Anonymous # 1

1. **What will be the likely economic impact of pharmacogenetics on the development of new medicines?** It will be modest initially. In some instances it will shorten the time needed to develop new drugs, and in other instances pharmacogenetic issues will increase the cost of new drug development as companies are forced to address genetic variation as a possible reason for an unpredictable adverse drug event(s). The economic impact on a given drug will all depend on whether gene variation(s) are believed important prior to clinical trials. If one or more gene variation(s) is considered highly likely to be therapeutically important it will be evaluated as part of the clinical protocol during drug development. However, it will be more likely rare genetic variation(s) with uncertain relevance will be evaluated after some problem develops in a small subset of the population. These patients will be screened to test for rare mutations in functional genes that could be associated with adverse drug outcomes to see whether the causative gene(s) can be identified. This will be combined with proteomics that attempts to try and elucidate the biochemical pathways that are altered in these rare individuals and to help identify the likely source of the genetic problems. This will increase the cost of drug development by may in the end save a useful medication from being removed from the market.

   Pharmacogenetics will likely increase the profit margins for some drugs as Pharmaceutical Manufactures try to market test kits with their drugs under the auspices of improving therapeutic care. In some cases the test kits will probably add marginal value to the safety of the drug, but much to the bottom line of the manufactures, but they will be marketed as providing value or safety. Pharmacogenetics will be used for any marketing advantage it may provide. Regulatory agencies and the public in general are so poorly informed about the economic issues surrounding genomics and genomic testing they will pay the cost associated with such increased testing.
2. **Are further regulatory measures needed to encourage the development of clinically desirable but economically unprofitable medicines?** NO. It is generally unwise for regulators to try and dictate what market forces do far more efficiently. Regulation is critical to preventing exploitation and illegal practices. Regulations aimed at dictating what drug companies develop makes little sense. It is better and far more efficient for the market itself to define what medicines get developed and which do not. Forcing companies to develop unprofitable drugs will increase the cost of drugs for everyone and decrease the efficiency of the market system.

   When the government wishes to encourage a certain behavior that makes little market sense, it is far more effective for them to use incentives for business to get companies involved rather than regulation. Incentives should be used to encourage development of economically unprofitable medicines.

3. **Should pharmacogenetic testing of participants in trials be a regulatory requirement for the development of medicines in the future?** No. It should be something which is encouraged to improve safety and efficacy when it makes sense to do so. Making a genetic testing or any test a blatant requirement for participants in trials makes little sense just because you can do it. There must be value to performing a test. We can do PET, CAT and NMR brain scans. Should we make those a requirement for any CNS active drug in clinical trials? Let the regulators and the company decide if genetic testing would add value to the information they collect in clinical trials. Ultimately it is the company that has its neck on the line if there is something they overlook and get a poor product to market. Market forces dictate that companies use diligence and caution in how they develop a new drug, or their costs for drug development and legal expenses will increase and their ability to stay competitive will be lost.
4. **Who should be responsible for genetic tests?** This is where regulation makes sense. It doesn't matter who does the genetic tests so long as the results are reliable. Make sure that whomever does the testing meets certain performance criteria (the job of regulators), then let market forces and interests determine who can provide that testing service most efficiently, most conveniently and at the least cost to the consumer. What I care about as a consumer is who is it that does a good job for the least money and whom can I count on for their quality. Why should genetic testing be any different? Regulate the parts that are critical for ensuring confidentiality, reliability and dependability. Let the market decide who can deliver that best for the least to the consumer. I would not encourage a monopoly in this area by providing the market to a single group. That only encourages inefficiency, over billing and waste.
5. **What are the implications of pharmacogenetics for Pharmaceutical companies and providers of healthcare regarding legal liability for adverse drug reactions?** People are going to sue whenever they have an opportunity and whenever someone tells them they have a case where they might be able to make some money. If someone has a severe adverse drug reaction and they were told a genetic test would have helped prevent this but it didn't, chances are they will visit their lawyer and start a lawsuit. The lawyer will make the Company, the healthcare provider and the genetic testing firm defendants in the lawsuit. Lawyers are not selective in who they sue for their clients, their goal is to get the client some money by proving negligence on the part of each or some defendant with money.

