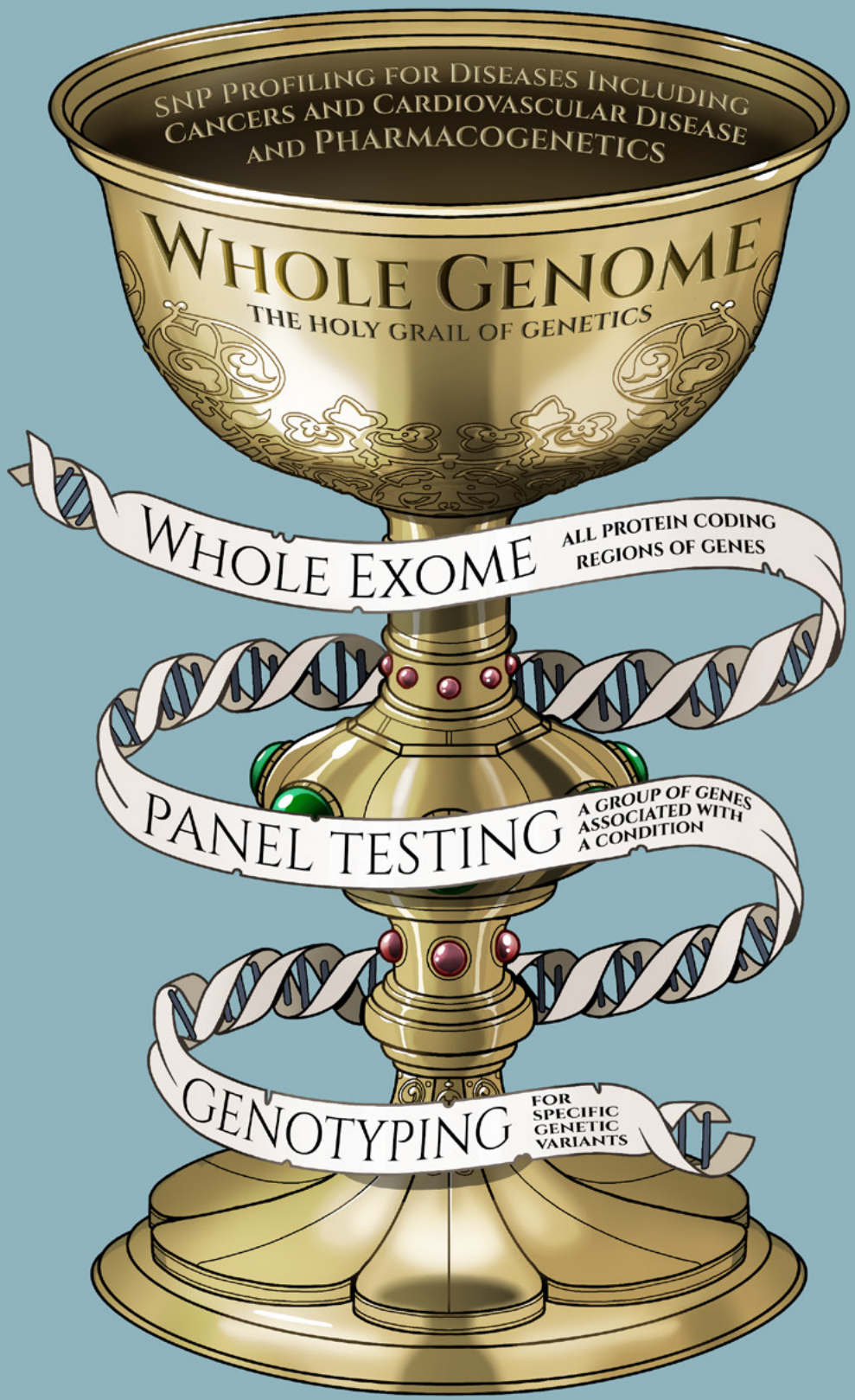


The London Genetics Centre

90 Sloane Street

Veritas Intercontinental

THE LONDON GENETICS CENTRE

SLOANE STREET 90

Targeted Whole Genome Screening (WGS)

The Holy Grail of genetics: all in one coverage

Ultimate Screening The London Genetic Centre with Veritas Intercontinental

The full utilisation of Whole Genome Screening:

- Major risk genes
- Cancer & cardiovascular polygenic risk scores (SNPs)
- Pharmacogenetics
- Recessive disorders (carriers of gene alterations)

Interpretation of Whole Genome Screening by experts:

Five eminent consultant geneticists led by Prof Ros Eeles, Dr Gabi Pichert, Dr Lucy Side, Dr Tessa Homfray, Dr James Ware with team members Dr Ann-Britt Jones and Dr Elizabeth Bancroft.
Study co-lead: Dr Michael Sandberg.

For many of us we may choose to avoid things that we fear, metaphorically ‘hiding under the pillows.’ But this attitude can be dangerous, puts us at greater risk and leads to diagnostic delay. When we do targeted Whole Genome Screening **we are only looking for gene alterations where, if we find them, we can do something positive to improve future health.** It does require a **philosophical leap**, but it is one that will save millions of lives if we can help the world to understand the enormous gains.

The Modeling studies show instituting Whole Genome Screening and acting on the results will reduce the cancer mortality by a Fifth. The sooner this advance is actualised huge numbers of lives will start being saved.

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

Whole Genome Screening (WGS) is the sequencing of your entire genome. If you printed all 6.4 billion letters it has been quoted that it would fill 4,200 books of 500 pages each. Veritas has selected a targeted 566 genes relating to more than 650 conditions. This targeting means we are only analysing actionable gene alterations. So if you find you have them then you are able to do something significant to improve your outlook. Therefore, we do <u>not</u> analyse the neurological genes such as Parkinson's or Dementia.

This brochure is to introduce you to genetics and your genetic health.
Everyone who has done targeted WGS has done something major to improve their future. Many people pay a fortune for education, insurance and houses, forgetting that good health is a most precious and life-enhancing priority. Knowing your genome is for life and is highly cost effective.

