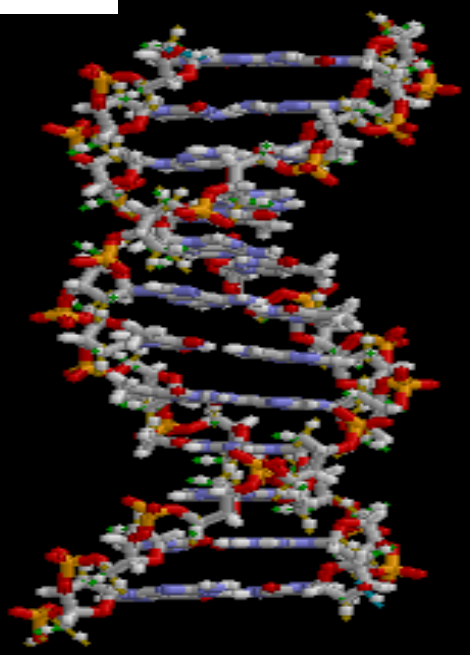


Dr Julian Barwell Dr Pradeep Vasudevan

Consultants in Clinical Genetics at the University Hospitals of Leicester and Honorary Professors in Genomics Medicine at the University of Leicester

jgb8@le.ac.uk

The Dawn of Genomic Medicine and Personalised Medicine

Leicester Medical Society March 2019

Types of genetic testing

The rise of Genomics

The rise of machines

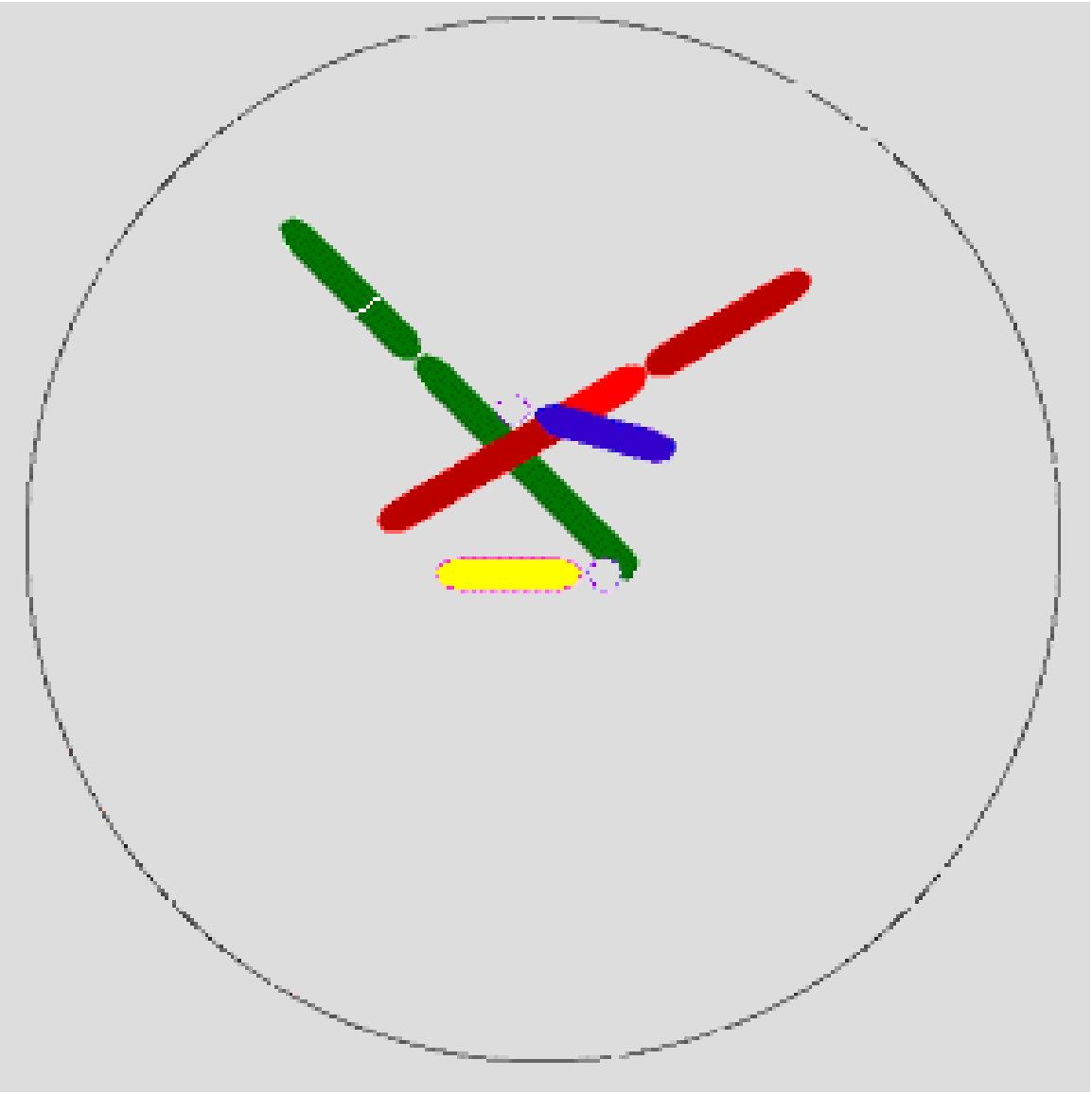
Variant Analysis

Triage

Population stratification

Ethical problems in counselling

Precision Medicine



Aberdeen	**Inverness**
Belfast	**Leeds**
Birmingham	**Leicester**
Bristol	**Liverpool**
Cambridge	**London**
Cardiff	**Manchester**
Dublin	**Newcastle**
Dundee	**Nottingham**
Edinburgh	**Oxford**
Exeter	**Sheffield**
Glasgow	**Southampton**

http://www.contexo.info/DNA_Basics/Meiosis.htm

What's more important-your DNA code or post code?
DNA code currently wins in less than 5%
Sanitation and immunisations key

40 years for post code internationally
2 months lost per kilo overweight
7 years lost per packet per day
20% variation in life-span inherited

Question Seven

A 12 year old boy

A 12 year old boy is taken to see the paediatric endocrinologist because of obesity, abdominal discomfort and poor behaviour. His father previously had kidney stones and his older sister is being investigated for galactorrhoea.

What are the causes of galactorrhoea in a women with no history of previous pregnancy?

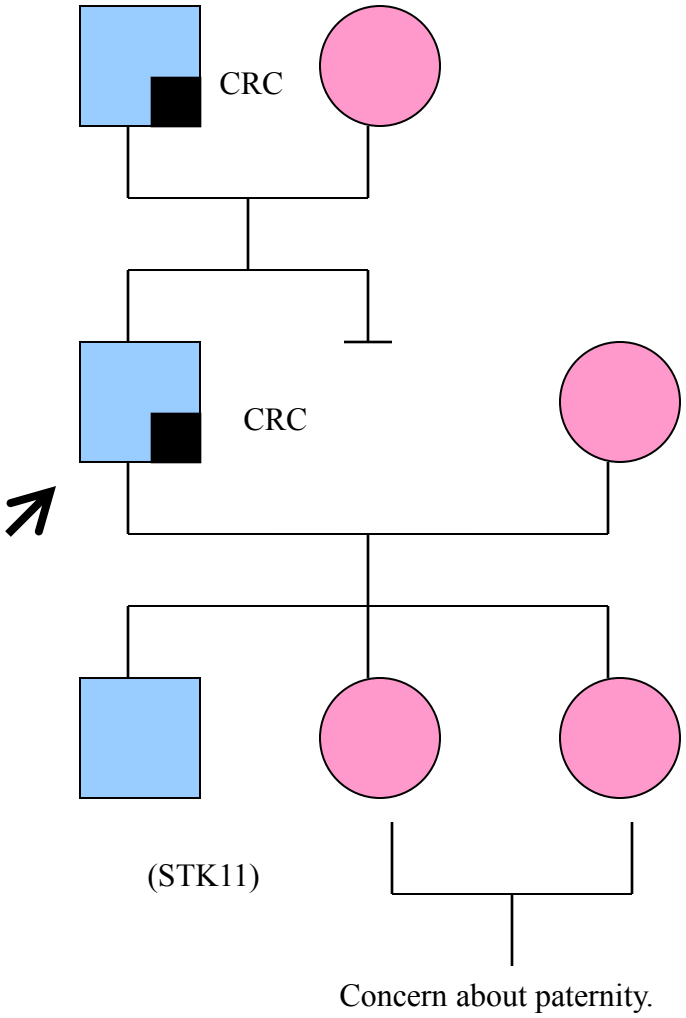
What are the causes of kidney stones?

Which abdominal tumour can cause increased appetite and poor behaviour?

Which syndrome can link all of these things?

Is our role of making a diagnosis changing?

Who has a right to know?



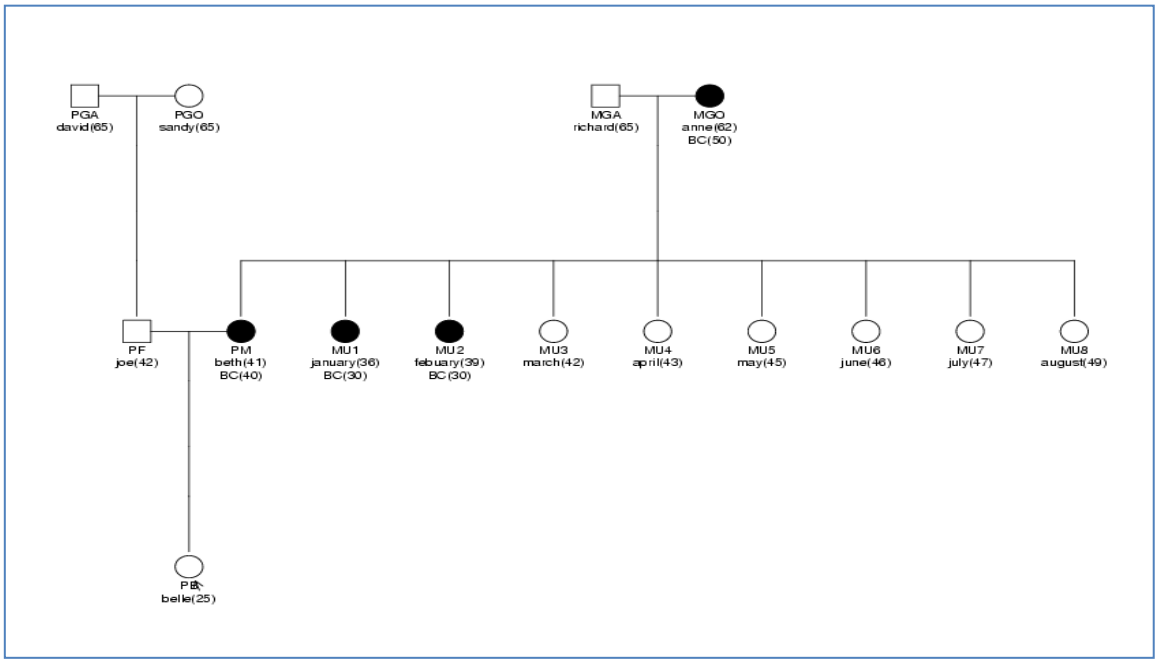
Genethics Club

Pradeep Vasudevan HoD
Julian Barwell
Emily Craft
Huw Dorkins
Shirley Hodgson
Corrina Powell SpR
Neeta Lakhani

Vanita Jivanji Matron
Claire Curtis
Beckie Kaemba
Penny Van Besouw
Shanta Patel

Genomics
Jo Lowry
Luke, Rachel
Judith, Sandra
Patricia, Patrina
Terry, Lauren

Computer modelling and mendelian risk



http://ccge.medschl.cam.ac.uk/boadicea/

Can the machine beat the human in calculating risk?

