Incidental findings

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Scope of this presentation

- What are ‘incidental findings’?
- How did they become a problem?
- Biobanking legislation
- Impact of GDPR on notification
- How to develop a policy?
- Conclusions
- Q&A

Definition

"Incidental findings are previously undiagnosed medical or psychiatric conditions that are discovered unintentionally and during evaluation for a medical or psychiatric condition"

"… in a variety of settings, including routine medical care, during biomedical research, medical imaging, post-mortem autopsy, or genetic testing"

"creates a range of practical, legal, and ethical challenges for recipients and practitioners"

In fact most of the early literature is on genetic testing…

Wikipedia

History of reporting incidental findings

- mid-1990s statement by the international Human Genome Organisation* (HUGO), which declared that "choices to be informed or not with regard to results or incidental findings should... be respected"

- CIOMS** guidelines state that "individual subjects will be informed of any finding that relates to their particular health status" & "subjects have the right of access to their data on demand, even if these data lack immediate clinical utility" (1982, updated 1993, 2002)

* Established in context of Human genome Project 1989

**Council for International Organizations of Medical Sciences

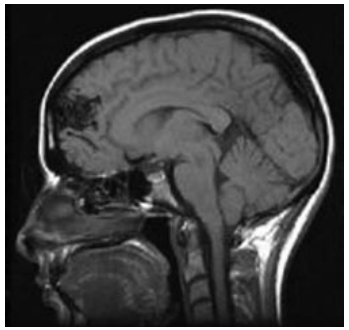
Incidental findings and more terminology…

- Incidental findings
  anticipatable incidental finding
  unanticipatable incidental finding

- Other terminology used:
  - Secondary findings
  - Incidental secondary findings
  - Incidental research findings
  - Discovery findings
    'when wide-ranging test intends to reveal anything of interest'

History of reporting incidental findings

Medical imaging IF meta-analysis



N= 27643 participants

3.9% (CI 0.4-27.1%) brain & body

½ suspected malignancies

"Such data could also help researchers calculate anticipated numbers of participants with potentially serious incidental findings in future studies, to inform the design of appropriate incidental findings handling policies."

Gibson et al. BMJ 2018;363:k4577

Findings in next generation sequencing

- Clinically **relevant to the diagnostic** question
- Clinically or socially **relevant** for the individual or his/her family members, for example, reproductive relevance to other members, but not relevant to the diagnostic question (‘**incidental findings’**)
- Not clinically relevant, (**‘neutral variants’**, which are not reported)
- Variants of ‘**unknown clinical significance’**, but potentially related to the primary clinical question (these findings may change status over time)

Hehir-Kwa et al. 2015

ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing

Robert C. Green, MD, MPH[1,2], Jonathan S. Berg, MD, PhD[3], Wayne W. Grody, MD, PhD[4–6], Sarah S. Kalia, ScM, CGC[1], Bruce R. Korf, MD, PhD[7], Christa L. Martin, PhD, FACMG[8], Amy L. McGuire, JD, PhD[9], Robert L. Nussbaum, MD[10], Julianne M. O'Daniel, MS, CGC[3], Kelly E. Ormond, MS, CGC[11], Heidi L. Rehm, PhD, FACMG[2,12], Michael S. Watson, PhD, FACMG[13], Marc S. Williams, MD, FACMG[14] and Leslie G. Biesecker, MD[15]

2013

American College of Medical Genetics

"incidental (or secondary) findings are results that are not related to the indication for ordering the sequencing but that may nonetheless be of medical value or utility to the ordering physician and the patient"

"minimum list of 56 highly-penetrant and medically actionable genes was recommended in any case of diagnostic WES/WGS, irrespective of the indication for testing and of the patient's age and preference "

"We recognize that there are insufficient data on penetrance and clinical utility to fully support these recommendations, and we encourage the creation of an ongoing process for updating these recommendations at least annually as further data are collected. "

ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing

ACMG Board of Directors[1]

2015

"… regardless of the specific indication for testing, laboratories will routinely analyze the sequence of a set of genes deemed to be highly medically actionable so as to detect pathogenic variants that ***may predispose to a severe but preventable outcome***.

Patients should be informed during the consent process that, if desired, **they may opt out of such analysis**. However, they should also be made aware at that time of the ramifications of doing so."

