# Potential implications of genomic medicine in general practice

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## ABSTRACT

- Genomic research can link specific molecular genetic information with specific diseases.
- Implications of genomic medicine in general practice include developments in screening and diagnosis, predicting disease prognosis, and optimising preventive and therapeutic care.
- As users or co-producers of genomic information, or as collaborators in genomic research, general practitioners can help realise the potential of advances in genomic research.


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General practitioners don't want to be gene gnomes labouring in the caverns of genomic research, but neither should we avoid the torrent of data, information and useful knowledge that new discoveries in the post-genomic world will provide.[1] The volume, however, is a problem: in February 2010, the United States National Center for Biotechnology Information's GenBank reported 200 billion base pairs in its database and a continued exponential growth rate in genetic information leading to a doubling every 18 months.[2] Much of the information provided by these research activities is still remote from the concerns of everyday practice, but some is being integrated into our work and more will follow.[3,4] A significant outcome of this new science is the ability to link specific molecular genetic information to specific diseases:

> Perhaps the most important single contribution of the new genetics to health care is that it will create a biological rather than a phenotypic framework with which to categorise diseases.[5]

Here, we review a range of current and potential developments in genomic research from the perspective of practising GPs, some of whom may also become engaged in genomic research.

## Methods

A scoping review of PubMed and Web of Science was undertaken using Medical Subject Headings (MeSH) terms for general practice, family medicine and primary care with terms for genetic, genomic and post-genomic research during the period 2001–2010. The results have been combined with our existing knowledge of the field and contacts with laboratory, hospital and community-based colleagues during discussions. Examples are expressed as clinical consultations in general practice with "Dr Paterson", a GP who has recently been reading about the potential implications of genomic medicine in general practice.[6] Examples of diseases for which genetic testing is available are provided in Box 1, and a glossary of genetic terminology is provided in Box 2.

## Screening

The first patient seen by Dr Paterson this Monday morning has read an article in a weekend newspaper suggesting that haemochromatosis is a serious disease and that all adult males should be screened genetically. Dr Paterson knows that the responsible use of genetic screening to determine susceptibility to disease is currently limited to those at increased risk.[7] For example, the option of genetic screening for haemochromatosis should be discussed with first-degree relatives of individuals with hereditary haemochromatosis, and with relatives of those already known to be genetically susceptible to the disease. The phenotypic expression of hereditary haemochromatosis depends on genetic susceptibility, usually C282Y homozygosity or C282Y/H63D compound heterozygosity of the *HFE* gene, plus sufficient iron in the diet. There is a further factor in that regular menstruation appears to protect against clinical disease, so that in a recent study 28% of men but only 1% of women homozygous for the C282Y mutation developed the disease over 12 years of follow-up.[8]

In Australia, the costs of testing for relevant mutations in first-degree relatives and in patients with persisting elevation of transferrin saturation or serum ferritin are reimbursed through Medicare. Asymptomatic relatives found to be susceptible are likely to benefit from ongoing surveillance of iron status, along with advice on diet and other measures that may reduce progression to clinical disease.[9] Indiscriminate screening in people who have a low likelihood of disease could lead to identification of many people with the genetic predisposition but who are protected by their environment and would never progress to clinical disease.

Indications for screening relatives of patients with other diseases that have a genetic aetiology are more complex. It is possible, for example, to screen individuals with a family history of venous thromboembolic disease for mutations of genes encoding Factor V, prothrombin and other molecules involved in coagulation, but the clinical benefits are less clear. Screening relatives of individuals with neuropsychiatric disorders that are attributed to an expanded number of trinucleotide repeats, such as Huntington disease, can enable affected individuals to make family planning choices and other decisions about their lives. Clearly, such screening should only be undertaken with expert support and following specialist counselling.

A growing number of genetic mutations are recognised as being associated with a variety of cancers. Certain mutations of the *BRCA1* and *BRCA2* genes, for example, convey increased risk of breast, ovarian and prostate cancer. Consideration should be given to referring individuals with unusual family histories of cancer, such as multiple affected relatives or relatives developing cancer early in life, to a family cancer clinic. The Australian National Breast and Ovarian Cancer Centre has an online calculator for the assessment of breast and ovarian cancer risk based on family history.[10]