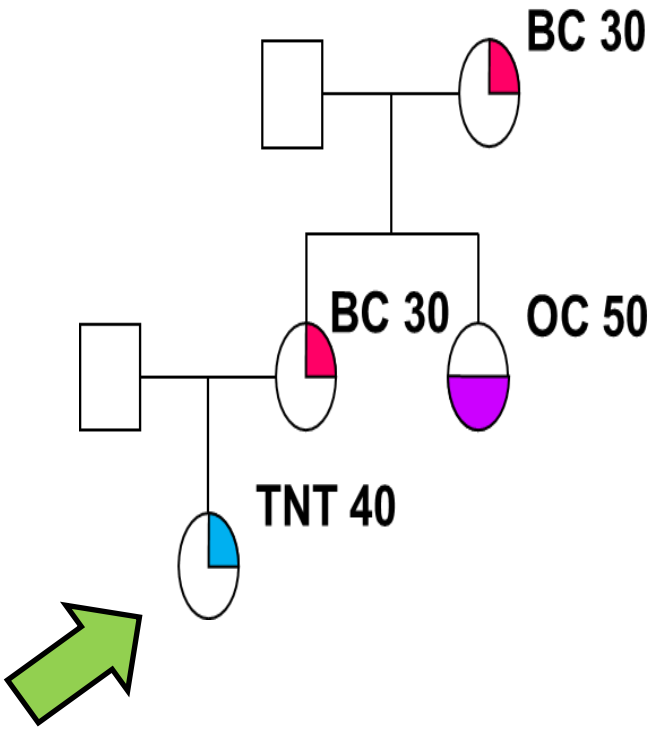
BOADICEA

Computed results are as follows...

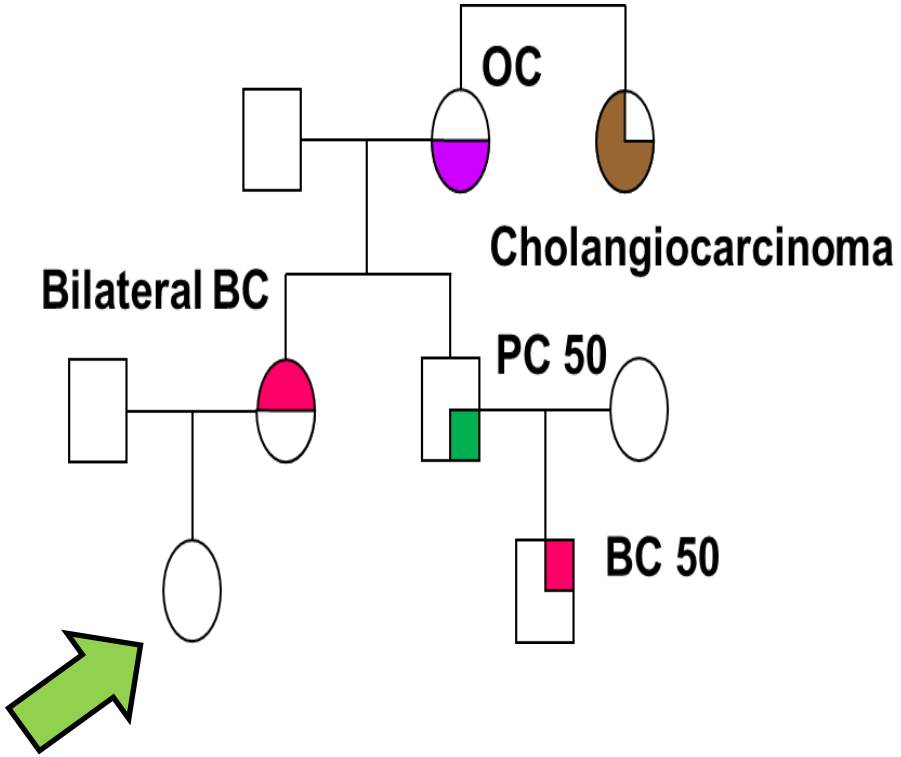
Family member:belle(PB)

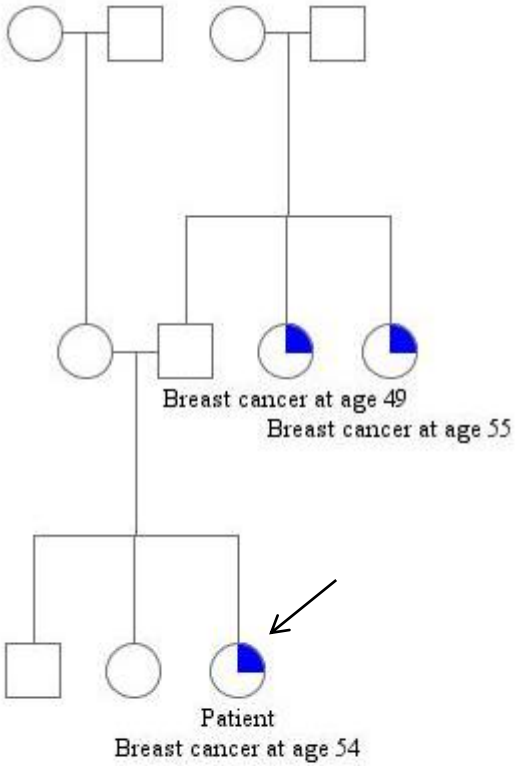
Genetic status	Mutation carrier probabilities
No mutation	0.7800
BRCA1	0.1169
BRCA2	0.1031

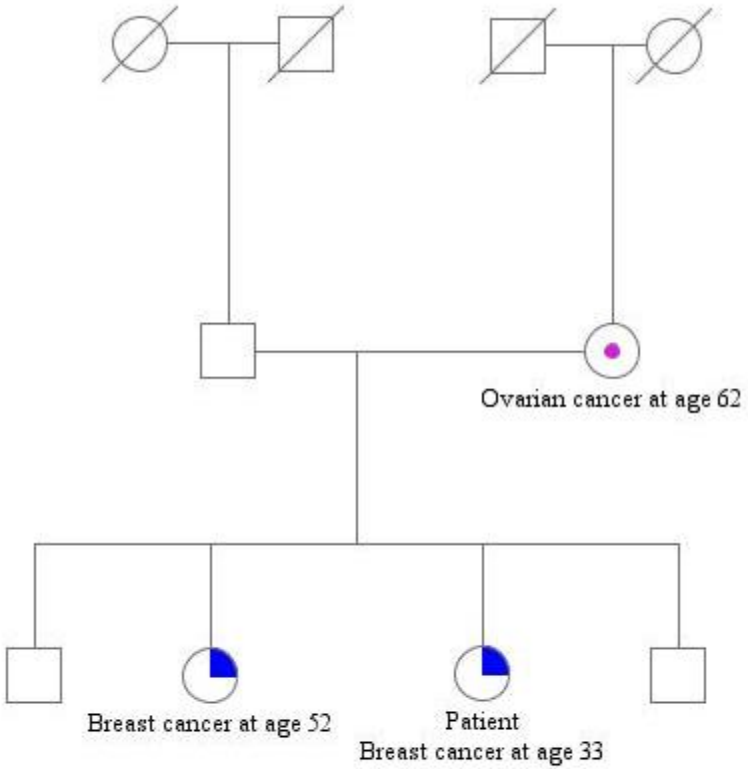
Classic BRCA1 pedigree



Pedigree showing bilateral breast cancer, male breast cancer and prostate cancer, which are common in BRCA2.





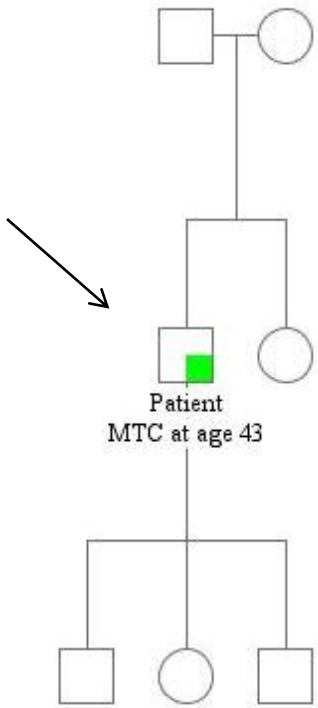


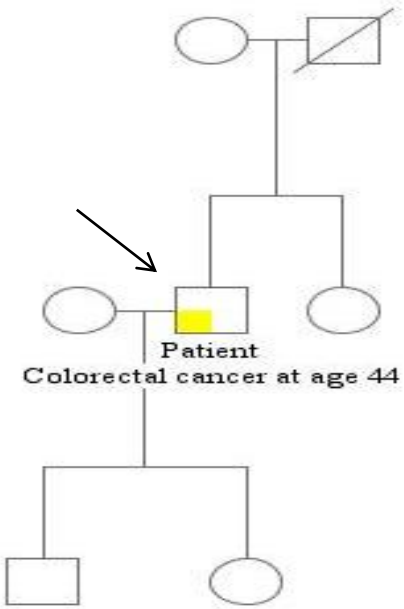
3,2,1 score:

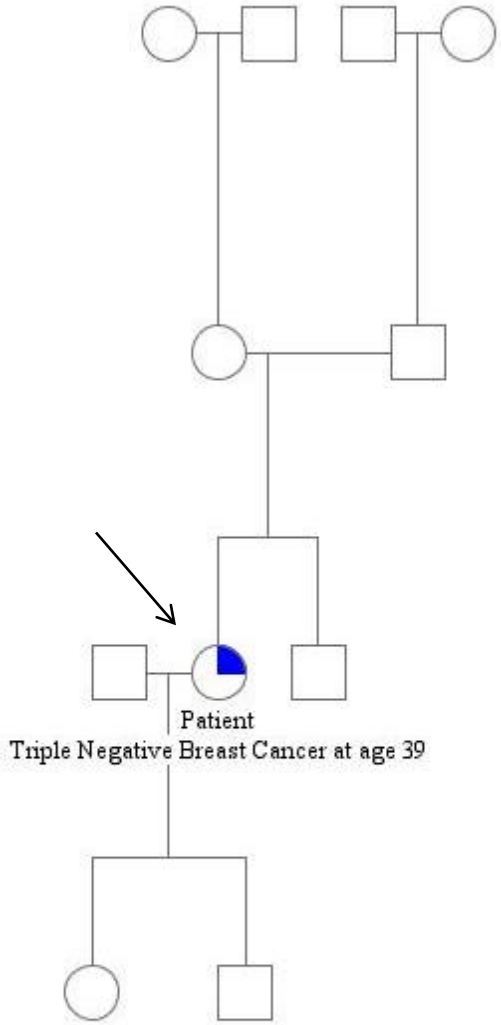
Action:

1. Missed opportunity: Refer
2. Refer
3. Seek advice
4. Do not refer: Relatives seek advice
5. Do not refer: Referral not indicated

Rory O'Sullivan







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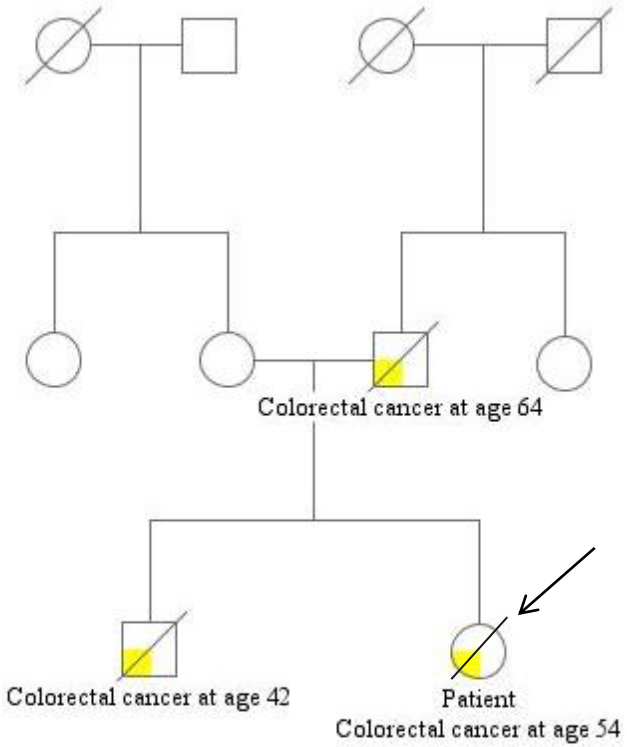