Criticism of initial recommendations

- Labelling IF in context of WES is paradoxical, because technique provides a host of 'incidental findings'
- '**incidental**' has a connotation of '**insignificance**'
- Difference between detecting an 'actual disorder' versus a (future) 'probability'
- Intentionally looking for additional results that exceed the indication for a test or consult, ***is not a routine action in general medical practice***
- Trend of medicalization, in which additional screening is ***a priori*** considered as ***beneficial***
- Obligatory reporting results, also against patients' will, violates right ***not to be informed***

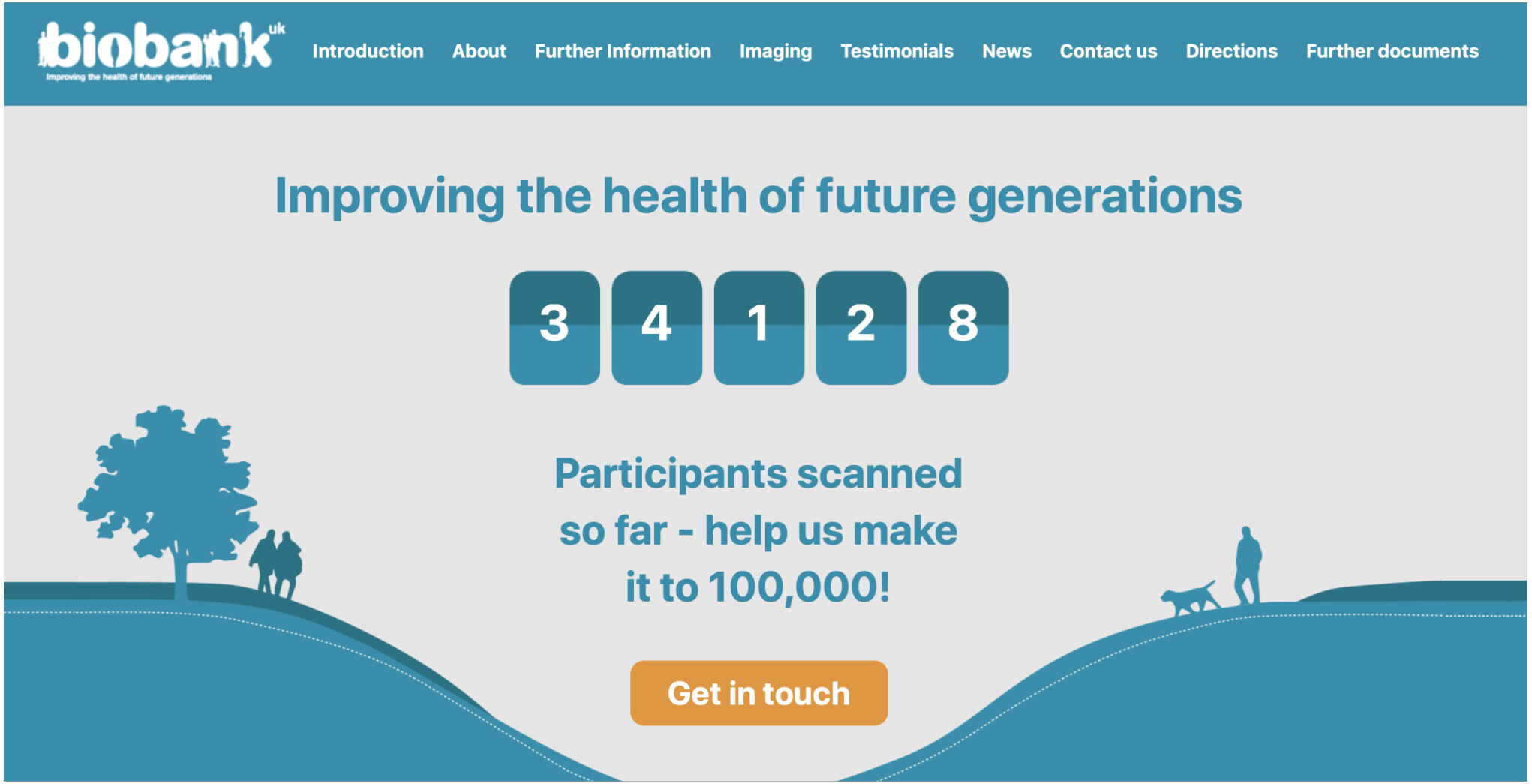
Saelaert et al. 2018

With **large cohort studies** reporting incidental findings became a problem…

"But, given the lack of knowledge at recruitment about the tests that might be done in this research context (and, hence, the inability to provide specific counselling), **UK Biobank will not provide participants with information** (genetic or otherwise) about their own individual results derived from examination of the database or samples by research undertaken after enrolment."