Your genes could be compared to a pack of invisible health cards.
WGS reveals the key cards so that you can then act on the revealed knowledge.

Whole Genome Screening tests the largest number of genes
It covers major monogenes for cancer, cardiac, iron overload, clotting conditions, aortic aneurysms and many hundreds of conditions, together with Pharmacogenetics (how you personally metabolise drugs). It is truly extensive.

We are also able to do **polygenic risk scores** from the single nucleotide polymorphisms (SNPs) - a technique for discovering which people are at greatest risk. This is a separate paradigm from the major monogenes such as *BRCA*.

SNPs and the resulting polygenic risk scores, while still a research area, will probably double the number of high cancer-risk patients we find when added to usual monogenetic major gene testing. (SNPs will be explained in detail later).

Cancers

20%-30% at least are due to hereditary factors

***BRCA* gene alterations and Lynch syndrome:** less than 10 % of people with these genetic alterations know that they have them so they are utterly unaware of their risk profile. If they have genetic knowledge their outlook is vastly improved compared to those people who do not know.

***BRCA* gene alterations occur in 1 in 250 people,** increasing to 1 in 40 of the Ashkenazi population. They confer a 60-80% chance of breast cancer and 10-60% of ovarian cancer in a lifetime. Prophylactic ovary and fallopian tube removal is a day case procedure and reduces ovarian cancer risk by 95%.

Lynch syndrome affects 1 in 250 people and causes several cancer types, particularly bowel and endometrial (uterine) cancer. Knowing it is present improves the mortality rate by 25% with colonoscopy screening.
Taking 600mg aspirin daily reduces colon cancer by 40% in these patients and this gene alteration also means they respond exceptionally well to immunotherapy.

Sudden cardiac deaths

20% are due to genetic abnormalities related to cardiac muscle and cardiac rhythm disorders or aortic aneurysms.

Hereditary thrombosis

6% of the population are at 4-5-fold increased risk. Most people are unaware of it and the first time they know is when they have a deep vein thrombosis, potentially fatal pulmonary embolism or stroke.

Genetic variants

17% of us have genetic variants increasing the risk of specific diseases.

Panel Tests

Cancer panels look for germline cancer predispositions that are known to be associated with a particular cancer. Panel tests have the benefit of not missing large gene deletions, which can very rarely happen with WGS, but panel tests **do not** have the massive wide gene coverage of WGS.
The landscape of genetic testing has shifted from single gene testing, say for *BRCA* alterations, to larger gene panels.

For everyone in the 90 Sloane Street Study programme we do both cancer and cardiac panel tests in addition to the WGS as a double-check.
If you are found to have a significant genetic risk for ovarian cancer you can make decisions on surgery if you wish as the alteration found has been confirmed on two tests.

Gene panels are beginning to be used in cancer care, testing for germline genetic alterations that can cause cancers and which can give treatment options. For instance, **the latest breast panels include: *BRCA 1/2, PALB2, ATM, CHEK2, PTEN, STK11, TP53, BARD1, RAD51 C &D***. The NHS currently only tests for *BRCA 1/2 & PALB2.*

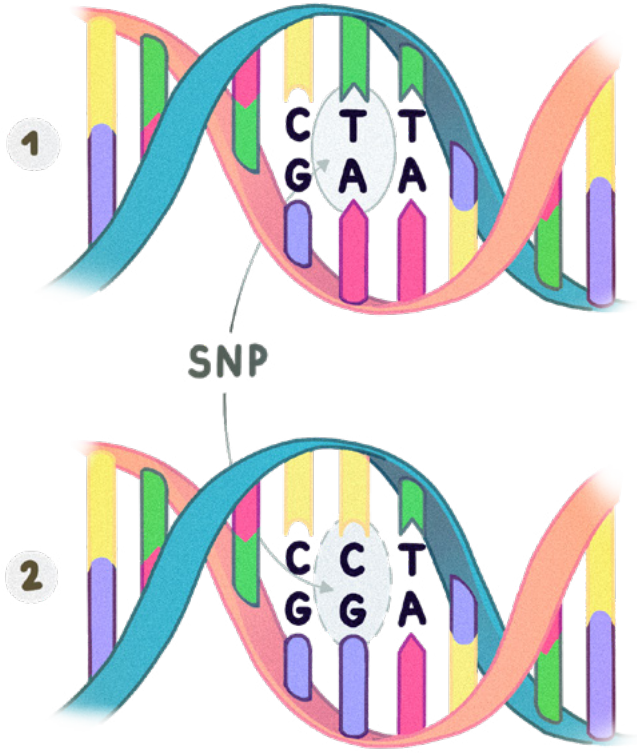
Germline variants refer to the DNA you have in every cell that you are born with, whereas **somatic variants** are seen in tumour cells and cannot be inherited unless they are directly related to your germline. Theoretically, if a germline alteration such as *BRCA* is the cause of your breast or ovarian cancer it will be found in your tumour. But occasionally it is lost, so knowing your germline by doing WGS can give specific treatment opportunities that you would not otherwise be aware of, such as PARP inhibitors or immunotherapy.

5 COMMANDMENTS OF GENETIC SCREENING

- **Accuracy**
- **Actionability** - we are only testing for genes you can do something about – we are **not** doing Parkinson's or Dementia genes
- **Full medical background and family history** known to geneticists
- **Multidisciplinary meeting of full team of genetic consultants** to review all results producing producing a summary document for every patient
- **Informed consenting and clear feedback communication by** consultant geneticists covering cancer, cardiac, children's genetics and Pharmacogenetics

SNP profiling and Polygenic risk scores (PRS) *finally we explain!*

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) on 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 monogenes such as *BRCA* gene alterations.

We are doing SNP profiles for breast, ovarian, colorectal and prostate cancer and will soon be doing cardiovascular risk SNPs using the raw data files from the sequencing of your genome.

