phgfoundation
making science work for health

Harm, Discretion or Duty: the Changing Nature of the Return of Individualized Results in Genomics Research

The Legal and Ethical Challenges of Precision Medicine

Alison Hall

April 08 2016

The PHG Foundation

The PHG Foundation is a UK independent think-tank in with a special focus on **genomics** and other **emerging health technologies** that can provide more accurate and effective personalised medicine.

MISSION - to make science work for health

- We provide knowledge, evidence, tools and opportunities for policymakers to deliver rational and responsible changes in health policy and practice
- Member of Cambridge University Health Partners and Cambridge Institute of Public Health
- Active since 1997

Emerging questions about return of results in genomic research

? Normative

Should individualized genomic results be returned?

? Ethical

How can this be done in an ethical manner?: provide benefit, not be harmful, promote autonomy, and justice

? Legal

Compatible with existing legal principles, regulation and governance

phg foundation
making science work for health

Return of individualized results in genomics

'Return'

- Miss-description
- *Informing* a research participant (or their legal representative) of results of tests performed as part of the research

'Genomics' the study of all of a person's genes (the genome), including interactions of those genes with each other and with the person's environment.

phg foundation
making science work for health

Return of individualized results?

‘Pertinent’

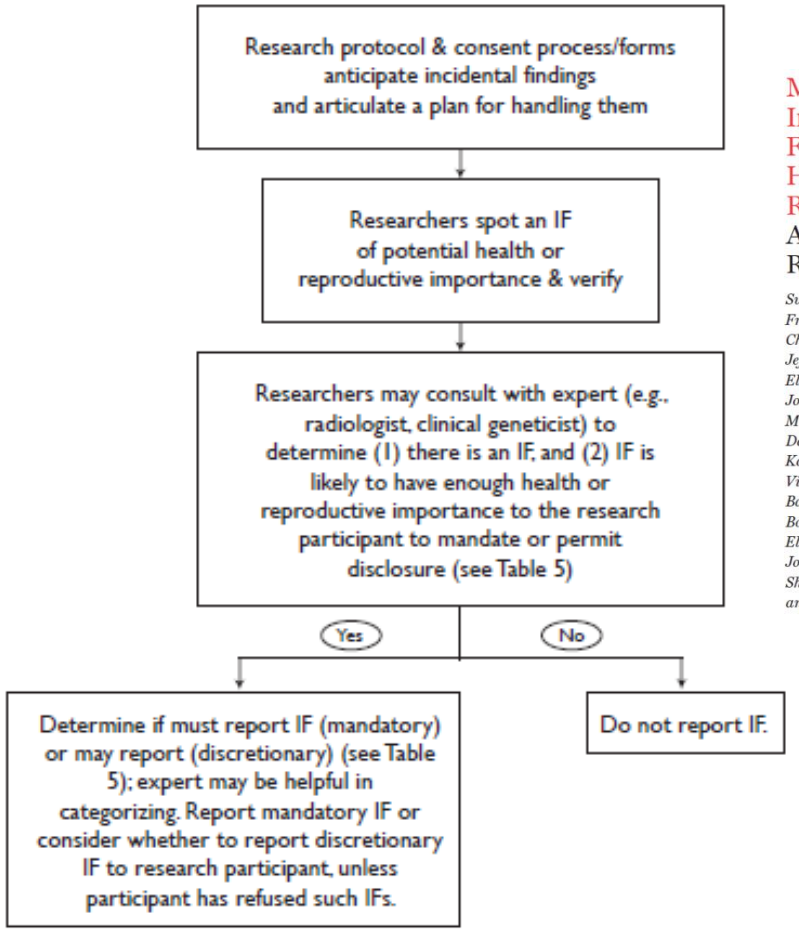
Findings relating to the primary purpose

‘Incidental’

A finding concerning an individual research participant that has *potential health or reproductive importance* and is *discovered* in the course of conducting research but is beyond the aims of the study. This means that IFs may be on variables not directly under study and may not be anticipated in the research protocol (Wolf et al)

