

# Genomics for Rare Diseases

Gemma Chandratillake & Karola Rehnström

East of England NHS Genomic Medicine Centre  
21<sup>st</sup> March 2018



# Overview

- The genetic basis of rare disease
- Why is it useful to know the genetic change that causes your rare disease?
- The problems of traditional genetic testing
- What is genomic testing?
- Genomic testing for rare disease: a brief history
- The 100,000 Genomes Project
- Types of results from a genomic test
- Things to consider if taking part in a genomic study
- After the project: genomics in the NHS

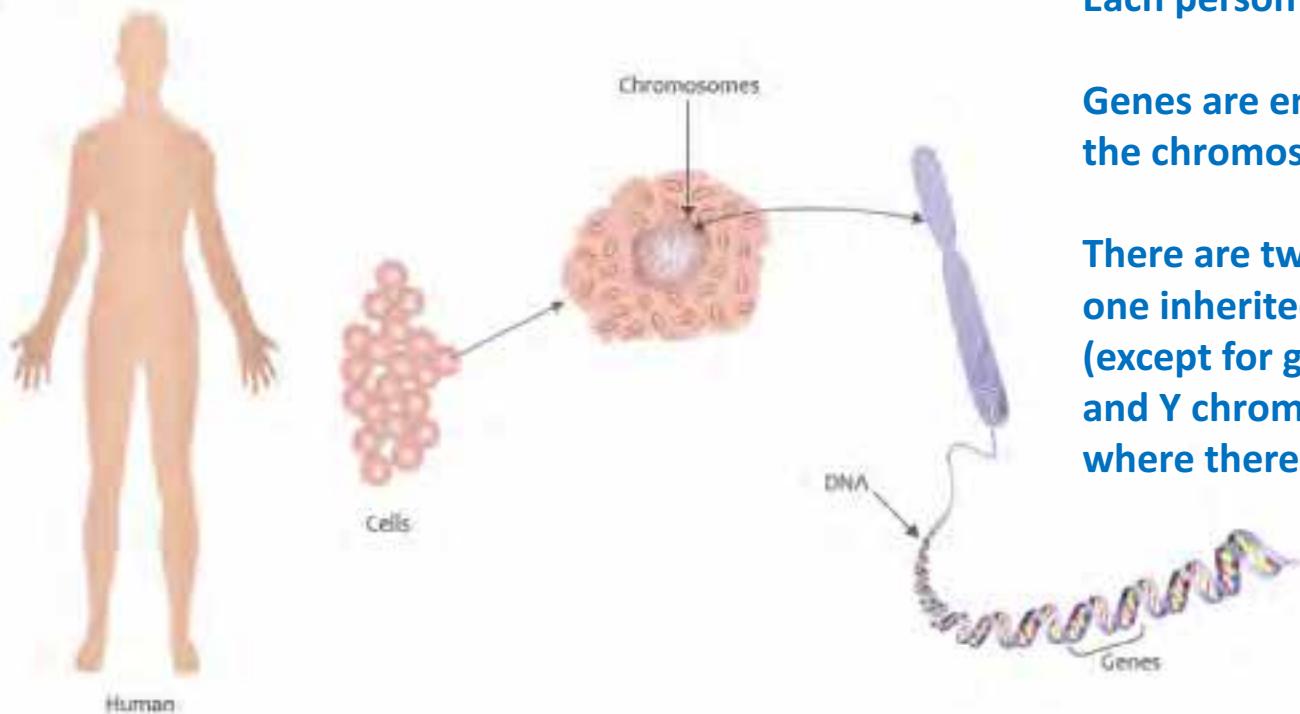
# Genes and DNA

Genes are the instructions for building our bodies and making them work.

Each person has ~20,000 genes.

Genes are encoded in the DNA of the chromosomes in each cell.

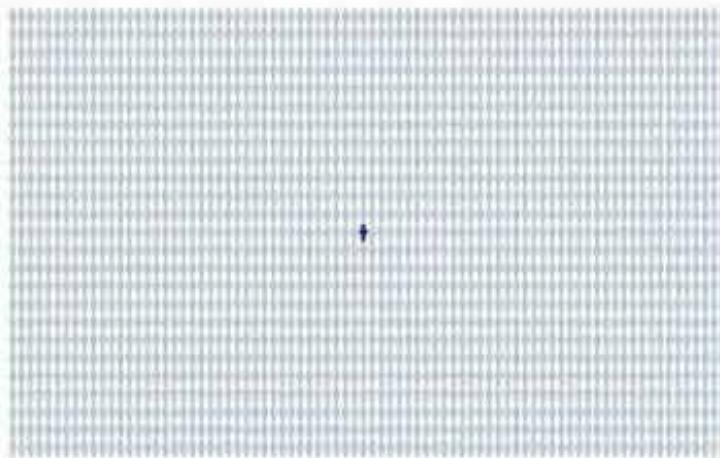
There are two copies of each gene, one inherited from each parent (except for genes that lie on the X and Y chromosomes in males, where there is only one copy).



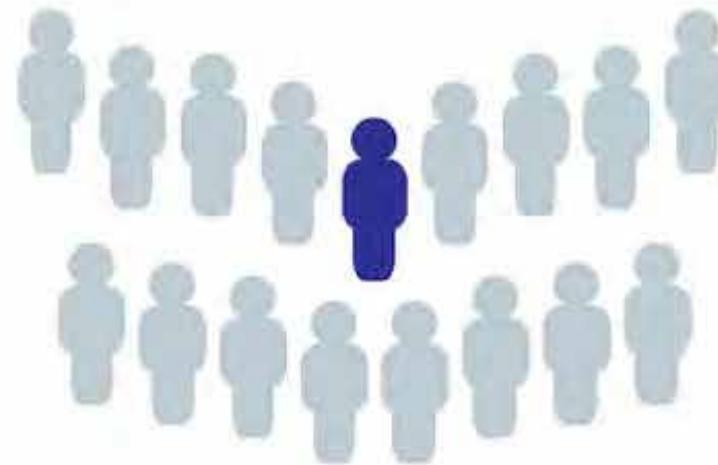
# Genetic Basis of Rare Disease

## Rare diseases: facts and figures

The UK defines a 'rare disease' as one that affects **1 in 2,000** or less of the population...



