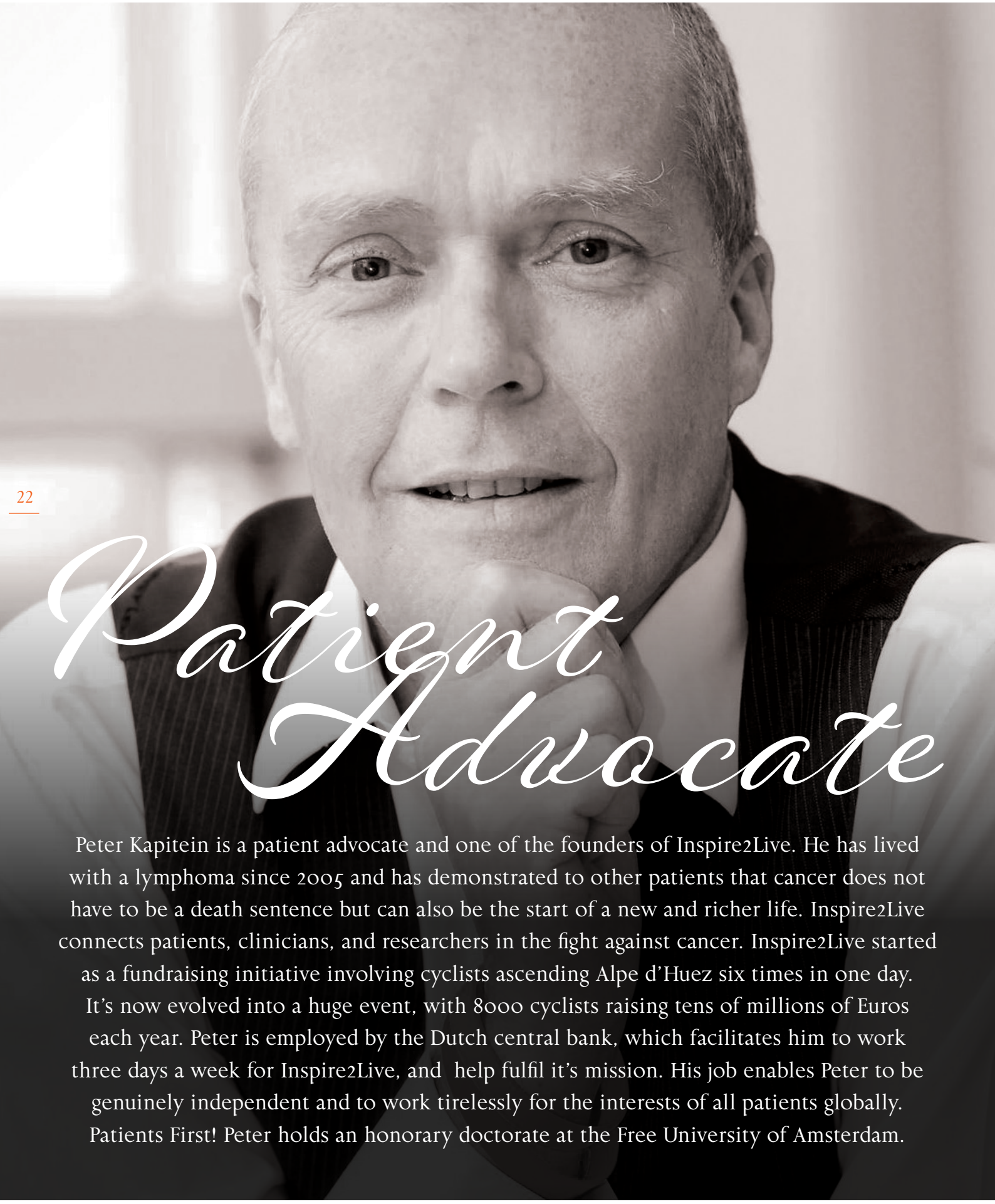


Patient Advocate

Peter Kapitein is a patient advocate and one of the founders of Inspire2Live. He has lived with a lymphoma since 2005 and has demonstrated to other patients that cancer does not have to be a death sentence but can also be the start of a new and richer life. Inspire2Live connects patients, clinicians, and researchers in the fight against cancer. Inspire2Live started as a fundraising initiative involving cyclists ascending Alpe d'Huez six times in one day. It's now evolved into a huge event, with 8000 cyclists raising tens of millions of Euros each year. Peter is employed by the Dutch central bank, which facilitates him to work three days a week for Inspire2Live, and help fulfil it's mission. His job enables Peter to be genuinely independent and to work tirelessly for the interests of all patients globally. Patients First! Peter holds an honorary doctorate at the Free University of Amsterdam.

