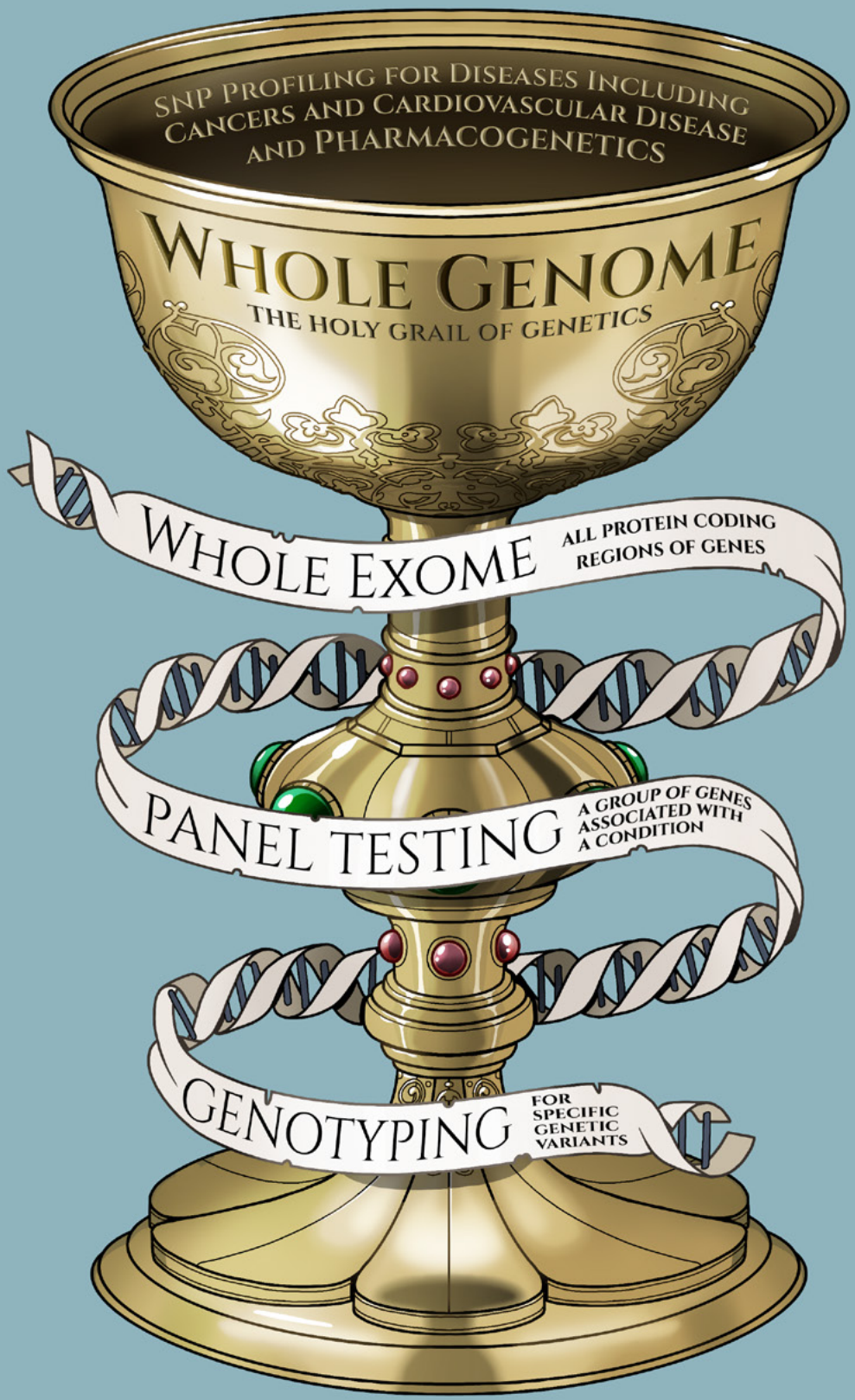


The London Genetics Centre
90 Sloane Street

Veritas
Intercontinental

CONTENTS

1- Our two main Genetic testing pathways

THE LONDON GENETICS CENTRE
90 SLOANE STREET

Our aim is to save lives and reduce the suffering of illness and treatments. We test for Single Risk Genes and Polygenic Risk Scores to find areas of personal genetic risk where we can significantly lower your risk, and that of your children and grandchildren.

We offer two main Genetic Screen pathways:

New Preventive Screen - Whole Exome to analyse 83 cancer and 76 cardiac genes, 5 other key genes and 4 cancer Polygenic Risk Scores (PRS) run by our Genetic Counsellor. A Consultant geneticist overviews all results and family histories with patients seen by the genetic counsellor. Cost £1,100

Whole Genome Screening - is more extensive, including 583 selected actionable genes combined with a Full Medical, Bloods, ECG, Echocardiogram and then a multidisciplinary meeting with the Genetic Consultants to review your results, producing a summary document, and finally an appointment with a Consultant Geneticist. Cost £4,995

In this booklet we give an overview of the extensive areas where gene testing can benefit you and some of the basic principles.

2- The Psychology of Genetic Testing

For many of us we may choose to avoid things that we fear, burying our head in the sand. But this attitude can be dangerous, putting us at a greater risk and leads to diagnostic delay.

When we do targeted 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 potentially save millions of lives if we can help the world to understand the enormous gains.

The modelling studies show instituting genetic screening and acting on the results should reduce the **cancer mortality** in the general population by nearly a fifth. The sooner this advance is actualised huge numbers of lives could start being saved.

3- Whole Exome Sequencing vs Whole Genome Sequencing

Our new preventive screen uses Whole Exome Sequencing to look at all the major cancer and cardiac genes with Polygenic Risk Scores (PRS)

WHOLE EXOME SEQUENCING

Our **New Preventive Screen** offers a more affordable method to test for **actionable gene changes.** At £1,100 **it includes all the same cancer genes (83) and cardiac genes (76) (optional) and Polygenic Risk Score (PRS) as in our Whole Genome Screening.**

This targeted approach means we are only analysing actionable gene changes: if we find you have any harmful changes in these genes, then we can do something to improve your outlook. We do **not** analyse the neurological genes such as those related to Parkinson's disease or dementias. It is important to note that some smaller risks associated with these gene changes may **not** be actionable.

The Preventive Screen is done via Whole Exome Sequencing (WES), which is the sequencing of all the **coding** parts of our genetic information.

