EGAN
Patients Network for Medical Research and Health

# Personalised Healthcare Frequently Asked Questions

## Foreword

In one sense, personalised healthcare is nothing new. It is what doctors have aimed to provide for their patients through the exercise of their clinical judgement, backed up by specialist knowledge and the use of appropriate diagnostic procedures.

However, as research advances and we begin to understand more about the complexity of common diseases and their molecular mechanisms, it is clear that a standard approach to the treatment of cancer, heart diseases and other common physical and psychological disorders will not yield the results patients need. Increasingly therapies are being selected based on an understanding of the underlying genetic components of a condition and how these interact.

This has come to be known as Personalised Healthcare. Properly applied and adjunct to the clinical skills of doctors, it will open up new opportunities for preventing, treating or curing many currently intractable diseases. It is an area where there has been much hype (both positive and negative) about possibilities for progress.

We hope this booklet steers a middle way between these extremes and gives a balanced view of Personalised Healthcare as it is now and for the immediately foreseeable future. It is the result of a collaboration between the patient group EGAN (European Genetic Alliances' Network) and Roche, with EGAN collecting commonly asked questions and Roche experts formulating answers that have then been checked by independent specialists.

We welcome comments and feedback. Please send these to me at alastair@geneticalliance.org.uk.

Alastair Kent
President, EGAN

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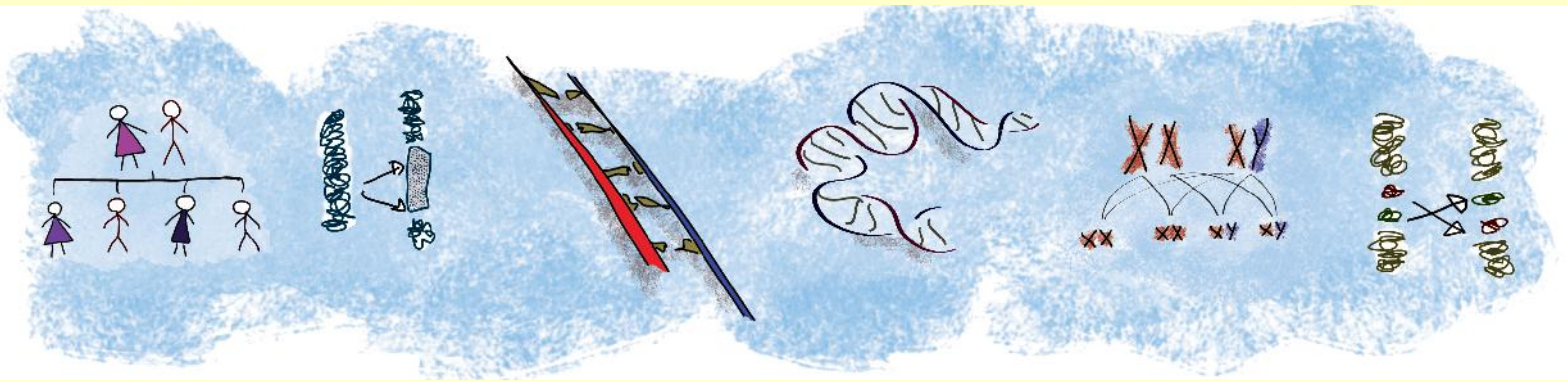
## 1. What is Personalised Healthcare?

Personalised Healthcare is based on the observation that patients with the same diagnosis react to the same treatment in different ways; while a drug can be highly effective for one patient, the same drug might not show the desired results when given to a second patient with the same diagnosis. Disease-related as well as disease-independent individual characteristics influence the way drugs work, and treating all patients diagnosed with a certain disease with a broad-brush approach disregards those differences.

In other words, conventionally practised healthcare is not as effective as it could be, with a considerable number of patients receiving treatment that is inappropriate for them or treatment that might even cause adverse reactions in some cases. Personalised Healthcare thus has the potential to increase the efficacy and safety of treatment. It is an approach which capitalizes on our increasingly sophisticated understanding of differences among patients, of the molecular basis of diseases and of how medicines work.



## 2. How is Personalised Healthcare achieved concretely?

Personalised Healthcare is an approach which is based on our increasingly differentiated understanding of disease causation, of how medicines work, and how hereditary factors influence both. It takes the differences between patients into account. Its foundation lies in research, aiming to learn more about disease pathways and subtypes with the aid of specific diagnostic tests. The ultimate goal is the translation of this improved understanding into better medical care.

