Ethical Considerations in the Genomic Era

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Abstract Pharmacogenomics is a powerful molecular tool in biomedical research aimed at providing personalised medicine in everyday clinical practice, best described as the provision of 'the right drug for the right patient at the right dose', that is safe, effective therapy, with minimal adverse reactions. The patient, is the main beneficiary but is also the indispensable key player, providing biological material for research.

This chapter focuses primarily on ethical issues as they affect the patient undergoing pharmacogenetic tests for personalised treatment, the subject enrolled in a clinical trial or participating in genomic research or the healthy person donating biological material for biobanking and research. Issues affecting the other stakeholders will also be pointed out, but again mainly from the perspective of the consumer.

Discussion centres on the right to beneficience, explored through benefit to risk ratio and the right to autonomy, exercised through informed consent with safeguards to ensure privacy and confidentiality in the handling of biological samples and data. Elements of justice will be introduced in relation to the target of equitable access to healthcare.

The basic ethical principles must be upheld through regulatory frameworks. States have embraced various instruments, from local and international guidelines to national legislation, but as genomic research increasingly moves into the global non interventional arena, the vision is of facilitation of international cooperation through harmonised regulations.

Keywords Informed consent · Ethical approval · Pharmacogenetic test uptake · Data protection · Clinical trials · Biobank

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1 Introduction

The concept that genes play a part in controlling response to drugs was recognised in the late 1950s [1]. The speciality of pharmacogenetics [2–4] led to the discovery of specific DNA polymorphisms, notably in drug metabolising enzymes. As molecular techniques developed, in the late 1990's, pharmacogenomics emerged as a new discipline [5, 6] with an important role in the field of drug development. The identification of person to person 'variations of DNA and RNA characteristics as related to drug response' [7] can be applied to the quest for new drug targets and for safe drugs, balancing efficacy with minimal adverse reactions.

Though pharmacogenetics and pharmacogenomics are terms that are often used interchangeably, pharmacogenomics is centred on information from the entire genome. In fact it was the advent of new technologies, such as whole-genome sequencing, that drove research swiftly. Next generation sequencing, whole-exome sequencing and the development of bioinformatics, make the possibility of carrying out large population studies and data analysis, more feasible and will prove effective tools to identify biomarkers related to an individual's likely reaction to a particular medicinal product. This shall support the development of drugs and the required predictive genetic tests and companion diagnostic tests. Once such clinical application becomes an everyday reality, the promise of personalised medicine, the ideal healthcare programme, will finally be realised.

Such a goal requires solid interaction between the scientific and medical communities and the public. The index patient, or the healthy person seeking a predictive test, may well be seen as the ultimate beneficiary of personalised medicine but he is also the key player in the quest for the 'right drug for the right patient at the right dose' [8] since he is the one to contribute the biological material. This complex relationship must be fostered and nurtured on a sound foundation of ethical principles that enhance trust between all stakeholders.

Ethical behaviour in medical science, and specifically in genomic research, offers the foundation for the protection of the basic human rights of an individual and of society, but is also relevant to the other parties involved in research practices, the healthcare providers, the scientific investigators, the pharmaceutical and diagnostic companies, the funders and the policy makers. The perspectives of each group will vary but as all have a vested interest in a successful outcome, and since they depend on each another, there is a willingness to harmonise effective practices to move forward. However to guarantee that ethical issues are respected, this is not enough and there is a requirement for good governance, with a variety of regulatory instruments applicable at various stages of research.

This paper will focus primarily on ethical issues as they affect an individual, as a patient undergoing pharmacogenetic tests for personalised treatment, or as a subject enrolled in a clinical trial or participating in basic scientific research or as a healthy person donating biological material for research. Issues affecting the other stakeholders will also be pointed out, but again mainly from the perspective of the donor.

Ethical aspects will centre on the right to beneficience, explored through benefit to risk ratio, the right to autonomy, exercised through informed consent with safeguards of privacy and confidentiality, and on elements of justice, in relation to the target of equitable access to healthcare.

2 Personalised Therapy

2.1 Benefits v Risks

The pharmacogenomics target is to change healthcare management, in particular drug therapy, from general to personalised prescribing of evidence based effective and safe medicines. The benefits of taking the right medicine at the right dose, with minimal side effects are obvious. There can be little doubt that this is the ideal situation for the patient but it also embodies a prime objective in the provision of healthcare. Moreover providing optimum treatment is also a lack of maleficience, one of the main tenets of ethical medical practice. However the benefits must be weighed against the risks.

Personalised medicine is most practised in oncology [9]. For some tumours, genetic testing has become essential, and sometimes mandatory for Good Clinical Practice, before therapy is started. A success story is the clinical application of mandatory pharmacogenetic testing for gefitinib by the European Medicines Agency, EMA. Gefitinib, a tyrosine kinase inhibitor, is an epidermal growth factor receptor, EGFR, antagonist, and when used in patients with advanced non small cell lung cancer with EGFR activating mutations, it provides a significant increase in median survival [10].

However the best known example of pharmacogenomics testing is for variants of the enzyme CYP2D6 [11, 12] in the treatment of breast cancer with tamoxifen [13], where response to tamoxifen is reduced. Ethnic differences in genetic polymorphisms are very variable, with decreased activity, more commonly present in non Caucasians, making them less likely to benefit from tamoxifen [14]. Yet so far there is no mandatory regulation for pharmacogenetic testing prior to starting therapy. In fact recent review and meta-analysis concluded that there is ‘insufficient evidence to recommend CYP2D6 genotyping to guide tamoxifen treatment’ [15]. This exemplifies the problem of translation of genomic research to clinical use, some issues giving rise to risks for the individual, as will be discussed below. It also highlights the need for assessing the benefit to risk ratio for a particular individual.