   What needs to be made clear to the public is no genetic test is going to be 100% accurate at predicting anything. The tests may reduce the risk and chance of an adverse drug event, but it can't totally eliminate it. This is the message that the public, the healthcare providers and the patients must understand. It is lack of understanding about the limits of this technology that will lead to lawsuits, although at times it may be simple human error. In any

case, all three groups will need to carry liability coverage (a standard for all business these days anyway).

6. **Should medicines that have been developed for administration in conjunction with a pharmacogenetic test be distributed to countries with which there are no testing facilities?** That depends on the drug and exactly what the test is meant to prevent/avoid. If the test is to prevent a common life threatening adverse event and marketing this drug without the test is going to expose many patients in the population to this adverse outcome, then it may be hard to justify the release of that drug into 3rd World countries. However, I doubt a Pharmaceutical Company would ever develop such a drug, because the liability issues would be tremendous for failure to prevent such a severe adverse event even at home.

   Most would say, take the high road and do more good than harm and not play Russian Roulette with peoples lives. But we must also be cognizant of reality. Many drugs that are on the market right now are capable of causing serious adverse effects under the right clinical conditions. When tricyclic antidepressant use was at its peak in the late 1980's, 500,000 people/yr were overdosing on these drugs just in the US. Yet we did not pull them off the market because at the time there was no other drug available that was as good for treating depression. These drugs were the best. Even when we knew CYP2D6 expression influenced tricyclic therapy, it was not evaluated to try and prevent these problems. Doctors developed some degree of expertise in using these drugs and tried to prevent/avoid problems. When the SSRI's became available they replaced the tricyclic drugs as the major drugs for treating depression. However, CYP2D6 testing is still not used in medicine and tricyclic drugs are still prescribed.

   Don't be too hasty in passing judgment about what should be allowed or not allowed. These are issues that should be worked out between the company and the countries and their people that may benefit or suffer from these drugs. I am not sure you can make hard and fast rules even with drugs that may produce severe toxicity in some individuals, if the drug adds real value to the therapeutic agents available in a country. Should 10 people die to prevent one severe drug reaction? Should 100 people suffer, so that one person is not put at risk from a moderate side effect? Where would one draw the line? I don't advocate dumping drugs on an unsuspecting population so a company can make more money. Nor do I think we should ignore the need for allowing for flexibility in human decision making. In an imperfect/uncertain world there are no absolutes, and so we allow humans to decide the best course of action and hope the decision makers are wise and compassionate.

   We impose regulations when we find someone abuses the system. Let's not make something into a problem because we think it might be. Regulations are costly and add additional burdens on the market system. Use regulations when needed, not because a regulation might be beneficial.

7. How should predictions of efficacy and safety, as well as cost, be integrated in deciding whether to provide a particular treatment to patients in a public healthcare system or a private healthcare system?

The answer is based on simple economics. Tests which do not provide a real value have no practical utility. For example, suppose you want to prevent an adverse event by performing a genetic test. The genetic test is fairly predictive of the adverse event so it seems there is some basis for doing it. However, it costs $100 to perform the genetic test, and the savings realized from the test is <$100. Each time the test is performed, someone has to pay that difference. Compare that to simply not doing the test. There are some adverse events, but the patients survive and the overall cost of health care is lower because it is not being wasted on a test that costs more than it saves.

Efficient use of resources dictates that we use tests when they are cost effective to use, not simply because it is possible to carry out a test. Some private patients may wish to have a test done in hopes they can avoid a potential problem or to ensure they will respond to a particular drug when it is prescribed. However, that is their choice. Those who manage health care resources should make their decisions based on the most efficient overall use of health care dollars, not the whims of a select few.

