A BLIND HITTING NAIL: A REVIEW ON GENOMIC MEDICINE

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ABSTRACT

Precision medicine promises to improve patient outcomes, but much is unknown about its adoption within health-care systems. A comprehensive implementation plan is needed to realize its benefits. "Genomic medicine is an emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g. for diagnostic or therapeutic decision-making) and the health outcomes and policy implications of that clinical use. Pharmacogenomics involves using an individual's genome to determine whether or not a particular therapy, or dose of therapy, will be effective. Currently, more than 100 FDA-approved drugs have pharmacogenomics information in their labels, in diverse fields such as analgesics, antiviral, cardiovascular drugs, and anti-cancer therapeutics.

Keywords: *genomic medicine, personalised medicine, transformation, emerging medicine.*

Introduction

Gene therapy is an experimental technique that uses genes to treat or prevent disease. In the future, this technique may allow doctors to treat a disorder by inserting a gene into a patient's cells instead of using drugs or surgery.When we visit the doctor, we are commonly asked to fill out a questionnaire about our family medical history, including major diseases such as cancer and heart disease experienced by our parents, siblings, and children. This is a rough way of gauging our risk of inheriting the factors leading to these diseases. All this information and more, however, reside encoded in our genome, and the current revolution underway in medicine is to decode and interpret our genomes to predict, prevent, and treat disease on an individualized basis.

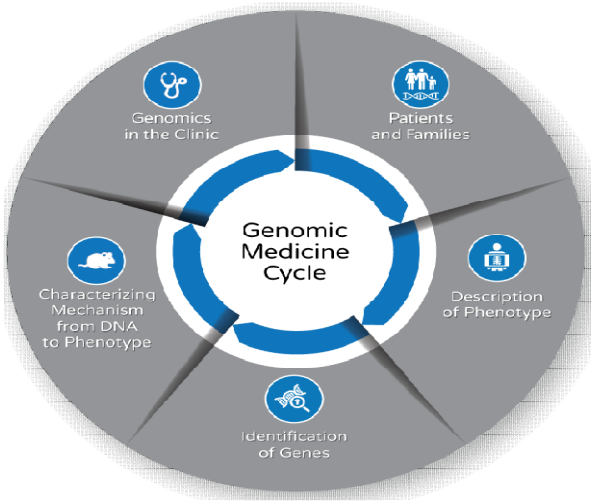

Figure 1: Genomic medicine cycle

What is personalized medicine?

Personalized medicine is an expression embracing ideas and a concept of making the treatment of a patient as individualized as possible. The therapy should be guided by clinical, genetic, genomic, and environmental information, which is different for every patient. The data offered are about the underlying mechanisms of the patient's disease, and can be used for drug selection ("selecting the right drug") or to determine the appropriate dose ("selecting the right dose"). The individual response to drugs depends not only on the mechanisms of the disease (pharmacodynamics), but in addition on the handling of the drug by the patient (pharmacokinetics).In 2002, the successful sequencing of the human genome was greeted with much enthusiasm. It was announced that the era of molecular medicine has begun and scientists and some physicians were promising that the field of personalized medicine would come at a fast pace. The hopes of many patients, which the high flying promises have provoked, have still to be fulfilled. In addition, it is to be noted that this progress will not come without costs in the health care system and that there are financial interests intertwined with the science and with the good intentions to provide the patients with the best medical care they deserve. Personalized medicine also encompasses the management of patients' personal data and medical information by

information and communication technology (ICT). It should however be noticed that frequently the medical doctors and patients are reluctant to make this information available on ITC platforms because of fear that the data could leak into the public domain. In some countries, there may be unwanted corollaries if the information is available with respect to employment and health insurance. Hence, the progress might come with some expenses that have to be weighed against the benefits it brings with it.

What are those personal factors that impact our personal health?

