L'Institut Servier scientific colloquia

2017 Colloquium
PRECISION MEDICINE AND TARGETED THERAPIES:
REALITIES AND PERSPECTIVES

Thoughts about precision medicine: what is its scope? The reflections of an innocent on precision medicine

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Springer Healthcare

Notes are linked to the references page.

The innocent that I am, with an unbounded enthusiasm for science, has been impassioned by this subject.

I would like to offer the following thoughts from this standpoint, as an innocent. These will consider in succession the scope of precision medicine, the expected benefits from its advances and the potential uncertainties relating to it. I will add to these the other challenges faced by precision medicine in terms of the future of medicine. After briefly describing these issues, I will offer a series of basic questions instead of concluding remarks.

PRECISION MEDICINE: WHAT IS ITS SCOPE?

The success in mapping the human genome, combined with the digital revolution, has enabled a rapid shift from 'reactive medicine' to 'proactive medicine'[1]. The speed of this transition is undoubtedly closely related to a phenomenal decrease in the cost of the full sequencing of the human genome, from 100 million dollars in the 2000s to a few thousand dollars in 2016. In parallel, the number of new genetic tests available has increased considerably, and now exceeds 65,000[2]. The amazing advances in this 'new patient-centred intensive medicine'[3] have been referred to in succession as 'genomic medicine', 'proteogenomic medicine', 'personalised medicine' and now, more often, 'precision medicine'[1,4]. So called 'precision' medicine is designed to incorporate all of the information possible about the same person, his/her environment, lifestyles, family history and the risks identified by new '-omics' technologies. Incorporating these various complementary data should enable personalised information to be generated, facilitate early clinical decision-making and offer new, targeted safe and effective medical treatments[1,4]. Precision medicine should therefore enable care based on a person's precise features of each person to be offered in the context of that person's own life [5]. This approach should enable a shift from the treatment of a disease to its prevention, promoting the wellbeing of the affected person[5].

This holistic approach, incorporating vast collections of personalised information about millions of people, has given rise to the new concept of 'precision health'[1,4]. Clearly, however, this label, suggesting overall health of a human in his/her vast living environment, is vigorously debated[6,7].

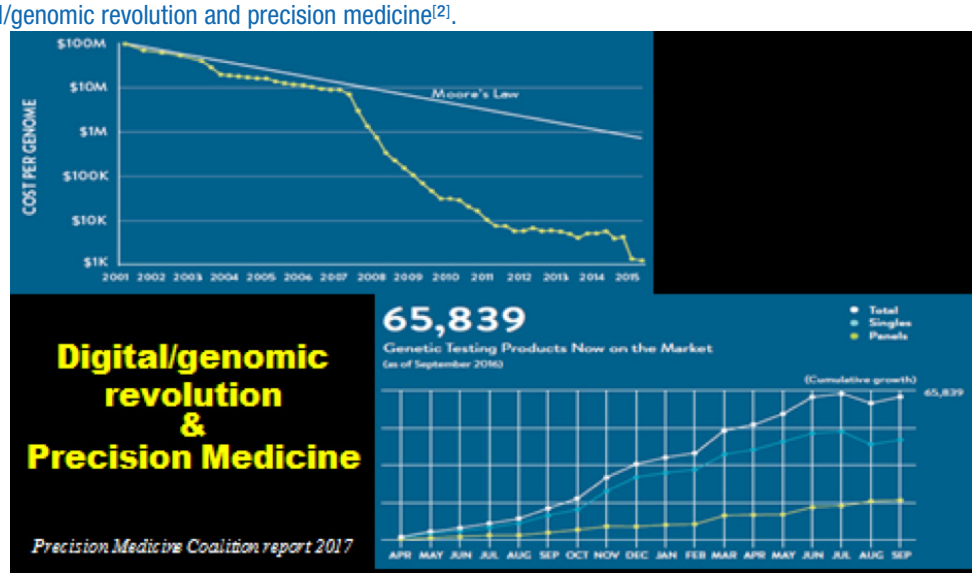
Regardless of the above, and to summarise, the scope of precision medicine involves:
- Diagnosis: identification of genetic predispositions and risk factors;
- Personalised prevention: interventions on lifestyle, nutrition and medical supplements;
- Continuous monitoring of the main indices recorded, including the use of connectivity items (eg, watches, spectacles, clothes);
- Improvement in the prescription of treatment through new clinical trial protocols, necessary because of the personalisation of regenerative gene therapy and reproductive medicine[3].