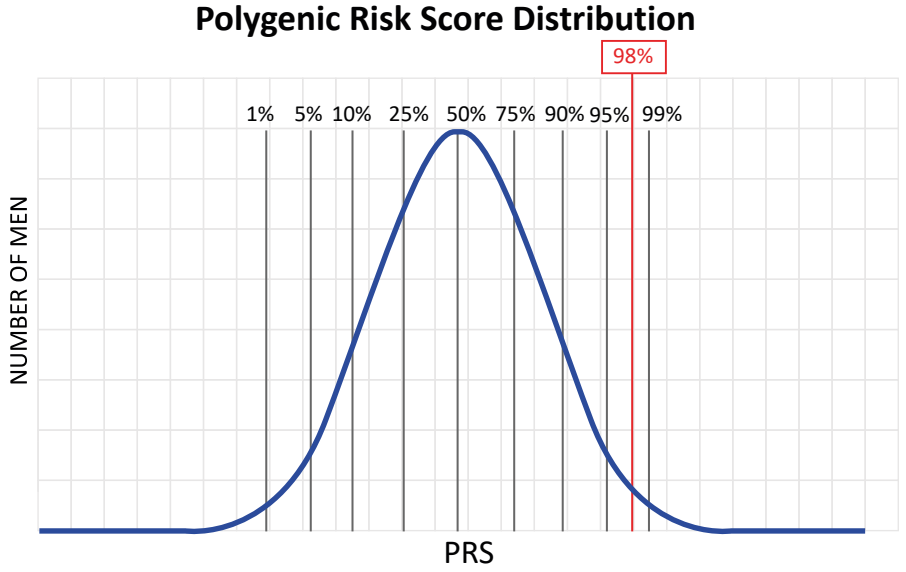
Prof Eeles' laboratory at The Institute of Research Sutton, with her co-investigator Dr Kote-Jarai, has in the last few years discovered two-thirds of the world's prostate cancer SNPs. From this work we now have the addition of 269 SNPs for prostate cancer to form your polygenic risk score. This team is well-placed to pioneer our study.

Two recent patient examples showing the role of polygenic risk profiles:

1) A 58 year old Scottish patient's * prostate SNP profile gave him a polygenic risk on the 98th centile.

The following chart shows the colorectal and prostate scores for this patient, then the PRS centile and relative risk calculated for colorectal cancer and prostate cancer. The final calculation shows he has a **more than a 6-fold increased risk of prostate** cancer compared to the normal population. He can now benefit from being offered research studies investigating the role of targeted screening in high-risk people. It may save his life.

gender	Colon Ca	Colon Ca relative risk	Prostate Ca	Prostate Ca relative risk
male	81%	1.53	98%	**6.23**



The above chart shows the position of the patient on the 98th centile for prostate cancer
RR stands for relative risk compared to the normal population.
Courtesy of Dr Kote-Jarai

2) A French patient underwent surgery aged 30 for bowel cancer. He is now 52. We had detected that he had an ***APC*** gene alteration which gives him only a two times increased risk of colon cancer. It was likely there was some other factor. Then we had his SNP profile score come through. The answer was there: it gave him a **3.78-fold increased colon cancer risk**. Scientifically we do not yet know whether his monogenic *APC* gene alteration interacts with his high-risk SNP profile but have seen this phenomenon with other monogenic gene alterations and SNPs and suspect it will.

*Identifiable characteristics in both profiles are changed for anonymity.

The polygenic risk score result means that his children may not necessarily have such a high risk as their father. It differs in the way they are passed down compared to the 50% hereditary risk of monogenes. **All the SNPs are reshuffled like a pack of cards** in the way they are passed down.

Prostate cancer: The pie-chart below shows the contribution of the SNPs to excess familial risk is large at 38% compared to so called major genes, (also called monogenes) such as *BRCA 1/2* which contribute in a smaller way together with the other listed genes.