The prime risks of a medication are the adverse drug events. Side effects exist for all drugs. In fact ‘any drug involves some kind of risk-taking on the part of the patient’ [16], but particularly burdensome are the serious adverse drug reactions requiring hospitalisation. However they are difficult to quantify, both as to prevalence and severity. Research has focused on the resulting hospital admissions, but often in individual hospitals rather than national [17] studies. The often quoted

meta-analysis study by Lazarou [18] way back in 1998 had estimated they were the 4th to 6th commonest cause of mortality in the states, when hospital admissions due to serious events were 6.7%. In a more recent overview of 95 published studies, related to hospitalisation following adverse drug events, with admissions ranging from 0.1 to 54%, there was such great variation in methodology that it was concluded that 'extrapolation based on a meta-analysis of unselected studies may be biased' [19]. Some have also attempted to quantify the economic impact from the burden on healthcare management [20, 21].

Marketing of drugs is based on a balance between efficacy and safety but for the patient, the decision to take a medicine depends on the benefit to risk ratio, which 'must always be compared with existing alternatives' [16], that is one must ensure that the proposed new therapy is better than the current treatment and management available [22] for each specific patient. However patients with disease causing serious morbidity may be prepared to take more risks, such as use a medication with higher adverse reactions than normally accepted by less ill individuals. Also one might be prepared to try a drug with serious adverse reactions if there is no other alternative available.

Availability and access to a specific therapy and its accompanying diagnostic test may be related to area of residence or may be a question of cost of treatment, not necessarily whether a medicine is actually on the market. This of course raises issues of justice and will be discussed later on in this paper.

3 Pharmacogenomic Tests

To benefit from personalised therapy, the patient needs to know whether his genotype puts him at risk for serious side effects or if a drug will be inefficacious or if an adjustment in dose is required. He has therefore to submit to a pharmacogenomic test developed for the relevant predictive biomarkers.

To put this into perspective, at present, pharmacogenomic information in drug labelling, by the Food and Drug Administration, FDA, is only available for about 150 drugs [23], with 16 having information about more than one gene. However mandatory pharmacogenomics testing prior to starting therapy is only required for 31 and recommended for 6 drugs by the FDA and for 17 by EMA [24]. Ideally regulation of diagnostic tests and drugs should occur together [24].

3.1 Informed Consent

The personal choice to consent to take a pharmacogenomics test respects the right of the patient to be personally involved in his own healthcare management. For valid consent, an adult must be competent to understand and evaluate options and so come to a decision. However for autonomy to be entirely respected, consent must

be genuinely informed and not be reduced to the legal requirement of validity and signing a form. The patient must be given the tools to reach a decision, specifically sufficient information, in a language they can understand, to effectively be engaged in evaluating the benefits versus the risks.

Consent by vulnerable patients such as the elderly or the very young may prove problematic as the person may not be fit to fully comprehend information regarding the state of health, let alone the relevance of a genomic test or of treatment options. These groups of people are well protected by regulatory mechanisms that insist on a guardian or legal representative to give consent.

Information should be provided about the specific indication for the pharmacogenetic test, the genetic abnormalities being detected and the interpretation of the result in relation to treatment options available. However the patient must also be made aware of issues regarding handling and secure storage of the sample and the data generated, including the long term dispositions and particularly if there are plans for use in future research. This allows the patient to assess the level of privacy and confidentiality afforded.

The patient must also be given enough time to consider all options and time to ask questions and clarify any confusing issues. The patient has the right to be informed as to benefits and risks, common and unusual. It stands to reason that choice must be free of any coercion. Healthcare professionals are ethically bound to offer only tests that are relevant to the medical problem and tests that are clinically valid, in keeping with good medical practice guidelines.

However there is also a fundamental right not to know [25] and such refusal of consent must be accepted, provided it is a genuine autonomous decision based on evaluation of adequate information.

3.2 Benefits: Uptake of Tests

For therapeutic purposes, when there is a definite recommended medicinal available, with the promise of beneficial impact on choice of treatment as well as a better patient outcome, most physicians value the tests [26]. Such tests are generally well accepted also by patients [27, 28] since the patient expects to benefit greatly from knowing the genetic variations which will predict the efficacy of the recommended treatment and/or whether there is any significant toxicity or if the dose needs to be adjusted. A 2009 study among a diverse US population revealed that 77% were ‘very likely’ or ‘somewhat likely’ to take a pharmacogenetic test [29]. A US patient survey, with just a response rate of 42%, showed that 73, 85, 91 and 92%, respectively were in favour of obtaining a test to identify if they were likely to have mild side effects, suffer serious side effects, to have the appropriate dose prescribed or to choose a specific drug [30].

Moreover it has been argued that a patient whose genetic test identifies an expected good response or at least an absence of serious side effects, is much more likely to comply with medication [31]. Taking a test may also be beneficial as it reduces anxiety [32].

3.3 Risks: Limitations to Uptake of Tests

3.3.1 Understanding the Value of Genomic Tests

For an individual the decision to take a test may actually prove to be a very difficult and painful decision. The primary reason may be that few patients can really comprehend genetic and genomic tests [33, 34] and appreciate the real benefits or risks. Healthcare providers use the term 'genetic tests' loosely for a multitude of different procedures that explore the function of genes and their products. So it is not surprising that there is a 'confused public perception of genetic testing' [35]. Just the mention of a genetic test to a patient can be a highly emotive experience, with the spectre of genetic exceptionalism in the background, leading one to immediately equate all tests with the possibility of establishing identity. There is also the immediate association that any genetic test must necessarily indicate inheritable disease of the monogenic type. The patient must be educated as to the possible value of a pharmacogenomic test, one that only provides estimates of risks for a particular variant, not definitive results [31].