WHOLE GENOME SEQUENCING

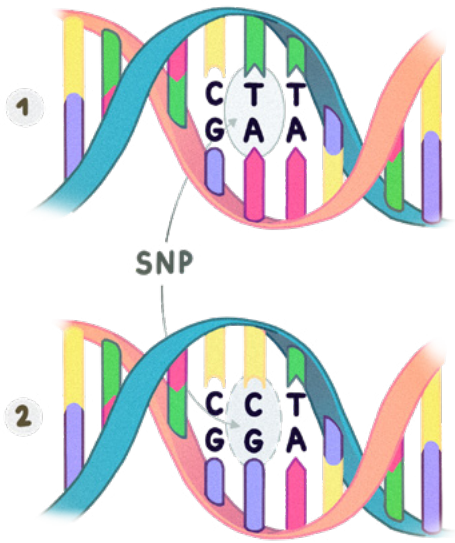
Whole Genome Sequencing (WGS) is the sequencing of your entire genome (all our genetic information) and costs £4,995. With Veritas we have selected a targeted 583 genes to analyse, relating to more than 650 conditions.
It also includes **250 recessive carrier genes**; which will not usually have any implications for your own health, but could be relevant to your wider family. WGS also includes **pharmacogenes**, the genes that control how we as individuals metabolise medicines. With our WGS we double check the result, doing WES as well. WES has the benefit of not missing large gene deletions which can happen on rare occasions.

WES and 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, CHEK2* and *ATM.)*

Germline changes refer to the DNA you have in every cell that you are born with, whereas **somatic changes** are seen in tumour cells and cannot be inherited unless they are directly related to your germline.

4- SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs) AND POLYGENIC RISK SCORES (PRS) EXPLAINED

Single nucleotide polymorphisms (SNPs) are single base letter changes in the genome as shown in the diagram. You can see the T and A pair in the middle has become a C and G – this is a SNP.



Some SNPs can cause a very small increased risk of developing certain diseases. However, when we combine and add up all the SNPs with their individual risk weighting for a particular condition to form a polygenic risk score (PRS), it can significantly increase the risk for developing a disease. The increased Cancer PRS risk for a condition, for example Prostate Cancer, can be as large as from a harmful single gene change such in BRCA. **So if you are trying to help find people who have a higher risk of a condition – i.e. cancer, you need to go to a genetic team that is analysing both single genes and polygenic risk scores.**

5- The Preventive Screen - What does it test?

The London Genetics Centre

The New Preventive Screen

Making genetics more affordable at £1,100

A newly introduced alternative to our more extensive whole genome screening medical of £4,995

High quality genetic testing combined with a team of 185 years of genetic expertise

Counselling and Results given by genetic trained counsellor with Consultant Geneticist seeing all results together with family history

Combines single gene changes & Polygenic Risk Scores - our genetic risk comes from both these areas

83 Cancer Genes
76 Cardiac Genes

5 extra genes - in key areas

Familial Hypercholesterolaemia
Iron overload for haemochromatosis
Factor V Leiden and F2 Prothrombin - both are clot risk genes
Alpha 1 antitrypsin for emphysema and cirrhosis

Polygenic Risk Scores for 4 cancers

Cancer PRS

Breast cancer
Prostate cancer
Colorectal cancer
Ovarian cancer

We plan in the future to bring in the tests below as research:

Kidney cancer
Melanoma cancer

Cardiovascular PRS

Coronary artery disease
LDL cholesterol
Systolic blood pressure

Other conditions

Osteoporosis
Inflammatory bowel disease
Premature ovarian failure
Coeliac disease
Diabetes

This new genetic screen has been developed by the London Genetic Centre together with Veritas Intercontinental - our sequencing and analysing partner. It has been produced with the knowledge we have gained from running the 90S London Genetics Centre Whole genome study.

6- Cancer and Cardiac Conditions - Examples

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, however, 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 60-85% 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%. Taking aspirin daily reduces colon cancer by 40% in these patients, and this gene alteration also means that they respond exceptionally well to immunotherapy.

Sudden cardiac deaths

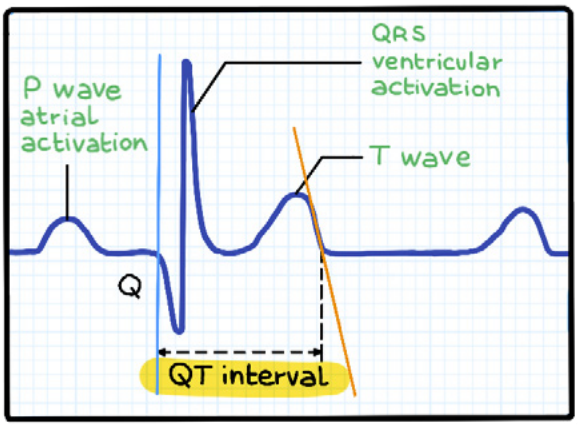
20% are due to genetic abnormalities related to cardiac muscle and cardiac rhythm disorders, or aortic aneurysms.

Hereditary thrombosis

6% of the population is at 4 to 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.

Cardiac Genetics

Inherited arrhythmia syndromes can cause sudden cardiac death through a dangerous rhythm called ventricular tachycardia. **Long QT Syndrome** occurs in 1 in 2,000 people, with a specific genetic type identified in 75% of cases. Genetically defined drug treatment and risk factor avoidance advice can then be instituted.



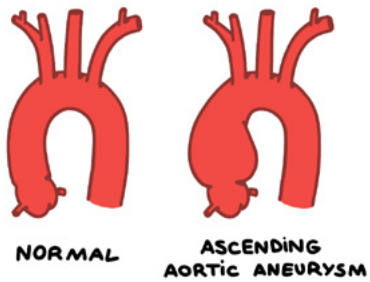
The electrocardiogram (ECG) shows the QT interval. Many patients respond to beta blockers, and QT prolonging medicines should be avoided to reduce the risk. **QT prolonging drugs** *include antidepressants, macrolide antibiotics, antihistamines and many other medicines.*

Dilated cardiomyopathies are a common cause of heart failure and the need for transplantation. We identify a gene change in 15-25% of cases.

Hypertrophic cardiomyopathy occurs in 1 in 500 people where the heart muscle is thickened. A gene change is identifiable in 30-60% of cases. We do an echocardiogram in all participants in the WGS Study as cardiac gene penetrance can be low.

Aortic aneurysms: the aorta enlarges with the potential to burst, or the wall can **dissect** with a tear in the inner lining, the blood flowing between the layers. Aneurysms occur in the abdomen and chest. Their progression can be reduced or they may be operable.

Ascending aortic aneurysms: 20-25% have specific genes. Known associations include Ehlers-Danlos syndrome, Marfan syndrome, Loeys-Dietz syndrome and Familial thoracic aortic aneurysms.



