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Friday 22nd March 2013

Dear Sally,

In December last year you asked me to convene a small group to provide advice on how the Government might address the ethical issues associated with a recent commitment to deliver the whole genome sequencing of 100,000 NHS patients. The recommendations below represent the result of our deliberations.

We hope that these will help guide discussions by the Genomic Strategy Board, and others, as the detail of this work is better defined in the coming months. This programme offers the prospect of a paradigm shift in our approach to diagnostic testing and the alignment of research and clinical care. Ultimately this holds promise in terms of better diagnosis, prognosis and treatment of patients. It also provides an unprecedented opportunity to address related ethical, legal, and governance issues in a broad and consistent manner.

We believe this programme to have huge potential to bring benefits both for existing and future patients within the NHS, and additional benefits for the UK's reputation as a world leader in genomic research. An appropriate and rational approach to the ethical issues outlined below will be essential to inspiring public confidence in this programme, and to ensuring that participants have the assurances they need to allow them to take part.

While there is much that is exciting and new in this proposal, we are aware that there are existing projects with the potential to provide models of good practice and feed into this programme. Ethically, it is important that this programme builds on, rather than duplicates, existing research or clinical practice and draws wherever relevant upon existing models of good ethical practice.

As a group, and as individuals, we would like to extend our offer of continued help to this programme as it develops.

1. Principles

Five core principles will need to underpin this programme:

- The programme should be guided by a commitment that whole genome sequencing will bring benefit to current patients, future patients and to the NHS.
- The findings of research associated with the programme should be available to patients in the NHS, and drive the development of resources for improved diagnosis or care within the NHS.
- Decisions about the use of the data generated by this programme should be subject to careful scrutiny by an appropriately constituted and accountable governance process and made in the public interest.

- A well-resourced model of best consent practice should be developed and put in place to ensure that participants understand the implications of participation for themselves and of this programme more broadly.
- The initiative should be supported by a well-designed and comprehensive programme of public engagement.

2. Key assumptions

2.1 This programme will focus on areas most likely to bring clinical benefit for patients in the short term. It is also intended that data collected from participants will be used in research aimed at bringing clinical benefit for patients in the future.

Based on feedback from the science priorities group, our understanding is that for the majority of participants whole genome sequencing *may* have a clinical benefit. Information collected as part of this programme will also be directed to research and development with the aim of leading to a better understanding of whole genome sequencing which will have benefit for patients in the future. The programme aims to build a platform for the future of genomic sequencing and, as knowledge and expertise grow, it is intended that whole genome sequencing will be better integrated into routine clinical practice.

We expect, therefore, that over time the balance will move towards one where all patients will directly benefit from whole genome sequencing. This trajectory has implications for consent, feedback, and patient and public involvement. Further work will be required to tease out and clarify these important distinctions and their implications for good practice (see below for further discussion).

2.2 Consent will be obtained from patients in the context of their routine clinical care.

It is our understanding that patients will be offered genome analysis in the appropriate clinical setting for the disease being investigated. Whole genome sequencing will be of a quality such that it is clinically applicable and will be subject to robust quality control.

It is our assumption that there will be no therapeutic disadvantage to being involved and that if patients choose not to participate in this programme they will continue to be entitled to the highest quality clinical care.

As plans for the initiative evolve, further work will be required to inform the development of an approach to best consent practice (see below for further discussion).

2.3 A mechanism will be developed to oversee the use of data associated with this programme.

While every effort should be made to secure anonymisation of data, irreversible de-identification of whole genome sequence cannot be fully guaranteed for technical reasons. We are therefore working on the understanding that access to data associated with this programme will be bound by data-access agreements which can provide participants, and the public, with the assurances they require and promote acceptability and involvement.

We also assume that data-access will be subject to the scrutiny of an appropriately constituted and accountable governance process capable of ensuring that research and clinical uses are appropriate and in the public interest. Work will be done to establish how

current legislation applies to, and whether this is sufficient for, this programme (see below for further discussion).

2.4 Public/private partnerships will be key parts of this programme.

Maximising benefit to patients will require the involvement of public/private partnerships. Public and private sector organisations will be invited to participate in the design of systems and mechanisms for carrying out whole genome testing and possibly the development of services for patients. Subject to approval through the governance processes outlined above and discussed further below, public and private companies will also be able to use data in research.

A clear policy will be required on commercialisation, detailing the extent of data sharing, IP, exclusivity, feedback requirements, how commercial researchers will interact with clinicians and academic researchers, and what oversight will be put in place to ensure that any commercialisation is in the public interest and brings benefits to the NHS. This will be crucial to ensure public confidence in the programme and that patients, clinicians, and NHS scientists are not deterred from taking part. Without information about such uses and reliable procedures that the public can trust, they are more likely to refuse to participate in such research.

