INTRODUCTION
Since the mid-1980s there has been an explosion in our understanding of the basic molecular genetic defects that underlie the pathogenesis of various diseases, including cancers and infections. Earlier articles in this series dealt with various technologies for nucleic acid analysis and the use of nucleic acids in diagnosis and genetic testing.1,2 This article deals with salient representative examples where knowledge, gleaned from identification of the molecular fingerprints of individual disease, is being used to develop increasingly accurate assays for monitoring the efficacy of treatment and determining the prognosis in these diseases.

MOLECULAR ANALYSIS OF CHROMOSOMAL ABERRATIONS IN LEUKAEMIAS

Acute lymphoblastic leukaemia (ALL)
The application of molecular diagnostic tools to the study of residual leukaemia has significantly advanced our understanding of the pathophysiology of leukaemia during and after treatment. Polymerase chain reaction (PCR) assays for specific translocations or for clonal immunoglobulin G (IgG) heavy chain or T cell receptor (TCR) gene rearrangements have facilitated the detection of leukaemic cells at previously unattainable levels. Whereas the detection of transcripts resulting from specific chromosomal translocations is limited to about one-third of cases, PCR assays for rearrangement of the IgG heavy chain or the TCR genes provide clonal markers in more than 90% of cases of ALL.5 A number of cases have been analysed by PCR for evidence of occult disease (minimal residual disease, disseminated tumour cells) using IgG heavy chain and TCR gene rearrangements as clonal markers.6 The conclusions from this study have been that a negative PCR assay at the end of therapy appears to predict long term disease-free survival, and persistence of a high level of disease by PCR at the end of induction therapy correlates with a poor overall prognosis.

Chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL)
In a majority of patients with CML and in nearly one-third of those with ALL, there is a characteristic reciprocal translocation between chromosomes 9 and 22 [t(9;22)], resulting in the so-called Philadelphia chromosome.7 The genes involved in this translocation are BCR and ABL. As a consequence of the BCR–ABL recombination, BCR sequences activate the ABL F-actin binding domain and deregulate the ABL tyrosine kinase activity via the ABL–SH2 domain. Two different BCR–ABL transcripts can be formed depending on their break point localizations and they encode 210 kDa and 190 kDa BCR–ABL proteins.8 This translocation can be detected by cytogenetic methods, Southern blot or reverse transcriptase-PCR (RT-PCR).

Cells derived from both the bone marrow and peripheral blood can be collected and assayed for residual BCR–ABL transcripts. The products of the PCR reaction can be analysed by hybridization with probes specific for the three known BCR–ABL fusion sequences.9 However, the detection of occult disease does not yield any information on the malignant potential of the BCR–ABL rearranged cells.10 It raises the possibility that a small number of non-clonogenic or suppressed leukaemic cells persist after successful therapy. An RT-PCR assay for this fusion transcript can also be used for disease monitoring after treatment, e.g. bone marrow transplantation. Adaptation for quantitative evaluation of cells carrying the BCR–ABL fusion transcript is, therefore, more suitable for the long term follow up of the activity of the residual BCR–ABL positive clone. Competitive PCR and real-time PCR (Roche Molecular Diagnostics, USA) assays are available for this detection, albeit as clinical research tools as of now.

Acute myeloblastic leukaemia (AML)
Monitoring the treatment efficacy is an important aspect of management of acute promyelocytic leukaemia (APL), because high complete response rates and relatively good overall survival rates are possible with appropriate therapy. Therefore, distinguishing between patients who will relapse and those who will remain in long term remission is desirable. RT–PCR for [t(15–17)] translocation involving promyelocytic leukaemia/retinoic acid receptor (PML/RARα) genes is one such useful assay. It could serve as a useful tool for determining the need for supplementary treatment during clinical remission.