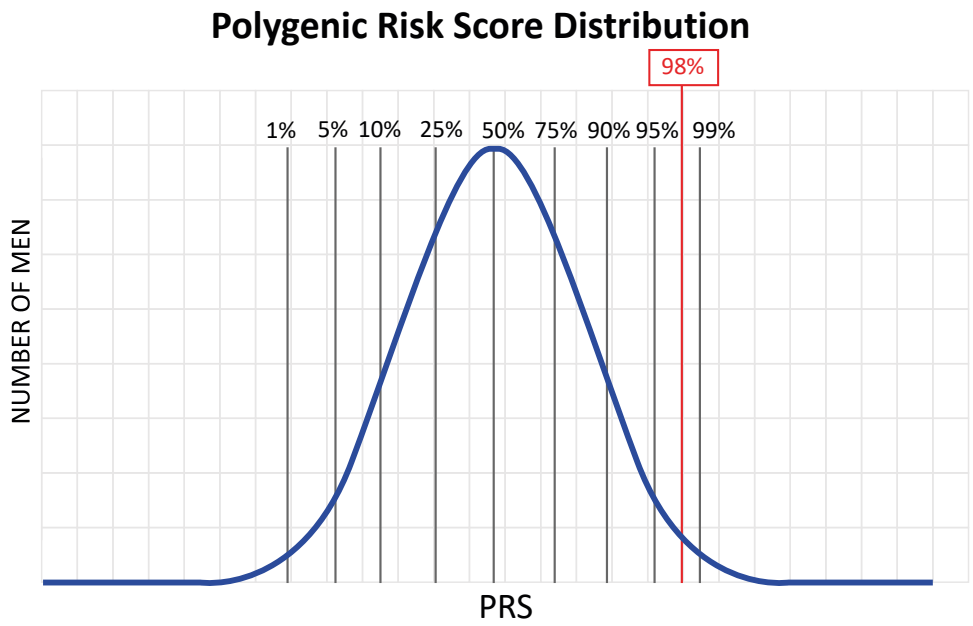
Aneurysm rupture is usually catastrophic.
Preventive surgery is generally carried out on those with 5 and 5.5 cm aneurysm diameter. The specific gene type influences the timing, some aortas being more vulnerable.

7- POLYGENIC RISK SCORES - PROSTATE AND COLON CANCER

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 prostate cancer. The final calculation showed he has a **more than a 6-fold relative 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.



The above chart shows the position of the patient on the 98th centile for prostate cancer
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 change which gives him only a two times increased risk of colon cancer compared with the general population. It was likely there was some other factor. Then his PRS was calculated. This conferred a **3.78-fold relative colon cancer risk**. Scientifically we have learned recently that his monogenic ***APC*** gene change likely interacts with his high-risk SNP profile, majorly combining to increase his risk.

*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. SNPs and therefore PRS differ in the way they are passed down compared to the 50% hereditary risk of single gene alterations. **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 SNPs to excess familial risk is large at 38% compared to so called single gene changes, such as *BRCA 1/2,* which contribute in a smaller way together with the other listed genes.

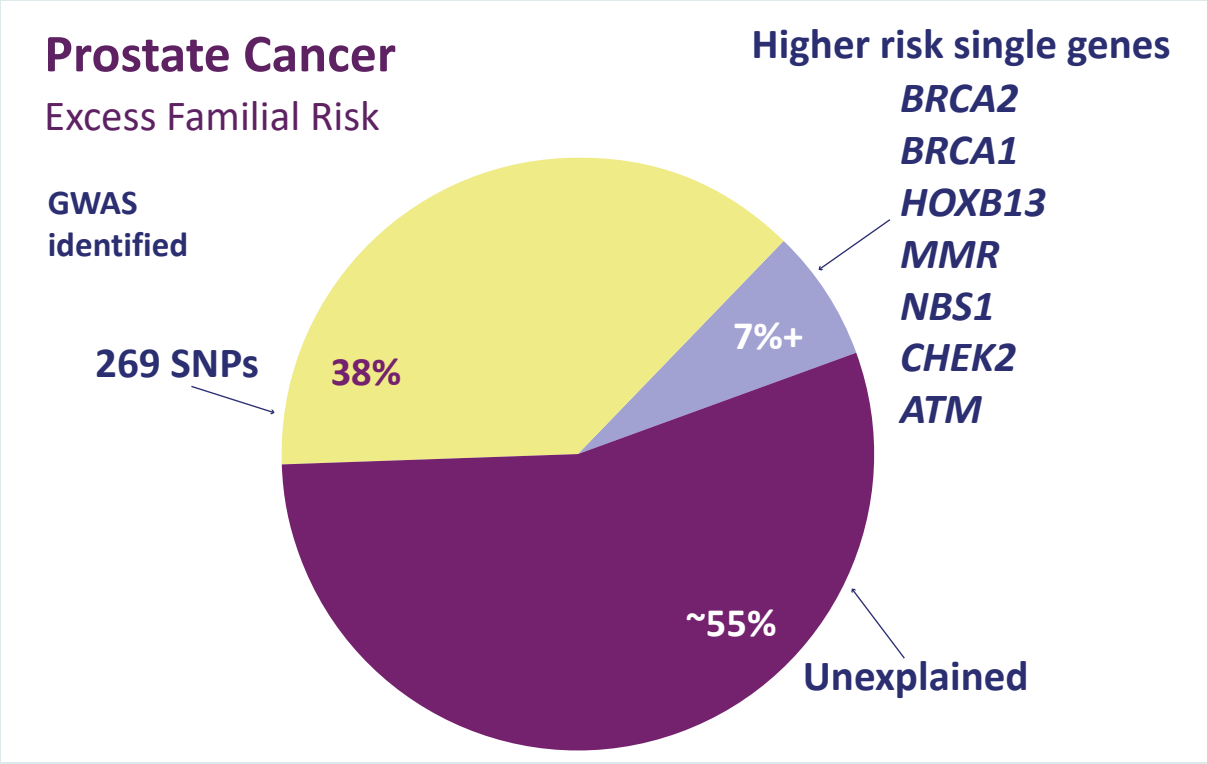


Figure courtesy of Dr Kote-Jarai

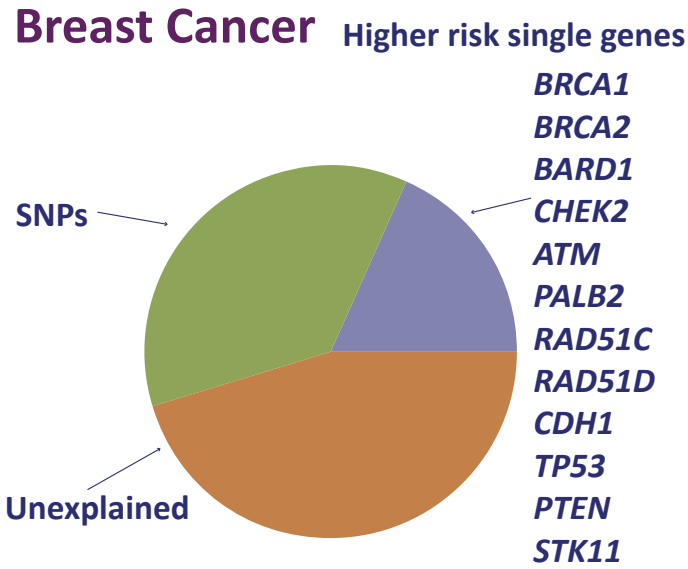
If we are to best identify people at highest cancer risk we need to do both single gene analyses and SNPs.

