



# Ethics and Genomics

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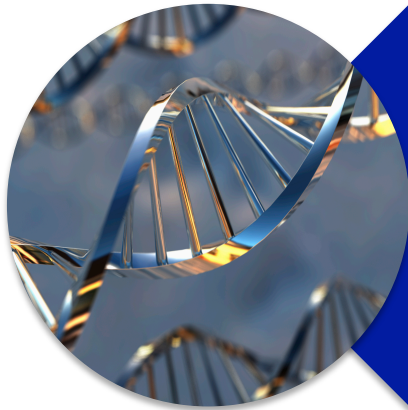


# Remit of this talk

- Overview of the Deciphering Developmental Disorders study in the UK
- Our results from the ethics study
- Influence on policy
- Sequencing in the UK (100k genomes project)



# Deciphering Developmental Disorders Project (DDD)



Molecular Study



Ethics Study

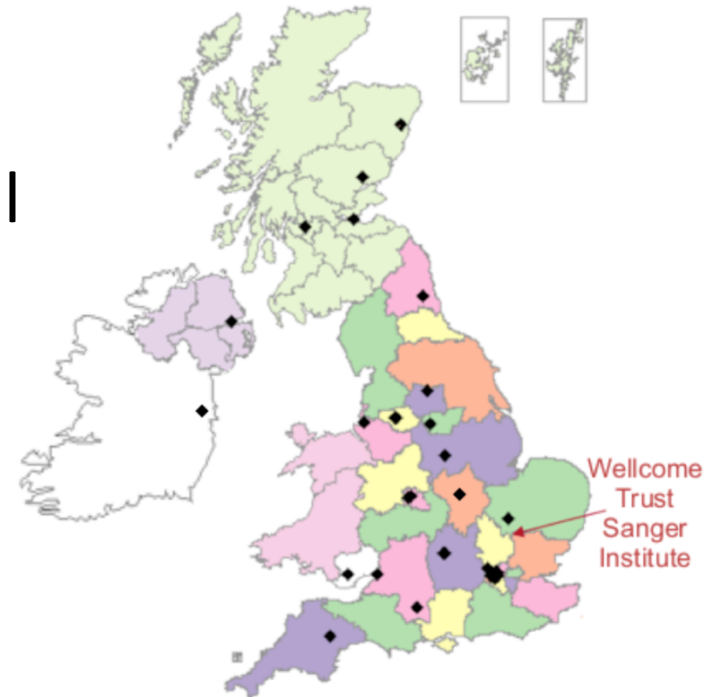
# DDD Molecular Project

## Objectives

- RESEARCH: understand genetics of developmental disorders

## A UK-wide collaboration:

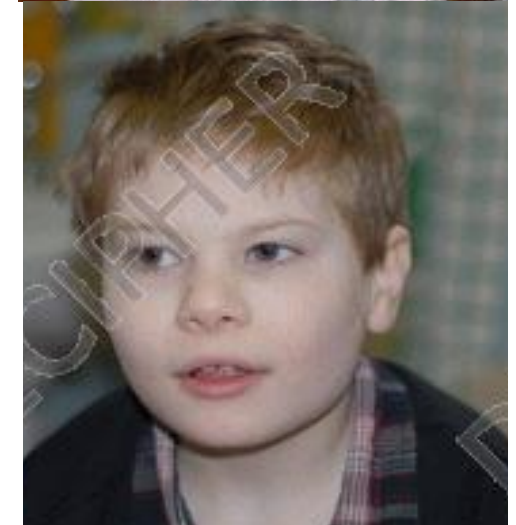
- Every regional clinical genetics department is involved (> 180 clinical geneticists ++)
- NHS - recruits patients and deliver results
- Sanger – offers exome sequencing



# DDD Molecular Project

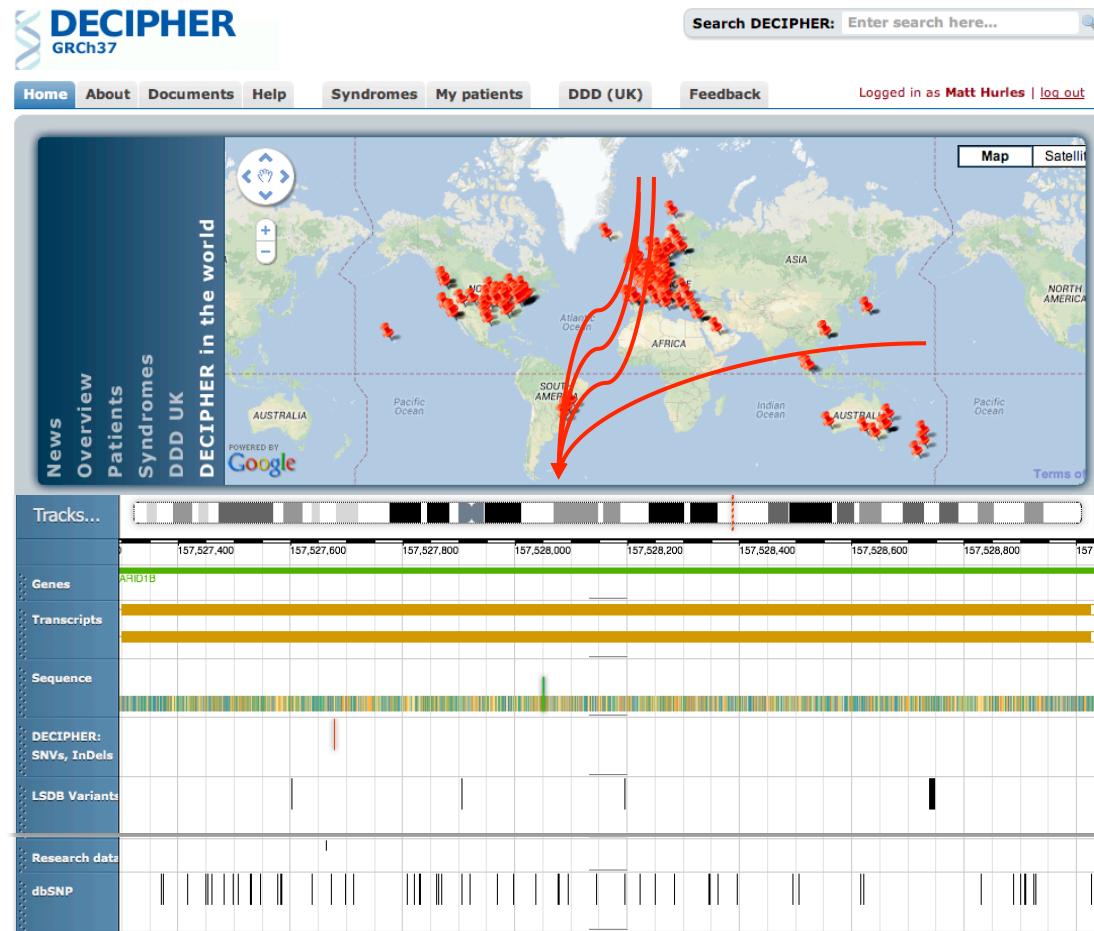
## Strategy:

- Recruit 14,000 children plus parents, i.e. 40,000+ samples
- Deep phenotyping
- NHS testing revealed no diagnosis
- Exome Sequence
- Feedback likely diagnoses (yield 36% and increasing)



# DECIPHER: Genomic Matchmaking

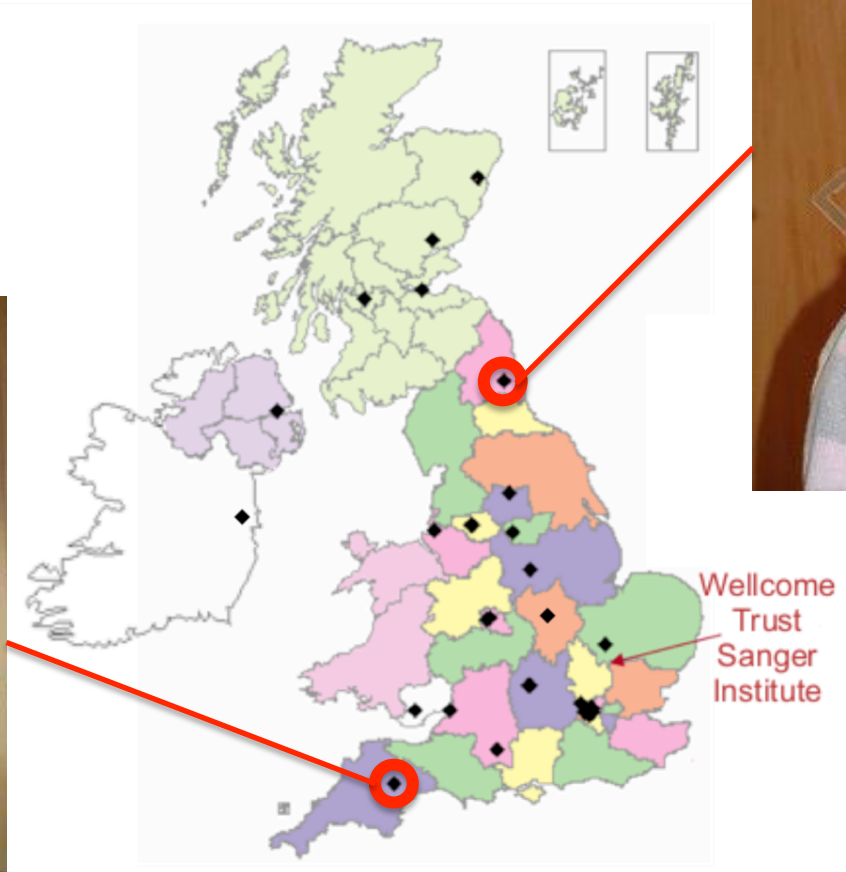
- Sharing of minimal **genotype and phenotype**
- Data deposition and visualisation
- Global: 206 centres, >28k patients
- Will include all DDD patients



