in that case

A multi-national pharmaceutical company wishes to recruit some of your patients to a pharmaco-genetic study. In the first instance, the company wishes to match asthma sufferers with medications. You will be required to recruit asthmatic patients who respond well to a specified inhaled medication and others who respond poorly to the same medication. The objective will be to discover whether there is a genetic basis for the variation in the drug response as measured by lung function tests. The frequency of a functionally relevant genetic marker will be compared between the two groups. The study will involve a minimally invasive collection of tissue samples which will be subjected to DNA analysis. The company also requests that they be allowed to store the tissues for future research. Should you agree to assist in this enterprise and, if so, on what conditions?

response

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This is an interesting case which has a number of parallels with studies the Southampton Asthma Genetics group have undertaken in the past. It raises issues relating to consent, storage of samples, commercial research and genetic testing.

(a) Consent: When recruiting individuals for genetic studies of asthma we routinely use a two stage consent as follows:

> Part A: Consent for specific project as outlined in information for participants.
>
> Part B and C: Consent for linked-anonymised/ unlinked anonymised samples gifted for storage and use in future in specified types of studies. For example permission is asked for samples to be used for treatments/investigations of medical conditions relating to asthma and other lung diseases.

As outlined in the guidelines on the use of human tissue and biological samples in research published by the Medical Research Council UK (MRC, 2001), the use of a two stage consent recognises that often there can be subsequent use of samples for new experiments that cannot be foreseen, while making the donor aware this may happen and giving them the opportunity to specifically give approval for this. Unless the sample is to be anonymised and unlinked prior to storage, unconditional blanket consent is not sought from the donors. In the majority of our studies, and especially for genetic studies, blanket consent is not sought. Rather, possible future research is restricted to specific types of studies that may be done, and the types of diseases that can be investigated.

The storage of samples for future unanticipated research has a number of benefits, including the reduction in use of invasive sampling procedures, a reduction in the numbers of subjects used in research projects and moving medical research forward more quickly with the potential benefits that it may bring to patients. However the benefits must be weighed against the potential for harm to the patients including invasion of their privacy. The benefits should be carefully outlined to donors,

consent given and donors should be given the reassurance that all secondary use will require approval by an ethics committee and that no tests of known clinical value for diagnosing or predicting disease on samples that can be linked to them individually will be done without their consent.

(b) Commercial research: In those studies that are to be undertaken in collaboration with commercial partners we specify that:

1. Donors are to be informed that their samples are being used in commercial research.

2. The samples are to be used only for what is outlined in the initial study description approved by the local ethics committee – generally this is a disease area restriction, and following completion of the study the samples are either destroyed or in the case of joint research programs returned to the academic research group if further research is continuing.

3. Any proposal for other uses of the samples is to be re-approved by the ethical committee.

Subjects participating in commercially funded research projects often have concerns with the idea of a company making a profit out of research material that they have freely donated. Hence it is important subjects are made aware of the potential benefits of allowing commercial access, and that the role of any one individual's sample in the generation of future profits is likely to be minimal as well as impossible to quantify. Given the possible sensitivities, it is essential that research participants know that their sample or products derived from it may be used by the commercial sector, and that they will not be entitled to a share of any profits that might ensue.

(c) Genetic testing: Public sensitivity to genetic research must be considered in studies involving collection of genetic material. Often genetic information obtained for research purposes is of unknown or uncertain predictive value. The MRC guidelines specify that:

> 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.

This advice is based on the Department of Health (UK) Advisory Committee on Genetic Testing's guidance to Research Ethics Committees (Advisory Committee on Genetic Testing, 1998). In the majority of our studies we include the following statement in the consent form:

> I understand that the project/future research using the sample I give may include genetic research aimed at understanding the genetic influences on asthma and lung diseases but that the results of these investigations are unlikely to have any implications for me personally.

In this case however, the results obtained may impact directly on the patient's health in terms of the suitability of a particular medication for treating their asthma. Therefore the possible benefits to the patient of informing their doctor of the suitability of specific medications for the patient should be weighed against the possible implications to the patient and their family of knowing the results of the tests. If this is to be the case, then the patient must be fully informed about the test(s) and prior specific consent sought.

Finally, outside of the ethical implications of participation in the proposed study there are a number of ethical implications of pharmacogenetics research in general that need to be considered. These include such things as individuals being classed as 'therapeutic orphans', too difficult or expensive to treat on the basis of their genotype, and the ethical implications of recruiting participants to clinical trials based on genotype which may exclude individuals from certain ethnic groups (Rothstein and Epps, 2001).

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response

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At the outset, I will have to say that the response here is not given in the capacity of a physician but given in the capacity of a Health Policy and Ethics Advisor. In light of the general information about the case as outlined, I will focus selectively on three main issues that primarily relate to obtaining the free and informed consent of participants to the study, and will then make some additional comments.

