NICE Health Technology Appraisal

Liquid based cytology for cervical screening

Submission from British Society for Clinical Cytology (BSCC)

EXECUTIVE SUMMARY (Page 1 - 3)

1. Background

1.1 BSCC and its role in LBC technology

The BSCC is a registered charity whose members are medical practitioners and senior biomedical scientists with a special interest in the practice of cytopathology, one aspect of which is the core speciality of the cervical screening test. As the main scientific society involved in this field of medicine, the BSCC has a duty to examine the evidence for the superiority of LBC over conventional smears, to make sure it provides genuine benefits to the public. Potential risks of substituting a new technology for a well-tried (even though widely mistrusted) conventional method must be identified and faced.

1.2 BSCC submission and data collection

The Chairman of Council commissioned a member of Council (Dr Sanjiv Manek) to consult widely among the membership of the Society, and provide a “corporate” view of the new technology. The BSCC submission has drawn extensively on that review. Evidence about LBC that has been published since the first NICE report is also submitted, as well as an overview of the reasons for the pressure to introduce a new technology. The submission has been written by the Chairman of the Society, in collaboration with the President, Vice Chairman, Dr Manek and two past Presidents, and was circulated to all members of Council for their comments before submission. This submission takes no account of the results of the pilot site projects, which only one of us (the President of the Society) has seen.

1.3 Current BSCC impressions of LBC

There is mostly a positive attitude towards LBC, which is perceived as the only major change to occur in cervical cytology since its formalisation several years ago, which brings hope to a service under attack from the media, public and under threat from various crises.

2. Epidemiological and Health Care Issues

2.1 Effectiveness of conventional screening

Evidence is presented to indicate that conventional screening is far more effective than generally recognised, and as long as LBC is genuinely as sensitive as conventional smears an *increase* in sensitivity is not so important.
3. Clinical effectiveness

3.1 Inadequate test rates Page 7
It would seem common sense to welcome a new technology that so clearly improves the adequacy of samples. However, there may be a potential problem with the reduction in inadequate tests, which is discussed in detail in this section of the main text.

3.2 Sensitivity and specificity Page 8
Ever since LBC was accepted by the FDA as an alternative to conventional smears, there has been concern about the reliability of many of the published studies claiming superior sensitivity for LBC. Reference is made to recent meta-analyses and trials.

3.3 Choice of machine Page 9
There are no published studies comparing the two systems directly in the same study population. It would be important to ensure that there was no monopoly.

3.4 Training Page 10
Training of medical, technical staff, nurses and other smear-takers for LBC is critically important if the clinical effectiveness of the technology is to be realised. It is acknowledged by most that this will be a major challenge in terms of “roll-out” whilst maintaining the current service level using conventional methods.

It is beyond the remit or expertise of the BSCC to comment on the cost-effectiveness, except to say that all aspects of cost must be considered.

5. Wider NHS Implications

5.1 Research and development Page 12
One of the main advantages of LBC is the availability of material for research, development of automation and ancillary tests, but it is not essential for HPV testing. Research into the effectiveness of LBC itself would be precluded if the technology were introduced nationally, except for comparisons between different machines.

5.2 NHS Cervical Screening Programme Page 13
The potential advantages of LBC must be looked at for the NHSCSP as a whole, and one advantage may be that the technology is so well accepted by smear-takers and patients. It is important that the benefits of LBC are not exaggerated, particularly during a period of training and implementation that would take several years. Since improved sensitivity has not conclusively been established, the NHSCSP as a whole should recognise the risks of possible reduced sensitivity.
6. Summary

There is no doubt that most of those currently engaged in cytology are willing to take on this new technology. As a scientific society, the BSCC must express concern about introducing a new technology without the possibility of a clinical trial or longitudinal study for a complete screening round. Many of us would be more comfortable about taking on LBC if we were confident that NICE, the NHSCSP and government had knowingly accepted those risks.

7. References
1. Background

1.1 BSCC and its role in LBC technology

The BSCC is a registered charity whose members are medical practitioners and senior biomedical scientists with a special interest in the practice of cytopathology, one aspect of which is the core speciality of the cervical screening test. The aims of the Society are:-

i. to advance the science and art of clinical cytology by encouraging higher standards in clinical cytology for the benefit of the public,

ii. to encourage research and the publication of useful results thereof.

