Ethical issues in genomic research: proposing guiding principles co-produced with stakeholders

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Abstract

Ethical guidance for genomic research is increasingly sought and perceived to be necessary. Although there are pressing ethical issues in genomic research – concerning for example the recruitment of patients/participants; the process of taking consent; data sharing; and returning results to patients/participants – there is still limited useful guidance available for researchers/clinicians or for the research ethics committees who review such projects.

This report outlines the ethical principles and guidance for genomic research co-produced with stakeholders during two workshops which took place in the UK between November 2016 and May 2017. The stakeholders involved in these workshops included: healthcare professionals, genomic research teams, academics, patients, biobank managers, and representatives from the Health Research Authority (HRA), NHS Research Ethics Committees, patient support groups, pharmaceutical industry, and health policy think tanks. The co-produced principles and guidance are specifically aimed at researchers/clinicians and members of NHS Research Ethics Committees, and are formulated with the intention to be clear and accessible, both in terms of content and language, to these groups.

Introduction

Ethical guidance for genomic research is needed to improve research processes, to facilitate the translation of research in clinical practice, and to foster trust (and trustworthiness) amongst patients/participants and researchers, and other stakeholders. Whilst there is ethical guidance on clinical trials and broad research practice [1-4], there is scant relevant guidance available for researchers/clinicians undertaking genomic research, or for the research ethics committees who review projects [5].

Therefore, such guidance is increasingly sought and perceived to be necessary. There are pressing ethical issues in genomic research concerning in particular: the recruitment of patients/participants; the process of taking consent; data sharing; and returning results to patients/participants. These issues are creating serious challenges to researchers, patients/participants, research ethics committee members, and other groups involved in genomic research. For example, genomic research increasingly involves recruiting patients receiving health care to research, thus blurring lines between research and clinical practice. Feeding back individual findings to research participants, who are also often patients, may raise particular issues for participants concerning ongoing and future treatment decisions.

One of the main benefits of the ethical debate in genomic research is to promote constructive interactions among research stakeholders. Ethics can inform the design and regulation of genomic research by helping to identify and to protect the needs of the diverse stakeholders. It is also important to note that current debates on the ethics of genomic research tend to exclude from meaningful engagement important stakeholders: the pharmaceutical industry, and other industry partners such as Contract Research Organisations (CRO).

We have conducted three workshops with the objective of bringing together key stakeholders to reflect on the ethics of genomic research. The stakeholders involved in these workshops included: healthcare professionals (n=4), genomic research teams (n=5), academics (n=5), patients (n=2), patient support groups (n=1), biobank managers (n=2), and representatives from the Health Research Authority (HRA) (n=1), NHS Research Ethics Committees (n=1), pharmaceutical industry (n=2), and

health policy think tanks (n=1). One of the patients participating in this workshop was involved in genomic research. Some, but not all the representatives from the above groups participated in all three workshops. This reflected our commitment to strike the balance between continuity of engagement and an inclusive participatory agenda.

The aim of the first workshop was to identify important ethical issues, areas of best practices, general principles, and practical guidance [6]. Building on these themes, the two subsequent workshops were organised to co-produce ethical principles and guidance specifically aimed at researchers/clinicians and NHS Research Ethics Committees (REC) members, with the understanding that these principles would also be relevant and accessible to other stakeholders involved in genomic research. Consensus on the principles and guidance was reached in the following way:

During the second workshop we identified best ethical practice/approaches, and agreed upon general principles. These principles were subsequently shared with the participants via email, and additional feedback was incorporated.

The aim of the third workshop was to further refine these principles and guidance. After the third workshop we shared the refined principles with the participants again, until we reached the version in this paper.

To facilitate such interdisciplinary and 'participatory' discussions, we used in both the second and third workshops real cases and challenges encountered by the researchers/clinicians co-authors (CB, JM, TA) (see *Supplementary material*).

This paper reports the outcomes of the last two workshops. It outlines the ethical principles for genomic research agreed by the participants, followed by some specific considerations about the main challenges concerning informed consent, and suggestions about how these could be addressed. Particular attention has been given by the participants to the clarity and accessibility of the principles, both in terms of content and language.

