Pharmacogenomics for General Practitioners:

Time for clinical application

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Pharmacogenomics tests are not yet available to general practice. The purpose of the following article is to inform primary care clinicians about the existence of such tests and to generate discussion about what role, if any, they may play in future medical practice. – Professor Murray Tilyard, Editor-in-chief, Best Practice Journal

Most medical practitioners will be aware of the variable nature of medication response. Until recently prescribing the correct medicine, at the correct dose, to the right patient has largely been empirical. Skilled prescribers take into account age, body weight and other co-morbidities when making a treatment choice. However, there are many other important factors that can be considered, such as genetics.

Pharmacogenomic testing will soon be available to GPs and encompasses what has previously been out of reach, the molecular dimension of patient care. The exciting promise of genomics and other molecular technologies is to make medicine more predictive, preventative and personalised.

What is pharmacogenomics?

The field of pharmacogenomics has existed for several decades, however, its clinical application has been limited by a number of factors. Although good science and clinical data exists to support the use of the technology, there are barriers to its implementation. These include cost, availability, speed of turnaround in results, education and opposition from industry. Since the completion of the human genome project in 2003, the cost of genotyping has reduced exponentially. Alongside this, there has been an explosion in the methods to perform genotyping and sequencing. A complete genome is not necessary to make important clinical decisions – single individual genetic variants (also known as single nucleotide polymorphisms, "SNPs") can be useful tests in isolation. The cost of testing

SNPs has now dropped to under $200 and each test needs to be performed only once in an individual's lifetime.

Pharmacogenomic testing generally involves the testing of a number of SNPs within key genes that encode for metabolic pathways, transporter systems or drug targets. Alterations in SNPs may alter the function of an enzyme or protein to make it more or less active, contributing to the phenotype or physical characteristics of an individual. It is important to understand that the genotype does not always correlate perfectly with the phenotype.

Considerations for healthcare professionals

As personalised medicine enters primary care, it will be important for it to be understandable and relevant to both the patient and practitioner. Unfamiliar data for general practitioners will be potentially confusing. For a SNP test to be worthwhile, it has to provide a result that is able to be actioned and also must provide additional benefit compared to current management strategies.

Pharmacogenomic tests fall into two categories (though some may provide information on both):

1. **Predictive tests** that are actionable and change treatment. These tests provide information about a patient's response or non-response to a medication.

   Examples of this include:

   a) Warfarin – genetic information combined with clinical information provides an accurate maintenance dose estimate (within 0.5 mg). In the future those at high risk for bleeding may be prescribed dabigatran.[1]

   b) Clopidogrel – provides the ability to identify non-responders who are at higher risk for stent thrombosis and death. Non-responders can be given alternative treatments when they become available in New Zealand.[2]

2) **Prognostic tests** that assess risk.

   Examples of this include:

   a) Simvastatin – provides a relative risk for the development of myopathy on 80 mg of simvastatin. Homozygotes are at a sixteen times higher risk of myopathy.[3]

   b) Abacavir - provides a risk for developing Steven's Johnson syndrome.[4, 5]

   c) Carbamazepine - provides a risk for developing Steven's Johnson syndrome in Asian people.[6]

Two considerations for the prescriber about pharmacogenomic testing are:

1. What is the likelihood of the adverse event?

   In the instance of statin myopathy the clinical trial event rate is uncommon and testing every patient may not be cost-effective.

2. How common is the genetic variant in the population I am testing?

   In some populations genetic variants that code non-response are more prevalent, meaning that testing may be more cost-effective.

Ethics and privacy

Genetic testing may be viewed as discriminatory by some groups. This concern is well founded as employers and insurance companies have shown an interest in using genetic information to assess prospective employees and load policies. General practitioners need to be aware that entering genetic information into patient's clinical notes may allow them to be viewed by third parties. Also, a non-functioning or deficient enzyme could quite easily be considered a label of a "deficient individual."

Other concerns with genetic testing include racial ancestry and paternity. Rare variants that are common in some ethnic

Current and future personalised medicine tests available in New Zealand

Biomarker test	Provider/Developer	Utility and Accuracy	Cost	Benefits
Stool-based molecular diagnostic test	Exact Sciences	Detects the presence of bowel cancer and adenomatous polyps	Unknown	Higher uptake of screening Improved specificity compared to faecal occult blood test
Renin[8]	Diagnostic Medlab	Predicts success of monotherapy to antihypertensive treatment (chlorthalidone vs atenolol)	Low	Avoids cycling through therapy and may reduce number of pills needed
Urine-based molecular diagnostic test	Pacific Edge Biotechnology Ltd	Detects the presence of bladder cancer	Unknown	Screening tool for bladder cancer, allows early diagnosis and treatment
Clopidogrel pharmacogenetic test	Theranostics Lab	Predicts risk of adverse events and efficacy	$150	Prompts treatment increase or change in treatment to reduce stent thrombosis
Statin pharmacogenetic test	Theranostics Lab	Predicts myopathy risk	$150	Improved adherence to treatment
Warfarin pharmacogenetic test	Theranostics Lab	Dose prediction and bleeding risk	$150	Reduced bleeding events
ACE inhibitor pharmacogenetic test	Theranostics Lab	Prediction for ACE inhibitor-related cough	$150	Prevents ACE cough, patients could possibly switch to ARB treatment

Notes: Other genetic tests of note include TPMT for azathioprine, KRAS for cetuximab and BRAF for melanoma treatment (see Phase III study from Plexxikon). Pharmacogenetic testing for SSRIs and tamoxifen are also emerging areas. Clopidogrel and warfarin tests have proven cost-effectiveness.

groups may be used as a surrogate for race. Presence or absence of a variant may imply paternity. Discussing genetic results with patients can be fraught with problems and genetic counselling is advised for any genetic test that has the potential for significant psychological impact to an individual and their family. Genetic testing of an individual, in effect, is also indirectly testing family members.

The future of personalised medicine

It is clear that the future of medicine is heading in the direction of personalised risk and treatment decisions. Historically the practice of medicine has largely focused on the physical (or phenotypic) manifestations of disease. However, many diseases begin at earlier stages that may not be apparent to most modern methods of diagnosis. These disease stages are sometimes detectable using molecular methods of diagnosis. Pharmacogenomics is the first in a number of scientific fields that is emerging as clinically valuable. The goal for these fields is to improve on the efficiency of current medical practice, rather than add to their cost. An example of this is a recently developed molecular stool-based test for bowel cancer screening (sensitivity 85%, specificity 90%). This test potentially may increase adherence to screening programmess and reduce negative colonoscopies.[7] In addition, genomic medicine is revealing highly targeted therapies, such as a new melanoma treatment produced by the company Plexxikon.

Cost is an important consideration when reviewing all of these new technologies. Making medicine more efficient by identifying high risk individuals using genomics, and applying non-invasive molecular screening tools, should lead to reduced cost, which is currently consumed by procedures and specialists applying healthcare that is not widely accessible. A smaller market for the pharmaceutical industry is unattractive and drugs developed for a few may unfortunately cost a lot, putting them out of reach for patients in New Zealand. General practitioners are likely to be at the very forefront of personalised medicine which seeks to provide a more global and holistic approach to healthcare.

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