Most medical members of the Society are also engaged in histopathology or diagnostic cytopathology, and biomedical scientists have many professional duties apart from cervical cytology. Cervical screening occupies a major part of their workload as well as being an academic special interest of many of them. However, even among this highly committed group, the intense pressure of the cervical screening workload since the introduction of the NHS Cervical Screening Programme (NHSCSP) in 1988, with its rigorous quality control requirements, has dominated the daily professional work of many pathologists and biomedical scientists to an extent that some regard as undesirable. Recruitment of biomedical scientists and cytology screeners has long been a problem, partly because of levels of remuneration of non-medical NHS staff in general, but also because of poor public perception of the effectiveness of cervical screening and intense media interest in any incident regarded as a “screening failure”. Similarly, at a time of general shortages of pathologists at medical staff at consultant and trainee levels, recruitment and retention of staff in such a high-profile stressful environment has been difficult.

It is against this background that considerable enthusiasm has built up for the introduction of a new technology that is widely believed to have the potential for being more accurate and less time-consuming. At the time of the NICE guidance in June 2000, the evidence suggested that liquid-based cytology (LBC) might improve sensitivity of cervical screening by reducing false negatives as well as reducing the number of unsatisfactory specimens (1). It seemed likely that the slides would be easier to screen, as blood and exudate would be removed, that there would be the added advantage of residual material being available for special techniques such as HPV testing and that the development of automated screening would be facilitated.
Following the recommendation of NICE, three laboratories in England and two in Wales have introduced this technology as pilot sites. Their reports are eagerly awaited, and it is no secret within the profession that the technology has been well accepted and is generally liked by technical and medical staff, as well as by nurses and doctors taking the cell samples. A decision has already been made in Scotland for all laboratories to convert to LBC, having piloted its use in five centres for several months and reported on its benefits (2).

As the main scientific society involved in this field of medicine, the BSCC has a duty to examine the evidence for the superiority of LBC over conventional smears, to make sure it provides genuine benefits to the public. This must be established without reasonable doubt, especially when such a major investment in professional time and public money would be involved in its implementation. New technology tends to follow a pattern of early enthusiasm followed by later disillusion, before its natural place is found.

Potential risks of substituting a new technology for a well tried (even though widely mistrusted) conventional method must be identified and faced, particularly when there has not been a randomised controlled trial in the UK to compare the effectiveness of the old and new methods.

1.2 BSCC submission and data collection
In view of the likelihood of NICE inviting a professional opinion from an organisation such as the BSCC, the Chairman of Council commissioned a member of Council (Dr Sanjiv Manek) to consult widely among the membership of the Society, and provide a “corporate” view of the new technology. The BSCC submission has drawn extensively on that review, which Dr Manek is preparing for publication in the BSCC journal Cytopathology (it is not yet available). The BSCC submission also draws on a meeting held on 5th November 2002, which forms the basis of the Royal College of Pathologists submission to NICE, when presentations for and against LBC were openly discussed.

Evidence about LBC that has been published since the first NICE report is also submitted, as well as an overview of the reasons for the pressure to introduce a new technology.

The submission has been written by the Chairman of the Society, in collaboration with the President, Vice Chairman, Dr Manek and two past Presidents, and was circulated to all members of Council before submission. This submission takes no account of the results of the pilot site projects, which are confidential, and only known to one of us (the President of the Society).

1.3 Current BSCC impressions of LBC
To quote from the report of Dr Manek “there is mostly a positive attitude towards LBC and its implementation throughout the UK. There is a significant momentum for LBC as more and more is published, researched and talked about it. There is almost an excited anticipation for it….LBC is perceived as the only major change to occur in cervical cytology since its formalisation several years ago, which brings hope to a service under attack from the media,
public and under threat from various crises.” The author of this submission visited one of the sites, and was impressed by their enthusiasm. It was hard not to be affected, but at the same time concerned, by the newspaper cuttings on the walls of the laboratory implying that “blunders” and “screening failures” would be a thing of the past. It has to be recognised and explained to the public and media, that for all its advantages LBC relies on a subjective assessment of cell changes, and that false negatives will never be abolished in any such screening process. Nevertheless, except for the introduction of a highly successful centrally organised NHS Cervical Screening Programme (NHSCSP) in 1988, replacing a system that was justly discredited (3), the introduction of LBC would be "the most significant change to occur in the history of cervical screening in the UK."