Table 4

Recommended Pathway for Handling IFs in Research



Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations

Susan M. Wolf, Frances P. Lawrenz, Charles A. Nelson, Jeffrey P. Kahn, Mildred K. Cho, Ellen Wright Clayton, Joel G. Fletcher, Michael K. Georgieff, Dale Hammerschmidt, Kathy Hudson, Judy Illes, Vivek Kapur, Moira A. Keane, Barbara A. Koenig, Bonnie S. LeRoy, Elizabeth G. McFarland, Jordan Paradise, Lisa S. Parker, Sharon F. Terry, Brian Van Ness, and Benjamin S. Wilfond

Incidental Findings in Human Subjects Research
Journal of Law, Medicine and Ethics Summer 2008 pp 219-248

Wolf et al: recommended classification (2008) (summary)

Category	Relevant incidental findings	Recommended action
Strong net benefit	• Condition likely to be life threatening • Grave condition that can be avoided or ameliorated • Significant risk of a condition likely to be life-threatening • To avoid or ameliorate a condition likely to be grave • Reproductive decision making to avoid or ameliorate a significant risk of offspring having a life-threatening or grave condition	Disclose unless P elected not to know
Possible net benefit	• Non fatal grave or serious condition which cannot be avoided or ameliorated (likely to be viewed as important) • Significant risk of a non-modifiable grave or serious condition (likely to be viewed as important) • Reproductive decision making to avoid or ameliorate offspring having a condition likely to be serious	May disclose unless P elected not to know
Unlikely net benefit	• A condition not likely to be of serious health or reproductive importance • Condition whose likely health or reproductive importance cannot be ascertained	Do not disclose

Return of individualized results?

‘Secondary’

Findings that are *anticipated* and *can be actively sought* with a given procedure, but are not the *primary* target of the research evaluation

Presidential Commission for the Study of Bioethical Issues 2013

Context-Specific Recommendations

Clinical Recommendations

Consent in the Clinical Context

Empirical Data in the Clinical Context

Clinical Judgement in Managing Incidental Findings

Research Recommendations

Consent in the Research Context

Planning for Incidental Findings in Research

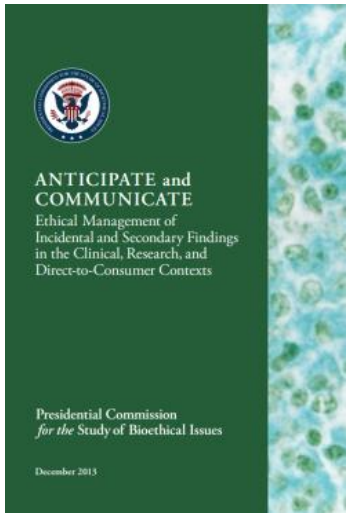
No Duty to Look for Secondary Findings in Research

Direct-to-Consumer Recommendations

Consent in the Direct-to-Consumer Context

Government Regulation in the Direct-to-Consumer Context

Industry-Wide Best Practices in the Direct-to-Consumer Context



phg foundation

making science work for health

Return of individualized results?

Additional 'looked for' findings

Genomic changes that are *unrelated* to the cancer or rare disease, and *known* to cause serious, life threatening conditions. 1:100 will have one of these conditions

- Estimates of 1-3% 'high risk of serious disease that could be mitigated by timely medical intervention

  Darnett AJ et al (2016) A Clinical Service to Support the Return of Secondary Genomic Findings in Human Research AJHG 98, 435-441 March 3 2016

- 1% candidate variants in the 56 ACMG genes (1000 Genomes dataset)