Over 500 publications citing DECIPHER in past 5 years

# PCGF2

G→A Chr17:36,895,854





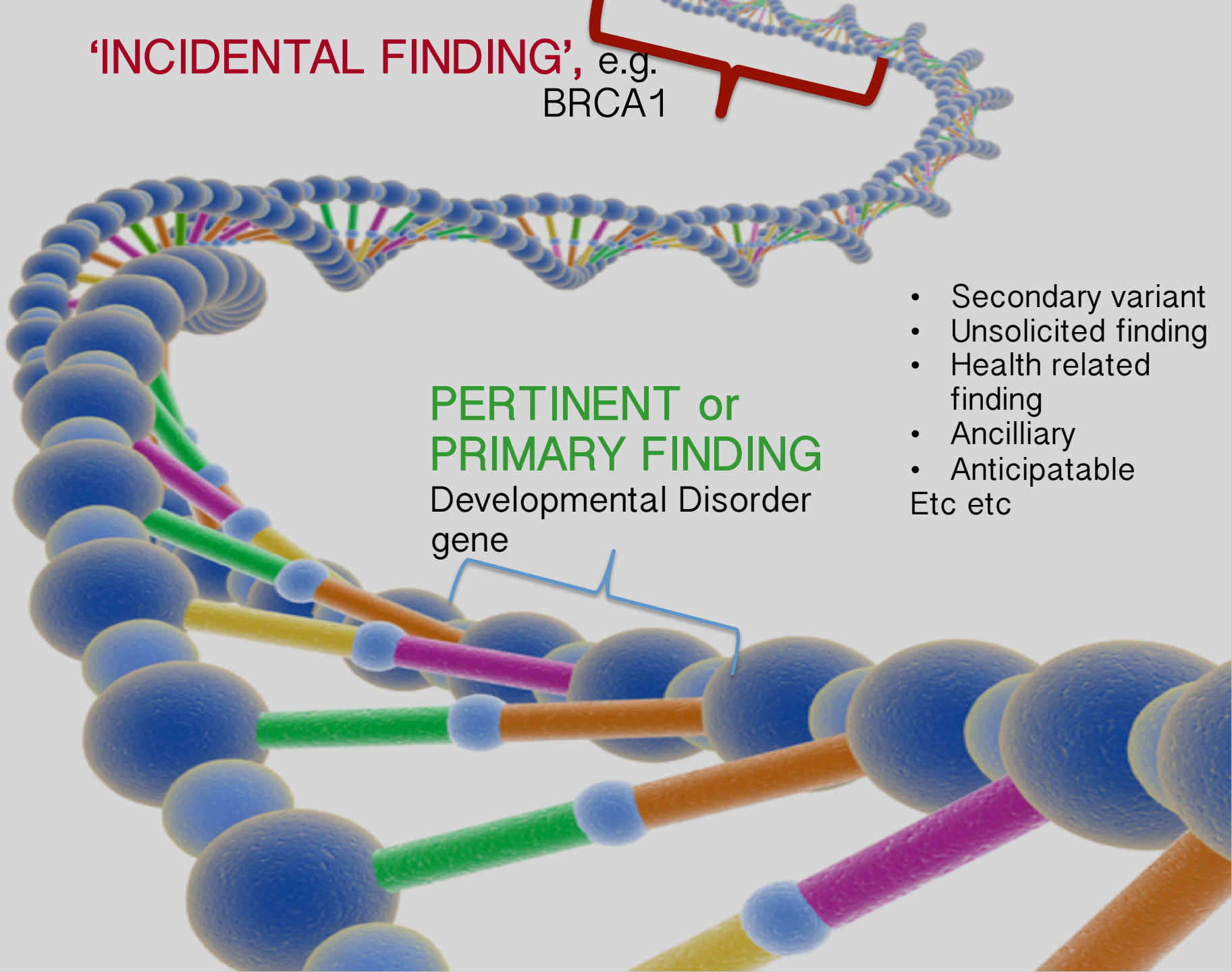
# **Ethics, Social Sciences Study**



© From left to right: Wellcome Library, London; Anthea Sieweking, Wellcome Images; Wellcome Library, London

- Sequencing studies like DDD aim to unlock a clinical diagnosis
- What to do with info unrelated to clinical diagnosis? = an Incidental Finding (IF)

**'INCIDENTAL FINDING'**, e.g.  
BRCA1



**PERTINENT or  
PRIMARY FINDING**  
Developmental Disorder  
gene

- Secondary variant
- Unsolicited finding
- Health related finding
- Ancillary
- Anticipatable
- Etc etc

# In DDD

- We are not exploring or sharing IFs
- Want to focus on the clinical question
- Difficulties with interpretation
- No firm position taken in clinical practice, thus in 2010 establishing a position in research was premature

# IFs are not new in medicine

- If something genuinely unexpected is seen, it is often shared
- This happens with aCGH in clinic
- Sequencing is slightly different because of the way data is filtered
- Can make pre-determined choices about what to look at
- Choices on a large scale

# Informatics

Presidential Commission for the Study of Bioethical Issues (2013):

“[T]his idea of data sort of popping out at you and being unexpected doesn't really reflect...the way that genomic data have to be analyzed... you have to decide what things you are going to look for”

# Types of IF: Opportunistic Genomic Screening



- As per ACMG recommendations
- Screen for 24 cancer and cardiac conditions when an exome/genome is done
- 100k Genomes Project aim to search for 'additional looked for findings'

# Secondary findings

## Adult onset

- HNPCC/Lynch syndrome genes
- MYH Associated polyposis
- BRCA1/2

## Child onset

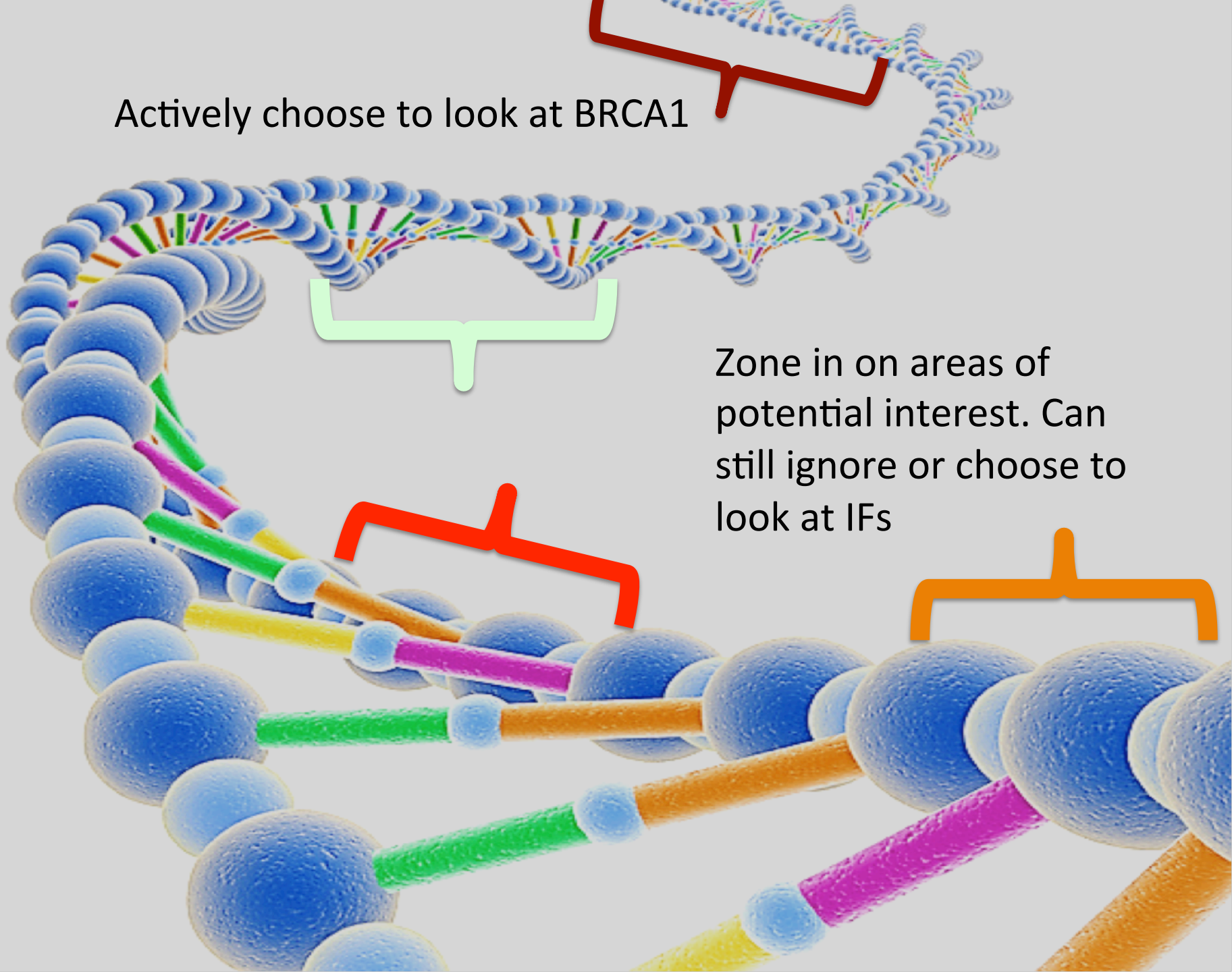
- Retinoblastoma
- FH
- FAP
- VHL
- MEN types 1 and 2
- Familial medullary thyroid cancer