Medical and non-medical cytologists involved in providing the service are rightly anxious not to miss this opportunity of introducing a less time-consuming technology, which would concurrently reduce the number of tests (if inadequate tests were reduced). The current manpower crisis is well known, and the average age of cytology screeners shows that it is likely to get considerably worse. As the technology is said to be easier and more pleasant to use, and potentially occupies less staff time with less chance of error, it is undoubtedly attractive both to government and management.

2. Epidemiological and Health Care Issues

2.1 Effectiveness of conventional screening
Before there is nationwide implementation of LBC, we must ask why we need this new technology. The current conventional methodology has been very successful in reducing incidence of mortality from cervical cancer, almost certainly reversing a significant upward trend in risk of disease (4,5). Although primarily intended to control squamous cell carcinoma, there is also evidence that conventional screening has reversed an upward trend in the relatively less common adenocarcinoma, which is far more difficult to detect at a pre-invasive stage (5), and is a recognised cause of false negative cytology (6). Over the years, particularly since the improvements in training, quality control and continuing professional education since the introduction of the NHSCSP, the art and science of reporting conventional cervical smears has been modified and improved and there is now far better recognition of pitfalls and patterns (7,8). Consistency in reporting has improved through monitoring high and low-grade cytological abnormalities (9), and it is likely that the vast majority of high-grade pre-invasive lesions are detected before cancer has a chance to develop. Kornek returns (KC61 form C) collect national data for cytology/histology correlation for April – June each year (10). In those 3 months in 2001/02, 6,975 cases of histologically proven cervical intraepithelial neoplasia, grade 3 (CIN3) and adenocarcinoma in-situ (AIS), 4946 cases of CIN2 and 308 invasive cancers were detected through conventional screening. Data from two demographically different populations (Southampton and South London) indicate that about 40% of cancers are cases with early invasion detected through screening (11), from which an approximation of the number of symptomatic cancers can be calculated (Figure 1). The calculated figure matches reasonably well with the latest known annual figure for invasive cervical cancer (2,784 in 1997). The true sensitivity of screening may be appreciated by looking at Figure 1. Important information about screening history is not available nationally,
because screening centres have been reluctant to publish their figures after the publicity arising from a cervical cancer audit in Leicester that was never formally published. However, data from the Leicester audit, supported by one from Guy’s, King’s and St Thomas’, indicate that around 40% of cancers develop in women with no cervical screening record, representing 7.9% of the eligible female population (10).

In summary, conventional screening is far more effective than generally recognised, and as long as LBC is genuinely as sensitive as conventional smears an increase in sensitivity is not so important.

So why do we need to consider a change? Essentially the reasons for introducing a new technology would be (i) to reduce inadequate rates, (ii) to improve productivity, (iii) to facilitate carrying out ancillary tests (particularly HPV testing) and (iv) to facilitate automated or semi-automated screening when it becomes available.

Sadly, another reason to introduce a new technology could be that the effectiveness of screening has not been put across to media, medical profession or women at risk of cancer, and screening coverage is declining. A new test perceived to be better, with new technology might encourage more women to be screened. As long as sensitivity was not compromised by the new technique, it might save more lives simply through being more acceptable.

3. Clinical effectiveness

This will be considered with respect to (i) inadequate test rates, (ii) sensitivity and specificity, (iii) choice of machine and (iv) training.

3.1 Inadequate tests

Although the pilot site results are not available for this submission, reporting rates have been published for all laboratories, and it is evident that pilot site laboratories showed a dramatic fall in rates of inadequate smears since using LBC (10), similar to results in the Scottish pilot sites (2). In terms of clinical effectiveness, introduction of LBC could be justified by a reduction of inadequate rates alone, which are reported on average in 7% of tests in the UK. Women dislike being asked to return for a repeat smear, and the vast majority of those women will have no significant abnormality on their cervix, because of the low prevalence of high-grade disease (reported on 1-2% of tests). Furthermore, there are wide variations in reporting rates in laboratories and it has been difficult to define criteria for adequacy of conventional smears (9). It would seem common sense to welcome a new technology that so clearly improved the adequacy of samples.

