Take it personally

Personalized Medicine: Past, Present and Future

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Looking at the history of medicine use, it is clear that personalized medicine has always been practiced. Physicians took patients' age, gender and the state of health and disease affecting major organs such as liver and kidneys into consideration when deciding to prescribe a medicine. In oncology, samples were taken from the tumor site and examined under microscope for pathological examination and then a therapeutic plan or surgery was decided based on the observations made on that sample obtained from the tumor of an individual. Therefore, personalized medicine is not a new field. It has been always here. Practitioners always took into account the mental, physical, spiritual and emotional aspects of their individual patients. Pharaohs and Kings had personal physicians so that they could receive the best possible medical care tailored to their individual needs according to standard of care of the time.

Over past century, physicians began to practice a more advanced form of individualized medicine using biochemical assays, pathological examination of tissues obtained from patients, radiological examination and imaging techniques to diagnose diseases, watch for drug side effects and/or assess the function of major vital organs such as liver, heart, or kidney. For instance, physicians started to use creatinine and BUN levels, and the presence of albumin in urine to investigate kidney function. Liver enzymes, serum albumin, bilirubin, and serum coagulation factors were used to investigate liver function. The laboratory information was used to assign a correct diagnosis, and tailor therapy to the individual needs of the patient who suffered from kidney or liver disease. CK-MB, troponins and myoglobin were used to investigate myocardial infarction and the patients were then treated based on these cardiac biomarkers. Hence, in comparison to ancient time, this was of course already a very futuristic form of individualized medicine practiced by clinicians.

In the investigation of albumin levels, hemoglobin levels or CBC clinicians look at a value which is then compared with a reference range established in an apparently healthy population. Hence by using biochemical tests the degree of the disease could be quantified and compared to a reference point or range for assessment of severity of disease. For example, in diabetes patients serum glucose levels and HBA1c are used in the diagnosis and assessment of the patients' compliance with the therapy or recommended life style changes. These are the examples of modern personalized medicine in every day practice of today. However, in this model all patients who have an elevation in blood glucose or lipids are placed in one category, which means that it is more likely we tailor therapy to an individual disease, and not to an individual patient.

We are now at the interface of traditional personalized medicine and personalized molecular medicine in which a molecular test can be used for diagnosis, prognosis, the selection and tailoring of a specific medication or therapeutic plan, follow up, outcome assessment, implementing preventive course or even discovering new therapy based on novel molecular therapeutics according to individual needs. What makes personalized molecular medicine different is that we look at the molecular level to stage a disease instead of gross pathology or tissue staging under a microscope.

The good news is that we have made progress. From a technological perspective, we are able now to investigate variation in genes, gene expression, protein and metabolites levels as well as developing new treatments based on novel molecular targets to correlate the findings with disease stages, prognosis, drug response and outcome to individualize therapy according to the molecular characteristics in patients. These new features have been made possible because of the advancement in molecular biology, nucleic acid research, chemistry, biology, development of novel technology and the completion of the human genome project. We are now able to look at the characteristics of specimen individually and use the information to detect disease at an early stage, select optimal therapy with minimal toxicity, increase patient compliance, select new targets for development of novel drugs, and reduce the time and cost of developing new medication, and shift medicine from treatment to early detection and prevention when the cure rate is significantly higher.

Success stories of personalized molecular medicine today include use of HER2 profiling for breast cancer therapy in women, who respond well to Herceptin®, an antibody which was developed to block this receptor. Breast cancer tissues that over-express this growth factor receptor respond well to the drug. Therefore a combination of diagnostic tests and a specific drug such as HER2 and Herceptin® can be used to target the drug towards a specific population of cancer patients who benefit the most from this type of approach. Hence using diagnostic tools to investigate a disease at a molecular level can be a powerful tool in therapy something that was not possible in the past.

Another example involving breast cancer patients involves patients whose biopsied tissue samples were found to ▸

be positive for estrogen (ER) and progesterone receptors (PR). These patients are found to respond better to hormonal therapy (drugs such as tamoxifen). Again in this example a diagnostic test was used to investigate a molecular target to decide on personalized therapy. Recently it was discovered that tamoxifen, although active, needs to be metabolized by CYP2D6 to an even more powerful metabolite called endoxifen. It appears that ER and PR positive patients who are slow metabolizers and have inactive forms of CYP2D6 enzymes do not respond well to tamoxifen therapy. Hence a combination of ER, PR and CYP2D6 tests may be used to assess the effectiveness of tamoxifen in these patients. For instance, endoxifen may benefit the breast cancer patients who are ER and PR positive but have low CYP2D6 activity whereas tamoxifen may be prescribed to ER and PR positive patients with normal CYP2D6 activity. The effectiveness of such approach should be investigated in a carefully designed clinical trial.

