wellcome trust sanger institute

WELLCOME GENOME CAMPUS
LIFE-CHANGING SCIENCE

Ethics and Genomics

Dr Anna Middleton

Principal Staff Scientist
(social science and ethics)
Genetic Counsellor

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)


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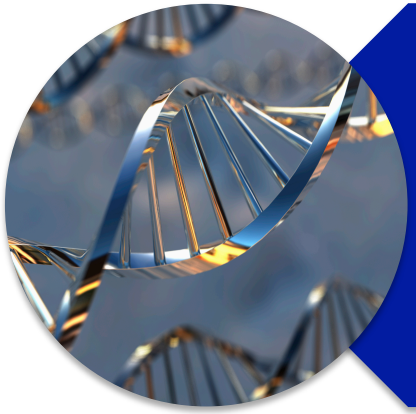
News

Deciphering Developmental Disorders Project (DDD)



Molecular Study

+

Ethics Study

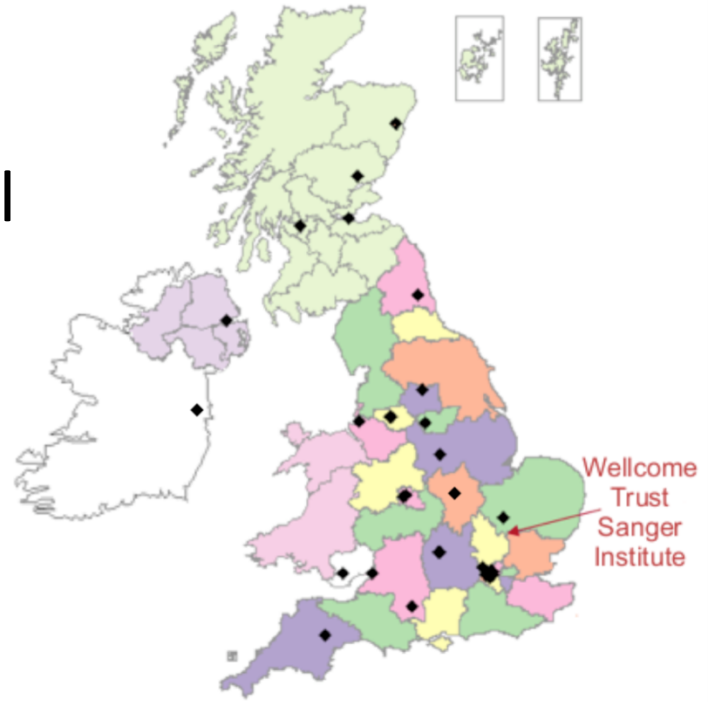
DDD Molecular Project

Objectives

- RESEARCH: understand genetics of developmental disorders

A UK-wide collaboration:

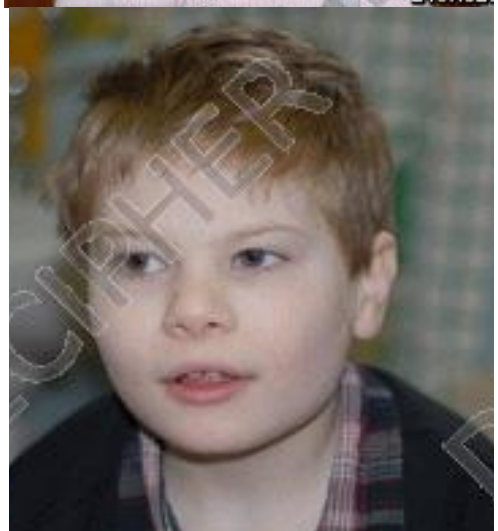
- Every regional clinical genetics department is involved (> 180 clinical geneticists ++)
- NHS - recruits patients and deliver results
- Sanger – offers exome sequencing