Genetic testing can find a third of those at highest risk of ovarian cancer and after having had a family, if you are at high risk you can decide to have relatively simple day case surgery to remove the ovaries and fallopian tubes which reduce 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, reducing ovarian cancer by a third.

Current ovarian screening with ultrasound and CA125 (a tumour marker) is sadly not effective. Ovarian cancer usually presents when it is widespread and too late for a good chance of cure.

The charts below elegantly show 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 single gene changes - monogenes so whereas in ovarian cancer SNPs play only a very small part compared to single gene changes. In prostate cancer the SNPs are dominant.



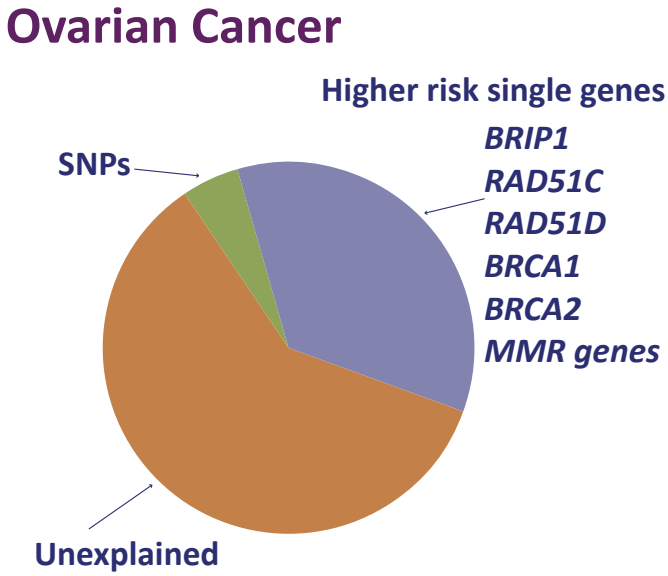
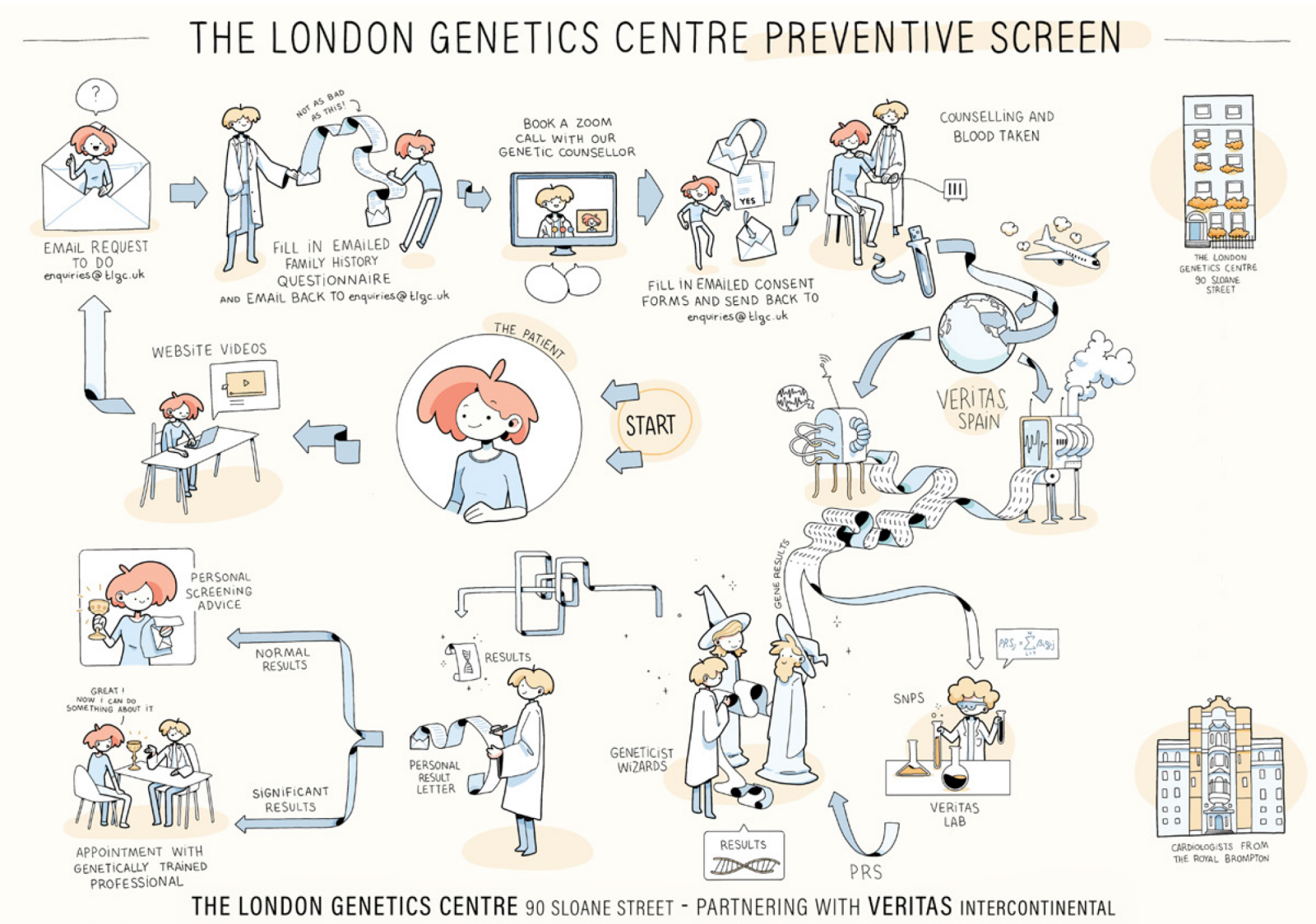


Figure created from amalgamated estimates from publically available data.