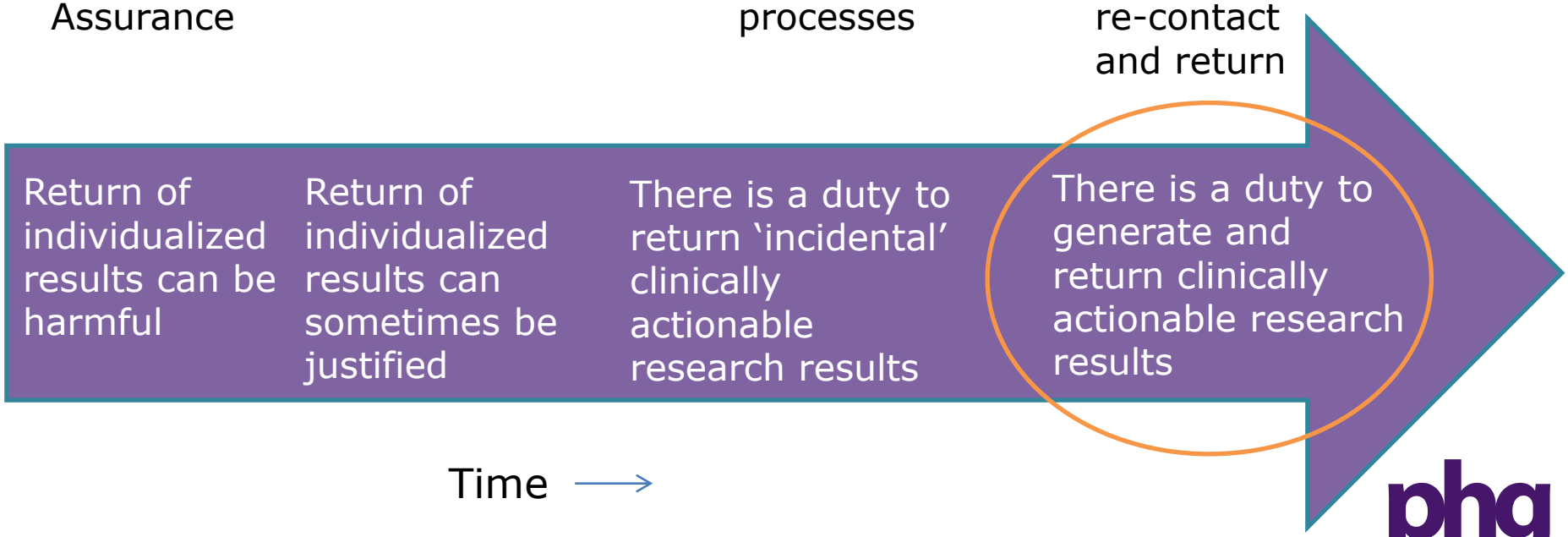
  Olfson E et al (2015) Identification of Medically Actionable Secondary Findings in the 1000 Genomes Plos One Sep 2 10(9):e0135193

- But the relationship between genotype and phenotype likely to be 'promiscuous'

  Lu JT et al (2014) Genotype-Phenotype Correlation – Promiscuity in the Era of Next Generation Sequencing NEJM DOI:10.1056/NEJMp1400788

The inexorable change in responsibilities around 'return' of results

Scientific validity	**Clinical utility**	**Operationalising return**	**Defining scope**
Validation Quality Assurance	Distinguishing subtypes	'No surprises' Consent processes	Extent of duty Logistics for re-contact and return