The latter point is important because major personalisation requires:

- a rapid shift from individual medicine based on clinical studies/trials which provide population-based results (what the English-speaking world calls 'one size fits all');
- to personalised care based on precise knowledge and monitoring of unique health and life features of each individual person, an approach the English-speaking world would describe as 'this treatment is not for all, it is only for you'), which makes the clinical trials limited to one person (hence the concept of the 'cohort of one')[4].

This last approach can be applied perfectly to the 6000 single gene diseases identified until now, such as sickle cell anaemia, cystic fibrosis, hereditary haemochromatosis, Huntington's disease, Marfan's syndrome, neurofibromatosis and many others[8].

Figure 1. Digital/genomic revolution and precision medicine[2].



PRECISION MEDICINE: WHAT ARE ITS BENEFITS?

Precision medicine, which is based on identifying molecular markers integrated into all of the features of the individual person in his/her living environment, should provide many benefits in areas as various as prevention, targeted medications, revision of some treatment indications, reduction of side effects of medicines and improved adherence to treatments.

The focus of precision medicine on prevention and early therapeutic interventions

- The significant benefits of precision medicine can be illustrated by the following two examples:
  - The first is inherited familial hypercholesterolaemia. This single gene disorder is due to a mutation of the low-density lipoprotein (LDL) PCSK9 receptor gene. This discovery has led to the development of a new treatment described generically by the term 'PCSK9 inhibitors'. This new category of targeted treatments has completely changed the previously dreadful prognosis of patients suffering from this disease[9].
  - The second example, which I shall return to later, is the involvement of the BRCA1 and BRCA2 genes in the incidence of breast and ovarian cancer. During a woman's life, the risk of developing breast cancer is 13% in the general population compared with 83% in women with the BRCA1 and BRCA2 genes. And while about 1.3% of women in the general population will develop ovarian cancer sometime during their lives, it is estimated that about 44% of women who inherit a harmful BRCA1 mutation and about 17% of women who inherit a harmful BRCA2 mutation will develop ovarian cancer by the age of 80[10].

Precision medicine also enables targeted medications to be prepared.

Targeted therapy has become possible with improved knowledge of the genes involved in the development of a long series of malignant diseases, including melanoma (73%), thyroid cancer (56%), colorectal cancer (51%), endometrial cancer (43%) and lung cancer (41%)[2].

As described above, breast cancer is closely determined by the presence of the BRCA1 and BRCA2 genes, and tumours with BRCA1 and BRCA2 expression respond well to treatment with polyADP ribose polymerase (PARP) inhibitors[11]. In addition, proteogenomic studies have shown that many breast cancer patients have an abnormality of the HER2 surface proteins. This has enabled the development of targeted drugs (Herceptin and Tykerb), which are among the most commonly prescribed agents for breast cancer at present. Also in breast cancer, it has been possible to identify genomic prognostic indicators (Oncotype DX and MammaPrint), which help to guide the choice of treatment in patients with malignant disease towards surgery, in combination with the medications described above or other treatment solutions[2]. It should also be noted that new prognostic indicators have developed to monitor the progress of colorectal and prostate cancers.