DDD Molecular Project

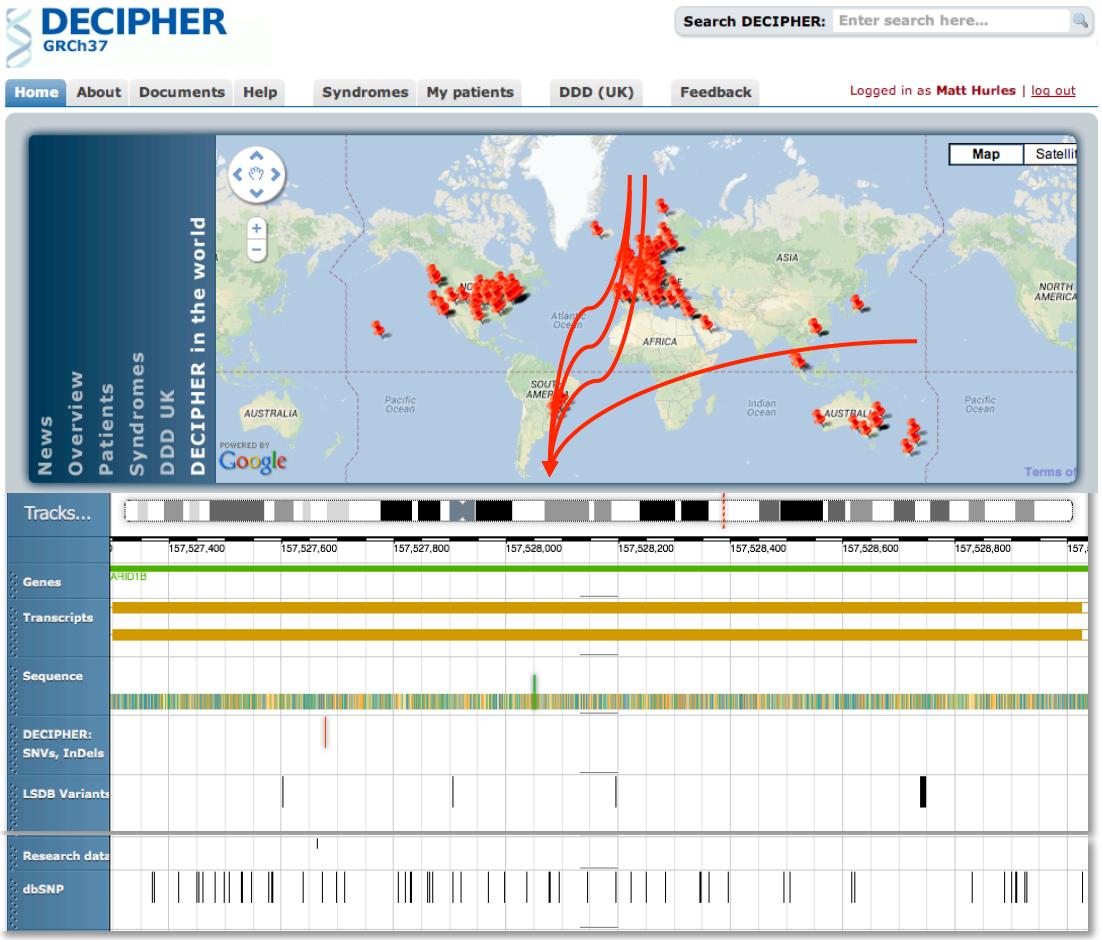
Strategy:

- 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

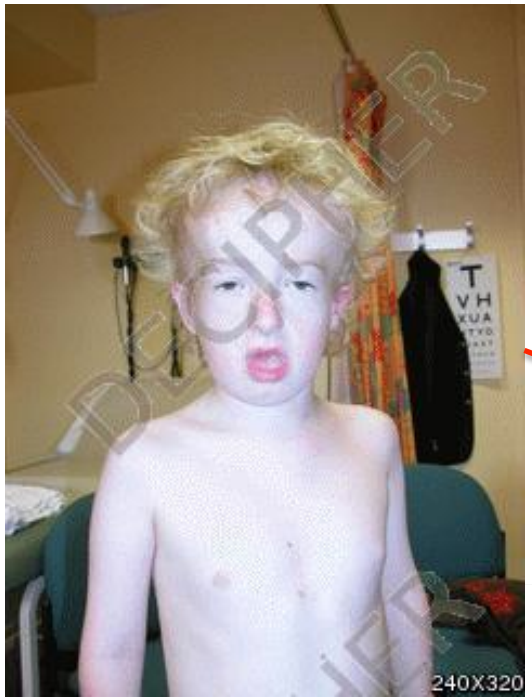
- Sharing of minimal **genotype and phenotype**
- Data deposition and visualisation
- Global: 206 centres, >28k patients
- Will include all DDD patients



