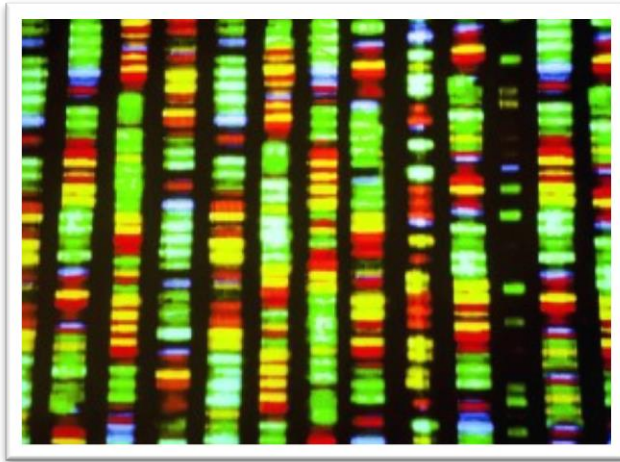


‘omics’ and ‘omes’ – the future of personalised medicine

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2500 years on, the human genome is shedding new light into the cavernous depth of Hippocrates’ quote: “*It’s far more important to know what person the disease has than what disease the person has*”. Knowing the person is what personalized medicine (PM) is all about, right down to their genome, transcriptome, epigenome, microbiome. The end game for personalized medicine is to provide the most effective individual treatment by providing “the right patient with the right drug at the right dose at the right time.”

Personalized/ individualized/precision medicines are used synonymously as the catch-phrase. Meanwhile multiple definitions of PM float about:

“Personalized medicine is the use of diagnostic and screening methods to better manage the individual patient’s disease or predisposition toward a disease....

– NHLBI Strategic Planning, Theme #10

Personalised medicine is an emerging practice of medicine that uses an individual’s genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease.

– NHGRI Talking Glossary of Genetic Terms

To get a better understanding of PM, let’s dissect this statement further “the right patient with the right drug at the right dose at the right time.”¹

‘The right patient with the right drug’

Often a very high % of patients will not respond to an initial treatment. Cancer is a prime example, where on average about 75% of patients don’t respond well to the initial drugs prescribed. Some examples of the right drug are as follows:

- Herceptin® for HER2 breast cancer. If genetic testing shows that a patient’s breast cancer shows overexpression of a cell surface protein called human epidermal growth factor receptor2 (HER2), then the recommended drug is Herceptin® (trastuzumab) used in combination with chemotherapy, which can reduce recurrence of a tumor by 52% compared to chemotherapy alone. About 30% of breast cancer patients are HER2 positive.

- Zelboraf® for melanoma. If genetic testing reveals a certain mutation (V600E) in the BRAF gene then Zelboraf® (vemurafenib) is recommended to treat melanoma that can't be surgically removed.

These examples show how information from our genomes has given us the answer to why 'One size does not fit all' when it comes to drugs. They also hint at the sweeping changes personalized medicine will bring in cancer diagnostics & treatment. Cancer diagnosis will move away from the traditional tissue of origin classification (lung, breast, prostate) to focus on profiling individual tumors (in other words the number and type of genetic mutations present). Treatment will be tailored based on this molecular diagnosis. For example, Pfizer carried out a trial on a drug to treat lung cancer which failed miserably. However retrospective analysis concluded that this drug is actually > 60% effective in just 4% of lung cancer patients who carry a specific genetic alteration (ALK translocation). So in other words this particular lung cancer drug can be used to very successfully treat 4% of patients, but 96% of patients would get no benefit and may even suffer adverse reactions.

Another important point is that identical mutations can be found in different cancers so the same drug can be used to treat different tumors. For example, BRAF V600 is found in melanoma and hairy cell leukemia, so vemurafenib can be an effective treatment for both. A 2014 report lists > 100 drugs whose labels now include pharmacogenomics information.

The right dose

It's a matter of getting the right drug *and* the right dose. Some people metabolize drugs more slowly than others which means the drug hangs around in their body for longer causing "overdose toxicity"; others metabolize the drug too rapidly so it doesn't have enough time to be effective. These adverse drug reactions are often due to differences in genes that code for key drug-metabolizing enzymes, such as cytochrome P450, or CYP, enzymes. Testing a patient's genes prior to administering a drug can facilitate more precise dosing rather than the conventional trial-and-error approach, which can be damaging, or even fatal. Warfarin dosing based on CYP2C9 gene testing provide a well know example. Warfarin is a drug used to prevent blood clots and the CYP2C9 gene encodes one of the main enzymes involved in its metabolism. Two single nucleotide polymorphisms (SNPs) in the CYP2C9 gene reduces warfarin metabolism. The FDA recommends testing for all patients before warfarin treatment, to allow more precise dosing and prevent excessive bleeding in slow metabolizers. CYP genes play a role in metabolising about 25% of all drugs currently prescribed.