This approach is largely based on new diagnostic tests that are carried out as part of or in addition to the conventional diagnosis of disease. Such tests are aimed at further analysing the respective disease, at improving the characterization of patients by disease subtype, so that the optimal treatment can be identified. Personalised Healthcare approaches can also help us understand which factors lead to differences in drug response. In some cases, the use of these tests can also help improve dosing decisions for a drug by making a distinction between certain patients who metabolize drugs more rapidly and others who metabolize drugs more slowly.

These tests measure so-called **biomarkers** – biological factors that serve as indicators of disease status or of drug response, e.g. proteins or DNA in body fluids and tissues or images, such as MRI or CT scans.

## 3. Which are the aspects that Personalised Healthcare currently focuses on?

Current research in the area of Personalised Healthcare is mainly covering the following fields:

- Individual patients' risk factors of developing a disease / disease subtype
- The biological factors that contribute to a disease / distinguish a disease subtype
- The likelihood of a treatment being effective in a disease / subtype
- The inherited or acquired patient-specific factors which affect efficacy or adverse drug effects

## 4. How does a prescription based on Personalised Healthcare differ from a traditional prescription?

It's difficult to describe this in black-and-white terms, as modern medicine already includes many elements of Personalised Healthcare. Put simply however, the difference is that instead of prescribing a drug (or dose of a drug) that, based on empirical evidence, *generally* yields good results based on the patient's diagnosis, a doctor will prescribe a drug (or dosage of a drug) that has been shown to be *more specifically* useful in patients that share a particular set of characteristics (such as an abnormal way of metabolising medicines or the presence of a specific tumour subtype).

In other words, the basis for medical decisions is no longer empirical knowledge, but increasingly detailed scientific evidence. Trial-and-error or one-size-fits-all approaches to treatment will gradually be replaced by more sophisticated approaches

Personalised Healthcare takes into account the subtype of the disease which the patient is suffering from (e.g. the characteristics of the tumour or the identity of the virus or bacteria that are the cause of the disease) as well as certain key aspects of the patient, e.g. their ability to metabolize particular drugs.[1]

[1] Aspinall, M. & Hamermesh, R. (2007) Realizing the Promise of Personalized Medicine: *Harvard Business Review*, October 2007, p. 110

## 5. What are the benefits for the patient?

By taking the individual characteristics of patients and their diseases (e.g. cancer subtypes) into account, Personalised Healthcare has the potential to:

- Improve medical outcomes and quality of care
- Predict which patients will most likely benefit from a treatment, also helping to avoid treatment that is unlikely to provide benefit
- Provide guidance on how long to treat a patient or at which stage of a treatment strategy a given therapy should be applied
- Aid in the development of safer and more effective treatments, thus reducing the risk of side effects
- Save patients' lives and improve their quality of life

## 6. The sooner a sick patient is treated, the better. Won't all this testing and diagnosing simply delay things?

On the one hand, it is true that the need to wait for the result of a diagnostic test will delay a prescription by anywhere from mere minutes to several days. However, when it comes to a prescription that is actually *effective*, Personalised Healthcare may enable the attending doctor to significantly abbreviate, or altogether avoid the current trial-and-error process of prescribing a drug - which often means waiting to learn that it is ineffective in a given patient, prescribing a second drug and then waiting again for it to show results.

So, while it is true that with more conventional healthcare practices, a patient might be fortunate enough to be given the ideal prescription on the first try, in many situations it is more likely that the treatment will be suboptimal, delaying the patient's recovery. Instead of trying out different medicines to eventually find the right one, a diagnostic test may reveal the underlying molecular mechanism which causes the patients' clinical symptoms and thus allow the doctor to choose the optimal treatment right away.

There are, however, also situations where presumptive treatment - i.e. treatment without the use of a predictive test - is the best course of action e.g. the use of broad spectrum antibiotics in serious infections. The value of a Personalised Healthcare approach depends very much on the time needed to get a test result versus the time it takes to see if a patient is responding to the treatment. The potential consequences of not treating a patient while waiting for a result versus the potential consequences of giving a patient the wrong treatment must also be taken into account. These and other factors have to be taken into consideration carefully and on a case-by-case basis.