Over 500 publications citing DECIPHER in past 5 years

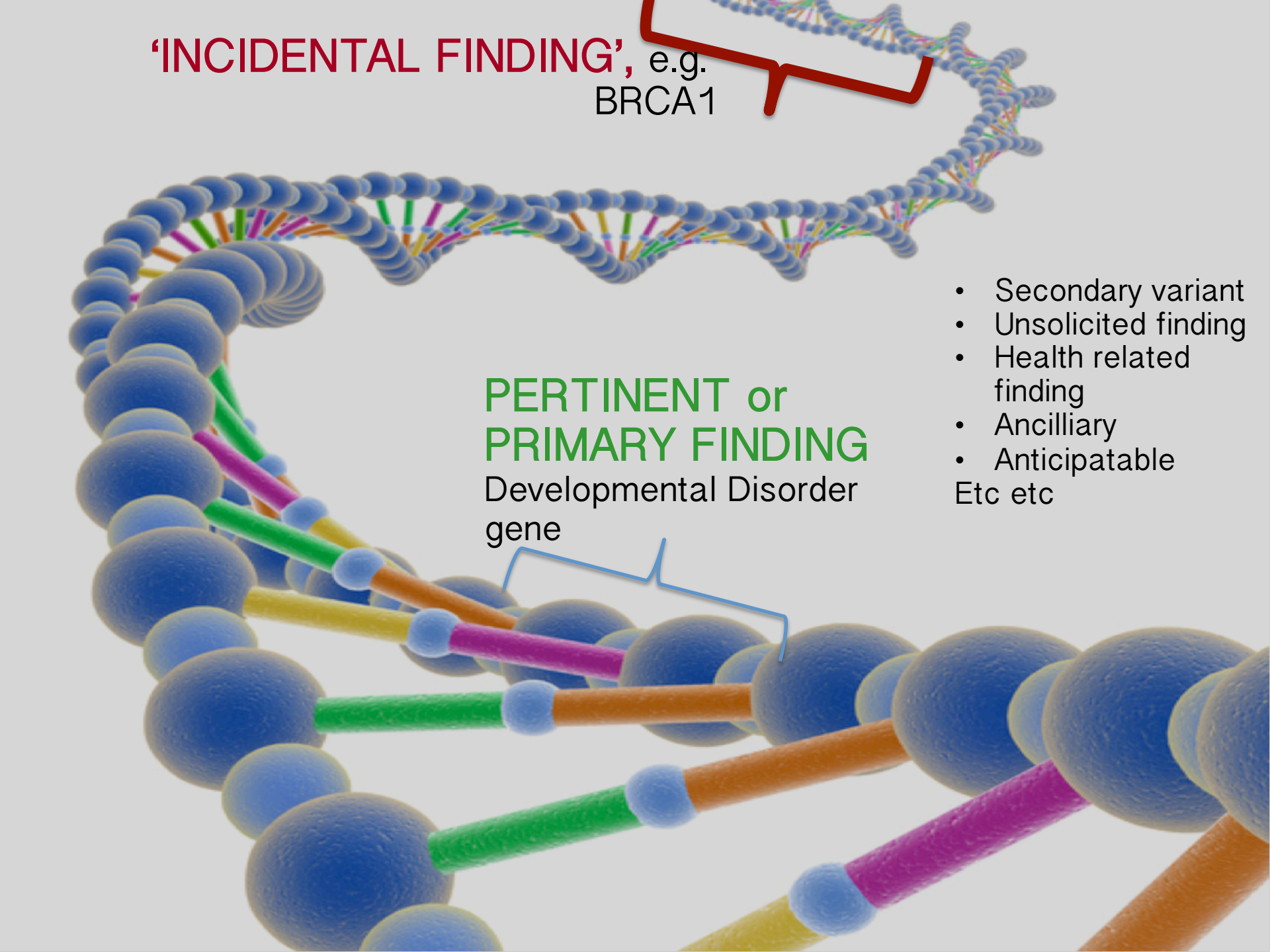
PCGF2

G➔A Chr17:36,895,854



Ethics, Social Sciences Study

- 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
• Ancilliary
• 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]this 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

ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

- 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

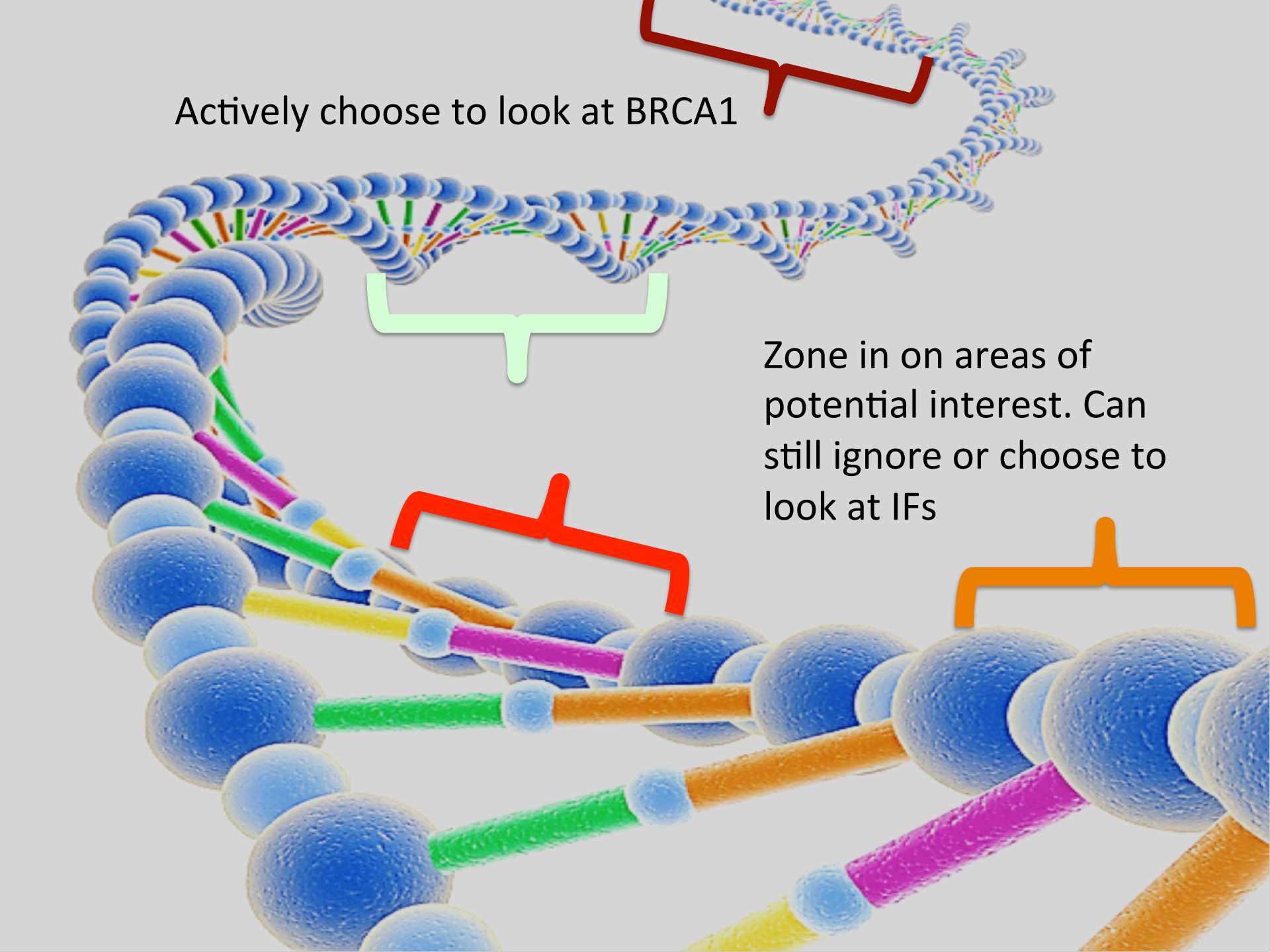
- HNPCC/Lynch syndrome genes
- MYH Associated polyposis
- BRCA1/2

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

Ethics and Genomics Survey

reset & start again

- ✔ 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

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Questionnaire designed by Dr Anna Middleton; Software developed by Eugene Bragin; Films by NeonOtter.com. www.ddduk.org, Wellcome Trust Sanger Institute, Cambridge UK

This site is hosted by the Wellcome Trust Sanger Institute.

