

Additional Best Practice Commissioning Guidance For developing Haematology Diagnostic Services

(In line with the NICE Improving Outcomes
Guidance for
Haemato-oncology, 2003)

Gateway number: 17241



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Content:

Introduction

Original Rationale and Evidence

The Integrated Diagnostic Pathway and Report

Review of rationale and anticipated benefits

- Quality assurance
- Cost effectiveness
- Technical and organisational developments
- The need for accurate data

Key components and processes

- Organisation
- Diagnostic pathways and technologies
- Components of the Specialist Integrated Haematological Malignancy Diagnostic Service
- Interface with clinical haemato-oncology
- Training/ research and development

Summary

Annexes:

- Responsibilities of the cancer network board & network site specific groups – annex A
- Service specification – annex B
- Glossary of terms – annex C
- Abbreviations – annex D

Foreword

There can be no doubt that improvements have been made in cancer services in the last 10 years. The local and regional implementation of the advice in a series of documents, including Improving Outcomes Guidance, has led to significant improvement in the quality of evidence-based services for patients across the country. There remain areas, however, where full implementation of the IOGs has not yet been achieved. We believe that the recommendation that specialist laboratories should have an integrated diagnostic process and produce an integrated report is crucial for the diagnosis of haematological malignancies to ensure diagnoses are consistent and accurate.

This guidance has been drafted by the National Cancer Action Team and the Royal College of Pathologists, to assist those teams that have had difficulty in implementing the IOG recommendation by clarifying the rationale and providing more practical help in the form of a service specification. The pace and extent of change in the management of the NHS and of postgraduate education make it even more important that we have clear and secure operational means of preserving excellence in our practice and training.

We recommend this guidance to you now and will continue to work to provide practical help and exemplars of high quality services to help providers and commissioners provide the highest quality services possible for patients.”



Professor Sir Mike Richards
National Cancer Director



Archie Prentice
President of the Royal College of Pathologists

Introduction

1. Improving Outcomes Guidance for Haematological Oncology (IOG) was published in October 2003. This has been one of the most complex to achieve and eight years later, implementation remains incomplete¹. Many cancer networks have been unable to work with providers and commissioners to ensure full compliance with some of the key recommendations. The most challenging recommendation has been the requirement to develop integrated laboratories for the diagnosis of haematological malignancy, commissioners will want to commission IOG compliant services to ensure accuracy and certainty of diagnosis for their populations.
2. Accuracy and certainty of diagnosis remains an ongoing problem, which particularly applies to lymphomas with concordance of diagnosis for lymphomas, is less than 85%². There is a human and financial cost of diagnostic errors even though the financial costs of a precise diagnosis are a small fraction of treatment costs. Additionally no nationwide, validated and comparable epidemiology/population based data exist for service planning or monitoring of clinical outcomes.
3. The purpose of this document is to provide best practice advice to commissioners that will enable them to commission services that are fully compliant with the NICE Improving Outcomes Guidance for Haematological Oncology, it will:
 - examine and update the original rationale;
 - clarify specific areas of the guidance;
 - define the key components, processes and benefits of an integrated diagnostic service;
 - provide a template service specification.This will help inform commissioner discussions with providers and bring clarity as to what an IOG compliant service might look like.
4. In order to ensure that they commission best practice Haematology Diagnostic Services that are compliant with NICE Improving Outcomes Guidance, commissioners need to commission specialist haematological malignancy diagnostic services for their populations. Specialist Integrated Haematological Malignancy Diagnostic Services (SIHMDS) should cover a catchment population of at least 2 million. There are already existing SIHMDSs above this threshold which could support all networks, although more than half of networks continue to commission services from local non-specialist laboratories. If commissioners were to switch from using local diagnostic services to a specialist service (possibly located in a neighbouring network), the optimal scale for these services would be reached.
5. Commissioners should ensure that the roles and responsibilities, in delivering these specialised services, of Cancer Network Boards, Network Site Specific

¹ National Institute for Clinical Excellence, Guidance on Cancer Services. Improving Outcomes in Haematological Cancers, The Manual, 2003, http://www.nice.org.uk/nicemedia/pdf/NICE_HAEMATOLOGICAL_CSG.pdf

² Ireland R, Haematological malignancies: the rationale for integrated haematopathology services, key elements of organization and wider contribution to patient care, *Histopathology* 2011; **58**: 145–154

Groups and providers are clear, that the service specification sets out appropriate standards for the service and that services are measured against appropriate outcome/ quality standards. This guidance provides background information, advice and templates to help commissioners to do this.