To understand personalized medicine requires an understanding of the factors that contribute to our health (Figure 2). In general, our health is determined by our DNA, our lifestyle, and the things to which we are exposed, namely, our environment. Our DNA is inherited from our parents. Our lifestyle includes behaviors such as how much we exercise, whether we smoke, and what we choose to eat and drink. Most of us know that environmental factors such as the quality of the air we breathe, ultraviolet rays from the sun, and the presence of certain chemicals in household items can affect our health. Important environmental exposures, however, go well beyond these

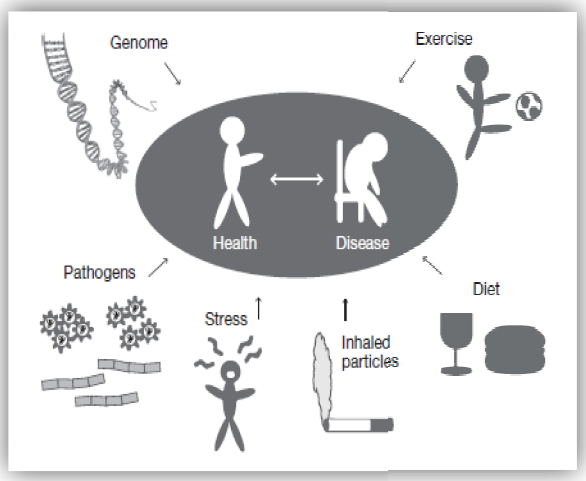

Figure 2: personal factor which impact on our health

Side effects of drugs and genetic markers

It has been known for a long time that the genetic disposition is important for the development of side effects of drugs. Liver injury is one of the most important side effects because it is severe and even life threatening. In genome-wide association studies, the human leukocyte antigen (HLA) system has been identified to play a role in eliciting major and clinically important side effects. Until now, the knowledge on the genetic basis of the drugs' side effect has only partially transformed into the clinical handling of these drugs. For example, testing is required before abacavir is given to a patient. However, testing before prescribing was not required for other drugs until now, although the information is mentioned in the drugs' information sheet (so-called labelling) at least for drugs approved by FDA.

Case study

For Cardiovascular diseases

Genomics in the cardiovascular field is directed toward understanding biological mechanisms of diseases and translating that knowledge to select the appropriate drug for the individual. During the past 5 years, hundreds of cardiovascular loci have been discovered. Genome-wide association study has been undertaken by the international consortium for blood pressure and it identified in 200 000 Europeans 29 single-nucleotide polymorphisms (SNPs) at 28 loci associated with regulation of the blood pressure. It is understandable that this information is of interest for the possible development of new drugs targeting specific regulation mechanisms. Molecular findings, however, have not yet found the way into clinical practice. The Seventh Report of the Joint National Committee on Prevention (www.nhlbi.nih.gov/guidelines/hypertension/) discusses clinically determined criteria helpful for selecting the appropriate antihypertensive drug, such as concomitant renal insufficiency, diabetes, and left ventricular hypertrophy. Currently only phenotypic factors but no genotypic factors influence the selection of antihypertensive drugs for the individual patient.

Pharmacogenomics might explain the variation in drug efficacy and more consideration needs to be given to the clinical context to define where pharmacogenomics would be an additional tool to monitor or predict therapeutic

success. As, at present, the place of pharmacogenomics in cardiovascular medicine is not defined, further studies are needed recruiting tens of thousands of patients with cardiovascular disease that combine tests of genome-wide association with sequencing. The genomic studies have to be supplemented by functional studies aimed to characterize molecular and cellular pathways. It should also be noted that there is more than the genome that influences treatment outcome, namely clinical, biological, or environmental factors that have to be meaningfully integrated to support personalized decision making in cardiology.

Cancer

The field of oncology is the area in medicine where genomic data and information is used on a daily basis. Here we can present several well established examples of the advantage of its use in identifying somatic mutations in the genotype of the tumour that are strong determinants of drug response.

Breast cancer: The HER2 (also called ErbB-2) receptor belongs to the epidermal growth factor receptor family of receptors characterized by an extracellular ligand binding domain, a Tran's membrane domain, and an intracellular domain. Epidermal growth factor receptors have an activity as plasma membrane-bound receptor tyrosine kinases. Their intracellular domain can interact with a multitude of signalling molecules in the cell. Signalling through HER2 or other members of the receptor family promotes cell proliferation and opposes cell death by apoptosis. In normal life, signalling through this pathway is tightly regulated to prevent uncontrolled cell growth. Amplification of the gene regulating the receptor protein or gene over expression is seen in 15%-20% of breast cancers. Gene amplification or over expression is a prognostic marker and indicates a poor outcome of the disease. During the past decade, treatment, specifically targeted at HER2, has improved disease-free survival in patients with breast cancers that over express HER2 but it has not convincingly increased the overall survival. Nevertheless testing is necessary, before treatment is initiated, in order to predict whether drugs directed toward HER2 will have a chance to be effective or whether the treatment will only cause side effects.