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

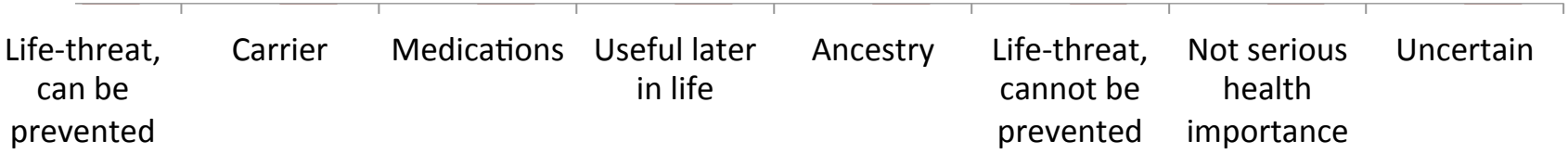
Other Health Professionals

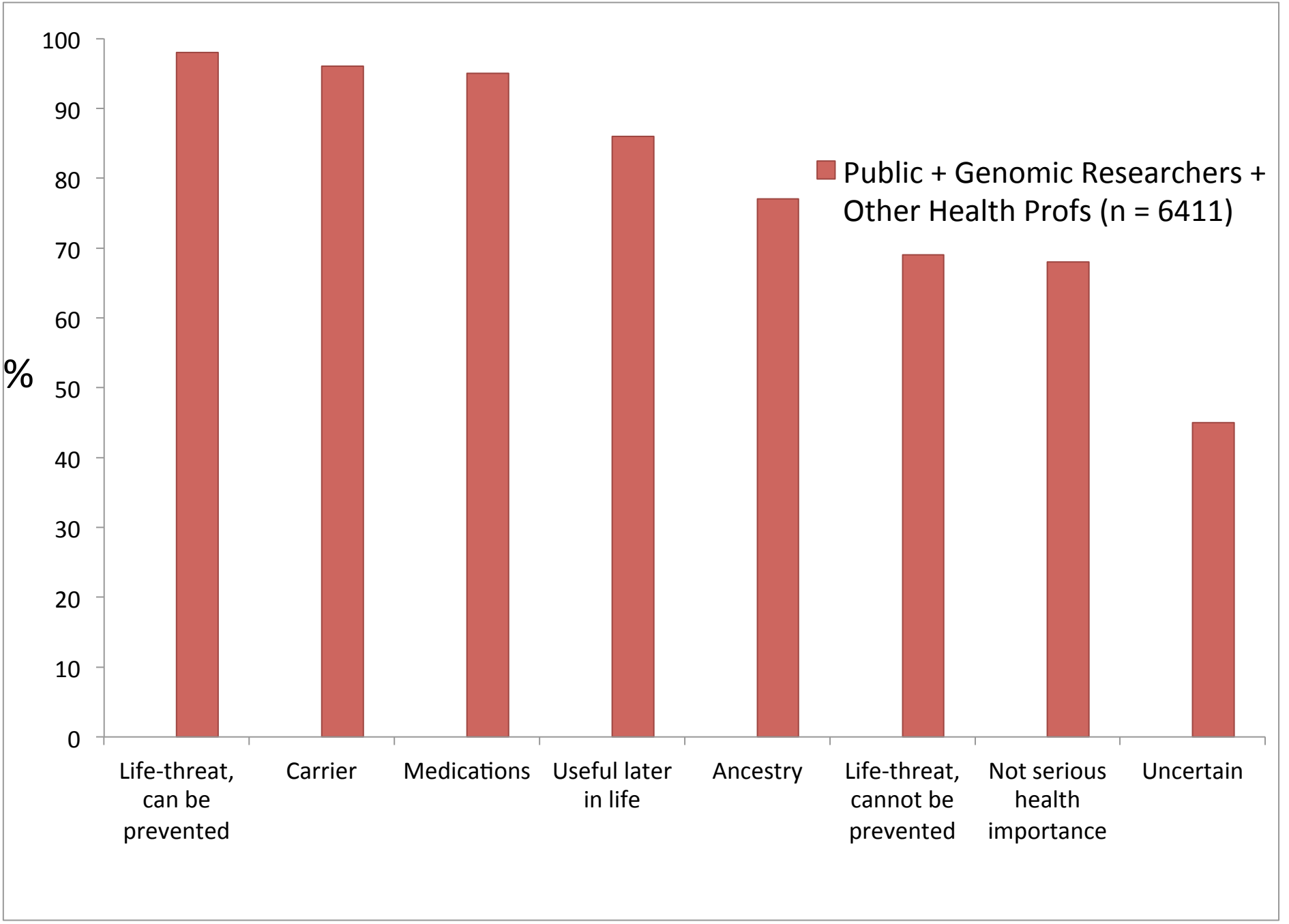
Genomic Researchers

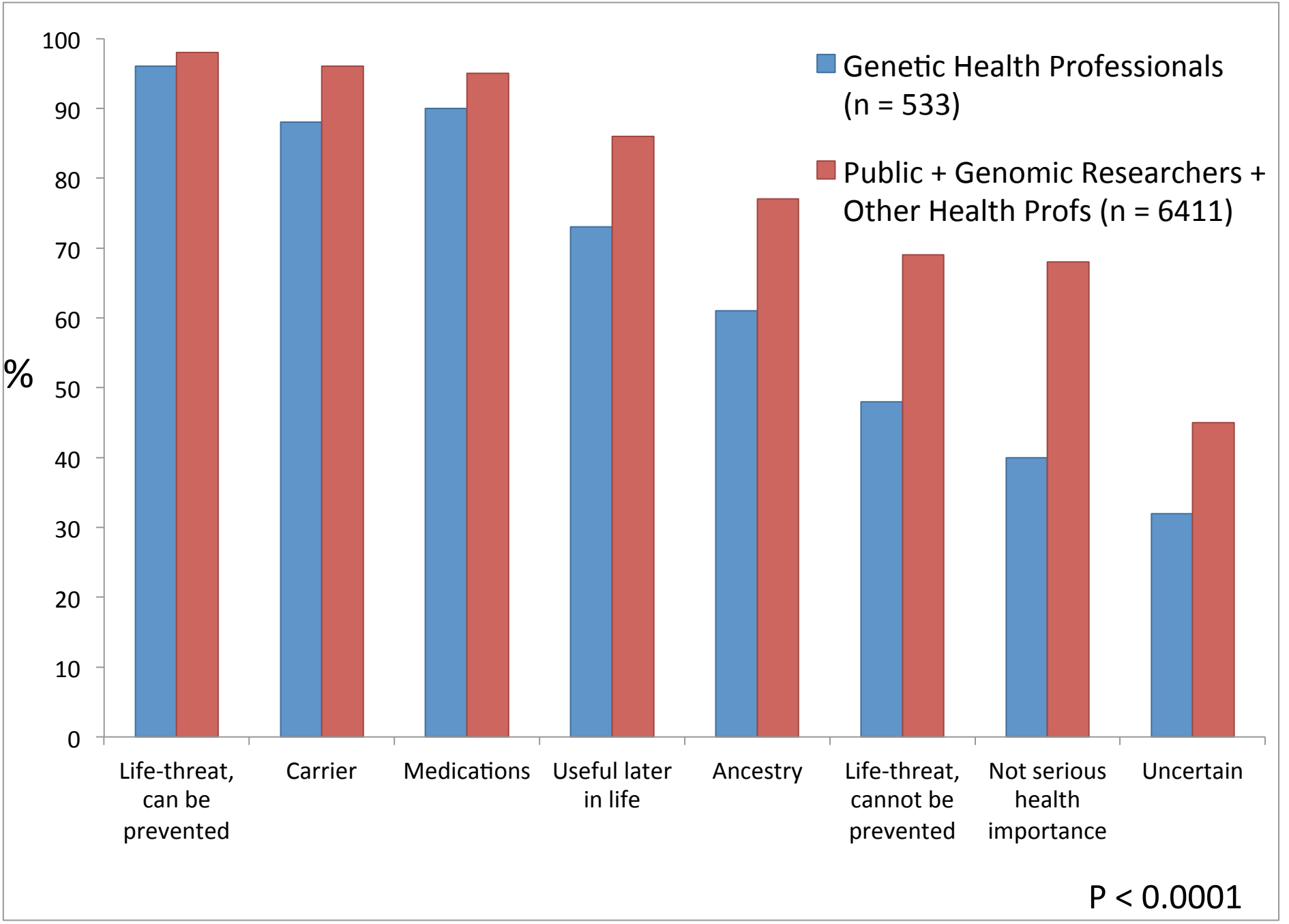
Public

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

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




100
90
80
70
60
50
40
30
20
10
0
%
Public + Genomic Researchers + Other Health Profs (n = 6411)
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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Life-threat, can be prevented
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Uncertain
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

