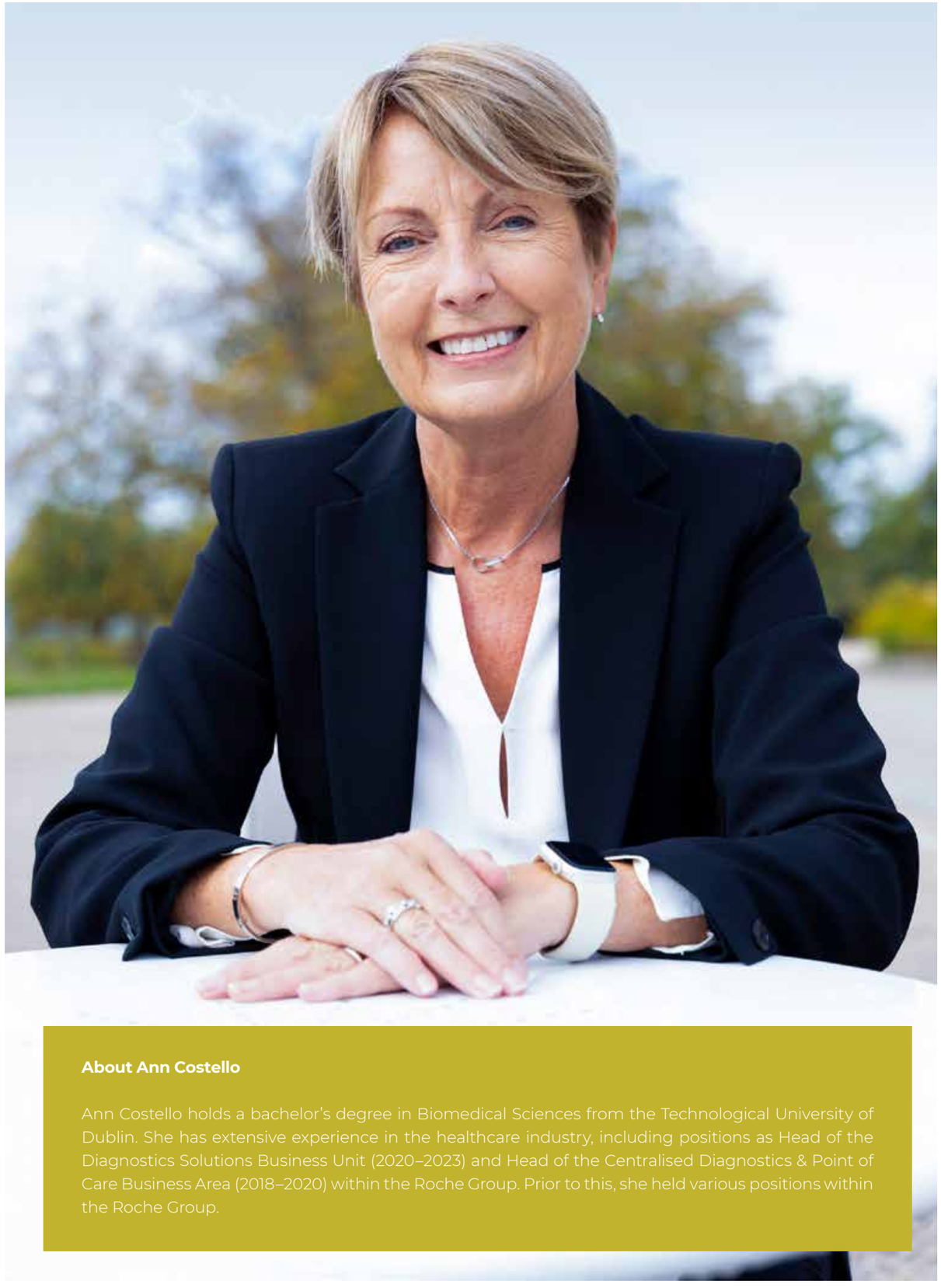
Therapy implementation

Patient monitoring/ aftercare

Quality control

Further steps

Every cancer is different and unique. Diagnostic tests help to gain important insights that enable better outcomes for patients during their treatment.



For diagnostics, automation is fundamental

As a former Roche Diagnostics senior executive, Ann Costello has witnessed the enormous progress in cancer diagnostics over the course of her 30+-year career. For her, the key success factors in diagnostic device development are clearly defined customer requirements, open communication and collaboration between all partners as well as customer involvement throughout the entire development process. As they need to master new skills such as Artificial Intelligence and Machine Learning, diagnostics companies must create interdisciplinary product development teams to remain competitive and innovative.

