PHARMACOGENETICS
a review of concepts and contents

Pharmacogenetics represents a logical and consequent step in the history of medicine, but what are the immediate benefits and where do the hurdles lie in its implementation?

By Professor Klaus Lindpaintner

It is common knowledge that today's pharmacopea – in as much as it represents enormous progress if compared with what our physicians had only 15-20 years ago – is far from perfect. Many patients fail to respond completely, or at all, to the drugs they are given, and others manifest often severe adverse effects. If we accept, reasonably, that all common complex diseases – ie the health problems that are the main contributors to public and private health spending – are the results of complex, multifactorial interactions between inborn predispositions and susceptibilities on the one hand, and external, environmental factors on the other, then the problem of inter-individual variance of response to medication is but one of the aspects of this complexity, and may, likewise, be assumed to have as much to do with external influences (eg non-compliance, wrong dose) as with inherent (ie inherited, genetically determined) ones.

Clearly, a better, more fundamental understanding of the nature of genetic predispositions to disease as well as to drug action is essential for future progress in healthcare. Current progress in molecular biology and genetics does indeed provide us with the prerequisite tools to reach this more refined understanding.

Drugs, among all the 'environmental factors' that we are exposed to, may be particularly likely to 'interact' specifically and selectively with the genetic properties of a given individual, because their potency pitches them precariously between being potent potions or perilous poisons. We would predict that, based on a patient's innate, individual biological make-up – as it affects the interaction with a drug – one or the other of these properties may manifest itself; this phenomenon is captured by the term pharmacogenetics.

Three different scenarios

Three conceptually very different scenarios of such individual-specific drug response can be differentiated. They include, on the one hand, to differential pharmacokinetics (on which we shall not dwell here as this topic has long been recognised and studied, and is covered well by many excellent reviews) due to inter-individual differences in absorption, distribution, metabolism or excretion of the drug, and on the other hand to differential pharmacodynamics, which again may represent two quite different conceptual scenarios that relate to the two principal mechanisms by which drugs act: etiology-specific and palliative. The former relates to drugs that work by targeting and mitigating or correcting the actual cause of the disease or one of its etiologically contributing elements. In contrast, palliative drugs modulate disease-phenotype-relevant pathways that are not dysfunctional but can be used to counterbalance the effect of a disease-causing, dysfunctional pathway, without directly addressing the underlying cause or etiological contribution. Since a causative treatment will only work if the mechanism it addresses is indeed contributing to the patient's disease, such a treatment may be ineffective if that mechanism is not operative. There is general agreement today that any of the major clinical diagnoses, such as diabetes or cancer, are comprised of a number of etiologically (ie at the molecular level) distinct subcategories. In the case of an etiologically acting drug this implies that it will only be appropriate in that fraction of the patients that carry the clinical diagnosis; namely in those in whom the (dominant) molecular etiology matches the mechanism of the drug given. Thus, unrecognised and undiagnosed disease heterogeneity at the molecular level provides an important explanation for differential drug response and likely represents

a substantial fraction of what is today somewhat indiscriminately called pharmacogenetics. On the other hand, in the case of a drug that works palliatively, inter-individual differences in the activity of the targeted pathways (and thus in the relative disease-counterbalancing effect of inhibiting or enhancing them) or molecular variations in the structure of the drug's biological target that affect the target's interaction with a drug provide a second, conceptually different explanation for differential drug response based on pharmacodynamics. Here we are faced with disease-etiology-unrelated, interindividual variability as the root cause for differential drug response.

The branching tree of differential diagnosis

Thus, the 'practice' of pharmacogenetics will, in many instances, be marked by progress along the very same path that has been the main avenue of medical progress for the past several hundred years: differential diagnosis. An increasingly sophisticated and precise differential diagnosis of disease, arising from a deeper, more differentiated understanding of pathology at the molecular level, will foster these advances. Therefore, the sequence of events commonly expected as characteristic for a 'pharmacogenetic scenario' –namely, exposing patients to the drug, recognising differential response, discovering a marker predicting this response and creating a diagnostic product to be co-marketed with the drug henceforth – is likely to be reversed. Rather, we will search for a new drug specifically, and a-priori, based on a new diagnosis (ie a newly-found ability to diagnose a molecular sub-entity of a previously more encompassing, imprecise clinical disease definition). Thus, pharmacogenetics will not be so much about finding the right medicine for the right patient, but about finding the right medicine for the disease, as we have aspired to provide all along. This is, in fact, good news: the conventional pharmacogenetic scenario would invariably present major challenges from both a regulatory and a business development and marketing standpoint, as it will confront development teams with a critical change in the drug's profile at a very late point in the development process. In addition, the timely development of an approvable diagnostic in this situation is difficult at best, and its marketing as an 'add-on' to the drug a less than attractive proposition to diagnostics business.