When a genetic test is capable of producing a savings because the overall efficacy and safety of a drug is improved substantially by knowing what the patient's genetic profile is, then the test should be applied. This is a great incentive for its clinical application, because each time the test is utilized properly it will save a certain amount of healthcare dollars that can be invested elsewhere. On the other hand, employing a genetic test to improve the safety and efficacy for some at a greater cost to everyone else only increases the health care burden on society. One may be able to justify this if that extra cost is low relative to the expected benefit to some, but when the benefit is modest and the cost is large it makes little sense.

The driving force to instituting genetic testing in clinical practice is MONEY. Safety and efficacy are what people like to talk about with regard to genetic testing because those are feel good issues. However, it is only when safety and efficacy significantly impact cost of care that they truly influence the economics and the decision making process.

A good example is CYP2D6 deficiency and codeine therapy. Many people know codeine is converted to morphine by the CYP2D6 enzyme and people without this enzyme get no analgesic benefit from codeine. This is clearly a therapeutic failure due to a well defined genetic variation. So why not test for the CYP2D6 polymorphism? Simple. While efficacy is affected, there is no indication it alters patient care costs sufficiently to justify routine testing for this polymorphism in pain clinics. If a patient doesn't respond to codeine it doesn't take the patient long to find that out and the doctor can prescribe another analgesic. The gene variation must modify efficacy and/or safety sufficiently to influence overall cost of care before the genetic test makes economic sense to employ.

8. **Application of Pharmacogenetics – will it exacerbate inequalities in healthcare? Will the benefits only be affordable or available to the wealthy?** Rich people can always do whatever they want to do with their money and they will always be able to afford more than the average Joe on the street. If the wealthy want a private hospital room and private nurse and they can afford to pay for it, does that mean everyone should be provided the same level of comfort in the hospital?

   Pharmacogenetics will be provided routinely to the public when it can be shown that it is cost effective to do so, and not unless it is. Everyone gets a basic level of genetic testing support. Some wealthy individuals may very well have their entire DNA sequenced in the future, and all their important variations identified. Just because it is possible, doesn't mean it should be done routinely. The rich are welcome to spend their money however they wish, whether it is cost effective or not, that is their choice because it is THEIR MONEY. We can't support that kind of excess in the public healthcare system, that would be a disaster.

9. **Is the storage of genetic information for the purpose of pharmacogenetic analysis categorically distinct from the storage of other kinds of genetic information, for example susceptibility to disease?** Categorically distinct is a very strong term since certain gene variations that affect drug metabolism could also affect disease risk and have often been investigated for such links. That said, the purpose of pharmacogenetic analysis is certainly very different from studies aimed at finding susceptibility genes, and it is the later work that has tainted the former. Most of the concern about genetic information and its potential abuse, risks for the patient, etc. are based on poorly understood concepts about what the information collected really can do and can predict, when it is of value and when it is not.

   Most genetic variations that are predictive of disease are genetic variations with high penetrance, that is they have a major effect on the disease process. The most practical genetic variations in pharmacogenetic research are likely to be genes that also have high penetrance with regard to therapeutic outcomes. It is unlikely (no evidence to date) these genes are going to be the same. Gene variations with low penetrance both in pharmacogenetics and disease will ultimately have limited utility, because they will not be predictive enough in a routine setting with all the other variables to allow decision makers to draw conclusions about what they mean. I disagree that doctors are going to look at a genetic test and use probability statistics to determine what drug to use. Doctors want something predictable and reliable to guide them. In the absence of that, they simply will disregard the test and the money to perform the testing will be wasted.

   It would help in research if people understood the difference in purpose between pharmacogenetic research and disease susceptibility research and their different ethical implications. Pharmacogenetics is aimed at defining risk for therapeutic problems, to identify genetic variations that may alter drug response for the purpose of using that information to avoid and prevent drug

toxicity and improve drug therapy. Disease susceptibility research is aimed at locating genetic variations associated with disease for which there may be no drug treatment and no method to prevent the disease. In my view, those two have extremely different ethical issues. However, ignorance is pervasive in genomic research.

