

**Additional Evidence for the House of Lords
Genomic Medicine Committee**

Professor Sir Bruce Ponder
(Oral evidence October 24th 2008)

(1) Testing for individual susceptibility using risk profiles based on SNPs (single nucleotide polymorphisms) because of risk

The Committee examined this in their second session on October 22nd at which I was not present. The witnesses at that session were from the commercial sector.

My colleagues and I have been concerned by recent publicity about tests which are, or are about to be, marketed which claim to predict individual risk from SNPs, alone or in combination with other risk factors. The publicity for these tests has attracted the attention of media and the cancer charities, and we have received several requests for our advice.

Our concern is that some of these tests may not be well founded. Very rigorous statistical criteria are needed, together with independent replication, before a claimed association of an SNP with susceptibility can be believed. For example, in the International Breast Cancer Association Studies Consortium, only one of the top ranked 27 SNPs identified as possibly associated with breast cancer susceptibility by member laboratories, was actually replicated when tested in the entire Consortium set of 20,000 breast cancer cases and 20,000 controls. The main reason for this is that the prior probability of any “candidate” SNP actually being involved in susceptibility is very low. As a result, most apparent associations will be chance, and rigorous statistical criteria must be satisfied before they can be accepted.

I do not mean to imply that all such tests that are currently being offered are unreliable. Some almost certainly are; some are based on real associations, but the risks attributed to those associations may not be reliable; other tests will be well founded. In my view and that of my colleagues regulation is needed to ensure that before tests are advertised to the public, their scientific and statistical basis has been adequately scrutinised.

(2) Genomic medicine over the next 20 – 50 years

I would like to amplify a point which I was able to make only briefly in oral evidence. The Committee’s discussion was about the “personalised medicine” that may flow from genetics and genomics, and which may promise greater efficiency and effectiveness in health care.

My point is that we will be moving from the genetics of the past 30 years, which for the most part dealt with rare conditions and small numbers of individuals, to a population based medicine which will involve very large numbers of people, but – for each individual – only small increments of risk.

This brings a problem of numbers. The populations that will need to be involved initially in the research studies, and later in the applications within the NHS of these approaches, will be large. The structures and resources to deal with this will take several years to establish, and must be thought about now. This is a challenge; but because of the structure of the NHS, we could potentially take a world leading role.

I will give one example. Early detection and prevention of cancer are NHS priorities set out in the Cancer Reform Strategy. One approach to prevention is to give generic advice – stop smoking; eat five pieces of fruit a day. But another approach to early detection and prevention, which is the approach that is based on genomics, is to identify high risk groups and target them. For example, high risk groups for early detection and prevention in lung cancer and oesophageal cancer could be identified by some combination of genetic risk factors, medical history (smoking, indigestion), and pathology (abnormal cells in the sputum). However the high risk group is identified, it is likely that there will only be about one cancer per year for every 200 people in that group. So a research study to investigate better means of detection, of prediction of the outcome, and the effectiveness of an intervention, will require a minimum of 4,000 individuals to “yield” 20 cancers a year, which is about the smallest number on which statistically reliable evaluations could be made.

The practicality and expense of this depends on the sorts of observations that are needed. If the high risk lung or oesophageal cancer cohorts must be followed by regular bronchoscopy or oesophagoscopy, then arranging this for 4,000 people on an annual basis as part of a research study will be expensive and (in the current research setting) at the limits of feasibility. And of course if the research suggested that such surveillance was of benefit and that it should be adopted as standard of care in the NHS, the resource implications would be even larger because now the whole population would be eligible. It may be possible in time to arrive at “nested” designs in which complex investigations are reserved for small subgroups at the highest risk, and these subgroups were identified by less expensive initial screening of the starting group. But to get to this point will almost certainly need larger studies in the first place.

The numbers problem could be even more challenging if, as is likely, the pre-cancerous conditions that we aim to detect are heterogeneous. We already have an example of this in early detection of prostate cancer by PSA where some “cancers” are aggressive, but the majority are not life threatening. So we must bear in mind that as we get better at early detection, we run a risk of identifying a whole new population who will be stigmatised as “cancer patients”, but who could more happily have been left undiscovered. Sorting this out is part of the challenge for research; but it may require even larger numbers to provide statistical power.

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The above paragraphs related to susceptibility, risk, and early detection. The other potential application of genomic medicine in cancer also has resource applications. Here, we aim to match treatment to the molecular make-up of each individual cancer. The implications here are that, if this were to be applied on a population scale, district hospitals as well as tertiary centres would have to be set up for collecting frozen tissue samples under defined conditions, and pathology laboratories would have to be available to carry out the required analyses. This type of genomic cancer medicine will be worked out first in tertiary centres; my own view is that one or more regional pilot studies will then be necessary to examine the costs and benefits of this approach in the more general NHS context.

Summary:

- (1) "Personalised medicine" is potentially applicable to the whole population, and will require large scale studies to develop, and to demonstrate its efficacy.
- (2) This will require recruitment of individuals into research cohorts, collection of large number of blood samples and tissue samples under defined conditions, collection of the related clinical information, and long-term surveillance of different levels of complexity to evaluate programmes of early detection and intervention. Studies of this sort on this scale are expensive.
- (3) The current hospital environment is generally not ideal for the development of early detection and intervention. It may be that both the research, and subsequent application, would be better developed from community centres built for this purpose.