About Ann Costello

Ann Costello holds a bachelor's degree in Biomedical Sciences from the Technological University of Dublin. She has extensive experience in the healthcare industry, including positions as Head of the Diagnostics Solutions Business Unit (2020–2023) and Head of the Centralised Diagnostics & Point of Care Business Area (2018–2020) within the Roche Group. Prior to this, she held various positions within the Roche Group.

How has the importance of diagnostics in oncology changed in recent years?
The role of diagnostics in oncology and patient care has always been important. Accurate diagnosis is a prerequisite for successful treatment. But over the course of my career, the field of oncology has undergone a huge transformation. In particular in the area of genetic sequencing capabilities, completely new possibilities have opened up.

Thanks to Next-Generation Sequencing (NGS), we can now identify genetic alterations in individual cancer tissues and develop personalized therapies. The synergy between scientific and technological advances in diagnostics has been instrumental in the significant increase in survival rates of cancer patients.

What are the current trends in cancer diagnostics?
NGS technologies are becoming increasingly precise and cost-effective. For example, a few years ago there were only three or four markers for lung cancer, but now there are more than 20 and researchers continue to discover novel genetic alterations that contribute to the disease. This is great news for patients because depending on the genetic profile of their tumor their oncologist can tailor their therapy.

Another exciting area is the evolution of liquid biopsies. They may become an important alternative to the often painful and risky removal of tissue samples to diagnose cancer. Liquid biopsy uses Next-Generation Sequencing (NGS) to detect minute amounts of altered DNA sequences in the blood, derived from dying cancer cells. The

technology is already being used to monitor treatment. In the future, it may also be used for cancer screening. However, specificity and sensitivity still need to be improved.

And histology, which has long been the number one diagnostic tool in oncology, will it disappear?
Personally, I don't believe histology will disappear as the primary diagnostic tool in oncology. Pathologists will continue to rely on the ability to visually examine cancerous tissue directly. In addition, histology itself is evolving. Automation has made a huge impact on the turnaround time of results and more importantly on the accuracy of the result for the patient. In addition, histology, like many other fields, is becoming increasingly digitized. For example, Digital Pathology which uses whole-slide imaging (WSI) of histology slides to analyze samples on a computer screen and AI-based (Artificial Intelligence) algorithms to assist in the identification of cancerous regions, the evaluation of tumor features and the grading of cancer. AI has the potential to augment the diagnostic capabilities of pathologists to further improve accuracy and consistency in cancer diagnosis.

You mention automation. How important is it to modern cancer diagnostics?
Automation is fundamental. Historically, cancer diagnostics techniques were largely manual. Processing tissue samples, running assays, and conducting genomic or molecular analyses required significant human involvement, increasing the potential for errors and limiting throughput. Automation ensures consistent and reproducible results and reduces the likelihood of human error leading to more accurate results.
Another area where automation plays a key role is in drug discovery and cancer research. Automated systems allow researchers to rapidly test thousands of compounds, speeding up the identification of potential drug candidates. And automation will also help to reduce the cost of cell-based immunotherapies such as CAR T-cell.

Are the benefits of automation limited to higher throughput rates and lower costs?
Automation accelerates diagnostic testing, enabling quicker patient diagnosis. However, another important element of automation is consistent results, which is critical for accurate diagnosis and treatment planning for patients.

Laboratories also have other requirements like scalability. As demand for diagnostic services grows, automation allows laboratories to scale up their operations without increasing their workforce.

During your career you oversaw the development of automation solutions at Roche Diagnostics. What are the biggest challenges in your experience?
One of the biggest challenges is to create a team with different specialists from different disciplines and departments across company boundaries and integrating their combined knowledge of biology, medicine, and engineering to tackle the challenges together. This requires transparency, excellent communication, mutual understanding and respect.

What does mutual understanding mean in relation to the engineers developing the device?
For engineers developing a medical device, mutual understanding is key. It refers to shared knowledge and goals between

all stakeholders involved, engineers, assay development scientists, regulatory experts, and most importantly the end users. This concept ensures that everyone has a clear, aligned perspective on the customer requirements, design, functionality and regulatory requirements. Words can be ambiguous, therefore it's essential that there is close and continuous communication between all parties involved.

