scientific dishonesty: European reflections

Dr Riis provides a cool Nordic analysis of scientific dishonesty and concludes that there is a need for a national independent control body that should take initiatives for strong preventative action. I disagree. There is no real evidence that scientific dishonesty is on the increase. Even if it were, it does not matter. Unsound data are already published for a variety of reasons, the chief of which are unsound methodologies and authors' inept expectations of laboratory and other data. Fraudulent data are, almost certainly, trivial by comparison. The published literature is not a source of truth. The only test of its validity is whether or not it is convincing to the discerning individual. This requires what used to be called scholarship. Neither popularity nor fashion are valid tests in this field. The ultimate responsibility is on readers to come to their own decision about the value and meaning of any given report. Unless an individual is prepared to exercise these critical faculties they should get out of the business. Passing the buck to "independent national control bodies" and thereby side stepping personal responsibility, as Dr Cavill mentions, for preventive education. The purpose of the institution will be exonerating falsely accused scientists and to make medical schools more responsible. Such an institution will be suitable for medical schools which have demonstrated a need for a national independent control body that should take initiatives for strong preventative action. However, once one accepts that screening should be carried out, the truth remains that although the trials of NT screening appear convincing, they can be criticised as flawed. They do not allow a true comparison with other biochemical screening programmes because immediate intervention prevents the assessment of natural intrauterine lethality. Second trimester testing was introduced into a relatively virgin field in which there was no established regimen of care. Despite the many potential advantages of NT screening, it has to break into an already occupied medical niche, meaning that extra momentum is required to change what has already become firmly engrained practice.

In an ideal world, we would carry out a trial that ignored significant first trimester results until a comparator test could be carried out in the second trimester. Clearly, however, given what we know about NT this would be completely unethical, and we are permanently reduced to debating the effect of intrauterine lethality in an attempt to identify comparable first and second trimester detection rates. If in the fullness of time early ultrasound is more advantageous than second trimester screening it will take over, and biochemical screening will justifiably disappear. The ethics of screening for cystic fibrosis are already being queried because the CFTR gene has been sequenced and a possible cure is expected. Who knows whether the human genome project will make trisomy 21 a treatable condition? We can only wait and see.

Microsatellite unstable colorectal cancer

The paper by Shiito et al. on the pathogenesis of non-familial colorectal carcinomas with high microsatellite instability (MSI) indicates little clinicopathological difference from microsatellite stable cancers and a similar distribution of mutation in the adenomatous polyposis coli (APC) and TP53 genes, and loss of heterozygosity (LOH) at 17p. The authors claim that their data fit with earlier studies, but several of the pioneering studies do not distinguish clearly between MSI low (MSI-L) and MSI high (MSI-H) cancers. Their findings are very different from multiple studies that adequately distinguish between sporadic MSI-H and MSI-L cancers. By way of explanation, the authors suggest that other studies may include hereditary non-polyposis colorectal carcinoma (HNPCC) cases. It is more likely that their own series includes HNPCC cases, because a lack of a family history does not exclude this diagnosis. Given that somatic mutations of hMLH2 and hMLH1 in their MSI-H cases, these could be examples of HNPCC because methylation of the promoter region of hMLH1 is regarded as the usual pathogenetic basis for non-familial examples of MSI-H colorectal cancer. Again, the failure to identify a germline mutation in these six cases does not exclude HNPCC: polyomerase chain reaction single strand conformation polymorphism (PCR-SSCP) is not a very sensitive technique for detecting germ-line mutations in HNPCC.

Down's syndrome screening: a controversial test, with more controversy to come!

