CHAPTER

218 Personalized Medicine: Making Effective Therapy Safe for Every Individual

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INTRODUCTION

The Institute of Medicine (IOM) USA, in a 1999 report "to Err is human" estimated that about 100000 deaths occurred annually in USA alone due to adverse effects of therapy. In 2006 the IOM estimated that medication errors harm 1.5 million people, costing the nation at least $3.5 billion annually. IOM recommended that by 2010 all prescriptions should be written electronically, with builtin warnings about drug – drug interactions and side effects. Alas, this has not happened yet.

It is a sobering thought for all doctors that about 10-20 percent of Hospitalized patients and 2-5% of out patients develop adverse effects of medications. A small group of frequently administered drugs account for the majority of adverse reactions. Most adverse drug reactions occur soon after administration. Many effects are seen after a month or more e.g. INAH hepatitis; many effects occur after several months e.g. chloroquine. Some adverse effects take years (mutagenesis, teratogenesis). Some effects are seen in the next generation (e.g. thalidomide in pregnant women, slibesterol given to mothers causes vaginal tumors in off springs).

During the first trimester of pregnancy, when organogenesis is taking place, the risk of drug induced effects is the greatest, but exposure any time during pregnancy may delay or distort normal fetal development.

Advanced age lowers kidney glomerular filtration, reducing drug clearance from the same dose. Hepatic and renal disease alter drug pharmacokinetics. Inherited enzyme defects like G6 PD deficiency can cause drug complications.

UNIQUENESS OF EACH INDIVIDUAL

Ayurveda (science of life) embodies experiential wisdom of over 5000 years. Charak Samhita States: "Every individual is different from another and hence should be considered as a different entity. As many variations are there in the universe, all are seen in human beings" Personalized medicine has been a distinct feature of Ayurveda, Unani and homeopathic practice of medicine. R.D. Lele[2] observes that safety record of homeopathy is 100%.

The greatest impact of the Human Genome project (2000 AD) on clinical medicine is the appreciation of the extra ordinary molecular and biochemical individuality of each person. Gene polymorphism occurs in 1 in 1000 DNA base pairs in the human genome. This is reflected in the diversity of the gene products – structural proteins, channel proteins, transporters enzymes and binding proteins, receptors and post receptor signaling cascades. Polymorphism can occur not only in the protein coding sequence but also in the upstream promoter sequence. Such polymorphism influences the activities of several enzyme mediated processes. The most common gene polymorphism is the single nucleotide polymorphism (SNP). Of the 3 million SNPs in the entire human genome only 60000 are in the exons or coding regions of DNA (CSNPs) which help in the hunt for genes of clinical interest. There are on an average 4-8 SNPS in every gene either in the exons or in the nearby exon intron boundaries in the upstream regulatory regions. Genes of interest can be pin pointed using SNPs. At the molecular level mutations in gone, leading to alteration in gene products or altered regulation of gene expression provide an understanding of disease. New techniques such as complementary DNA micro assay (CDNA) are now available which will facilitate analyses of individual variations in the whole genome and the expression profile of all genes in all types of cells and tissues.

Table 1 summarizes recent advances in this field.

DRUG – DRUG INTERACTIONS

As important as predicting the efficacy of a drug is predicating and thus preventing adverse drug reactions. In general practice and in hospitalized patients several drugs (4-8) may be taken concurrently. Hence it is essential to understand the basic mechanism of drug – drug interactions.

1. Pharmacological incompatibility e.g. Penicillin + gentamicin / heparin / phenytoin neutralization.
2. Pharmacokinetics: Antacids interfere with absorption of antibiotics.
3. Metabolism: Enzyme induction. Enzyme inhibition: isoniazid enhances hypoglycemic effects of anti-diabetic drugs.

Pharmacogenetics defines DNA sequence variations in genes encoding transporters receptors, drug metabolizing enzymes such as CYP2C19 etc. Tamilian populations in India have poor or intermediate metabolism compared to Caucasian populations.

Concept of chirality: A pair of molecules which are mirror images of each other are called enantiomers. S-amlodipine, S-pantoprazole, S-atenolol, S-metoprolol at half doses are as effective as the racemic mixtures. S-Thalidomide is teratogen while R thalidomide is sedative.

