

Tailor-made Medicine: A step towards future of Diagnostics and Therapeutics

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ABSTRACT

The goal of tailor-made medicine is to maximize the likelihood of therapeutic efficacy and to minimize the risk of drug toxicity for an individual patient. It involves right drug & dose, right patient and at right time administration of a medication. By averting the knowledge of gene sequence and their functions, biomedical research are diversified towards inter-individual variations that are expected to become an eminent part of treatment planning in terms of efficacy and toxic side effects of drugs. Tailor-made medicine focuses on individualized drug treatment according to each patient's molecular diagnosis and genetic makeup. Genomic-based diagnostics can play a key role in creating a more efficient healthcare system by directing patients toward beneficial therapies and away from therapies that pose substantial risk or are unlikely to improve outcomes for the patient.

Key Words: Pharmacogenomics, SNPs, FDA, Proteomics, Cancer, tailor-made medicine.

INTRODUCTION

By empowering the knowledge of gene sequence and their functions, biomedical research are more focused towards inter-individual variations that are expected to become eminent part of treatment planning in terms of efficacy and adverse effects of drugs. Existence of genetically distinct races is the reality and so is the pharmacological variations known to occur in varying frequency in different people. The way a person responds to a drug either positive or negative reactions is a complex trait that is influenced by many different genes. Without knowing all of the genes involved in the drug response, scientists have found it difficult to develop genetic tests that could predict a person's response to a particular drug. Once scientists discovered that people's genes show small variations or changes in their nucleotide (DNA base) content, all of that changed- genetic testing for predicting drug response is now possible.^[1-3] Our key ethical question is this: Does every individual faced with cancer have a just claim to receive treatment with one of more of these targeted cancer therapies at social expense? If any of these drugs literally made the difference between an unlimited life expectancy (a cure) and a premature death, that would be a powerful moral consideration in favor of saying that such individuals had a strong just claim to that drug. However, what

we are beginning to discover is that different individuals with different genotypes respond more or less positively to these targeted drugs with some in a cohort gaining a couple extra years of life while others gain only extra weeks or months. Should only the strongest responders have a just claim to these drugs at social expense when there is no bright line that separates strong responders from modest responders from marginal responders? This is the key ethical issue we address. We argue that no ethical theory yields a satisfactory answer to this question, that we need instead fair and respectful processes of rational democratic deliberation.^[4]

HISTORICAL ASPECTS AND "-OMICS" TECHNOLOGY

Genomics is a discipline in genetics concerning the study of the genomes of organisms. The field includes intensive efforts to determine the entire DNA sequence of organisms and fine-scale genetic mapping efforts.^[5]

Another technology is known as proteomics gaining much attention now days. The most important tools here are microarrays and bioinformatics. Study of the full set of proteins in a cell type or tissue, and the changes during various conditions, is called proteomics. PROTEOMEX, representing a combination of proteomics and serology which is most widely used in the bio-marker's discovery. As

the proteome is dynamic unlike genome which depends on the tissue, cell type and environmental factors. Thus, genomic approaches alone are insufficient to investigate the causative mechanism underlying disease.^[6] In short scientific, economic, and social circumstances all indicate that “tailor-made” medicine is likely the way of the future. Personalised medicine is defined as: ‘the capacity to predict disease development and influence decisions about lifestyle choices or to tailor medical practice to an individual’.^[7]

METAGENOMICS

The microbiome is a complex community of Bacteria, Archaea, Eukarya, and viruses that infect humans and live in our tissues. It contributes the majority of genetic information to our metagenome and, consequently, influences our resistance and susceptibility to diseases, especially common inflammatory diseases, such as type 1 diabetes, ulcerative colitis, and Crohn’s disease. Here we discuss how host-gene-microbial interactions are major determinants for the development of these multifactorial chronic disorders and, thus, for the relationship between genotype and phenotype. We also explore how genome-wide association studies (GWAS) on autoimmune and inflammatory diseases are uncovering mechanism-based subtypes for these disorders. Applying these emerging concepts will permit a more complete understanding of the etiologies of complex diseases and underpin the development of both next-generation animal models and new therapeutic strategies for targeting personalized disease phenotypes.^[8]

BIOMARKERS

Advances in studies of protein–protein interactions, protein expression profiling, annotated proteomics databases, and sophisticated protein function methodologies will no doubt provide an increasing spectrum of biomarker and therapeutic candidates. The biomarkers obtained by this technological intervention are classified in to three classes:

1. DNA biomarker

Mutations in oncogenes, tumor suppressor genes, and mismatch-repair genes can serve as DNA biomarkers. Promoter region methylation of MGMT, an enzyme that reverses 5'-guanine alkylation,

predicts the response or resistance of tumors to nitrosourea alkylating agents.^[9]