Original Rationale and Evidence - NICE guidance 2003

6. The National Institute for Health and Clinical Excellence (NICE) laid out the rationale, evidence and recommendations for haemato-oncology services in 'Improving Outcomes in Haematological Cancers – The Manual' in 2003.
7. The NICE guidance clearly identified that the haematological malignancies are a complex group of neoplastic diseases and the current WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 2008 identifies approximately 125 diagnoses in 12 major disease groups³. Scientific advances have transformed diagnosis, classification and patient management so that specialist immunophenotyping, cytogenetics and molecular methods are as important as traditional morphology for accurate disease classification. Accurate diagnosis and sub-classification requires integration of the morphological, immunophenotypic and genetic features. These techniques are now fundamental not only for diagnosis but also for patient treatment in the era of targeted monoclonal antibodies and novel agents for specific molecular abnormalities. Their conclusion was that '*Individual patient management should be based on sound and comprehensive information to define the most appropriate treatment.*'
8. Central to the NICE guidance was recognition that consistency and accuracy of diagnosis was the starting point, and probably '*the single most important aspect of improving outcomes in haematological cancers*'.
9. NICE identified concerns about provision, access and accuracy of diagnosis:
 - Heterogeneity of services ranged from single-handed pathologists with little access to specialist diagnostics, through to fully integrated specialist diagnostic laboratories.
 - When key investigations are carried out in separate laboratories, there may be duplication and contradictions in results.
 - There is consistent evidence of a significant level of inaccuracy of diagnosis and that expert review improves diagnostic accuracy. This was derived from audit and reviews which showed significant errors in diagnosis that would affect treatment. These are summarised in the table below: i.e. post reorganisation of Haematology Multi-disciplinary Teams (MDTs) but in the absence of reconfigured laboratories.

All Wales Lymphoma	2 year central review of 275	Major diagnostic discordance in 20% of cases: -5 cases diagnosed as benign were lymphoma.
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³ Swerdlow SH, Campo E, Harris NL et al., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC; 2008

Pathology Review Panel⁴	lymph nodes(1998-2000)	-13 cases diagnosed as lymphoma were benign or a non-haematological malignancy. -15cases changes from NHL to HL or vice versa. -16 cases of NHL assigned to a different prognostic group. -21% diagnosed as lymphoma but no REAL classification -17 cases would have had a change in management strategy and first-line treatment was altered in 12.
Lancashire Hospital⁵	Regional centre review	-36% had major discrepancies
NE England audit⁶	100 lymph nodes	-26% diagnostic discrepancy rate that would have changed management
Scottish and Newcastle Group⁷	574 cases of Hodgkin Lymphoma	-28% had revised histological subtype and a resulting change in management in 10%

- Extrapolation of the evidence above (up to 5% of patients treated for lymphoma in Wales had benign disease) suggests that annually 400 people might receive an inappropriate cancer diagnosis and unnecessary treatment in England.
 - The All Wales Lymphoma Pathology Review Panel found a diagnostic error rate of 17% and estimated costs of inappropriate treatment at around £200,000/year excluding legal costs. Cost savings from avoided misdiagnosis in England are unknown but could be substantial.
 - In addition, many more patients may receive sub-optimal treatment because their disease is incorrectly classified.
10. These problems are by no means limited to the United Kingdom. Similar problems in the diagnosis of acute leukaemias were reported from the USA⁸ and support the view that expert review of pathology improves diagnostic accuracy. The financial costs of precise diagnosis are a small fraction of the cost of treatment and the human cost of diagnostic error is potentially significant.
11. The NICE guidance made important recommendations about service organisation and delivery that supported:
- Local initial assessment of specimens leading to appropriate referral to specialist services;

⁴ Lester JF, Dojcinov CD, Attanoos RI *et al.* The clinical impact of expert pathological review on lymphoma management: a regional experience. *Br J Haematol* 2003;123:463–8.