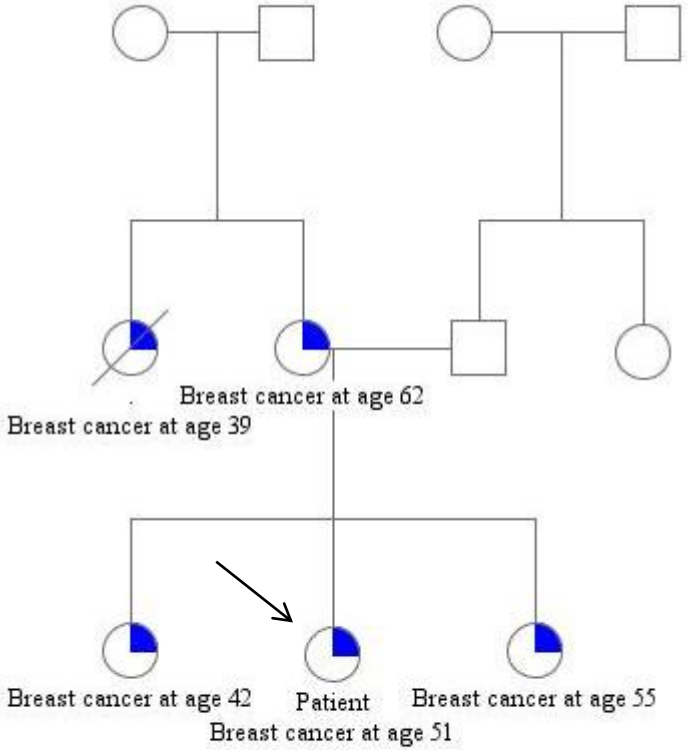

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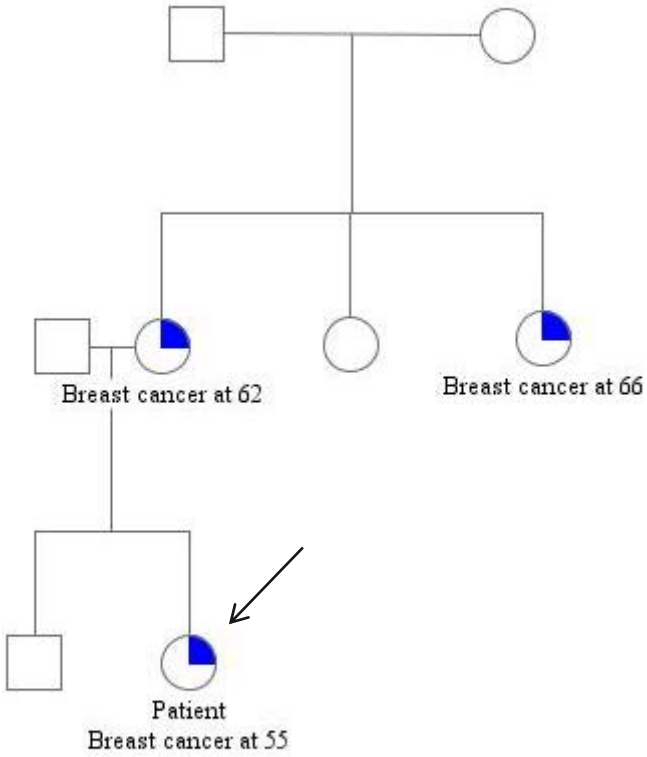

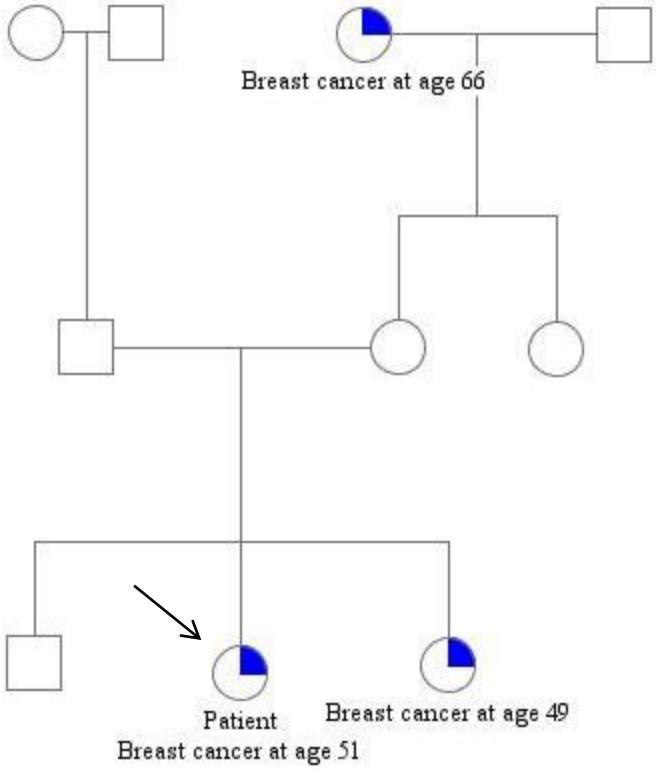

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J Community Genet (2017) 8:267–273
DOI 10.1007/s12687-017-0317-5

ORIGINAL ARTICLE

Inclusion of diverse populations in genomic research and health services: Genomix workshop report

Savio S. Mathew[1] · Julian Barwell[2] · Nasaim Khan[3] · Ella Lynch[4] · Michael Parker[5] · Nadeem Qureshi[6]

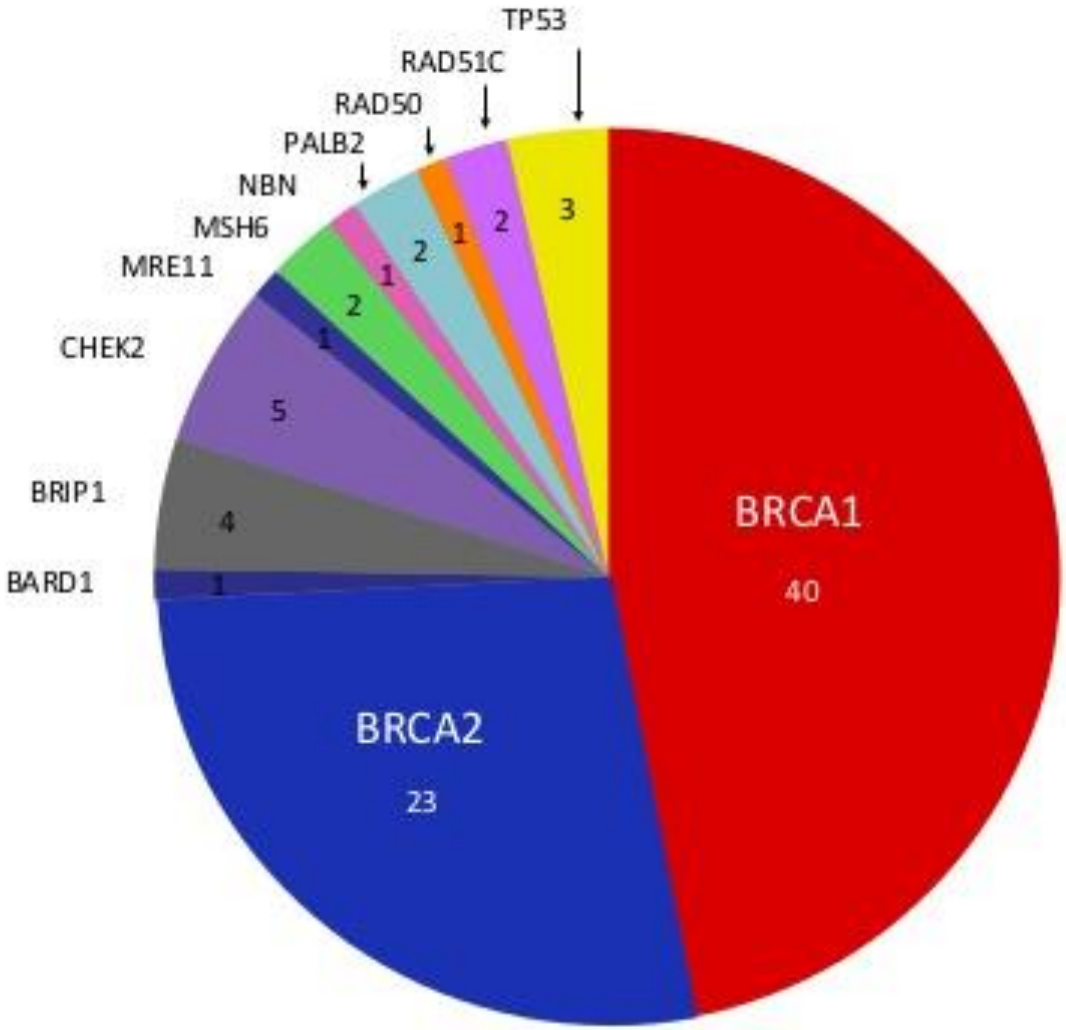
Received: 16 April 2017 / Accepted: 29 June 2017 / Published online: 28 July 2017

Abstract Clinical genetic services and genomic research are rapidly developing but, historically, those with the greatest need are the least to benefit from these advances. This encompasses low-income communities, including those from ethnic minority and indigenous backgrounds. The "Genomix" workshop at the European Society of Human Genetics (ESHG) 2016 conference offered the opportunity to consider possible solutions for these disparities from the experiences of researchers and genetic healthcare practitioners working with underserved communities in the USA, UK and Australia. Evident from the workshop and corresponding literature is institutions involved in funding research, commissioning and redesigning genetic health services also need to be adequately represented by underserved populations with intrinsic mechanisms to disseminate good practice and monitor participation. Further, as genomic medicine is mainstreamed, educational programmes developed for clinicians should incorporate approaches to alleviate disparities in accessing genetic services and improving study participation.

Keywords Disparities · Genetic services · Ethnic minorities · Indigenous populations · Genomic research

BRCA1/BRCA2 mutations in ovarian cancer (UW, Seattle, USA)

Ovarian cancer: BRCA1/BRCA2 mutations in **63/360 (18%)** patients not selected for family history or age at onset