Researchers should respect the rights of patients and genetic information should remain as confidential as any other part of the patient's medical information. But the uninformed ignorance surrounding genetic tests and their potential value/risk is appalling. I disagree that it is of any value to tell a patient about every genetic test you run if you cannot verify it has therapeutic relevance. If you can confirm its therapeutic relevance then I think it is ethically required for you to let the patient know this. Thus, I agree with maintaining records that would allow you to contact the patient if possible at some future date, but not to contact a patient about anything you find. You are not doing the patient or the research any good with that policy..

10. **What level of anonymity should be accorded to genetic information stored as part of research in pharmacogenetics?** That depends on the purpose of the pharmacogenetic research. If the purpose is for data snooping, to try and see if there might be a relationship between some genetic variation and a drug response, one should anonymize the sample as much as possible. You may wish to be able to relate the genotype to some clinical information, but you do not need to related it back to the patient. Most of these studies will be too preliminary to know how predictive that genotype would be. They would need further research for confirmation, which the investigator may or may not be able to perform.

On the other hand, if there is a strong reason (previous work) to believe a particular genetic variation will have therapeutic utility for patients, it would be unethical to anonymize the sample and be unable to provide that information back to the patient. A major goal of pharmacogenetics is to use it to improve patient therapy. Clinical researchers should not view themselves as performing independent investigations with no responsibility to the individuals who participate in their research studies. When important information is collected that has direct importance for the patient, that information should be conveyed to them. The distinction lies in when to anonymize and when not to anonymize. This is NOT a hard decision in pharmacogenetics. It is based on the level of confidence one has that a particular genetic test is likely to prove therapeutically useful prior to the execution of a study.

I think one can view this the following way. You find a $20 bill on the street. and you may ask generally if anyone lost some money. You ask a general question, because you cannot ask specifically if someone lost a $20 bill and expect to get the money back to its rightful owner. There is a large degree of uncertainty to whom a $20 bill belongs and the honesty of those who might claim it. On the other hand, if you pick up a wallet and find $20 in it, keeping the money is equivalent to stealing. In this case you know who the owner is and you have an obligation to return the money and the wallet to them. Research should not be

governed by a set of morals different from that of society in general.

11. **What kinds of consent should be required for the collection of samples for research in pharmacogenetics? Should pharmaceutical companies which collect samples in the course of research in pharmacogenetics be able to use such samples for any purpose, or should consent of the donor be restricted to allow usage only for specific kinds of research?**

    The consent can do both things. The consent can allow the patient to donate the blood for other uses if they wish, or stipulate the sample be destroyed after the planned testing is completed. It depends on what the research subject is willing to allow. Some individuals are willing to donate DNA just like they are willing to donate organs or blood for other purposes, with the intention and hope it will help others. Clinical research has depended on the generosity of these individuals for decades. If the consent clearly informs the subject their sample may be used to test for any number of genes, and if the company anonymizes the sample, I see nothing wrong with this. There certainly will be times a company will not know what adverse effect will show up in the population and it needs to be free to investigate genetic variations it may not have anticipated being involved in those adverse effects prior to beginning clinical studies. Tying the hands of the companies in their efforts to address those types of problems that may have a genetic relationship is foolish and counterproductive.

    The subject should be given the option of donating their blood for a specific purpose or not. Thus, the consent should allow the subject to deny the use of their sample for other purposes. After the immediate tests are done those samples should be destroyed. When the subject donates their sample for other testing, the company is free to use it for other purposes.

12. **Do you think researchers should provide individual feedback about genetic information obtained from participants in research in pharmacogenetics?**

    Yes, when it is of use! Suppose I tell a patient they do not express the GSTM1 enzyme. Fifty percent of Caucasians don't have this enzyme. What does it mean? Does it affect the response to any drugs in any significant way? How useful will that knowledge be to the patient? If I collect that information and I cannot relate it with anything in a meaningful way, why should I or the patient be bothered with knowing this? Alternatively, a deficiency in TPMT may be a very important risk factor for a toxic response to some anticancer drugs. A CYP2C9 *3/*3 genotype holds a substantial risk for an adverse response to standard doses of Coumadin. These genotypes are very predictive of problems and it is the obligation of researchers who know this to convey that information back to the patient, as it may be of importance to them someday, and that information may help them avoid a therapeutic problem. When we know genetic information has therapeutic utility we should let the patient know this. When we do not know the therapeutic relevance, we should not confuse the public, try to inform them about something we don't understand or mislead them (either purposely or through our own ignorance).