Very recently it has been demonstrated that acting on the same target by adding pertuzumab to a treatment with trastuzumab and docetaxel does improve progression-free survival in patients with HER2 positive metastatic breast cancer (control median: 12.4 months; addition of pertuzumab 18.5 months). However, the positive influence on overall survival of the patients is still to be documented.

Colo-rectal cancer: Another example where diagnostic testing is used is the anticancer therapy directed toward epidermal growth factor receptor (EGFR). Similar to HER2, the EGFR receptor is on the surface of cancer cells. Monoclonal antibodies have been approved to treat EGFR-expressing late-stage colorectal cancer (CRC) in patients who had become resistant to chemotherapy. It has been found out that the drug is not effective in patients whose tumours have a mutated KRAS gene, which is associated with resistance to drugs that are anti-epidermal growth factor receptor (EGFR) antibodies. The tumours of patients with metastatic colorectal cancer are now profiled for seven KRAS mutations before receiving monoclonal antibodies. Polymerase chain reaction-based kits (e.g., Therascreen, Quiagen) can provide information about the KRAS gene mutation in patients who's CRC has metastasized. These tests have been approved recently by FDA to determine if the absence of a gene mutation would indicate the treatment with a monoclonal antibody. In one clinical study with cetuximab, in patients whose tumours did not have a KRAS mutation, median survival was 8.6 months compared with 5 months in the control group. In patients with a KRAS mutation, median survival was similar in those who received the drug as in the control group (4.8 months and 4.6 months, respectively). Hence, testing is helpful for predicting the outcome. However, we have to admit that we still wait for therapeutic breakthroughs as even in the most favourable case survival was prolonged for a few months only. In a recent study, other mutations, namely BRAF, NRAS, and PIK3CA exon 20

mutations, were also found to be associated with a low response rate. From this study, it can be concluded that additional genotyping of BRAF, NRAS, and PIK3CA exon 20 mutations in a KRAS wild-type population may help to identify patients with a good therapeutic outcome.

Application

The application of genomic medicine that's really relevant to a lot of people and gaining in popularity in that is family planning in vitro fermentation and pre-implant action genetic diagnosis that is a human embryo now screen this embryo for serious genetics defeat at this stage before it's implant into the women's for pregnancy so if you are going through IVF one of these cells can be removed from the embryo doing no damage to the embryo it can be screened for serious diseases but wouldn't it be great if we could actually have prevented medicine & the impact of genomic medicine from the first breath rather than waiting to her adults meet nick.

IDIOPATHIC DISEASE of unknown causes have you ever know figure out way IDIOPATHIC so patient was normal until about age 2 when fistula began to form and those are holes that formed between rectum and outside of his body faces leaked through holes and made him sick year high fevers become septic almost died many times in fact by hundreds general anaesthesia surgical patient had his colon restated and then completely removed they inserted a G-tube so all food drink went through a G-tube and exceeded his but by genomic medicine they sequential genome and found a mutation in a protein called EIAP if we do a bone marrow transplant which was not obvious and it was risky that we would be able to cure his illness.

Thus far, for the vast majority of mystery genetic diseases, exome and whole genome sequencing has been successful indentifying the likely disease- causing mutations in about 25%–30% of cases. Furthermore, when the causative mutation isidentified, only in a handful of these cases has the information been valuable for optimizing treatment. Often whole genome sequencing or exome sequencing generates a short list of possible disease-causing mutations; narrowing the list further requires additional tests and experiments. There have been, however, a few spectacular successes.

Conclusion

Genomics can have a direct impact on drug treatments for cancer and mystery diseases. In a patient with cancer, it may be possible to use that patient's DNA sequence to guide treatment to chemotherapy or to target pathways that are genetically or epigenetically affected in the patient.The molecular basis of variability in effective drug doses was understood several decades ago. Understanding, however, does not transfer automatically in therapeutically important improvements. Whereas the concept of testing for molecular changes to explain metabolic differences is accepted, we have to note that the clinical influence of a changed metabolism is modest in most of the cases. Somatic mutations are important for detecting whether the patient will respond to new drugs targeted for tumour specific molecular features. Success is limited by tumour heterogeneity, which is not easily detected and by development of tumour cell resistance at the molecular and cellular level. There is a long way to go to fight these obstacles. The concept of personalized medicine is intellectually attractive and scientists are convinced that this is the way forward. However, dissemination of the current status instead of unrealistic promises will be a cornerstone for the acceptance by doctors and patients alike.

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