First, it seems to me that the issue of recruitment involves two distinct groups of participants. The first group comprise asthmatic patients who respond well to a specified inhaled medication (therapeutic research), and the second comprise those who respond poorly to the same medication (non-therapeutic research). It appears that the interests of the second group of patients are different from that of the first group, and so, in obtaining informed consent for participation in the study, the second group of patients will need to understand that participation may not offer direct or immediate benefit. A safeguard that the recruiting physician may wish to adopt is to have another physician, who is not engaged in the study and who is independent of a patient-physician relationship with the individual who is to be recruited, obtain informed consent from the second group of patients.

Second, in response to the statement that minimally invasive collection of tissue samples is involved, the observation needs to be made that the study involves tissue samples collected prospectively in the context where it is clearly for the specific purpose of research. The information that would need to be communicated when recruiting participants should include: the purpose of the research, the type and amount of tissue to be collected, the location where the tissue is to be taken, and how the tissue will be taken, stored, and subsequently handled. The statement that minimally invasive collection of tissue samples is involved appears to indicate that there does not appear to be an issue about risk of harm in taking samples from participants.

The third issue, which is the most interesting and perhaps also quite difficult, relates to the storage of tissue samples for future research. There are really two matters that should be considered here – the first is readily apparent, and the second is not immediately obvious. The first is the issue of storage itself and related questions about consent; the second is the issue about the use of the tissue samples for future research and related questions about consent.

Storage of the tissue samples for future research raises questions about labelling and coding, with implications for privacy considerations, and can be conceptualised as falling into four categories: Identified Samples, Coded Samples which may be Single Code Samples or Double-coded Samples, Anonymised Samples, or Anonymous Samples. For a clear discussion of the different terminologies, refer to the EMEA Position Paper (European Medicines Evaluation Agency, 2001).

Briefly, Identified Samples are labelled with personal identifiers such as the individual's name, date of birth or address, and so can be directly traced to the individual.

Coded Samples are labelled with specific codes. Where a single specific code is attributed to the sample, the sample is 'single coded'. Where an additional code is added to a Single Code Sample, that sample is 'double coded'.

Anonymised Samples are typically double coded samples but with the key linking the first or second code (or both codes) deleted.

Anonymous Samples were originally collected without any identifiers and are impossible to link with their sources.

The general approach that should be adopted is that identification of samples be limited to the minimum necessary to achieve the objectives of a study. Hence, consideration of

whether collection should involve anonymous samples or the extent to which (identifiable) samples should be de-identified must be balanced against consideration of whether the purposes of the research can be met in accordance with good science.

In the case before us, it seems clear that anonymous samples would not serve even the purpose of the immediate study requiring that tissue samples, which are subjected to DNA analysis for the frequency of a functionally relevant genetic marker, be linked to specific participants.

In so far as the physician carries out the immediate study on her/his patients, the question about whether the samples are identified, coded, or anonymised seems to be a non-issue. However, if the samples are transferred by the physician to another person/organisation, for example to the multi-national pharmaceutical company, the samples should be coded – whether 'single coded' (with the code key being held by the physician) or, for added protection, 'double coded' (with the code key linking the double coded samples and information to the single coded sample being kept by an independent and trusted third party). De-identification to the extent of the samples being anonymised in this context would make future research requiring correlation between the samples and specific participants very difficult to undertake. I avoid saying 'impossible to undertake' as I have come across the comment that with modern DNA identification techniques, it is possible even in anonymised collections to link a sample with an individual if one wishes to spend the effort and if the individual provides a fresh sample for matching (Wertz, 1999).

With regard to the use of the tissue samples for future research, the question that should be posed is to what extent the future proposed study (or any future proposed studies) will be an extension of, or bear close relation to, the immediate study that will be conducted. This is important in the context of the specificity or scope of consent that is now being sought for the future research use. The options that would need to be thought through include considering whether consent should be obtained for any study relating to the immediate study, or whether consent should be obtained for any kind of future study whether or not that study is related to the immediate study. Depending on the circumstances, the physician may need to consider the additional safeguard of asking for permission to re-contact the participant in some future time for a future study (or for any future studies). Some issues related to disclosure of research findings (whether those findings arise from the immediate research or future research) can also be considered, for example the circumstances (if any) that might justify research findings to be communicated to participants or added to their medical records. The latter touches on the issue about whether it is appropriate in the context, particularly where DNA analysis is involved, to have a system that keeps the boundary between research and clinical practice clearly separated.

Finally, moving on to some general comments, the patients should be informed that they may abstain from participation in the study or withdraw from the study at any time - and also request the destruction of the tissue samples that have been collected and stored. The patients should be informed that refusal to participate or withdraw from participation will not interfere with the patient-physician relationship. The physician would also need to ensure that specific protections are in place when recruiting vulnerable patients or patients who are unable to give legally valid consent (for example, children and the legally incompetent). Circumstances may also require sensitivity to relevant cultural or religious concerns.

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