There is, however, a potential problem. ThinPreps (SurePath preparations are not quite the same) are made by concentrating a sample of a cell suspension on a glass slide, to a maximum of about 40,000 cells. Without counting the cells before or after making the ThinPrep, which might technically be possible, there is no way of knowing whether those cells represent all of a few cells in a specimen, perhaps otherwise composed mainly of exudate, or is a representative sample of a good, cellular specimen (15). The cellularity
of the original sample depends largely on the competence of the smear-taker, and its adequacy cannot be assessed by examining a ThinPrep slide.

Examination of the data in some published split-sample studies shows low rates of cytological abnormalities in tests with inadequate conventional smears and apparently adequate ThinPreps, supporting the hypothesis that those ThinPrep slides may not be representative, and may include some false negatives (15,16,17,18). With a screening interval as long as five years, a false negative test might allow 10 years to elapse between adequate tests, which would be longer than the period of protection against invasive cancer that a negative test affords (19).

If a conventional smear appears inadequate, the woman is offered a repeat as soon as convenient, and colposcopy is recommended if three tests are inadequate (9). Longitudinal studies have shown high-grade rates on follow-up are equal to, or slightly in excess of, those expected in a normal population, suggesting that women with inadequate conventional smears are essentially un-screened (12,13). Furthermore, data from KC61 form C (2001/02) shows that above average rates of high-grade CIN (4% compared with 1-2%) are found in women referred for colposcopy with persistently inadequate smears (14).

Some BSCC members believe that further work is needed on criteria for adequacy (which could include cell counting) before implementing LBC without a clinical trial or even a longitudinal study through a full round of screening. Others believe this problem has been exaggerated, and that it would be resolved if expected numbers of high-grade pre-invasive lesions and cancers were detected in the pilot site studies. Many of those approached for opinions agreed that only a randomised, controlled prospective trial could answer the question on the significance to the screening programme of the reduction in inadequate tests.

3.2. Sensitivity and specificity
There is no way accurately to measure sensitivity without knowing the prevalence of high-grade CIN in the population screened. Reporting rates for high-grade dyskaryosis and detection rates of histologically proven disease may be used as surrogates. Specificity is also difficult to measure, but overcalling may be assessed from positive predictive values, and indirectly by borderline smear rates.

Ever since LBC was accepted by the FDA as an alternative to conventional smears there has been concern about the reliability of many of the published studies claiming superior sensitivity for LBC (20-24). This has been one the reasons for the technology not being recommended for routine screening in New Zealand, Australia and the Netherlands (21,24,25). Similar decisions are likely (personal communication) in Germany (26,) and France, where a controlled trial was not favourable to LBC (27). Randomised controlled trials, based on histological outcome, have unfortunately been rare, and it should be noted that the first such study was not favourable to LBC (28).
Nevertheless, members of the BSCC were impressed by the consistency of published studies, so many of which show improved detection rates for LBC compared with conventional smears, citing a number of papers (29-33). They did not accept that improved sensitivity could be explained by shifting diagnostic goalposts (15,23). One of those authors had published his concern about potential bias in the Scottish pilot studies (34), suggesting that the reported increase in sensitivity in might be dependent on the new sampling device and improved training of smear-takers prior to the introduction of the technique. Sensitivity improved more strikingly in laboratories with low rates for high-grade abnormalities prior to the study, suggesting that recent intense training might have affected the results (2). Also, differences in case-mix in the conventional and LBC groups had not been taken into account, since the method used for tests taken in colposcopy clinics was not stated. Manek found that BSCC members in general remained impressed by the improved performance with the new technology. Theoretically, it would be easy to argue the reasons why there would be improved sensitivity: the better visibility of cells, lack of artefacts and the even distribution of abnormal cells within the “spot” of a LBC preparation. Furthermore, women would benefit from improved detection of high-grade abnormalities, whatever the reason, such as a different collection device or improved training in smear-taking.

Although the lack of exudate and blood may be seen as an advantage on LBC, their presence on conventional smears acts as a signal for identification of high-grade dyskaryosis and cancer (23). Those sceptical of LBC cite that apparent advantage as a potential pitfall, as so few abnormal cells may be present on a LBC slide making decisions about their nature more difficult (15,23). This may be particularly important in known areas of difficulty such as glandular neoplasia, its look-alikes and their potential for false negative and false positive cytology (8). These matters are dealt with as training issues, and are only mentioned in this section on sensitivity because small numbers of abnormal cells and glandular abnormalities are a known causes of false negative cytology (6,35).