Are there success factors that are often neglected in device development?
Diagnostic devices – just like consumer products – need to be developed with the customer in mind, which is not always the case. The challenge for product development teams is to keep the customer requirements front and center.

In terms of key success factors, ease of use is becoming more and more important. In many parts of the world, medical laboratory professionals are in short supply, which means non-specialist technicians must be able to operate the instrument reliably with little training. Maintenance must also be simple and kept to a minimum. To achieve this, the R&D team needs to have a good understanding of the customer requirements and to take a customercentric approach to the development process.

What exactly do you mean by customer-centric development?
Customers must be involved throughout the development process, not just at the beginning and end, which is often the case. Product development teams must involve users right from the outset where customers provide direct input on their workflow as well as features and functions. It must be an iterative process with regular feedback loops during prototyping and testing. Of course, this means much more work upfront for the team. However, it pays off in several ways. Firstly, the device will be much closer to what the market wants, and secondly, customers who have been involved in the development will have a stronger relationship with the manufacturer and the device.

In your opinion, are there key skills that diagnostics manufacturers will need to master in the future?
I believe Diagnostics manufacturers will need to master new skills to remain competitive and innovative, especially as the field evolves with emerging technologies like AI and personalized medicine.

AI and machine learning (ML) improve the analysis of large datasets to identify patterns and gain valuable insights to improve accuracy and efficiency in diagnostics. AI-powered tools can potentially assist in predictive diagnostics, identifying diseases at earlier stages, and tailoring treatments to individual patients, which is a key component of personalized medicine.

To do this, manufacturers will need experts with an entirely new skill set such as bioinformatics to analyze and interpret large data sets, for AI algorithm development and the integration of AI with diagnostic platforms.
However, the development and deployment of AI in diagnostics is still in the early stages, and there are several technical and regulatory challenges that must be overcome before this technology can reach its full potential.

Sample quality determines the success of the diagnosis

HSE·AG possesses extensive and profound expertise in handling a wide variety of medical and biological samples, as well as the full spectrum of processing technologies. The engineers are well-versed in the specific requirements of various applications, ranging from multiplex PCR and NGS libraries to proteome analyses and tissue staining assays, and even the emerging spatial biology platforms.

"The reliable automation of nucleic acid purification for analytical and diagnostic applications is practically the DNA of HSE·AG," emphasizes Felix Westhoff, Head of Projects and Quality Management at HSE·AG. CEO Michael Collasius and CTO Konstantin Lutze were responsible for launching the BioRobot 9600, the first device to automate the purification of nucleic acid samples in microtiter plates, at assay specialist Qiagen back in 1996.

Experience with all kinds of samples and technologies

Today, HSE·AG has a uniquely broad and deep experience with the whole range of sample preparation technologies: from centrifuge-column-based systems and procedures based on magnetic or non-magnetic beads, to the optimal distribution of tissue sections or cell smears on slides, to flow-through methods performed in cartridges and cytometry procedures.

Which preparation technology is optimal in each individual case depends, among other things, on the type of sample and the specific requirements of the assay. Depending on whether multiplex PCR is to be performed, a library is to be prepared for an NGS method, a proteome is to be analyzed, individual cells are to be assessed, or tissue material is to be prepared for spatial analysis of the molecular processes in the cells, other factors are decisive.

"However, the basic principle always remains the same, regardless of whether whole blood, saliva, swabs or tissue sections are available as starting material," clarifies Westhoff. The substances to be examined are extracted or isolated, then the samples are chemically prepared and finally analyzed.

Quickly translating established technologies into new areas

Thanks to its extensive experience, HSE·AG is able to efficiently transfer tried-and-tested processes from one area to another, as Westhoff explains: "For example, we were able to adapt an established centrifuge column application from nucleic acid processing to the specific requirements of protein samples. By not having to develop the process steps from scratch, we were able to provide our customer with a reliably functioning system much more quickly."

According to Westhoff, the current trend is towards cartridges. Assay manufacturers want to get as close as possible to the patient with their tests. For this purpose, the sample is already placed in the cartridge when it is taken from the patient – ideally as self-service – and the automated analysis is then carried out in the cartridge. The reaction steps of the assay are then carried out using flow-through technology.

The consistency achieved by the cartridges reduces the need for highly qualified personnel on the user side. Moreover, hardly any additional consumables such as tips, reaction vessels or plates are required for the analysis.