PRECISION MEDICINE ALSO MEANS AN EXCELLENT DIAGNOSIS

by Dr. h.c. Peter Kapitein

I was recently introduced to a beautiful lady, immaculately dressed and wearing a wig. She told me she had cancer and was is in her third round of chemotherapy. She said she was doing reasonably well and was looking forward to completing her final therapy. Her hope was that she would recover quickly and resume normal life. I asked her what were the genetic underpinnings of her tumor. "I will hear that in two weeks", she replied. "And what if it becomes clear that chemotherapy was not really necessary?" "Then there's a big problem." was her response.

Only in recent years has it been possible to determine whether chemotherapy would or would not be effective for a certain type of cancer. This is possible in a growing number of cases. Sometimes there is a prevailing probability; sometimes there is a little less certainty. Now due to the proliferation of new data and ways to anatyse that data and improved communication with patients, he/she can make an informed decision as to whether or not to make the choice of abandoning treatment, either because it is possible to predict whether the patient will be a good or a poor responder or that the side effects are deemed likely to be too severe when balanced with a possible advantage. In short: the decision to either treat a patient with a certain medicine or not is more and more supported nowadays with data. Current data still shows that surgery is still by far the most successful approach in the treatment of cancer, combined with radiotherapy and intervention oncology (a form of operating without incision). The paucity of effective oncology drugs is supporting the patient's decision to renounce therapies and choose traditional treatment options. However, there is hope that we are approaching an era where we will be able to prescribe the right drug for the right patient at the right time.

An example of a test that was evaluated recently is the MammaPrint. This test is used for the diagnosis of breast cancer and has been on the market for more than a decade. This test was developed by Laura van 't Veer and René Bernards. MammaPrint is a diagnostic test that assesses the risk that a breast tumor will metastasize which helps physicians determine whether or not the patient will benefit from chemotherapy thus preventing potential debilitating side effects (like sickness, loss of hair, chronic tiredness and permanent damage to various organs). Such a test lasts a week, i.e. a biopsy is taken and researched by checking the activity of 70 genes.

MammaPrint is not the only test for breast cancer and indeed there are other diagnostic tests like Oncotype DX for prostate cancer that enable physicians to make informed decisions for the benefit of the patient, however despite this progress, are these tests done correctly and can they be used for everybody?

What are the advantages of the test?

Are the tests reliable? By in large yes. There will always be issues of sample integrity and reproducibility but this is improving. Clearly there is more uncertainty in the absence of a test altogether. Testing is critical and leads to extra information, but both physician and patient must continue to assess. A good doctor will go through the options, certainties and uncertainties with the patient, so that the patient can weigh up the pros and cons. It is important that the patient is well informed in this process. For the patient runs the risk, not the doctor, not the manufacturer, not the hospital and certainly not the regulator.

The advantage is clear: the patient gets the possibility to be treated without chemotherapy with all of the associated side effects. All cancer patients know what side effects they have to go through and they are very happy when it can be determined that such treatment is not necessary. An additional advantage is that considerable cost savings can be made in the treatment of side effects. The latter aspect deserves more attention, often this perspective gets neglected. A decrease of the treatment of the side effects is not only advantageous

economically (fewer costs, more profit through faster and complete recovery), but also has the most important advantage:- the patient's quality of life. This improves enormously.

Every year, 2,500 women in The Netherlands get treated unnecessarily with chemotherapy for breast cancer. This has been well documented in the Anthony van Leeuwenhoek Hospital for the last decade! MammaPrint has been used there for many years. The MammaPrint story is an excellent example of how technology based on rigorous scientific research by talented scientists can be used for the benefit of patients, obviating the need for lengthy trials with thousands of patients and unnecessary delays. It was implemented and used with diligent monitoring to assess effectiveness and safety and has been a great success story in preventing the over-treatment of breast cancer patients over the last 10 years.

Why is it unjust not to implement it fast?