⁵ Prescott RJ, Wells S, Bisset DL *et al.* Audit of tumour histopathology reviewed by a regional oncology centre. *J Clin Pathol.* 1995; **48**; 245–249.

⁶ Department of Health. Measures for the Manual for Cancer Services 2004: Haematology, head and neck and cancer registry. Department of Health Publications, London, 2005..

⁷ Jarrett R F, Krajewski A S, Angus B *et al.* The Scotland and Newcastle epidemiological study of Hodgkin's Disease: impact of histopathological review and EBV status on incidence estimates. *J Clin Pathol*; **56**: 811-816

⁸ DeLima M, Albitar M, O'Brien S, *et al.* Comparison of referring and tertiary cancer center physician's diagnoses in patients with leukemia. *Am J Med* 1998;**104**:246-51

- Identification of specialist immunophenotyping, molecular biology and cytogenetics services and facilities by Cancer Networks. This was incorporated into Cancer Peer Review measures (1A-248, 249 and 250);
 - Development of clinical networks in pathology across Trusts to build capacity, reduce fragmentation and provide enhanced levels of equipment and expertise;
 - Organisation of haematological services at network level, with collaboration between networks to achieve economies of scale and with specialist services serving one or more networks.
12. In order to reduce errors it recommended that every diagnosis should be reviewed by specialists in haematological malignancy. This would involve integrating the results of specialist tests into a final report with an overall interpretation and diagnostic opinion authorised by a single designated pathologist (Cancer Peer Review Measure 1C-122). The following would be needed to achieve this:
- Locating all specialist haemato-pathology diagnostic services in single laboratories;
 - integrated diagnostic processes with a systematic approach to the choice and sequence of tests;
 - use of computer software designed to support precise identification of haematological malignancies.
13. Results are integrated into a single interpretative report containing all of the information relevant to the management of the patient. This would be a collaborative process supported by a dedicated IT system. This avoids the duplication and possible contradictions that may arise when key investigations are carried out in separate laboratories.
14. Quality of the new organisation and diagnostic systems is assured by:
- All laboratories participating in CPA and external quality assurance schemes;
 - A systematic approach to diagnostic testing with a specified range of tests carried out on each sample in a systematic way, following protocols that define order and choice of test;
 - Results of tests being integrated and interpreted by experts who work with local haemato-oncology MDTs and provide a specialised service at network level.
15. The specialist multi-disciplinary meeting is the final quality check confirming that all clinical, imaging and pathology results are concordant.
16. Of major concern is the fact that there are no precise or reliable figures for incidence or survival rates for haematological cancers in England and Wales and it is not possible to judge whether clinical outcomes are better or worse

than elsewhere in the world. To enable commissioners to plan future service needs, the NHS requires knowledge of incidence, prevalence and survival rates, all of which are changing in the UK.

17. The development of an accurate dataset for haematological malignancies to support commissioners is a major objective of the National Cancer Intelligence Network. The difficulty in achieving data quality comparable to other cancer sites is a direct consequence of the fragmented nature and quality of diagnostic service for haematological cancers.
18. Commissioners should ensure that diagnostic laboratory providers utilise updatable computer software designed to support precise identification of haematological malignancies to facilitate accurate population-based studies of epidemiology and clinical outcomes.
19. The Improving Outcomes Guidance also identified resource implications for setting up these services. Specialist laboratories have high capital and revenue costs. However, rational selection of diagnostic tests following defined protocols can conserve resource by only selecting tests yielding useful information. There are also substantial economies of scale that can be achieved by batching tests and analysis.
20. Cost implications vary according to:
 - The degree of centralisation already achieved;
 - The additional equipment required;
 - Inclusion of gene sequencing facilities;
 - Size of population served.
21. Costing exercises originally predicted national capital set-up costs of approximately £5.8million with annual running costs of £7.5 million but with cost-effectiveness linked to the size of population served; i.e. a low-cost scenario with an anticipated catchment population of 3 million or more and a high-cost scenario for smaller populations down to 1.5 million. The Specialist integrated haematological malignancy diagnostic service (SIHMDS) should cover a catchment population for the service of at least 2 million but there should be no new SIHMDS services set up as a result of this guidance, where none previously existed. In fulfilling this requirement, the network may obtain this service from another network.

