The Next Generation Health Screen

How Can Genetics Revolutionise Primary Care Practice?

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We share the results of our Whole Genome Screening (WGS) and how The London Genetics Centre can help to collaborate with doctors and their patients to fully gain the benefits of this new medical programme.

WGS is more likely to help your health than any other single test in your lifetime. It can also help your family.

We have an exclusive agreement with Veritas in the UK for WGS and panel tests. This is a joint project and we have worked closely together for the last 2 years. 566 genes are analysed for pathological alterations which are related to more than 650 diseases. We are only analysing actionable gene alterations. So, if you find you have them, then you can do something significant to improve your outlook. We do not analyse the neurological genes such as Parkinson's or Dementia.

Modelling suggests that WGS should be able to reduce the cancer mortality by a fifth. For example, we should be able to stop one third of ovarian cancer deaths by the day case procedure of bilateral salpingo-oophorectomy for those with high-risk gene alterations. We know that CA 125 and ultrasound screening have finally been proven not to help, so we must move on to WGS and start saving lives.

The main result categories are: Major monogenes, SNP profiling and Polygenic Risk Scores (PRS), Recessive disorders and Pharmacogenes.

Major monogenes e.g. BRCA and Lynch Syndrome. Less than 10% of people with BRCA alterations and Lynch Syndrome are aware they have them. Both syndromes are common, each occurring in about 1 in 250 people.

With WGS hundreds of conditions can be identified including haemochromatosis, dilated cardiomyopathies, and some thrombophilias such as Factor V Leiden. Such knowledge identifies the risks, leading to the best screening options, risk reducing options and therapeutic choices.

Cardiac Genes

Some cardiac genes in the asymptomatic population may only have a penetrance of 10-20%, such as in dilated and hypertrophic cardiomyopathies, whereas penetrance in Long QT syndrome is high. 25% of ascending thoracic aneurysms will have a WGS-detectable genetic condition.

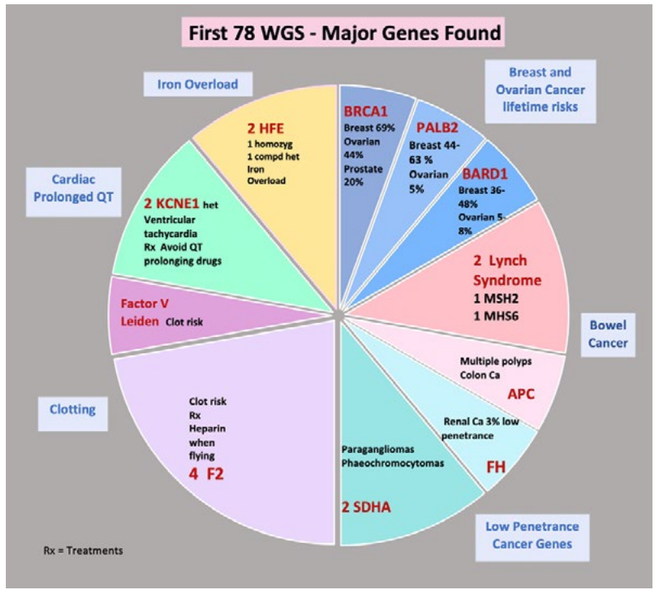

Figure 1 – This shows the monogenes from the first 78 patients.

The massive diversity of Whole Genome Screening

Examples of beneficial findings: Factor V Leiden or F2 alterations – procoagulant conditions – increasing the risk of pulmonary emboli.

Haemachromatosis gene alterations are frequent and a leading competitor for one of the most underdiagnosed and mismanaged areas in medicine. Failure of optimal management increases the risk of cirrhosis and hepatocellular carcinoma.

SNP profiling and Polygenic Risk Scores (PRS) Single nucleotide polymorphisms (SNPs) are single base letter changes in the genome. Polygenic risk scores (PRS) quantify the cumulative effects of a number of gene variants (SNPs) associated with a trait. Individually each SNP has a very small effect (e.g. 1.2 times risk) but, when all the SNPs for a particular condition are added to form a polygenic risk score, some scores can be very high. The increased cancer risk from this can be as large as in those who have high risk monogene alterations such as those in the BRCA gene.

We are doing SNP profiles for breast, ovarian, colorectal and prostate cancer and will soon be doing cardiovascular SNPs together with other common conditions.