Another example for the use of molecular medicine in oncology is TPMT (thiopurine s-methyltransferase). TPMT genotyping is used to identify individuals that are susceptible to 6-mercaptopurine therapy. TPMT is a phase II drug metabolizing enzyme that inactivates 6-mercaptopurine, which is used for treatment of ALL (acute lymphoblastic leukemia). The drug can cause severe myelosuppression and even death in individuals who have inactivated forms of TPMT genes. Another example includes irinotecan which is used for treatment of colorectal cancer. Irinotecan is a prodrug which needs to be metabolized to its active form. The active metabolite is very potent and can cause severe diarrhea and other serious side effects. It was determined that individuals who have the inactive form of UGT1A, a phase II drug metabolizing enzyme, cannot detoxify irinotecan effectively. Hence if the genotype of the individual patient is known, the drug dose may be tailored to the personalized need of the patient who carries the ineffective form of the UGT1A1 gene.

CML (chronic myelogenous leukemia) is another example of a success story in personalized molecular medicine. CML patients who are positive for bcr-abl gene respond favorably to Gleevec®, an antibody against the abnormal bcr-abl protein which can stimulate cell division in white blood cells. Another example in oncology includes patients with colon cancer with p53 gene mutations who respond better to doxorubicin than 5-flurouracil. The list of using molecular medicines to tailor and implement a personalized therapeutic plan for patients is growing fast not only in clinical oncology but also in all area of medicine such as cardiovascular, psychiatry and infectious disease. Hence, the future is now.

What will personalized molecular medicine look like in 2025? This is a question we often ask ourselves. By then, we believe that the medical community and clinical laboratory would be routinely able to use and screen arrays of 3,000 genes and 140,000 SNPs on a single chip. We would be able routinely to screen for the expression of 3,000 genes at mRNA level. Proteomics techniques make it possible to screen and detect 100-1000 proteins in blood specimen and biopsied tissues simultaneously in one run. Reference ranges will be established for staging and sub staging all the diseases. New definitions will emerge for diseases based on molecular medicine and molecular profile rather than clinical presentations of the disease. Presence of a specific molecular profile will warrant a specific therapy for the diseases even though the clinical presentations may be different. We anticipate that future clinicians will increasingly move towards practicing personalized molecular medicine and that PhD scientists will be involved to a greater extent in patient care by providing highly complex diagnostics services and support in decision making and interpretation of the results.

In the future to be truly able to implement personalized molecular medicine we have to carry out significant amount of translational research. We will need PhD scientists with fellowship training in clinical diagnostic laboratory and pathology to be able to decipher the clinical aspects of developing novel diagnostic tools using molecular staging, biochemical, proteomic and genetic testing. We will need PhD scientists who work side by side clinicians to establish and validate new molecular profile and refer-

ence ranges for various stages of diseases. Physicians and pharmacists will be required to participate in research so that they can assist in addressing complex issues and problems associated with the development of new tests and the interpretation of the results for clinical staging and implementation of personalized therapeutic plan.

Considering the advances that we have made in technology, the only problems that we see that prevent us from achieving a fully integrated personalized molecular medicine in today medicine is an urgent need for education and the development of human resources. Arguably, the future of personalized molecular medicine depends solely on education.

Hence, to address the need for education in this area a new Special Interest Group was established on "Individualized Medicines" by International Pharmaceutical Federation in 2004. This is because scientists and medical communities are attempting to develop and tailor therapy for patients based on their individual needs, genetic makeup and uniqueness of the patient's disease to optimize therapy, reduce toxicity and minimize morbidity and mortality as a result of drug therapy or the disease itself. In this approach each patient is treated as an individual rather than just prescribing a drug or protocol or applying a procedure to all patients without considering the patient as a unique individual. Furthermore, individualized medicine will have a substantial influence on the design and development of new drugs in pharmaceutical companies, and on the medical care and pharmaceutical care provided by physicians, pharmacists and clinical scientists, respectively. The aims of establishing this focus group include: 1) Dissemination of the latest research and technology of individualized medicine to pharmacists and pharmaceutical scientists. As new knowledge emerges physicians, pharmacists and pharmaceutical scientists will need to learn about this new information which will shape how we will select a drug for specific therapy and monitor therapy in patients. And 2) To foster discussion about the regulatory, ethical and medico-legal issues related to use of individualized medicine.

In brief, personalized molecular medicine will provide us with a unique opportunity to redefine the practice of medicine by addressing important questions related to clinical problems that are unique and personal to patients. ■

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