Except for the implications of reducing inadequate test results already discussed, there is little, if any evidence to suggest a difference in specificity between LBC and conventional cytology, since both depend on the same subjective assessment of morphological cell changes. There is no convincing evidence that LBC increases or decreases the number of borderline results.

### 3.3. Choice of machine

The FDA recognises SurePath as different from ThinPrep. Its approval for ThinPrep states that the system is better than conventional screening whereas FDA approval for SurePath states that it is equivalent to conventional methods. The results of the English pilots may be crucially important in terms of whether neither, either or both systems could reasonably be implemented in the setting of the NHSCSP currently, or whether further trials are needed. To the best of our knowledge only one laboratory in the UK has piloted SurePath (there were none in Scotland), and all the rest were ThinPrep. Assuming that a choice were made in favour of LBC, decisions would depend on (i) performance in terms of pick up rate (ii) ease of use, (iii) degree of automation, (iv) space required, (v) ease of implementation and (vi) costs.
There are some potentially significant differences in adequacy of samples using ThinPrep and Surepath, partly because of the difference in the way that the samples are processed. Surepath regards a specimen as inadequate if the broom is not left in the fluid, because they have evidence that cells may be retained on the device, whereas ThinPrep depends on the smear-taker washing the cellular material into the fluid. Members of the BSCC do not find it possible at this stage to comment on which is the better system, although some members are concerned that the morphology is different with the two techniques, because of the use of a different fixative.

There are no published studies comparing the two systems directly in the same study population. It would be important to ensure that there was no monopoly of a single system and that training schools between them had the ability and flexibility to train in both systems.

3.4 Training
Training of medical and technical staff for LBC is critically important if the clinical effectiveness of the technology is to be realised. It is acknowledged by most that this will be a major challenge in terms of “roll-out” whilst maintaining the current service level using conventional methods. There are various issues to be addressed and these include:

1. It is likely that nationwide training might take up to four years. If the CSP were not to be suspended serially for a few months in each centre, while laboratories and smear-takers trained and converted to LBC, then backlogs would inevitably rise whilst the staff was engaged in training.

2. There would be difficulty in keeping up with conventional cytology, and other professional commitments, while learning the new technology at a time of severe manpower shortages. There is a genuine widely held concern that some “older” cytopathologists might chose not to retrain, potentially making the manpower crisis worse and losing valuable expertise, and also that even more general histopathologists might decline to carry out cervical cytology.

3. Training centres might have to provide LBC training in both systems, although this might not be necessary in all of them, which would require sharing of slide material between pilot sites and training schools.

4. Initial training courses represent only part of the learning process, which would require time and experience to build up competence and confidence. There is concern that experience in pitfalls and potential false positives and false negatives is naturally limited when a full round of screening has not yet been experienced in any of the centres.

5. Training of smear takers is also a major consideration, and would involve the use of both techniques, and continuing education to ensure maintenance of good practices.
6. Examinations for pathologists, cytology screeners, biomedical scientists and advanced practitioners would require collection of case material in both types of LBC.

It is easy to envisage the need for new books, illustrations and courses to discuss the new pitfalls and diagnostic criteria as these are gradually learnt with the two systems, in much the same way as has taken place with conventional cytology over the last 2-3 decades. Many do believe, however, that there are more similarities than differences between conventional and LBC methods, and that the “pitfalls” will not be significantly different once those associated with artefacts (blood, inflammatory exudate, etc) are excluded. However, morphology of conventional cytology often depends on signals provided by exudates and blood, and the differences should not be underestimated. It also depends on subtle variation in chromatin pattern between reactive and dyskaryotic cells (7), which is certainly different with the methanol fixation used with ThinPrep. Screening will need to be a more rigorous process, because it is well recognised that conventional smear patterns are destroyed and abnormal cells may be fewer in number. This is one of the main areas of emphasis in training, and may also be a factor in productivity, and the time taken to primary screen and re-screen (for internal quality control) a slide.

4. Cost-effectiveness

It is beyond the remit or expertise of the BSCC to comment on the cost-effectiveness, except to say that all aspects of cost must be considered. It may be an advantage, and even a necessity to centralise slide preparation of LBC, but costs of transporting slides to remote laboratories for screening should be taken into account. Cytology screeners are a scarce resource, often living locally, and may not be prepared to travel to centralised laboratories.

