Cesagen, the ESRC Centre for Economic and Social Aspects of Genomics, was established in October 2002 as a collaboration between the Universities of Cardiff and Lancaster. Cesagen is a multidisciplinary centre in which staff from social sciences and humanities work closely with natural and medical sciences to address the social, economic and policy aspects of developments in genomics.

For the purposes of this Nuffield consultation, our response focus on the issues around direct-to-consumer (DTC) genetic testing, as dealt with in questions 11-14, although we wish to emphasise that many of the issues raised by these kinds of tests have previously been addressed in the literature (Clarke 1995).

Our first point centres on the basic science (and its interpretation) underpinning the kinds of broad-based risk profile offered by companies such as 23andMe, Navigenics and deCodeMe. These companies claim to be able to assess a person's risk of developing conditions such as heart disease, diabetes and some cancers, often using the results of scientific studies that seek to link small genetic differences (Single Nucleotide Polymorphisms – SNPs) to increased risk for particular conditions. There are a number of problems in the way in which these companies take results out of the academic literature, and, within a short space of time, add them to their DTC information.

One problem is that there is considerable scientific uncertainty over how such small genomic differences actually contribute to increased disease risk. What has become apparent from a number of large Genome Wide Association Studies (GWAS), is that the genetics of many common conditions are characterised by the involvement of a large number of SNPs, each of which contributes a very small increase in overall disease risk (for a review see Maher 2008). Even in the case of characteristics that are known to have a high inherited component, height for example, the underlying genetics looks extremely complicated, with 20 recently identified polymorphisms contributing only 3% to the population variation in height (Goldstein 2009). While companies could accept this and make clear in their literature the assumptions that support the risk profile they offer, any current risk assessments can only be viewed as provisional, since further research may reveal the involvement of more SNPs impacting on the possible risk (Kraft and Hunter 2009). It is the inherently provisional nature of these tests that challenges these companies' assertions that because no over the counter medical test (a pregnancy test, for example) is 100% accurate (producing both false positives and negatives), DTC genetic tests' variability is not problematic. While over the counter pregnancy tests are not 100% accurate, it is extremely unlikely that the scientific knowledge that underpins these tests is going to be significantly altered in such a way that the test becomes a great deal less accurate. Yet such change is inherent in the knowledge base that underpins DTC genetic tests.

For some SNPs, it is likely that the GWAS-detected association is the result of one or more instances of genetic variation elsewhere (but nearby) that are in linkage disequilibrium with the SNP rather than effects of the SNP itself. This means that the interpretation of some GWAS results will probably be substantially refined in the coming 5+ years.

Another issue concerns standardisation between the different companies offering these tests. All of the big three DTC companies claim to only include results in their risk profiles on the basis of stringent academic standards. For example, 23and Me require genetic associations in their database to be from studies using over 1,000 case samples, high statistical significance (p-values less than 0.01) and independent replication (Hsu and Naughton 2008). Yet the same DNA sample sent to different companies has, on at least one occasion, resulted in very different risk profiles. For example, in the case of age related macular degeneration, a condition where the genetics is relatively well understood, a deCODEme test put the risk at 20% below average while 23andMe gave it as 62% higher than average (Fleming 2008). Given that the DTC companies claim authority on the scientific basis of their services, it is not unreasonable to expect them to provide roughly the same risk estimate, when given the same DNA sample.

The second main theme that we wish to raise is the 'additive' model of risk information that the DTC companies work within. As Peter Kraft and David Hunter note; "One argument in favour of using the available genetic predictors is that some information must be better than no information" (Kraft and Hunter 2009: 1701). This position, which allows DTC companies to claim that the genetic risk information they provide can be 'added into' broader decisions about healthcare, is deeply flawed. Take for example, PROCAM (Prospective Cardiovascular Munster study) a well-acknowledged tool for assessing cardiovascular risk that uses a range of tests (including total cholesterol, triglycerides, systolic blood pressure) as well as body mass index and family history. If one's genetic risk profile from a DTC company is added to one's PROCAM score to help make a decision about treatment or behaviour change, is this a problem? If the information from the DTC test supports the conclusions of the PROCAM (for example that one's risk is elevated and behaviour change is suggested) then the DTC test has done little harm. Yet if the DTC test *contradicts* the risk score given by PROCAM, then the dangers of 'adding in' scientifically provisional information becomes clear. If DTC genetic tests challenge and contradict more established and reliable medical tests, then the potential harms could be considerable. It is unlikely that DTC genetic tests will operate where there is no information, but rather where there is already some medical information. The question then becomes, are DTC genetic tests reliable enough to be combined with well-recognised, standardised medical tests? Many biomarker tests such as blood pressure or serum cholesterol are likely to be mediating much of any effects identified through DNA-based information. To the extent that this is the case, the DNA-based tests will simply be irrelevant, adding nothing (and if this is not allowed for, then to include the genetic tests will actually increase errors).

The final point we wish to raise concerns the 'rational user' model that the DTC companies operate with. The firms assume that people who receive a genomic risk profile will act in a rational manner, for example, stopping smoking if they discover they are at increased risk of lung cancer. Often the claim is also made, that further research is required to know for sure how people respond to this kind of information (Anon. 2008; Prainsack et al 2008). We think both these points are flawed. While more research is never a bad idea,

over the past fifteen years there has been considerable psycho-social research into the effect of, not just monogenic disease tests, but also genetic risk susceptibility information. What is clear from this work is that while it is hard to predict how people will respond to this information, "Threat representations that include genetic causes are often seen as ones that are less controllable than threats with behavioural or environmental causes" (Marteau & Weinmann 2006: 1363). It is simply not the case that people act as rational agents in the face of genomic risk information. Given that most of this research took place in the context of genetic counselling sessions, it is not unreasonable to assume that in the context of current DTC testing (where there is little or no counselling offered) people's reactions to and understanding of this information will be even less predictable.

For example, research by members of Cesagen indicates that information about genetic risk is often interpreted in ways that do not reflect the intentions of professionals providing such information. Genetic information (such as risk values and susceptibility) is interpreted by individuals and family members in accordance with lay theories of inheritance, lay understandings of risk values, and the dynamics of family communication (Featherstone, K, 2006; Arribas-Ayllon M, 2008 a,b).

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