The Integrated Diagnostic Pathway and Report – Clarification of the original NICE guidance.

22. The guidance relating to unified reporting was more far reaching than the collating of individual results into a single overall report, with or without adding a comment. It was also clear that it is not appropriate to have a local report produced and then sent on for central review or integration into the final diagnostic report. This undermines the integrated diagnostic process, internal

validation and quality assurance given by systematic investigation processes. It also delays the turnaround of a meaningful, high quality diagnostic report within a time frame that allows for timely decision-making.

23. The underlying principle is that effective working requires an integrated diagnostic pathway. This process is characterised by:
- A predefined diagnostic pathway that is followed systematically for each specimen type or clinical problem. The design of the pathway includes two components:
 - Selection of the most appropriate diagnostic platforms for a particular clinical situation and avoiding unnecessary duplication.
 - Selection of a panel of investigations for each specimen to provide maximum levels of internal cross-validation using the WHO principle of multi-parameter disease definitions.
 - Comprehensive diagnostic testing facilities, technologies and interpretation including cytomorphology/histology/ immunocytochemistry /cytogenetics-Fluorescent in-situ Hybridisation (FISH) and molecular genetics.
 - Review of all of the results and compilation within the laboratory of a fully integrated report by senior laboratory staff with appropriate levels of expertise that is then released to the referring clinician. This should be completed in a timeframe that allows additional investigations to be carried out if inconsistencies or uncertainties remain after the primary investigations have been completed. This affords the opportunity for internal validation and cross-checking, at source, before a misleading and potentially inaccurate report leaves the laboratory.
 - An integrated report that includes all information needed for initial patient management should be available at the multi-disciplinary team meeting.
 - The final report should summarise the results of investigations performed, contain an interpretative comment and a final diagnosis using the terminology of the WHO classification/ICD-O-3.
 - An effective system of quality assurance that should include an audit trail for each sample demonstrating that the diagnostic pathway has been followed, as well as traditional external quality assurance requirements.
24. In many cases this would require significant re-engineering of existing services to achieve the benefits described below. However, in most cases many of the core resources required to do this will already exist within the network.
25. It is not expected that clinicians would devolve all morphology to the centre and would be encouraging them to combine both their clinical and laboratory skills. It is believed that local reporting of the bone marrows is a final quality assurance test for the MDM where treatment decisions are made and is beneficial to all parties. What the IOG offers is a coordinated, systematic, integrated approach to multi-technology diagnostics and a definitive final integrated report.
26. Specialised testing should be centralised for immunological, genetic and molecular techniques that is essentially, what the IOG is recommending. The

IOG is, however, taking it one-step further by suggesting that morphology also needs to be undertaken centrally in conjunction with the specialist testing as these are all inter-related and need to be considered in totality. This should also include the immunohistopathological reporting of trephine biopsies by histopathologists.

27. This does not prevent the local clinician reviewing the bone marrow and we would expect this to happen as treatment decisions may need to be made rapidly, often before all results are available. However, this should happen in parallel and delay in referral should be minimised so that the final definitive diagnosis to the patient is not delayed. Extensive, but often incomplete, local testing followed by specialist referral and further retesting will not provide an efficient, patient centred approach.
28. These changes in integrated specialist testing do not reduce the need for skilled reporting of blood films and marrow smears at the ends of the spokes in a hub and spoke arrangement. There remains a need for accurate and vigilant detection of potential haematological malignancies in the first round of investigations at all DGHs, followed by prompt referral of specimens for specialist testing.

Review of Rationale and Anticipated Benefits

Quality Assurance

29. The original rationale for the guidance was the recognition that the error rate in the diagnosis of haematological malignancies was unacceptably high and had clinical consequences. This was based on publications and audit data. There is no evidence of any substantial change in this underlying problem and this has been confirmed in a recent audit carried out in Greater Manchester (A Norton and R Byers 2008)⁹ who found the serious and critical error rate to be 15%. These data refer to the diagnosis of lymphoma but similar results would be expected in other diagnostic categories. The second review was undertaken in a North London Cancer Network and whilst error rates have fallen between 2003 and 2008, they are still substantial (13-15%) resulting in minor or major changes in treatment or delay in treatment¹⁰

North
Central
London
Lymphoma
Network

1,949 patient
samples were
subject to expert
review between
2003 and 2008.