Recently, Professor Reynolds eloquently highlighted some of the current controversies surrounding the provision of Down's syndrome screening, primarily from a biotechnical standpoint, and most of those involved in this field would certainly agree with the last part of the title. Nevertheless, there are several issues raised in the article, which require some further clarification to achieve a balanced discussion. First, the issue of intrauterine lethality and detection of affected fetuses that may spontaneously abort is one that potentially impacts on prenatally diagnosing and screening, not just ultrasound screening for nuchal translucency thickness (NT), as implied. Second, this issue only becomes important, in terms of evaluating detection rates, if those fetuses that are destined to abort spontaneously are preferentially detected by the screening test. In a study on this issue using data from individual pregnancies, rather than epidemiological models, there is indeed a significant use in intrauterine lethality, but only when the NT thickness is considerably raised (which accounts for only a small proportion of fetuses with trisomy 21), resulting in only a small impact on the issue of screening efficiency, with an estimated reduction in live birth rate of about 70% for an 80% detection rate at 12 weeks. Third, and by far most importantly, an ultrasound scan at 11-14 weeks has other benefits for antenatal care, allowing the accurate assessment of gestational age, the detection of multiple pregnancy, the detection of most major structural defects, the definition of markers for major cardiac defects, all in addition to the measurement of NT thickness for the assessment of risk for trisomy 21, with or without the addition of first trimester biochemical assays to improve detection rates. At the time of the scan, the findings and risks can be discussed with the patient and questions answered without delay to allow the parents to decide about further invasive testing. From a political point of view, a national screening policy makes sense, but only if it makes the best use of resources (which might be used not just for Down’s syndrome screening, but to improve all aspects of antenatal antenatal care), and is welcomed by the “clients”, most of whom choose to have a first trimester ultrasound examination if given the option, with early diagnostic testing if appropriate. I declare the following financial and family interests in Down’s syndrome screening: (1) patents, none; (2) grants, none; (3) software, none; (4) consultancies, none; (5) medicolegal, none.

The author replies

A doubtul or unreliable methodology or the unrealistic use of laboratory data certainly can invalidate results of biomedical research. But they are usually unintended parts of research publications and can be disclosed by critical readers if such shortcomings should happen to pass the referee and editorial gatekeepers. On the contrary the deliberate creation or change of research data via fraudulent behaviour is not always possible to detect, as a large number of serious international cases have demonstrated.

On this background, the Nordic attitude (as expressed in my leader) is based on the fact that scientific fraud is an existing phenomenon, and that for this reason an independent national body is recommendable. Such an institution will be suitable for exonerating falsely accused scientists and to collect national and international real cases for preventive education. The purpose of the latter is precisely to strengthen scientists’ personal responsibility, as Dr Cavill mentions, and certainly not to side step it.

The author replies

Dr Sebire is absolutely correct about the apparent benefits of the early antenatal ultrasound assessment, not just the ability to measure nuchal translucency (NT), thereby indicating that it is necessary to carry out earlier diagnostic tests, to allow earlier “therapeutic” intervention. Here of course it is possible to raise the level of controversy with the provision of Down’s syndrome screening, primarily from a biotechnical standpoint, and most of those involved in this field would certainly agree with the last part of the title. Nevertheless, there are several issues raised in the article, which require some further clarification to achieve a balanced discussion. First, the issue of intrauterine lethality and detection of affected fetuses that may spontaneously abort is one that potentially impacts on prenatally diagnosing and screening, not just ultrasound screening for nuchal translucency thickness (NT), as implied. Second, this issue only becomes important, in terms of evaluating detection rates, if those fetuses that are destined to abort spontaneously are preferentially detected by the screening test. In a study on this issue using data from individual pregnancies, rather than epidemiological models, there is indeed a significant use in intrauterine lethality, but only when the NT thickness is considerably raised (which accounts for only a small proportion of fetuses with trisomy 21), resulting in only a small impact on the issue of screening efficiency, with an estimated reduction in live birth rate of about 70% for an 80% detection rate at 12 weeks. Third, and by far most importantly, an ultrasound scan at 11-14 weeks has other benefits for antenatal care, allowing the accurate assessment of gestational age, the detection of multiple pregnancy, the detection of most major structural defects, the definition of markers for major cardiac defects, all in addition to the measurement of NT thickness for the assessment of risk for trisomy 21, with or without the addition of first trimester biochemical assays to improve detection rates. At the time of the scan, the findings and risks can be discussed with the patient and questions answered without delay to allow the parents to decide about further invasive testing. From a political point of view, a national screening policy makes sense, but only if it makes the best use of resources (which might be used not just for Down’s syndrome screening, but to improve all aspects of antenatal care), and is welcomed by the “clients”, most of whom choose to have a first trimester ultrasound examination if given the option, with early diagnostic testing if appropriate.