## 7. How accurate will Personalised Healthcare be?

Accurate predictions of treatment success will continue to be very challenging. Personalised Healthcare approaches seek to improve patient care through better predictions of treatment success, but, like all other aspects of medical practice, they will never be 100% accurate. The accuracy of Personalised Healthcare approaches depends on many factors, such as the diagnostic test in question, the disease being treated, and the drug used for therapy. The complexity of human biology and disease poses an extraordinarily difficult scientific challenge, meaning that ongoing research efforts will be required to continuously improve the predictive accuracy of Personalised Healthcare approaches. A single diagnostic test alone will often not be enough to give a complete answer, and it is envisioned that not infrequently several tests, along with careful consideration of a patient's medical history, lifestyle etc. will have to be taken into consideration.

## 8. If common diseases such as diabetes or heart disease divide up into small sub-sets, how will health care systems be able to generate enough evidence to decide what works and for whom?

In many cases the patient population characterized by a biomarker may still be sizeable enough not to raise such concerns. For example, there is a Personalised Healthcare treatment that specifically benefits that 15-25% of all women with breast cancer who test positive for a particular biomarker that indicates that the treatment is likely to be effective – still more than enough to generate satisfactory evidence for its effects.

Should a disease-subtype really be so rare that scientifically sound evidence is hard to come by then the problem is very similar to that of drugs for rare diseases, so-called orphan drugs. There are several criteria that make a drug an orphan drug; the most important being that the patient population affected is relatively small (i.e. fewer than 5 patients per 10,000 population; sometimes, more common diseases that have been ignored because they are far more prevalent in developing countries than in the developed world - such as tuberculosis, cholera, typhoid, and malaria - are also included in the definition).

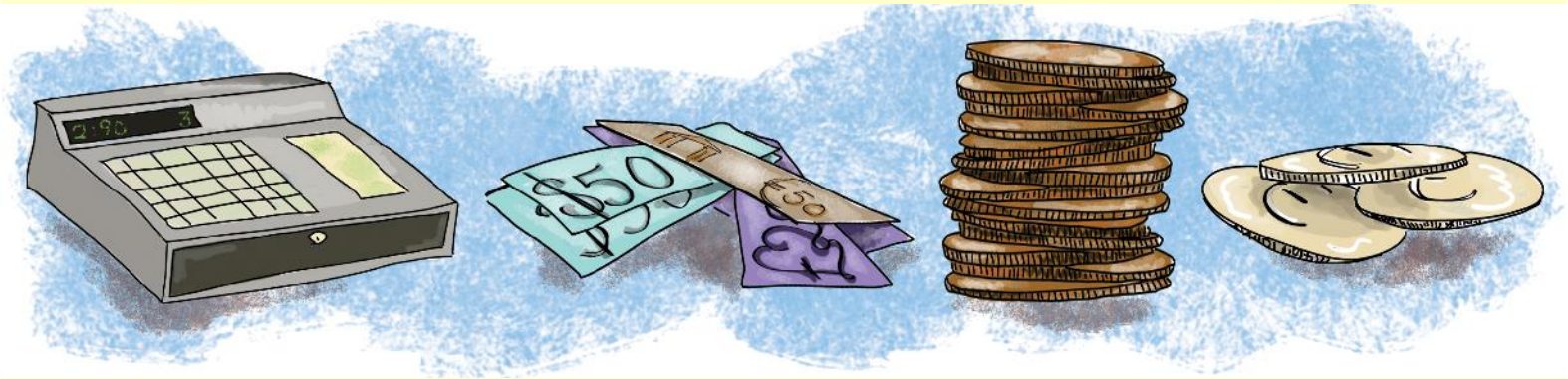
For orphan drugs, a range of different designs for clinical trials has been specifically developed in order to reduce the number of patients necessary to gather enough evidence to assess the risks and benefits of a drug. Here, regulators have the difficult task of balancing patients' right to safe and effective treatment with their need for any treatment at all in the case of severe or life-threatening diseases. It is for this very reason that regulators judge the scientific requirements needed to obtain a marketing authorization for an orphan drug on a case-by-case basis, so as to ensure an adequate balance between the risk that comes with taking a drug that could not be tested as intensely as one might desire, and the benefits that a new drug might bring to patients in great need of treatment.

## 9. If patients are part of a group where current medicines are no good, who will want to develop a treatment (especially if there are only few others like them)?

Should this be the case, the challenge is basically the same as the one posed by rare diseases, so-called orphan diseases (see Q 8): If patient groups are small and development costs are high, private companies may be reluctant to invest in research. In order to ensure that drugs for rare diseases are developed nevertheless, orphan drug policies have been enacted in many countries. By providing companies with accelerated review cycles by regulatory agencies, extended exclusivity of marketing rights, and (in some jurisdictions) tax incentives, these regulations, supported by a combination of funding by donations and the public sector have successfully allowed the development of a number of such medicines.