phg foundation
making science work for health

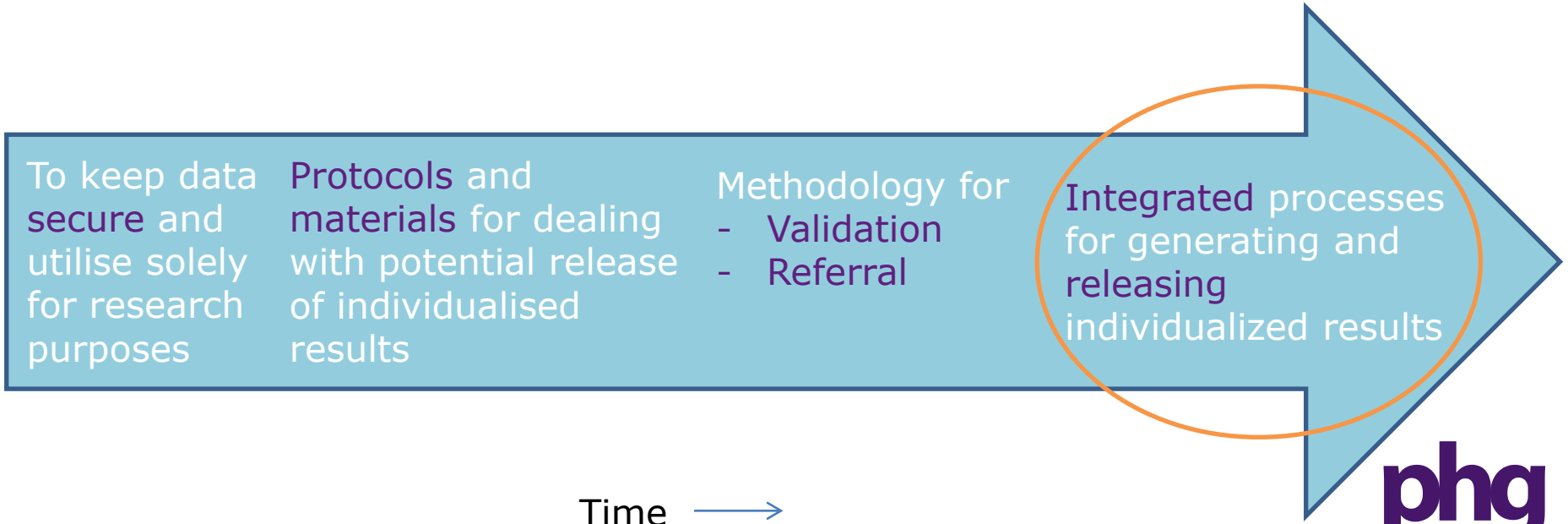
The nature of that responsibility

Non-maleficence
Paternalism
Release of data has potential to cause distress

Beneficence
Infrastructures
Protocols
Information sheets
Consent forms

Justice
Elements
Provision
Expertise
Insurance
Funding

Respect for Autonomy
Looking beyond participants
- Children
- Biological



phg foundation
making science work for health

The current position (1)

- Literature and policy review
- Empirical research with stakeholders

Sénécal et al Statement of Principles on the Return of Research Results and Incidental Findings in Paediatric Research: A Multi-site Consultative Process DOI:10.1139/gene-2015-0092

- 'a continuum of decisions to return research results depending on numerous contextual factors
  - Best interests of children
  - Clinical significance of findings
  - Need to adhere to professional standards
  - Obligations should not extend beyond the duration of the research

Rahimzadeh V et al (2015) To disclose, or not to disclose? Context matters *EJHG* (2015) 23,279-284

phg foundation
making science work for health

The current position (2)

- A plethora of guidelines acknowledging the potential for communicating individualized results
- *Empirical work*
  - Marked differences between stakeholder groups
  - Participants tend to favour disclosure even if findings are not clinically significant
  - Willingness amongst research ethics committees to countenance feedback BUT limitations are lack of skills and resources to identify, verify, interpret and return results

Darnell et al A Clinical Service to Support the Return of Secondary Genomic Findings in Human Research http://dx.doi.org/10.1016/j.ajhg.2016.01.010

- In the short term – practices are likely to be:
  - Highly variable
  - Potentially detrimental effect

phg foundation
making science work for health

What are the principles governing desirability of return ?

A Clinical Service to Support the Return of Secondary Genomic Findings in Human Research