## Carrier testing

- Sickle cell disease
- CF
- Beta Thalassemia
- Congenital adrenal hyperplasia
- Alpha thalassemia
- SMA type 1
- F5 Leiden
- Haemochromatosis
- Alpha 1 antitrypsin deficiency
- DMD
- Adrenoleukodystrophy
- Haemophilia A



Actively choose to look at BRCA1



Zone in on areas of potential interest. Can still ignore or choose to look at IFs

# Objectives

Attitudes towards sharing incidental findings  
(inc deliberate searching)

Sequencing in a research setting



- ✓ Questions about you
- ➔ Sharing of Pertinent Findings
  - Sharing of Incidental Findings
  - Categorizing Incidental Findings
  - Relations with Risk
  - Raw data
  - Duty of Genomic Researchers
  - Filter of Genomic Information
  - Consent for genomic research
  - Last few questions about you

## Sharing of Pertinent Findings

- Should Pertinent Findings from genome studies be made available to research participants?
  - Research participants should be able to receive pertinent findings if they want them
  - I don't think pertinent findings from research projects should be available
  - I don't know

« Previous

Next »

Public = 4961



Genomic  
researchers = 607



Genetic health  
professionals = 533



Other health  
professionals = 843



**Q: What influences attitudes the most?**

**A: Our professional background rather than the country we are from**



Genetic Health  