8- THE PREVENTIVE SCREEN PATHWAY



9- Polygenic Risk Score (PRS) - How we display the results

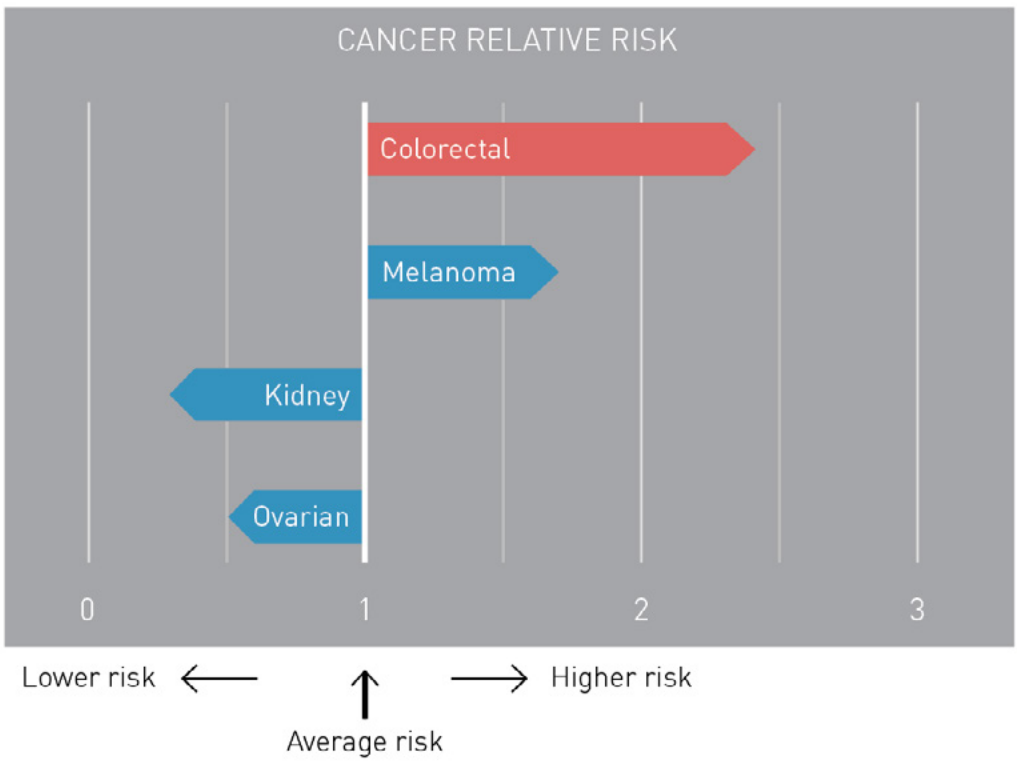
In the following two pages we show how the report comes, individual to each person

POLYGENIC RISK SCORE REPORT SUMMARY

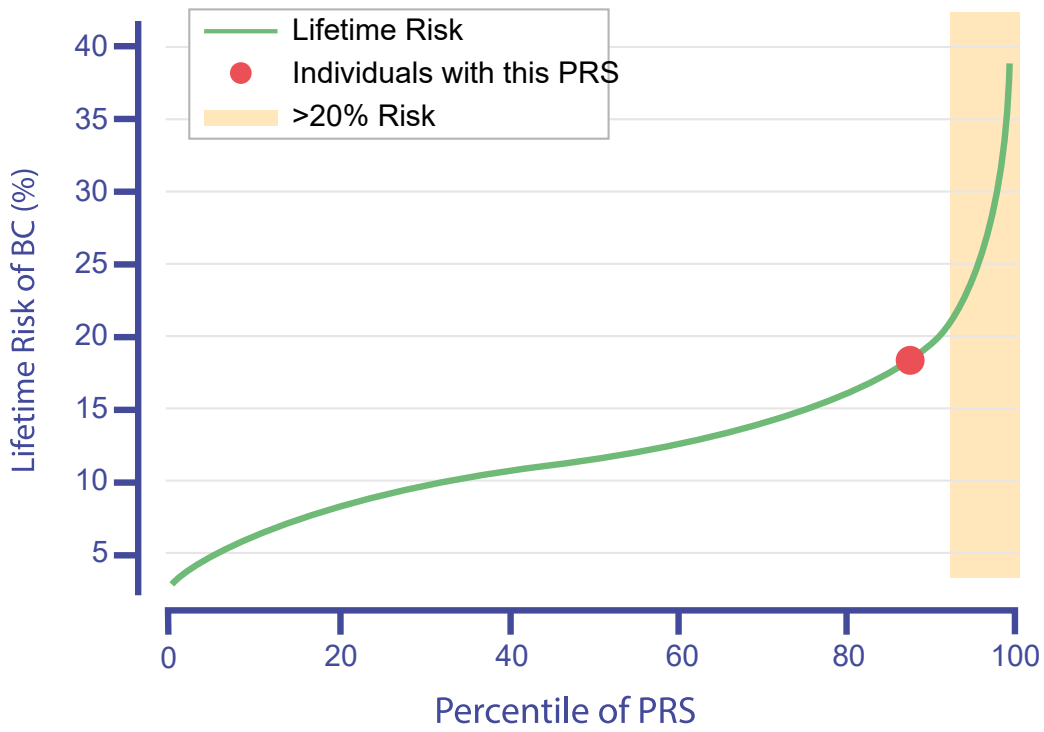
CANCER		
DISEASE/TRAIT	PAGE	RELATIVE RISK
Colorectal	3	2.40
Melanoma	5	1.70
Kidney Cancer	7	0.30
Ovarian Cancer	9	0.50

*The average person has a relative risk of 1

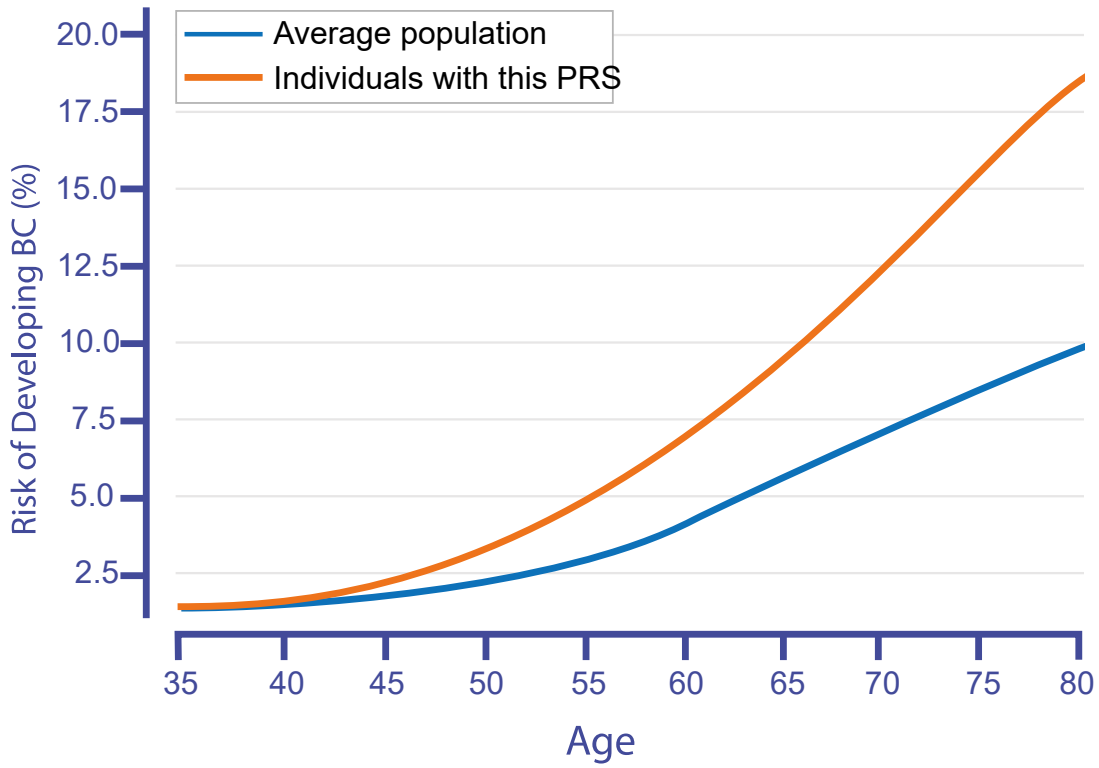
*Red if >2-fold risk



Breast Cancer PRS on the 89th Centile: This patient's position on the risk curve gives her an 18% chance of breast cancer in her lifetime. If on the 5th centile it would be 4%.