Rather, the sequence of events in this case would likely involve, first, the development of an *in-vitro* diagnostic test as a stand-alone product that is marketed on its own merits, allowing the physician to correctly establish a state-of-the-art diagnosis of the molecular subtype of the patient's disease – even in the absence of any as yet developed pharmaceuticals (if for no other reason than the one that developing a drug takes two to three times longer than developing a diagnostic). The marketing of such a tool is likely justifiable by the advantages the thus obtained knowledge provides in terms of the likely response –or lack thereof – to existing medicines, and the potential applicability of non-drug treatment modalities such as specific changes in diet or lifestyle. When a medicine tailored to the particular differential diagnosis becomes available, the development process, based on the by then existing body of knowledge about the nature of the molecular disease (sub)-entity will allow a prospectively planned, much more systematic approach towards clinical and business development, with a commensurate greater chance of actual success.

Practically speaking, guesswork will remain, due to the nature of common complex disease. First, any and all diagnostic approaches will ultimately only provide a measure of probability, not of certainty, and we will see shades of grey rather than blacks and whites as a result of this. In addition, based on our current understanding of the polygenic and heterogeneous nature of these disorders, we will – even in an ideal world where we know about all possible susceptibility gene variants for a given disease and have treatments for them – only be able to exclude, in any given patient, those that do not appear to contribute to the disease, and therefore rule out certain treatments. We will, however, most likely find ourselves left with a small number – two to four, perhaps – of potentially disease-contributing gene-variants whose relative contribution to the disease will be very difficult if not impossible to rank in any individual patient. Likely then, trial and error, but on a more limited and sub-selective basis, will still play a role.

Candidate gene v whole-genome pharmacogenetics

The alternative scenario, where differential drug response and/or safety occurs with a 'palliative' drug, or despite having prescribed an 'etiologically applicable' medicine, will pose, as discussed, much greater difficulty in planning and executing a development programme, even if one were to find a marker/diagnostic that predicts the drug's efficacy/adverse events. In addition, there are considerable obstacles towards finding such a marker, unless it is one of the 'obvious' candidate genes implicated in the disease physiopathology or the treatment's mode of action. Although screening for

molecular variants of these genes, and testing for their possible associations with differential drug response is a logical first step, more often it will likely be necessary to embark on an unbiased whole genome screen, using Single Nucleotide Polymorphisms (SNPs) as molecular flagpoles. Despite recent progress in high-throughput genotyping, the obstacles that will have to be overcome on the technical, data-analysis and cost levels are formidable. They will limit the deployment of such programmes, at least for the foreseeable future, to select cases in which there are very solid indications for doing so, based on clinical data showing a near-categorical (eg bimodal) distribution of treatment outcomes. Even then, we may expect to encounter for every success – that will be owed to a favourably strong linkage-disequilibrium across considerable genomic distance in the relevant chromosomal region – as many or more failures, in cases where the culpable gene variant cannot be found due to the higher recombination rate or other characteristics of the stretch of genome that it is located on.

Pharmacogenetic testing for drug efficacy v safety

In principle, pharmacogenetic approaches may be useful both to raise efficacy and to avoid adverse events, by stratifying patient eligibility for a drug according to appropriate markers. In both cases, clinical decisions and recommendations must be supported by data that have undergone rigorous biostatistical scrutiny. Based on the substantially different prerequisites for and opportunities to acquiring such data, and to applying them to clinical decision-making, we expect the use of pharmacogenetics for enhanced efficacy to be considerably more common than for the avoidance of adverse events.

The likelihood that adequate data on efficacy in a subgroup may be generated is reasonably high, given the fact that unless the drug is viable in a sizeable number of patients it will probably not be developed for pharmacoeconomic reasons. Implementation of pharmacogenetic testing to stratify for efficacy, provided that safety in the non-responder group is not an issue, will primarily be a matter of physician preference and sophistication, and potentially of third-party payer directives, but is less likely to be a matter of regulatory mandate. Indeed, an argument can be made against depriving those from being eligible for the drug who carry the non-responder genotype, but who individually, of course, may respond to the drug with a certain, albeit lower probability. From a regulatory aspect, use of pharmacogenetics for efficacy, if adequate safety data exist, appears largely unproblematic –

the worst-case scenario (a genotypically inappropriate patient receiving the drug) resulting in treatment without expected beneficial effect, but with no adverse consequences, ie much of what one would expect under conventional paradigms.