Uptake of these genomic tests by society may depend on the perception of individuals as to the uncertainty of results of predictive testing. Patients require assurance as to the value of tests, that development is in line with the US ACCE framework model [36], which applies to analytic validity, clinical validity, clinical utility and associated ethical, legal and social implications that ensure adequate safeguards to the scientific measures.

Analytical validity is the ability to measure the relevant biomarker, with reproducible accuracy and reliability, which is the first step before any test can be developed further for the market. Estimate of errors in identifying a gene variant in whole genome sequencing is given as less than 0.5% [37] but this does assume great importance when dealing with rare variants of disease. Different results in genome sequences of the same sample have been quoted as between 4–14% [38]. Such variances may give rise to imperfect or erroneous deductions in the interpretation of a predictive test.

Many cannot appreciate that the clinical validity lies in the ability of the test to identify the phenotype from the genotype [39]. Clinical validity is a function of the complex relationship between penetrance of the genomic variant, gene heterogeneity and the test sensitivity and specificity. Genomic tests, though less invasive than phenotypic tests, often have lower sensitivity and specificity [40]. Variations of the latter two test characteristics will give rise to false positives and false negatives.

A low predictive value may be one of the reasons why a test is underused [39]. However it may be even harder to explain that clinical validity may be much lower than expected because response to drugs is not limited only to genetic factors. There is interrelationship with the environment, lifestyle, age, race, comorbidities and other drug treatments [6, 39]. Moreover gene variants are sometimes pleiotropic [41], and are associated with more than one disease or drug response. The contribution of the genotype to a particular drug response is reported as very variable, anything between

20–95 % of all variability [42]. For warfarin, over 40 % of variability in dose requirement cannot be attributed to any known genetic or non genetic factor [43].

Moreover genuine laboratory errors may also occur, for example analysis of the wrong sample or a problem with techniques or equipment. Laboratories providing genetic tests should be accredited and there are established practice guidelines and standards for laboratories conducting pharmacogenetic tests [44] and for ensuring quality assurance of genetic tests [45].

To be useful in clinical practice, a predictive test requires to show clinical utility [39]. It must reflect the expected health benefit attributed to the result of the test, which may include adherence to the drug, for which the patient was tested [46]. Realising there is a specific treatment might actually improve compliance to drug taking [31].

A new concept is that of personal utility [47] that is how a test will prove of benefit to the patient in terms of disease outcomes. Obviously for pharmacogenomics tests, this relates to how useful is the drug therapy available or how important it is to avoid a particular drug with serious adverse reactions. This may be a very individual assessment, depending on the seriousness of the disease being managed. Clinical utility may however also spur a healthy person to take a test in the asymptomatic stage, just for relief of uncertainty. This alone may provide psychological benefit. On the other hand lack of sufficient clinical utility may still push a patient with a serious disease to ask for the therapy even though the test result may not be promising [48].

The test result will always have a psychological effect with the risk of anxiety and depression from false positive tests to misplaced relief or a euphoric state from false negative tests. However a negative test, or one that suggests a reduction in drug dose, may not only cause anxiety but may make the patient unduly worried of the inability to take the recommended therapy at the usual dose, and so the patient may not adhere to what is regarded as less than best therapy [31]. The latter scenario may prove most difficult since it gives a false hope, which is doomed to total shattering effects if the disease actually manifests itself, let alone opening the spectre of litigation for the clinicians. An unexpected lack of response or increased risk may thus occur leading to possible litigation [31, 49]. This alone should encourage the doctor to think twice about which information to give the patient and the reliability of the test is one piece of information which should always be imparted.

Understanding pharmacogenetic tests is even more difficult when the patient has a lower educational level [50]. In a survey of oncology services providers, many cancer patients are thought to be unable to ‘adequately comprehend the purposes and complexities of pharmacogenomic testing’ [9], in particular in appreciating differences between somatic and germline testing and that only the latter have potential for inheritance and an effect on family members.

It is also probable that uptake of tests depends on the effort made by the healthcare provider in obtaining consent. The onus of promoting a test through enhancing the patient’s understanding lies with the medical provider, who is morally and professionally expected to aim at maximising benefit to patients. Yet studies indicate that there is little expertise in genomics among clinicians in oncology [9]. This leads

to problems in provision of services [26] and in giving the right advice to patients and/or in interpreting genetic results [51].

Clinicians also worry that they do not have adequate guidelines how to use tests [52], although now there are many such guidelines [52, 53] to consult. Canadian cardiologists, oncologists and family physicians identified various difficulties that prevented use of pharmacogenetic tests, mainly lack of clinical guidelines (60%), lack of personal knowledge (57%), no evidence based clinical information (53%) and expense (48%). 37% also recognised that they did not have the time and resources to educate patients [26]. US primary care physicians also reported being uncomfortable with the level of knowledge expected to interpret the genomic tests [54]. There is little formal training of healthcarers, with as many as 92% reporting no formal undergraduate training [26, 55] and there is a good argument for introduction or increase in the teaching of pharmacogenomics in medical curricula [56–58].

Such physician surveys highlight the need for adequate explanation and counselling by well trained individuals. Counselling requires ensuring that the patient understands the implications of testing, whichever result is obtained. This requires commitment by the healthcare providers to explain in lay man's terms and to ensure there is adequate understanding. Such consultation is time consuming. With regard to counselling for hereditary disease, there are recommendations for counselling pre and post test when the disease is severe, with the counsellor giving the patient sufficient time to weigh up the odds [59].