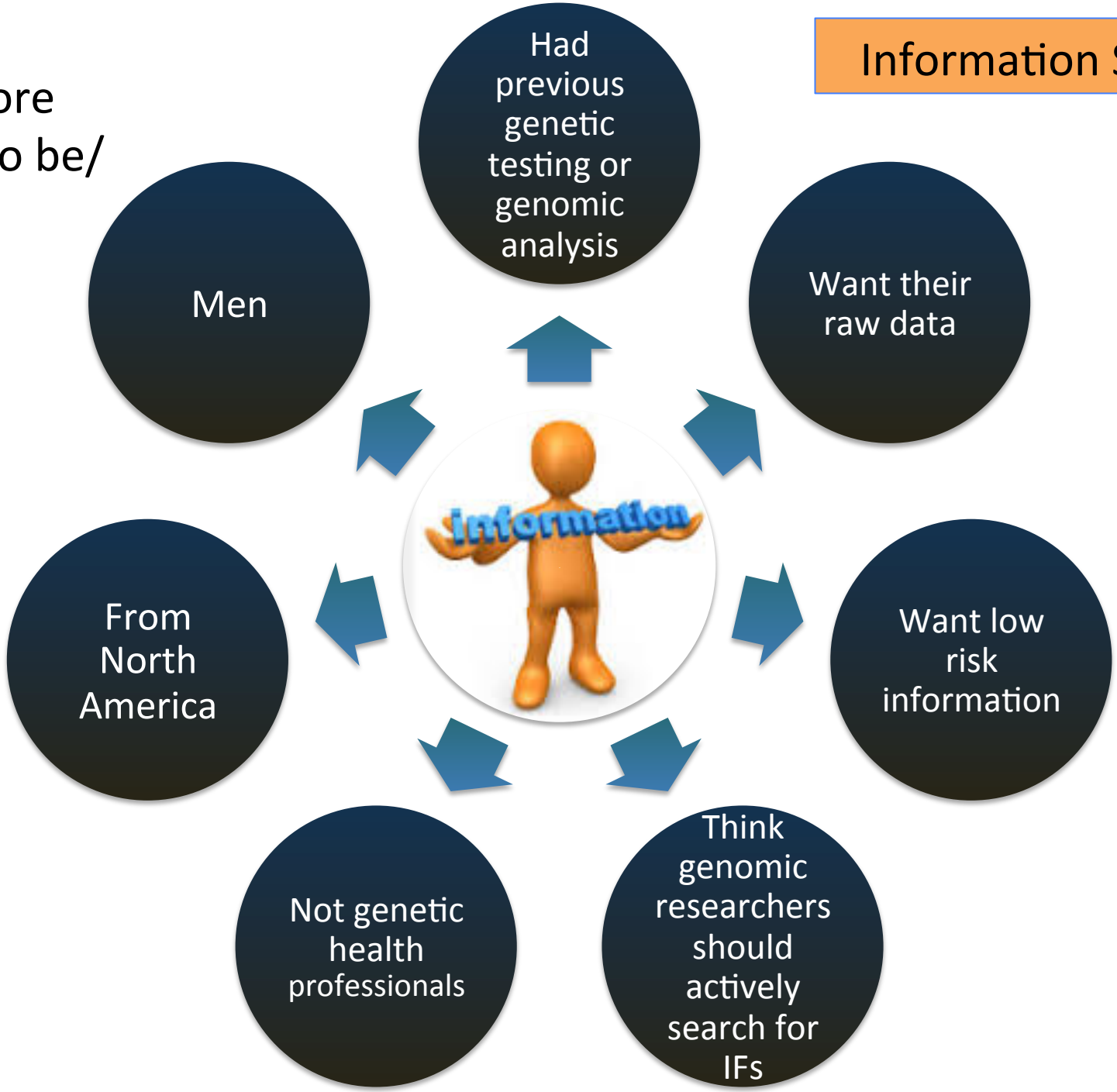
Information Seeker

Information Discriminator

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

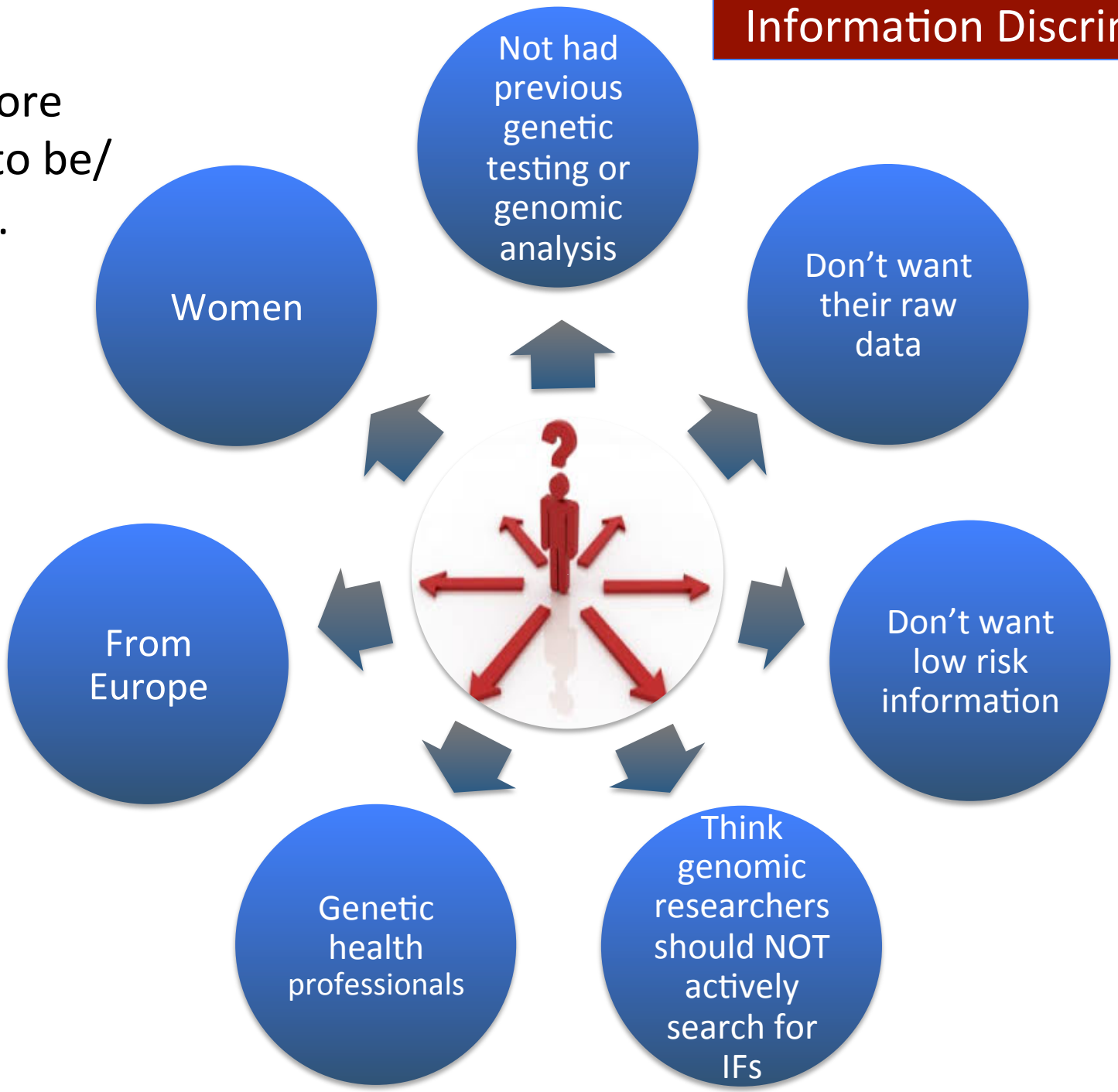
Information Seeker

Are more likely to be/ want…



Information Discriminator

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…