The utility and clinical application of pharmacogenetic approaches towards improving safety, in particular with regard to serious adverse events, will meet with considerably greater hurdles and is therefore less likely expected to become reality, for a number of reasons: first, in the event of serious adverse events associated with the use of a medicine, withdrawal of the drug from the market is usually based almost entirely on anecdotal evidence from a rather small number of cases – in accordance with the Hippocratic mandate *primum non nocere*. If the sample size is insufficient to statistically demonstrate a significant association between drug exposure and event, it will most certainly be insufficient to allow testing for genotype-phenotype correlations; this becomes progressively more difficult as many markers are tested and the number of degrees of freedom applicable to any analysis continues to rise. Therefore, the fraction of attributable risk shown to be associated with a given at risk (combination of) genotype(s) would have to be very substantial for regulators to accept such data. Second, the very nature of safety issues raises the hurdles substantially because in this situation the worst-case scenario – administration of the drug to the 'wrong' patient – will result in harm to the patient. Therefore, it is likely that the practical application of pharmacogenetics towards limiting an adverse event will be restricted to diseases with dire prognosis, where a high medical need exists, where the drug in question offers unique potential advantages, and where the side-effect of interest is both relatively common and tolerated in favour of the drug's beneficial effects, eg in areas like oncology or HIV/AIDS. In contrast, the proposed, conceptually highly attractive, routine deployment of pharmacogenetics as a generalised drug surveillance practice following the introduction of a new medicine faces the sobering biostatistical and regulatory considerations discussed; barriers that are unlikely to be overcome.

Ethical-societal aspects of pharmacogenetics

No discussion about the use of genetic/genomic approaches to healthcare can be complete without considering their impact on the ethical, societal and legal level. Arguments have been advanced that genotype determinations for pharmacogenetic characterisation, in contrast to 'genetic' testing for primary disease risk assessment, are less likely to raise potentially sensitive issues with regard to patient confidentiality, the misuse of genotyping data or other nucleic-acid-derived information and the possibility of stigmatisation. While this may be true when pharmacogenetic testing is compared to predictive genotyping for highly penetrant Mendelian disorders, in it is not apparent why in common complex disorders predictors of primary disease risk would be any more sensitive in nature than predictors of likely treatment success/failure. Indeed, two lines of reasoning may actually indicate an increased potential for ethical issues and complex confrontations among the various stakeholders to arise from pharmacogenetic data.

First, while access to genotyping and other nucleic acid-derived data related to disease susceptibility can be strictly limited, the very nature of pharmacogenetic data calls for a rather more liberal position regarding use, and thus dissemination of this information, if it is to serve its intended purpose, ie improving the patient's chance for successful treatment. Thus, the prescription of a drug that is limited to a group of patients with a particular genotype will unavoidably disclose the receiving patient's genotype to anyone of a large number of individuals involved in the patient's care at the medical and administrative level. The only way to limit this quasi-public disclosure of this patient's genotype data would be if he or she were to sacrifice the benefits of the indicated treatment for the sake of data confidentiality.

Second, patients profiled to carry a high disease probability along with a high likelihood for treatment response may be viewed, from the standpoint of, for example, insurance risk, as quite comparable to patients displaying the opposite profile, ie a low risk to develop the disease, but a high likelihood not to respond to medical treatment, if the disease indeed occurs. For any given disease risk, then, patients less likely to respond to treatment would be seen as a more unfavourable insurance risk, particularly if non-responder status is associated with chronic, costly illness rather than with early mortality, the first case having much more far-reaching economic consequences. The pharmacogenetic profile may thus, under certain circumstances, even become a more important (financial) risk-assessment parameter than primary disease susceptibility, and would be expected – in as much as it represents one stone in the complex-disease mosaic – to be treated with similar weight, or lack thereof, as other genetic and environmental risk factors.

Evidently, the critical issue is not only, and not so much the sensitive nature of the information, or its disclosure and dissemination, but how it is used. Obviously, generation and acquisition of personal medical information must always be contingent on

the individual's free choice and consent, as must be all application of such data for specific purposes. Beyond this, however, there is today an urgent need for the requisite dialogue and discourse among all stakeholders within society to take place to develop and endorse a set of criteria by which the use of genetic, indeed of all medical information should occur. It will be critically important that society as a whole endorses, in an act of solidarity with those destined to develop a certain disease, guidelines that support the beneficial and legitimate use of the data in the patient's interest while at the same time prohibiting their use in ways that may harm the individual, personally, financially or otherwise. As long as we trust our political decision processes to reflect societal consensus, and as long as such consensus reflects the principles of justice and equality, the resulting set of principles should assert such proper use of medical information.

Conclusion

Pharmacogenetics, in the different scenarios included in this article, will represent an important new avenue towards understanding disease pathology and drug action, and will offer new opportunities of stratifying patients to achieve optimal treatment success. As such, it represents a logical, consequent step in the history of medicine – evolution, rather than revolution. Its implementation will take time, and will not apply to all diseases and all treatments equally. If society finds ways to sanction the proper use of this information, thus allowing and protecting its unencumbered use for the patient's benefit, important progress in health care will be made. DDW

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