At present in Australia, neonatal screening for genetic conditions is based on biochemical testing, with subsequent confirmatory DNA analysis following detection of some abnormalities. This is partly because of cost. As the price of genetic testing falls, and the genetic basis for more diseases is characterised, the opportunities for prenatal, neonatal and subsequent genetic screening will grow.[11] There is a risk, however, that the technology may outstrip our understanding of the associated costs, benefits, and legal and ethical issues.[12]

**1 Examples of diseases for which genetic testing is available**

| Disease | Comment |
|---|---|
| Hereditary haemochromatosis* | Useful for confirmation of susceptibility |
| Coeliac disease* | Useful for exclusion of uncertain diagnosis |
| Inherited thrombophilia* | Useful for assessment of risk |
| Fragile X syndrome* | Useful for assessment of developmental delay |
| Huntington disease | Available through specialist services |
| Early-onset familial Alzheimer disease | Available through specialist services |
| Cystic fibrosis | Prenatal diagnosis is available |
| Haemoglobinopathies | Useful for complex and prenatal diagnoses |

*Costs of testing are reimbursed through Medicare in Australia (specific conditions apply). ◆

**2 Glossary of genetic terminology**

**Alleles:** different variants of the same gene locus.

**Chromatid:** one of two identical DNA copies which makes up a chromosome.

**Codon:** a sequence of three adjacent nucleotides constituting a unit of the genetic code (eg, a codon might specify the insertion of a specific amino acid in a polypeptide chain).

**Exome:** the portion of the genome which includes all the coding DNA.

**Exon**: a coding segment of DNA.

**Genetic medicine:** the use of knowledge about single genes to improve the diagnosis and treatment of single-gene disorders.

**Genome:** the entirety of an organism's genetic material.

**Genomic medicine:** the use of knowledge about interactions between the genome and non-genomic factors, from which new diagnostic and therapeutic approaches are emerging.

**Haplotype:** a combination of related genes on the same chromosome, which are usually inherited together, or a set of single-nucleotide polymorphisms which are present on a single chromatid and statistically associated.

**Heterozygous:** an individual is said to be heterozygous for a particular gene when different alleles occupy corresponding gene loci on homologous chromosomes.

**Homozygous:** an individual is said to be homozygous for a particular gene when identical alleles occupy corresponding gene loci on homologous chromosomes.

**Intron:** a non-coding segment of DNA which interrupts the coding segment of a gene.

**Locus (plural, loci):** the specific location of a gene or other DNA segment on a chromosome.

**Null allele:** a mutant copy of a gene which completely lacks function.

**Pharmacogenomics:** the study of the influence of genetic variation on drug response and toxicity.

**Phenotype:** the complete, observable characteristics or traits of an organism resulting from interaction between genetic expression and the environment.

**Polymorphism:** multiple alternative alleles at a locus that result in different phenotypes.

**Single-nucleotide polymorphism:** DNA sequence variation in which a single nucleotide differs between members of a species.

**Trinucleotide**: a polymer consisting of three nucleotides. ◆

## Diagnosis

The next patient has come for the result of a genetic test for coeliac disease and here genomic medicine is more helpful. As 99% of people with coeliac disease express HLA-DQ2 or HLA-DQ8, exclusion of these haplotypes virtually excludes the diagnosis in a patient with clinical suspicion of the disease but who has no antibodies to tissue transglutaminase, or a patient who does not wish to consume a gluten-containing diet before biopsy.[13] Coeliac disease provides a good example of a pathological interaction between an individual's genome and their environment. Development of clinical disease requires both genetic predisposition and exposure to specific environmental factors.[14]

At present, the diagnostic usefulness of genetic testing in general practice is limited to few situations (Box 1), but this is likely to change rapidly. A recently published article described an unexpected diagnosis of congenital chloride diarrhoea, an extremely rare condition, after the patient's whole exome was extracted, sequenced and analysed.[15] As the cost falls, such "exome scanning" may become commonplace in the context of unexplained illness.

## Prognosis

During his lunch break, Dr Paterson reads through his mail. A letter from the local children's hospital reports on the recent admission for asthma of one of his patients, an 8-year-old boy named Jake. During his admission, Jake had a buccal swab, from which homozygous null alleles of the filaggrin gene were demonstrated. In 2007, asthma in patients with null allele mutations of this gene was shown to require more aggressive treatment.[16] Asthma is a complex condition with a multifactorial aetiology: genetic research is starting to unravel the molecular basis of the disease and challenge conventional views on pathogenesis. Using genetic markers to classify subgroups of asthma patients, it may be possible to predict individual drug response and prognosis. In the meantime, Jake can be monitored more closely and treated more aggressively: future population-based studies will increase our ability to individualise treatment and minimise exacerbation risk.