The MammaPrint test is not used in many hospitals in The Netherlands. As a breast cancer patient you undergo chemotherapy and through a process of experimentation it is decided if it works or doesn't work. If it doesn't work, you have become sick and bald with no benefit at all. *"Then there is a problem."* This is a distressing situation with serious physical and mental consequences. Moreover, it costs a lot of money because of the medical proceedings to restrict the side effects and of course for the wig. I think it is strange and unjust that for many years already we have allowed this to exist not only in The Netherlands, but also undoubtedly in other countries as well.

But still, this is not all there is. Testing with MammaPrint, Oncotype DX, etc. is important, but it is not sufficient. Nowadays we can do much more in the field of diagnosis, but it is applied in a fragmented way and is not accessible for all patients. Everyone is aware, that an excellent diagnosis is a condition for the best treatment plan. And an excellent treatment plan leads to a better treatment with a better result. Keep in mind that for a patient, science, diagnosis, treatment plan, treatment and aftercare are essential, but not the final goal. This is the quality of life for herself and her loved ones. And believe it or not, Precision Medicine can make that possible. Precision Medicine, provided it is applied correctly, offers the hope that is so often deprived of those that need it most.

Precision Medicine offers hope.

In the paragraph above I talked about excellent diagnosis. I have to modify this. Excellent diagnosis in 2016 will in all probability be less excellent diagnosis in 2017 or 2018. Developments are fast, but this does not mean that we can wait, with the hope that next year will bring improvement "Perfection is the enemy of good". There are patients in front of us and they have to be treated now. In that way "excellent" is relative and good enough for now.

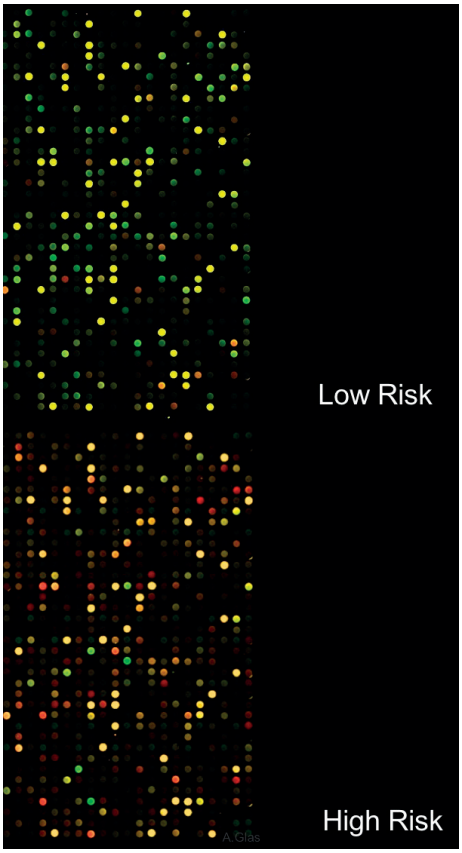


Image of MammaPrint Microarray Results

In the last few years Precision Medicine has evolved through a development of individualized approaches. It started when the patient was classified into a certain group of mutations: BRAF, KRAS, BRCA 1 and 2, etc. It was called Personalized Medicine. This specific mutation of the hereditary material was treated then. For example intestinal cancer patients with a BRAF mutation received a combination therapy of Cetuximab and Vemurafenib. The basket trial was born and this proved to be a great discovery. Rene Bernard's work played a critical role in this. Beside the Antoni van Leeuwenhoek Hospital, various other institutes have applied it and it is being applied in many institutes worldwide. Blocking pathways and the tumor's escape route proved to be an intelligent breakthrough and some of the first successes were witnessed here. Meanwhile we have arrived in a truly individual era. We diagnose a patient at this moment, with this specific mutation and we realize that the tumor "doesn't sit still" and mutates either as a consequence of the treatment or by itself or through a combination of these two. This is why biopsies are taken repeatedly to adjust treatment if required. We play chess with cancer and diagnosis plays a crucial role in this.

How to diagnose correctly?

A good diagnosis of cancer in the 21st century includes the following parts and techniques:

The patient's story.

It is important to listen to "the patient's story" well. We cannot make data the leading principle and forget to look at the patient. To illustrate this point: when my father, who had prostate cancer, was seen by his doctor in his sickbed, his reaction was: "If I look at the data, my conclusion would be that your father's condition is not as bad as expected, but when I look at the bed, I see a man that is very ill". And the patient's reality needs to be the reality of the physician and the treatment required.