Advances in the molecular knowledge of many cancers have completely changed the use of some anti-cancer drugs which are now prescribed in new indications. Two examples are shown below:

- Iressa was approved in 2003 for use in all types of lung cancer. It was withdrawn from the market in 2005 because it was found to be ineffective, before being reintroduced in 2015 with the single targeted indication for epithelial growth factor receptor positive (EGFR+) lung cancers.
- Xalkori was first approved to treat small cell lung cancers including EML4-ALK+ cancers. Later it was shown to be effective in other ALK+ tumours, such as aggressive forms of childhood neuroblastoma[11].

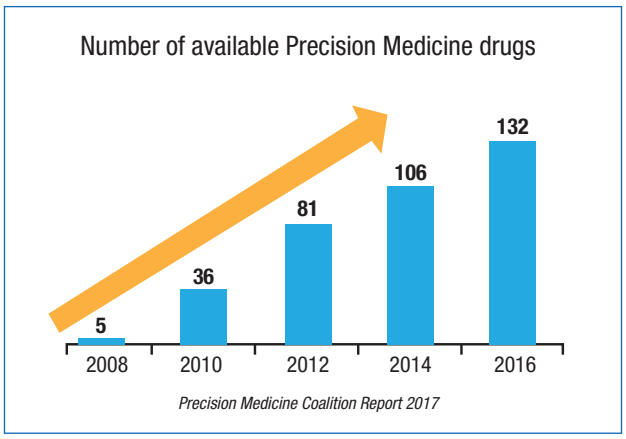
In parallel, the advances in pharmacogenetics and pharmacogenomics have improved our understanding and reduced the side effects of drugs:

- Pharmacogenetics can help to explains inherited metabolic variations, responses to treatment and adverse drug effects. One of the best examples the predominant role that genetic variations in cytochrome P450 has in explaining drug–food interactions and differences in the efficacy or toxicity of certain drug combinations.
- Pharmacogenomics is the overall study of multiple genes which influence the effectiveness of a drug. It has been found that the VKORC1 gene activates the action of vitamin K, whereas the CYP2C9 gene modifies the metabolism of warfarin, at the same time explaining both the lack of treatment efficacy and the bleeding problems caused by this treatment.

By improving the specificity of treatment, precision medicine can also improve specificity of treatment, which itself improves adherence to treatments. This undoubtedly explains part of the amazing success of the targeted drugs available, which have increased in number from five in 2008 to 132 in 2016 (Figure 2)![2]

Before these appeared, the same treatment given to a population of patients suffering from the same disease could produce either excellent results, cause adverse effects or be totally ineffective. In the era of precision medicine, each patient should receive the most appropriate treatment for his/her unique profile based on the inclusion of data about molecular biomarkers and lifestyle. Is this possible? This point will be discussed below, although what is certain is that, if it becomes possible, adherence to treatment will be optimised[2].

Figure 2. Changes in the number of targeted medicines available over time



The possible advantages of precision medicine appear to be major, but what about the uncertainties and risks of this new type of medicine?

PRECISION MEDICINE: UNCERTAINTIES AND POTENTIAL RISKS

Precision medicine has implications for individual health, conventional public health systems and national and international regulations, which appear to be poorly suited to the advances made through technological and digital advances.

The uncertainties and risks to individual health

It is essential to list these:
- As described above, the rapid transition from traditional clinical trials based on patient cohorts (‘one size fits all’) to individual monitoring of personalised treatment for a single patient (‘cohort of one’) raises enormous management and application problems.
- Unpredictable physical, emotional and mental reactions will be a concern when patients are told about their own specific genetic abnormality.
- High quality genetic counselling will be essential to facilitate effective communication with the patient and their family members.
- Patient uncertainties and of course uncertainties of the patient’s family circle about the safety of treatment and its long-term consequences will be inevitable.
- As long as national and international regulations are not appropriate, it will be possible for some ill-intended organisations to provide low quality services at excessive prices.
- Finally, ethicists may describe catastrophic scenarios of potentiating human capacities purely as a result of personal or financial interests[12].