Dr Paterson then takes a call from Claire, a 55-year-old woman with type 2 diabetes and a strong family history of cardiovascular disease. Claire wants to know if she can have a genetic test to predict her risk. To date, the use of genetics in this area has been disappointing: no single allele which has an influence on risk that is large enough to improve current risk calculations has been identified.[17] A polygenic approach seems to be promising; this would involve testing for several alleles that convey risk, and assessing risk based on this information and known phenotypic risk factors.[18] Advances in this area will increase our understanding of the pathogenesis of cardiovascular disease and allow more targeted treatment of patients who are at risk. Dr Paterson reassures Claire that her current risk-reduction strategy is the best treatment at present, and tells her that genetic testing may eventually provide a more individualised treatment plan and risk calculation.

## Treatment

Afternoon consultations start with a patient who has depression. Dr Paterson has already made a referral for cognitive behaviour therapy and the discussion has now turned to drug treatment. The patient, 25-year-old Morna, is keen to receive medication. She was

treated with antidepressant medication several years ago but stopped after 2 months. Morna says that she felt terrible on the tablets, with lots of nausea and diarrhoea, and that they didn't seem to improve her mood. However, her depression persists, it is interfering with her college course, and she is very motivated to try treatment again.

Dr Paterson is prompted by his electronic health record that researchers at the local university have recently started recruiting for a trial which is assessing the performance and utility of genetic testing for antidepressant action and metabolism. He prints off and discusses more information about the study, and Morna agrees to participate.[19] The aim of this pharmacogenomics research is to determine genetic predictors of response and side effects. Morna's outcome will be followed up by the research team. Perhaps genetic factors have been the cause of her previous treatment failures? Perhaps Morna does not efficiently metabolise the drug, causing excessive side effects, or perhaps her molecular receptors for the drug have reduced affinity, meaning it is less effective.[20] This technology is controversial, which is why the university researchers are investigating it further.[21] Morna feels this might improve her chances of recovery and let her contribute to the development of "personalised medicine", which she keeps hearing about on television.

Personalised medicine can be defined as the systematic use of information about an individual patient to guide and optimise that patient's preventive and therapeutic care. Increasingly, the term has come to refer to the use of genomic and molecular data to guide health care. In the context of treatment, there is currently much interest in the genetic basis for variation in drug metabolism. For example, more than 30 single-nucleotide polymorphisms have been reported in the gene encoding cytochrome P450 2C9 (CYP2C9), resulting in considerable variation in the activity of this enzyme. Many drugs are metabolised by cytochrome P450 enzymes, and differences in activity between individuals are thought to be an important cause of variation in therapeutic response.

## Keeping up to date

To keep up to date with new developments in genomic medicine, and to revise his knowledge of genetic science, Dr Paterson has identified the need to include improving his understanding of genomics in his professional development plan. He will attend a 2-day course which has been developed by the local genetics service and university departments of genetics and primary care. The emphasis will be on current service provision and rapid translation of research findings into practice, including the use of clinical decision support systems.[22] He will also aim to develop his awareness and understanding of the potential implications of genomic medicine.[23] As an advocate for the health of his patients, he knows that it is imperative that he firmly grasps the impacts of genomics, both positive and negative, on individual patients and their families, as well as at a societal level. Dr Paterson knows that he needs to understand the science and the ethical and legal issues if he is to provide adequate advice to patients considering direct purchase of genetic tests over the internet, or who may require life or disability insurance after a genetic test. His attendance at such training sessions will be supplemented by involvement in continuing professional development organised by his professional body or other provider. Dr Paterson is excited that, by doing so, he will help shape future health policy.[24]

## General practitioners and genomic research

General practitioners may be users or co-producers of genomic information, or collaborators in genomic research, and some may find themselves in all three roles. The user role is unavoidable because we all want our patients to benefit from the developments in health care that genomic medicine will provide. If we want to ensure that the results of basic research are more relevant to our practice and more rapidly translated into useful knowledge, then we might collaborate with the large groups of international researchers undertaking such work.[25] Laboratory science is not the only area that would benefit from GP engagement. Research in communication, behavioural and social sciences, such as exploration of ethical and legal issues, is likely to be very relevant to general practice.[26] Through our involvement as fully engaged members of a post-genomic medical profession, the full potential of advances in genomic research will be realised.[27]

## Competing interests

None identified.

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