3.3.2 Discrimination

Patients do refuse to take tests because of fear of the test results finding their way into the wrong hands, such as an employer, or an insurer, which exposes them to discrimination. Those with higher levels of education express fewer concerns about possible misuse of genetic information [34]. Despite anti discriminatory laws being enacted in all democratic countries, patients are still worried [9]. In a Canadian study, 40% of clinicians admitted that their patients had suffered from the fear of discrimination in relation to genetic testing [26].

Even when there is legislation against discriminatory practices, it may not offer comprehensive protection. The US Genetic Information Nondiscrimination Act, GINA, prohibits employers from discriminating against their employees on the basis of genetic information and prohibits health insurers from refusing to provide insurance, or asking for higher premiums, on the basis solely of genetic tests, but it does not offer protection for life insurance or disability insurance.

Legislation usually takes a firm stand against discrimination in terms of employment because the right to work is a fundamental human right but as to insurance, this is often a personal voluntary choice of the consumer to buy certain products. There may be instances where the consumer feels coerced into making a choice, for example in requiring insurance related to certain transactions, like obtaining a bank loan or buying a house.

3.3.3 Ethnicity

Certain gene variants will be predominant in particular ethnic groups. So clinical validity is higher in such groups. In a multicultural society, due to heterogeneity and cross culture, gene variations within a racial group, may differ more than the variations between different races and so there seems to be no need to have gross racial sub classifications [60]. A focus on race might not take into account the environmental factors. However one cannot negate the fact that certain drugs are certainly contraindicated in certain ethnic groups, e.g. ACE inhibitors in African Americans, so there certainly remains scope for more research into racial genetic differences. African Americans are more likely than other groups to believe that genetic test results will be misused [34], that genetic test results lead to racial discrimination [61] or for the racial/ethnic group to be labelled as inferior [33, 62].

3.3.4 Privacy and Confidentiality

Patients also feel threatened by the risk of breach of privacy and confidentiality. In a telephone survey of US adults, 78% stated that they were unlikely to have a pharmacogenomic test if there was a risk that their DNA sample or test result could be shared without their permission [30].

The family doctor offering companion diagnostic tests may also be put in a dilemma as to whether they should inform the family, of any positive results, especially when they are also the doctor's patients. This disclosure is always to be considered as unethical professional behaviour, without the consent of the index patient. In fact a person may refuse to be tested just because of fear that they may be asked to make their test results available to relatives. Although one can argue, from an altruistic point of view, that such disclosure should occur, most patients are reluctant to show others their disease status. Also, patients may be prepared to tell their family doctor the result of a pharmacogenetic test but they may have some reservations at sharing the results with other healthcarers involved in their health care management [63].

If tests become widely available, a healthy patient might decide to take a test years before he is likely to develop a disease. So the result will end in his medical file [64]. Protection of data from access by third parties must therefore be ensured through regulatory instruments. Patients should be reassured as to storage facilities for samples and data from results, both paper and electronic formats.

What does the physician do if a patient refuses to take a pharmacogenomic test? Should the medication still be provided, even if there may be adverse reactions? The answer lies in ensuring real informed consent has been obtained because an individual retains the fundamental right of refusing treatment. However physicians are concerned as to possible litigation in the future from the patient or the family.

The American College of Medical Genetics recommends that incidental findings obtained in a clinical (not research) setting should be disclosed to the patient and the clinicians [65]. However not everyone agrees with these guidelines [66–68] and

it is best to have an agreed policy at the time of the initial consent, with the added safeguard of utilising counselling if there are unexpected results.

3.4 Direct to Consumer Tests

It is increasingly possible now to obtaining genetic information without direct consultation of a physician by purchasing personal genome tests, PGTs, also called direct to consumer tests, bought directly through the company developing and marketing the test, or via retailers. Commercially available tests, based on whole genome sequencing are now widely available for multifactorial diseases and some also for pharmacogenomic tests. The companies may offer a bundle, with tests providing results about several diseases or groups of diseases, or about therapy options, which vary in nature and therefore also have differing ethical implications. Some pharmacogenomic tests for antidepressants are also being combined with susceptibility tests [69] in psychiatric disease and this raises concern in relation to clinical validity of such tests [70].

Common to all there is the central issue of consent and how to ensure that it is really informed. Article 7 of the Additional Protocol of the Council of Europe on Genetic Testing for Health Purposes [71] states that 'a genetic test for health purposes may only be performed under individualised medical supervision' with a view to offering protection to the person tested and also the possibility of informed consent and counselling.

Bunnik et al state that 'because of the complexity and the quantity of the information offered in PGT, informed consent cannot be fully specific' [72]. They propose a model of consent, with three layers, tiered, layered and staged, which can also be intertwined. Tiered consent is based on giving a choice to the individual as to which type of disease the consumer is interested in. The layered consent relates to the amount of information made available at different times, starting with a minimum basic amount of knowledge, labelled as the first layer; so there are options to know more, with the choice left freely to the consumer. Staged consent refers to provision of information over a specific timeframe, when the consumer has to give consent at various stages of the process, in relation to a certain process, for example pre purchase of the test, prior to being sent the results and prior to receiving updates.

The other ethical dilemma is disclosure of information. The companies provide different levels of assurance as to confidentiality and disclosure of information for their clients. Consumers have expressed a preference for tiered consent schemes that allow individuals to specify the level of data sharing permitted with respect to their genome [73]. Of course not everyone is prepared to share their results, not even with their doctor [74].