UK BIOBANK ETHICS AND GOVERNANCE FRAMEWORK Version 3.0 (October 2007)

UK Biobank imaging study



"You have taken part in UK Biobank on the understanding that you will not receive any results from the assessment visit other than the few simple measures, such as blood pressure, that you were given immediately after your visit. Neither will you receive feedback on the results of analyses carried out on your samples or data." (FEB 2019)

Why and how feedback on incidental findings?

- Autonomy
- Reciprocity
- Accountability
- Respect
- Ownership
- Continuity
- Health gain
- Counseling

- Biobank => donor
- Therapeutic relationship

- Letter to donor or physician
- Direct access to data (‘portal’)

When is an incidental finding '**medically relevant and actionable**'?

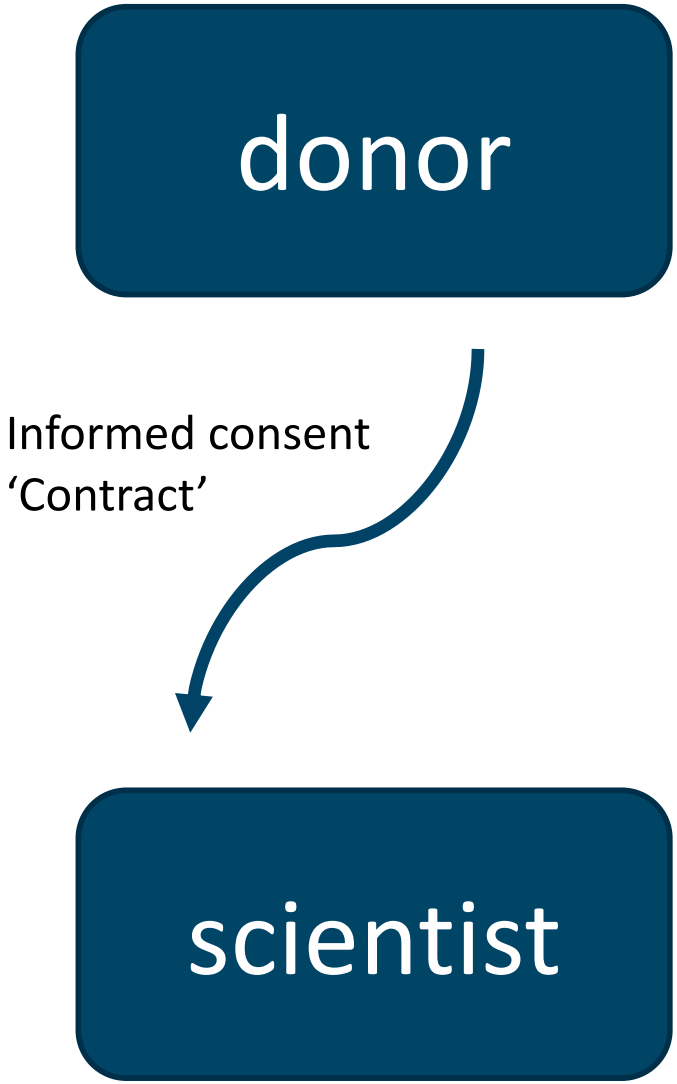
- Diagnostic NOT research context
- Validated in an accredited lab, GLP conditions
- Re-test for diagnostic purposes
- Clinically relevant – individual, not population level
- Prevention or therapy available
- Treating physician agrees with feedback
- Informed consent of donor on feedback

