



Personalized medicine—but this time for real!

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Abstract: Personalized Medicine is not a new treatment for patients with more possibilities for the stakeholders in the medical industrial complex. It's the hope for patients to get a treatment on an individual level: this patient, with her specific defect, needs a treatment at this moment. With the modern technologies of pathology, imaging, sequencing and proteomics we can realize a lot but not enough. We need more and better molecular testing to realize our goal and transferring hope into a better quality of life. Several hurdles need to be taken. This is possible when cooperation of the stakeholders takes place. And when there is the urgency, opportunity and willingness to change. Some other industries have done it before so why should healthcare not be able to do so?

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The vision

Personalized medicine is about using molecular characteristics of the tumor cells in individual patients as relevant targets to predict better responses and get better results. This adds to the experience driven and statistics driven approaches of developing new treatments. This is why personalized medicine is another way of treating patients that comprises the design of diagnostic tests for treatment stratification, clinical trials for effective treatment testing, the registration of how the patient responds to the trials and treatment, another evaluation of the market registration for the new treatment, reimbursement of the treatment and aftercare for patients and their loved ones.

It is important to realize that we are in the midst of a development towards a treatment that is tailor-made and biomarker driven for each individual patient. In this article, I use the term “personalized medicine” for this, to avoid confusion with other terms like “precision medicine” and with other concepts that try to identify groups for treatments. Personalized medicine is about treating an individual patient with an individual treatment at this moment. This is the inevitable evolution for treating patients.

❖ Inevitable because we simply want to know how to

treat an individual patient and therefore science will deliver the necessary tools, hopefully as quickly as possible;

- ❖ Evolution because each phase of treating patients needs the phase before it to build on it further. We started treating “cancer” long ago, after that we treated “prostate cancer” and nowadays we treat “BRCA-mutated prostate cancer” with Olaparib. Meanwhile we know that Olaparib is a good drug, but that it does not help all patients with BRCA-mutated prostate cancer (1). There is more. Of course, we know that patients are unique and that one patient with “the same tumor” reacts differently from another, but we do not yet know how to identify this uniqueness in patients. However, we are getting closer. In the near future, we will treat BRCA-mutated prostate cancer with a specific protein defect. Then we will be able to treat patients individually and adapt their treatments in the future because of the mutations that have taken place over time in their tumor because of changes over time and because of the order in which treatments has already been given.

Our reaction to this evolution is too often: “*This is impossible, because it is getting much too costly.*” A correct

response to this is that we might not have looked deeply enough into possibilities. There is always a solution when there is urgency, when the pressure is high and there is intensive cooperation. If we continue to think in the way we have thought for decades, we will find the same solutions that do not work properly. Therefore, let's think differently and be creative.

Let's see how the energy industry is dealing with a change that comes from outside and to which it adapts its business model. In 30 years, there won't be any energy producers like we have today. There will only be two endless sources of energy left: sun and wind. All tiles and windows will be solar energy collectors and we will all have become producers of energy and consumers of "our energy". Sometimes you may produce too much and you give while at other times your production is insufficient and then you take. Energy companies like Nuon and Shell will evolve towards setting up and managing this infrastructure. They will ensure that energy flows from A to B to C and back to A again. The business model of these companies is adjusted to this, simply because they realize that sun and wind are the best solution for the population, climate, customers and therefore their business as well. They will profit, but with a product quite different from what they market now. Just as the taxi company Uber makes a business without possessing a single taxi and Airbnb is the largest hotel chain without a single hotel, energy companies will make profit from a product that is not theirs.

The pharmaceutical industry will go through a similar development. There will be infrastructures, set up by the industry, where it will be possible to produce high quality intermediate compounds fast (this is already being done). These compounds can be assembled into clinical grade compounds by pharmacists and prescribed by physicians on the basis of a refined molecular high-grade diagnosis of the patient in a specialist cancer center (I will restrict myself to the production of intermediate compounds for the more complex and therefore more costly cancer treatments). This all happens for each individual patient at a critical time for them. The pharmaceutical industry will develop a business model that creates revenue and profits from drugs, or rather, treatments, which is a better description of the new way that the industry will work. They will not produce their own product themselves any longer. Their business model is based on the infrastructure they facilitate like the energy industry does. Not for profit organizations who specialize in blood and tissue products will use this infrastructure for

disseminating the pharmaceutical company's products and treatments. This is what is going to happen, and of course this takes time. We will have to deal with intermediate measures, but in general, we will evolve in this direction.

So, what are the hurdles?