... so, collectively, rare disease will affect **1 in 17** of the population at some point in their life

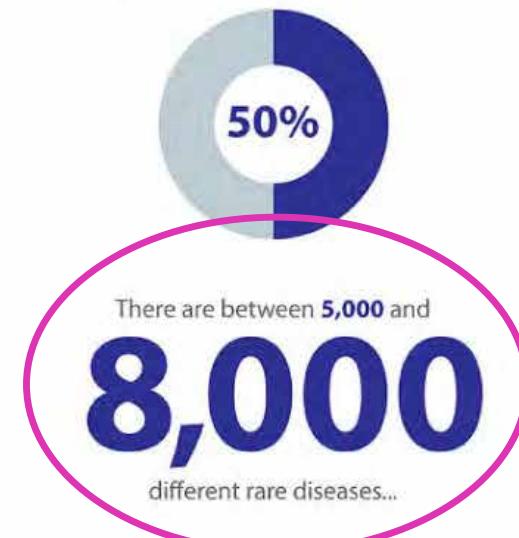


# Genetics Basis of Rare Disease

In total, that's about **3 million** people currently in the UK who will be affected by a rare disease



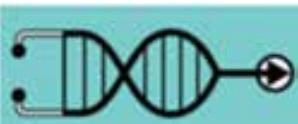
**50%** of newly diagnosed cases of rare diseases are in children



... and **80%** of them have a known **genetic origin**



© National Genetics and Genomics Education Centre

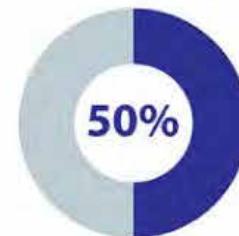


# Genetics Basis of Rare Disease

In total, that's about **3 million** people currently in the UK who will be affected by a rare disease



**50%** of newly diagnosed cases of rare diseases are in children

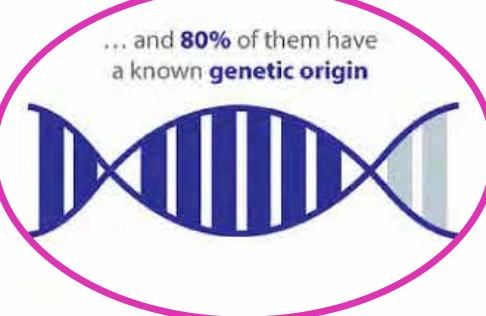


There are between **5,000** and

**8,000**

different rare diseases...

... and **80%** of them have a known **genetic origin**



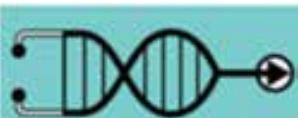
© National Genetics and Genomics Education Centre

 @genomicsedu

[www.genomicseducation.hee.nhs.uk](http://www.genomicseducation.hee.nhs.uk)

 /genomicsedu

  
**East of England**  
NHS Genomic Medicine Centre



# Genetic Testing for Rare Diseases

The goal of genetic testing is to make a **molecular genetic diagnosis**, meaning to identify the change(s) in the person's DNA that is causing their condition

- If they *don't have a clinical diagnosis*, genetic testing can provide one
- If they *do have a clinical diagnosis*, genetic testing can further *clarify* that diagnosis and/or *provide information for family members*

# The Importance/Utility of a Diagnosis

- To guide care (treatment, preventative)
- To provide prognosis, anticipatory guidance
- To put an end to unnecessary testing/treatment
  - Psychologically and financially costly
- To provide an answer, sense of closure
- Family planning (for individual and/or family)
  - Recurrence risk counseling
  - Pre-natal testing
  - Pre-implantation genetic diagnosis
- Family member testing
  - At-risk relatives (early intervention)
  - Carrier testing
- Participation in more relevant support/advocacy groups
- Participate in, and drive, research
  - Participate in clinical trials
  - Increasing availability of targeted therapies for rare diseases



Genet Med. 2015 Jun;17(6)

But...

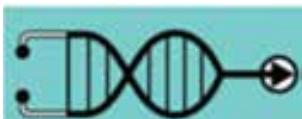
## **diagnostic odyssey**

/dajəgnastɪk ədəsi/

*noun*

1. The time taken between a patient first developing symptoms of their condition and receiving a correct medical diagnosis.

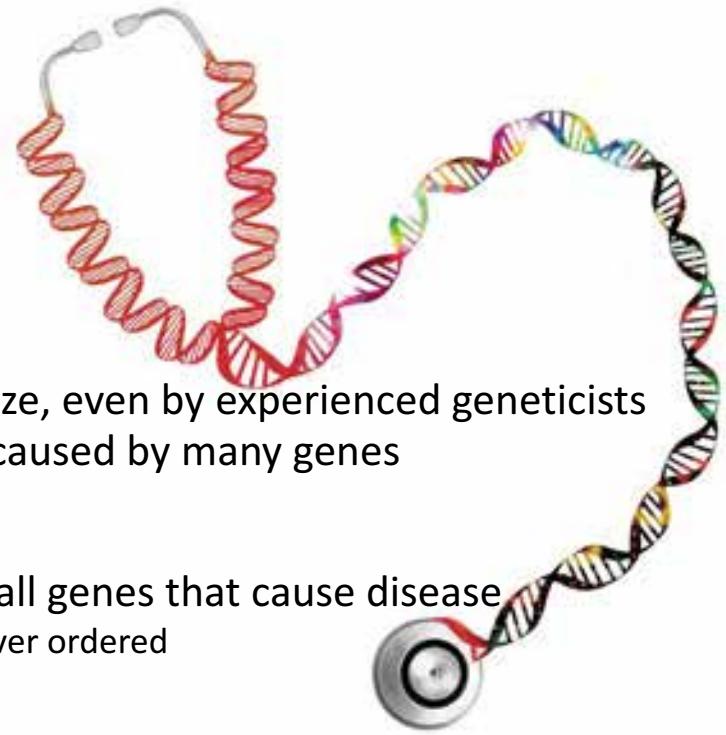
*“A rare disease patient’s diagnostic odyssey lasts on average four years.”*



# Genomics

- **Genome:** An individual's genetic information, made of DNA, contains genes but lots of other DNA too
- **Gene:** a sequence of DNA in the genome that is required for the production of a *functional product* (polypeptide/protein or RNA)
  - We have >20,000 genes in our genome
- **Exome:** the combined regions of the genome that contain the genes (only 1-2% of the genome), essentially the bit of the genome that we can interpret
- **Genetics:** the study of a particular gene
- **Genomics:** the study of many genes -> all of a person's DNA
  - Micro-arrays, multi-gene panels, exomes, genomes
  - Study made possible by development/advances in microarray technology and DNA sequencing technology (Next Generation Sequencing, NGS)

# Genomics & Rare Disease: The Promise



## The problems of traditional genetic testing:

- Many rare genetic disorders are difficult to recognize, even by experienced geneticists
- Many genetic disorders with clinical diagnosis are caused by many genes
  - difficult to pin-down exact underlying genetic cause
  - e.g. Retinitis pigmentosa, Charcot-Marie Tooth
- Clinical genetic tests have not been developed for all genes that cause disease
  - not cost-effective to develop/maintain a test that is never ordered

## The promise of genomics for individuals with a rare disease:

- Interrogate the genome to immediately identify the genetic cause of a disorder without the need for costly, time-consuming sequential genetic testing
- **Do away with the “diagnostic odyssey”**

# Genomics for Rare Disease: A Brief History

- 2010: First research showing exome sequencing could be used to identify new rare disease genes

# Genomics for Rare Disease: A Brief History

## **Exome sequencing identifies the cause of a Mendelian disorder**

- **Sarah B. Ng<sup>1,\*</sup>, Kati J. Buckingham<sup>2,\*</sup>, Choli Lee<sup>1</sup>, Abigail W. Bigham<sup>2</sup>, Holly K. Tabor<sup>2</sup>, Karin M. Dent<sup>3</sup>, Chad D. Huff<sup>4</sup>, Paul T. Shannon<sup>5</sup>, Ethylin Wang Jabs<sup>6,7</sup>, Deborah A. Nickerson<sup>1</sup>, Jay Shendure<sup>1,†</sup>, and Michael J. Bamshad<sup>1,2,8,†</sup>**