In the EU, once a drug has been designated as an orphan drug, the manufacturer can take advantage of several incentives put into place by the current regulation to foster the development of orphan drugs. For instance, the administrative hurdles for orphan drugs are lowered significantly because the European Medicines Agency (EMEA) assists the investor in submitting the protocol necessary to obtain a license for the drug. In addition, orphan drugs can obtain a central license for all member states of the European Union, at a lower than the usual cost or no cost at all, relieving the producer of the burden of submitting an application to each member state. The most important incentive for producers of orphan drugs is a guaranteed right to be the sole distributor of the drug in question for a period of ten years, and that no drug for the same disease and with similar characteristics will be licensed in the EU. Similar incentives are in place in the U.S. and a number of other countries.

All these tools ensure incentives fostering the development of drugs for rare diseases, thus making it much more likely that companies are willing to take on the risk that comes with investing into such an enterprise.



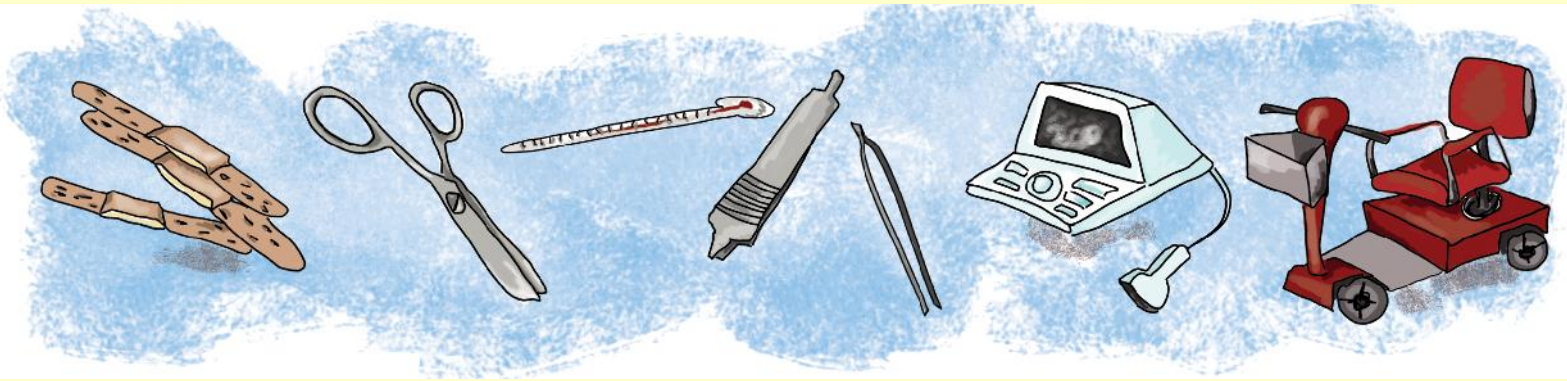
## 10. How will it be affordable if a disease breaks up into a number of gradually distinct subsets?

Improvement in our ability to diagnose disease more precisely or to identify better those patients who are most likely to respond to a specific treatment will generally have a beneficial effect on the overall cost effectiveness of a specific treatment. At first glance, this might be a confusing prediction considering how a smaller target group generally leads to higher unit prices for medicines. While this rule of thumb is also expected to apply to Personalised Healthcare, it is likely

that the increase in efficacy and safety will result in overall gains in cost effectiveness. In other words, when applying Personalised Healthcare concepts, fewer units of a higher priced drug are necessary to achieve the same or better results. This will save money compared to a more indiscriminate administration of such a drug to a less selected patient group.

It may make it less affordable to develop new treatments for those who do not adequately benefit from existing treatments, especially if these groups of patients are small, but, as discussed in the answers to Questions 8 & 9, Orphan Drug legislation has been put in place to address this issue.

In addition, we believe that it will become increasingly difficult to develop new medicines for many diseases and unmet medical needs without applying Personalised Healthcare approaches.



## 11. What is the ethical challenge of Personalised Healthcare?

An example: A diagnostic test predicts that a patient is unlikely to respond satisfactorily to a certain treatment, or belongs to a group in which only a small percentage of cases responds to the treatment – assuming that the treatment is still the best available option, should the patient receive it regardless of his potentially insufficient response?