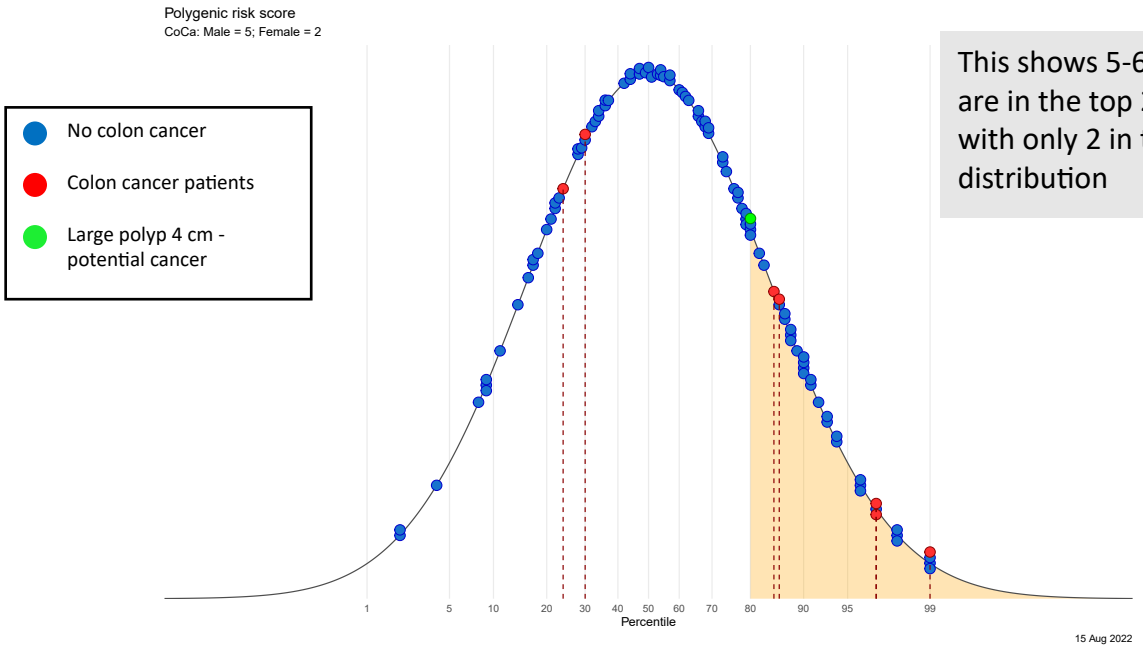


An average PRS lifetime breast cancer risk curve shown in Blue, the patient with PRS on the **89th Centile is shown in Orange.**

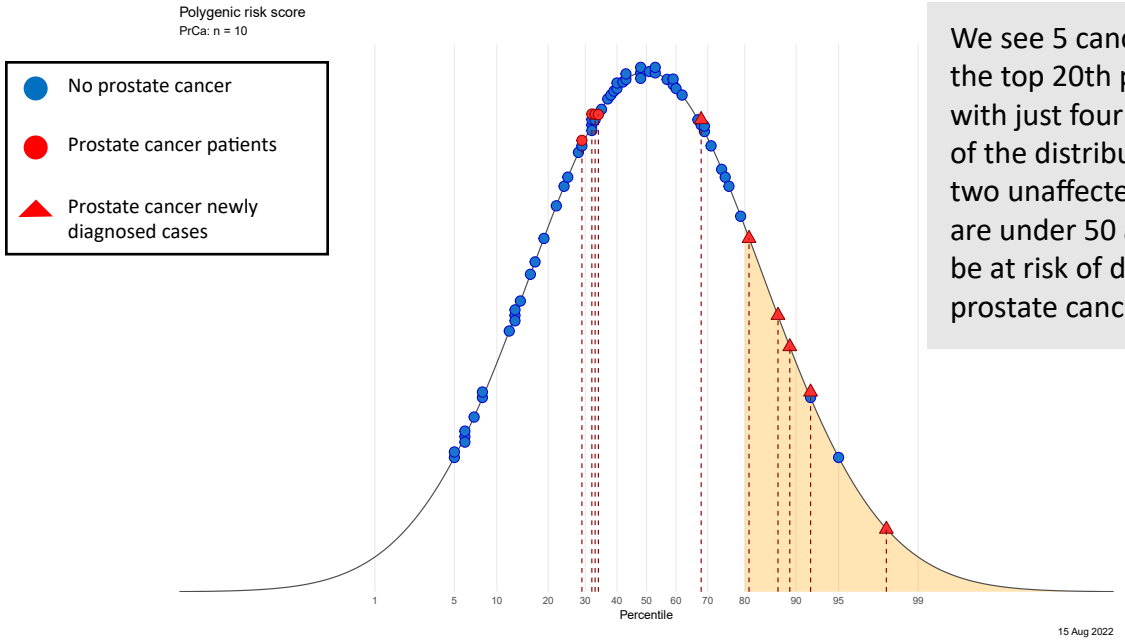


10- PRS results - The first 104 patients of the 90S Study

Colon cancer (CoCa) polygenic risk scores (PRS). Each circle represents an individual



This shows 5-6 colon cancers are in the top 20th percentile with only 2 in the rest of the distribution



We see 5 cancer cases in the top 20th percentile with just four in the rest of the distribution. The two unaffected cases are under 50 and will be at risk of developing prostate cancer.

Using polygenic risk scores for colon cancer and prostate cancer can help find those at greatest risk with more to gain from colonoscopy/starting at a younger age. Knowing a person has a high PRS for colon cancer and starting screening earlier in high PRS cases should save lives. The same paradigm should also apply to prostate cancer screening.

11- Veritas Intercontinental: Our Partners in Genetic Screening

Veritas provides the sequencing and interpretation of our whole exome and whole genome, providing 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.

Working collaboratively with Veritas over the last three years has given us an exceptional pioneering developmental opportunity. Genetics really is teamwork.

The London Genetics Centre has an exclusive UK agreement with Veritas Intercontinental.