# Genomics for Rare Disease: A Brief History

## **Exome sequencing identifies the cause of a Mendelian disorder**

- **Sarah B. Ng<sup>1,\*</sup>, Kati J. Buckingham<sup>2,\*</sup>, Choli Lee<sup>1</sup>, Abigail W. Bigham<sup>2</sup>, Holly K. Tabor<sup>2</sup>, Karin M. Dent<sup>3</sup>, Chad D. Huff<sup>4</sup>, Paul T. Shannon<sup>5</sup>, Ethylin Wang Jabs<sup>6,7</sup>, Deborah A. Nickerson<sup>1</sup>, Jay Shendure<sup>1,†</sup>, and Michael J. Bamshad<sup>1,2,8,†</sup>**
- 2010: Lupski sequences *his* genome to identify molecular basis of *his* CMT

# Genomics for Rare Disease: A Brief History

ORIGINAL ARTICLE

- Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy

James R. Lupski, M.D., Ph.D., Jeffrey G. Reid, Ph.D., Claudia Gonzaga-Jauregui, B.S., David Rio Deiros, B.S., David C.Y. Chen, M.Sc., Lynne Nazareth, Ph.D., Matthew Bainbridge, M.Sc., Huyen Dinh, B.S., Chyn Jing, M.Sc., David A. Wheeler, Ph.D., Amy L. McGuire, J.D., Ph.D., Feng Zhang, Ph.D., Pawel Stankiewicz, M.D., Ph.D., John J. Halperin, M.D., Chengyong Yang, Ph.D., Curtis Gehman, Ph.D., Danwei Guo, M.Sc., Rola K. Irikat, B.S., Warren Tom, B.S., Nick J. Fantin, B.S., Donna M. Muzny, M.Sc., and Richard A. Gibbs, Ph.D.

N Engl J Med 2010; 362:1181-1191 | April 1, 2010 | DOI: 10.1056/NEJMoa0908094

a Mendelian disorder

Bigham<sup>2</sup>, Holly K. Tabor<sup>2</sup>,  
Jabs<sup>6,7</sup>, Deborah A.

# Genomics for Rare Disease: A Brief History

**ORIGINAL ARTICLE**

- Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy

James R. Lupski, M.D., Ph.D., Jeffrey G. Reid, Ph.D., Claudia Gonzaga-Jauregui, B.S., David Rio Deiros, B.S., David C.Y. Chen, M.Sc., Lynne Nazareth, Ph.D., Matthew Bainbridge, M.Sc., Huyen Dinh, B.S., Chyn Jing, M.Sc., David A. Wheeler, Ph.D., Amy L. McGuire, J.D., Ph.D., Feng Zhang, Ph.D., Pawel Stankiewicz, M.D., Ph.D., John J. Halperin, M.D., Chengyong Yang, Ph.D., Curtis Gehman, Ph.D., Danwei Guo, M.Sc., Rola K. Irikat, B.S., Warren Tom, B.S., Nick J. Fantin, B.S., Donna M. Muzny, M.Sc., and Richard A. Gibbs, Ph.D.

N Engl J Med 2010; 362:1181-1191 | April 1, 2010 | DOI: 10.1056/NEJMoa0908094

**a Mendelian disorder**

Bigham<sup>2</sup>, Holly K. Tabor<sup>2</sup>,  
Jabs<sup>6,7</sup>, Deborah A.

- March 2011: First paper published using exome sequencing to make a diagnosis, **Nicholas Volkner**

# Genomics for Rare Disease: A Brief History

**ORIGINAL ARTICLE**

- Whole-Genome Sequencing in a Child with Tooth Neuropathy

James R. Lupski, M.D., Ph.D., Jeffrey Chen, M.Sc., Lynne Nazareth, Ph.D., Ph.D., Amy L. McGuire, J.D., Ph.D., F Chengyong Yang, Ph.D., Curtis Gehring, B.S., Donna M. Muzny, M.Sc., N Engl J Med 2010; 362:1181-1191

**a Mendelian disorder**

**Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease**

*Elizabeth A. Worthey, PhD<sup>1,2</sup>, Alan N. Mayer, MD, PhD<sup>2,3</sup>, Grant D. Syverson, MD<sup>2</sup>, Daniel Helbling, BSc<sup>1</sup>, Benedetta B. Bonacci, MSc<sup>2</sup>, Brennan Decker, BSc<sup>1</sup>, Jaime M. Serpe, BSc<sup>2</sup>, Trivikram Dasu, PhD<sup>2</sup>, Michael R. Tschannen, BSc<sup>1</sup>, Regan L. Veith, MSc<sup>2</sup>, Monica J. Basehore, PhD<sup>4</sup>, Ulrich Broeckel, MD, PhD<sup>1,2,3</sup>, Aoy Tomita-Mitchell, PhD<sup>1,2,3</sup>, Marjorie J. Arca, MD<sup>3,5</sup>, James T. Casper, MD<sup>2,3</sup>, David A. Margolis, MD<sup>2,3</sup>, David P. Bick, MD<sup>1,2,3</sup>, Martin J. Hessner, PhD<sup>1,2</sup>, John M. Routes, MD<sup>2,3</sup>, James W. Verbsky, MD, PhD<sup>2,3</sup>, Howard J. Jacob, PhD<sup>1,2,3,6</sup>, and David P. Dimmock, MD<sup>1,2,3</sup>*

# Genomics for Rare Disease: A Brief History

**ORIGINAL ARTICLE**

- Whole-Genome Sequencing in a Child with Tooth Neuropathy

James R. Lupski, M.D., Ph.D., Jeffrey Chen, M.Sc., Lynne Nazareth, Ph.D., Ph.D., Amy L. McGuire, J.D., Ph.D., F Chengyong Yang, Ph.D., Curtis Gehring, B.S., Donna M. Muzny, M.Sc., N Engl J Med 2010; 362:1181-1191

**a Mendelian disorder**

**Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease**

Elizabeth A. Worthey, PhD<sup>1,2</sup>, Alan N. Mayer, MD, PhD<sup>2,3</sup>, Grant D. Syverson, MD<sup>2</sup>, Daniel Helbling, BSc<sup>1</sup>, Benedetta B. Bonacci, MSc<sup>2</sup>, Brennan Decker, BSc<sup>1</sup>, Jaime M. Serpe, BSc<sup>2</sup>, Trivikram Dasu, PhD<sup>2</sup>, Michael R. Tschanne, BSc<sup>1</sup>, Regan L. Veith, MSc<sup>2</sup>, Monica J. Basehore, PhD<sup>4</sup>, Ulrich Broeckel, MD, PhD<sup>1,2,3</sup>, Aoy Tomita-Mitchell, PhD<sup>1,2,3</sup>, Marjorie J. Arca, MD<sup>3,5</sup>, James T. Casper, MD<sup>2,3</sup>, David A. Margolis, MD<sup>2,3</sup>, David P. Bick, MD<sup>1,2,3</sup>, Martin J. Hessner, PhD<sup>1,2</sup>, John M. Routes, MD<sup>2,3</sup>, James W. Verbsky, MD, PhD<sup>2,3</sup>, Howard J. Jacob, PhD<sup>1,2,3,6</sup>, and David P. Dimmock, MD<sup>1,2,3</sup>

- April 2011: Launch of Deciphering Developmental Disorders (DDD) Study in UK
- Sept 2011: Clinical exome sequencing test available in US (Ambry Genetics)
- 2012: ACMG guidelines for exome/genome sequencing
- December 2012: 100,000 Genomes Project announced
- July 2013: Rare Disease focus for 100,000 Genomes Project announced
- 2015: ~12 US labs offering clinical exome sequencing for rare disease diagnosis
  - >>10,000 patients sequenced, considered standard of care in US

# The 100,000 Genomes Project



Announced by the Prime Minister in December 2012.