Ethical Guiding Principles for Genomic Research

Foundational requirement: appropriate training for research teams and NHS REC members is needed

Structured e~~E~~fforts are needed to create or improve the **training** and **resources** available to support the design and ethical approval of genomic research studies. Training for both **researchers** (in particular those who are taking consent) and **NHS REC members** (who review research protocols) should be consistent and aligned. It should include information, resources, and, where possible, points of contact for REC members and researchers requiring specific scientific and ethical guidance (e.g. a bank of Scientific Officers as described in the Department of Health's 'Report of the Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees'[7]).

1. Balancing the variety of research with ethical requirements

There are **different types of genomic research** (understood as research on a complete set of DNA and /or its genes using biotechnological techniques). For example, there are exploratory projects (e.g. projects that look across populations rather than being focused on one disease), disease specific projects (e.g. studies to find the genetic causes of Inflammatory Bowel Disease), or gene-drug interaction projects. In addition, ~~such~~ projects employ different levels of genetic analysis e.g. candidate gene analysis, Genome Wide Association Studies, whole genome sequencing, RNA arrays. The objectives, nature, and obligations related to such different projects are ~~likely to be~~ diverse. Therefore, while it is important to follow legal and regulatory requirements, a one-size-fits-all policy to project design and ethics approval is ~~unlikely to be the best~~not a good approach. A **balance** among the variety of research and ethical requirements needs to be found as this can have an impact on all of the ~~below~~ principles listed below.

2. Appropriate information ~~at the appropriate time~~

Researchers should give patients/participants a **suitable** level of information about the research project[1] ~~at the right time~~. ~~This information~~ given ~~also needs to be sufficient to~~meet ~~the requirements for compliancey with relevant data protection laws~~ – but ~~, but the question of legal compliance is outside the scope of this paper.~~

What is suitable depends on characteristics of the potential participants: Are they vulnerable? Are they highly educated? Are they already research participants? Do they belong to an underserved group? In other words, suitability is influenced by **different levels of vulnerability** and the potential for emotional pressure (e.g. participants can include healthy volunteers or patients with a serious health condition looking for a diagnosis/treatment). Patients/participants have **different needs** concerning the amount of information they wish to know about a project, and at what time.

Information given to potential study patients/participants might be best provided in the form of a research **'mission statement'**. A research '**mission statement**' should cover the **main aim(s)** of the research project; **risk and benefits** for patients/participants; **commercial involvement**; and a policy about **returning results** (see also §4). The research mission statement should be written in plain English, and be short, clear, and transparent.

An **information resource centre** should be made available for patients/participants who wish to know further or additional information than that provided at the initial point of consent taking. This will include further information about the project design, what will happen to the participant/patient data, contact details of the research team (e.g. the type of information generated as part of the NHS Research Ethics applications), and already existing institutional/educational information about genomic research (e.g. educational animations produced by Genomics England). The idea is that the participants/patients will be able to access further information that will answer any questions they may have, when and how they choose. This approach is in line with existing work such as: the HRA guidance on Proportionate Consent [1]; the Trust-based approach to consent developed by the European School of Molecular Medicine and the European Institute of Oncology [8-10]; Prainsack and Buyx's approach to solidaristic data governance[11] and the Global Genetic Alliance consent policy [12]. It

[1] This information given also needs to meet the requirements for compliance with relevant data protection laws – but the question of legal compliance is outside the scope of this paper.

ensures that individual patient needs and values are at the centre of genomic research, and that the recruitment and consent process is more patient focused, and more efficient for research teams.

3. Research objectives and methods

It is important to recognise the difference between the **objectives** of a research project (what are the questions that the research aims to address) and the **methodology and technology** adopted (how researchers plan to answer the research questions). This distinction has important implications for the generation of the project mission statement, the design of the research project, the research ethics approval process, and the development of any information given to participants/patients. Any materials made for the patient/participant, should be broad enough to keep up with any future changes to the research. This would ensure that only changes to the research mission statement would require ethical review and re-consenting by the participant/patients. Patients/participants generally understand that **research methods and technologies used evolve quickly**, they also expect researchers to use the latest most powerful tools to answer their research questions [13].

4. Policy about reporting results (broad, individual, and additional)

Research teams should make an **informed decision** at the **planning stage of a project** about the **strategy** to adopt to **report results**. There should be a clear **policy** about what type(s) of results may be reported, by whom, how, and when, and how decisions on these aspects are made. The plan needs to be clearly outlined in the research mission statement and tailored to the specific type of genomic research (see §1, 2).