The right time

The right time is as early as possible. Personalized health care can detect disease at its earliest stages, enabling doctors to treat proactively rather than reactively. We're back to the old adage, prevention is better than cure. Medicine of the future will focus on maintaining health rather than curing disease.

Realising the mantra 'the right patient with the right drug at the right dose at the right time' will increase patient adherence to treatment and help control the overall cost of health care.

Technology is the driving force behind personalized medicine. NGS (Next-Generation Sequencing) has given us the power to unlock the secrets of the human master plan with the \$1,000 genome a stone's throw away. It's a very significant price because it's comparable to costs of existing medical

tests and will make routine whole genome sequencing a reality, not only for patients but for healthy ‘consumers’ who maybe want to carry their genome around on their cell phone. A gargantuan task lies ahead according to the ENCODE (‘ENCyclopedia Of DNA Elements’) project which grabbed the headlines with a claim they had found “biochemical functions for 80% of the genome”, even though 20% may be closer to the truth. ‘Big Data’ generated by sequencing hundreds of thousands, or eventually millions, of human genomes will be fed into bioinformatics pipelines to extract the actionable data. New DNA diagnostic tests will aim for high analytical & clinical validity as well as high clinical utility.

Epigenetics

Epigenetics is also an important part of the genomic jigsaw puzzle and an intense area of research. Epigenetic changes alter the chemistry and structure of our DNA, but not the sequence. Could epigenetic changes represent a ‘fine-tuning’ of our stoic DNA to allow certain genes to be turned on or off in response to our environments/lifestyles?

The role of biomarkers

In addition to information we can glean from DNA biomarkers, protein biomarkers can also be used to detect the earliest onset of disease and to track a patient’s response to therapy. The ideal biomarker is reliable and easy to measure non-invasively (e.g. in a blood sample). The level of a biomarker must accurately reflect both the burden of disease and how this changes in response to drug treatment. In other words a biomarker must be significantly correlated with the clinical state. The development of new biomarkers will increase as we elucidate the molecular pathogenesis of different diseases.

Pharmacogenomics

The Pharmaceutical industry is a big player in this genomic revolution. Companies are now integrating genomics into drug development, identifying responders and non-responders from their genome and designing clinical trials with just 100 people (Instead of 000’s) that can be approved in a short period of time. In the US it’s predicted that the FDA will require genome sequencing to be an integral part of every drug trail before the end of this decade. The significant reduction in cost and time for clinical trials could increase the rate of new drugs being approved and entering the market by 10 fold. This will in turn catalyse the availability of safer and more effective treatments.

Into the future

The futuristic vision is one where clinicians can access a patient’s electronic data instantly (including their genome and microbiome) and within minutes computers will recommend a personalized treatment based on the latest scientific and evidence-based medicine from around the world. These electronic health information systems could be linked nationally, or ideally worldwide, to create the most up to date “learning health care system” that is continuously fed with real-time data collected in clinics and research institutes. In addition, after discharge from hospital patients can be monitored

remotely at home, offering a less stressful environment for recuperation. In the US health the infrastructure for information technology is being put in place. From 2016 on, hospitals and physicians will face penalties for not using health IT such as electronic health records with molecular information in a meaningful way.

Education for clinicians and patients is currently the missing link in this new futuristic vision. In addition, health insurance policies will need to be designed for personalized medicine to ensure both patient access and benefits for the healthcare system. Policies based on the least expensive treatment will discourage PM because it may cost more up-front, but will result in substantial clinical and economic benefits in the long-run. Accountable models of healthcare focus on paying for the outcome (making the patient better), rather than paying for an MRI scan here, a blood test there ('fee for service' approach). Laws to protect privacy and safeguard against discrimination by employers and health insurers will have to re-align to personalised, predictive, preventive, and participatory medicine.

Armed with a clear understanding of the genome, epigenome, microbiome and all the other omes and omics, futuristic healthcare will focus on prevention rather than cure. Whole genome sequencing as a routine newborn test in the first 1-2 days of life, uploaded to an electronic medical record, is the Holy Grail. The ultimate visual proof that each human genome is a unique code will come into focus with the ability to print a 3d image of someone's face or brain from their genetic code.