There has not been any strong evidence of harm to consumers from availability of direct to consumer tests. In fact a study revealed that the type of information received did not result in any psychological harm [75]. Possibly this reflects the personality of the person willing to obtain such tests.

Other concerns relate to criminal abuse, such as the possibility of submitting biological samples of third parties who have not actually consented, as well as lack of transparency as to what type of research is carried out on the samples submitted [76].

4 Research

4.1 Clinical Trials

4.1.1 Informed Consent

The ethical issues related to research in general and to clinical trials in particular are well established and safeguards are faithful to the principles in the Declaration of Helsinki, with its latest amendment in 2013 [77]. From a participant's point of view, informed consent, privacy and confidentiality are guaranteed through scrutiny by Research Ethics Committees, RECs, based in universities and in health departments and institutions, sometimes covered by state legislation. For clinical trials there is specific legislation in most countries reflecting the higher stakes. In Phase I research there may be healthy volunteers while in Phase II or III clinical trials, the patient may get the placebo or the least effective drug. So the information prior to obtaining consent has to be comprehensive and transparent and well explained.

In the EU, states have transposed the EU Directive [78] into national legislation. The Directive lays down detailed guidelines as to what the RECs should assess. Again there are guidelines available through the Oviedo Convention [25] and the Additional Protocol [79], which clearly distinguish subjects capable of giving consent from those who for some reason (age, mental infirmity, and emergency situations) are unable to consent. Research on such vulnerable people, including persons with mental impairment and minors, carries the same problems in relation to consent, as that for diagnostic purposes but there are some specific issues. The subject should only participate if the trial is personal of benefit, or to others suffering from the same type of disease, or if there is no other way of obtaining the same information. Although not able to understand all information, vulnerable individuals may be able to decide and consent to simple procedures and to take part in the decision making process. With respect to children, a child should be involved in evaluation of the benefits and risks of participating in research, and in coming to a decision, in accordance with maturity but consent from the parent or legal guardian is also required, though the minor is allowed to object [80, 79]. Moreover if a competent child refuses trial participation, they must not be coerced to participate just because the parents agree to participation. Ethics mandates that their wishes should be respected, even though legislation only requires consideration of their views [80]. Yet again the main problem here is ensuring adequate information and time to enable the potential trial participants to make up their minds.

Obtaining consent in multicentre clinical trials may be hampered by lack of harmonisation of law. Even in the EU states this has this been possible, for example there is no harmonisation of standards for ethical committees.

4.1.2 Consent for Genetic Studies

Consent for genetic tests, either on blood or tissues, in a clinical trial is usually obtained completely separately from the consent for the rest of the protocol. However the content of the legally binding form to be signed and the information supplied, vary from one trial to another.

The main problem is obtaining consent for future studies. The Oviedo Convention allows additional use of biological materials if 'done in conformity with appropriate information and consent procedures' [25]. The pharmaceutical companies claim that often it is impossible at the first instance to outline exactly the future research. So researchers have sought different models of consent, focusing mainly on broad [81, 82] or open consent for any future research, whether of a genetic nature or not, that is, there would be no need to get back to the trial participant to ask for consent for future studies, or for studies not contemplated in the original design of the trial or because new technologies become available. However broad consent does not mean 'vague' [83] but broad in relation to the original idea of consent to a specific protocol. It usually implies consent related to future research, either on the same disease or some new biomarker, but not tied to a specific project. Effectively this is 'consent to governance' [81] by some authority or person to take the decision in future as to whether to use the material or data for research. However sometimes such distinctions are not even mentioned and this actually amounts more to 'blanket' rather than a broad type of consent. The only safeguard is the requirement to have the future project reviewed by a REC, which is always a prerequisite for substantial amendments to a trial.

Other researchers may opt to give the participant the option to choose whether to be recalled in the future for further consent. Yet this is very cumbersome, not to mention that of course it limits anonymisation of material collected, as the participants have to be traced to be recalled, thus compromising privacy.

There is some disagreement as to whether broad consent can ever be equated with genuine informed consent [85, 86] although most ethicists are in favour of its use and agree that this is a decision that fulfils the original intention behind the introduction of informed consent, that of ensuring the participant's autonomy is protected [82]. Similarly the trial participant may affirm that they do not want to be re-contacted in future and are prepared to give authorisation for the researchers to use their material anyway. From an ethical perspective such a position would also be a voluntary decision and thus guarantees the principle of autonomy [87].

Legally, broad or open consent or waiver of consent cannot by its very nature be considered as informed consent as covered by the EU Directive or by the Council of Europe. However the Nuffield Council on Bioethics did approve broad consent for the 'use of samples that are anonymous or anonymised' [88] while it recommended collection of a separate broad consent if the samples where identifiable.

The possibility to opt out of the trial, must be present for the length of the trial, but also for the stored samples and data. It may be possible at the outset to refuse to be part of the genetic research arm, or to refuse to all future research, although often these comprise exclusion criteria from the trial. When opting out occurs after destruction of the biological sample, the data already collected is generally retained for the research - this must be highlighted in the original consent.

Finally, the issue of coercion arises when a patient agrees to being a trial subject if they obtain access to a new medicine, which they hope will work [88]. Is this a valid consent? One can argue that this decision is conditioning a better outcome in the participant, akin to a placebo effect.

4.1.3 Privacy and Confidentiality

Participants may be worried about privacy and confidentiality of stored biological samples, and sharing of data and results, which in the EU are offered protection through the EU Directive [88, 89]. However Data Protection laws are not comparable in non EU states.