Genomics is one of the Prime Minister's 19 priorities.

1. To bring benefit to NHS patients
2. To create an ethical and transparent programme based on consent
3. To enable new scientific discovery and medical insights
4. To kickstart the development of a UK genomics industry

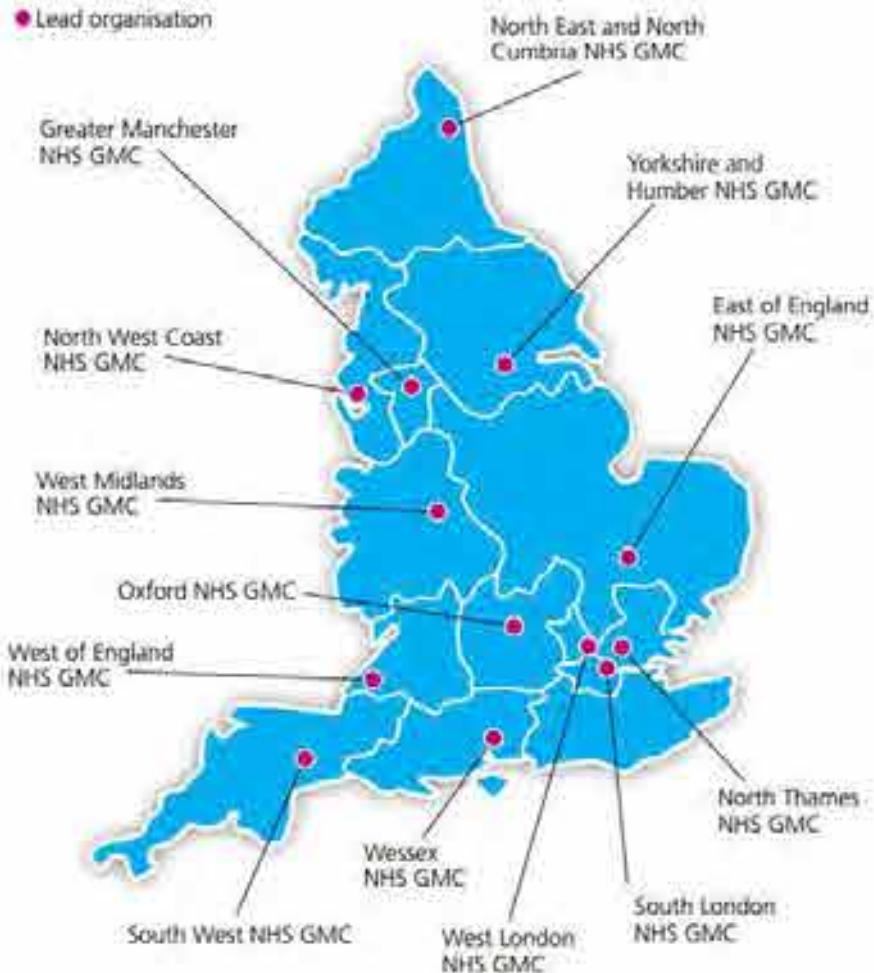


# NHS Genomic Medicine Centres

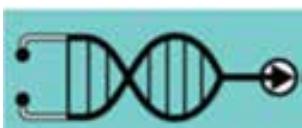
NHS  
England

Creating a lasting legacy for genomic medicine

● Lead organisation



NHS  
East of England  
NHS Genomic Medicine Centre



## What it is all about?

Patients who take part in the project may be able to get diagnosis.

For some, genome sequencing may mean a specific treatment can be recommended.



But for most, taking part means knowing they are helping medical research for future generations.



Research on genomes will help us understand diseases and what's causing them.

It can help researchers develop treatments and new diagnosis.

# The 100,000 Genomes Project by numbers



## Your genome

is found in almost every cell of your body and it is the instructions for making you.

It contains all your  
20,000 genes

It is all 3.2 billion letters of your DNA.

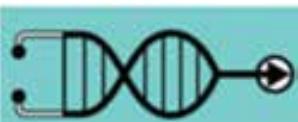


1 genome = 3.2 billion letters of DNA. If it was printed, your genome would fill a stack of paperback books 51m high or fill 200 telephone directories.

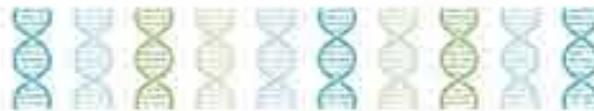
1 sequenced genome equals 2 billion bytes or 200 GB. That's enough to fill the memory of an average laptop.



East of England  
NHS Genomic Medicine Centre



# The 100,000 Genomes Project in numbers



**100,000** genomes



**70,000** patients and family members

```
1100010101001010100101010000101  
110110111010101010001011101000101  
110101010001001101010001010100010  
00100100111001000100001010101010100  
100111101100101010110101111001101
```

**21** Petabytes of data.  
1 Petabyte of music would take 2,000 years to play on an MP3 player.



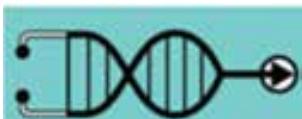
**13** Genomic Medicine Centres, and  
14 NHS Trusts within them are involved in recruiting participants



