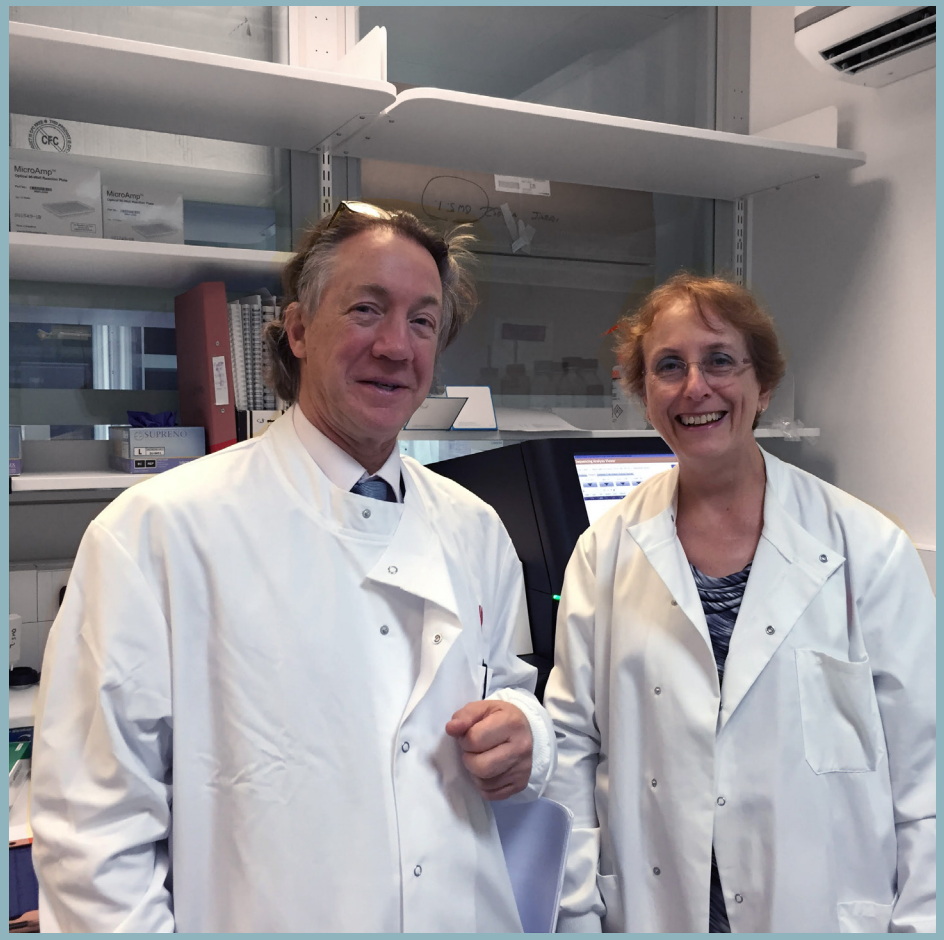
Whole genome screening at 90 Sloane Street

90 Sloane Street Genetic Centre
The Institute of Cancer Research
The Royal Marsden hospital
Cardiologists from the Royal Brompton hospital

Content

Whole Genome Sequencing (WGS) is the process of determining the complete DNA sequence of your genome. In 2008, it cost $350,000. At 90 Sloane Street we are offering WGS as part of a full medical combined with bloods, ECG, Echocardiogram, Abdominal Ultrasound and Pre-Counselling in one appointment. When the results are through, you will have a 30 minute meeting with a consultant geneticist. We are also doing polygenic risk scores as part of ongoing research.
All tests are anonymised.



Dr Michael Sandberg visits Prof Eeles at her Laboratory at The Institute of Cancer Research Sutton

Whole Genome Sequencing

Whole Genome Sequencing is Highly Accurate:
Until now, most people's contact with genetics has been the so called non-medical grade 'direct-to-consumer testing' such as AncestryDNA and others.