The EU Directive on Clinical Trials does emphasise the 'rights of the subject to physical and mental integrity, to privacy' in accordance with the Data Protection Directive. In general privacy issues related to fear of discrimination are not an issue, as occurs in the diagnostic field. However subjects need to know that insurance companies do not get access to data. For this reason, they may be more likely to agree to participate in a trial if there is anonymisation of samples, though they may be satisfied by coding which allows them potential access, particularly if they trust the pharmaceutical company or researcher.

However the problem of confidentiality is paramount for uncommon orphan diseases, particularly in a small community. With rare diseases, it seems pointless to have anonymity when it might be beneficial to contact the participants to impart individual results. Should there be disclosure of results to such participants, and/or to other family members, particularly if the information is beneficial to them or their family? Potential participants should be encouraged to speak with their families regarding genetic trials, so that the subject can share information with family members [90–92].

4.1.4 Data

There is a duty on the scientists to impart sufficient information at the time of recruiting participants to a clinical trial to enable informed consent. The potential trial subjects should be told about the benefits and risks of the research but there is a need to balance the knowledge divulged with what a reasonable person would expect to be told and to express consent forms in a straightforward unambiguous language. The investigator should find out what is important to a specific group of persons or ethnic group or study group in the inclusion criteria.

Subjects must be informed as to the length of time and site of storage of biological samples and data, the security provided and who has access to the data, whether

only researchers or local authorities or third countries, in conformity with Data Protection legislation.

In the process of data sharing, data should be anonymised and some countries have regulatory mechanisms in place, particularly in the case of clinical trials, e.g. EMA guidelines. Data sharing is of course enhanced and expedited through publication in open access journals but this needs to be funded. A survey among trialists reported willingness to share data among respondents (albeit there was only a 46% response) but they were concerned about appropriate interpretation of data, protecting their own interests with respect to publication or academic recognition, as well as some concern about patient confidentiality being maintained [93]. In the interests of the public, negative results should be reported, so trials can be repeated.

There has been a campaign to increase the transparency of clinical trials and to make results available to the public. It is not clear how companies decide which information to make available to the public or third parties. RECs should actually make sure that both trial registration and the publication of results are mandatory prior to ethics approval [94]. EMA's policy of providing clinical trial data to third parties was weakened due to legal action from pharmaceutical companies. Similar incentives are happening in many countries. Once the EU Directive regulating clinical trials is repealed in 2016 and replaced by the Clinical Trials Regulation [95] registration of all trials in the EU will become mandatory as will the publication of trial results. A full study report must be published in line with guidelines by ICH [7] and again this would become available in the public domain.

Trial subjects may worry about the commercial interests of the company overriding their basic rights. They have to be informed as to commercial interests of the company as well as to the fact that intellectual property rights are vested with the sponsors or the pharmaceutical company.

Drugs that are new on the market need to be followed up for a considerable length of time, in fact ideally throughout the drug's lifetime, the so called 'life-cycle approach to risk management' [96]. This will ensure that rare side effects are identified [16, 96]. EMA guidelines [97] aim to strengthen evidence about the effect of genomic labelling and the use of genomic biomarkers in the post marketing stage, to use it in clinical practice. Post marketing surveillance is when certain rare adverse reactions are identified. These may be due to complex interactions of genetic variations with environment and lifestyle. The pharmaceutical companies may proceed to utilise these results to develop personalised medicines.

4.2 Genomics Research and Biobanks

4.2.1 Informed Consent

Genomics research may lead to development of new drugs, which can then be assessed through clinical trials. By its very nature such research requires a large database so as to enable examination of genomes from a large number of individuals, to obtain meaningful results that identify either susceptibility genes for specific diseases or for variability in drug responses.

This has led to the establishment of biobanks, repositories of biological materials and / or data derived from such samples, from specified populations, sometimes healthy individuals, invited to participate in being donors for research purposes. Some material is in private collections but most is in the public domain. Many banks contain more information, in the form of personal data, which may be also linked to medical and lifestyle data. This data is necessary because of the interrelationship between genes and the environment but it is often linked to other information held on a national level, for example social security or tax information.

Such biological collections are now often managed by multinational groups or consortia. This means we have entered the global era of research where international collaboration is the only way to obtain sufficient research material that can be shared globally for meaningful results for practical clinical application.

Recruitment is increasingly coming indirectly through the use of the biological material already stored in national archives or biobanks. Consent is obtained at the time of donation of samples, often long before the research project is fashioned. The commonest type of consent used currently is broad consent [98]. Such research is non interventional and offers a low risk to participants [99], seeing that most results do not apply directly to the individual who has submitted the material; this renders broad consent more acceptable. To donors, 'practical utility' may be more important than knowing the details of each project [84].

As for clinical trials purposes, broad consent is acceptable provided certain safeguards are in place; these would include measures to maintain confidentiality by ensuring all personal information, whether in the form of biological material or data, is stored securely in a suitably coded fashion. Anonymisation is not usual as it would preclude clinical monitoring or adding new data to the bank. Maintaining privacy is important because of the links to other data. Consent should include information related to who has access to data and with whom data is shared. The principal investigator should not be involved in obtaining consent but a contact person needs to be identified.

The autonomy of consent can also be preserved if, within the constraints of the biobank set up, donors are allowed the possibility to have samples and data withdrawn [100]. A crucial safety measure is to ensure adequate governance regulations of the biobank facility and to have RECs approval for any new research project that uses material from the bank.

Because most of the research is carried out by international collaboration, of different bodies, difficulties arise in obtaining consent from the individual national RECs. In an effort to simplify such authorisation and to ensure it is timely, there is a need for setting up a framework based on cooperation between the multiple research centres, be they health institutions or industry based companies, with consideration of the local policies, regulatory mechanisms and legislation.