13. **What, in your view, would be appropriate methods of regulating scope, storage and access with respect to pharmacogenetic information used in**

clinical practice?

Again, at issue is: "what is the purpose of pharmacogenetic information?" Is it to try and improve our understanding of the relevance of genetic variations on drug response and outcomes? If so, then it really needs to be made available to those on the health care team that can use it to avoid drug problems (doctors and pharmacists). This is no different than any other important clinical information that is used to make therapeutic decisions. Most patients will not be as aware of the meaning and implications of their genetic information as a doctor or pharmacist might. Making sure the information is part of the confidential Medical Record seems appropriate. There is no need to broadcast it, nor is there any need to restrict access to information that could help clinical personnel guide patient therapy. However, the only genetic information that needs to become part of the medical record is that information KNOWN to have a clear impact on drug response. Genetic variations that may have questionable relevance should never be placed in the medical record. The question should be: "at what point is pharmacogenetic information conclusive enough to incorporate into a patient medical record?" The issue should not be about restricting access to valuable and potentially important therapeutic information. That is the wrong question and direction to take.

Use of DNA for testing genes not relevant to the patient may be allowed provided the sample cannot be related back to the patient and the patient has no objections to the use of his DNA for this purpose. However, that information should be restricted to the researchers, not clinical personnel. DNA should be destroyed immediately after it is analyzed for its original purpose if not approved for further use by the patient.. When in doubt, destroy the sample after it has served its initial purpose. Consent forms should clearly provide the patient the right to decide this issue, not the researcher or clinical lab.

14. **Do you think that the ethical and legal issued raised by the use of pharmacogenetic tests in primary care differ from those raised by other forms of genetic testing? What about non-genetic tests, such as tests for cholesterol?** The ethical and legal issues of genetic testing in general are the same regardless in what venue one finds them applied. The issue should focus on the type of tests, their use and potential abuse. Why stop at cholesterol testing? How about EKG's, high blood pressure and glucose level. How about medical history (which really has a strong genetic component to it). How about ABO blood groups and Rh tests – those are really phenotypes are they not? Aren't the ethical and legal concerns already there with regard to medical information in general? All people have done is add another medical test to the mix, only this time it is something over which the patient has no control – their genes. Somehow that makes the problems with this so much worse? The purpose of pharmacogenetic tests is to identify genetic variations that affect drug response and outcomes. What is the problem? Don't doctors test patients now for various conditions that may affect their response to drugs and attempt to dose them accordingly? Somehow this simple concept has gotten mutated by genetic testing for disease that is not necessarily treatable, avoidable and has major

ethical issues associated with it.

15. **What might be the psychological implications for individuals of pharmacogenetics tests? Are such tests likely to reveal information that is of relevance outside the context of testing for response to medicines?** Are we are moving toward a GATTACA like society where your future is decided by your genetics, not your interests or your desires? It makes for great science fiction, but there are a number of factors that will prevent that from happening, much as there were a number of factors that prevented George Orwell's 1984 vision of society from becoming a reality. The basic premise of these extrapolations to the future is that technology will rule society rather than society controlling the technology. However, all technology has always been controlled by humans. That technology must provide humans with a clear benefit or they will not use it or allow it to be used. If people attempt to abuse genetic information, people will not provide doctors with access to their genetic information anymore. They will not allow tests to be run. They will not provide samples. If the medical community abuses its rights and privileges, patients will not trust them.

    Could genetic tests reveal information beyond the context of their original purpose? Sure they could. Is that bad? It depends on how it is used or abused.