Professionals



Other Health  
Professionals



Genomic  
Researchers



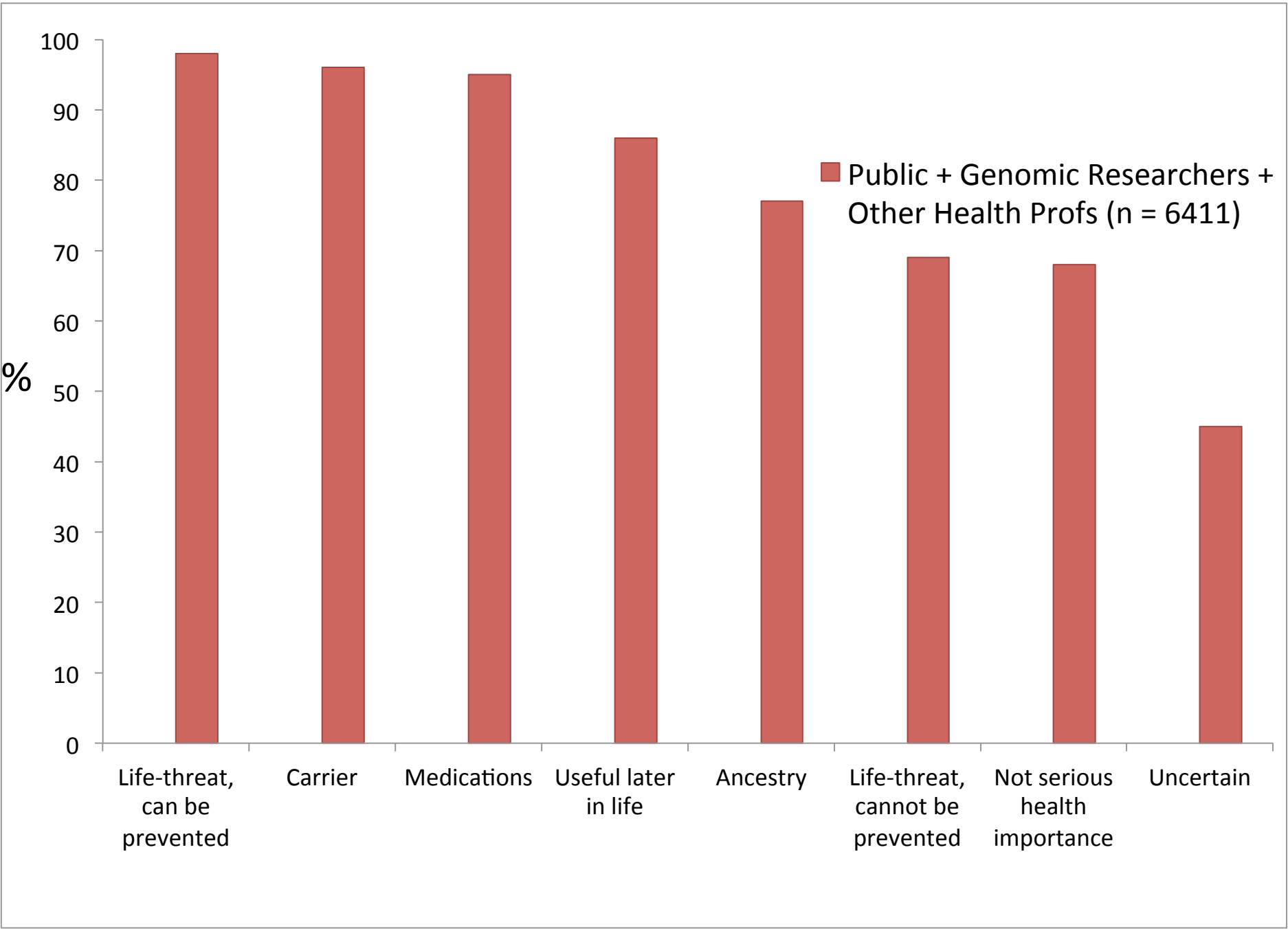
Public

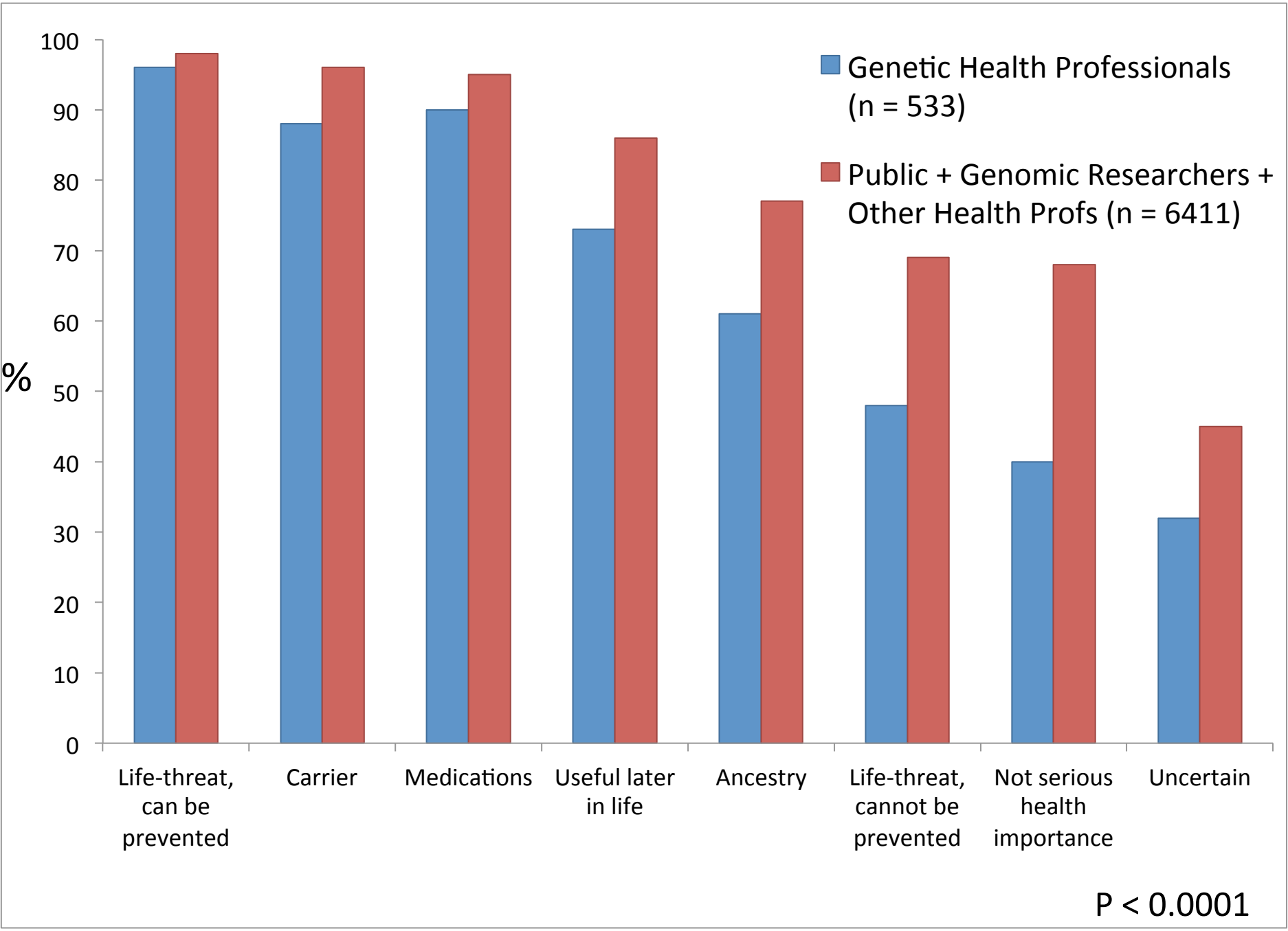
**Q: If Incidental Findings were categorized in the following ways (↓ below)**

**should research participants be able to choose to receive information in these categories?**

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Life-threat, can be prevented	Carrier	Medications	Useful later in life	Ancestry	Life-threat, cannot be prevented	Not serious health importance	Uncertain
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$P < 0.0001$



# Three key messages

- On the whole, all stakeholders would be interested in receiving IFs
- Actionability is important to people
- Genetic health professionals are more conservative
  - Most realistic about how this would work in clinic

I want to  
know  
**EVERYTHING!**



Information Seeker



I just want  
some  
things.....

Information Discriminator

- Explored the profiles of each



Information Seeker

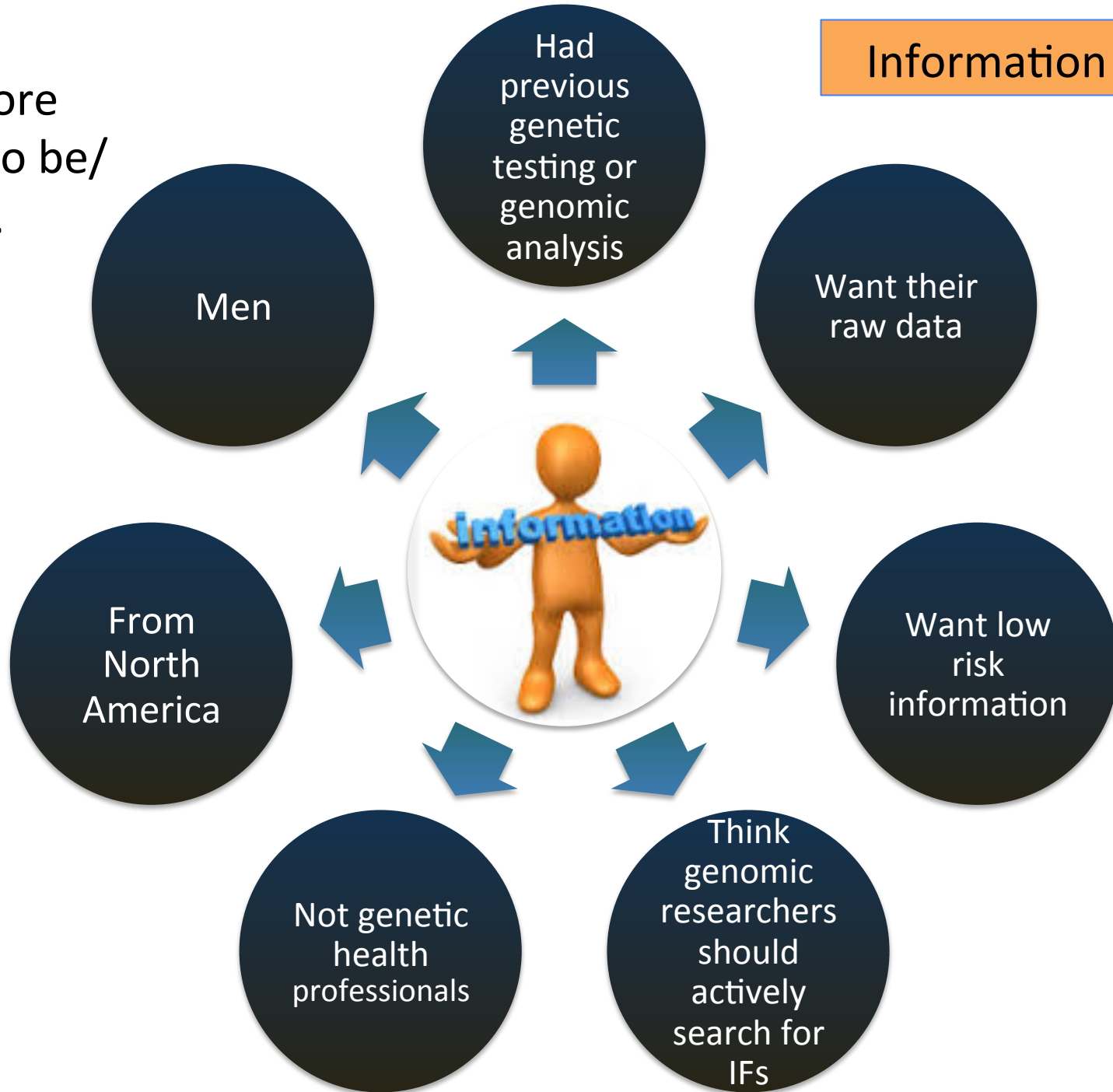


Information Discriminator

- Adjusted for all potential confounding effects
- Only show data relating to significant odds ratios

# Information Seeker

Are more likely to be/  
want...