2. RNA biomarker

RNA biomarkers include differences in the transcription levels, or RNA molecules that take part in regulation. Pattern based RNA expression analysis of clinical breast cancers has identified previously unknown molecular subtypes.^[2,9]

3. Protein biomarker

Not protein quantity but its function can be utilized as marker. Single RNA markers in tumor classification, prognosis or prediction of response to therapy, protein-based ‘fingerprints’ may outperform individual protein markers.^[2,9]

PERSONALIZED DRUG DISCOVERY

If the hypothesis is extended backward into the drug discovery phase where researchers administer drugs to tumor derived human cell lines, it suggests that only a small fraction of the cell lines would respond to any given drug. Many drugs could be getting ruled out unnecessarily as inactive before they even reach the clinic. An ideal human tumor cell line profiling panel should consist of between 2,000 and 6,000 cell lines. However, there are only between 1,500 and 2,000 tumor-derived cell lines available in total today. It is also important to detail the molecular pathways through which a drug halts a tumor in order to identify new targets once the cancer becomes resistant to the drug in patients. “Every patient is making a sacrifice in order to participate in these trials, especially when a drug is entirely experimental and we have no evidence the drug is going to work,” says Mellman. “We have to recognize that as a sacred trust.”^[10]

FUTURE PERSPECTIVES

Our current understanding of genetic variability does not yet allow us to fully interpret the outcomes of specific drug treatment, in particular for common diseases. The reasons for this are:

- The pathogenesis of most diseases is polygenic in nature
- Most drugs exert their actions or effects in a multigenetic manner

There are complex interactions between the genes, disease, environment, drugs, and even pathogens (such as viruses, bacteria, parasites and tumor cells)^[10-13]

APPLICATIONS OF TAILOR MADE MEDICINE

Tailor made Medicine can be used as predictive medicine or in treatment optimization.^[14] Tailor made Medicine can facilitate disease prediction, prevention and treatment strategies by:

- Determining if someone is at increased risk of developing a disease, followed by promotion of and support for compliance with available prevention strategies;
- Diagnosing disease earlier in development using optimal surveillance, thereby allowing more effective interventions or treatment options;
- Enhancing therapeutic efficacy by ensuring the most appropriate drug is used and that the dosing regimen takes into consideration any genetic variants, which may influence metabolism of the drug; and
- Avoiding preventable drug related complications and side effects resulting from generic “one size fits all” drug prescribing.^[15]

BARRIERS TO PROGRESS IN PERSONALIZED CARE ^[6, 15-17]

As mentioned earlier in this manuscript that the – omics technologies are in emerging phase and have to pass many barrier before it actually commercialized.

1. Complexity of finding gene variations that affect drug response: SNPs occur every 100 to 300 bases along the 3- billion-base human genome, therefor millions of SNPs must be identified and analyzed to determine their involvement (if any) in drug response. In simple term it requires huge amount of efforts, time and money.
2. Limited drug alternatives: Only one or two approved drugs may be available for treatment of a particular condition. If patients gene variations that prevent them using these drugs, they may be left without any alternatives for treatment.
3. Financial loss for drug companies to make multiple alternative pharmacogenomics products:

4. Educating Healthcare Providers: As mentioned earlier physician should be through with gene knowledge so as to tackle any problem during therapy. To interpret the diagnostic accurately and recommend the best course of treatment for each patient, all prescribing physicians, regardless of specialty, will need a better understanding of genetics.

CONCLUSION

Tailor made Medicine is the application of genetic information to predict disease development, influence decisions about lifestyle choices, and tailor preventative interventions or medical treatment to the individual needs of each patient. Tailor made Medicine can allow screening, early intervention and treatment to be concentrated on those who will benefit, reducing expense and side effects for those who are not likely to benefit. Nobody is interested in investing huge money, time and efforts for only single fit medicine. At this stage, without government support in terms of subsidies and exemptions, it seems unclear. Apart from this there are certain ethical and social issues which need consideration. One should also not forget patient’s affordability! Successful personalized medicine research programs will not only require strategies for developing and validating biomarkers, but also coordinating these efforts with drug discovery and clinical development. The realization of personalized medicine is not without challenges, yet many of these challenges are being addressed. By encouraging public dialogue and debate, we expect that there will be continued progress forward. Lastly, as we take on more and more of the burden of our own health and well-being, educational forums must be developed for patients and physicians alike to understand the complex nature of the genomic information that is being used for decision making. Then we will have truly fulfilled the promise of the future.

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