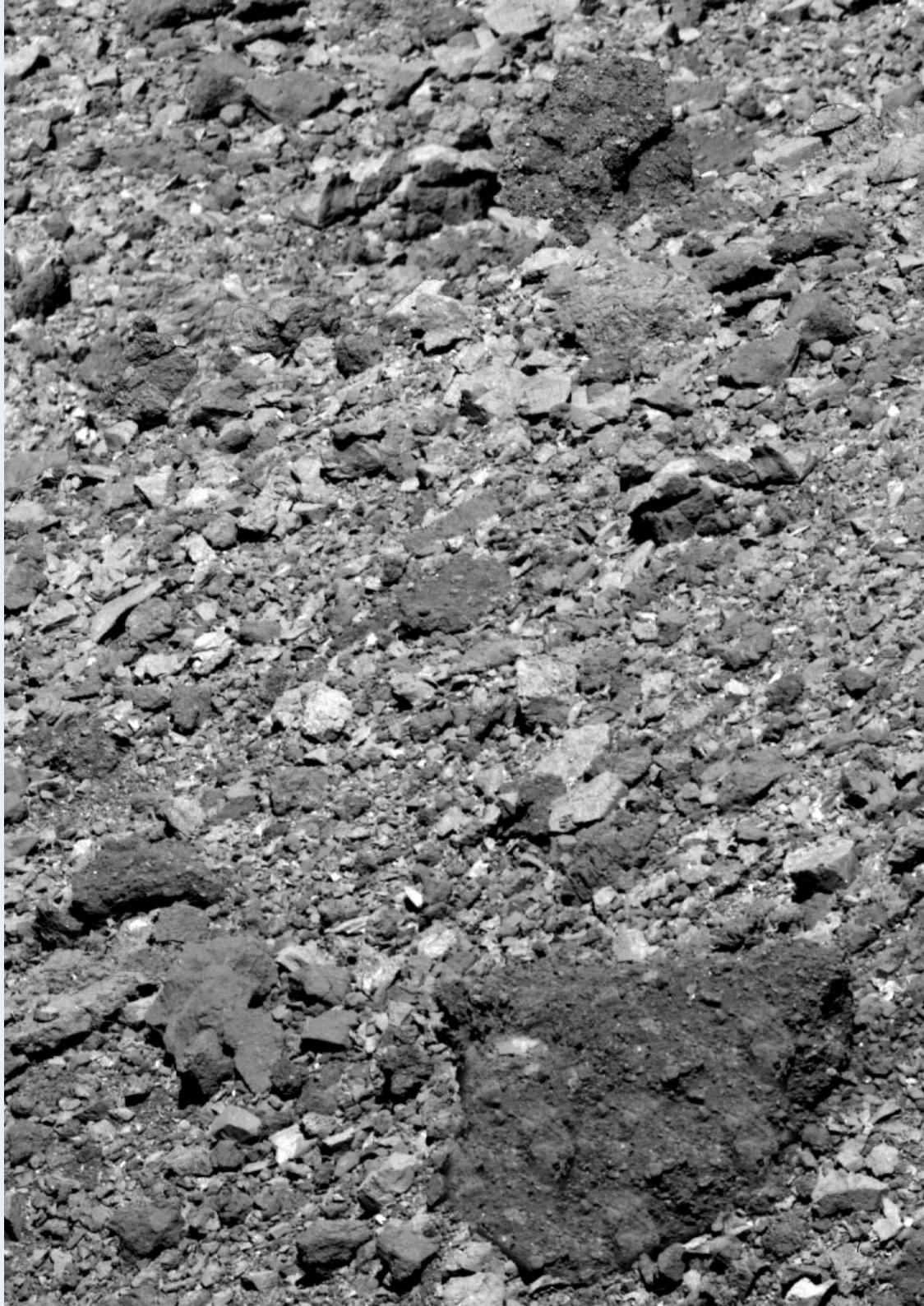
Newly available Whole Genome Screening is of a very different quality, it is highly accurate. "Direct-to-consumer testing" kits have characteristically been wrong up to 45 percent of the time when they suggest a genetic risk is present. They also give false reassurances i.e. not detecting genetic defects when they are in fact present. They are not recommended for medical diagnostic use. We refer you to the **October 2019 Statement from The Royal College of GPs and The British Society for Genetic medicine** which puts the issue most directly.