Walsh, Swisher et al. *PNAS* 2011

Courtesy of MC King, UW

Genetic Testing in Phaeos

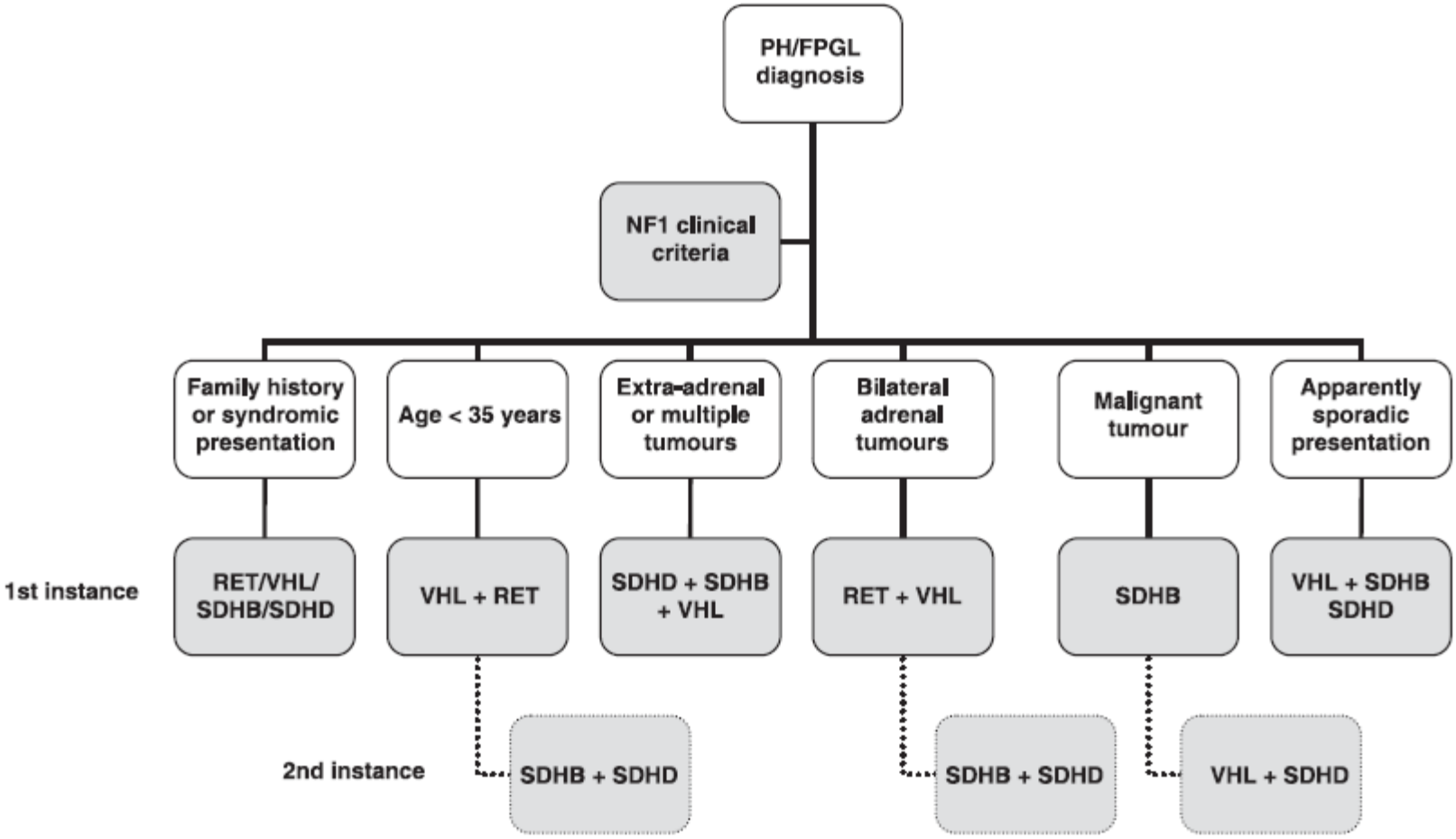
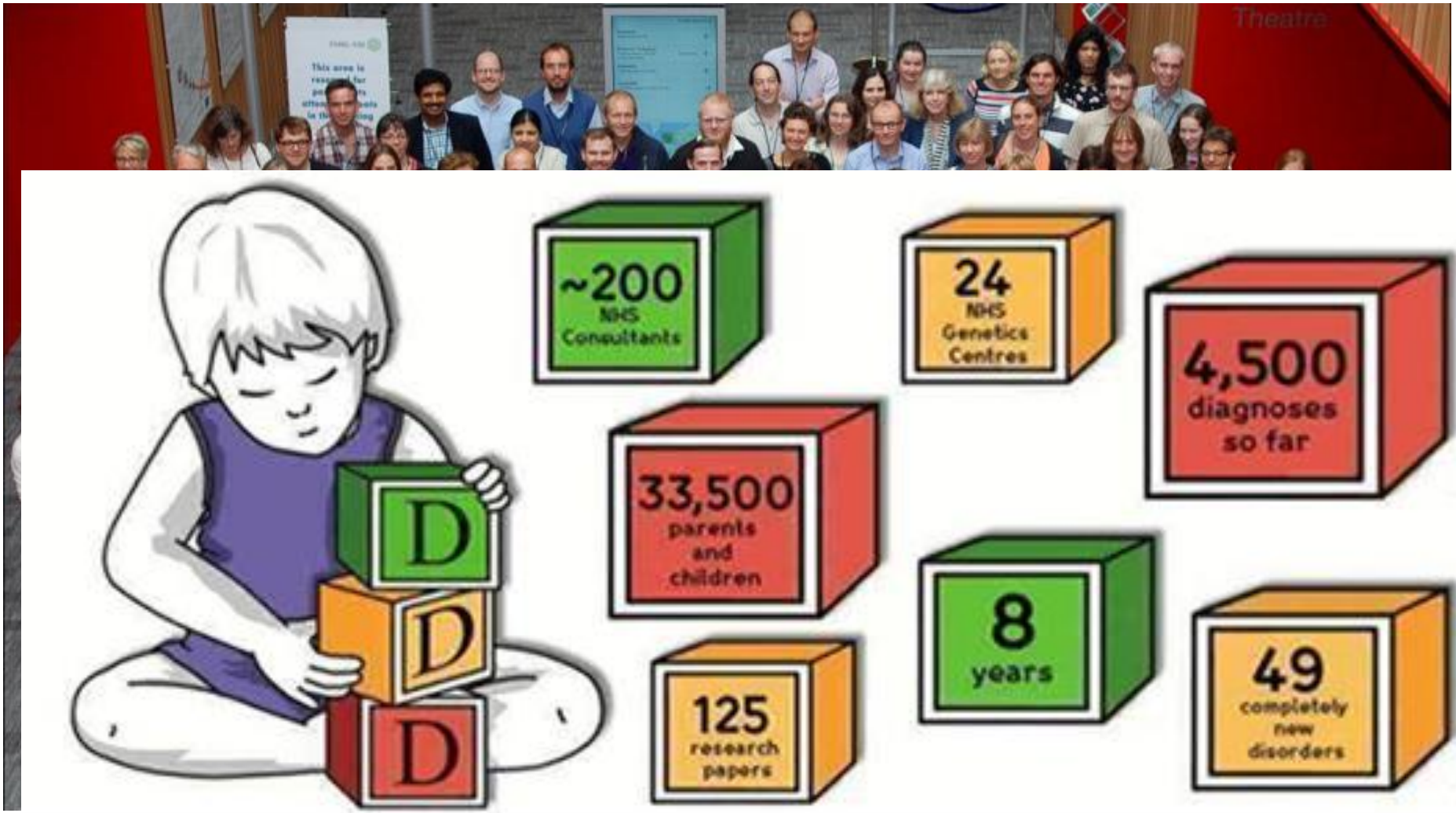


Fig. 1 The ENS@T PH/FPGL genetic screening algorithm.



National Institute for Health Research

Health Innovation Challenge Fund

Department of Health

wellcome trust

wellcome trust sanger institute

Highlights of DDD

- **Recruited: 13,963 families consented**
- **Discovery of more than 50 new genes**
- **125 Publications including Lancet, Nature, Science and Nature Genetics**
- **Diagnostic yield from trio exomes up to ~43%**
- **Ongoing research analyses of 4,295 families**
- **Growing portfolio of >100 Complementary Analysis Projects**
- **Partnership with Genomics England**
- **Securing core institutional funding at Sanger to continue research analyses until 2021**

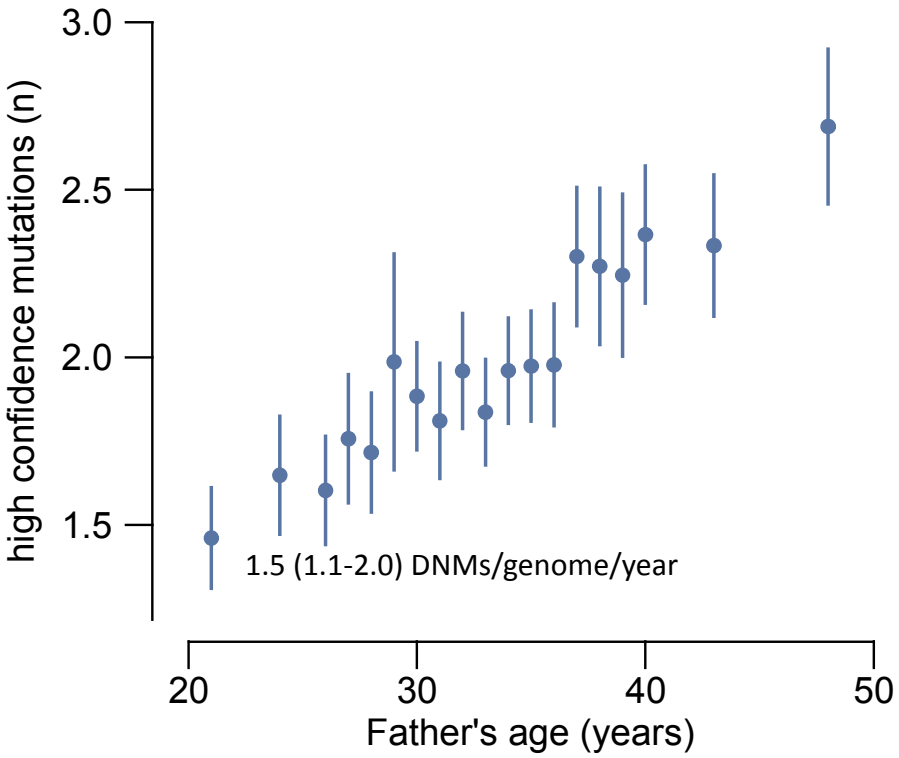
Prevalence of severe dominant disorders

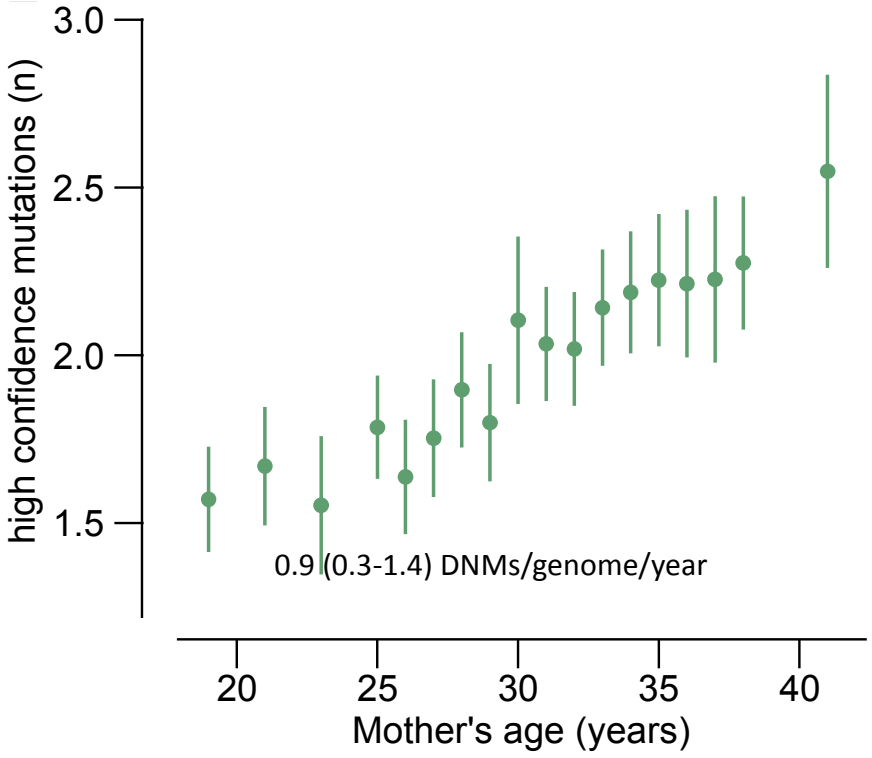
- Based on 4,300 families from the DDD study
- Estimate 1/300 pregnancies carry new, pathogenic mutation
  - >500 genes associated
  - Only know gene for ~60% of these disorders
  - Many not visible by ultrasound (e.g. severe intellectual disability)
- Equivalent burden to trisomies
  - Doesn't include recessive disorders
  - Single gene disorder burden > trisomy burden
- Can we identify subset at high risk?
  - Neither parent affected
  - Pre-conception testing is uninformative