Table 2 given examples of genetic determinates of responses to drugs. Pharmacogenomics now provides an opportunity to analyze the drug metabolizing enzymes (super family of cytochrome P450 CYP 1 CYP2 and CYP 3). Determination of an individual patient's genotype will be particularly important in use of antipsychotic drugs. For example, the drug remoxipride has to occupy 70-85% of dopamine D2 receptors in the brain to be effective. To achieve this end, point some patients need only 50mg / day while others may need 1 g / day. Use of radiolabel receptor ligand and external detector probe can enable determination of optimal dose by receptor occupancy. Similarly, to block 80% of platelets some patients need as little as 30 mg aspirin per day while at the other end some patients may need 1 gm/day. Hence for those in the first category the standard 300 mg dose is toxic while for the second category the dose is only a placebo"

Illustrative examples: Role of genotyping in optimizing warfarin dosage in prosthetic valve replacement – genetic variations of CYP 2Cq and VKORC1; dose determination by pharmacogenetic algorithm.

Clopidogrel dosage determined by CYP2C192 and iT744C of P2Y12.

NEW TOOLS FOR SNP ANALYSIS AND EDITING

Affymetrix, based in Santa Clara California USA, founded by Dr. Stephen Fodor in 1992 developed methods for fabricating DNA micro arrays called "Gene chip". In 1994 an HIV genotype Gene chip was introduced. Affymetrix Gene chip arrays assist in quick scanning for particular genes in a biological sample with oligonucleotide microarrays. A single chip can be used to analyze 20,000 SNPs to probe 6817 genes in one assay. Chips can be used only once.

Affymetrix uses photolithography to manufacture its quartz gene chips. Various inexpensive plastic based technologies are being produced at lower prices than Affymetrix quartz chips.

In January 2014 USA FDA cleared a first of its kind whole genome post-natal blind test – Cytoscan Dx Assay to diagnose genetic causes of development delay, intellectual disability, congenital abnormalities or dysmorphic features in children who have some sort of intellectual disability.

The current cost of Affymetrix chip is US$ 3000. The challenge is to make the chip affordable to the Indian population as early as possible. Drug companies have an enlightened self-interest in making this happen. This will save them billions of dollars paid by them in compensation for drug induced damage.

The future of health case lies in preventative genetic testing. Genome Patri[JM,] MapmygenomeJM Indian Genomics company founded in Hyderabad has developed in 2013, simple saliva based test which gives genetic predisposition for many chronic and life threatening diseases, genetic traits that influence medical outcomes, response to drugs, drug sensitivity and drug dosage, carrier status, diet and fitness well-being and life style improvement. The cost is Rs. 25000.

Baby Map DNA test Covers 171 developmental, genetic and metabolic disorders after drawing a simple drop of blood 24-28 hours after birth. The cost is Rs. 25000. A genetic counselor is available to discuss the results.

While 99.9% of the genome is the same in all humans, the 0.1% that varies from person to person is the key to all the diversity among humans.

Map My Genome provides personalized health solutions and actionable steps for individuals towards a healthier life, preventive health care. The aim is to touch 100 million lives and save a million lives by 2013".

Genome patri decodes DNA and predicts genetic risk for more than 100 diseases, traits inherited conditions, carrier status and drug responses, predictive assessment of cardiovascular, neurological and oncological conditions, women's wellness and reproductive health.

In the recent Rio Olympics India got only one silver and one bronze medal. SMART. SPORT assesses individual genetic predisposition to either sprint / power muscle exercises.

CVD SNP 55K Bead chips and illumine Micro assay system PLINK software and Kyoto encyclopedia of Gene and Genomics software. Illumina's veracode golden Gate Genotyping Assay of entire genome in 3 days for $100. The challenge is to make this technology available and affordable to every individual Indian.