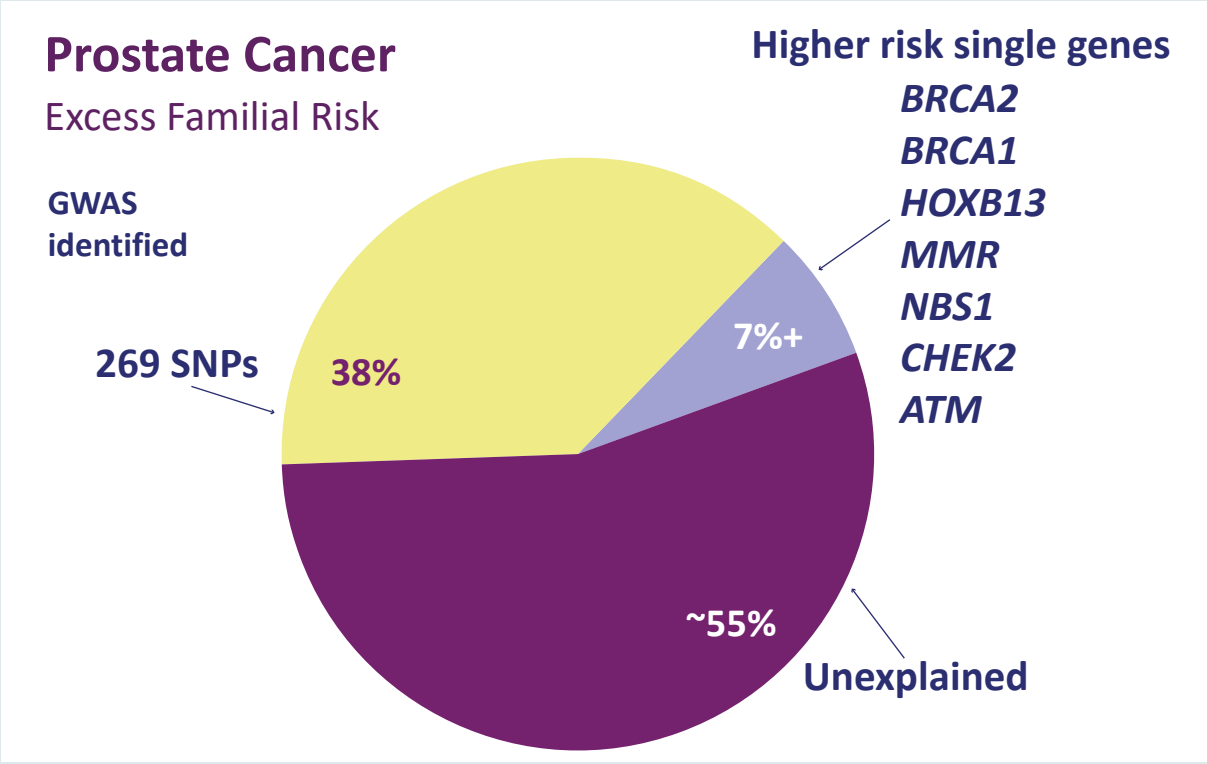


Figure courtesy of Dr Kote-Jarai

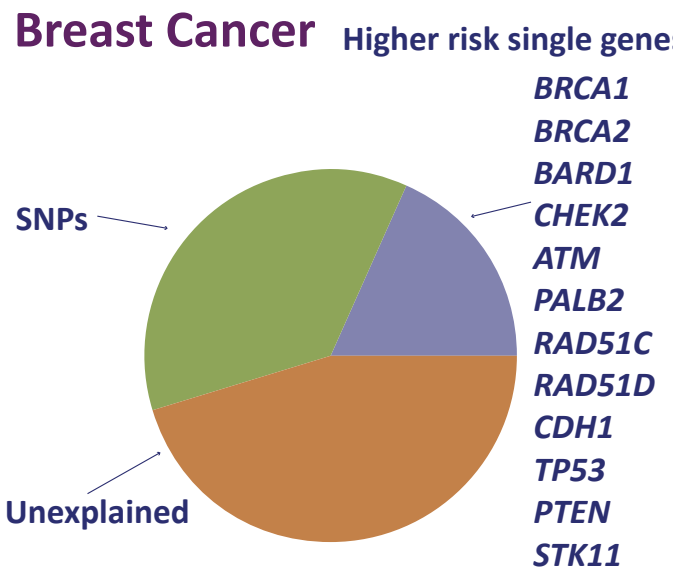
If we are to best identify people at highest cancer risk we need to do both major monogenes and the SNPs. This is the advantage of Whole Genome Screening. We have the added value being able to do the analysis of the whole genome data in a research setting to produce a polygenic risk score.

WGS can find a third of those at highest risk of Ovarian Cancer and after having had a family, you can decide to have relatively simple day case surgery to remove the ovaries and fallopian tubes which reduces the risk of suffering ovarian cancer by 95%.

We could save 2000 lives a year lost from ovarian cancer in the UK by using WGS to find those at risk.

Current ovarian screening is sadly not really effective. Ovarian cancer usually presents when it is widespread and too late for a good chance of cure.

The charts below show so well the concept of what the contribution of genes are compared with SNPs and how this varies for different cancers. The SNP contribution in breast cancer is nearly equal to that of major monogenes, whereas in ovarian cancer SNPs play only a very small part compared to major monogenes. In prostate cancer the SNPs are dominant.



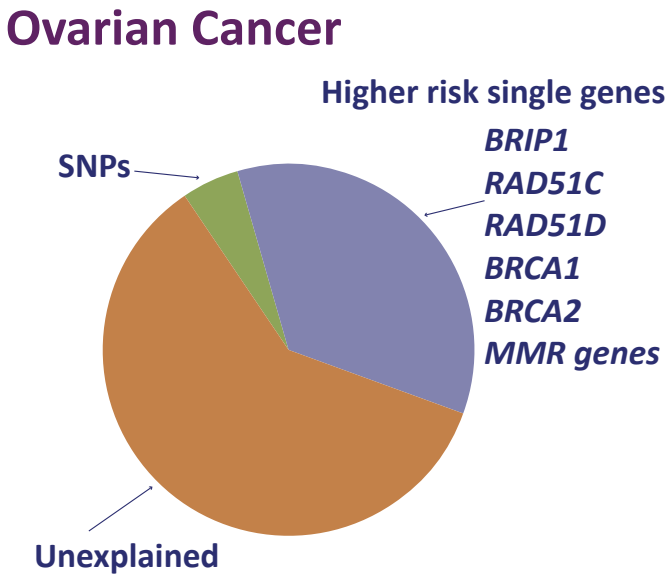
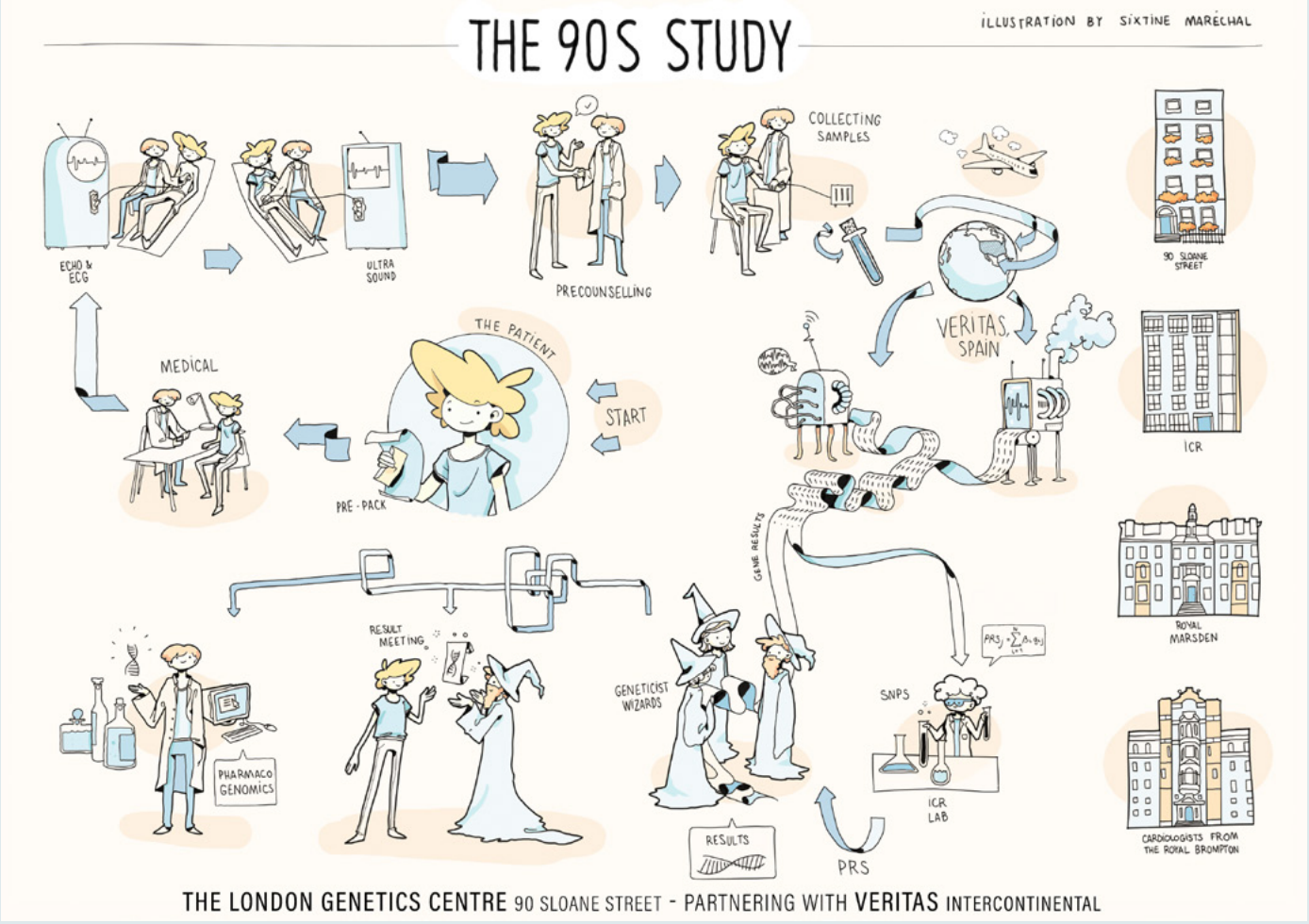