Veritas
INTERCONTINENTAL
The Genome Company

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. They will not ask for or take into account the result of a predictive genetic test with the only exception being Huntington's disease. If you are doing genetic testing when you already have a condition they can ask for the genetic results associated with the that specific condition.
For other countries you would need to see their guidelines.

5 Commandments of Genetic Screening

- **Accuracy -** our tests are the highest quality
- **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
- **A genetic consultant reviews all results**
- **Informed consenting** and clear feedback by a genetically trained professional

12- Gene-Associated Risk Chart

TYPE OF CANCER:	BREAST (female)	OVARIAN	PROSTATE	PANCREAS	OTHER
UK Cancer deaths per year (2017-2019)	**11,400**	**4,142**	**12,039**	**9,558**	-
Lifetime risk of cancer in general population	12%	2%	18%	2%	-

Prevalence	MAJOR BREAST CANCER GENES:	BREAST (female)	OVARIAN	PROSTATE	PANCREAS	OTHER
1/381 1/40 with Ashkenazi ancestry	***BRCA1***	85%	40-60%		1-3%	
1/277 1/40 with Ashkenazi ancestry	***BRCA2***	80%	17-25%	18-25%	higher risk with positive family history 2-7%	**Melanoma** 3-5%
1/770	***PALB2***	44%	5%		2-3%	
1.8/1000	***BARD1***	25%	7%			
1/3555 1/5476 90% chance of cancer by age 60	****TP53***	90%			10%	**Soft tissue** 20% **Brain** 15% **Bone** 10%
1/200,000	****PTEN***	67-85% av. age of diagnosis in the 40s'			other: **Melanoma** 5% **Kidney** 30% **Thyroid** 15-35% **Uterus** 25% **Bowel** 9%	
1/25,000-1/280,000	****STK11***	32-54%	10-21%			
1/100	****ATM***	20-25%		40%	6%	
1/100-1/200	****CHEK2***	25%		25%		**Bowel** 12.5%
1/1,000,000	****CDH1***	39-52%				**Stomach** 45%

XX% Number in circle represents lifetime risk of developing respective cancer for each gene change

* Large variation in lifetime risk: dependent on type of gene change found and family history

** Encompasses kidney/ureter and bladder cancers. Risks vary between different organs.

For a more extensive list of the genes included in our Preventive Panel and their associated risks please see our website:

https://thelondongeneticscentre.com/

There may be additional cancer risks associated with a given gene change where % lifetime risk is currently under discussion. Therefore, recommendations based on a test result may differ from what is suggested by the table.

TYPE OF CANCER:	BOWEL	UTERUS	OVARIAN	STOMACH	OTHER
UK Cancer deaths per year (2017-2019)	**16,808**	**2,453**	**4,142**	**4,216**	-
Lifetime risk of cancer in general population	6%	3%	2%	1%	-

MAJOR BOWEL CANCER GENES:

*In addition to **ATM, CHEK2, STK11** and **PTEN** genes as above*

Prevalence			Bowel	Uterus	Ovarian	Upper GI tract	+Urinary tract	Brain	Prostate
1/200,000	Lynch syndrome	***MLH1***	35-65%	37%	11%	18%	*5-7%	*2%	
1/3000	Lynch syndrome	***MSH2***	47-51%	50%	17%	17%	15%	*3-8%	24%
1/800	Lynch syndrome	***MSH6***	20%	41%	11%	11%	*1-8%	*1-2%	24%
1/714	Lynch syndrome	***PMS2***	13%	13%					
1/13,500		***APC***	70-95%						
1/40,000 (2 gene changes)		***MUTYH***	70%						
very rare		***BMPR1A***	30%			15-21%			
very rare		***SMAD4***	10-38%			15-21%			

MAJOR OVARIAN CANCER GENES:

*In addition to **BRCA1** and **BRCA2** gene changes – as above which are major contributors, lesser contributing gene changes include **PALB2, BARD 1, PSTK11** as well as some of the Lynch syndrome genes above.*

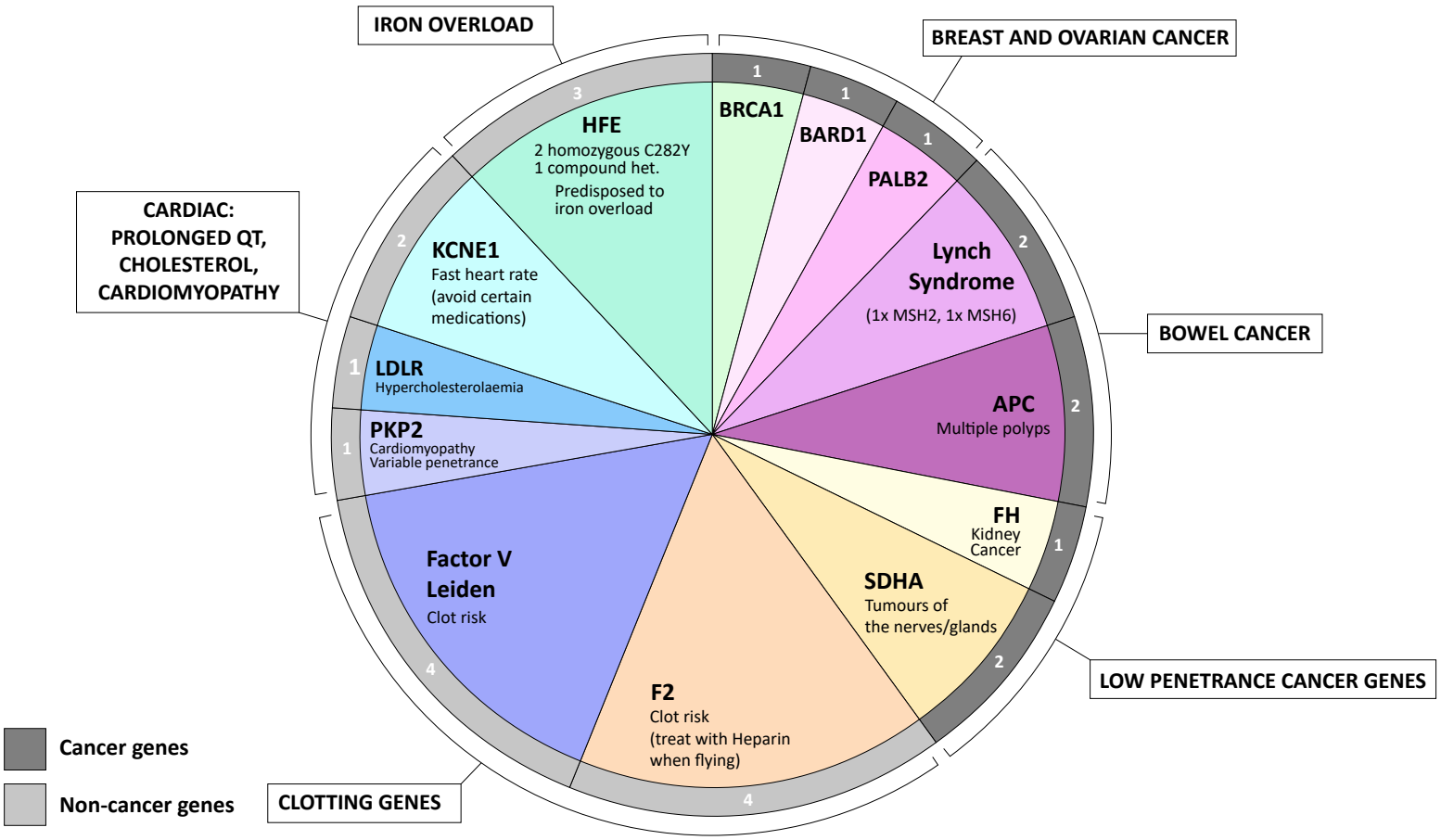
		Ovarian		Breast
1/416	***BRIP1***	9%		possible increase
very rare	***RAD51C***	10%	triple negative	20-40%
very rare	***RAD51D***	10-20%	triple negative	20-40%