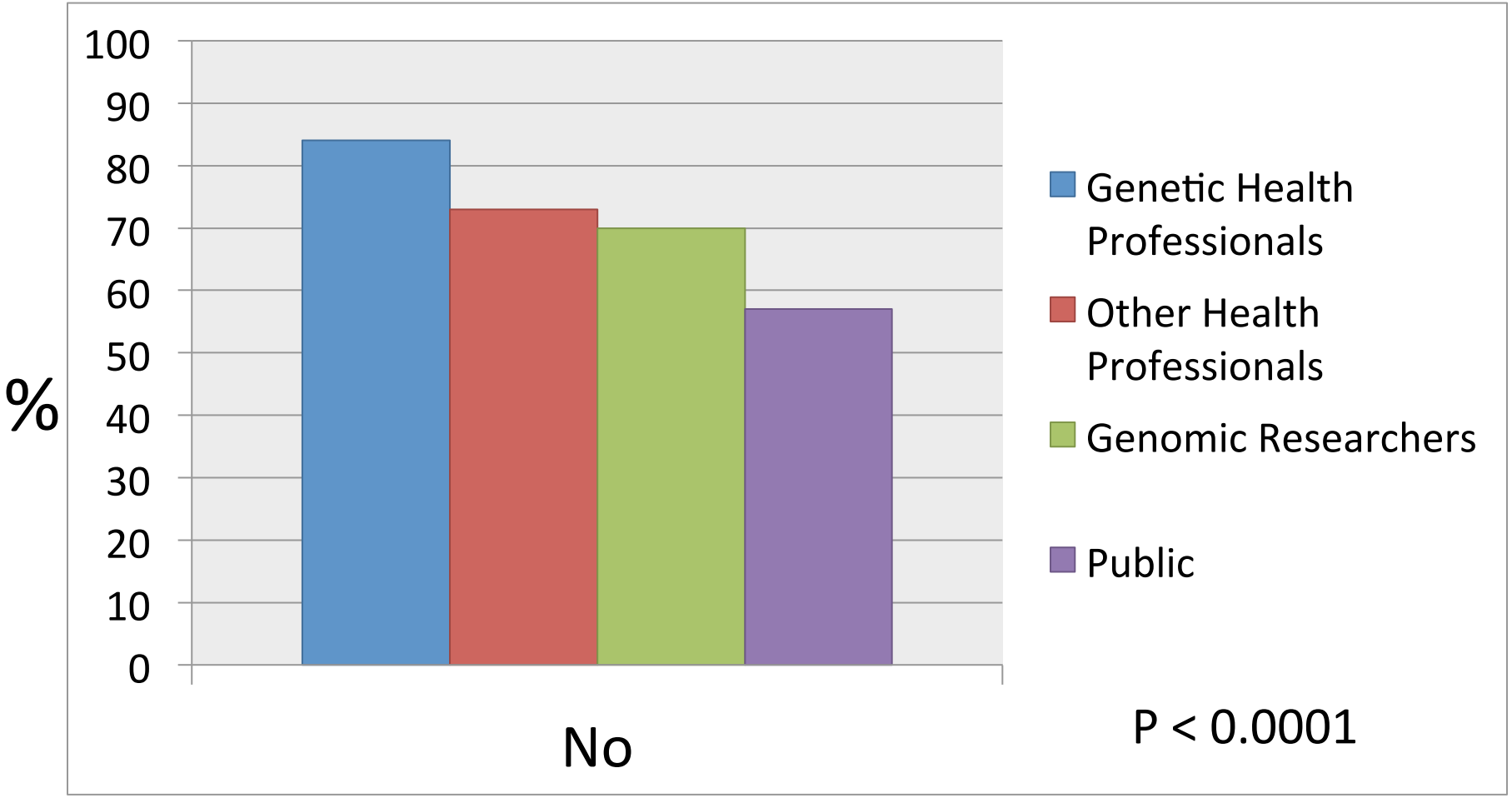
- 79% thought there should be a committee of people who did this including:
  - Genomic researcher
  - Health professional
  - Independent ethics personnel
  - Patient representative

- 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?