Relevant Legal Principles

Duty of care

Potential clinical utility

Proximity

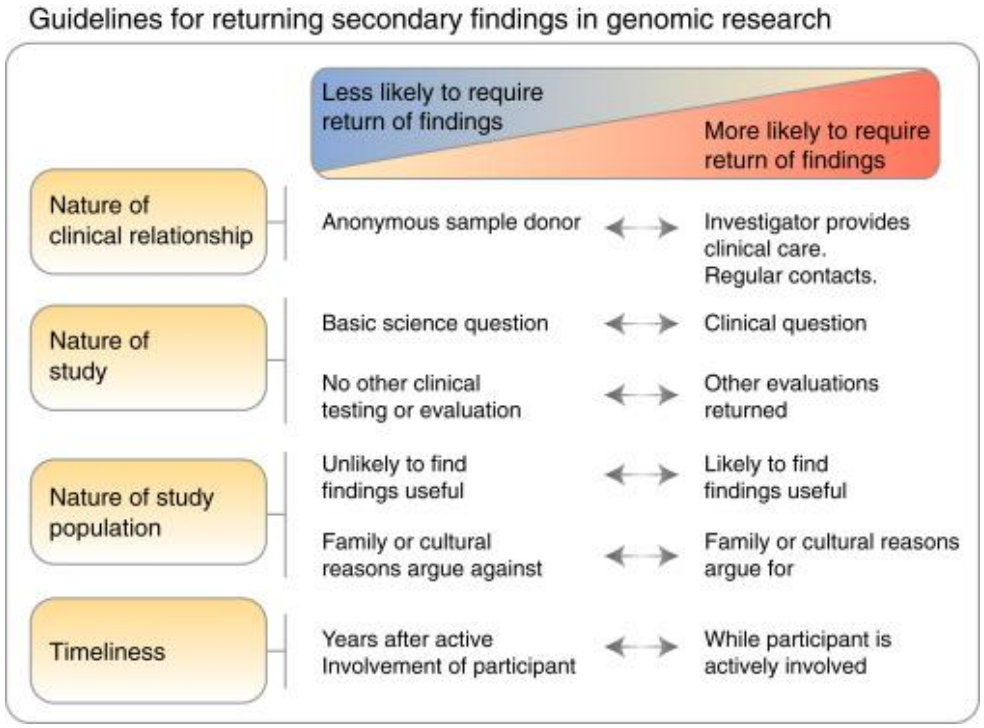


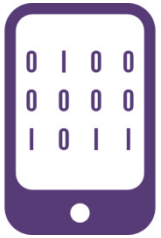
Figure 1. Graphical Representation of Some Key Attributes of Research Studies that Argue For or Against Seeking and Returning Secondary Findings

Andrew J. Darnell et al et al
http://dx.doi.org/10.1016/j.ajhg.2016.01.010

phg foundation
making science work for health

How might a duty to return individualized research results be characterised?

- Is this a normative obligation or legal duty?
- What form of duty (care, warn or rescue)
- By whom is it owed? (interpretation and disclosure are multidisciplinary activities)
- To whom is the duty owed?
- What could it involve?
  - Examining data for secondary and incidental findings (and relevant pertinent findings)
  - Stipulating the actions to be taken (e.g. to validate/refer)
  - Setting out what research participants are told and when
  - Provision for guardian/legal representatives
  - Full descriptions in protocols/apportioning liability



What is the likelihood of such a duty developing? *And bringing a successful claim?*

Montgomery v Lanarkshire Health Board [2015]

- Is a duty 'fair, just and reasonable'?
- *Montgomery* – 'risks are patient-centred'
- Displaces *Bolam* – 'to exercise the care and skill of a reasonable professional'

➢ Applied different tests to risk communication and to treatment/diagnosis

➢ The obligations arising in clinical care and research are very different but the boundaries between these activities are often blurred

➢ Increasing instances of generating and disclosing clinically actionable results (whether pertinent, secondary or incidental) in genomic research

➢ Clinical care and research practice are becoming inexorably linked

phg foundation
making science work for health

What thresholds must be met to establish liability for negligent non-disclosure?

