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Overview

- The problem
- The traditional solution
- Why the traditional solution may not work any longer – disappearance of the distinction between clinical and research results
 - Pharmacogenomics
 - Pleiotropic genes
 - Genome Wide Association scans
- The future and the \$1000 genome

The problem

During gene-epidemiological research information may be generated about a particular identifiable individual that is of *prima facie* importance to that individual

Should that information be given back to the individual?

The traditional solution

No obligation to feed back information to the individual unless immediately clinically relevant

The justification for this view is:

- The interpretation of the results are uncertain
- The results have been produced using research methods that are less reliable than “clinical” methods
- Feeding back information may be unwanted or may cause distress – paternalism?
- Researchers are not medical doctors, therefore no professional obligation or duty of care

“MRC *Ethics Series* Human Tissue and Biological Samples for use in Research” – An example of the traditional approach

8.3 Incidental clinical findings

Where a result that can be linked to an individual has immediate clinical relevance (for example, if it reveals a serious condition for which treatment is required), the clinician involved has a clear duty of care to inform the research participant, either directly or via the clinician responsible for his or her care. The clinician responsible for care should always be notified, and participants should be informed that this will occur. A research result should not be relied on as the sole basis for diagnosis, since quality control standards in research laboratories generally differ from those used for clinical testing. Research participants or their clinicians should be advised to seek a repeat or confirmatory test by a clinical diagnostic laboratory where possible. Where a confirmatory test is not available via the NHS the diagnosis might need to be verified by the research laboratory using a new sample.

8.4 Research results

There is currently no consensus on whether, or under what circumstances, it is appropriate to feed back research results to participants on an individual basis⁵. Often the clinical relevance or predictive value of a research result is unclear, at least initially, and there will be no individual data of value to be fed back.

It will always be difficult to define the point at which a research hypothesis becomes a clinical fact. Where consent is being sought for a specific research project at the time a sample is collected, the potential relevance, if any, of the results for the participant should be explained and the opportunity to receive feedback of individual results should be offered where appropriate. There should be a mechanism in place for participants to change their minds (for instance, a contact telephone number). If feedback is requested, they should be given appropriate instructions about how to notify researchers of a change in their address.

Researchers feeding back individual results must be prepared to explain their significance to the participant and to advise on access to counselling or treatment where indicated.

It is good practice to offer research participants the opportunity to be kept informed about the general results of research projects done using the samples they have donated, though this may not be appropriate in all circumstances. Participants could be informed by posting information on research outcomes on a website, or by offering them the opportunity to receive a newsletter.

Where the clinical relevance of research results becomes clear some time after the sample was obtained, or where the results obtained from secondary research may impact on the donors' interests, these routes should be used to inform donors that results of potential interest may be available and offer them the opportunity to receive individual feedback or advice if they wish. Similarly, when new predictive tests of clinical value become available as a result of the research, participants can be informed how to access these tests if they wish.

Where samples may subsequently be used for secondary studies, a mechanism should be put in place to allow participants the opportunity to seek individual results that might impact on their interests. It is acceptable for the onus to be on the participant to seek the information rather than on the researcher to be pro-active in providing it. The research protocols for secondary studies and the arrangements (if any) for feeding back results to participants must be reviewed by an ethics committee, preferably the committee that oversaw the making of the collection. If samples from a collection are shared with other researchers, the custodian of the collection is responsible for all contacts with donors, including providing any information on research results with a possible impact on individuals.

8.5 Specific issues related to genetic research

Much genetic information obtained for research purposes is of unknown or uncertain predictive value. Genetic tests of known clinical or predictive value should not be done on samples that can be linked to an individual without their specific consent, and appropriate counselling should be available if consent for such a test is sought. Participants should be advised of the possible implications of genetic information for other family members and the potential impact on family relationships, and also of the implications of genetic risk information for employment or their ability to obtain insurance, before they decide whether to give consent to the test or whether they want to know the result. The feeding back of other genetic information, the significance of which is currently unknown, could also have similar implications in the future. The clinician responsible for care should always be notified, and participants should be informed that this will occur.

A research result should not be relied on as the sole basis for diagnosis, since quality control standards in research laboratories generally differ from those used for clinical testing. Research participants or their clinicians should be advised to seek a repeat or confirmatory test by a clinical diagnostic laboratory where possible. Where a confirmatory test is not available via the NHS the diagnosis might need to be verified by the research laboratory using a new sample.

The traditional solution under pressure - Pharmacogenomics

A significant proportion of pharmacogenomic research involves typing for different variants of the main drug metabolising CYP450 enzyme system and studying the correlation between CYP450 types and drug effects and side-effects

Some CYP450 enzymes metabolise very commonly used drugs

Typing for CYP450 will therefore very frequently produce information that is likely to be of current or future clinical relevance to the individual

The traditional solution under pressure – Pleiotropic genes

Many genes are pleiotropic, that is influence two different phenotypic traits

One example is apoE which produces a protein involved in blood lipid regulation and is a risk factor for Alzheimer disease

The research project may investigate “one side” of a pleiotropic gene where there is uncertainty about function and phenotypic expression, but there may be no uncertainty on the other side which may be clinically relevant

The traditional solution under pressure – Genome Wide approaches

In genome wide approaches a very large number of markers spaced across the genome are typed in order to pinpoint associations between common diseases and genomic regions

Most of the markers have no (known) function but some have

A genome wide scan therefore often, as a side-effect produces results that are important for the individual

What creates the pressure on the traditional approach

- More information generated in each project (no longer “one project – one gene”)
- Some of the information generated has well known interpretation (no uncertainty)
- *Changes in general use of genetic information in clinical practice may change requirements for analytic accuracy*

The future

Technological developments:

- Number of markers in genome wide scans rapidly increasing
- The advent of the “\$1000 genome”
- Tools for “lay interpretation” of genetic information

Social developments

- Routine use of genetic information in clinical medicine

Result: many more clinically relevant and interpretable results produced in more and more research projects