Men

Had previous genetic testing or genomic analysis

Want their raw data

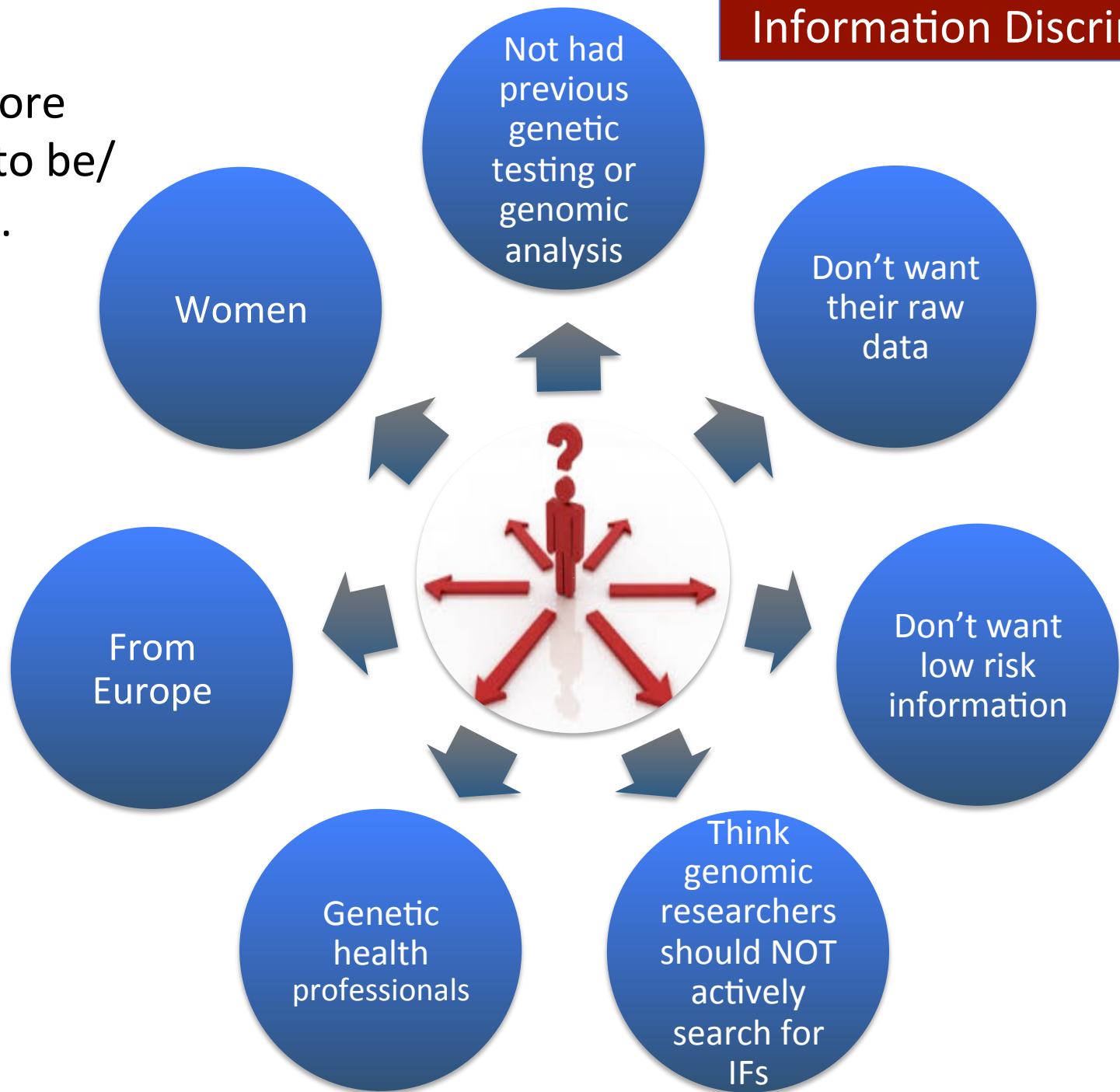
From North America

Want low risk information

Not genetic health professionals

Think genomic researchers should actively search for IFs

Are more likely to be/want...



# Key Messages

- No 'one-size fits all'
- Information seeking behaviours are important
- Should be reflected in consent processes

# Issues for Consent



- Patients/research participants should be aware :
  - Possibility of IFs being identified (true IFs or opportunistic screen)
  - Plans for disclosure and management (e.g. ?follow up studies to explore pathogenicity)
  - Scope of the IFs that might be disclosed (i.e. no to uncertain data but yes to actionable serious conditions?)
  - What choices are available (or not)

# If the decision is made to share IFs

- Who chooses the categories?
- Who decides what is 'actionable'?
- Very subjective