The hurdles

Regulations and "the way we work" are preventing us from implementing personalized medicine. I try to avoid using the expression "the system", because you cannot make contact with "the system": no individual takes responsibility for results or for an alternative solution. Responsibility is connected to individuals, which means us: you and me. I have written about it in my book that was published in 2016 (2). In practice, it is difficult to get personalized medicine off the ground. We are continuously talking about it and so many parallel meetings, initiatives and congresses take place all the time, but in practice, with a few exceptions in the academic setting, colon cancer is still being treated with a strategy that has existed for many years in parts of Europe.

What are the hurdles? I have elaborated on the problems below, in which I make clear that so many are interwoven. It is inevitable that when you work on one problem, you influence another.

It is important to recognise that according to legislation, drugs have to be tested in a phase 1, 2 and 3 trials to firstly determine safety, secondly, efficacy in a more general sense and thirdly, the efficacy in a limited and randomized group. If there is evidence that the drug works better than the placebo or an existing drug, it then meets "the state of science and practice" requirements and it is registered, thus gaining market authorization. European Medicines Agency (EMA) registration is, however, the first step to be taken and procured after being proved safe and effective. Because the pharmaceutical company already has a patent on the particular molecule in question, it benefits a monopoly from the legislator, for many years, to market the product. In the Netherlands, "The state of science and practice" is important for reimbursement; in the EU, this differs from country to country. However, we must evolve towards a European situation where this is equal and it works for each country. In the Netherlands, the minister can still halt any move on the advice of "Zorg Instituut Nederland" (Health Care Institute of the Netherlands) or can decide to put negotiations "on hold" in order to negotiate the price.

Hurdle 1: we treat, register and compensate per organ

With personalized medicine, it is becoming clearer that a patient's cell contains a defect and that it has to be repaired. Of course, this has been known for years, but now it's essential for what science does know to be put into practice. For example, we know about a *BRAF*-defect in the colon for which there is a recommended drug from the legislators. This drug has been tested in a phase 1, 2 and 3 clinical trial, has been registered, comes with a marketing authorization and is reimbursed. This drug also proves to be suitable for *BRAF*-mutated melanoma patients. Yet, we have to go through similar phase 1, 2 and 3 trials again and register the drug for melanomas, get a marketing authorization and bring it to the market. This takes years! This process is too long and too expensive. There are not many who want this: the patient wants to have the drug quickly, the industry wants to sell it fast, the doctor wants to prescribe it right away and health insurance companies are willing to reimburse the costs. However, regulations are preventing this from happening. This is tragic. In my view, it is not regulations that stop us, but "the way in which we work". You and I made those rules so you and I can also change them. The good news is that the FDA approved pembrolizumab (Keytruda) as the first drug for patients whose cancers have a specific genetic feature (biomarker), making them more responsive to immunotherapy specific to the biomarker rather than treatment for one particular organ (3).

An example of this is olaparib. This has been registered in the Netherlands for ovarian cancer with a *BRCA*-mutation; it has been approved and there is a marketing authorization. It is reimbursed because it complies with "the state of science and practice". For breast cancer with a *BRCA*-mutation it had not been registered until this year, there was no marketing authorization and therefore it cannot be reimbursed for 3 years. The same applies for *BRCA*-mutated pancreatic and prostate cancer patients. For each organ, a phase 3 trial needs to be carried out in order to comply with "the state of science and practice". Then there is registration and marketing authorization to follow. This takes precious time and takes lives or it unnecessarily shortens lives. Mind you, a registered physician is allowed to give it to patients with a tumor for which it's not registered yet, but then it's mostly not reimbursed. The hospital will have to pay for the costs and in the case of expensive drugs the hospital won't. Patients hear that there is a possible treatment, but that they will have to wait for it. And they die.

Hurdle 2: combination therapies and science

Everyone involved in personalized medicine knows that a solution for a complex problem will not be simple. We know it is likely that a combination of agents will be necessary rather than a single agent in order to make the difference. Surgery, radiotherapy, intervention radiology, immunotherapy and targeted therapy can be used in combinations. New developments in metabolic approaches can add to the possible combinations. Besides age, lifestyle and genetic factors, cancer also has specific metabolic characteristics. The problem is that science does not like combinations of drugs. Surgery, radiotherapy and one drug are okay, but two or more drugs in a newly developed treatment are becoming inconvenient and often rejected. When the patient is given three or more drugs at the same time, it's not easy to indicate how it exactly works. The patient says: "The combination" and is glad. The scientist replies: "Yes, but what is the substance that is really effective and how does it work?". For patients, this does not matter, but we understand that science does have a point. This problem plays a big role in the innovation of treatments and since science might slow down the process for patients that need new and better treatments, this aspect has to be taken seriously. It deals with the scientific paradigm and switching that is extremely difficult. Of course, there are good examples of combinations of drugs or combinations with surgery and 2 or 3 drugs. So, it can be done and this hurdle can be taken.