3. Key ethical issues for consideration

Against this backdrop, the ethical issues we believe will need to be addressed to ensure the success of this programme are outlined below. There is significant overlap between these issues and as such they will need to be addressed in parallel. We are aware that much work has already been done on these issues elsewhere and that it will be important to draw upon this in any future deliberation.

3.1 Consent

We consider that broad consent is possible and acceptable. Consent should be thorough without being overly burdensome on clinical staff or patients who are undergoing treatment. Training for staff and appropriate resources to support the taking of consent and to ensure that such consent is valid will need to be built into the planning assumptions.

The precise form and content of the model of consent adopted will need to be informed by the approaches taken to the other ethical issues discussed below. It is already clear however that consent will be taken for whole genome sequencing in the clinical setting and the resulting data used in treatment and research. We therefore recommend that patients should be asked to consent to a 'package' comprising:

- The search for a clinical diagnosis, prognosis, treatment option or other aspect of a patient's clinical management.
- Depositing genome data in a repository to allow pooling and ongoing analysis and a link to clinical data.
- Research on repository data.

It would be impractical for it to be possible for patients to place restrictions on the research undertaken on the data, for example by limiting it to 'non-commercial research'.

Patients will be given the option to choose not to participate in this programme and, if they do so, they will be entitled to a high quality standard programme of care.

Conversations at the time of consent will need to cover: data-access; the challenges of anonymisation; approaches to and reasonable expectations in relation to feedback (see below for more discussion); possible use of results for the benefit of family members; and any current uncertainty around interpretation of data where this is relevant. Consideration will also need to be given to implications for families in the development of a model of good consent practice.

Special consideration may also be needed for consent regarding sequencing for public health in the context of infectious disease, where such consent is required.

As the detail of future research will be unknown at the time of consent, participants should feel confident that they are giving consent to research governed by a clear process guided by the public interest. An outline of how decisions will be made about who gets access to their data should be included in the consent process. It should be made clear to participants that additional consent will not be sought before access is granted to anonymised data and that research will be performed by NHS academics and industry partners, non-NHS academics and researchers in other countries. Participants will also need to understand that consenting to research involves a waiver of any personal rights to benefit from commercial exploitation. Mechanisms will need to be introduced to ensure that the NHS benefits where data from this programme are put to commercial use.

Thought will also need to be given to whether and how patients will be able to withdraw their consent at a later date and whether it will be possible to remove data from the system. This might be particularly important in the case of those who are recruited as children or whilst lacking mental capacity and later achieve majority, Gillick competence, or capacity. Special consideration will need to be given more broadly to the obtaining of consent for the involvement of children, particularly in relation to the feedback of future findings, for example those that only become clinically significant in adulthood.

We are aware that there are a number of existing models of good consent practice including the approach taken by the UK Biobank, and the consent form template developed by the Joint Committee on Medical Genetics, which could perhaps be used as models for this programme.

3.2 Data-access

It is our recommendation that decisions about the use of clinical information, sequence data and samples are made by an appropriately constituted and accountable body set up for the purpose of acting as a guardian of probity and a guarantor of the public interest.

Agreement will need to be reached about the way in which decisions about access to data are to be made and overseen. It is likely that this process will be managed by a data access committee. An important ethical consideration for data access is that arrangements are clear within, and that decisions about access later reflect, the patient consent. Consideration will also need to be given to the appropriate response to participants who request access to their own genomic and related clinical data.

The programme will need to be open from the start about the possibility that patients might

in theory be identified from their data. Given this, it is essential that sufficient constraints on the uses of data are built into the programme to ensure well-founded public confidence. As mentioned above, it is likely that a key element in this will be the requirement on researchers to sign a binding data access agreement. Were the view to be taken that these would by themselves be inadequate, additional safeguards would need to be considered to avoid unauthorised identification of individuals from their genomic data.

Management of sensitive issues such as the chain of transmission involved in investigation of a disease such as HIV or transmission events in TB should be addressed by confidentiality requirements as set out in GMC and other guidance. However, careful thought will need to be given to ensure that adequate protections are in place.

By taking samples from patients, with consent, a duty is also taken on to maximise the benefit from the samples. This means actively encouraging researchers to apply for access to the resulting data to carry out research in the public interest. However, it is clear that this will need to be justified if it is seen to lead to commercialisation. A key component of this programme, and one of the challenges in ethical terms, will be the arrangements for commercialisation of genomic data. A clear policy will need to be developed on this. This should reflect that there are, and take steps to maximise, benefits (either financially or through access to clinical benefit) to the NHS. It may be that the public should be assisted in a step wise way to seeing more benefits as trust is developed, and therefore only be asked to agree to a limited amount in the first instance.