**Who should filter results?**



# If results were to be filtered...

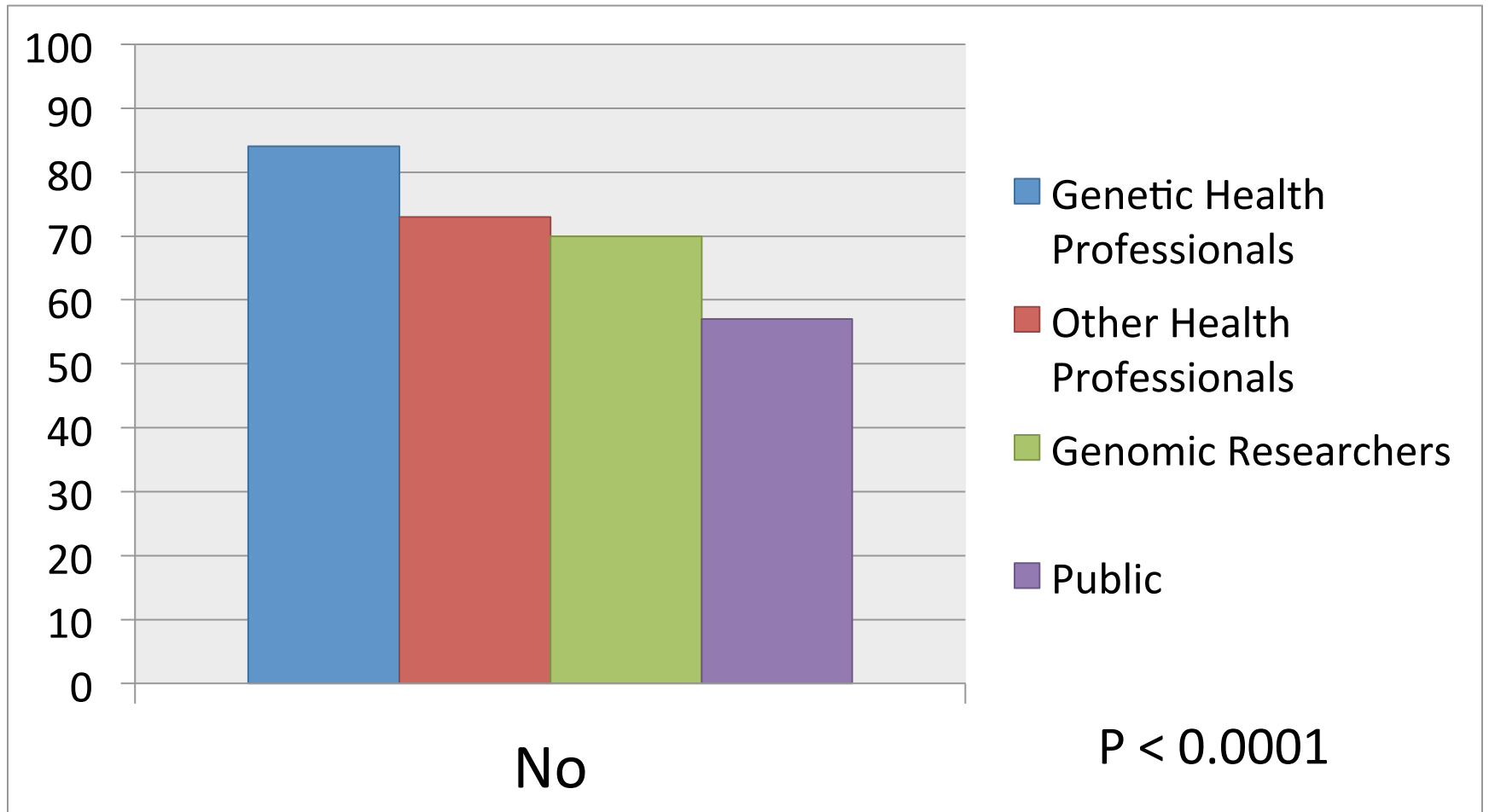
- 79% thought there should be a committee of people who did this including:
  - Genomic researcher
  - Health professional
  - Independent ethics personnel
  - Patient representative
- Lots of comments about the patient/research participant being involved



**Q: Do you think genomic researchers should actively search for Incidental Findings that are not relevant to their research study?**

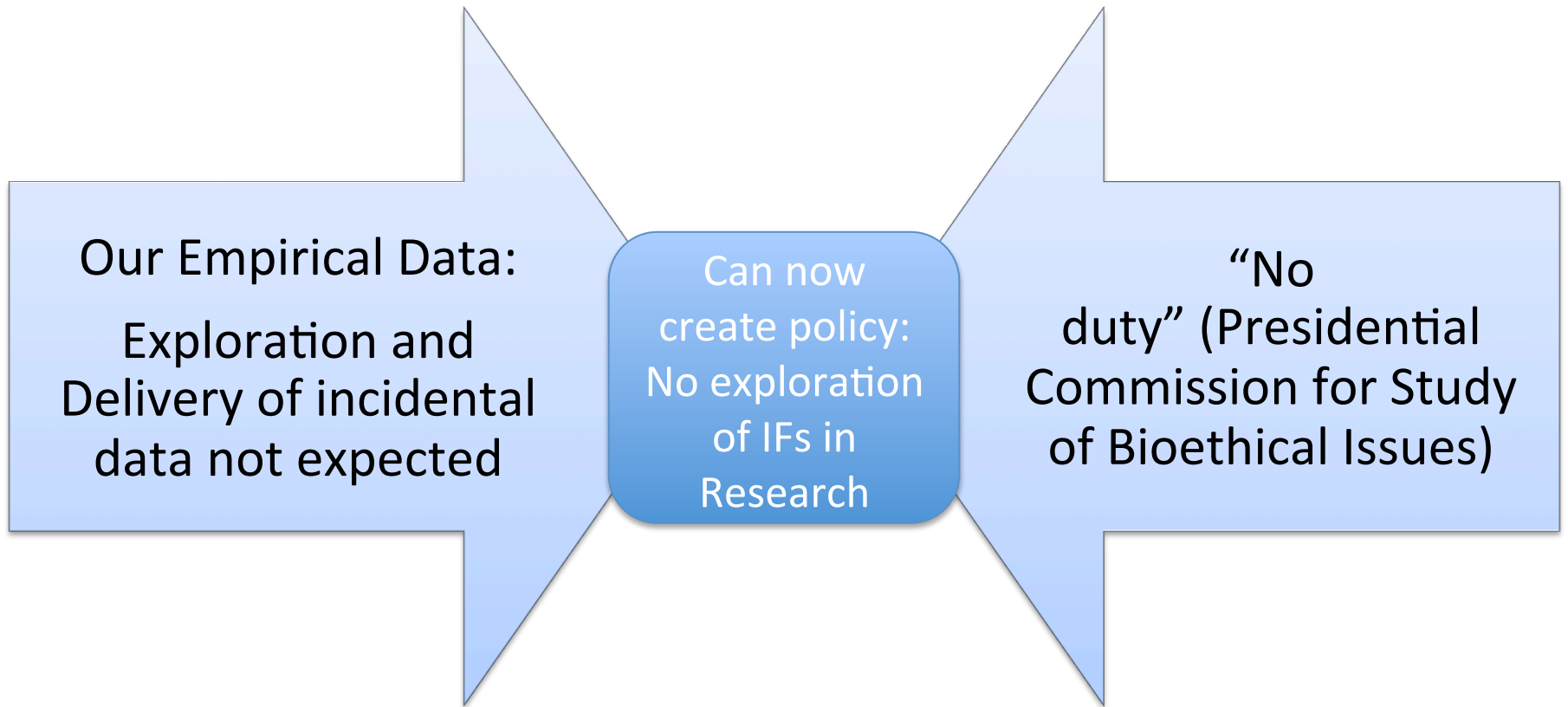
**[There may be a cost...]**

# Should actively search for IFs?



**Drawing this together...**

# Sequencing in a research setting:



## No expectation to share incidental findings in genomic research

Genomic sequencing studies can answer questions about the genetic contribution to complex medical disorders such as developmental disorders. Although findings relating to the disorder of interest will be communicated to patients along with appropriate counselling, there is pressure on researchers to return secondary or incidental findings (ie, additional health-related data unrelated to the research question).<sup>1</sup> But few studies have actually asked relevant stakeholders what their expectations are of researchers.<sup>2</sup>

Analysing and returning extensive data from genetic studies poses a particular dilemma simply because of the scale—with potentially hundreds of relevant variants that could be linked to future medical health. For many researchers, an exploration of such variants would have implications for time and resources that could compromise the ability to do research.