Figure created from amalgamated estimates from publically available data.

How do we do Whole Genome Screening



To obtain the full benefits of Whole Genome Screening in The 90 S study all patients have a medical, detailed family history together with bloods, ECG, cardiac echo and abdominal ultrasound. Your own doctor can do the medical.

Veritas Intercontinental - our partners in Whole Genome Screening

Veritas provides the sequencing and interpretation of the whole genome and provides a comprehensive report of the information. This information is then further analysed and interpreted by our geneticists, generating a personalised action plan for each of our patients. Veritas also passes on to us the raw data of your genome so our scientific team can produce a polygenic risk score, which at the moment is a research initiative.

Collaboratively working with Veritas over the last two years has given us an exceptional pioneering developmental opportunity. Genetics really is teamwork with the patient results being evaluated by a dynamic multidisciplinary team. The strategic partnership we have with Veritas has demonstrated continuous improvement as the programme has evolved.

The London Genetics Centre has an exclusive UK agreement with Veritas Intercontinental. The London Genetic Centre and Veritas jointly wanted to give WGS the safest start in the UK, so all Veritas genomes in the UK are now reviewed at The London Genetic Centre Multidisciplinary Team Meeting (MDT) and are anonymously collated as part of the overall programme. The evaluation of all results at a macro level allows for continuous improvement as we progress through this new frontier of preventive medicine.

Veritas
INTERCONTINENTAL
The Genome Company

Pharmacogenes

Pharmacogenes control how you metabolise drugs. We currently report on genes which are involved in controlling the metabolism of 150 drugs. Pharmacogenetics is a new science that will help to reduce the 5% of hospital admissions due to adverse drug reactions. It is a massive medical advance.

Your personal pharmacogene knowledge may show that certain drugs won't work for you. For example, **Clopidogrel** is a drug given to millions of patients with coronary artery stents or for stroke prevention; it stops platelets sticking together blocking your arteries. However in about 2% of patients it is ineffective due to gene variants. Clopidogrel itself is inactive and **needs to be metabolised to its active component in order to work.** In some people a gene variant means they cannot metabolise it, **so it remains inactive and useless** with both the doctor and patient being utterly unaware.

Other drug gene alterations may mean specific medicines such as antidepressants or statins. **In some cases, a drug could be life threatening to you.** Patients with **DPYD deficiency** if given **5 Fluorouracil** - one of the most commonly used drugs in cancer medicine - may die due to this gene-controlled deficiency, meaning there is little metabolism of the drug, so the patient effectively has an enormous overwhelming dose. Pharmacogenetics detects if you could be at risk.

Why do you need geneticists?

You need **a full genetics team**, as the areas to be covered include cancer, cardiac, children genetic disorders', as well as pharmacogenetic knowledge. You simply would not find this with only a couple of geneticists.

90 Sloane Street geneticists are at an international level.
Dr Tessa Homfray recently delivered a lecture to 15,000 people.

Our cancer area has three top specialists, who are fundamental for the discussions we have in our **multidisciplinary meetings** to give the best opinion.

There are often areas of uncertainty:
It requires extensive experience to help judge whether a gene variant found may be pathogenic disease-causing, or whether it may actually be benign (harmless).
What is the **penetrance of a particular gene?** In some areas gene variants may be found that are rarely expressed phenotypically i.e. disease- causing.

Such knowledge and wisdom are only gained by years of experience and deep technical understanding of the underlying scientific genetic mechanisms.
This is the under-the-bonnet knowledge that is so crucial.

We believe that in time carrier screening will be routinely offered to couples

Pre-natal Genetic Diagnosis (PGD) and congenital disorders

It is time to offer the chance of avoiding the 1 in 300 births that are recessive disorders, many of which are devastating for the baby and its family.

86% of people are asymptomatic carriers of recessive disorders. If their partner is a carrier of the same disease, 1 in 4 of their babies will inherit the condition. If on testing, a couple is both found to have the same recessive carrier variant, for example for Tay Sachs disease, they can still have a baby together using IVF, with embryo selection to avoid the disorder.