➢ Not only medically *relevant* and *actionable*, but also *reportable*

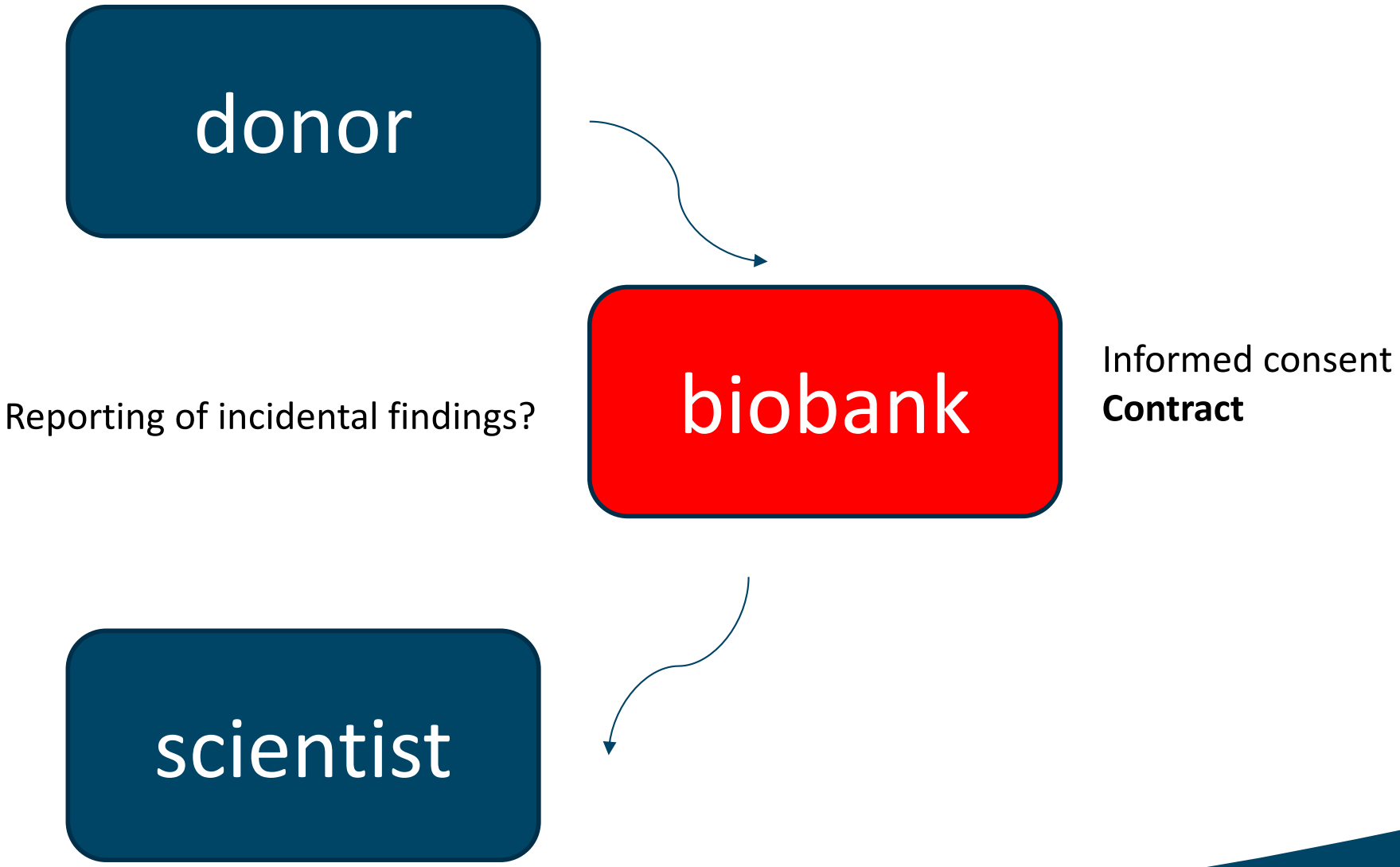
Human Tissue and Medical Research: Code of Conduct for responsible use (2011)

What about ‘incidental findings’ in biobanks?

Biosamples for scientific experiments



Biosamples for scientific experiments



Biobanking research

- a structured resource that holds human biological samples **and/or data** to facilitate research over time
- have become crucial to the conduct of genetic and genomic research, especially large-scale genomic research
- **donor should be informed of what will happen to the samples** taken and how the residual portions of samples will be used for research purposes
- **use is conditional** upon either the lack of opposition (*opting out*) by the patient or by the obtention of formal consent (*opting in*)

Biobanking ethics

- Consent and withdrawal of consent
- Protection of privacy and confidentiality
- Ownership of data and samples
- Benefit sharing
- Commercialization
- Sharing of data and samples with other (secondary) researchers
- ***Ethical responsibilities of biobanks with respect to the return of incidental findings***

Ethical arguments in reporting incidental findings

FOR

- researchers have a responsibility to make clear to research participants whether IFs and IRRs will or will not be offered back
- participant vulnerability and researcher fiduciary duties mean researchers owe a limited duty of "ancillary care" (care beyond that required to carry out the research safely)
- obligation to return IFs is rooted in the researcher's professional relationship with the participant

AGAINST

- return of individual findings will divert scarce resources
- invite research participants to mistake research for clinical care
- may involve return of findings that are not yet adequately understood and validated

Wolf et al. 2012

Current state of affairs?