**1,500** NHS staff  
(doctors, nurses, pathologists, laboratory staff, genetic counsellors)

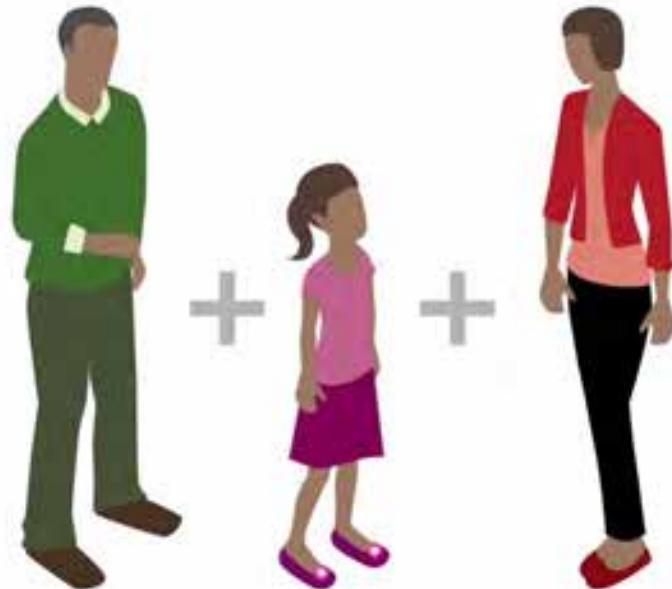


**2,500** researchers and trainees from around the world



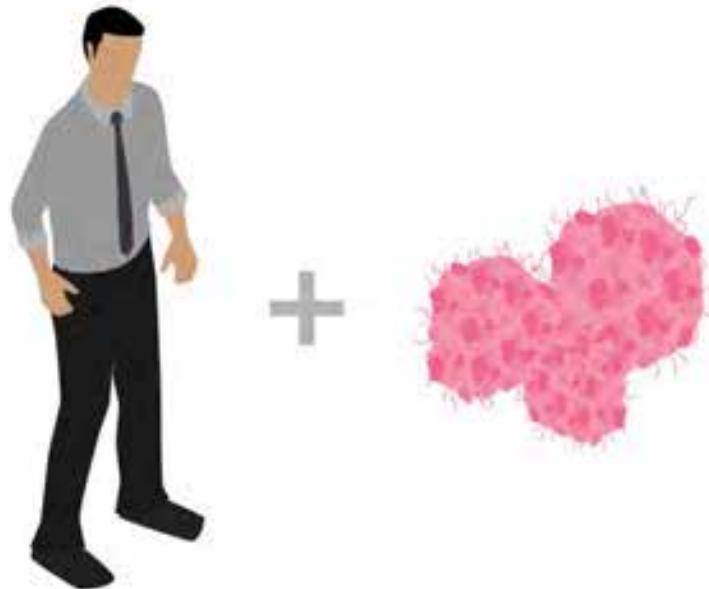
# Who can take part?

Rare disease



Blood sample required from the patient  
and, in some cases, from their close relatives

Cancer



Blood sample required from patient,  
and tissue sample from their tumour

# What happens if you take part?



+



+



# How do you sequence a genome?





1

Participants in the 100,000 Genomes Project are enrolled through NHS Genomic Medicine Centres. Their DNA is extracted from a blood sample and loaded on to a **sequencing machine**.

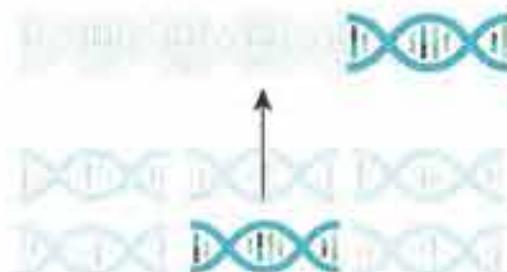
2

The machine determines the sequence of short pieces of DNA, 150 letters long. These are called **reads**.



3

The 'reads' from the sequencing machine are matched to a reference sequence. This is called **mapping**.



4

This image shows what bioinformaticians see when they are viewing a genome on a computer.



Reference human genome sequence

Each line of letters is one 'read' from the sequencing machine – approx. 150 letters long

A red letter indicates a difference to the reference sequence

## 5 Analysis



Amongst the 3 billion letters in your genome are 20,000 genes. These make up about 2% of the sequence. The position of most of our genes is known, and is marked on the [reference sequence](#).

Every person has millions of differences (called [variants](#)) to the reference sequence.

Most of these differences are harmless – they are the reason we are different from each other. Some differences could be causing a disease.

Bioinformaticians use a variety of tools and techniques to filter these differences down from millions to just a handful that could be harmful.

In the [100,000 Genomes Project](#), if a difference is thought to be the cause of someone's condition, it is fed back to the NHS. They then confirm the result. The diagnosis and its implications are discussed with the patient.

If it is not clear which difference is causing disease, researchers analyse the genome further.



[www.genomicsengland.co.uk](http://www.genomicsengland.co.uk)



[@genomicsengland](https://twitter.com/genomicsengland)



[info@genomicsengland.co.uk](mailto:info@genomicsengland.co.uk)



# Be research-aware: Use of your data



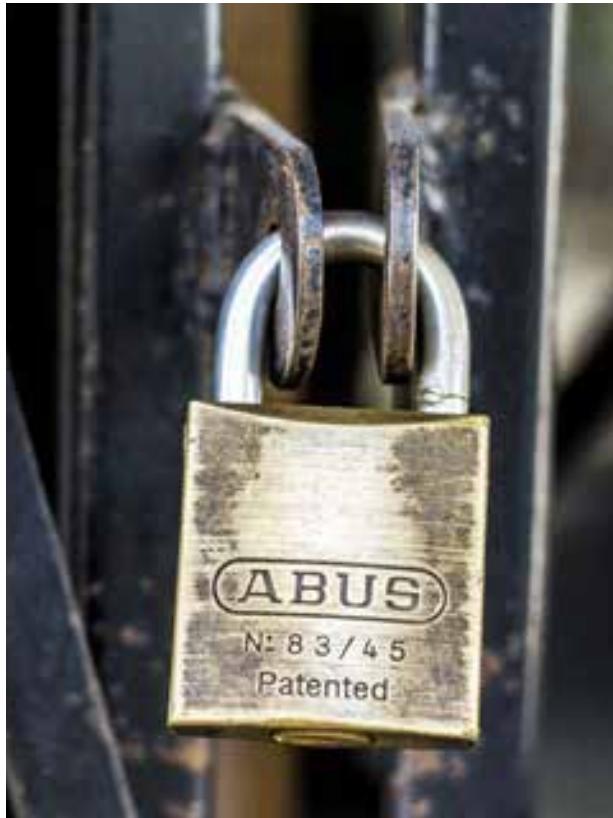
- “If you consent to take part, you will need to agree that: Researchers and organisations approved by Genomics England can look at your data in a way which protects your identity, including for-profit healthcare companies like those developing medicines or diagnostic tests” (Introduction to the 100,000 Genomes Project Leaflet)

# Be research-aware: Who looks at the data and why?



- “The data will be de-identified (that’s where everything that might identify you has been removed) and stored in the Genomics England data centre along with data from tens of thousands of other people. Approved researchers can then look at the de-identified data, but they can’t take any of it away.”
- “Comparing data from many people can give new understanding about the cause of a disease and how to treat it.”
- “Drugs have never been developed by the NHS – this is done by for-profit companies.” (Introduction to the 100,000 Genomes Project Leaflet)

# Be research aware: Privacy



- “We make it as hard as possible to identify you from your data, but we can’t rule it out. Trying to find out who data belongs to is illegal and could lead to a prison sentence. Genomics England monitors and records everything scientists do with the data, so re-identification is very unlikely.” (Introduction to the 100,000 Genomes Project Leaflet)

# Be research-aware: results

- Some research projects won't return any results
- Other research projects will return results of various levels – this could be anything from a summary report to results which relate directly to you (could be genetic, or other measurements such as your blood cholesterol level, a summary of a psychological test etc.)
- You should always find information about any results returned to you in the information leaflet

## Types of potential feedback to participants



### Main findings

All participants agree to receive results about the main condition for which they were referred

### Additional findings

Participants can opt in to receive feedback on a selection of known genetic alterations of high clinical significance

### Carrier status

Eligible adults can opt in to find out their carrier status for certain genetic diseases



# Results about the main condition

- There may not be any results which relate to the participant's condition.
- At the moment it takes over a year to receive results.
- Results will be returned to the participant's referring clinician who can discuss the findings with the participant.
- If no results are found, the data will continue to be part of the project, so results could be returned in the future.