The London Genetics Centre

Recessive Carrier Genes alterations

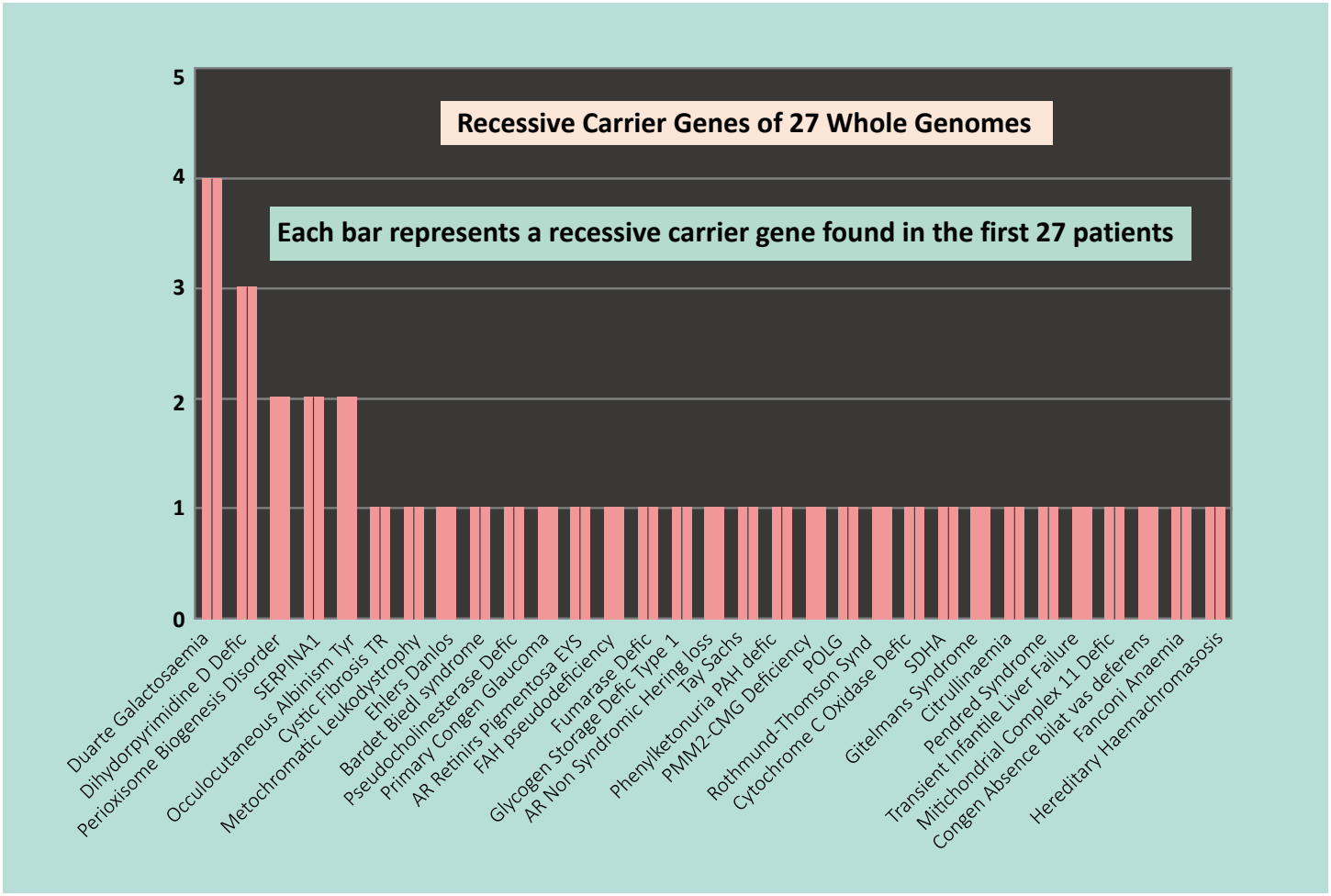
- 85% of participants had a minimum of one recessive alteration
- Some participants had 4 recessive gene alterations
- 1 in 300 live births are recessive disorders