In future editing our genes will be possible with a low cost very precise gene editing technique **CRISPR** (Clustered regularly interspersed, short palindrome repeats). Prashant Mala, born in Rajasthan and educated at IIT-B, Johns Hopkins and Harvard explains the intricate working of CRISPR. "Ability to target a new genomic site simply requires one to alter the sequences of the guide RNA. It is a very easy to use and cost effective. A DNA strand is slit open; target portion sniffed off by CRISPR – prefab desired portion is inserted and DNA joined up again. This can be used for removing disease – causing genes and inserting genes with desirable characteristics.

As an illustrative example Steven Johnson Syndrome, a fatal reaction to drug abacavir is due to a mutation in HLA B5701.Identification of this gene and elimination of this gene is now possible. A well-known physician of Kolkata was sued by his own student for the death of his wife due to Steven Johnson Syndrome caused by medication (and granted compensation amounting to Rs. 9 crores).

CPIC: CLINICAL PHARMACOGENETICS IMPLEMENTATION CONSORTIUM

Patients suffer because doctors fail to warn them about side effects of drugs.

C M Gulhati, editor MIMS has been championing the cause of safe drugs for decades. Pregnant women and children below 12 are particularly vulnerable.

Table 1: Recent Advances

Genomics: Study of gene sequences 3.5 billion DNA base pairs in exons (Coding regions) and introns has pairs (non coding regions)

Structural genomics: Precise 3 dimensional structure of proteins by X-ray Crystallography.

Transcriptomics: Study of variations in the expression level of different genes under different environmental conditions.

Tissue transcription profiling will be routine for planning appropriate treatment of cancers.

Proteomics (functional genomics) study of all proteins – 1278 families of proteins doing all the work in cells. Proteomics is center stage for new drug discovery.

Metabolomics deals with metabolizing enzymes: Over 50 cytochrome P450 enzymes determine the fate of drugs in the body. Biological networks with cybernetic relationship in cellular, biochemical and metabolic reactions.

System Biology: Biological switch boards with differential combinations of homodimers helirodimers and heterodimers initiating signaling and cell activation in several systems.

Metabolic phenotyping in health and disease: The human metabolome Database contains 41500 entries including water soluble and lipid soluble metabolites, 5680 genes and protein sequences and 440 human metabolic and disease pathways. For instance, the multiple genes and their poly morphisms in metabolic syndrome with their SNPs, are now known.

Epigenetics and transcriptional gene silencing

Nutrigenomics – Nutrition gene interactions

Future drug delivery systems: Site specific, pathophysiology – driven optimizing pharmacokinetic and pharmacodynamic and pharmacogenetics responses tailored to meet individual therapeutic responses.

It should be mandatory to provide readable package inserts regarding safety risks and precautious in using the drug. Millions of patients suffer because Pharma Companies and doctors fail to forewarn about drugs side effects. Pharmaco vigilance for every drug old or new, should be a continuous process. Drug related deaths can occur during clinical trials for which adequate insurance cover is mandatory.[7]

Sometimes rare but important adverse drug reactions (ADRs) are not detected in randomized controlled drug trials prior to FDA's drug approval e.g. Troglitazone's hepatotoxicity or viovax's adverse effect on CAD. The internet now makes available a wide range of information about ADRs almost instantaneously. CDIC (clinical pharmacogenetics implementation consortium) gives pharmacogenetics information in the package inserts eg.

Abacavir (HLAB5701)

Capecitabine

Carbamazepine (HLAB 1502, 3101)

Irinotecan (UGTQ, A128 allele)

Valproic acid (PULG mutation)

Warfarin (VKD RCIrs 9923231 allele)[8]

Marcia Angel M.D. former editor of NEJM, in "The truth about drug companies: how they deceive us and what to do about it". Random House 2004, observed that the pharmaceutical industry is corrupted by easy profits and greed. $35 billion are spent on "promotion of drugs" in doctors- marketing masquerading as education. She has given guidance for the mission to make drugs better, safer and more affordable.

EHR AND COMPUTERIZED PRESCRIPTIONS

In my book "Computers in Medicines: Progress in Medical informatics (Tata McGraw Hill 2005, 3rd reprint 2009). I have given action plans for introducing electronics Health Record and computerized prescriptions in India. Dr. N. J. Rao (Hyderabad), Dr. Anil Vij (Delhi), and Dr. Rohini Chougulay (Mumbai) have developed them successfully.