The aim of this chart has been to communicate gene risk association, but we should add there are many more genes and conditions which are not included for reasons of space. Please refer to our website https://thelondongeneticscentre.com/ for wider coverage.

13- Gene Changes Found In The 90S Study

This chart demonstrates the gene changes that we have found in the 90 Sloane Street Study

First 120 WGS - Major Gene Changes Found

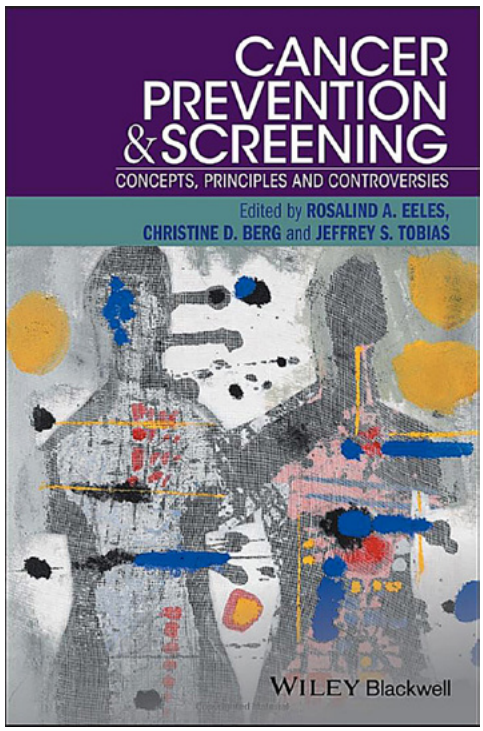


For risks associated with BRCA1, BARD1, PALB2, MSH2, MSH6 and APC see Page 17-18 Gene-Associated Risk Chart. For a more comprehensive list of the genes in the Preventive Panel see our website: https://thelondongeneticscentre.com/.

14- MEET OUR LEAD INVESTIGATORS

Figure 1 Co-lead investigators of the 90 Sloane Street Whole Genome Screening Study, Dr Michael Sandberg and Professor Ros Eeles.

Dr Michael Sandberg is the Medical Director of 90 Sloane Street and jointly set-up The London Genetics Centre with Professor Ros Eeles, who is a world-renowned Consultant in Cancer Genetics and Oncology and is also a radiotherapist. She has led an extensive number of worldwide genetic trial collaborations, repeatedly moving the boundaries in the world of prostate cancer and genetics. Professor Eeles' work has changed the management of prostate cancer internationally.
Her book on screening, published in 2019, is a global multi-authored definitive document in this area. The book is aimed at both medical professionals and the lay public and is the winner of the BMA Chairman's Prize for the 2019 book of the year.



15- NEWS AND MEDIA

The Times, June 2022

British scientists have developed a way to screen patients for "actionable"mutations - faulty genes that increase the risk of disease but can be mitigated through lifestyle or treatment

A study has revealed that one in four people carry potentially harmful genetic mutations that can be picked up through a simple blood sample.

Dr Michael Sandberg, a GP at 90 Sloane Street in London, which co-ordinated the research, said: "This study is pushing the boundaries of genomic screening by showing that it is feasible as part of GP care.

The Telegraph, June 2022

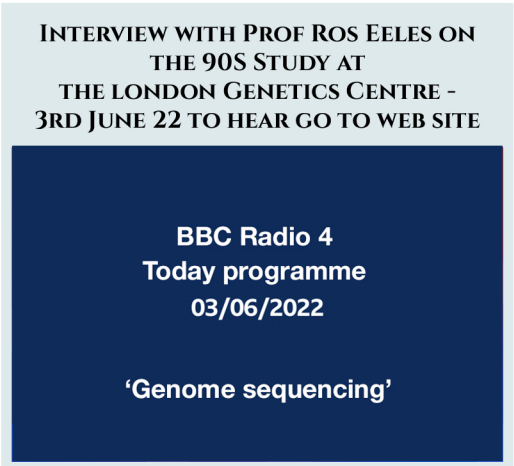
DNA testing revolution' at the GP could detect patients at risk of cancer

Using genomic sequencing in primary care means patients can get early treatment for health conditions before they become life-threatening, the first UK study of its kind has found.

Early modelling based on the study findings suggests thousands of lives a year could be saved by the tests, the researchers said, by reducing mortality by at least a fifth for breast and ovarian cancer.

The Health Secretary said on Thursday that the technology was "changing the future of healthcare", and opened up the possibility for patients with life-changing illnesses to be diagnosed early via their GP.

https://thelondongeneticscentre.com/clinical-news/



You can listen to Professor Eeles talking about the 90 Sloane Street Study at the annual American Society of Clinical Oncology (ASCO) Conference in 2022.

She explained that routine screening could prevent couples who are planning a family, from passing on genetic diseases. Couples who carry harmful gene changes may then have the option to undergo assisted reproductive procedures (IVF). This involves testing embryos for harmful genetic changes present in a family, and only returning those embryos that **do not** carry the harmful gene change for a potential pregnancy.

16- Meet the London Genetics Centre Team

Professor Ros Eeles

Dr Gabriella Pichert

Dr Lucy Side

Dr Tessa Homfray

Dr James Ware

Liz Bancroft

Catrina Willliams

Sophie Hicks

Lucinda Seymour

In the UK there are only around 250 consultant geneticists. The geneticists on our team have over 180 years of experience between them. The team are also joined by Genetic Counsellor, Catrina Williams, and Genetics Associate, Sophie Hicks and genetics secretary, Lucinda Seymour.

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 the London Genetics 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 Hospital, 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 practice 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 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, ablations and pacemakers.

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

Dr Denis Pellerin is consultant cardiologist at St Bart'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

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