Results ~~which~~ that may be reported to participants may fall into three major categories: ~~**broad**~~ **general results** (the main research outputs e.g. publications); **individual level results** (either uninterpreted or interpreted patient/participant data, should the individual samples have been tested) and **additional findings** (e.g. sought-for secondary findings or incidental findings). Some patients/participants, especially those seeking for a diagnosis, may also want to know whether their samples have been tested.

Ethical and practical considerations should inform the decision about whether and how to report

research results. For example, some long term projects may have systems to communicate with patients/participants which could be used to report research findings (e.g. a newsletter). Research that is very close to the clinical end of the spectrum may have these systems in place, especially where the research is conducted on patients who have an ongoing clinical relationship. Such situations will not only have an influence on the practicalities of whether the team might want to or find it easy to report back the results, but also potentially to what the participants/patients might expect.
However, other projects may not have such systems and may not influence such expectations.

Researchers should also consider that returning different types of results may have **clinical and/or psychosocial implications** for participants/patients who may require support (e.g. counselling).

5. 'Ethical' Planning

At the planning stage of a research project the potential **questions**, **needs** and **risks** to patients/participants should be considered. Researchers should also plan the most efficient, clear, and timely way to communicate with patients/participants and stakeholders through the life cycle of the project. This will depend on the type of project (see §1, 4), and may require training for both researchers and Research Ethics Committee members. Researchers should also consider the **different educational background and understanding of genomic information** of patients/participants [14]. This ensures patient/participant focused research, builds trust and promotes transparency and reciprocity between researchers and patient/participants [15].

6. Ethical guidance should enable participation

Ethical regulations and **guidance** are there to support researchers to implement the above principles. They **help researchers** to **identify** and **engage with stakeholders as part of the design of a project**. Ethical regulation and guidance enable researchers to be more aware of how they (and their **research**) are situated within the broader **community, the scientific environment,** and the **legal and regulatory** and **policy** frameworks.

Some notes on Informed consent

Informed consent **is needed**, but we recognised that there are **difficulties with current forms of consent** [16]:

- The sheer quantity of information and the considerable number of forms to read/documents to sign may burden participants/patients and researchers – ultimately hindering research. Various types of information should be available for those participants who are interested in them; but not all available information may need to be given to participants at the time of recruitment (instead participants could be given guidance on how to access further information if required), in a layered fashion.
- The complexity of the information conveyed to patients/participants – also due to the current need to balance different requirements from REC members, regulators, the law, etc. (clauses, adoption of particular types of form etc.). Consent serves different purposes for different stakeholders. However, there is no need for patients/participants to know the specific laws and regulations that the consent is holding to. It is more important that the consent coveys to patients/participants the **general principles** that it is following (e.g., confidentiality) in an accessible fashion, in the form of a **mission statement**.
- The lack of flexibility to patients/participants' needs (see below)

Best practice

The Informed Consent document should:

- Be seen as the basis for a conversation, as a process that engenders – and builds on – trust and trustworthiness, rather than a box ticking exercise that often serves the purpose to protect institutions rather than patients/participants

- Be short, easily comprehensible, and transparent. It should use simple language, supported by background information (an **information resource centre).** This could represent a starting point to promote genuine education and engagement and reduce knowledge and power imbalance amongst stakeholders [17]. The adoption of such sources of background information may also reduce the time of the so-called 'consent conversation' for a specific research project between researcher and patients/participants.
- Be flexible, exploring different modalities to convey the same information, and responding to the different ways in which patients/participants learn and look at information (e.g. video, media etc.). It should also be flexible in how it incorporates the requirements of regulators, law etc.
- Not over-promise (e.g. promising to keep patients/participants' identity entirely secure is inappropriate, as research has demonstrated that it is possible for anonymous data in genomic research to be re-identified [18].

Researchers/Clinicians should:

- Engage patients/participants in the process of developing the consent (and other patients/participants facing material), as early as possible in the design of research projects and certainly before applying to Research Ethics Committees. -Patient and Public Involvement groups – commonly composed of volunteers – are becoming more common across hospitals and research institutions [2] , and are playing an important role in ensuring that research is relevant to the needs of the public.
    - This would circumvent the phenomenon of '*double- paternalism'*: both researchers and committee's members claiming to represent/protect the interest of patients/participants, or claiming to respond to what patients/participants are interested to know, without involving patients/participants

[2] See for example https://www.england.nhs.uk/participation/

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Conflict of interest statement

The authors declare no conflict of interest

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