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It is interesting that of the six MSI-H cases with mutation of TP53, three show somatic mutation of hMSH2 or hMLH1. Of four MSI-H cases with LOH at 17p, three show somatic mutation of hMSH2 or hMLH1. Three of the 11 MSI-H cancers with mutation of hMSH2 or hMLH1. The finding of APC mutation is expected in HNPCC cancers because these are associated with traditional adenomas. 3 The relatively low mean age at onset of their MSI-H cases (67.5 years) also suggests the inclusion of some HNPCC cases because sporadic MSI-H cancer is age related. In HNPCC cancers identified in the course of population based surveys, distinguishing clinicopathological features—notably site and mucinous differentiation—are not as obvious as they are in large kindreds ascertained through cancer family clinics. 4 This would explain an earlier report by the same group that fails to associate mucinous adenoma with mutation of TP53, three show somatic mutation of hMSH2 or hMLH1. 

Three of the 11 MSI-H cancers with somatic mutation of hMSH2 or hMLH1. 5We believe that these data support the notion that most of our cases were non-HNPCC cancers. We think that the two pathways (one via serrated polyp and one via flat adenoma) are very interesting, as Professor Jass mentioned. We hope that we will be able to verify this pathway in the near future and we believe that the β catenin–Tcf signalling pathway may be a key factor in the carcinogenesis of MSI-H cancers. 


The authors reply

We thank Professor Jass for having read our article 1 carefully and for his comments. When investigating non-familial colorectal carcinoma cases, the criteria for defining these are very important. We guess that the non-familial colorectal carcinomas excluded familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal carcinoma (HNPPC) in most reports from Western countries. Viewing the criteria of non-familial colorectal carcinoma, our criteria were supposed to be stringent. In fact, a lack of a family history does not exclude HNPCC as Professor Jass mentioned. However, stringent criteria for a family history should be applied when evaluating the non-familial colorectal carcinoma cases. In addition, the characteristics of our microsatellite instability (MSI-H) cases were different from those of HNPCC, as reported previously. 

We detected normal bands in polymerase chain reaction single strand conformation polymorphism (PCR-SSCP) analysis of the matched normal tissue DNA from all six cases of hMSH2 or hMLH1 mutation. We agree that PCR-SSCP is not a very sensitive technique for detecting germline mutation in HNPCC, as mentioned by Professor Jass, because the alternative splicing cases could not be detected by this method. However, we do not think that we missed the germline mutations in these six cases because of the existence of normal bands in normal tissues. We believe that all these six mutations were somatic. 

Jass mentioned that the finding of adenomatous polyposis coli (APC) gene mutation is expected in HNPCC; however, we think that mutations in the gene encoding β catenin mainly contribute to HNPCC colorectal carcinogenesis, as reported previously 2 and that the frequency of APC mutation is lower (~20%) in these cancers. The frequency of APC mutation in our MSI-H non-familial colorectal cancers was higher than in HNPCC cancers. Interestingly the β catenin–Tcf signalling pathway, through either β catenin or APC mutation, frequently contributes to carcinogenesis of MSI-H non-familial cancers, similarly to HNPCC cancers. 3 We think that most MSI-H cancers (both HNPCC and non-familial colorectal cancers) are associated with traditional adenomas. In HNPCC cancers identified in the course of population based surveys, mucinous-type tumours were three times more likely to occur in HNPCC kindreds than in the non-HNPCC familial group, and no HNPCC cases were detected in the over 65 years age group. 4 We believe that these data would again be worth investigating.