3.3 Feedback

An appropriate model for feedback from whole genome sequencing will need to be developed and agreed before participants are recruited into the programme. This will need to be the result of careful analysis of the range of feedback which may be appropriate as part of this programme. These discussions will need to take into account relevant professional guidelines. The issue of appropriate feedback is complicated by inevitable need for further validation of genomic data and the ongoing development of whole genome sequencing as a technique. A number of organisations have mapped different possible approaches to feedback. However, there is not yet consensus on which of these is the most appropriate model and further work is needed to establish how issues related to feedback might be addressed as part of this programme.

An effective model of feedback will need to address:

- The criteria by which decisions about what researchers will be required to feedback to clinicians should be informed. These seem likely to include considerations relating to the significance of the finding and the availability of an intervention to ameliorate the resulting condition.
- How clinicians will be empowered to make informed professional, patient-centred judgements about what they feedback to patients.
- How to counsel patients to receive feedback.
- How the implications for family members other than the patient will be managed, including situations where the patient has died.
- How feedback over time will be managed. We envisage that clinically relevant results may become apparent some time, possibly years, after consent is first obtained.
- How expectations for feedback are to be incorporated into consent. It is our view that the model for feedback adopted and the criteria to be used in judgements about feedback should be explained at the time of consent.

Knowledge and expertise are very likely to evolve over the life-span of this initiative. Better understanding of the implications of genetic findings might mean that more clinical information could be derived from samples taken earlier in the programme. This will influence how the feedback process is structured and have implications for the continuing professional development of clinicians and the development of approaches to and resources for recontacting patients. This developmental aspect of the initiative will need to be clearly communicated to participants at the time of consent.

3.4 Public confidence and involvement

Public trust and confidence are crucial to the success of this programme.

Beyond the potential participants, this broad reaching initiative will need to engage, inform and involve a range of publics. Public involvement must be integrated into the programme. We believe that confidence will be lost if public involvement is not central from the beginning. In addition to the general public, the media and critics of this programme, medical professionals not directly involved in the programme will need clear advice to support them in providing information to patients. Other interested parties such as employers and insurers should also be aware of the implications of this programme for their work.

Given this range of publics it will be important that messages are consistent and that there are opportunities for greater involvement for interested individuals. It is our recommendation that resources should be made as publicly available as possible, and include consistent and thorough 'frequently asked questions'.

There are three key principles that should run through any public engagement and involvement activities:

- Transparency – subject to the need to preserve patient and family confidentiality, or commercial confidentiality, information should be publicly available and accessible.
- While this programme is likely to bring real benefits for patients both now and in the future, the direct clinical benefit for participants should not be overstated.
- Effective communication about the commercialisation aspect of this work will be essential from the outset.

3.5 Oversight and governance

It will be important that the oversight and governance aspects of this programme link to other ongoing initiatives on patient rights and the sharing of tissue and data for research. Where possible, the existing mechanisms that apply to related NHS services – accreditation and licensing of labs, diagnostic services and control of patient data should be applied to the programme. There are obvious overlaps with the review of the NHS Constitution and other relevant ongoing work by Fiona Caldicott.

How legislation such as the Data Protection Act and the Human Tissue Act apply to the activities undertaken as part of this programme will need to be further defined. If exemptions are needed efforts should be made to ensure that these are in place.

We are aware that there are particular public concerns about how genetic information may be used in insurance and employment. Whilst the latter may be adequately covered by anti-

discrimination legislation there may be a need, and an opportunity, to revisit the existing moratorium on the use of genetic data in the context of insurance as the programme becomes more clearly defined.

There are also examples of existing governance and oversight structures which will be helpful in supporting this programme as it goes forward. These include large clinical databases, which allow clinical data from individual patients to be used in research; electronic patient records to complement clinical databases and disease registries; and initiatives to improve early access to novel medicines.

4. Summary of areas where further work is required

As outlined above a number of policies will need to be developed over the course of the next few months. These include the following:

- A model of good consent practice, building on existing exemplars.
- A policy on how issues related to feedback will be addressed.
- An approach to how access to genomic data will be governed, including a review of whether additional safeguards may be required to deter malicious attempts to re-identify anonymised individuals from their data e.g. Data Protection Act applied to individuals by their employers.
- A policy on the management of commercialisation in the public interest and for the benefit of the NHS.
- An approach to the provision of appropriate training and support in ethics.

We look forward to continuing to work with you as this programme develops.

Yours sincerely,

Michael Parker
On behalf of the ethics advisory group