The London Genetics Centre

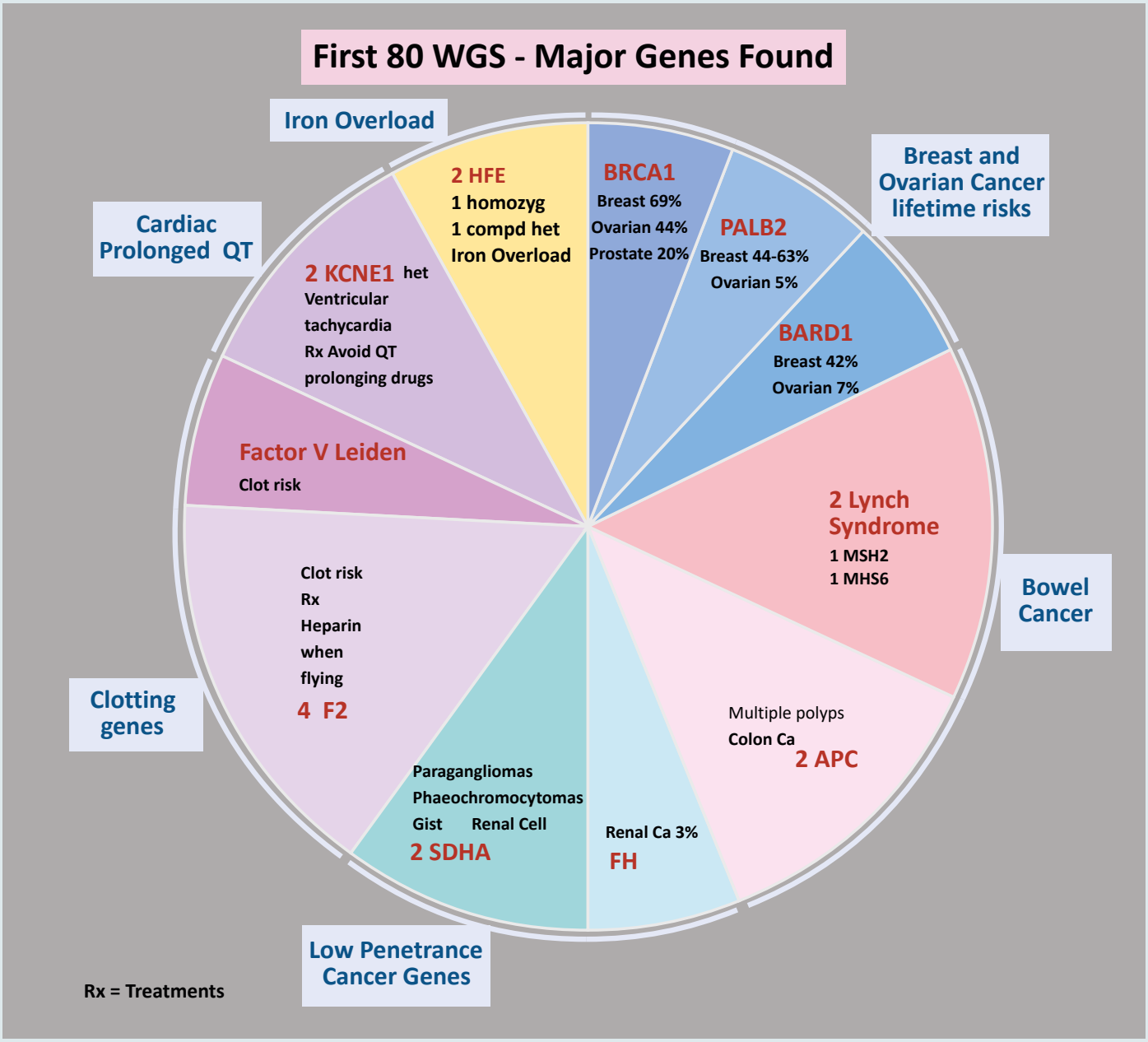
The Human Fertilisation and Embryology Authority has licensed over 600 conditions for PGD. This licence is only awarded where the disorder is severe. Our WGS does not detect all recessive carrier disorders, but is presently covering the most common 200.

Large recessive panel tests are available which cover 1,200 recessive genes.

Results from the first 27 patients showed that 85% of patients had a carrier gene. Four patients actually had 4 carrier genes.



This charts demonstrates the gene alterations that we have found in the 90 Sloane Street study.



Two of the patients with breast and ovarian cancer gene alterations had siblings with the same gene alterations explaining the higher pick-up rate of major (monogenes) than one would expect in 80 patients.

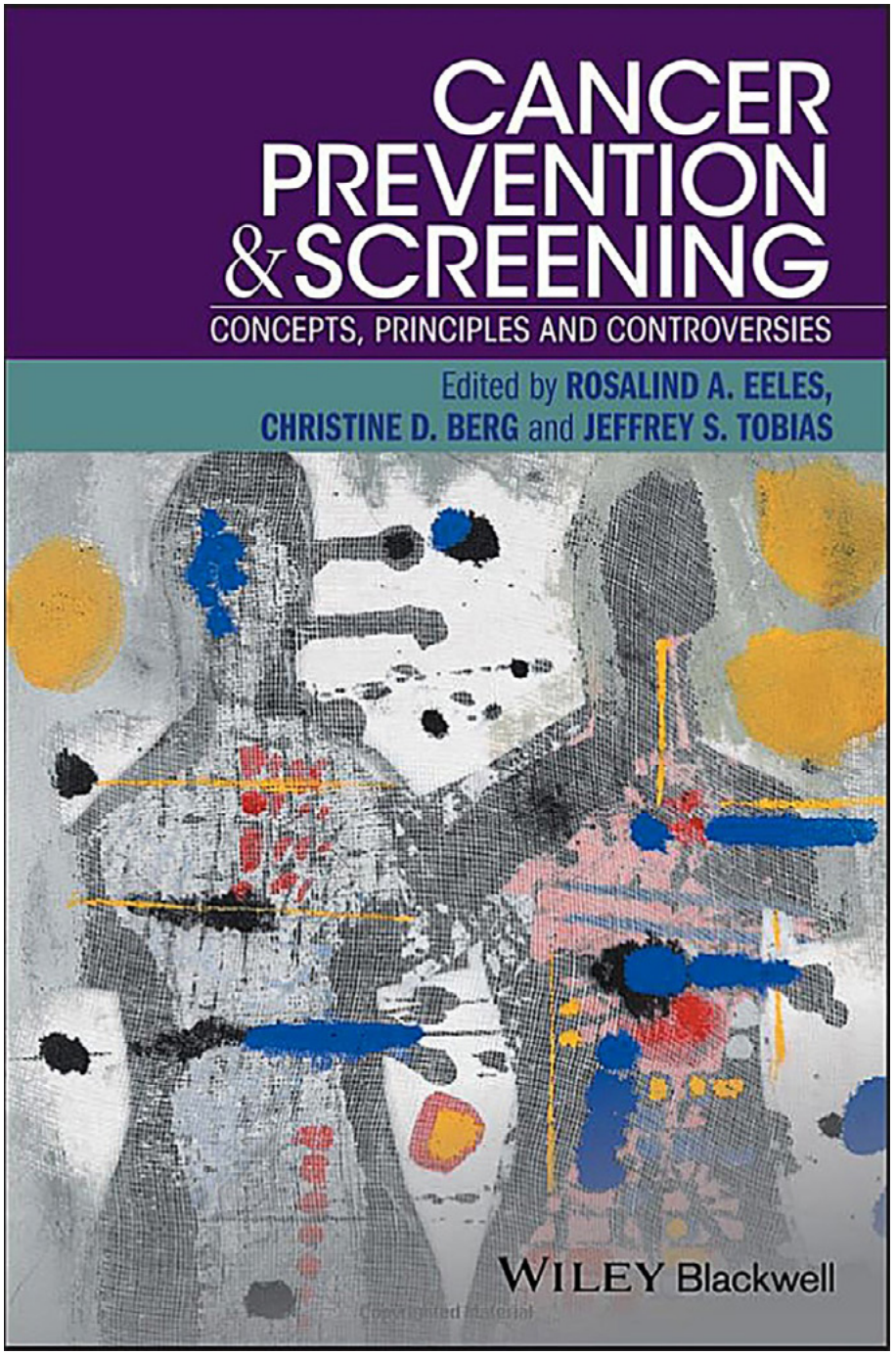
We have now done WGS on over 80 patients, recently picking up **Familial hypercholesterolaemia** and **Factor V Leiden** alterations, the latter increasing risk of clots by 5 times. Both patients will have the gain of awareness and protection from the effects of these gene alterations, for example by using statins for cholesterol lowering and heparin injections for flights, having operations and avoiding the combined contraceptive pill in those with Factor V Leiden. I.E. we only take into consideration **actionable gene alterations.**