CLONAL ANALYSIS OF LYMPHOMAS
A very important practical consequence of immunoglobulin gene rearrangement is the ability to utilize powerful molecular biological tools to study the clonal nature of a given lymphoproliferation. During the tumourigenic process, clonal expansion of the tumour progenitor cell takes place after the immunoglobulin gene rearrangement has occurred. Thus all the progeny cells will share identical immunoglobulin gene rearrangements. Hence, by simply assessing the status of the immunoglobulin gene in an unknown cell population, one can determine the clonality of the cells. Clonality is usually synonymous with lymphoma, though exceptions do exist. PCR analysis or the classical restriction fragment analysis using Southern blot can be used to assess the immuno-
globulin gene status. The sensitivity of Southern blot in these cases is such that the tumour cell population must account for about 5% of the cellular population. It is possible to achieve the sensitivity necessary for evaluating minimal disease settings using PCR technology. PCR is performed most frequently using primers that amplify a DNA segment spanning the junctional sequences of the rearranged heavy chain gene. Although this comes with the caveat that the rearranged immunoglobulin genes of normal B cells will be amplified alongside the tumour-specific rearranged genes, this analysis takes advantage of the junctional nucleotide alterations that occur during V-D-J (junction between the variable and diverse regions of the immunoglobulin molecule) joining generating clone-specific markers. In polyclonal populations of B cells there will be a distribution of amplified products whereas in a monoclonal population, a single PCR amplicon will predominate. Although the sensitivity of this form of PCR analysis is very low, it can be improved by about 2–3 logs by combining PCR with Southern blot and hybridization to a V-D-J junction-specific probe.

Molecular cytogenetic tests can also be performed using PCR analysis. The bcl-2/JH junctions are the most frequently studied targets of molecular cytogenetic analysis in B-cell lymphomas. However, PCR analysis has also been performed for bcl-1/IgH and c-myc/IgH joining sequences. Analysis of translocations by PCR is extremely sensitive; the rate of detection is in the range of 1/10^5–1/10^6 cells. For primary diagnosis and in certain instances such as monitoring the purging of tumour cells prior to autologous transplantation, these analyses are rapid and easy to interpret. However, in the setting of minimal disease, one must be very careful in interpreting positive results, as rare normal cells containing oncogene/JH junctions, particularly bcl-2/JH may occur at a low frequency in otherwise normal individuals.

The study of B-cell molecular biology and lymphoma pathogenesis has already made a major impact in medical diagnostics. Molecular genetic approaches to B-cell lymphoma diagnosis will be increasingly used in the years to come, for classification purposes, monitoring treatment and recurrence screening. We can also expect to see panels of molecular-based tests for oncogenes and other molecular markers which will not only define specific tumour subtypes, but also generate prognostic information and help shape treatment protocols. PCR techniques still hold great promise for monitoring the effect of therapy and screening for early recurrence of disease.

DETECTION OF OCCULT METASTASIS IN CARCINOMAS USING RT-PCR

A major proportion of cancer patients, who do not have residual disease by histopathological criteria, will develop metastases. Adjuvant chemotherapy benefits some patients, but treatment of all patients with tumours is unnecessary, since most will never have recurrence after surgery. Therefore, there is a need to identify patients with solid epithelial tumours who are at an increased risk of progression, or in whom this has already occurred but is as yet occult, because this group may benefit from adjuvant systemic therapy. Identification of occult metastases can reduce treatment-related morbidity in patients with a more favourable prognosis and in those who probably do not benefit from a chosen therapeutic regimen. Metastatic relapse in patients with cancer is caused by occult dissemination of tumour cells. The presence of tumour cells in the bone marrow and blood of patients with cancer can be detected mainly immunohistochemically or by RT-PCR methods to identify expression of tumour-specific mRNAs. Such detection has been found to be a clinically relevant prognostic factor in an increasing number of studies.