Nature, January 2017

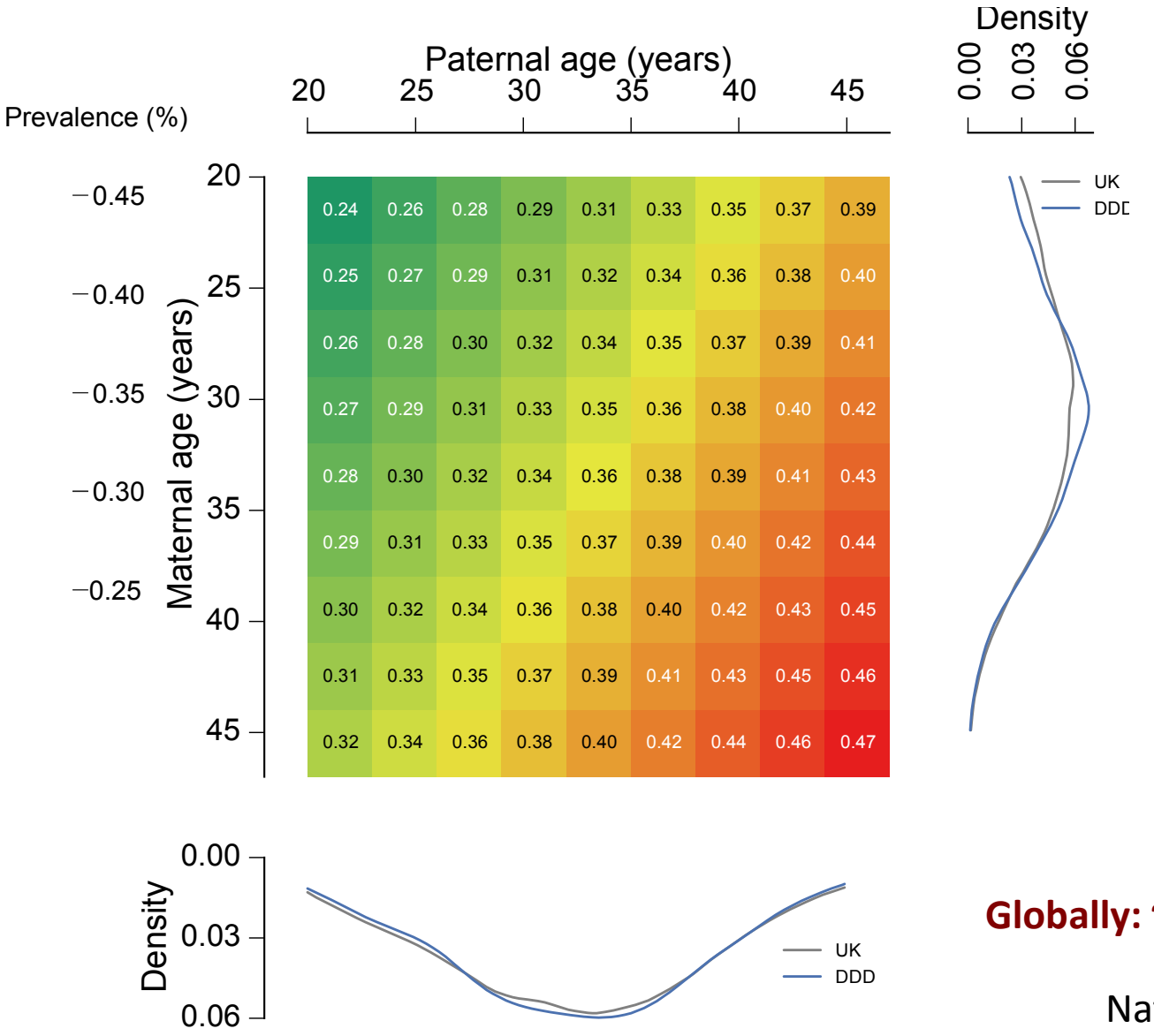
Increasing parental age, more mutations, increased risk

75-80% of *de novo* mutations come from Dad





Estimated age-dependent birth prevalence



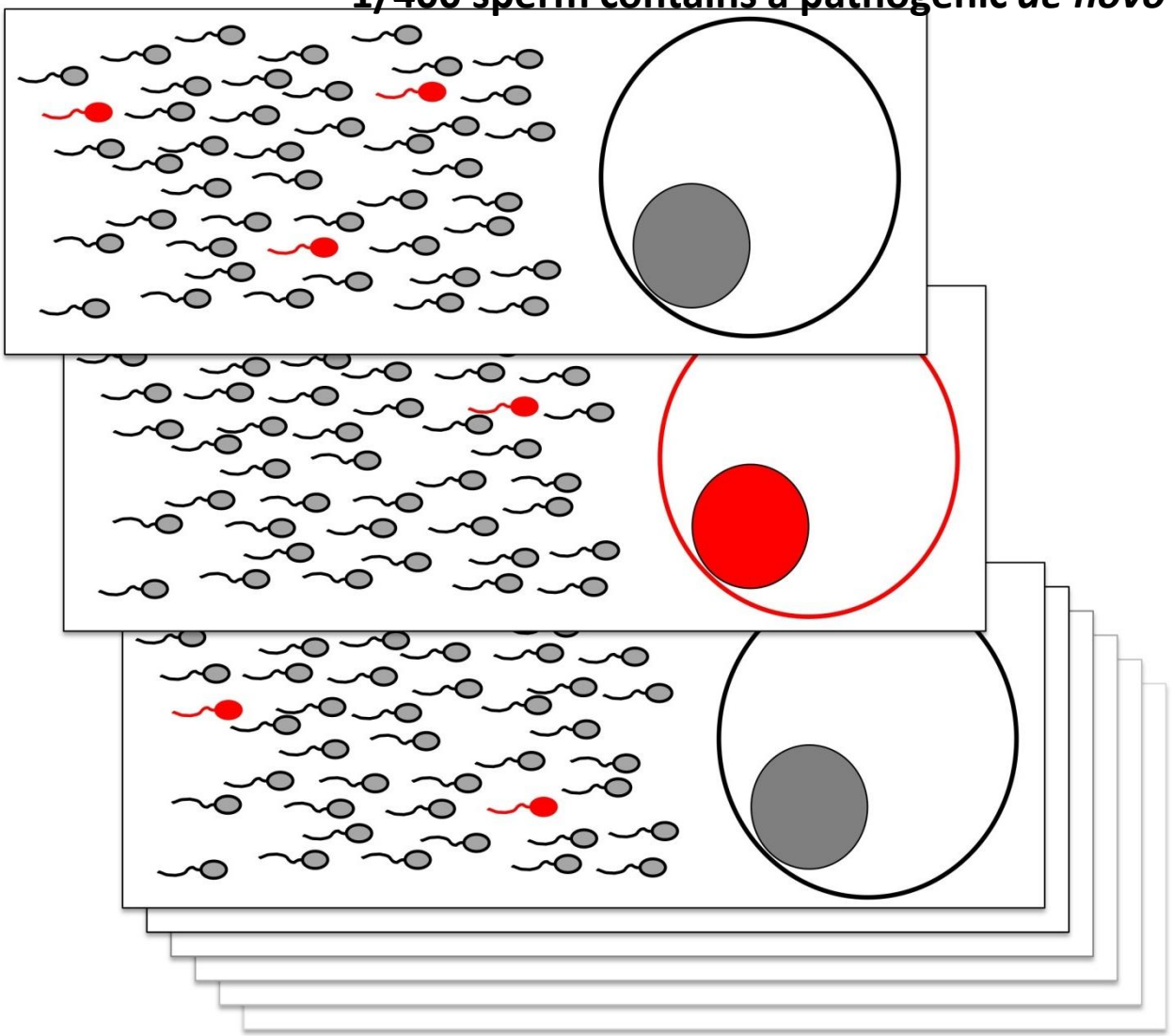
Globally: ~400,000 born/year

Nature, January 2017

Every conception is a lottery

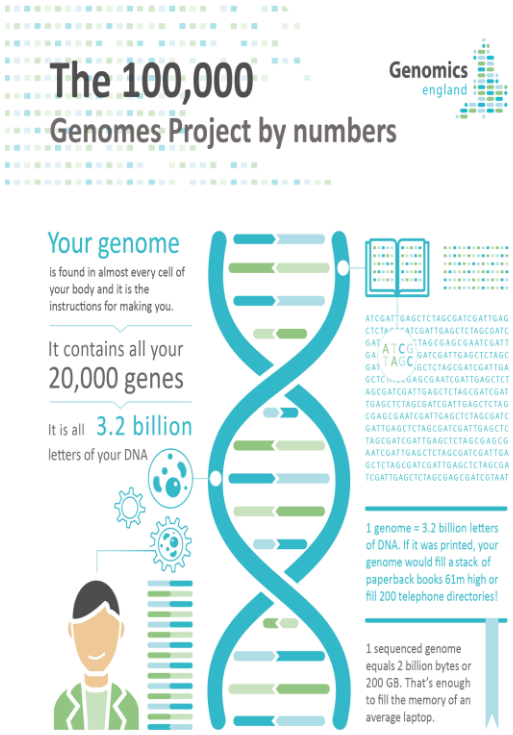
1/1,400 eggs contains a pathogenic *de novo* mutation

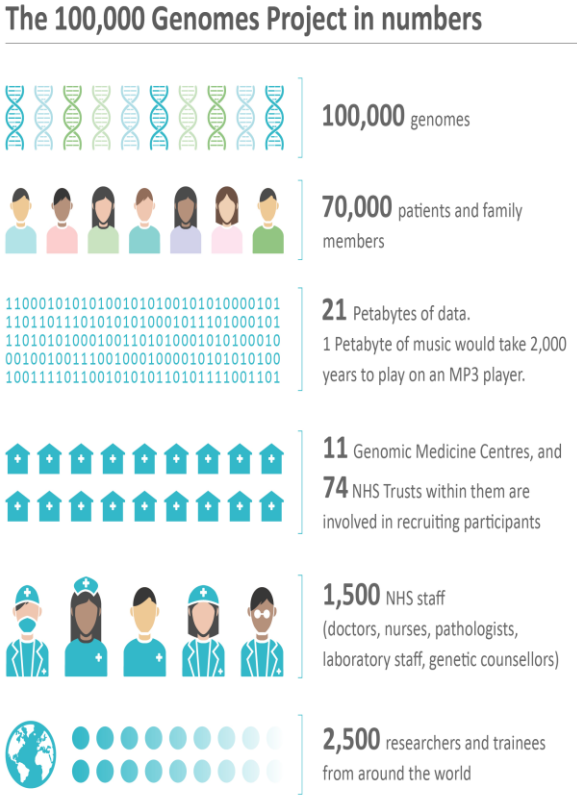
1/400 sperm contains a pathogenic *de novo* mutation

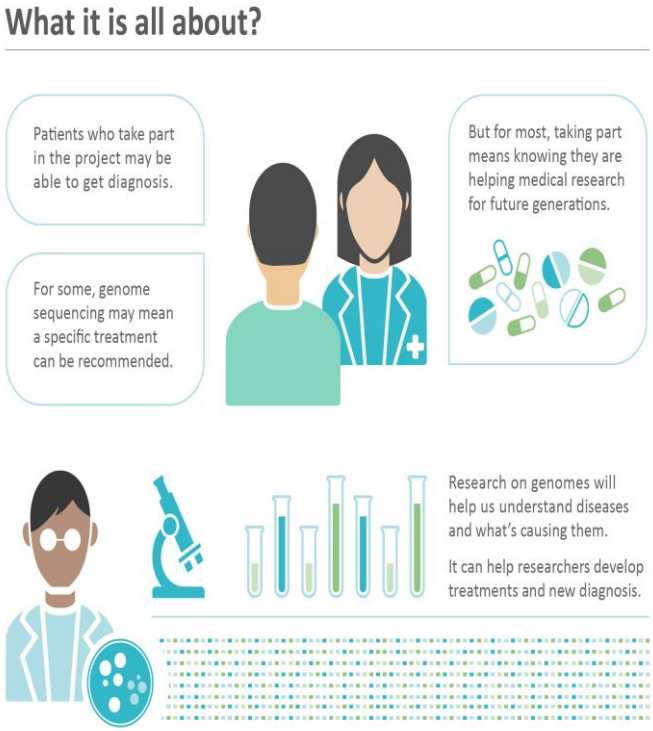


100,000 genomes project

Genomics england







Sir John Chisholm, Professor Mark Caulfield, Professor Sue Hill OBE and Tom Fowler

Discussion Points: Potential patients in the 100.000 Genome Project

Data Storage

- Integrated EPR, stored for life, for use in healthcare.
- Anonymised and data protected.
- Patient agrees to allow viewing of unidentifiable data with researchers and approved companies but the data cannot be taken off the database.
- Patient may be contacted by future research projects (participation optional).