"For us, automation always means increasing efficiency," emphasizes Westhoff: "Faster and greater sample throughput is the basis. We achieve additional added value when material consumption is also reduced and the qualification requirements for operating personnel are lowered thanks to ease of operation."

About Michael Collasius

Michael Collasius holds a Diploma in Biology from the University of Bonn, Germany, a Diploma in Molecular Biology from the Institute of Genetics at the University of Cologne, Germany, and a PhD from the Max Planck Institute of Biochemistry in Martinsried/Munich, Germany.

He has more than 25 years of experience in the life science and diagnostics industry. Michael Collasius has developed a broad portfolio of innovative laboratory sample preparation and analysis platforms for industrial and academic applications, held several leadership positions and built companies in the triple-digit million range from scratch. Michael was a member of the board of QIAGEN before co-founding HSE·AG in 2017.

Artificial Intelligence: between fascination and hope

Convincing answers to everyday questions and astonishingly accurate protein structure predictions are offset by limited creative inputs and predictive maintenance systems of limited usefulness. For Michael Collasius, CEO of HSE·AG, this dichotomy of artificial intelligence exemplifies where it can be best utilized in diagnostic applications and where, at least from today's perspective, it still does not offer many advantages.

Michael Collasius: Sometimes I feel a little lost when it comes to artificial intelligence (AI). On the one hand, there is this fascination: the precise answers and explanations that tools such as ChatGPT, Google Gemini, Mistral, Bing Chat or Perplexity provide me with to many questions in everyday life, the enormous accuracy of Google AlphaFold's protein structure predictions or the reliability with which an image recognition system verifies the correct filling of the work deck of a diagnostic device.

On the other hand, I am always disappointed: ChatGPT and its ilk haven't yet provided me with any truly creative and innovative answers that go beyond lexical knowledge. And it's not just the life sciences diagnostics and automation industry that hasn't made any noticeable progress in predictive maintenance in recent years.

Even Zuckerberg is still looking for the killer app

I am not alone in my dilemma. Even pioneers of the AI revolution such as Meta CEO Mark Zuckerberg, who is convinced that AI will transform large parts of our society, in an interview with the business podcast "Acquired," also states that he is not sure what the first applications of the technology will be. His platforms Facebook, Instagram, Threads and WhatsApp have not yet found the AI killer app either and are still experimenting in trial-and-error mode.

I increasingly suspect that this dual nature is a fundamental characteristic of AI. Whether the tools are extremely powerful or completely helpless depends less on the technology itself and more on the question at hand and the environment or, in other words, the data available.

Relationship and available data volume as restrictions

AI is obviously particularly powerful when the objects of investigation are closely related. This applies, for example, to languages or protein structures. Both develop through evolutionary processes from precursors, which automatically create patterns of relationships. In contrast, completely new things usually only allow AI to hallucinate by clinging to any apparent patterns. AlphaFold also fails with structure prediction if an amino acid sequence is artificial and has no relationship to known structures.

In addition to the necessary relationships, there is another limitation that stands in the way of many practical applications. If AI does not have enough reliable data at its disposal, it cannot generate reliable answers. This limits the application for questions that venture into unknown territory as well as for events that only occur very rarely.

The better the device, the more difficult predictive maintenance becomes

For example, if we at HSE·AG develop a device that works very reliably, error events will inevitably only occur very rarely. Predictive maintenance is therefore unlikely to ever work for such quality devices. If the devices were to produce enough fault data to train an AI model, they would be an imposition for users and therefore simply not marketable.

Sufficient data is generated, for example, where many images are created that are related to each other. This applies, for example, to the automatic evaluation of stained tissue sections or the video monitoring of processes on the work deck of an analytical

device. But even in these cases, AI is not a sure-fire success. Sudden light from outside – for example from sunlight when the device has been repositioned – can overwhelm the AI and lead to misinterpretations.

Acceptance for assistance systems is higher than for autopilots

Such errors can usually be detected and rectified sooner or later. However, they impair the acceptance of AI and this is particularly problematic in the medical environment. Doctors must be able to rely on the analysis results. Pathologists therefore prefer to assess the tissue sections with their own eyes. This is nothing but understandable, as they are ultimately responsible for the decisions.

For the time being, AI is therefore best implemented in the medical environment as an assistance system that makes doctors' work easier. For example, it can indicate where they should take a closer look. This is no different in medical practice than in autonomous driving. After all, most of us would feel uncomfortable if we had to leave control of the car entirely to a self-driving AI system. In contrast, assistance systems that park, keep in lane or maintain speed are welcome helpers for the vast majority of us.

