EDITORIAL

WILL PHARMACOGENETIC FINDINGS INFLUENCE OUR EVERYDAY CLINICAL PRACTICE?

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Receptionist: "Hallo, Dr. X office, can I help you?"

Patient: "I heard that your clinic performs individualized therapy on a genetic basis, is it true?"

Receptionist: "Yes, it is true, would you like to make an appointment?"

Patient: "Yes thanks"…

Two weeks later, in the doctor office, after a detailed interview, the doctor is looking to the results of the genetic analyses.

Doctor: "Well, your condition needs a specific drug treatment, I suggest to use the drug Y, one tablet twice a day, because your genetic analysis tells us that you will have a probability of 80% to have a favourable outcome".

Patient: "But, doctor, I read that in cases like mine, the chances of recovery with drug Y are about 70%. Why did you tell me to perform the genetic analysis and made me wait two weeks?".

Pharmacogenetic studies claim that they will change our lives with the promise of individualized therapies (Arranz et al. 2001, Weber 1997), however initial enthusiasms should be moderated in the light of some considerations. As the patient in the clinical case says, what is the point in having a prediction from a costly analysis, if its clinical impact is so small?

We should consider firstly the probabilistic nature of the genetic information. We are used to read laboratory data offering well definite information, for example if a specific bacteria is sensitive or not to a certain antibiotic. Conversely the genetic information is much less deterministic: we should never forget that genetic data gives information about the initial input we received from parents, and that a number of modulating events followed. The phenomenon "response to drug" therefore is a probability to have a certain reaction in a certain individual, and this probability is influenced by a number of factor, such as environment, drug-drug interaction and so on. In particular the environmental influence should not be overlooked: two cells, with identical genome, develop differently depending from the nutrition environment, two monozygotic twins are not phenotypically identical. Therefore the information coming from a pharmacogenetic analysis will tell us that a specific drug has a certain probability to be effective in a given individual, not certainty. The clinical usefulness of this information depends on how much this data will change the a-priori clinical knowledge, or, in statistical terms, how much is the variance explained; in reality only explained variances of 40-60% have substantial clinical impact. Unfortunately up to now many liability genes explain less than 10% of the total variance, as in the case of mood disorders (see my review and the one of Paola Artioli in this issue), as in many other fields of medicine, both for efficacy (Ameen et al. 2002, Anderson et al. 2003, Flexner 2003, Severino et al. 2003) and for side effect prediction (Phillips et al. 2001).

Notwithstanding those limitations, recently there were some initial attempts to apply pharmacogenetic findings: the most interesting case is that of antipsychotics as reviewed by Youssef K. Hassoun. For those drugs the prediction is clinically very meaningful because of the low rate and delay of clinical response and a kit for everyday clinical practice will be marketed soon (Kerwin 2003).

Are we therefore close to a change in our everyday practice? Most probably not. As a first point, pharmacogenetic prediction will not be useful in conditions where the drug has a very high expected efficacy. What is the point in having increased the rate of response from 70% to 80 %? The main issue for the choice of the drug will focus on other factors, such as side effects, or toxicity, or interactions. Conversely, in the case of drugs with low rate of response and high rate of side effects, it would be very useful to identify in advance those who will respond and not present side effects. For each individual a careful analysis of costs-benefits ratio of a genetic test should be performed.

The second issue is linked to ethical problems: What is the risk-benefit ratio of genetic knowledge for people? What are the problems concerning DNA banking and economical issues? Are informed consents really informed? How could we conduct researches with human beings respecting confidentiality? Those issues are now being dealt with for the first time, and guidelines will soon be ready (Freund and Wilfond 2002, Serretti 2003). Claus Møldrup deals in good detail those problems in this issue. Overall, we should consider that, whatever difficulties may be, the development of such analyses should not be stopped, for their potential large use in clinical practice.

New techniques of analysis are analyzed in the ar-

ticles of Cristina Lorenzi and Evangelia M Tsapakis in this issue. The possibility of a simultaneous analysis of thousands of genes and the analysis of their product such as proteins and metabolic processes are of great interest but they are not free of problems yet.

In conclusion, pharmacogenetic data will be useful but only when identified polymorphisms will explain a large part of the variance of drug response and/or side effects, when it will be technically feasible in a sufficient number of centers (see the paper of Cristina Lorenzi in this issue) and when common ethical and legal issues will be developed. Until then, it will have only research interest.

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