Besides these two methodologies, techniques have been suggested to detect circulating tumour cells at a molecular level. These involve detection of somatic events such as point mutations or chromosomal rearrangements. One such example is the mutant allele-specific amplification (MASA), which is a PCR-based assay for amplification of tumour-specific DNA sequences, which may detect a tumour cell in a background of thousands of cells. MASA is capable of detecting micrometastases in lymph nodes that are classified as histologically negative. MASA-detected tumour cells in lymph nodes correlate with an increase in local recurrence rates in patients with colorectal carcinoma. The limitation of the mutation detection method is that not all tumours contain mutations suitable for PCR amplification. Thus, p53 mutations are present in only 70% of colorectal and 30% of breast cancers, excluding a major subclass of cancer patients from analysis. Clinically overt bone marrow metastases have been observed only in patients with identifiable disseminated isolated tumour cells, indicating that these cells may indeed constitute the progenitors of metastases arising later. Thus, not surprisingly, the detection of occult metastatic cells in bone marrow, with regard to both the absolute number at the time of diagnosis and the kinetics of occult metastatic cells on follow up, has been associated with an increased risk of systemic relapse and decreased overall survival. Accordingly, monitoring of occult metastatic cells may constitute a surrogate marker for the estimation of prognosis and for the efficacy of therapeutic interventions in patients harbouring disseminated tumour cells in their bone marrow.

The rationale of usefulness of the RT-PCR method hinges upon the specific expression of the target molecular marker in malignant cells, with no expression in the surrounding tissue and blood cells. If these conditions are met, the RT-PCR assays can be used for detecting tumour cells in the lymph nodes, resection margins, blood, bone marrow and serum. However, the high sensitivity of this method is itself a matter of concern since high false-positive rates may result because of nodal contamination by DNA from non-viable tumour cells that have been shed.

The importance of RT-PCR assays in detecting occult metastatic cells can be best illustrated in the case of prostate cancer where this technique is used for the detection of two important markers—prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSMA).

PSA is a tumour biomarker for the clinical management of patients with prostate cancer. Serum PSA levels are useful not only in the early detection of prostatic cancer but also in determining the prognosis and monitoring the efficacy of treatment. PSA was initially described as a protein believed to originate solely from the prostatic epithelium. However, PSA and/or PSA gene expression has been detected at low concentrations in the endometrium, normal breast tissue, normal breasts and breast milk, female serum, adrenal neoplasms and renal cell carcinomas.

RT-PCR has been used in clinical urology with a focus on the staging of prostate cancer, primarily to detect haematogenous extraprostatic disease. Circulating PSA mRNA has been detected by RT-PCR in as many as 88% of men with known prostatic metastases. RT-PCR has also identified the mRNA of PSA in the serum of men following needle biopsy of the prostate. The available data suggests that false-positive results are exceedingly rare with RT-PCR. It has so far been applied to stage patients with prostatic cancer with pelvic lymphadenectomy and to detect bone metastases in a molecular fashion. Deguchi et al. have reported...
through the Primary Health Centre (PHC) in case of rural areas, and the municipal health office in case of urban areas. Tabulation is usually done at the state level but the statistics are published by the RGI. Until December 1998, the COD data for rural areas was collected under the Survey of COD-Rural (SCD-Rural) scheme, from a sample of villages using a lay diagnosis and reporting system. A paramedical person from the PHC is designated as the field agent to carry out the primary survey. (S)he identifies key informants and maintains liaison with them. A household register is then opened and updated half-yearly. For each death occurring in the villages, the field agent interviews the family of the deceased, and records the symptoms and circumstances of death in a form (Form 7). A structured questionnaire is used to determine COD on the basis of the symptoms and circumstances of death. A checklist supplements the structured questionnaire. The field agent infers the probable COD by applying the structured questionnaire to the symptoms and circumstances recorded in Form 7. The checklist entry against the probable COD arrived at is tallied with the symptoms and circumstances of death. The COD thus arrived at is reported in Form 3 (referred to as certificate of death here). The PHC statistician is designated the recorder of events reported by the field agent. The recorder does a half-yearly verification of the household list. The medical officer of the PHC is expected to check and certify the correctness of the COD assigned by the field agent. The structured questionnaire currently in use was adopted after taking into account 5 years of field experience with a provisional questionnaire. The non-medical list (NML) of causes of death was last revised in 1983 to correspond to ICD-9, RGI. SCD-Rural follows the verbal autopsy method to arrive at the CODs using paramedical personnel.