Mountains of data can no longer be managed without AI support

One field of application in which AI tools will be indispensable in diagnostics in the future is undoubtedly data analysis. Devices are producing ever more and ever more complex data. Without the help of intelligent systems, humans will no longer be able to distil the necessary findings from these constantly growing mountains of information. This is all the more true as in future there will be an increasing need not only to assess individual diagnoses, but also to combine the results of different analyses.

When and how AI should be used sensibly in diagnostic devices and where the limits of the systems lie are among the most demanding challenges for us device developers. In order to master them successfully, we not only need to have a technical handle on the application but also understand it in a laboratory context. We must also be able to assess the biology on which the assays are based. Only then can we reliably assess the responses of an AI and incorporate them into the development process.

Used correctly, AI tools will significantly advance analytics. In the wrong place, they generate false security at best and false results at worst.

Specifically developing Next-Generation Sequencing methods further

NGS technologies are becoming ever more powerful and ever more specialized. HSE·AG has many years of experience in all areas of high-throughput sequencing through to the development of a complete system. Our expertise in the area of direct liquid handling processes for integrated sample quality control is unrivalled.

Next-Generation Sequencing (NGS) has laid the foundation for personalized medicine and thus for the major advances in oncology. However, the fast, reliable and cost-effective sequencing of entire genomes has by no means reached the end of its potential in cancer diagnostics.

Long fragments, modifications and disease-specific panels

On the one hand, the latest methods such as nanopore or SMR technology (single-molecule real-time sequencing) can be used to read ever longer DNA fragments of up to several tens of thousands of base pairs at a time.

On the other hand, more and more specialized systems are being developed with which epigenetic modifications such as methylations or binding sequences of transcription factors can be analyzed.

In addition, so-called panels can be used to specifically detect certain disease markers in the blood. This allows, for example, a return of cancer or mutations in tumor cells to be detected at an early stage. This means that targeted countermeasures can be taken more quickly.

Many years of experience in all NGS areas

"We have many years of experience in the development of NGS systems," says Andreas Geipel, Principal System Engineer at HSE·AG. The engineers have developed components for all sub-areas; starting with sample preparation and library preparation, through reliable qualification of sample quality integrated into the liquid handling processes and the optical readout of gene sequences in flow cells, to the development of a complete end-to-end NGS system.

"In the area of library preparation, for example, we recently developed a beads-based system that allows DNA fragments to be selected based on their length in just a few steps," illustrates Geipel. This allows libraries to be generated quickly and reliably that optimally match the read length of the NGS technology used.

Unique expertise in integrated quality inspection

HSE·AG's experience in qualifying the quality of nucleic acid samples is unique. It ensures that no contaminated or overly diluted samples pass through the sequencing process and then produce unreliable results.

"With our OEM component eviDense UV, for example, the concentration and purity determination of NGS samples can be integrated directly into a liquid handler," says Geipel. The module, which only requires one microtiter plate space, uses four wavelengths in the UV range for the analysis of protein, RNA, salt or organic impurities and for precise concentration determination. Thanks to a sophisticated process, the analysis does not consume any valuable sample material.

Facts and Figures

Seven major corporations from Europe and North America used the services of HSE·AG in the 2024 financial year.

Operating income rose from CHF 12.0 million to CHF 13.1 million, an increase of 9.2 %. In the area of in-house innovation, a new product line was developed and is scheduled for market launch in mid-2025.

The financial stability of HSE·AG was further strengthened, resulting in a significant increase in the equity ratio from 47 % to 62 %.

The profit will be fully reinvested in the expansion of the company's own product range.

Retained earnings (in CHF)	**2024**	**2023**
Retained earnings, beginning of period	2'990'730.55	2'390'544.85
Profit for the year	810'007.86	790'185.70
The available retained earnings amount to	**3'800'738.41**	**3'180'730.55**

The Board of Directors proposes to the Annual General Meeting the following appropriation of profit:

Appropriation of profits	**2024**	**2023**
Payment of a dividend of	0.00	190'000.00
Allocation to the statutory reserves	0.00	0.00
Allocation to free reserves	0.00	0.00
Carried forward to new account	3'800'738.41	2'990'730.55
Total	**3'800'738.41**	**3'180'730.55**

62 %

Equity quote, previous year: 47 %

13.1 million CHF

Operating income rose by 9.2 %

80 employees

Including 5 apprentices

Audit of the annual financial statements

The financial statements of Hombrechtikon Systems Engineering AG for the financial year 2024, which covers the period from January 1, 2024, to December 31, 2024, were audited by Treu Control AG as external auditors in accordance with the Swiss Standard on Limited Statutory Audits, as of April 16, 2025.