Hurdle 3: combination therapies and the industry

A combination of multiple drugs in a trial often means more than one supplier and industry does not feel comfortable with this. Think of the inclusion criteria (these criteria determine whether a patient is included or not in a clinical trial). How will these combinations be composed? And when one of the suppliers seems to have an advantage, the others are unhappy and will take measures. Cooperation between competitors is possible, but it causes extra problems and this issue has to be solved.

Hurdle 4: combination therapies and the costs

A combination of therapies with 2 or 3 drugs might cost 2 or 3 times €80,000.00 which is unaffordable as is the treatment with CAR-T cells (a very innovative way of modifying T-cells and roughly estimated around €400,000.00 per

patient). This problem now exists in some European countries for only one drug and will be even worse with more than one targeted drug. This problem however can be solved with “Formula Magistralis”. European and WTO legislation makes it possible for local pharmacies to produce drugs that are prescribed by physicians for their own patients. This way, the costs of the drugs being produced can be lowered, sometimes for less than 10% of the price of the industry (4).

Hurdle 5: phase 3 and its relevance for hospitals

Personalized medicine and phase 3 trials do not relate to one another. It is a kind of a contradiction in itself. All sorts of reasons are put forward to continue phase 3 trials with dozens and sometimes more than hundreds of patients, but most of them are not valid. How can they be carried out when we realize that each patient and their cancer is unique? In the Global Alliance for Genomics and Health database there are already more than 22,000 variations of *BRCA*-mutated breast cancer described. Each variation has to be checked separately and depending on the patient, the doctor’s clinical experience and the data, the correct treatment is chosen. This is, by the way, what David Sackett meant with “*evidence-based medicine: data and science-based evidence, the doctor’s clinical expertise and the patient’s own experience with her disease*” (5). Phase 3 trials are expensive and for hospital laboratories, a way to generate money. This should, of course, not be the reason to continue with them, but we must realize that especially academic hospitals have a financial interest that is in conflict with the patient’s interest. This creates resistance against the abolition of phase 3 trials. So, simply telling the hospitals that perform phase 3 trials to stop performing these trials and not to take the financial aspect seriously, won’t be the way to act.

Industry, government, doctors, health care insurance companies and patients do not want most of the phase 3 trials any longer, but they all want to make available, prescribe and reimburse the new drug, or combination of drugs as quickly as possible. We have to carefully register what the effects are for the individual patient and stop the treatment if it appears to have no effect (for that individual patient) and continue the treatment if it does. It is important to be aware that the effectiveness of immunotherapy might take some time before it is clear whether the drug or combination of drugs works or not.

All this may only be a temporary situation and we may

develop a really permanent solution for Personalized Medicine so that we treat patients individually and make drugs “made to measure”, as described in the vision above.

The solution

In time, we will embrace personalized medicine and treat each individual patient with an individual treatment. Our vision is for industry to frame an infrastructure that supplies the compounds for treatment to each specific person. A couple of things have to be put in place for this. For some immunotherapies (the T-cell modification therapies), this is already taking place and will be improved. Although the development is inevitable, it takes some years. Until then, we must continue to do the necessary work that contributes to this and works towards this aim.

Excellent diagnosis

Few drugs that are developed really work well, and sadly, we do not give those drugs to the right patients. To enable this, we need to explore biomarkers and diagnostic tests that predict results with more accuracy. For the majority of patients these do not exist as yet, because biomarkers are not developed together with the drugs. This should be a priority for science and industry. Personalized medicine is not only a correct analytical execution of tests, but, more importantly, about the tests having predictive value for the result of a therapy on an individual basis, so that the choice of therapy is really supported and not only based on statistics. We may perform “thorough pathology”, if the result has none or little effect on the prediction of what therapy will have the best outcome for the patient, such a test is of little use. This is often the case with “old diagnostics” like pathology and also with “modern diagnostics”, like DNA sequencing methods and imaging. That is why molecular diagnostics are important for personalized medicine, because this contributes to the prediction of the result of a therapy on an individual basis. After we have sorted this out, and only then, will personalized medicine relate to the individual and on a personal level. Right now, pathology institutes can take care of existing diagnostics as well as new molecular diagnostics.

More and better use of patient data

Often patient data is locked up in hospital databases and

in the pharmaceutical company's files. Hospitals wrongly state that it's their data and industry seldom releases data that is derived from trials. This is an enormous "treasure chest" of information that would enable us to see which patients would be successful in trials and why. It would also tell us which patients for whom the trial would not be suitable. It is crucial that industry releases the data of their "failures". These are drugs that do not reach the market because they are not better than a placebo or any other existing drugs. This data needs to be released and reviewed, as the compound may be effective in inhibiting its initial prescribed target, but still have no effect on outcome because of other reasons, including escape of tumor cells due to the activation of alternative, escape mechanisms. This compound may still be a perfect candidate for combination treatment with other targeted compounds, and various examples have been published over the last years. The biggest challenge will be to conduct new trials with combination treatment of various targeted compounds, especially when developed by different pharmaceutical companies. Moreover, let's be aware that if it is effective for 4 percent of the patients, it could be vital for those 4 percent. We need to know! These drugs have to go to those patients. With this information, a database of these "pharmaceutical failures" can be realized and so many lives can be saved.