Co-lead investigators of the 90 S Whole Genome Screening study Dr Michael Sandberg and Prof Ros Eeles

Prof Eeles' work has changed the management of prostate cancer for the world

Prof Eeles is not only a leading cancer geneticist co-ordinating trials across the world but is also an oncologist and radiotherapist

She is at the heart of the drive to transform cancer screening and prevention. Her book, published in 2019, is the global multi-authored definitive document in this area. It was **winner of the BMA Chairman's Prize** for the 2019 book of the year. The book is aimed at both medical professionals and the lay public.



Insurance

In the UK the Association of British Insurers (ABI) has a trade agreement. (www.abi.org.uk).

All members of the ABI are signed up to the code on genetic testing and insurance. Companies who have signed up to the code agree to act according to its rules. They will not ask for or take into account the result of a predictive genetic test with the only exception being Huntington's disease.
For other countries you would need to see their guidelines.

NHS Pilot

We are planning to pilot targeted Whole Genome Screening in three NHS Practices combining our consultant genetics team with a genetically trained nurse counsellor. We will do this in a more straightforward way that is viable for the future from a cost effective aspect. We have begun to develop an initial small fund as the main cost areas will be the genes themselves and the genetic nurse.

General practice is where the realisation of WGS lies to improve health and save lives.

Introduction to The London Genetics Centre

Professor Ros Eeles

Dr Gabriella Pichert

Dr Lucy Side

Dr Tessa Homfray

Dr James Ware

Liz Bancroft

In the UK there are only about 250 consultant geneticists

Our geneticists have over 175 years of genetics experience between them

Prof Ros Eeles is a Professor in Oncogenetics at The Institute of Cancer Research and an Honorary Consultant in Cancer Genetics and Oncology at The Royal Marsden Hospital. She is also a radiotherapist treating prostate and bladder cancer. She leads many worldwide trials in prostate cancer genetics.

Dr Gabriela Pichert has over 20 years of experience in cancer genetics and was a consultant geneticist at Guy's and St Thomas Hospital for 8 years, some of them as joint lead in cancer genetics. She currently works at 90 Sloane Street Genetic Centre, and several private hospitals in Switzerland.

Dr Lucy Side was a consultant geneticist for 9 years at Great Ormond Street Hospital, before moving to Southampton, where she is clinical lead to the Wessex Clinical Genetics Service at the University Hospitals, Southampton.

Dr Tessa Homfray is a consultant geneticist at St George's Hospital and at the Harris Birthright trust as well as being a consultant in cardiac genetics at the Royal Brompton Hospital. She is world expert on foetal and children's genetic disorders.

Dr James Ware is a consultant cardiac geneticist at the Royal Brompton Hospital and Reader in Genomic Medicine at Imperial College, and a group head within the cardiovascular genetics and genomics unit.

Dr Zsofia Kote-Jarai is a senior staff scientist in the Division of Genetics and Epidemiology at The Institute of Cancer Research. She has two PhDs and over 20 years' experience as a molecular biologist. She has led and supported numerous research projects.

Dr Ann-Britt Jones is a clinical fellow in cancer genetics at the Royal Marsden Hospital and The Institute of Cancer Research. She has previous experience in epidemiology, infectious diseases and oncology. She has been a key researcher in this project.

Dr Elizabeth Bancroft PhD is a senior research nurse in cancer genetics. Her PhD was in the psychosocial aspects of genetics. She leads the psychosocial research aspects of this programme.

Dr Michael Sandberg is a GP and medical director of 90 Sloane Street and has Honorary Clinical Fellow contracts at the Royal Marsden Hospital and The Institute of Cancer Research. He is co-lead of the 90S Study and has trained in genetics and cardiology.

Dr Lisa Webber is a consultant gynaecologist working at 90 Sloane Street and 1 Welbeck Street specialising in fertility, polycystic ovarian syndrome and the menopause. She is a contributing author to the Oxford Textbook of Medicine.

Dr Luis Izquierdo is the Chief Medical Officer at Veritas Intercontinental. He is a Doctor of Medicine and Surgery and has a Master of Science in Medical Genetics from the University of Glasgow.

Dr. Vincenzo Cirigliano is the Chief Technical Officer at Veritas Intercontinental. He has an extraordinary doctorate award from the Autonomous University of Barcelona. He was previously Head of Molecular Genetics at Labco and SynLab.

Bibiana Palao is the Chief Product Officer at Veritas Intercontinental. She has over 15 years of experience in medical genetics and previously held the role of Director of Innovation at Synlab International.

We are very grateful to the consultant cardiologists working at 90 Sloane Street and supporting the project:

Dr Vias Markides is the head of cardiology at The Royal Brompton hospital. His subspeciality is arrythmias and ablations and pacemakers.

Prof Diana Gorog is consultant cardiologist at the Royal Brompton and the Lister Hospital in Stevenage. Diana as well as being an interventional cardiologist undertaking angioplasty also heads a research team in thrombosis and prevention of heart attacks.

Dr Denis Pellerin is consultant cardiologist at St Bartholomew's hospital. He is a world authority on Echocardiography having written many European guidelines. He established the largest Echo department in the UK. He specialises in Stress Echo and Transoesophageal Echo.

The London Genetics Centre

90 Sloane Street

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