Testing

- Uses whole genome sequencing and is the best chance of identifying a causative mutation. Finding no mutation does not exclude an inherited link.
- Not NHS diagnostic lab grade testing and results will need NHS lab confirmation.
- Need to confirm any findings through appropriate clinical and molecular investigations.
- Patient can withdraw at any time.

Incidental Findings

- Incidental findings are OPTIONAL and include;
  - Additional Findings (Table 1), Carrier status if both parents agree-mother only required if X-linked (Table 2). This list is likely to change through the project.
- May not detect all mutations with this technology e.g. SMA and thalassaemia
- Need to confirm any findings through appropriate clinical investigations.
- Findings of unknown clinical significance will not be reported.

Insurance

- Any findings from 100,000 Genome project DO NOT need to be disclosed to insurer
- Disclosure is not required if confirmed with NHS molecular testing
- Is disclosure required if confirmed with NHS clinical investigations i.e. if have a disease? Yes
- Need to disclose: Strong Family History, Medical investigations and Medical Treatment
- Diagnostic findings may affect ALL types of Insurance
- Predictive findings may affect: Life, Critical Illness, Income protection insurances, ONLY.

Table 1: Additional Findings

Adult onset:

- Hereditary non-polyposis colorectal cancer / Lynch-syndrome
- MYH-Associated Polyposis
- Hereditary Breast and Ovarian Cancer
- Child and adult onset:
- Familial Adenomatous Polyposis
- Von HippelLindau Syndrome
- Multiple endocrine Neoplasia Type 1
- Multiple endocrine Neoplasia Type 2
- Familial Medullary Thyroid Cancer
- Familial Hypercholesterolaemia

Child onset:

- Retinoblastoma

Table 2: Carrier Testing

Autosomal recessive conditions (both parents will be tested for these):

- Sickle Cell Anaemia
- Cystic Fibrosis
- Alpha Thalassemia
- Beta Thalassemia
- Congenital Adrenal Hyperplasia 21
- Spinal Muscular Atrophy Type I

X-Linked conditions (only the mother will be tested for these):

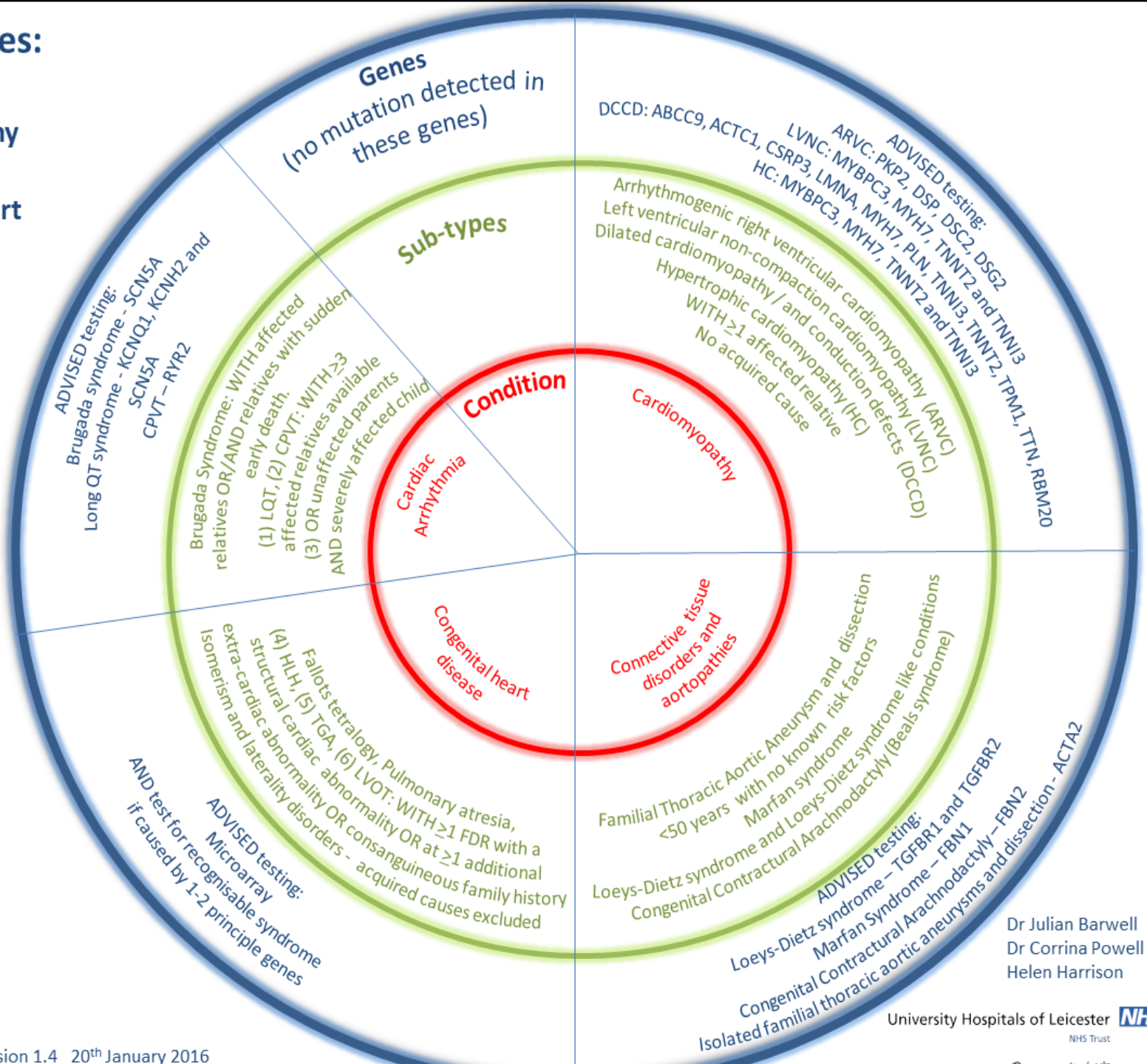
- Duchenne Muscular Dystrophy
- Adrenoleukodystrophy
- Haemophillia A

Dr Corrina Powell

Rare Diseases: Cardiology

Cardiomyopathy and Congenital heart disease

(1) Long QT Syndrome
(2) Catecholaminergic polymorphic ventricular tachycardia
(3) Over 3 generations
(4) Hypoplastic Left Heart
(5) Transposition of Great Vessels
(6) Left Ventricular Outflow Tract Obstruction disorders

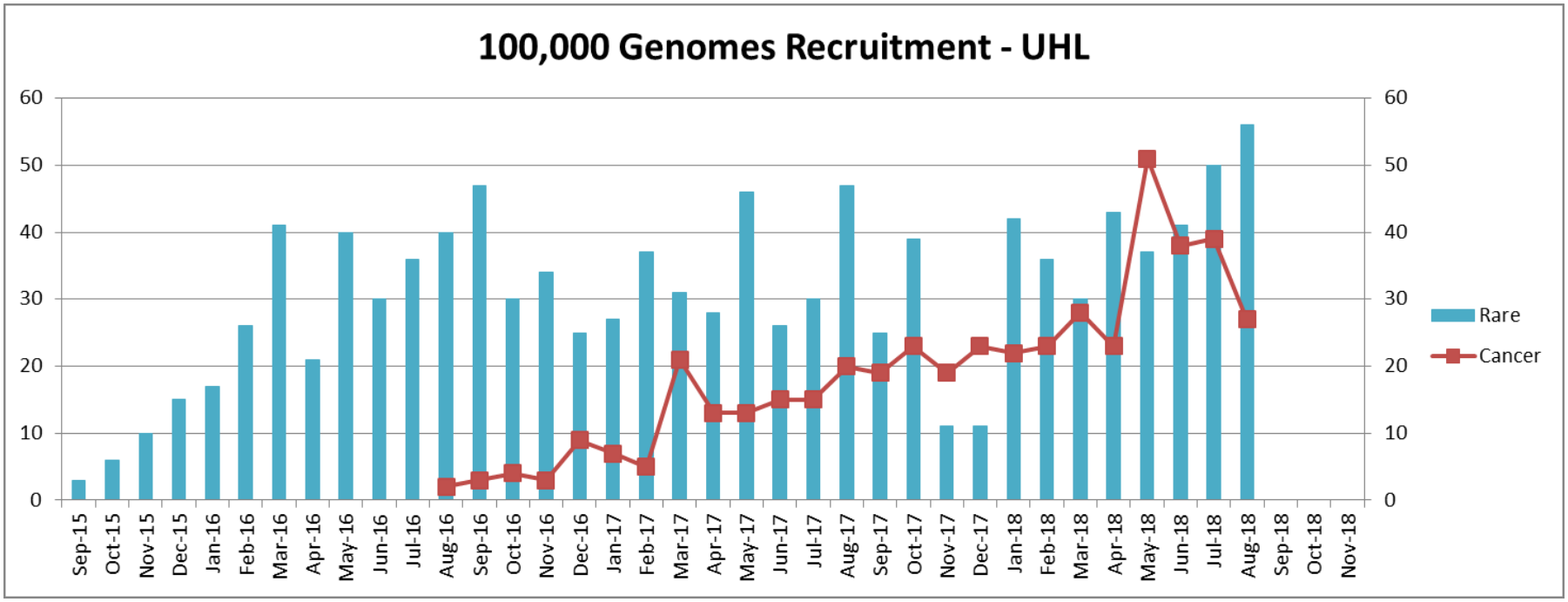


Dr Julian Barwell
Dr Corrina Powell
Helen Harrison

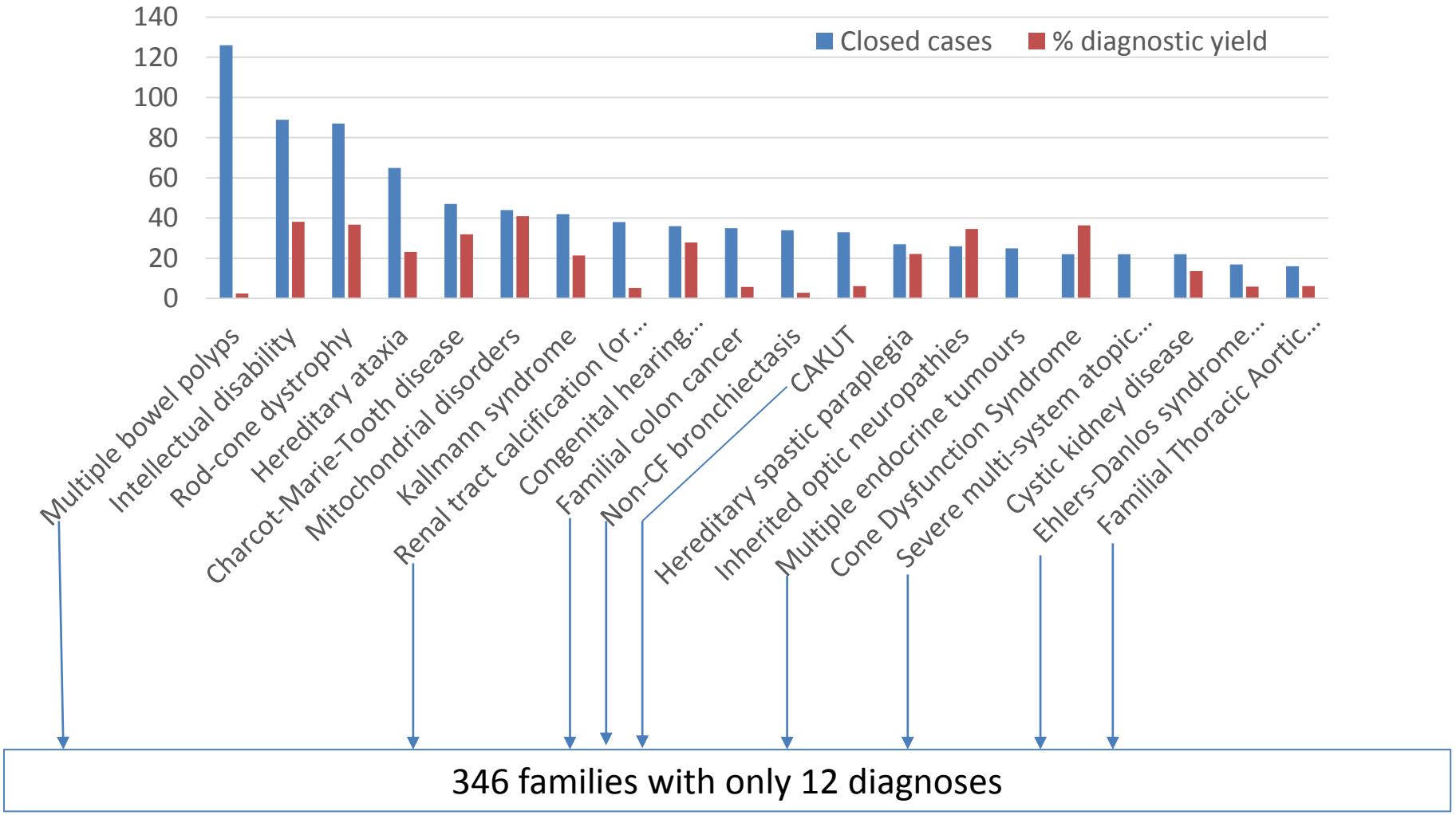
University Hospitals of Leicester NHS Trust