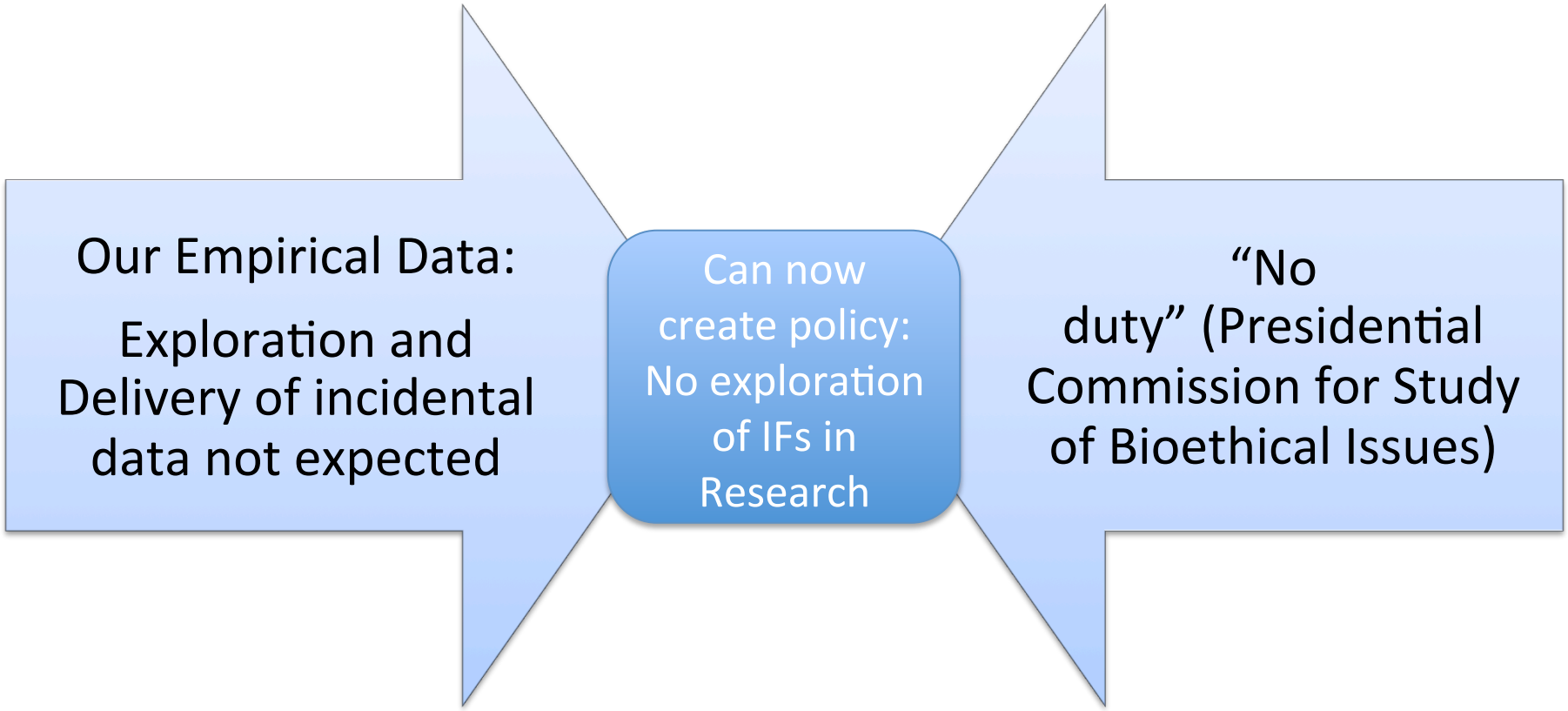
[There may be a cost…]

Should actively search for IFs?



Drawing this together...

Sequencing in a research setting:



THE LANCET

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).[1] But few studies have actually asked relevant stakeholders what their expectations are of researchers.[2]

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.[3] Whether to do such an opportunistic screen and what to do with incidental, health-related data, is subject to debate.[4]

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.[5,6] 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 respondees 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.[4] 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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1 Wolf SM. Introduction: The challenge of incidental findings. *J Law Med Ethics* 2008; **36:** 216-18.
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.

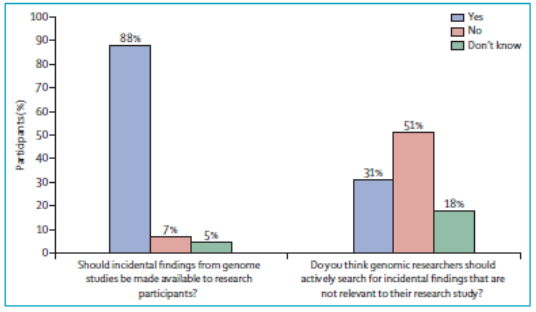

Figure: Attitudes towards sharing of and active searching for incidental findings

For the online survey see www.genomethics.org

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)

Anna Middleton[1], Chris Patch[2], Jennifer Wiggins[3], Kathy Barnes[4], Gill Crawford[5], Caroline Benjamin[6] and Anita Bruce[7] 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*[1], Anna Middleton *ethics researcher*[1], Hilary Burton *director and public health consultant*[2], Fiona Cunningham *Ensembl variation project leader*[3], Steve E Humphries *professor of cardiovascular genetics*[4], Jane Hurst *consultant clinical geneticist*[5], Ewan Birney *associate director*[3], Helen V Firth *consultant clinical geneticist*[6]

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

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