A recent recommendation is to set up a Safe Harbor Framework for International Ethics Equivalency [101], creating an International Ethics Review body that harmonises procedures based on the same principles and satisfying the varied national legislation [102]. Management will rely on electronic means to expedite matters.

One way to promote donation to biobanks is to induce patients to donate residual biological material after diagnostic procedures, material that may otherwise be discarded after biopsy [103] or even to obtain material during recruitment in clinical trials. This may be quite acceptable for donors as it benefits them by promoting a sense of altruism in helping society. Some ethicists argue that there is no need for consent [104], particularly if the material stored can be considered as having already been discarded by the patient. On the other hand there are advantages to the patient giving consent. This would enhance trust between patients and researchers, auguring well for future participation in research, since it would show respect for patients' views. They may have strong objections to being involved in any genomic research, especially if it has commercial potential but may be prepared to consent to use of their biological material if the research allows clinically relevant results to be passed on to the patient or their family [105]. Current opinion is that national banks should be able to inform clients of any positive results if it is going to be to their benefit.

In fact in a study [106] of the UK public in 2012, 55% of those surveyed believed that it was 'extremely important' and 25% that it was important to be asked to provide consent for residual samples, and the majority agreed to have an opt in type of consent, to speak directly to a healthcare professional and not just fill a form. 27% of those surveyed and 57% of those in focus groups did prefer an opt out type of consent. However this again would be broad consent at the time of collection.

Much biological material is already present as archived biological material, initially retrieved with another purpose in mind, in particular human tissues in pathology departments in all hospitals, previously collected with consent for diagnostic purposes. The question is whether such material should now be available for genomic research and then how to obtain consent to use such material. Recall of patients is very unlikely to be feasible. In some countries, legislation provides for use without consent if there is appropriate protection, such as ethics approval by RECs, for each new project. If samples are securely coded and stored and access to data is limited, and if the donor has not specifically refused consent, then most agree that specific consent is not necessary [107]. The Council of Europe provides for use without consent if reasonable efforts to contact the owner are not possible, provided the research is of important scientific interest and could not be addressed by using other biological material for which consent was available [108].

There should be a policy as to what to do with samples from minors. Should these be initially excluded from inclusion in a biobank until the minor turns 18?; should they then be contacted for consent?

Other models of consent may be used, such as the authorisation model [85], which allows the donor to decide for which type of research they are willing to contribute and it is up to the donor to lay down particular conditions as to the level of involvement they want in the future, especially regarding recall for future consent or not. Staged or stepwise [109] informed consent would allow potential donors to understand what is happening. Dynamic consent [110] takes involvement a step further as the donors are kept informed by the researchers as to what is happening and are asked to re-consent, with various interactions occurring between the donor and

the biobank, regarding samples and data use. It is claimed that this would increase recruitment, trust and transparency. However Segerdahl [111] has been critical of such consent, claiming that this places a lifelong burden on the donor while the researchers have the liberty to move on.

Another problem particular to biobanks is what would happen to banked material after death of the donor. The OECD [112] leaves the options to the biobank but the relevant policy must be made known to the participant from the outset. The sample and / or data could be withdrawn or the option given to relatives to decide or they can be anonymised.

Biobanks have variable policies [113] regarding return of unexpected findings to research participants, whether these are incidental findings unrelated to the aims of the research or whether they are 'individual research results' that are part of the study variables, with less likelihood of the latter being passed on to the subjects. Such policies must be clear before consent is obtained.

4.2.2 Data Privacy

Now that technology has really advanced, the limiting factor in genomic research is actually the data analysis. Electronic records facilitate the extraction of results but electronic data is never really completely safe. With today's bioinformatics tools it is possible to analyse large public data bases and use data linkage disequilibrium to identify individuals, even if data was anonymised.

Electronic medical records may be less secure than envisaged but even researchers have claimed that 'efficiency and utility of securing accurate personal genomic information through genomic testing and electronic medical records may outweigh patient privacy concerns if cancer treatment outcomes can be improved' [9]. The US has an electronic Medical Records and Genomics network, eMERGE, with biobanks linked to electronic medical records, specifically aimed at finding genomic markers and genotype-phenotype associations.

The Personal Genome Project [37] hinges on publicly sharing genome date from self referrals, such genomic data being combined with public health data. The participants are 'explicitly not promised anonymity' because the project leaders argue that although protection of data is possible in such research, privacy cannot be always ensured when there is public release of data for sharing among researchers.

Therefore it is crucial to ensure confidentiality. This is possible in EU states where it is covered by the Data Protection Directive [89]. However the collection, storage and sharing of samples is not harmonised. Data may be transferred across the EU in line with the Data Protection Directive but transfer to third parties is allowed if they are deemed to have data protection laws similar to the EU; this excludes the United States of America. In an attempt to solve this impediment to sharing information, in 2000, the European Commission and the US Department of Commerce agreed on a Safe Harbor Framework, agreeable to both sides [114] for ensuring privacy.

It is a much bigger problem if such material is unfairly disclosed to authorities for educational decisions, employment and legal decisions on culpability [87]. This

will erode donors' trust in the system but there is no specific legislation as yet, at least on an EU level, to give biobanks the right to protect their data at all costs. It is envisaged that the data may be useful for allocation of health resources. Accessibility to biobanks must therefore be controlled.

5 Responsibilities of Other Stakeholders

Commercial companies in the pharmaceutical industry have a duty to society to invest in research and development of new drugs to provide efficacious and safe drugs through properly conducted clinical trials. But Phase I development of new drugs is expensive and traditionally drugs have been aimed at 'one size fits all'.