Eligibility Statement version 1.4 20th January 2016

Recruitment



Top 20 recruited diseases (pilot) and diagnostic yield



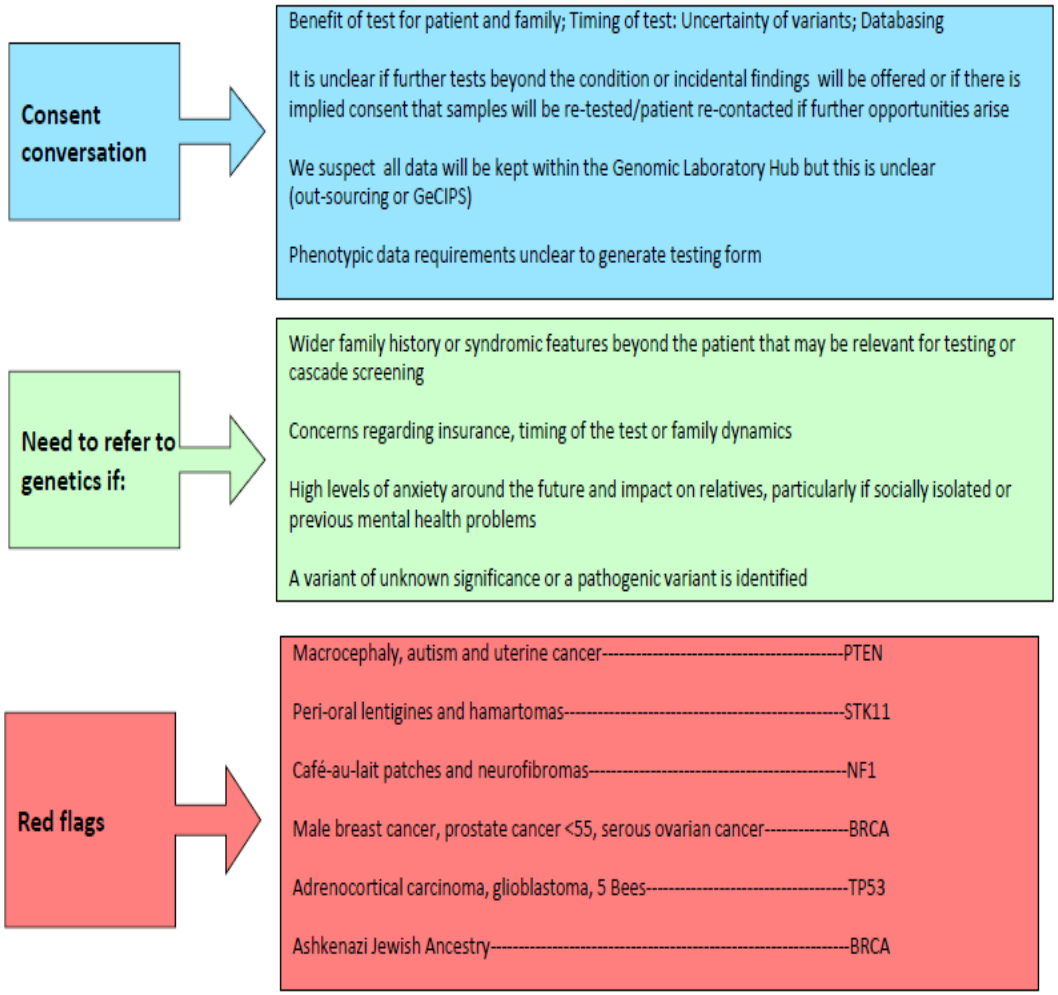
Test Directory: candidate clinical indications for WGS in 2018/19

- A range of conditions where Whole Genome Sequencing should be used have been identified
- NHS England will commission and fund WGS - Additional funding has been allocated

CANCER CLINICAL INDICATIONS
Neurological Tumour
Sarcoma
Acute Myeloid Leukaemia
Acute Leukaemia other
Blastic Plasmacytoid Dendritic Cell Neoplasm
Acute Lymphoblastic Leukaemia
Paediatric tumours

RARE DISEASE CLINICAL INDICATIONS
Acutely unwell infants with a likely monogenic disorder
Congenital malformation and dysmorphism syndromes
Floppy infant with a likely central cause
Moderate, severe or profound intellectual disability
Ultra-rare and atypical monogenic disorders
Rare syndromic craniosynostosis or isolated multisuture synostosis
Skeletal dysplasia
Neonatal diabetes
Likely inborn error of metabolism - targeted testing not possible
Arthrogryposis
Cerebellar anomalies
Cerebral malformation
Childhood onset hereditary spastic paraplegia
Childhood onset leukodystrophy
Early onset or syndromic epilepsy
Hereditary ataxia with onset in adulthood
Hereditary ataxia with onset in childhood
Holoprosencephaly - NOT chromosomal
Hydrocephalus
Other rare neuromuscular disorders
Severe microcephaly
Cystic renal disease

Recruitment to the GLH test directory



Personal communication of Dr Barwell, shared with permission

5 ways of interpretation of genetic result

Literature search for the variant in other individuals affected by bowel cancer
databasing

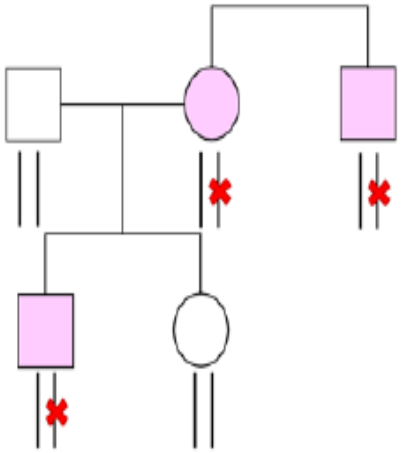
Do members of the family who have a mutation develop the disease-

co-segregation

Is the variant associated with change in amino acid or change in reading frame may have variable effect on the protein

Chemistry

Normal sequence: CAT GCT AAC
Frame shift: CAT GTA ACC *(truncated protein)*
Base change: CAT TCT AAC *(variable effect)*

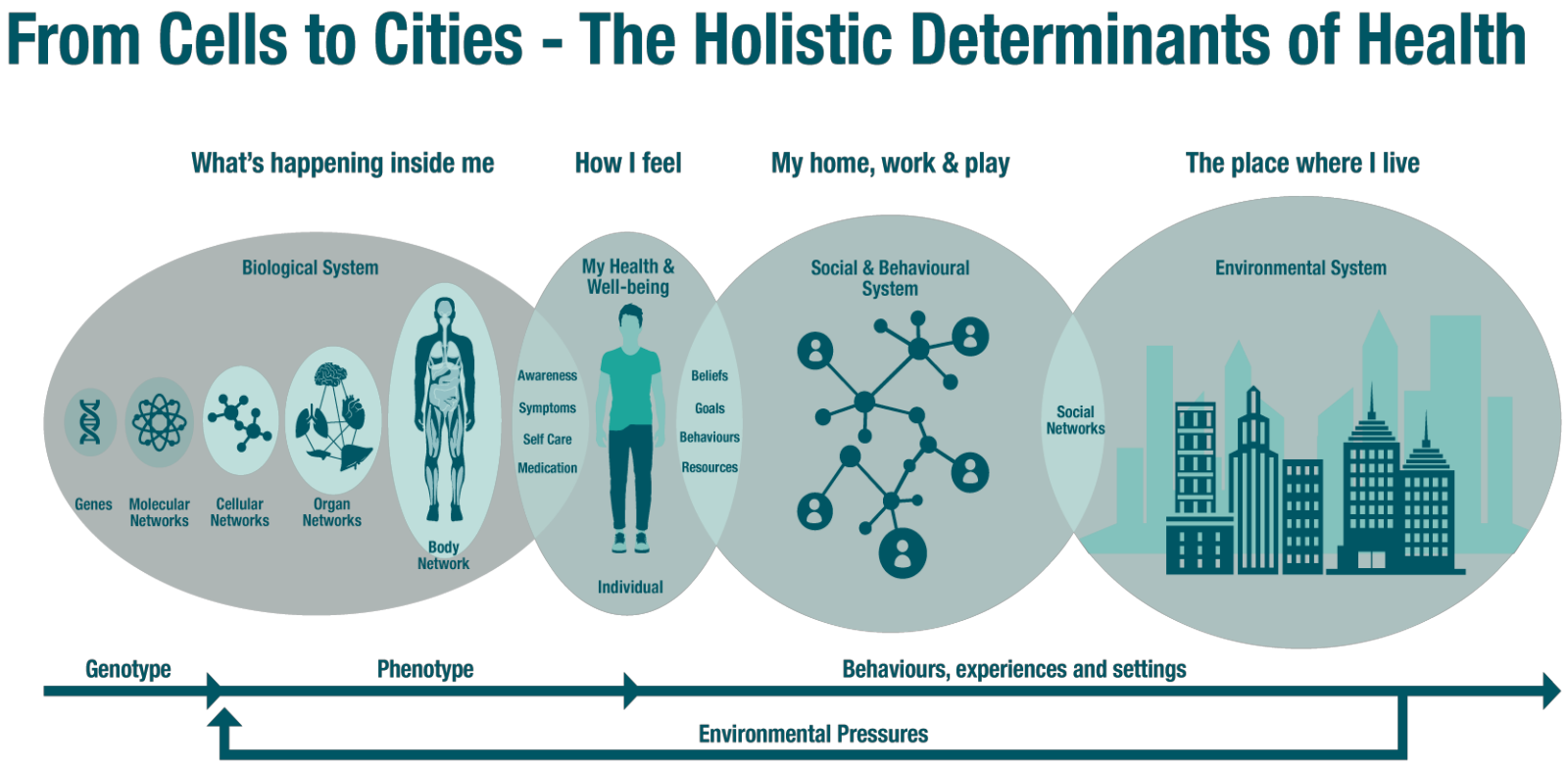


Is the protein produced result in normal function? Functional *in vitro* studies

Is the position preserved in other species which would be suggestive that it is important for survival

Sequence homology through evolution

The 21st Century health challenges call for a wider framing of the healthcare landscape

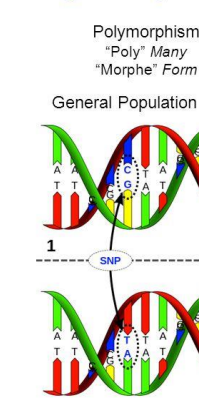


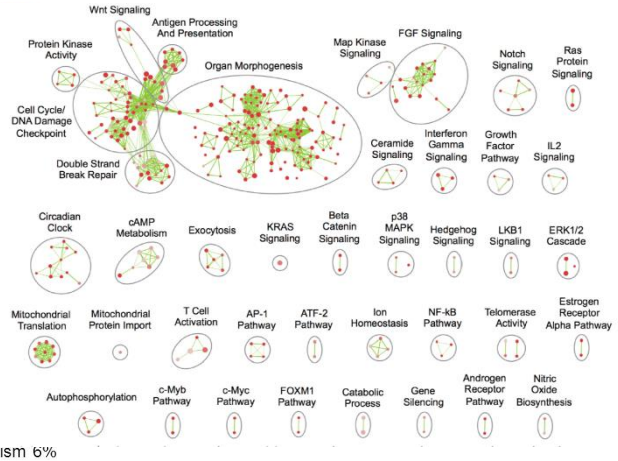
Can we improve on basic biomarkers?