From January 1999, the COD component has been added to the Sample Registration Survey (SRS), RGI (personal communication from Registrar General of India, Ministry of Home Affairs, on 11 January 1999 addressed to Prasanta Mahapatra, Institute of Health Systems). We call this the SRS-COD component. Two columns have been added to the SRS Form 5 (Columns 16 and 17) and Form 10 (Columns 12 and 13). The SRS Part Time Enumerator (PTE) records COD in column 16 and the code in column 17 of the revised Form 5. The SRS supervisor records similar information in columns 12 and 13 of the revised Form 10. A major departure from the SCD-Rural design is skipping the symptom record (SCD-Rural Form 7). Another departure from the SCD-Rural is doing away with the structured questionnaire. Instead, the instructions contain a list of causes, related symptoms for some, and the corresponding ICD-10 code. Hence, content validity of the verbal autopsy system is important. In addition, Ruzicka and Lopez’s perspective was usability of country-level COD data. They did not consider usability of COD data for sub-national political units and for small area analysis. In a large country like India, the usability of country-wise COD data is important (many Indian states have populations that far exceed the population of many countries in the world). Finally, timeliness and regularity in the availability of statistics improves usability by building confidence among potential users. Considering all these aspects, and building upon the criteria suggested by Ruzicka and Lopez, we identified the following criteria to assess the usability of any COD statistics:

1. The proportion of all deaths attributed to residual categories such as ‘Symptoms, signs and ill-defined conditions’ is within limits, say less than 10%.
2. The proportionate distribution of deaths by cause is consistent with the estimated mortality level for that country.
3. No COD with a clear age-sex dependency has been incorrectly assigned.
4. The age-sex distribution for major causes is consistent with what one may expect for each cause.
5. Data generated by the system are consistent with previous years.

These are essentially plausibility checks. A data set failing these criteria is likely to be biased. A data set satisfying these criteria may still not be usable on account of the poor statistical accuracy of the generated estimates, and biases that are not readily noticeable. These authors did not consider the effect of content validity on the accuracy of COD data based on verbal autopsy. In India, verbal autopsy provides COD statistics for the country’s rural population, which forms a large majority of the population. Hence, content validity of the verbal autopsy system is important. In addition, Ruzicka and Lopez’s perspective was usability of country-level COD data. They did not consider usability of COD data for sub-national political units and for small area analysis. In a large country like India, the usability of state-wise COD data is important (many Indian states have populations that far exceed the population of many countries in the world). Finally, timeliness and regularity in the availability of statistics improves usability by building confidence among potential users. Considering all these aspects, and building upon the criteria suggested by Ruzicka and Lopez, we identified the following criteria to assess the usability of any COD statistics:

1. Content validity of lay reporting systems, if any
2. Adequate coverage and compliance
3. Validity of statistics at sub-national levels of disaggregation
4. Minimal usage of residual categories, such as unclassifiable, or ill-defined conditions
5. Consistency of case-specific mortality proportion with general mortality level
6. Absence of incorrect assignment of causes with clear age and sex dependency
7. Incidence of improbable assignment of causes with clear age and sex dependency
8. Consistency of cause-specific mortality proportion over time
9. Timely compilation and publication of statistics.
We examine below the usability of COD statistics from the rural and urban areas, respectively. We take up each usability criterion, discuss its implications briefly and then examine how India’s COD statistics fare, using national statistics and state-level statistics from Andhra Pradesh. Where required, we supplement the published statistics with information about Andhra Pradesh, available to us from our study on COD. We call this the AP Rural COD (APRCD) study, 1998.