The General Data Protection Regulation that has become effective in May 2018 is particularly important for patients because, if this regulation is implemented in the wrong way, it prevents researchers from doing good research with important data. This is not what the law aims for but might be the result of it. I consider this issue to be an advocacy problem that has to be solved by patient advocates. No one else but patients and patient advocates can decide on the availability of their data for research.

Deliver drugs after phase 1 and 2 to the patients with unmet medical need

As I have said before, phase 3 trials and personalized medicine often do not relate to each other; drugs have to be available immediately after phase 2 and available as an initial therapy, to treat patients with unmet medical needs and who have a poor prognosis (think of glioblastoma, pancreatic cancer and lung cancer). This does not go along with the protocol of second line treatments, last resort and experimental treatments, for then, ideal strategy for these

patients has already been wrecked by chemotherapeutics and by treatments for them that are seldom effective. For pancreatic cancer, there are already good examples that show that this method is possible. Why not for other tumors as well?

Reimbursement for all drugs that have passed phases 1 and 2

Reimbursement is an obstacle. This is why this strategy has to be based on supplying drugs that have passed phase 1 and 2 and not on waiting for phase 3 trials for each organ type. Criteria relating to response can be closely monitored resulting in continuation or halting treatment, so that the implementation of these experimental and targeted drugs will not make healthcare more expensive. Moreover, it is important that we only pay for value based on results if the drug works. Whether a drug is effective or not is decided by the patient and their physician. Inspire2Live has already expressed our views on this, part of our position paper (in Dutch) with regard to experimental drugs (6).

What problems do we solve with this?

The problem of registration, treatment and reimbursement per organ type has disappeared. This does not mean that the tissue is not the issue but it means that we start from a different perspective. We do not only diagnose and treat on the basis of organs any longer, but treat on individual basis, led by specific biomarkers for the particular tumor involved. At any particular moment the individual patient, with their defect, gets a unique mix of compounds with which the tumor is treated. We have to accommodate the reimbursement by determining the composition of the treatments with agents/compounds (based on the excellence of diagnosis), the costs of these compounds and also putting them together. But this can be successful: it is much simpler than what we already do now!

The problem of scientists not liking three drugs in one trial can be solved. The composition with combinations of compounds is done on the basis of a refined diagnosis with pathology, imaging, sequencing and determination of the protein defect. This is all based on science, although it is very difficult to interpret and combine all this data. Based on this information it should be possible to accurately predict which drug or combination of drugs will be effective, based on science, and with higher success than we have had so far

with statistics.

The problem of multiple suppliers of multiple drugs will not exist in time, for the industry will not supply drugs any longer, but compounds, and their business model will be aligned to delivery, logistics and organization of all this. Nevertheless, this issue is difficult to address and needs further thought and debate but we can learn from what we see with the development of CAR-T and the way Novartis and other companies operate this.

The problem of high costs for combinations of 2 or 3 drug are non-existent for there are only compounds and patients are posing no obstacles. We've already stressed that "Formula Magistralis" will lower the prices significantly (4). Competition will be the same as always. The companies that deliver the most effective and efficient infrastructure will get the most revenue and profit.

The problem of phase 3 trials will instantly disappear, for there will not be phase 3 trials any longer. There will be an excellent therapy directed to the individual patient based on solid molecular testing. The models will be built up and fine-tuned in such a way that the function is guaranteed and the treatment is safe. The science has been done and verified before the prescription of the treatment.

The problem of hospital laboratories depending on trials for their financial resources can be solved. For this we have to come to agreements. Hospitals will manufacture the drugs themselves in their pharmacies and laboratories ("Formula Magistralis"), something that has already started for immunotherapy. Think of the modification of T-cells. This happens in the laboratories of excellent cancer centers or in industry facilities (think of CAR-T). We present a key role for government and health insurance companies. Dependence of hospital laboratories for money from industry can be taken away with good agreements between these hospitals and government and health insurance companies. And it should be taken away.

Finally

It is a complex and evolving process, but there are examples of this kind of process in other industries. So why not in healthcare? If it does not succeed, we have not looked carefully enough. Or to use Pipi Long Stocking's words: "*I have never done it before, so I think I can do it.*"

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Footnote

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