In other words, while Personalised Healthcare might help improve the efficacy of treatments, there might also be cases where it will suggest a likely lack of or poorer efficacy without offering superior alternatives. How to treat such cases is a highly complex question that poses an ethical challenge to policy makers and healthcare professionals, whereas the healthcare industry may see this as an incentive to work on creating superior alternatives for patients who are not adequately treated by existing medicines.

There could also be the opposite case; consider a biomarker that indicates whether a tumour is likely to return. Should all patients diagnosed with that biomarker then be treated with chemotherapy with all its side-effects, even the patients with very small tumours that would not otherwise have been treated with chemotherapy? Here, patients and health care professionals have to weigh the potential benefits against the risks of a certain course of action, and once again, there is no easy answer.

## 12. How will a doctor know that there are personalised interventions available that will assist a patient? Or, conversely, that they should not prescribe because the prescription would do more harm than good?

Special training courses for physicians and healthcare professionals are needed. They will have to take place in regular intervals to provide updates on the current state of research and knowledge. Also, drugs that receive regulatory approval contingent on the use of a Personalised Healthcare approach – e.g. on a test being performed before the drug can be administered – will of course be labelled accordingly.

If patients think that options for personalised treatment are available for their disease or condition which their physician is not aware of, they should not hesitate to address this. Reliable information from a healthcare or patient organisation may convince the doctor to agree upon a more personalised treatment for them, and future patients. In addition, patients may work with their patient organisation to stimulate this personalised treatment and/or its reimbursement in their country as a whole.

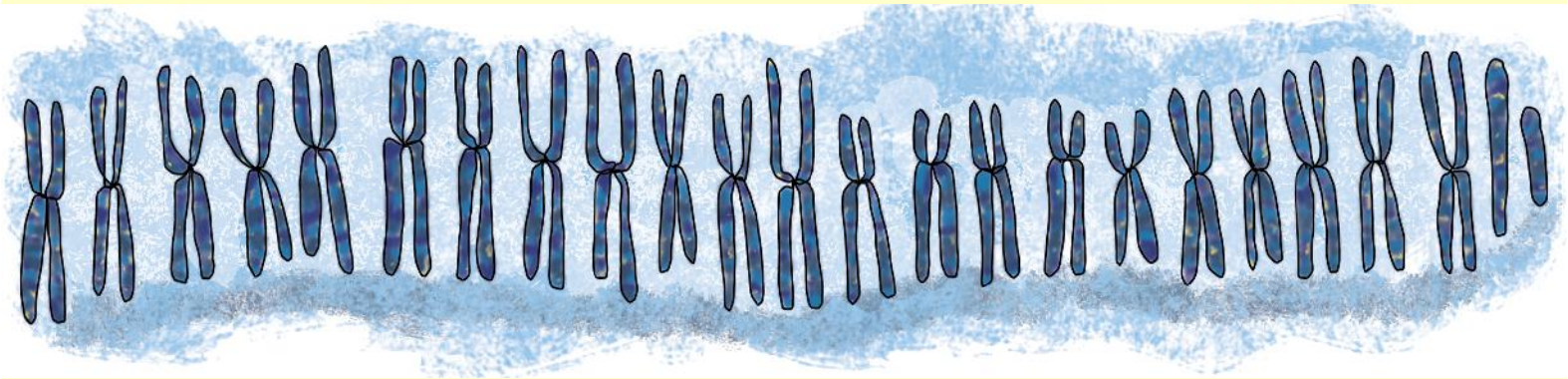
## 13. Won’t national healthcare systems simply take a broad brush and not bother with all this prescribing based on sophisticated differential diagnosis?

While it is true that an adjustment process won’t happen overnight, there are several incentives for policy makers and health insurance providers to react positively to Personalised Healthcare. For one, Personalised Healthcare has the potential to make therapies more cost-effective: Diagnostic tests may help contain the overall costs of treatments by targeting therapies at the patients who are most likely to respond, and by avoiding the prescription of expensive drugs to patients who won’t benefit from them. Additionally, diagnostic tests that recognize a patient’s predisposition for severe side effects can thus help avoid such complications and may help reduce the high costs associated with such adverse events. Since the cost of diagnostic tests is generally much lower than that of advanced treatments, there are clear potential benefits with regard to cost-efficacy.

By increasing efficiency and safety, Personalised Healthcare might thus enable policy makers and health insurance agents to utilize their healthcare budgets in a more efficient way.