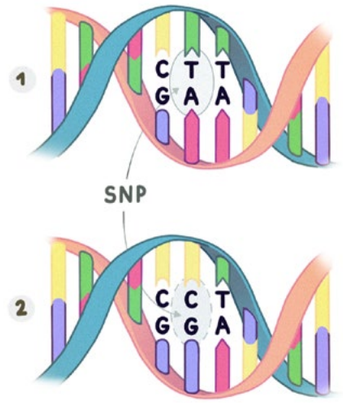

Figure 2 – This shows the base pair changes as an SNP example.

SNPs potentially contribute half the cancer genetic risk; so, if you want to know your cancer risk, you must analyse monogenes and SNPs. The balance of contribution of monogenes and SNPs varies: in ovarian cancer there is a dominance of monogenes, whereas SNPs are dominant in contributing to prostate cancer risk, where someone on the 99th centile will have a 11-fold risk of prostate cancer.

Bowel cancer SNPs identified high PRS in all 3 patients who had early bowel cancer at less than 42 years on one GP's list.

Figure 3 shows that two young cases had a high-risk genetic alteration and a high PRS, one case had an increased PRS alone, illustrating that risk can be due to a mixture of genetic components.

Recessive disorders

I in 300 births are due to recessive disorders, many of which are devastating; these could be prevented by offering pre-natal recessive carrier testing. If a couple has the same carrier alteration, for example cystic fibrosis, they can undergo IVF with a selected non-affected embryo being put back into the uterus, if the condition is one of the current 600 licensed by the HFEA. This is called Prenatal Genetic Diagnosis.

Pharmacogenes

Pharmacogenes control how we metabolise medicines. Genetic variation in this area means that we may need to adjust medicine doses and sometimes not use medicines at all in people who could have fatal reactions. For example, DPYD deficiency causing 5 Fluoro-uracil toxicity, the backbone of chemotherapy regimens for bowel cancer. Another example is that two percent of the population cannot metabolise the inactive prodrug Clopidogrel to its active metabolite, so that it is ineffective with neither the patient nor the doctor knowing.

Key areas of gene-defined metabolism can mean that patients need different doses of medications such as SRI antidepressants, warfarin, NSAIDs, PPIs, phenytoin and cancer medicines.

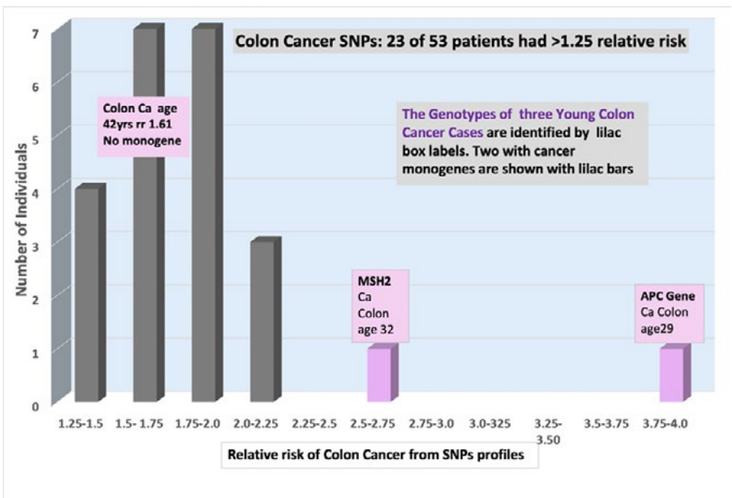

Figure 3

Pharmacogenetics should help reduce the 7% of hospital admissions that are caused by adverse drug reactions.

How can we fulfil the potential of genetics together, so your patients can fully benefit with a consultant genetics team behind you? Our aim is to increase our combined knowledge of genetics. We will be offering a series of educational talks/webinars starting in April for those doctors who want to involve their practices.

You can also join our MDT meeting to discuss your patients' results.

The London Genetics Centre is led by five eminent Consultant Geneticists: Prof Ros Eeles, Dr Gabi Pichert, Dr Lucy Side, Dr Tessa Homfray and Dr James Ware, with team members Dr Ann-Britt Jones and Dr Elizabeth Bancroft. Centre co-lead: Dr Michael Sandberg.

Some practices are now carrying out a medical in the usual way in their practices, then the patient is consented for Whole Genome Screening through The London Genetics Centre.

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