Good Pathology.

The fundamental question of 'is this cancer or not?' is essential for the next steps and helping give clarity and certainty to the patient. Keep in mind that the patient does not permanently live with the thought that he/she might get or have cancer. The first message causes almost all patients to clam up. In the first conversation they won't probably care what form of lymph node cancer is involved. "I have cancer". That is what it is about and what they want to know. Follow-up research defines the tumor and the stage more specifically and also takes care of a well-balanced choice of treatment, but within a short time (often less than a day) the pathologist can offer clarity about the first question: Is it malignant or isn't it?

DNA-sequencing.

For more and more forms of cancer it is important to know what DNA-defect the patient has. This is of great importance for determining the correct treatment. On the basis of this (surgery, radiotherapy, intervention oncology and/or a combination of drugs) is determined. Sequencing the tumor is becoming more available but is still not widespread enough to benefit all patients. The speed with which this new and important technique is implemented is unjustly slow. It is unjust because it is done for one patient and not for another. Why does one patient get an individually attuned treatment and another patient doesn't? In many cases this is about patients that are diagnosed in academic centers. Not only is this situation undesirable, it is simply unacceptable. And with the current price of sequencing (for whole genome sequencing this is about € 1.000,00 per patient in The Netherlands right now) it no longer can be seen to be an issue of cost. Moreover, the costs will decrease when there is a massive switch to sequencing patients.

It is an organizational problem and and this can be solved if we are committed.

Imaging.

The tumor has to be visualized to determine its size and location. and also assessed to see if it had spread into surrounding tissue and whether it is viable to remove through surgery. Think of brain tumors. In the past few decades these imaging techniques have become more and more refined and with the help of, for example, nano-ferro particles, we are now able with CT-scans to detect and localize metastases of 8 millimeters. MRI already has good results with metastases of 2 mm. For better survival this is of great importance. At the moment there is limited availability for this technique in The Netherlands, but Professor dr. Jelle Barentsz of Radboud Ziekenhuis in Nijmegen has made huge progress in this field to the benefit of his patients..

Clinical experience of the physician.

Ultimately you are the doctor's patient. There are many vital components in this process. The doctor combines many years of education and clinical experience, working with a highly skilled team with the relevant expertise. In addition to using the leading diagnostic technologies and communicating effectively with the patient concerning the diagnosis. We can make as many rules and protocols as we want, in the end it all comes down to made-to-measure human work. The doctor's judgement is based on his/her clinical experience. This is essential in determining the correct treatment for a patient at that moment. That is why it is essential that a doctor's clinical experience is considered an important part of the diagnosis.

Re-biopsies.

A tumor cell lives, just as healthy cells live. A characteristic of a tumor cell is that it can also mutate. The healthy cell may have mutated into a tumor cell, because hereditary predisposition may trigger a tendency to develop tumor cells, but it is also essential that the tumor cell doesn't "sit still" either. A tumor cell may change because its own cell division process brings this about. It may also change by means of the therapy we use and probably it can also be caused by a combination of the two. That is why it is important to check regularly (e.g. after three cures or three months) if the treatment is still effective or if an adaptation of the treatment plan is needed. This phenomenon is called re-biopsy and it appears that it can be carried out in a simpler and less aggravating way for the patient. With so-called "liquid biopsies" a new biopsy can be taken fast and painlessly via the blood to estimate if treatment is (still) successful.

A new development for the future: protein determination.

Meanwhile science continues to advance and we know that proteins are important for the question of what medicines (and how) are taken in by the body and attack the tumor. These techniques are relatively new and have seldom been applied so far. In Erasmus MC in Rotterdam among other hospitals, however, they have made progress with this and the first results have been shown. With a device, various medicines are brought into the tissue and it is determined what medicine works best for this tumor of this patient at this moment. In fact, the reaction of the cell is monitored on the basis of what the proteins do. In this way it can be determined if it is advisable or not to use a certain medicine. One limiting issue here using this form of diagnosis is in keeping the tissue alive. This is difficult because of logistics (tissue has to be transported from A to B). In addition, with some tumors it is difficult to cut the tissue into slices of the correct thickness to enable effective treatment by the drugs. It seems that these problems can be solved, but that it may take some time. Nevertheless it is an extremely important and hopeful development, because it seems it may open the way for very effective individualised treatments