# What your doctor should do on making a molecular diagnosis

## For the person with the condition:

- Tell them, and give them a copy of the genetic/genomic test report
- Determine management for disease and make appropriate referrals
- Refer to Clinical Genetics to further discuss condition/provide genetic counselling as necessary
- Provide information on patient support group for condition

## For their family:

- Ask about plans to extend the family. If the person, the person's parents, or the person's siblings plan to have children, refer them for Genetic Counselling
- Consider whether anyone else in the family should be offered genetic testing to determine whether they could be affected, at-risk, or a carrier for the condition. **If in doubt, call or refer to Clinical Genetics.**

# What if the results are uncertain?

## Results can be uncertain for different reasons:

- 1) The suspected condition is recessive and it is not clear whether the two variants found are on the same or different copies of the chromosome.
  - **Follow-up testing of family members (usually parents) is needed to clarify this result.**
- 2) One or more of the genetic changes identified was reported as a “Variant of Uncertain Significance”, (VUS):
  - **There is currently not enough information to know whether this genetic change can cause a genetic disorder or not. It may be helpful to test for this variant in other family members to help with the interpretation.**
  - **IMPORTANT: Variants of Uncertain Significance DO NOT provide a diagnosis and should not be acted on clinically.**
  - **Variants of Uncertain Significance are reported because their status may change in the future. Your doctor can check in with the lab in a year or two to see if there is any new information about the variant.**

If in doubt, call the lab or refer to Clinical Genetics.

# Why the report could be negative

A “negative” genetic test report, *even from whole genome sequencing*, doesn’t mean that person doesn’t have a genetic condition, it just means that *we haven’t identified a genetic cause for their condition at this time*.

Reasons that a genetic test can be “negative”:

**The person DOES NOT have a meaningful variant in the gene(s) that were tested**

- However, there may be **other genes** that can cause the person’s disorder that have not been examined because they **weren’t included in the test**, or they are **not yet known** to cause a genetic disorder.

**The person DOES have a meaningful variant(s) in the gene(s) that were tested**

- But it **could not be detected** by the test method that was used: no method is perfect.

# What your doctor can do if the test report is negative

**If a doctor is sure that the person's condition is genetic, they can consider:**

- Referring to Clinical Genetics who may be able to recommend further or different testing
- Checking back in with the lab or Clinical Genetics down the line to see if there is scope for re-analysis of the person's data, or further clinical testing to offer

# Optional – results about additional genetic conditions

- When signing the consent form, participants can decide if they would like to know about other genetic conditions which are not linked to their current condition.
- Not a full health MOT, but looking for pre-defined, serious conditions for which there is an intervention (treatment, screening etc.)
- Only about 1% of participants are expected to have an additional finding.
- Will identify individuals with a higher risk for certain conditions, but cannot exclude the risk of having one of the conditions even if no additional results are identified
- The list of conditions is likely to change in the future
- Part of the purpose of offering this information about additional findings is provide information about this information should become part of NHS standard clinical care.

# Optional – carrier status

- “a test to look for conditions that don’t affect you, but which might be a problem for your baby if you were found to be carrying them in your genome”  
(Introduction to the 100,000 Genomes Project Leaflet)
- “If you are joining the Project with your partner and you **both** ask us to look for carrier test results, we will look for these diseases which you both need to carry to affect your future children.” (100,000 Genomes Project Rare Disease Participant Information Leaflet)
- “Some of the diseases we will look for are only carried by one parent, but can still affect future children.”

# Public attitude to additional findings

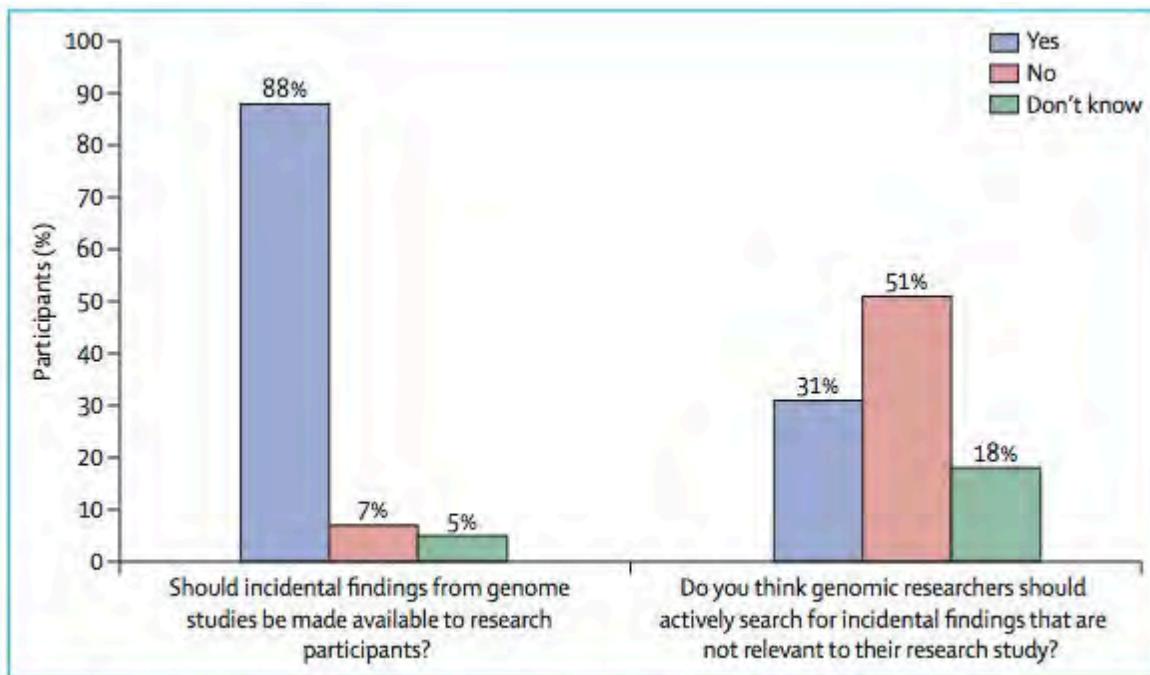
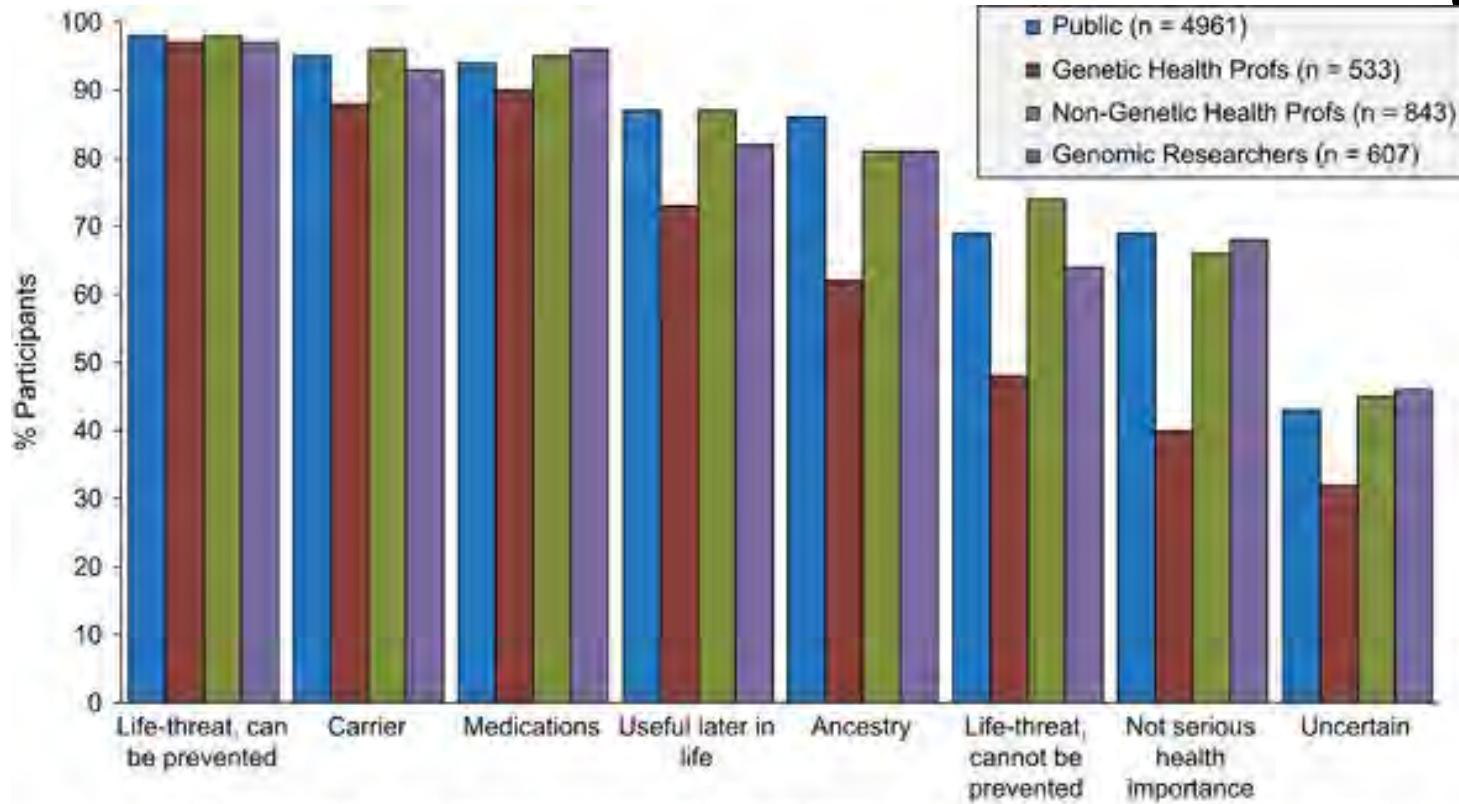