## 14. What is really new about Personalised Healthcare?

Personalised Healthcare is not an entirely new concept. The idea of tailoring medical treatment to patients has been around for a long time, and we have a number of successful examples such as the treatment of diabetes patients guided by blood sugar measurements. However, with rapidly growing knowledge about molecular processes and genetic variations we are now presented with an increasing number of opportunities for realizing this goal, using a scientific approach rather than the trial-and-error process that has been used so far in the majority of instances, for example in breast-, stomach, lung and skin cancer, infectious diseases or metabolic disorders. In all these indications, targeted treatments are now a reality.



## 15. How long will it be before Personalised Healthcare isn't just a promising future scenario anymore?

Personalised Healthcare holds great promise for patients and expectations are high. Significant advances in making this a reality have been made and a number of diagnostic tests and targeted medicines are already available for patients and their treating physicians (see question 14.) Yet this is only the beginning. There is enormous potential for further improvement of diagnosis, therapeutic approaches, and outcomes. It can both alleviate the negative impact of a disease and prolong a patient's life.
One challenge lies in the fact that the underlying biological causes of many diseases are highly complex, and, therefore, the chances of finding new biomarkers that are sufficiently predictive for use in clinical decision making are low – meaning that developing such tests will not always be possible. Personalised Healthcare is a great opportunity for patients to get
more customized treatment and, over time, it will provide benefits to more and more patients.

## 16. Are there any real examples of Personalised Healthcare working?

There are several examples for a successful implementation of Personalised Healthcare, the following being only a selection:

- One of the best-known examples is a drug for patients diagnosed with a certain type of **breast cancer**. It comes with a diagnostic test that serves to identify a specific **growth factor** (a protein produced by a specific gene with cancer-causing potential) that heightens the cancer's aggressiveness – the tumour is fast-growing, responds poorly to chemotherapy, and the likelihood of relapse is elevated. If the test signals high levels of this growth factor (found in 15 -25% of invasive breast cancers), the patient is treated with the associated drug. It specifically targets the growth factor, thus hindering further growth of the tumour. This combined test-treatment approach has increased both response rates and survival.
- The general mechanism described for breast cancer applies also to **stomach cancer**. Here approximately 16–22 % of tumours over-express HER2, leading to the diagnosis of HER2-positive metastatic stomach cancer.
- Another successful example of Personalised Healthcare is a drug prescribed on the basis of a diagnostic test, intended for patients with a certain type of **chronic leukaemia**. Unlike chemotherapy, the drug doesn't attack both healthy and cancerous cells indiscriminately, but **selectively targets cancer cells**, therefore reducing the side-effects of therapy. In the second half of 2011 the US Food and Drug Administration approved a new diagnostic test and medicine for the treatment of **metastatic skin cancer**. About 50% of this type of cancer is caused by a specific genetic mutation which leads to uncontrolled division of the skin cells. Once a companion test has identified this mutation, the new medicine attacks the protein product of the altered (mutated) gene.
- An **immunochemistry-based test** measures the level of a specific immunosuppressant factor after **transplantations**. The test enables doctors to both tailor the prescribed amount of a medication more accurately as well as to safely lower dosages of more toxic agents.
- In **hepatitis C**, the concept of Personalised Healthcare has led to **response-guided therapies**. Here, a number of diagnostic tests serve to identify patients who can profit from significantly shortened treatment duration (4 months instead of the usual 6-12 months) with full therapy benefits and a reduction of unnecessary drug exposure.
- A diagnostic test that identifies a **mutation of a specific gene** in patients with **colorectal cancer** has been found helpful in selecting appropriate chemotherapy – certain drugs are much less likely to work if this test is positive.

Several other examples show that **Personalised Healthcare is not a new concept** as such. There **exists a considerable number of products that are** tailored to patients' needs and have been on the market for quite some time:

- Tests for **diabetes patients** make it possible for them to monitor their own **blood glucose levels** in order to identify the right amount of drug (insulin)
- There is a broad range of tests to **assess the bone integrity** of **osteoporosis patients**. They also enable a physician to monitor the effects of a therapy aimed at keeping the bones from breaking down.
- Physicians have tests at their disposal to measure the **viral levels** in **HIV patients** before and during treatment, allowing them to monitor success as well as evolving resistance to a therapy.

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Leaflet with Glossary of terms:
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Euractiv.com – European Union Information Website
http://www.euractiv.com/en/health/personalised-healthcare/article-171796

**International**

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