Risk assessment

In the first year of its existence, HSE·AG established a quality management system in accordance with ISO 13485:2016 for the development of IVD systems (in-vitro diagnostics). This was successfully re-certified in November 2023. Risk management is an integral part of the system. In order to identify both risks and opportunities at an early stage, HSE·AG regularly reviews internal and external factors in the entire company environment. This review is based on the financial data determined for the financial statements in accordance with the Swiss Code of Obligations and the risk finance figures in accordance with regulatory requirements.

"Thanks to the HSE·AG invention eviDense UV, several new customers were acquired.

80 %

of employees own shares in HSE·AG

7

Major corporate accounts

22

Patent families granted or pending

Employee competencies

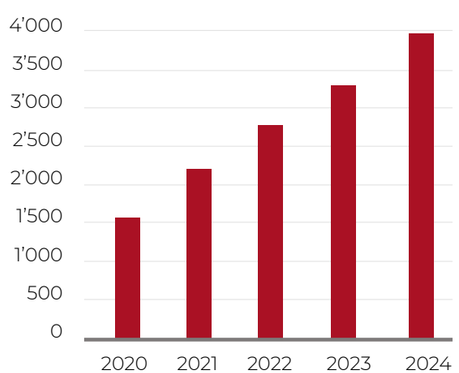
HSE·AG is characterized by its comprehensive and in-depth know-how. The skills of its employees cover the entire spectrum of technology and project implementation requirements, including the development and implementation of automation solutions in the field of molecular biology life science and diagnostics solutions. This in-depth knowledge, combined with many years of experience, gives HSE·AG a decisive competitive advantage.

Employee development

HSE·AG's workforce comprised 80 employees, including 5 apprentices. The low fluctuation rate of less than 10 % has been maintained. The fact that HSE·AG is still able to attract employees underlines its competitiveness in the international labor market for highly qualified specialists.

"The sale of eviProducts is progressing well and there is significant market interest.

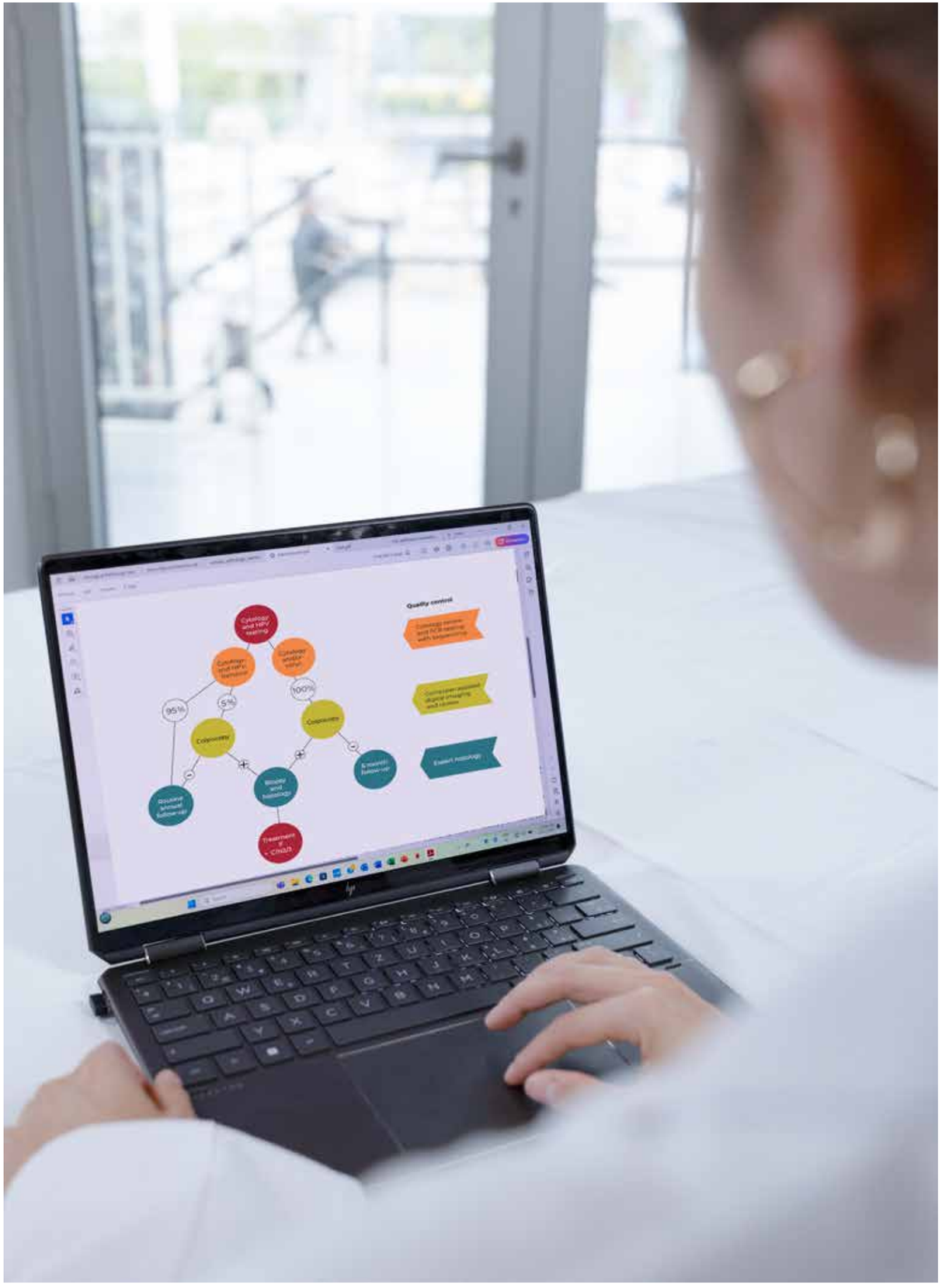
The diagram shows the growth of the equity capital in CHF thousands:

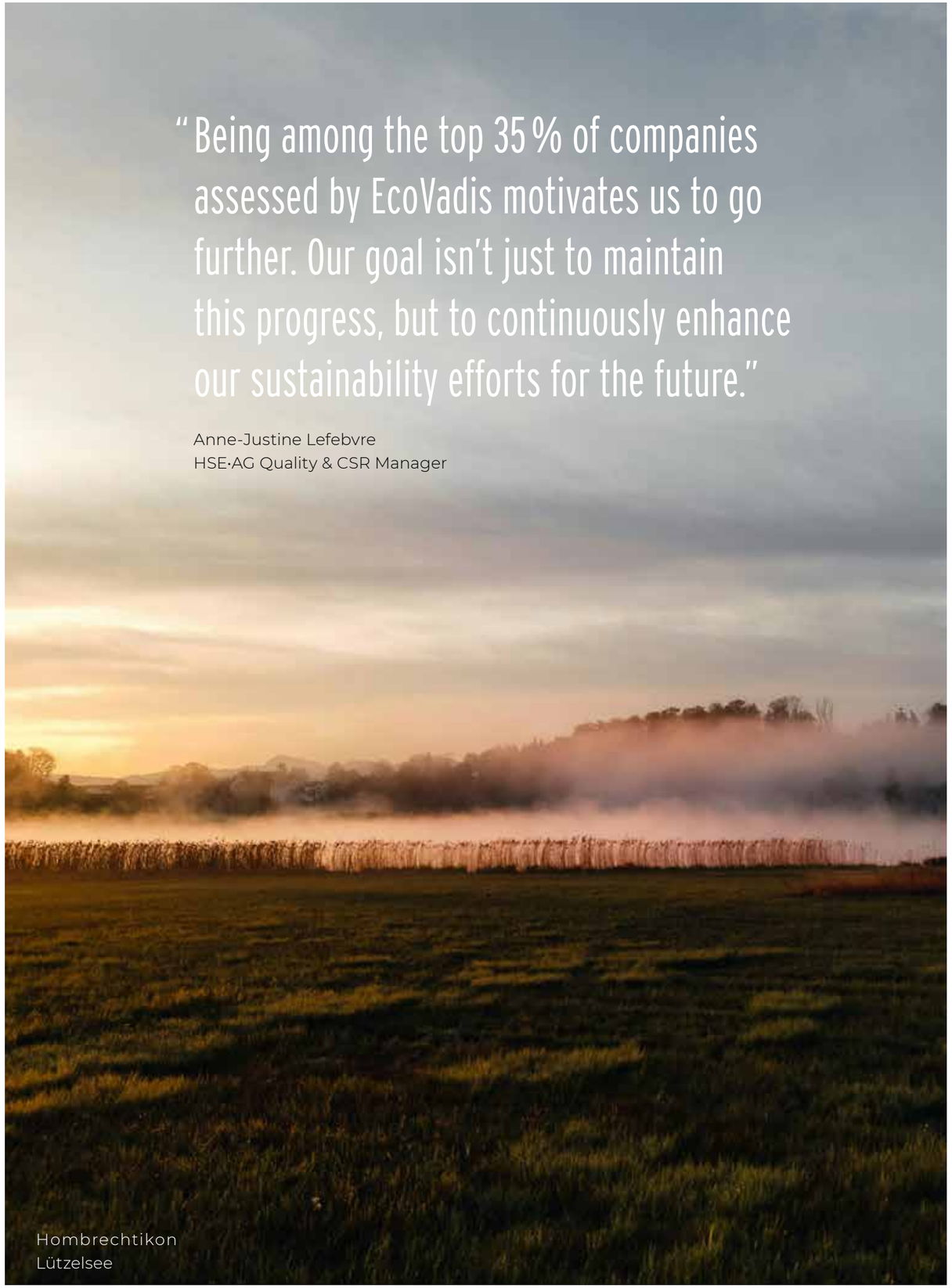


The following figures are in CHF thousands	2020	2021	2022	2023	2024
Working assets	4’949	7’053	8’007	6’672	5’415
Fixed assets	380	367	425	415	398
Intangible assets	1’986	836	6	-	606
Total assets	**7’315**	**8’257**	**8’437**	**7’087**	**6’419**
Borrowed capital	5’512	6’097	5’675	3’722	2’431
Credits	3’960	3’381	-	-	-
Equity capital	1’653	2’159	2’762	3’364	3’987
Total capital	**11’126**	**11’638**	**8’437**	**7’087**	**6’419**
Equity ratio in %	23 %	26 %	33 %	47 %	62 %

Employee participation program
An important pillar for the long-term business success of HSE·AG is the participation program for employees. This enables selected employees to acquire participation certificates. Their value is strongly linked to the success of the company. To date, around 80% of HSE·AG employees have participated in the company. This high proportion shows that employees also have great confidence in the sustainability of HSE·AG’s business model.

Development of PS value
The value per unit certificate increased from 1.9384 to 2.2672 Rappen.





Sustainability is key

EcoVadis Bronze Award Highlights Our Sustainability Efforts

At the heart of our business lies a commitment to sustainability, and our hard work is paying off. We are extremely proud to announce that our overall EcoVadis score has increased this year from 60/100 to 63/100.

EcoVadis, the world’s leading provider of trusted business sustainability ratings, evaluates companies across key categories: environment, labor and human rights, ethics, and sustainable procurement. Despite the notably more rigorous criteria for earning medals this year, we are proud to announce that we achieved a bronze award – a reflection of our ongoing commitment to sustainability and responsible business practices.