Incidental findings could be uncovered by accident while exploring a pertinent finding, or might be revealed through a deliberate search for particular genes linked, for example, to serious, life-threatening treatable disorders.<sup>3</sup> Whether to do such an opportunistic screen and what to do with incidental, health-related data, is subject to debate.<sup>4</sup>

With an **online survey** containing ten explanatory films, we gathered the attitudes of 6944 people from 75 different countries towards their expectations of genomic researchers with respect to sharing incidental findings.<sup>5,6</sup> These participants included four relevant stakeholder groups in sequencing research: members of the public (n=4961), genomic researchers (n=607), genetic health professionals (n=533), and other health professionals (eg, nurses, surgeons, paediatricians,

and general physicians; n=843). We asked participants whether incidental findings from genome studies should be made available to research participants; and whether they expected researchers to deliberately do an opportunistic screen to look for incidental findings of particular health relevance. 5628 of 6370 respondents thought that incidental findings should be made available to research participants (**figure**). However, despite such a strong interest in having access to data, only 1741 of 5653 participants expected genomic researchers to actively search for incidental findings not relevant to their research. These results remained consistent even after adjustment for potential confounding effects.

When asked, stakeholders do not expect researchers to search actively for incidental findings in a research setting. The US Presidential Commission for the Study of Bioethical Issues also suggests that researchers do not have a duty to actively look for incidental findings.<sup>4</sup> Although researchers might choose to explore and share incidental findings, within an appropriate ethics framework, our survey supports a policy that does not obligate researchers to search for and then communicate incidental findings to research participants.

We declare no competing interests

\*Anna Middleton, Katherine I Morley, Eugene Bragin, Helen V Firth, Matthew E Hurles, Caroline F Wright, Michael Parker, on behalf of the Deciphering Developmental Disorders Study  
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- 2 Jackson L, Goldsmith L, O'Connor A, Skirton H. Incidental findings in genetic research and clinical diagnostic tests: a systematic review. *Am J Med Genet* 2012; **158A**: 3159–67.
- 3 Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med* 2013; **15**: 565–74.
- 4 Presidential commission for the study of bioethical issues. Anticipate and communicate: the ethical management of incidental and secondary findings in the clinical, research and direct-to-consumer contexts. Washington, DC: United States Government, 2013.
- 5 Middleton A, Bragin E, Morley KI, Parker M. Online questionnaire development: using film to engage participants and then gather attitudes towards the sharing of genomic data. *Social Science Research* 2014; **44C**: 211–23.
- 6 Middleton A, Bragin E, Parker M. Finding people who will tell you their thoughts on genomics—recruitment strategies into social sciences research on genetics. *J Community Genet* 2014; **5**: 291–302.

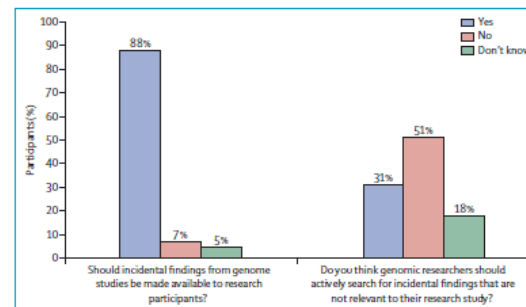


Figure: Attitudes towards sharing of and active searching for incidental findings

For the online survey see [www.genomethics.org](http://www.genomethics.org)

Submissions should be made via our electronic submission system at <http://ees.elsevier.com/thelancet/>



# Extrapolation of our data to the clinic?

- People want data
- No one size fits all (information seekers versus discriminators)
- Multi-disciplinary approach to decision making

# We focus on answering a clinical question

European Society of Human Genetics reports:

“When [sequencing] in the clinical setting, it is preferable to use a targeted approach... to avoid unsolicited findings or findings that cannot be interpreted”

# Contribution to policy

## European Journal of Human Genetics

European Journal of Human Genetics advance online publication 8 January 2014; doi: 10.1038/ejhg.2013.301



### Position statement on opportunistic genomic screening from the Association of Genetic Nurses and Counsellors (UK and Ireland)

(3)

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Anna Middleton<sup>1</sup>, Chris Patch<sup>2</sup>, Jennifer Wiggins<sup>3</sup>, Kathy Barnes<sup>4</sup>, Gill Crawford<sup>5</sup>, Caroline Benjamin<sup>6</sup> and Anita Bruce<sup>7</sup> On behalf of the Association of Genetic Nurses and Counsellors in the United Kingdom and Ireland

## ANALYSIS

### Policy challenges of clinical genome sequencing

Around the world, genome sequencing is moving from research into the clinic, and in the UK plans to sequence the genomes of 100 000 NHS patients are well underway. A clear policy on how to conduct genomic testing is therefore both essential and urgent, argue **Caroline Wright and colleagues**

Caroline F Wright *senior scientific manager*<sup>1</sup>, Anna Middleton *ethics researcher*<sup>1</sup>, Hilary Burton *director and public health consultant*<sup>2</sup>, Fiona Cunningham *Ensembl variation project leader*<sup>3</sup>, Steve E Humphries *professor of cardiovascular genetics*<sup>4</sup>, Jane Hurst *consultant clinical geneticist*<sup>5</sup>, Ewan Birney *associate director*<sup>3</sup>, Helen V Firth *consultant clinical geneticist*<sup>6</sup>

# 100,000 Genomes Project

- Whole genome sequencing in the NHS
- 100,000 sequences by 2017 (60k patients)
- Cancer, rare diseases and infectious diseases

# Enormous thanks to:

- Mike Parker
- Caroline Wright
- Helen Firth
- Eugene Bragin
- Matt Hurles
- Kate Morley
- DDD ‘actors’ in films
- DDD team