16. **What implications do you think pharmacogenetic tests might have for family members?** It may be very important, particularly the more rare the genetic variation. If a family member is homozygous recessive or heterozygous dominant, and there is a chance other family members carry the same trait, the other family members may want to know this, particularly as they may eventually be exposed to similar drugs at some point in their life. This may also apply to related family members not just immediate family members. I would let the individual tested know their test result if it was clinically valuable and encourage them to share that information with others in the family if they so wished. Remember, the purpose of pharmacogenetic testing is to predict and avoid therapeutic problems. Knowledge is power. The testing is not to hurt patients, but to prevent them from experiencing a problem. Family members could be tested if they were informed and wished to be tested. It is their prerogative and the prerogative of the propositus who may or may not wish to tell anyone.

17. **In your view, are controversies likely to arise about who ultimately decides which treatment is prescribed in light of a pharmacogenetic test?** No. The doctor will always have the final say about the treatment. But, he may have to do this with input from the clinical lab and a pharmacist who are likely to warn him/her of the dangers based on a particular genetic variation. Any clinician who does not understand the implications of this information will probably be risking a lawsuit if their neglect of important clinical information was ignored in their prescribing behavior. I do not hold to the futuristic view that pharmacogenetic tests will be used to select in a probabilistic way the most optimal therapy for a patient. Genetic testing will initially focus on tests that have a major impact on drug therapy and where

ignoring that genetic information will significantly affect treatment outcome. It will be many, many years before we actually combine multiple gene variations in optimal therapeutic management. Even then, drug selection will be a rational process based on a high probability for success, not based on selecting between low, average or moderate differences in treatment outcomes. There will not be a sufficient difference in cost to justify the cost associated with genetic testing in those situations.

18. **Should patients be able to refuse a genetic test to determine response to medicines but still expect to receive a prescription?** YES. Patients have a right to expect treatment for whatever ails them and they have a right to refuse testing if they wish. This does not change the obligation of the doctor to provide the best care they can for the patient. I can't even imagine a clinician thinking that way, and if they did the patient should have no trouble finding a better more qualified doctor.
19. **Do you think that providers of health insurance should have access to pharmacogenetic information? What about other parts of the insurance industry, for example life insurance?** Pray tell, what business is it of the health insurance providers to know about my genetic information, or life insurance companies to have this information? Their job is to provide coverage for which I pay. I can't imagine pharmacogenetic information would provide them much useful information about risk when the purpose of pharmacogenetics is to be used to prevent therapeutic problems with drugs. I don't see these issues as connected. The genetic testing avoids therapeutic problems. Allows better selection of specific drugs to improve outcomes. Insurance companies should applaud this improved efficiency, not look for ways to exploit it for assessing risk. I suspect it would not be very valuable to them for defining rates anyway, but they should not have access to it, period. They are not part of the health care team responsible for patient care.
20. **Do you think that pharmacogenetics will increase the likelihood of the grouping of patients according to racial or ethnic groups for medical purposes? If so, what might be the ethical and social implications of such an outcome?** No, I don't think it will lead to this, in fact I think just the opposite will happen. There is no doubt certain racial groups carry different frequencies of various mutations in specific genes that influence the function of gene products. However, in our multiracial society, the need to definitively characterize genetic risk will force broader testing to cover all ethnic groups. Drug therapy will be defined based on who is likely to respond based on their genetic make-up, not their race. Some racial groups may end up with more or less benefit from a particular drug, but it will be based strictly on likelihood or response, not race. I believe there is more racial grouping occurring now based on past trends and not actual individual factors. In the future, the genetics will direct therapy more towards the individual, not the race. In a society where intermingling of the races has already taken place for over 200 years or more, this is a step in the right direction as race has been a poor indicator of individual genetic variation.

The response reproduced below was submitted further to a consultation held by the Nuffield Council on Bioethics on its Report: *Pharmacogenetics- ethical issues*, during November 2002 – February 2003. The views expressed are solely those of the respondent(s) and not those of the Council.