In contrast, Whole Genome Screening, at 90 Sloane Street has only a one in several thousand risk of missing a genetic alteration. A gene alteration may be benign (not harmful), pathogenic(harmful), or a variant of unknown significance (VUS), most of which are unlikely to be upgraded to harmful.

Can genetic testing help improve our lifestyle health risks?

As a population we have not been effective in practicing preventative lifestyle medicine, other than diminishing the rate of smoking. Obesity is on the increase; our diet is suboptimal, and in general we are not exercising enough. The majority of the population is drinking outside the recommended limits for alcohol and we are not sleeping enough.
The hope is that if your personal gene profile suggests an increased risk of certain conditions, you will be better incentivised to positively change your lifestyle risks.

Genetics has the potential to have similar health benefits as with the other seismic health development eras, such as immunisation and in the 1940s the advent of antibiotics.



90 Sloane Street Genetic Guidelines

Whole Genome testing - the principles to ensure its true potential is fulfilled:

1. Accuracy of tests should be of the highest level

At 90 Sloane Street, the Whole Genome Test is being done at what is called 'thirty-times depth'. In addition, we are doubling up by doing 'panel tests' at eighty times depth - for 84 cancer genes and 80 cardiac genes. The reason for double checking the work in this way is that we are keen to minimise missing the risk of any genetic alterations. Also, having a result duplicated and corroborated by a different technique is usually recommended before any clinical action is taken.

2. Actionable genes should only be reported in healthy screening

In the healthy population we believe only in testing for actionable genes; i.e. those that would be beneficial to know about – so that you can do something constructively with that knowledge and reduce the potential health risks they may engender.

Gene testing for Dementia or Parkinson's disease are not in this category. Our sense is that the concerns and worries of knowing one has such a gene variant, potentially giving a risk of up to a 60 percent chance of developing dementia in one's life, are of a greater negative mental load than the currently smaller levels of ability to change the potential course of these conditions if picked up earlier.

We are not into fortune telling!

3. No genetic testing in isolation.

We are doing all WGS - in the long respected essential medical paradigm of history, examination and then blood tests and others, before moving to a complex test such as WGS.

Genetics testing should only be done with a medical professional involved who has full knowledge of that persons past medical history, their family history, and their current issues. Doing genetic tests in isolation is foolhardy, as has been seen with inaccurate 'direct to consumer testing'. It is just like having one piece of a jigsaw puzzle, you will not have the full picture.

4. Consultant geneticists should lead any testing programme.

We are led by Prof Ros Eeles, who with a team of four Consultant Geneticists, a genetics Fellow Ann Britt-Jones and a genetic specialist nurse Dr Liz Bancroft comprise the 90 Sloane Street Genetic Centre. We also link with Dr James Ware a Consultant Cardiologist at the Royal Brompton for abnormal cardiac tests.

The aims of the work at 90 Sloane Street are to help participants and to learn more about Whole Genome screening in the healthy population. This work is being undertaken in partnership with The Institute of Cancer Research, The Royal Marsden hospital and cardiologists from The Royal Brompton hospital.

5. Consenting and informing

Participants should be properly informed and consented to a good level of understanding. Consenting is done by genetically trained doctors with results given to you in a consultation with a consultant geneticist.

Key Genetics Concepts

Penetrance of Genes
Finding a patient with a cancer who has a specific genetic alteration that is involved in that cancer is one thing. What is not so clearly known - is the significance when one finds such a genetic alteration - in a healthy individual, without any significant family history. Little genetic work has been done in the healthy population, and it may be that in the healthy population the presence of such a genetic alteration does not have the same risks. The genetic alteration may only rarely express itself to cause disease as there maybe other factors involved which we do not yet know about, which alter the effects of such deleterious genetic alterations.

The penetrance of cardiac genes may be quite low; if we consider cardiomyopathies (heart muscle disorders of genetic origin - i.e. not coronary artery disease) it maybe that only 10-20 percent of people who have a genetic alteration for a cardiomyopathy will actually develop it. This is called **'reduced penetrance'**. It is important not to cause unnecessary worry to patients.