Med Docket – TM clinic management software developed Dr. Rohini Chouguley has following features

1. Linkage of drug names to diagnosis
2. More than 1200 generic drug names and drug trade names
3. Alerts for drug interactions
4. Pregnancy and lactation alerts
5. Alerts for drug allergies
6. Automatic dose calculations based on age, gender, body surface area
7. Auto calculation of total drug quantity prescribed based on dose, pregnancy and duration

Mobile phones now carry adequate information about drug – drug interactions, and reminders for appropriate changes in drug dosage in such situations. Every written prescription should have at the bottom in bold letters this printed caution: If you notice any untoward reaction stop the drug and report to your doctor immediately. Forewarned is forearmed.

CHECKLISTS

Dr. Atul Gawande in his book "The checklist Manifesto – How to get things right" states – "Clinicians now have at their disposal some six thousand drugs and four thousand medical and surgical procedures, each with different requirements, risks and considerations. Major complications for surgical patients in all hospitals fell by 36% after the introduction of checklists, deaths fell by 47%, infections fell by almost half. A checklist is a simple solution that makes the entire surgical team working towards solving a problem. Despite this doctors around the world resist checklists.

How to handle death?

Dr. Atul Gawande in his famous book "Being mortal"

Table 2: Examples Genetic determinates of responses to drugs

Polymorphism of drug metabolizing enzymes	Mechanism	Consequences
TPMT (Thiopurine S-methyl transferase)	(Inactivation of azathioprine and 6 mercaptopurine) = full activity enzyme EM : extensive metabolism deficient activity enzyme PM : Poor metabolism	PM phenotype patients show Excessive bone marrow toxicity with "Usual" dose EM phenotype patients show under treatment with" usual" dose of azathioprine.
NAT-2 (n-acetyl transferase)	Acetylation of isoniazid, hydralazine, sulfonamides, procainamide etc. "slow" rapid" and "intermediate" acetylators	Slow acetylators likely to produce INAH neuropathy
Cytochrome P450 mono oxygenases	Isoforms with different substrate specificities multiple pathways EM (extensive metabolizers) PM (poor metabolizers) IM (intermediate metabolizers)	Range of activity can vary tenfold between individuals on same dose. e.g. chlorpromazine
CYP2D6 antiarrhythmic drugs	Metabolic pathway for exaggerated drug effect B blockers, tricyclic antidepressants, neuroleptic drugs, selective serotonin reuptake inhibitors	PM phenotypes show on same dose of B blockers can be identified by test drug debrisoquine
CYP2C19	Catalyzes omeprazole Proguanil, diazepam and etalopram	EM genotype patients show only 29% cure rate for eradicating H. Pylori Vs 100% cure rate in PM genotype for same dose 20 mg omeprazole
CYP2C9	Metabolism of warfarin and phenytoin, loss of catalytic function in PM phenotype causes bleeding even with low warfarin dose.	100-200-fold difference in clearance of mephentoin between EM and PM phenotype increased toxicity in PM phenotype.
Genes coding ion channel proteins	Mutant genes, remain sub clinical until challenged by drugs such as quinidine which prolong action potentials	Prolonged QT and Polymorphic VTachycardia

has observed that doctors are trained how to keep their patients alive as long as possible but they are never taught how to prepare people to die. The last 8 days of a terminally ill patient in the hospital ICU can mean complete financial ruin for the entire family. A trusting doctor patient relationship will allow the doctor to explain to the relatives of the patient of the futility of heroic measures which only prolong his suffering. It is more humane for the terminally ill patient to die at home with his family around, rather than in the ICU.

In 1991 Greyon Thompson, a critical care specialist posed 4 questions to his patients.

1. Do you want to be resuscitated if your heart stops?
2. Do you want aggressive life support such as intubation and mechanical ventilation?
3. Do you want antibiotics?
4. Do you want gastric tube or intravenous feeding if you cannot eat on your own?

The written answers made management decisions easier and brought down end of life costs to half the national average. In the words of Mahatma Gandhi – "Death is the truest of friends, delivers us from agony".

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