Content validity of the verbal autopsy algorithm for lay reporting of COD in India

Certain general design features are crucial to the wide applicability, efficiency and validity of data generated by a verbal autopsy-based COD reporting system. Over the years, some degree of consensus on major design issues has emerged. Content validity of the verbal autopsy-based COD reporting systems in India has been examined in detail by one of us.4 Here we present a summary of the findings from the paper just cited. For our purpose, the SCD-Rural structured questionnaire was systematically examined for each of the conditions included in the NML. The questions were reviewed in the light of available research results on verbal autopsy. The SCD-Rural system appeared to satisfy most of the general design criteria for a good verbal autopsy system. Altogether there are 57 specific causes in the SCD-NML, excluding the residual categories. Accidents and injuries account for 12 of these. There is a strong consensus on the validity of verbal autopsy to code deaths due to accidents and injuries, since lay persons can easily recognize most of these. Cause-specific discussions of verbal autopsy on accidents and injuries are not available in the literature. This is also the case with deaths due to maternal causes under which the SCD-NML contains 7 items. Attributing these 19 causes to the general category of accidents, injuries and maternal deaths, there are 38 specific codes in the rest of the SCD-NML. At least some expert opinion or validity information is available for 24 of these 38 causes. For 21 of these 24 causes, the SCD questions appear to be in accordance with expert opinion and validity information available in the literature. The 3 causes for which there is major discrepancy are (i) cord infection, (ii) prematurity, and (iii) cancer. Most experts agree, and validation studies show, that verbal autopsy is good at detecting neonatal tetanus. In SCD-Rural, neonatal tetanus is included under cord infection. Thus an opportunity for accurate estimation of deaths due to an important cause from the public health point of view is missed. Experts opinion that it is usually difficult to distinguish between prematurity and low birth-weight.7,8 Hence, they ought to be clubbed together for accuracy of statistics based on verbal autopsy. The SCD list does not include low birth-weight in its causes. It can be added to prematurity without affecting the rest of the questionnaire. The SCD list places all cancers under one cause. Some expert opinion is usually available about the site of cancer. Moreover, some cancers may have symptoms that could be confused with the filter questions for other modules. For example, cancer of the stomach may be listed under deaths due to digestive ailments. In that case, the field agent may not consider cancer of the stomach at all, since there is no mention of it in the module on digestive causes. Lung cancer also suffers from the same problem. In spite of these deficiencies, the SCD-Rural system was reasonably valid in terms of its design and verbal autopsy guidelines. It appears to have been discontinued mainly on account of poor coverage and compliance at different levels of the COD reporting system.

The SRS-COD component relies on verbal autopsy to determine the COD. However, major departures from the SCD-Rural design are: (i) doing away with the structured questionnaire approach; and (ii) lack of a symptom record. The SCD-Rural symptom record (SCD-Rural Form 7) was similar in its information content to the WHO COD report format, which requires information about the underlying COD. The SRS-COD component requires field agents to record the COD and the code to which the COD is assigned. No further information about symptoms and circumstances of death need be reported (This information is required for systematic screening and coding of the COD reports). However, it is too early to make a judgement on the new system. It will be helpful if specific research studies are carried out to evaluate the performance of the new COD reporting system in rural areas. In particular, it will be desirable to assess the accuracy of classification of deaths due to various causes. We intend to take up this issue in our future studies and hope that other researchers will examine and assess the efficacy of the newly introduced SRS-based COD reporting system. We feel the content validity of the SCD-Rural system was ‘satisfactory’ and assign a rating of ‘tolerable’ to the SRS-COD component.

Coverage by COD reporting systems

Table I shows coverage of deaths by the SCD-Rural scheme from the sample areas from 1991 to 1995.5 Coverage is computed with respect to the estimated total deaths for the SCD-Rural sample areas, using the SRS death rates. Some states show more than 100% coverage for some years. This could be due to under-counting by the SRS, giving rise to a small denominator in the coverage estimate or under-counting of the population by the SCD-Rural system. At the national level, the SCD-Rural covers 70% to 90% of deaths. However, there is a great deal of difference among various states. Maharashtra has consistently maintained more than 80% coverage for all 5 years. The other states with a high yearly coverage include: Haryana, Karnataka, Tamil Nadu, Rajasthan, Andhra Pradesh, Orissa, Himachal Pradesh, Punjab and Uttar Pradesh. States such as Assam, Bihar and Madhya Pradesh generally show poor coverage by the SCD-Rural system. In West Bengal, the SCD-Rural system seems to be altogether defunct. The APRCD study catalogued all SCD-Rural reports from Andhra Pradesh for 1998. It was found that about 20% of sample PHCs in headquarter villages were not sending any reports.