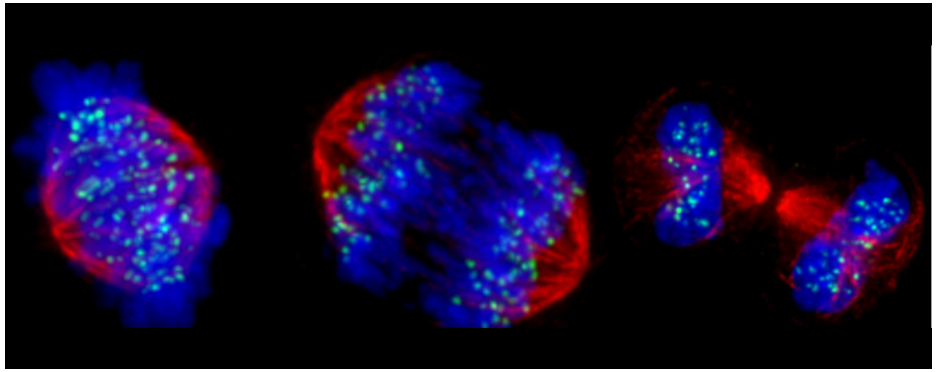
In the 90 Sloane Street Study (90 S) all participants prior to genetic testing have an Echocardiogram – a heart ultrasound. If the Echocardiogram – (which looks at the heart muscle) – is normal, then one can say if a participant is found to have a cardiomyopathy genetic alteration, but there are no signs of cardiomyopathy on the Echocardiogram, we would just repeat the Echocardiogram in three years' time.

Variants of Unknown Significance

These are changes in genes of which the significance is not clearly understood. Such variants may be in a particular gene that is known to cause certain conditions, but the reality is **probably only about 1 in 100 of VUS actually have clinical significance.**

Participants need the knowledge of a geneticist to give reassurance. For some people, it may be that when we look back in five years' time, more is known about the variant and its potential pathogenicity, or more likely benign nature.

Laura Trinke - Mulcahy Human Chromosomes at 3 Stages of Mitosis



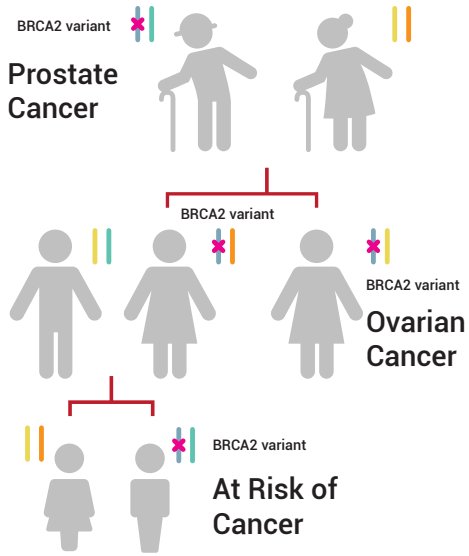
Recessive genes and carrier status

Human cells carry two copies of each chromosome - so they have two versions which are called alleles. Alleles can be either dominant or recessive.

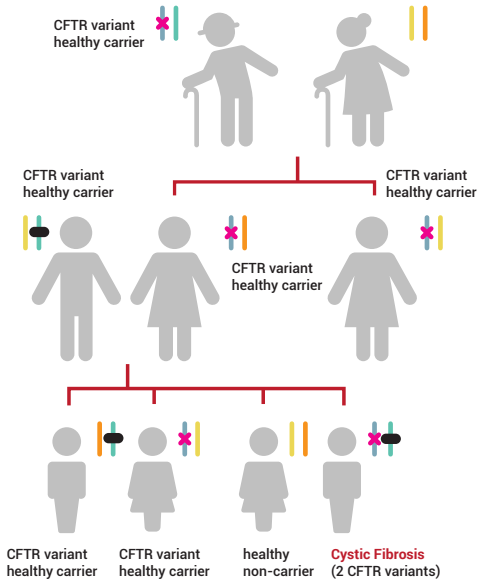
Dominant alleles show their effect even if the individual has only one copy of the allele - also known as being heterozygous.