Surveys of biobanks communicating incidental findings

- Participants expect feedback on ‘actionable’ IF
- “Code Goed Gebruik 2011” (NL): when does an IF become ‘actionable’?
- BBMRI.NL 144 biobanks, 73 responded, 23 (32%) reported IF
- Basic and clinical scientists seem to differ of opinion
- Structural and financial limitations

Human Tissue and Medical Research: Code of Conduct for responsible use (2011)
Vermeulen et al. 2014; Vaz et al. 2017

Biobank handling of incidental findings

Table 2 Return of information to individual contributors by type of biobank

	NIH (*n* = 43); ratio (percentage)			Other US (*n* = 30); ratio (percentage)		
	Yes	**No**	**NA**	**Yes**	**No**	**NA**
Will information of some sort be returned?	7/43 (16%)	14/43 (33%)	22/43 (51%)	6/30 (20%)	7/30 (23%)	17/30 (57%)

NIH, National Institutes of Health.

Adapted from Johnson et al.[3]

Wolf et al. 2012

Belgian biobank legislation

Information to the donor

When significant information is obtained on the donor health status when using his traceable human body material, he is entitled to this information.

How should this legal provision be interpreted?

The donor has the right to be informed when clinically relevant and validated information is available at his/her individual level.

The law of 22 August 2002 on the rights of the patient applies – *what about next of kin?*

Information to the donor

Information to the patient can be done:

1. when material was taken in a hospital: by the physician responsible for taking the human body material or the hospital's medical director;
2. when blood was collected in a blood collection unit: by the physician responsible for the collection of the human body material or the person responsible for the blood collection unit;
3. when material was taken outside the hospital: by the physician responsible for taking the material

Information to the donor

Can the donor waive the right to information in a consent form?

Yes, but this must be clearly stated in the consent form. If the lack of communication of certain information clearly causes harm to the health of the donor or third parties, the biobank manager may decide to inform the patient after consultation with another doctor.

Information to the donor

What are the responsibilities of the biobank manager?

The manager of the biobank is responsible for the various obligations that the RD and the law impose, including:

…

feedback to the donor;

…

The biobank manager may delegate his responsibilities, but he remains accountable.

GDPR - Rights of data subjects

a) **The right to be informed**: Data subjects have the right to be told about who will be processing their data and for what reasons.

b) **The right of access**: As with the existing legislation, data subjects have the right to access their personal data.

c) **The right to rectification**: Data subjects are entitled to have personal data rectified if it is inaccurate or incomplete.

d) **The right to erasure**: Also referred to as 'the right to be forgotten', individuals may request the deletion or removal of personal data where there is no compelling reason for its continued processing.

Policy on feedback of incidental findings

WHEN REPORTING

Ensure traceability

Include procedure in informed consent document

Describe procedure of feedback

Inform biobank of incidental findings

WHEN NOT REPORTING

Waiver in informed consent document (cfr. UK Biobank)

Lift traceability - anonymize

“therapeutic exception”?

Lifting of traceability

Once the human body material is included in the biobank, traceability can be lifted:

1. After receiving consent of the donor
2. If impossible or exceptionally inappropriate to seek this consent, after a positive opinion from an ethics committee
3. When the human body material has undergone a transformation

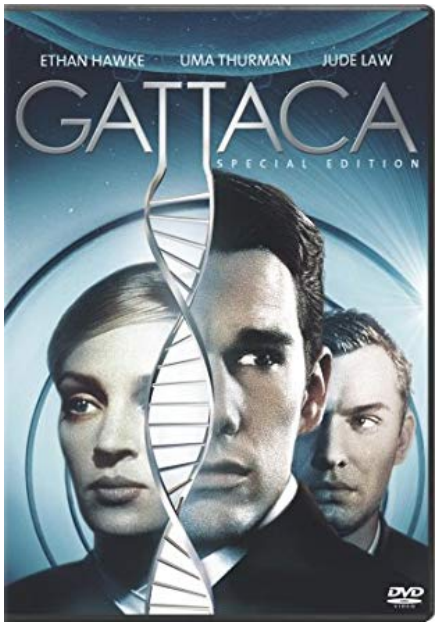
Conclusions

- Until present biobanks have no tradition of reporting incidental findings
- Respect for integrity of biobanks/scientific research as well as donors
- Biobanking legislation now instates feedback on significant health information
- Data should be valid, actionable, and reportable
- In drafting guidelines inclusion of perspective of donors and end-users is advocated
- Specific context of a donor's subjective perspective on incidental findings emphasized
- Right to information can be waived in informed consent

Research Club 6 juni 2019

"GDPR na 1 jaar: stand van zaken klinische studies en wetenschappelijk onderzoek"

Q&A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