Risks to conventional public health systems

Some countries such as China, the United States of America and Great Britain have made precision medicine a priority for all of their health systems, with major investment in this new area.

- However, the danger of this approach is that it focuses all development efforts on a treatment for a a minority of patients instead of investing in the development of a drug which is essential to a far greater population of patients suffering from a disease of similar severity.
- It is important not to forget that cost of developing a single targeted drug is currently estimated to be over one and a half billion euros.

Targeted therapies carry a danger of greater discrimination developing in care, i.e. increasing the healthcare inequalities which are already worrying throughout the world[12].

Dangers to current national and international regulations

The new scientific knowledge enables the collection of individual information to be concentrated in large population databases (molecular, genomic, environmental and behavioural), and this requires a complete revision and profound change in current regulations[13, 14]. The questions that must be rapidly addressed and then continually updated depending on advances in science include[13, 14]:

- who funds the setting up of databases?
- who standardises and decides on the data collected?
- who ensures that the data are anonymised and stored securely?
- how is information shared?
- who controls and limits their use?
- who funds the resultant research?
- who holds the intellectual property rights for each innovative stage?
- who owns the patents?

It is therefore absolutely essential to have updated harmonised international regulations as soon as possible, and to regularly update these recommendation in response to changes in scientific knowledge and worldwide technologies.

These many questions and major imperatives highlight the urgent need for considerably expanded ethical guidelines, which are accepted by the great majority of, if not all, countries.

THE OTHER CHALLENGES WE ARE FACED WITH FROM PRECISION MEDICINE

Everything described above already presents considerable challenges. The world, however, is faced with other challenges:

- The first is the huge acceleration of advances in science. We should remember that the concept of precision medicine or personalised medicine as it is currently understood globally was described for the first time by Langreth and Waldholz as recently as 1999[15]!
- The speed of the progress of ideas, concepts, knowledge and their application into the reality of everyday medicine is phenomenal, but it should raise serious concerns:
    - The very great majority of health professionals currently in practice and most young graduates do not have the requisite training to answer the basic questions asked by patients about precision medicine. Incorporating this new innovative discipline into all educational programmes is essential, but how should we do this?
    - Similarly, patients and their families appear to be either completely naive or ‘expect everything’ from treatment applications resulting from this hugely important scientific revolution. What should we do as new advances occur almost every day and the information is difficult to collect and communicate to the public even if the public has already been alerted?
- All of the challenges referred to in this article are well understood by some members of the ‘conventional’ medical community and reactions are beginning to appear in the literature, such as the series proposed from July 2017 onwards in the journal *JAMA Internal Medicine*:
    - Is it possible that the future of medicine will only involve this precision medicine based on technological advances[16]?
    - In response to this question, it has been strongly affirmed that ‘the future of medicine will rest on the basis of doctor–patient communication and shared decision-making’[17].

CONCLUDING MESSAGES, OR RATHER, QUESTIONS TO BE ANSWERED AS SOON AS POSSIBLE

As an innocent, and one who has had great pleasure in writing this review, it is logical to ask myself about several points which need to be examined in more detail and debated:

- Will precision medicine one day benefit all patients? My answer to this is negative, because as a geriatrician I know that a quarter of our genes are invariable in their expression during our lives[18]. This means that precision medicine, which is proactive by definition, will never be able to solve all global health problems.
- In my humble opinion, even 'precision health' closely involved in prevention (see above), must not make us forget the major roles of:
  - population-wide prevention programmes (hygiene, nutrition, vaccination, lifestyle and habits);
  - the importance of doctor–patient communication based on shared decision-making and treatment choices.
- Other essential questions for everyone:
  - Could precision medicine help to increase life expectancy?
  - But even more importantly, could it reduce functional handicap due to advancing age?

These questions, just like those about the potential of an 'augmented' mankind, are the subject of passionate debate, which is only just beginning and which neither we, as doctors, nor the politicians who govern us can ignore.

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