Recessive alleles only show their effect if the individual has two copies of that allele, known as being homozygous. For example, the allele for blue eyes is recessive, so to have blue eyes you need to have both copies of the blue eye allele. A hereditary carrier is a person who has a recessive allele but as they only have one and not a pair of recessive genes, they do not express that trait.

We test for some carrier recessive genes such as cystic fibrosis. If both parents have the Cystic Fibrosis gene alteration, there is a one in four chance a child will have both copies of the gene alteration, one from each parent and therefore have the condition.



Dominant gene inheritance



Recessive inheritance - Cystic Fibrosis

What other techniques are involved in Whole Genome sequencing that will help patients?

Polygenic Risk Scores are able to be done as part of research for all participants.
This is a technique for finding participants who have an increased risk of certain conditions. **Single nucleotide polymorphisms (SNPs)** are usually found outside genes. While the presence of an individual SNP may only cause a very small increased risk for a particular condition – for example prostate cancer. They can be combined to add up to a large risk.

If one looks for 170 SNPs known to increase the risk of prostate cancer, we will be able to find people who have five times the risk of the normal population. **The polygenic risk scores is calculated by adding up all the individual SNPs.**

Polygenic risk scores are a major gain of doing Whole Genome screening. This cannot be done by "whole exome screening" – which only looks at the genes themselves. Nor by "panel tests" – where just a specific group of cancer genes are investigated.

This is why Whole Genome screening is the "holy grail" of genetics.

Gene Examples

GENE EXAMPLES INCLUDING CANCER AND CARDIAC GENES

A Few Examples of actionable genes we are screening for :

NON-CANCER NON-CARDIAC EXAMPLES:

Genes which increase our risk for clots :

Factor V Leiden –
Factor V Leiden occurs in about 8 percent of the population This gene alteration gives an increased rate of clots (deep vein thromboses) of about five times the normal population. It is present in up to 30 percent of patients with a deep vein thrombosis or potentially fatal pulmonary embolism. **Another pro-clotting gene, the Prothrombin mutation,** occurs in 2-3 percent of the UK population and increases the risk of clots three-fold.

Haemochromatosis –
Haemochromatosis is a condition where patients retain excessive iron which is damaging and potentially fatal, due to toxicity to organs such as the liver, pancreas, and heart. Over 380,000 people in the UK have this genetic predisposition and yet only 10,000 are diagnosed.
1 in 200 have the genotype of both of their chromosomes having the so-called C282Y variant which causes 95 percent of haemochromatosis. If you are found to have the gene alteration, simply taking off some blood from time to time, successfully depletes the iron stores so preventing organ toxicity.

A FEW CANCER GENE EXAMPLES:

Some genetic anomalies such as **BRCA genes,** which are associated with breast and ovarian cancer occur quite frequently, ***one in three hundred people.*** In the Ashkenazi Jewish population, they occur as frequently as one in forty.

Ovarian Cancer - We test for alterations in 9 genes including *BRCA1* and *BRCA2*.