- **Duty**
- **Breach**
- **Damage**

Successful claims unlikely

Duty to exercise reasonable skill

'Informational harm'

Colin Mitchell, Helex 2016

Two ways in which liability for non-negligent disclosure in genomic research could arise:

(a) Greater personalization of the genomic sequencing process in research

(b) A failure to communicate clinically actionable individualized findings to family members in specified cases

phg foundation

making science work for health

Potential impacts of personalization of the return of results in genomic research

Elements of personalization might include:

- Inviting participants to select genes, disorders or categories in advance of secondary findings analysis
- Dictating the scale and timing of return (other than respecting a 'right not to know')

If this results in:

- Increased 'quasi clinical' contact between researcher and participant
- Tailored generation, analysis and feedback of results
- Heightened visibility ('service' performed with reasonable skill without breaches)

➢ Might imply that a **duty of care** exists

phg foundation
making science work for health

Extending the duty of care to relatives

A duty of care may be more likely to be recognized:

- Especially unclear boundaries between clinical care and research
- Close biological relatedness with the participant
- Where the family member is a parent or guardian
- Foreseeable harm (disease penetrance/ timeliness)
- Where the research participant has died

ABC v St George's Healthcare NHS Trust & Others 2015 (UK)

- Duty to families rather than individuals
- Requires a balance between right to confidentiality and risk of harm to others
- Possible emergence of a duty to consider warning relatives and exercise reasonable skill and judgment

phg foundation
making science work for health

Implications for practice

FOR THE SECTOR

- Need harmonized, multidisciplinary approaches
- Clarity - nature of the activity and its objectives
- Legally and ethically sound
- Build expertise within IRB/RECs
- Transparent and accountable (to build trust)

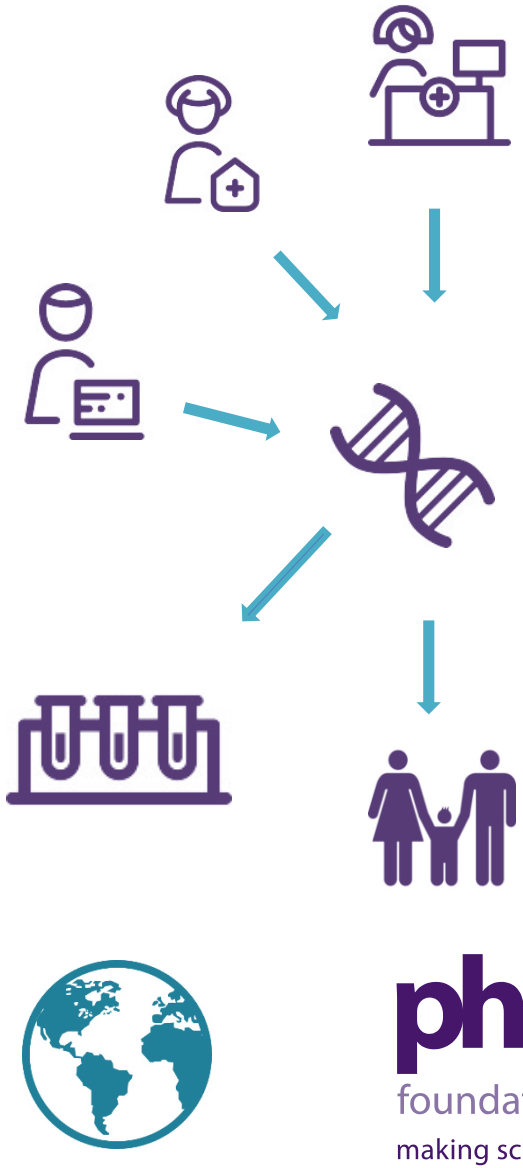
FOR INDIVIDUAL RESEARCHERS

- Consistent with existing legal principles, regulation and governance
- Strong leadership and appropriate clinical support
- Accessible patient facing materials (PIS, consent forms)
- Consider reasonable expectations of participants
- Provision for disclosure in funding, insurance

phg foundation
making science work for health

Summary

- Existing terminology is unhelpful and misleading
- Current proliferation of practices is likely to lead to inconsistencies
- Adopting more personalized approaches to communicating individualized research results could have unintended impacts
- Need for proactive policy development at a global level



phg foundation
making science work for health

phgfoundation

making science work for health

CAMBRIDGE UNIVERSITY
Health Partners

Knowledge-based healthcare

alison.hall@phgfoundation.org