Costs of capital equipment and maintenance as well as storage, transportation and disposal of samples will no doubt be considered by NICE. Cost-effectiveness should take account of inevitable increases in cost after initial prices have been agreed for large contracts, and consideration should be given to whether local or central funds would be made available for maintenance of the technology. It should be recognised that cost-effectiveness was a major concern of national screening programmes elsewhere deciding against implementation of LBC (21,24,25). It should also be recognised that improvements in technology might not seem so important in countries that have other priorities, such as improving quality control and screening coverage.

5. Wider NHS implications

These will be considered under the headings of (i) research and development and (ii) the NHS Cervical Screening Programme as a whole.

5.1. Research and Development

One of the main advantages of LBC is the availability of additional cellular material for research, development and ancillary tests. This was almost unanimously cited as a major
advantage by those approached by Manek, and was the main reason that the author of this submission was enthusiastic to train in LBC technology, purchase a machine with research funds and engage in that research.

It is well known that one of the main reasons for the development of LBC was to facilitate the development of automated or semi-automated cytology. LBC may also be a platform for in-situ hybridisation. However, it is not necessary for ancillary tests such as HPV or chlamydia testing. Experience has shown that LBC adds an additional step, which is to some extent a disadvantage (15). Many studies on HPV testing and even automation have been carried out during the last 30 years using material retained after conventional smears have been prepared. Indeed, the TOMBOLA study has been conducted using a swab taken during the same procedure, after preparing a conventional smear. The NHSCSP is currently funding at least one study of HPV testing alongside conventional cytology.

LBC provides a convenient method of providing additional material for ancillary testing on material taken at one visit, which is clearly an advantage for “reflex” HPV testing of borderline results. If LBC were not used for the screening test, it would still possible to use a plastic collection device to prepare a conventional smear, and to routinely retain residual material in an appropriate fluid medium. It is imperative for ancillary tests and research projects to be planned for in advance, which is mandatory anyway in order to obtain informed consent for such procedures.

Research into the effectiveness of LBC itself would be precluded if the technology were introduced nationally, except for comparisons between different machines. Experience with conventional cytology would rapidly be lost, and some members of the Royal College of Pathologists and BSCC believe that it would be wise for at least some centres to maintain that expertise.

5.2 NHS Cervical Screening Programme
The potential advantages of LBC must be looked at for the NHSCSP as a whole, and one of these may well that the technology is so well accepted by smear-takers and patients. However, it has to be said that much of that acceptance is based on a generally held assumption that LBC is “better” than conventional screening,

It is important that the benefits of LBC are not exaggerated, particularly during what would inevitably be a prolonged period of training and implementation. The NHSCSP should give careful consideration to reversing the inappropriate “negative image” of conventional screening, because it will be necessary to explain that women’s lives are not being put at risk in laboratories that have not yet introduced LBC. That would be even more important if NICE did not recommend immediate implementation, and the experience of commercial pressure when this happened in New Zealand should be born in mind (36)

Since improved sensitivity has not conclusively been established, The NHSCSP as a whole should recognise the risks of possible reduced sensitivity (i.e. increased numbers of false negatives), and the length of time that it would take for such problems to emerge.
It is essential that costs of the new technology should not be offset by other cost-saving initiatives such as extending the screening interval. There is strong evidence that risk of invasive cancer is related to the time since the most recent test, essentially because no individual screening test is 100% sensitive (19,37). It should be remembered that there is no country in the world considering the use of LBC as a sole method of screening with an interval as long as five years.

As stated in the report of Manek, “the most ideal situation would be to conduct trials in the UK, devoted particularly to the issues of adequacy, sensitivity, specificity, cost-effectiveness and productivity using LBC.”

6. Summary

There is no doubt that many, but by no means all of the pathologists, biomedical scientists and cytology screeners currently engaged in cytology are willing, prepared and even eager to take on this new technology. As a scientific society, the BSCC must express concern about introducing a new technology without even the possibility of a clinical trial or longitudinal study for a complete screening round. Many of us would be more comfortable about taking on the new technology if we were confident that NICE, the NHSCSP and government had knowingly accepted those risks. We are grateful to have had this opportunity to express our admittedly diverse opinions on this subject.
References


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