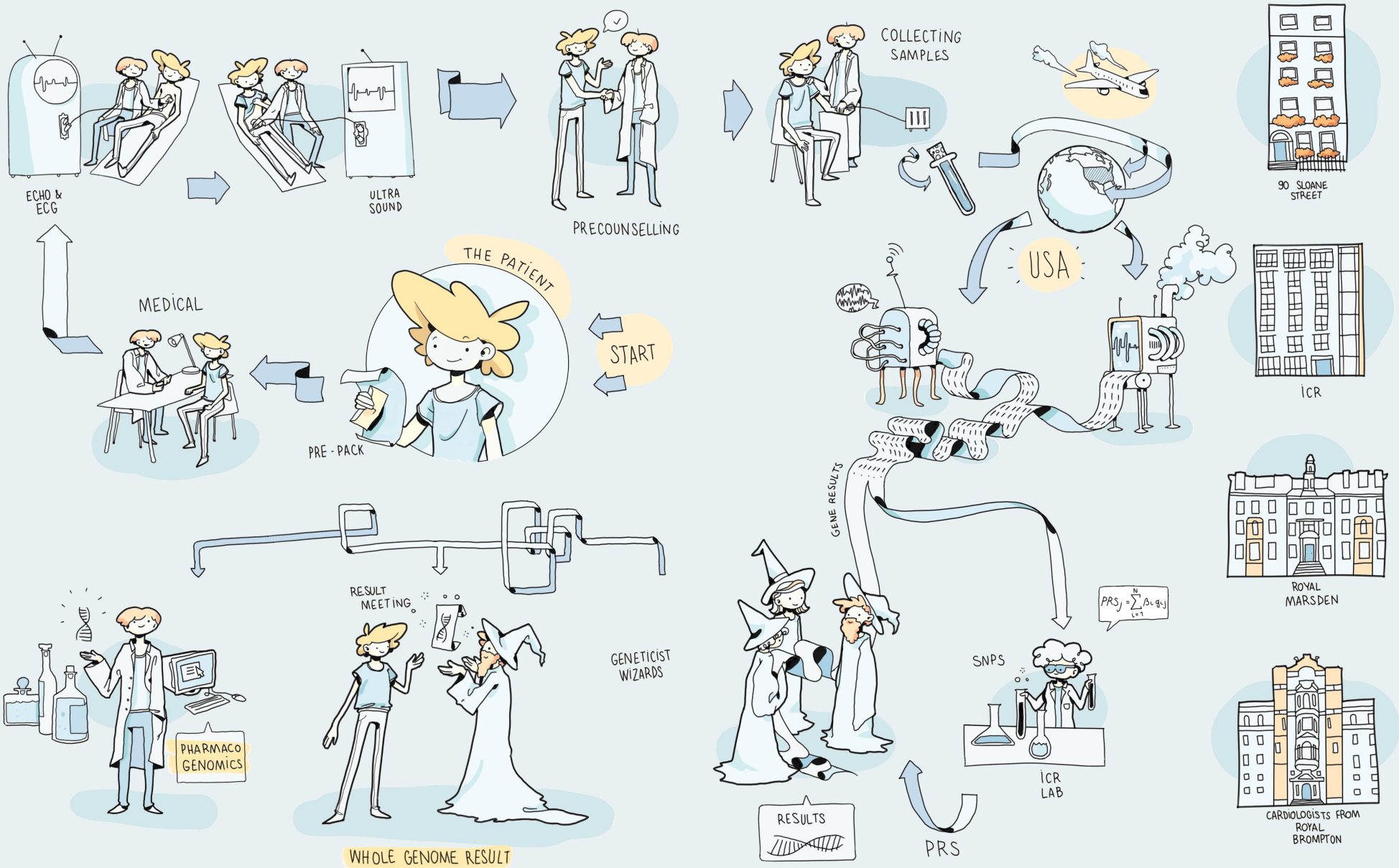
Lynch syndrome - Another genetically defined condition with a high risk of colon cancer, uterine cancer, and other cancers – it probably occurs in about ***one in two hundred and fifty people.*** Colonoscopy screening may reduce the colon cancer mortality by up to 70-75 percent. In the case of Lynch syndrome, colonoscopy screening should be started as early as 25 years of age, in some cases.

Prostate Cancer - Prof Eeles has published data to show that men who carry alterations in the *BRCA2* should be offered regular prostate screening. She is investigating whether screening other prostate cancer risk genes improves outcome.

We are testing for around 80 cancer genes; we have just given a few examples above.

THE 90S STUDY

ILLUSTRATION BY SIXTINE MARECHAL



CARDIAC GENES:

Our Whole Genome testing will also test for a range of cardiac risk genes.

Aortopathies - Certain genes may cause **aortic disease, such as aortic aneurysms - or aortic dissections,** where the main artery coming from the heart enlarges and can burst with usually fatal consequences. Knowledge of their presence may mean specific actions can be taken in order to dramatically reduce the mortality rate of such conditions.

Familial hypercholesterolaemia – A gene alteration which causes severely elevated cholesterol levels from birth results in men having an 80 per cent chance of a heart attack by the age of 60. (a woman's risk profile is about 10 years behind a man's.)