Figure: Attitudes towards sharing of and active searching for incidental findings

- 6944 people from 75 different countries
- 5628 of 6370 respondents thought that incidental findings should be made available to research participants
- 1741 of 5653 participants expected genomic researchers to actively search for incidental findings not relevant to their research.

Middleton et al. Lancet vol 385, 2015

# Public attitude to additional findings



Q: If you had the choice to receive information in the following categories, what would you want to know?

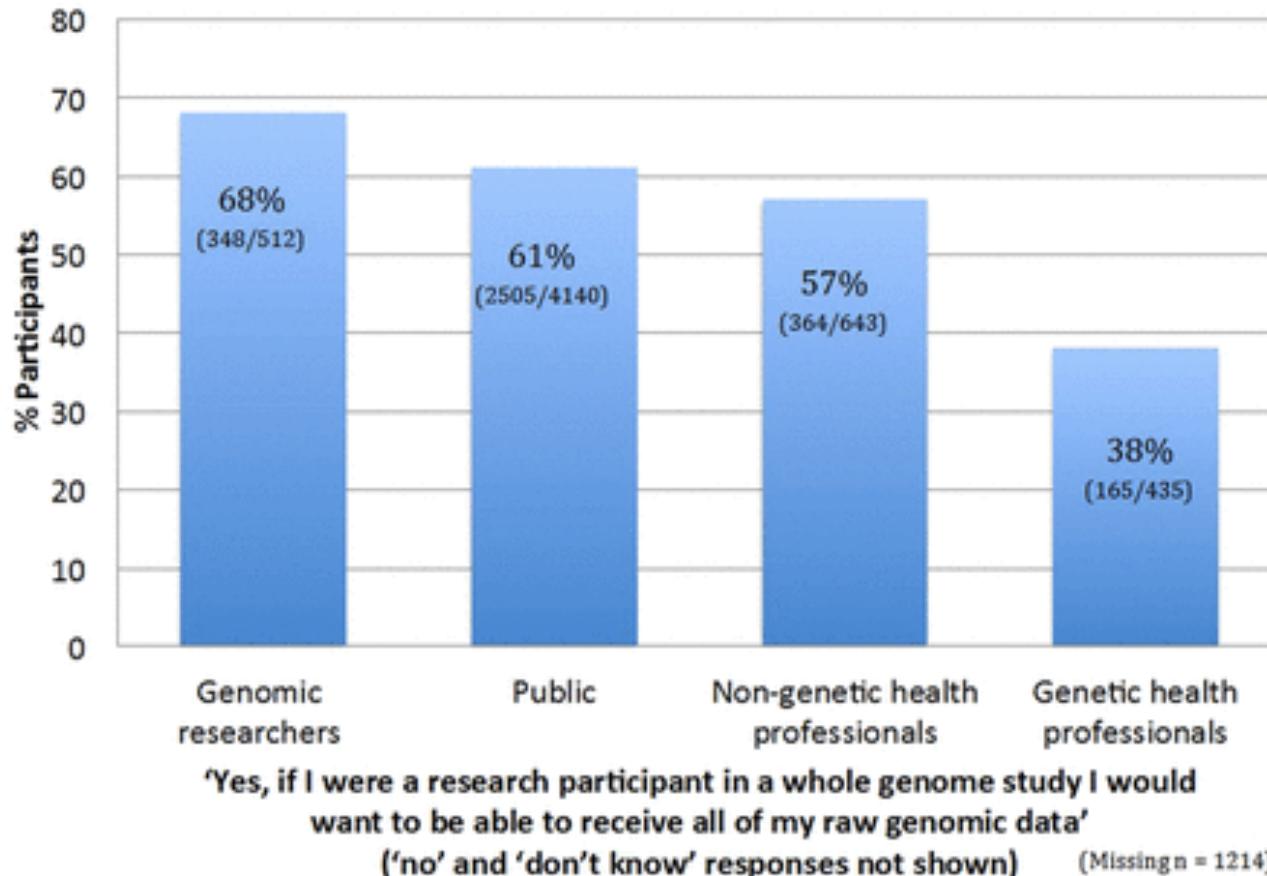
Life-threat, can be prevented = conditions that are life-threatening and can be prevented; carrier = tells me if I'm a carrier of a condition that could be relevant to my children; medications = demonstrates how I might respond to different medications or drugs (e.g. statins, anti-depressants etc.); useful later in life = information that is not immediately relevant but could be useful later in life (e.g. relating to a very late onset cancer or predisposition to strokes); ancestry = tells me about my ancestry; life-threat, cannot be prevented = conditions that are life-threatening and can be prevented; not serious health importance = is not likely to be of serious health importance (e.g. mild eyesight problems); uncertain = information that is uncertain and cannot be interpreted at the moment

Middleton et al. (2016), EJHG 24,21-29

# Return of genetic results

- All results from the 100,000 Genomes Project are returned to the participant's clinical care team who can provide further information
- These days many companies offer interpretation services for genomic data – changes in the data protection regulations will soon allow requests to be made for data held by researchers, and this could include your whole genome sequence.