Do we have anything to add for complex disease and treatment?

Single Nucleotide Polymorph

- The most common cause of genetic variation
- SNPs occur on average every 1000 bases
- Understanding SNPs has shown promise for improving disease detection and treatments





P3 Personalized Pharmacogenetic Profile

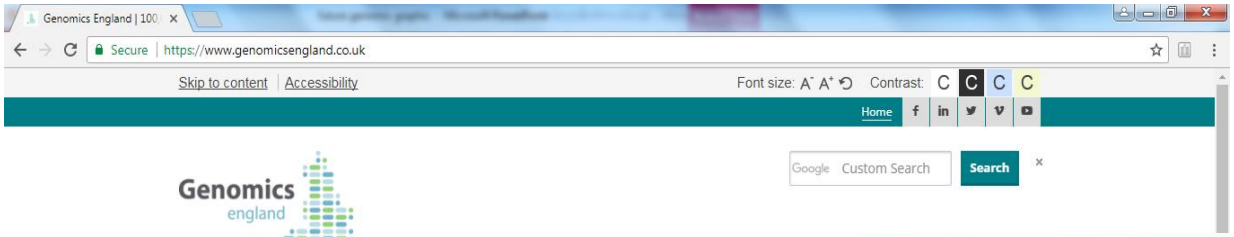
All patients with same diagnosis.

Not all respond to the same medications.

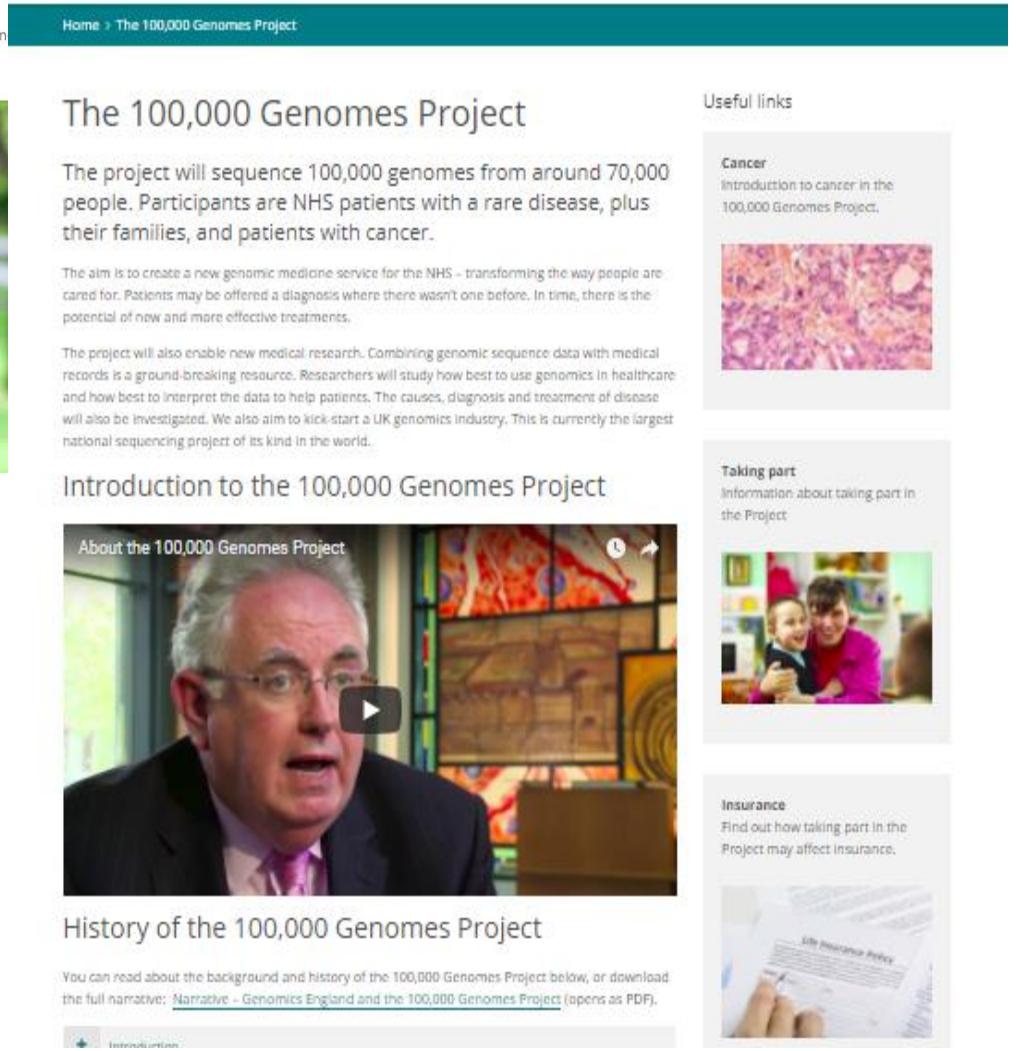
P3 - Normal
Treat with conventional dose

P3 - Moderate risk
Consider alternative drug or dose

P3 - Elevated risk
Treat with alternative drug or dose

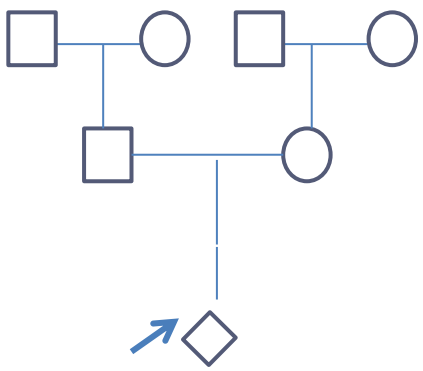


Germline, somatic, circulating DNA
Microbiome, pharmacogenomics



1. Treat disease for what it is, not what it looks like
2. Treat on risk, not age
3. Look beyond single genes
4. Machine learning and building an equation of life
5. Understand human variation

NIPD:FGFR3-Skeletal Dysplasia



Sheffield Diagnostic Lab
Compound heterozygous gene **ALPL**

CONFIRMED DIAGNOSIS HYPOPHOSPHATASIA

Orphanet Journal of Rare

BioMed Central

Review

Open Access

Hypophosphatasia

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The symptoms are highly variable in their clinical expression, which ranges from stillbirth without mineralized bone to early loss of teeth without bone symptoms. Depending on the age at diagnosis, six clinical forms are currently recognized: perinatal (lethal), perinatal benign, infantile, childhood, adult and odontohypophosphatasia. In the lethal perinatal form, the patients show markedly impaired mineralization *in utero*. In the prenatal benign form these symptoms are spontaneously improved. Clinical symptoms of the infantile form are respiratory complications, premature craniosynostosis, widespread demineralization and rachitic changes in the metaphyses. The childhood form is characterized by skeletal deformities, short stature, and waddling gait, and the adult form by stress fractures, thigh pain, chondrocalcinosis and marked osteoarthropathy. Odontohypophosphatasia is characterized by premature exfoliation of fully rooted primary teeth and/or severe dental caries, often not associated with abnormalities of the skeletal system.

The disease is due to mutations in the liver/bone/kidney alkaline phosphatase gene (*ALPL*; OMIM# 171760) encoding the tissue-nonspecific alkaline phosphatase (TNAP). The diagnosis is based on laboratory assays and DNA sequencing of the *ALPL* gene. Serum alkaline phosphatase (AP) activity is markedly reduced in hypophosphatasia, while urinary phosphoethanolamine (PEA) is increased. By using sequencing, approximately 95% of mutations are detected in severe (perinatal and infantile) hypophosphatasia.

Committees
Select Committee report lobbying
Patient resources
Patient Champions
Helplines
Research Space
Academic partnerships
International group advice
Webinar for professionals

A huge thank you!

https://www.youtube.com/watch?v=3HGwkK5LuoY
https://www.youtube.com/watch?v=IebHOk9SpwA
https://www.youtube.com/watch?v=hEU8IzGUmv4

You Tube
Triage support
Community events
Equality of access
Media
Study aids
Academic papers
Oversight & Insight
Support for adopted women

Commercial testing

Challenge/opportunities arising from commercial genomic testing	Why	Examples and specific technical details	Recommendation
1. Calibration	Do we trust the accuracy of the test? Could significant findings be missed	Not all tests look at DNA sequence/ amount from both parents in detail [SNP vs NGS, CNV and MLPA]	All labs have ISO 15189 accreditation thereby improving capacity
1. Consent prior to undergoing the test	Does the patient understand the limitations and implications?	The variety and complexity of potential results integrated into a person's socio-cultural and health background makes consent challenging	Ensure all companies have tests available and written information approved with medical device legislation and adhere to test directory standard of evidence
1. Context and validity of the result interpretation in unaffected patients with no family history	Without a relevant family history, is the interpretation and predictive power meaningful?	Ascertainment bias on how original data collected on inherited diseases can impact on interpretation of findings and alter predicted risk	Private companies should help pay for NHS validation and interpretation of findings
1. Clinical utility of the results and identifying carrier status in children	Does the result have a useful clinical intervention to lower disease burden?	Clinical grade genomic tests require linked evidence based interventions. Otherwise fatalism and carrier stigmatisation is a risk	Limit access tests for to non-actionable findings or insist on pre-test counselling. An ethical review on carrier testing is required.
1. Capacity to respond to the results	Can we offer downstream medical support to patient and family?	Cost effective and affordable are different in ring-fenced budgets	Health economic integration of diagnostics/therapeutic
1. Caldicott principle for data protection	Is the data secure and could it be used to identify or target people?	Highly sensitive data that predicts risks could be used to identify and discriminate against individuals	Legislation on the use and misuse of commercial data and moratorium with insurance companies
1. Cascading and Controls	Will the DNA be sent to NHS lab when testing at-risk relatives?	When cascading results in NHS to relatives, we need affected patient DNA (control)	All laboratories should release positive control DNA to NHS
1. Commercial forces and staffing in laboratories for clinical scientists	Will NHS trained staff join the private sector for higher wages?	The private sector may not have the training/governance challenges of the NHS and be more competitive	Public/Private partnership debate and consider STP training contract at outset
1. Continuing Professional Development for clinicians explaining results to patients	Will most doctors be able to understand/critically assess the data?	Many doctors find this a challenging area and a lack of results to date makes it feel irrelevant to their practice	Mandatory e-learning package for talking to patients, use of test directory and variant interpretation
1. Competition from other Countries	Can we compete at scale and pace with other groups keen to access big data sets?	A number of international competitors e.g. BGI/China National Gene bank are able to sequence at pace and scale	Drive life science industries and continue integration with NIHR and academic institutes

- A. Align commissioning between diagnostics and precision medicine taking into consideration proposed reconfigurations
- B. Develop local services with e-training for clinicians, staff retraining and recruitment of bioinformaticians
- C. Invest in digital health technologies for presenting actionable findings in a useful way for busy non-specialist clinicians
- D. Transform medical care predicated on accurate genomic information in a world beyond cultures and microscopes.
- E. Mobilise the Clinical Research Network to help assess change in practice in the longer term
- F. Defining the most useful tests may be different for each condition and requires economic modelling
- G. Develop and innovate inclusive genomic medicine access, diagnostics and therapeutic interventions
- H. Ensure confidentiality and data protection
- I. Commission additional research to discover how patients understand and respond to complex risk
- J. Clarify and evaluate impacts of Brexit on university grants and data/sample transfers