It has a ***frequency in the population of about 1 in 250*** and affects 250,000 people in the UK. So far three main gene variants have been found that cause 80 percent of this condition. The 3rd was found in 2003. The risks of these genes can be dramatically lessened by treatment.

Heart muscle disorders – Cardiomyopathy

Genetic alterations may cause up to 40 percent of cases of **Dilated cardiomyopathy,** so called familial dilated cardiomyopathy, where the heart muscle is like a floppy bag. ***The prevalence is 1 in 2,500 people.*** By detecting this condition early, medicines can be started that are highly effective and genetic counselling used to identify additional asymptomatic family members.

Hypertrophic cardiomyopathy

This is a genetic condition where there is harmful thickening of the heart muscle, which occurs with a ***prevalence of 1 in 500 p***eople. Early diagnosis can lead to an improved outlook.

Long QT Syndrome *(prevalence 1 in 2,500) -*

Alterations in specific genes can cause a prolongation of part of the electrocardiogram called the QT interval. This can then be associated with an increased risk of life-threatening cardiac rhythm abnormalities. The knowledge of such a genetic alteration being present can mean that patients are not given drugs that may increase their QT interval length, so reducing risk.

There are also preventative drugs in some types and other treatments that can reduce the risk. Sudden death can occur as the first fainting episode in 30 percent and there are 4,000 deaths each year in the USA.

PHARMACOGENOMICS

A GAIN FOR EVERYONE

We test for a large number of pharmacology genes. The metabolism of drugs varies hugely from person to person, being controlled by genes which can now be tested for. It may be that if a person has a particular gene variant affecting a specific drug's metabolism, that they should not be given the drug. A couple of examples:

Clopidogrel is a drug that stops platelets sticking together and is used to help prevent heart attacks and strokes. It is metabolised from the original **non- active drug** given, to an active component. In some patients this metabolism does not occur due to having a genetic alteration. This means that Clopidogrel is not effective for that patient.

A patient having a coronary artery stent procedure is typically put on Clopidogrel and aspirin to reduce the risk of the new stent becoming blocked by a clot. But it is no good if one of these two preventative drugs is inactive with neither the patient nor the doctor realising. There are substitute options.

5 flurouracil (5 FU). Another gene *DPDY* controls the metabolism of a commonly used cancer drug called ***5 flurouracil*** (5 FU) If there is an abnormality in the DPDY gene, then a patient cannot metabolise the drug and could be exposed to an absolute walloping dose which has been fatal. 2-8 per cent of the population may be at risk of toxic reactions to 5FU due to total or partial DPD deficiency.

These are just two examples of hundreds of drugs that can be affected by knowing the genetic pharmacology of a patient.

The era of personalised medicine really is here. In time, your doctor's computer will detail not just your allergies and drug interactions but also your genetic pharmacology profile. When the doctor types up a drug the computer may then suggest an alteration in the dose or advise not to prescribe that drug. This can already be done for drugs such as Warfarin, a blood thinner where a patient's dose can vary from as much as 1mg to 10mg from one person to another.

How about those of us who find it worrying enough going to the doctor to have our blood pressure taken! - The Ostragene!

The direct answer : We have what we have and doing the test does not give it to us.

The concept is not really different from a patient finding out they have high blood pressure and then going on to treat the condition. The result of this knowledge and subsequent action is that their risk of a stroke or heart attack may be reduced five times.

If the patient did not have the knowledge of having high blood pressure, as they were worried or could not be bothered, that person would have carried on oblivious of their 5 times increased risk. This is not the best life strategy!

The blood pressure analogy is not so very different from checking out and gaining the knowledge of any actionable health risk genes you may have. You can then take action if you know you have them, to improve your health outlook.

The 'Ostragene' - is a person who does not want to do any genetic tests. The Ostragene will have a higher risk in life compared to a person who undergoes genetic testing.

Procedure details

Anonymity

All samples are sent off anonymised. We are aware that databases and security can sadly fail, and we do not want to give patients any concerns in an area which is so personal.

Insurance

At present UK insurance companies have issued **an ongoing genetics moratorium** for those taking out insurance in the UK. This means you do not have to declare gene alterations that may put you at risk in the future. But this excludes Huntington's, (a degenerative neurological condition), for policies above 500K.