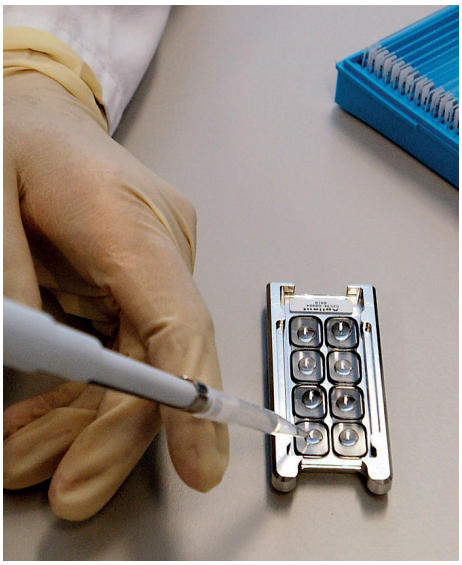
Now what does it get us?

When this takes place in good cancer centers, there will be an end to the unjust situation as just described. And the figures around breast cancer confirm that we are not talking about small change. 2,500 superfluous treatments of breast cancer in The Netherlands are large numbers already, but if the unnecessary treatments of all other tumors of patients are added, this means an enormous amount of money and much misery that can be prevented by a change in healthcare delivery. It will entail alot of hard work but ultimately it is a re-organization. We must put into practice what we already know. Having witnessed the advantages already in The Netherlands, the global opportunity for change is immense. What is essential is that we also look upon this development as a new and different approach for patients with cancer. If we see it as a new treatment, it is doomed to end up on top of the pile of ineffective and costly new treatments. This happens all too frequently with existing treatments and this is something we should avoid. I have written about this previously. With careful implementation, the costs of Precision Medicine will not get out of hand, but will decrease healthcare costs. Besides, money must not determine if one patient does get the best treatment and another does not.

As we scale, sequencing and other techniques like mass spectrometry will become more accessible. Eliminating superfluous tests and treatments along with prescribing the right drug and thus reducing the treatment of side effects will all contribute to cost reduction. Not to mention the huge benefits we would gain in quality of life and the benefit to society as a whole!

What can patients do?

Patients should question the treatments they are offered if they have any doubt on the quality and integrity of the diagnosis. The problem, of course, is the dependency of the patient on the doctor. Despite all of the



Scientist prepares sample for MammaPrint Microarray at Agendia lab in the Netherlands

modern means that can be used in those first few critical days and weeks to investigate what the best treatment should be, the patient is ultimately at the mercy of the doctor who is responsible for assessing what is available to you. A good doctor knows that this may not be restricted to the hospital where he/she works. A good doctor knows what is available in the world and does not only arrange the best cancer care, but also the access to it. And the best cancer care may be in a different institution from where the doctor works.

We aspire for a scenario where the patient has full confidence that they are being treated in the best cancer center, we're not there yet of course but things are moving in this direction globally. There are cancer centers that arrange the scale of early diagnosis, treatment plan, treatment and aftercare at the highest level imaginable. We have the knowledge and expertise, we just need to harness this and put together a new organizational framework. Healthcare cannot do this by itself, this is a collaborative effort. We strive for a higher goal, a good quality of life for patients and their loved ones. This leads to Precision Medicine in optima forma. And it might just be meant for that.

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Dr. h.c. Peter Kapitein, is a Patient Advocate of Inspire2Live. He connects patients, researchers and clinicians to further research, treatments and care; in the Netherlands as well as international. He organizes congresses, lobbies the matrix of public authorities, health care organizations, insurance companies and health research institutes. Peter also give lectures and talks to help patients and society to fight cancer where possible and live with cancer with a good quality of life. He is a writer of blogs, articles and books that also contributes to these topics.

Peter has been the co-founder of Alpe d'HuZes, the foundation that is most famous for the annual cycling event on Mount Alpe d'Huez. They raised over 100 million euro for the fight against cancer. Peter works at the Central Bank of the Netherlands as a program manager and advisor for complex and politically difficult problems. His employer facilitates him in his patient advocacy. Peter was honoured with a doctorate in October 2012 at the Free University in Amsterdam for connecting patients, researchers and clinicians all over the world and make them contribute to the quality of life of patients and their loved ones.