It is now accepted that it is unethical to ignore the needs of non responders, when such reaction is the result of recognised pharmacogenomic differences that can be targeted in drug development for the production of personalised drugs for these people.

However if the number of potential patients is low, it will not be economically feasible for a pharmaceutical company to invest in drug development specific to such patient groups since the drug will be too expensive to manufacture, even if altruistically this will be of long term benefit to such individuals, if not a life saver.

The company may need to look into allele distributions for specific populations before deciding to invest in developing drugs for such a group of people. Of course this seems unjust to a minority of people with orphan diseases.

Some have argued that companies have to be given incentives to pursue drug development, such as allowing them exclusive research for rare diseases for which they aim to provide therapy. This may be public funding [115], as happened for orphan diseases, for which research has been adopted by international networks. The US Orphan Drug Act of 1983 allowed tax refunds and 7 year exclusivity for drugs for orphan diseases.

Knowing which individuals are likely to benefit from a new drug based on their genetic variations can lead to clinical trials only in patients with the particular genotype, thus leading to a new personalised product at a quicker rate. This minimises costs.

Maybe this is why the major investment has been in personalised therapy in oncology. The increasing number of elderly people has brought about an increase in the prevalence of cancer and an easily available source of biological material to work on. However, one can argue that either someone looked far ahead and invested in oncology work, or it was fortuitous and initial success led to development of more drugs in oncology [9].

A company may also consider to rescue drugs that have failed to pass a clinical trial because the majority suffered toxic effects. Yet the drug may be developed for the relatively few responders. Such a scenario is more likely for specific ethnic groups [116], as happened with BiDil (isosorbide and hydralazine) [117]. Repurposing of drugs, the use of approved drugs for another indication, may also prove possible.

The Nuffield Council on Bioethics [88] had proposed that licences for marketing of medicines could be tied to a pharmacogenetic test to ensure that it is carried out and not bypassed in a measure to avoid costs.

5.1 Justice

Healthcare providers may be willing to allocate resources for pharmacogenetic tests or personalised drugs if there is evidence of the benefit in terms of savings in health expenditure, in the long term, for treating the rare conditions.

More commonly the problem is that the tests are still expensive [49] and for pharmacogenetically designed drugs they are likely to be more expensive tests, leading to inequalities in access [118]. In fact not all genomic tests are covered by insurance [119] and this deters patients from obtaining the test and moreover the availability of insurance cover is not uniform, for example in the US, this varies from state to state [120].

Access to genetic diagnostic testing may be limited for various reasons, including residence, distance from healthcare facility, socio-economic status and insurance coverage. It may not be available at all in certain countries or at least it may only be available in tertiary centres, rendering access difficult and entailing expenses to contact the providers. If the test is positive, there is the problem that the relevant therapy, again likely to be more expensive than for common diseases, may not be available or may not be free to all. Treatment for rare conditions is much more expensive than expected. Sometimes the impetus must come from lobbying by patient groups to put pressure on insurance companies to provide cover and on healthcare providers to make expensive tests available [3, 121].

Pharmacogenomics will benefit society by improving the benefit to risk ratio for a particular drug in a particular population but it can never guarantee improvement for an individual [49]. Putting the onus on a person to take decisions about their health can be interpreted as empowerment but it may also be placing a burden of responsibility on their shoulders, instead of healthcarers. Patients might have to conform to social expectations [122].

6 Outcome and Recommendations

It is the hope of all stakeholders, but primarily of the main beneficiary, the potential patient, that the promise of pharmacogenomics to provide ‘the right drug for the right patient at the right dose’ is fulfilled. Advances in molecular technology have enabled the application of genomics to the development of specific drugs for personalised therapy. At present the number of drugs with pharmacogenomic labels is limited and the challenge is to identify genetic variability of drug targets and develop biomarker diagnostic tests for common diseases. This requires investment

in large scale research and robust clinical trials on an international basis, with multidisciplinary international collaboration. However the starting point for such projects is the pool of biological material from the patient or potential patient.

This chapter has focused on the ethical issues that guarantee standards and promote cooperation by society. The primary emphasis is on informed consent, which is central to the involvement of the patient. It is a crucial step for the uptake of a pharmacogenetic test, for enrolment in a clinical trial or genomic research and for the donation of biological material for a biobank. Continuing cooperation of the patient is enhanced through safeguards to ensure privacy and confidentiality in the handling of biological samples and data. Consent is also promoted through dissemination of the knowledge that there is equitable access to personalised medicine and not solely a reliance on the cost effectiveness of the tests and the therapy.

So society must be kept fully informed about pharmacogenomic progress to encourage open interaction with scientific and medical researchers. There is a definite educational role for healthcare professionals, provided they are themselves also well informed and trained to explain the benefits of personalised medicine, to choose and interpret relevant genomic tests and to encourage research participation. Genomic training must be included in medical and health science curricula at all levels, with emphasis on continuing professional development to keep abreast of advances.

Participation in multidisciplinary international research may be enhanced by opting for broad consent for genetic studies in clinical trials and for collection of biobank samples. The move to increased transparency in the conduct of clinical trials will provide more information to individuals as trial results are made public. Post marketing surveillance of drugs needs to be pursued on a regular basis to identify the effects of genomic labelling, pick up rare side effects and identify potential new niches for specific drugs.

Ethical principles are now embedded in various regulatory frameworks and legal instruments, but states have embraced different norms. As genomic research increasingly moves into the global arena, the vision is to work towards establishing harmonised regulations to facilitate international collaboration and so achieve the goal of making personalised medicine a reality in everyday medical practice.

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