# Return of genetic results

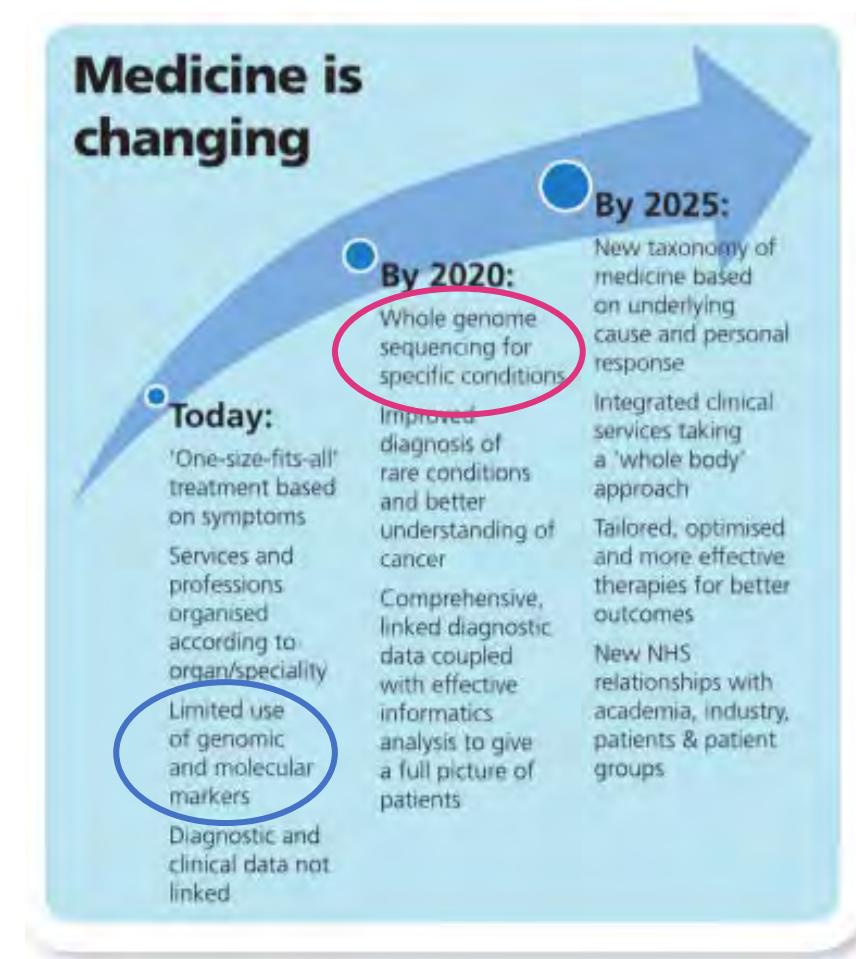
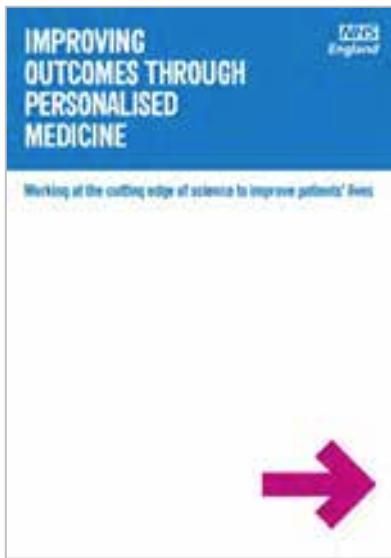


Middleton et al. (2015) J Med Genet 52

# Additional aspects of the 100,000 Genomes project

- There are other aspects of the 100,000 Genomes project in addition to directly trying to identify the genetic changes linked to genetic conditions
- Working groups for improving the current genetic reports
- Education of healthcare professionals
- Participant panel feeding into the project design, results, public documents, equity of access etc.

# NHS Vision: Personalised Medicine

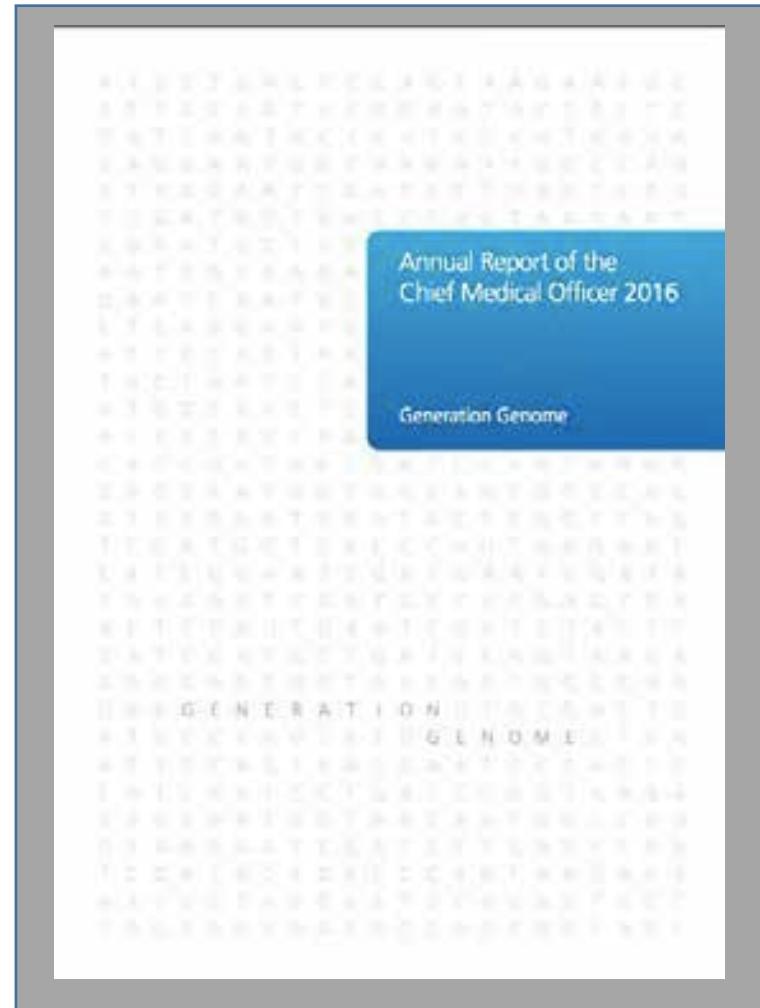


## Precision Medicine (4P Medicine):

- Predictive
- Preventative
- Personalised
- Participatory

# Generation Genome

- NHS CMO's Annual Report focused on Genomics
- How it will impact the way care is delivered in the NHS
- How this transformation in delivery of care can be achieved



# Find out more...

- <https://www.genomicsengland.co.uk/>
- <https://www.genomicseducation.hee.nhs.uk/>

A large, colorful word cloud centered around the words 'thank you' in various languages. The word 'thank' is in blue, 'you' is in yellow, and 'you' is in green. The background is white with a subtle grid pattern. The word cloud includes many other words related to gratitude and thanks in different languages, such as 'merci' (French), 'gracias' (Spanish), 'mochchakkeram' (Burmese), and 'mamnun' (Burmese). The text is in a variety of fonts and colors, including blue, green, yellow, red, and orange.