On August 14, 2024, we proudly received an overall EcoVadis score of 63/100. This success is largely driven by a remarkable 20-point improvement in our ethics score, which now stands at 70/100 – well above the industry average for comparable companies.

OUR VISION

is to enable the next break-through in the life sciences.

OUR MISSION

is to create tools to unravel the principles of life, by combining our applications and engineering know-how. We create and maintain systems and workflows in line with our customers' needs.

OUR ASPIRATION

Enjoyment
We like what we do and we enjoy working with the people around us.

Usefulness
Whatever we do should be useful to our customers, colleagues, and society. We continuously improve as individuals and as a company.

Ambition
We strive for excellence and continuously push past our limits to build something that is greater than ourselves. This is the source of our satisfaction.

Sense of reality
We utilize deliberate, fact-driven, decision-oriented thinking. We explore the harsh realities, draw conclusions, and focus on optimal execution. Time constraints do not compromise excellence.

Search for the best solution
We are curious and open-minded. Truth and transparency guide us. We encourage feedback and use this to learn quickly.

Fairness and respect
We treat everyone fairly and with respect. We communicate openly and honestly. This forms the basis for thoughtful disagreement.

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Gender-neutral pronouns and role descriptions have been used whenever possible and are to be understood in all cases.

For environmental reasons, our annual report is carbon neutral and printed on FSC-certified paper.

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