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PUBLIC HEALTH SITUATION 2000
The South African Health Review 2000' has just been published (516 pages; 24 chapters). The publication of these annual reviews began in 1995. Those involved or interested in the health scenario in our constituent populations wonder whether any real progress has been made. Have we regressed in some respects? What are the outstanding problems?

In order to provide a proper perspective, before describing the changes that have taken place in South Africa, we need to consider whether affluent western nations have any serious problems in their national health scenes. They do indeed. In the USA, 'health care continues to fail the poor and the non-White races.' 2 In the UK, a recent enquiry concluded that 'health of the nation deemed to be a failure' 3 and urged the authorities 'to begin a serious assault on the gross inequalities that have emerged in Britain in the past two decades.' 4 A further item, averred that 'one in three English hospital wards is filthy.' 5 Notwithstanding the extent of the problems depicted, they pale in comparison with those faced by developing populations, such as those in sub-Saharan Africa, where one-tenth of the world’s population lives on 1% of the world’s total income. 6

In the South African report, among the positive findings listed, primarily in relation to the African population, substantial progress has been made in antenatal care. There have been moderate improvements in immunization, family planning and postnatal care, but only slight improvements in sexually transmitted diseases and in the care of patients with tuberculosis. The turnaround times of various laboratory tests have improved considerably. Home visits are being conducted by a relatively high percentage of clinics. Nationally, nurses at fixed clinics now have a substantially lower patient load than that in 1997. The updating of skills in the field of HIV/AIDS has improved. The availability of electricity at fixed clinics has increased markedly from 65% in 1997 to 92% in 2000, and in 5 of the 9 provinces, electricity is available in all the clinics. Condoms, oxygen, methyl dopa, oral hydration solution, penicillin and oral contraceptives are more readily available than they were in 1998.

On the negative side, the availability of tests performed as part of primary health care (PHC) is unsatisfactory. Thus, the availability of HIV testing at fixed clinics remains low; indeed, 4 in every 10 clinics do not offer this extremely important test. Nationally, HIV tests are less available than those for syphilis. Only half the fixed and mobile clinics offer pregnancy tests. A quarter of the fixed and satellite facilities, and half of the mobile clinics, have no ambulances available for emergencies. Essential PHC equipment is not available at some fixed clinics. Although the availability of telephones at PHC facilities has increased substantially since 1998, the general situation is still unsatisfactory with no telephones in one-fifth of fixed clinics, and alternative means of communication in only 2 of 10 facilities. Despite the improvements in the availability of electricity, interruption of supply remains a major problem. In the month preceding the present survey, interruptions occurred at one-third of the clinics.

Poor water supply also remains a problem. At present, 12.5% of satellite clinics still depend on water delivered by a tanker; 5% of these obtain their water from a river or a dam; and 12.4% of fixed clinics rely on rainwater. Among the other drawbacks, one-third of mobile clinic health workers believe that their vehicles are unsuitable for the roads on which they travel. Iron tablets, doxycycline and erythromycin are less widely available than they were in 1998. The regularity of nurse supervisor visits to fixed facilities in the month preceding the survey has fallen substantially from 79% in 1997 to 67% in 2000; moreover, one-third of the facilities reported that they were ‘never’ visited. A preliminary investigation has shown that record-keeping of patients with tuberculosis is poor, especially in satellite clinics. Understandably, the above scenario varies considerably from province to province.

A recent enquiry in the Eastern Cape (perhaps the poorest of the