This means you currently do not have to declare genetic information in most circumstances. (It should be noted that there are some parts of the world where there is no genetic moratorium and patients do need to declare genetics results; such as in a couple of USA states.) We advise consulting the **Code of Genetic testing and insurance.** Possibly in combination with legal advice on how this applies to you. To refer to the code of the Association of British insurers, cut and paste the below url into your web browser.

www.abi.org.uk/globalassets/files/publications/public/genetics/code-on-genetic-testing-and-insurance-final.pdf

What is the cost of Whole Genome Screening and what does it include at 90 Sloane Street?

The current cost for Whole Genome Screening combined with all the above described tests and counselling together with a medical is **£4,995.**

The technical genetic sequencing component and initial analysis is about £3,000 to include the special **double-check system** we are using. The polygenic risk score assessment is so new that it is being done for free as part of ongoing research.

The remainder of the cost includes an hour long medical with a GP, an Echocardiogram, ECG, abdominal and pelvic ultrasound, general blood tests as well as a pre-counselling appointment and a 30 minute 'result appointment' with a consultant geneticist.

The first part is all done in a single 2.5 hours appointment at 90 Sloane Street.

14-18 weeks later when all the genetic tests have come through, every patient sees a consultant geneticist for a post result thirty-minute appointment. All results are seen by a consultant geneticist and abnormal ones are reviewed by a team of four consultant geneticists in a multidisciplinary meeting.

If patients have abnormal results they can either book for a longer appointment or a further consultation with the consultant for more support and advice (these extra appointments with a consultant geneticist would be not be included in the above price.)

Should one tell one's family about genetic testing?

Having one's own genome sequenced has implications for your family members. It may be sensible to discuss that you are going to have your whole genome sequenced with family members of adequate maturity and that you will share the results and potential health gains of this knowledge.

However, it would often be considered irresponsible to tell children until they have the maturity to take on the knowledge of gene testing. The risks for many conditions and the time when screening will become helpful is often around 25-30 years of age, such as in *BRCA* carriers. The delay until reaching mature adulthood, is not usually an issue. These are all considerations where a geneticist will help you inform family members if needed.

Is this 'IT' or will things change further?

Your whole genome – the order of your genetic letter code will not change.
It may be that we are at a level of playing a recorded symphony on a cassette- machine. In time it may transpire that the risk of errors may decrease from presently one in several thousand to one in say twenty or thirty thousand. So, technology may change from a cassette to a CD player, but the music i.e. the genetic letters are the same.

Where will there be changes in our knowledge of genes?
Our knowledge of **variants of unknown significance;** in most circumstances their non- significance will be affirmed.
More disease-causing genes will be detected and the triggers that turn them on and off. We will **find more deleterious SNPs for different cancers, expanding polygenic risk scores.**

Screening decisions will become based on genetic stratification of risk as to who and when to screen. The aim being to screen those at the very highest risk, as assessed not just on traditional risk factors including family history, but also on **the basis of genetic personalised risk.**

The importance and potential gain for a person to have prostate cancer screening, could be on the basis of their having a high polygenic risk score calculated from their SNP profiling when they had Whole Genome Screening. Equally, their having a *BRCA2* gene alteration will give them a much higher risk of prostate cancer.

A '**lookback review**' mechanism is sensible for the future. Three years on, it may be advisable to check if anything new has been discovered. Your whole genome can be reviewed in the light of new knowledge about genes and variants of unknown significance.

Expectations of Genetic Screening at 90 Sloane Street

If we have a room of one hundred people, we should pick up six on the basis of actionable gene screening who are at increased risk, and a further six patients on the basis of their polygenic risk score. In total maybe twelve people out of a hundred, will be helped by having had Whole Genome screening.

However all participants will be significantly helped by having their pharmacogenomic profile for how they metabolise medicines.

We also have details on Whole Genome Screening at 90 Sloane Street on our website:

90sloanestreet.com or
genetics@90sloanestreet.com

The Institute of Cancer Research joint press release :

UK-first study to assess role of whole-genome screening in primary care