-Overall discordance rate of 27.3% identified.

-Among the 10 most commonly referred lymphoid malignancies, the discordance rate varied between 3.6% and 34.1%.

Of the 512 discordant diagnoses, it was possible to assess 350 patients to determine whether expert central review would have altered patient management.

- In 39 patients (11%), would have resulted in a significant change to the clinical management of the

⁹ Unpublished

¹⁰ Ian E. Proctor, Christopher McNamara, Manuel Rodriguez-Justo, Peter G. Isaacson, and Alan Ramsay Importance of Expert Central Review in the Diagnosis of Lymphoid Malignancies in a Regional Cancer Network, North Central London Lymphoma Network, *Journal of Clinical Oncology April 10, 2011 vol. 29 no. 11 1431-1435*

patient; 19 of these patients (5.4%) were misdiagnosed with either reactive or malignant conditions.

- In 136 patients (39%), only minimal change(s) to patient care would have been made after central review
- In 175 patients (50%), the primary diagnosis provided insufficient or outdated information and would have resulted in either delayed or potentially inappropriate treatment.

-42% of samples required additional ancillary tests to confirm or establish the final diagnosis

-During the 6-year study, the discordance rate improved significantly, decreasing from 32% to 13%.

This is the essential context for the following discussion.

30. These concerns about standards of diagnosis serve to highlight a more fundamental problem that is almost unique to haematological oncology. For most types of cancer, the diagnosis made on an initial biopsy or cytology specimen will result in a secondary operative procedure and specimen which provides independent validation of the original diagnosis. Visualisation of the lesion at endoscopy or operation adds further steps in the diagnostic process contributing to overall confidence in the accuracy of the original diagnosis. For leukaemia and lymphoma a diagnosis made on a pathological specimen will generally lead directly to treatment by chemotherapy or radiotherapy. This may be based primarily on subjective morphological interpretation of cytology preparations or tissue sections by a pathologist. Unless a subsequent review is undertaken, serious errors will not be detected. External quality assurance schemes designed to test morphological interpretation are difficult to design for haematopathology given the very large numbers of possible diagnoses. More importantly, by their nature, they are retrospective and based on circulated material to test overall performance rather than detect and prevent errors in 'real time' diagnostic samples. A 'real time' quality assurance scheme should be a goal that a network of integrated diagnostic centres could explore and exploit.
31. Recent developments in classification and technology provide a solution to this problem. The WHO classification defines each type of leukaemia and lymphoma in terms of morphology, phenotype, molecular and cytogenetic features and clinical characteristics. If all of the defining features can be demonstrated, there is a high probability that the diagnosis is correct. This is the rationale for the integrated diagnostic pathway described above. Technical developments mean that it is now possible to design pathways that contain multiple levels of cross-validation between techniques. Adherence to these pathways is the critical element in diagnostic quality assurance and provides clinician and patient with the level of confidence in the diagnosis that is required before proceeding to treatment. In haemato-oncology the critical element is the ability to demonstrate that a diagnosis is likely to be correct through a process of internal validation using multiple independent diagnostic techniques. Where this process is absent, particularly where the primary diagnosis is based mainly on subjective assessments, there will be a major weakness in the quality assurance of the whole patient pathway leading to the

possibility of undiscoverable errors. As retrospective audit data have demonstrated, these risks are unacceptably high.

32. A systematic approach to the investigation of suspected leukaemia and lymphoma based around a carefully designed pathway is essential. If this is the approach taken, then important entities that cannot be reliably identified by morphology alone and will be mis-diagnosed.
33. A very striking recent example is the MRC LY10 trial in Burkitt lymphoma (BL)¹¹. This is a critical diagnostic area and about 50% of patients entered in the trial were proven not to have Burkitt Lymphoma on review and further investigation. The implications of these data are:
 - Half the patients in the trial had the wrong treatment – in this case expensive and toxic in-patient chemotherapy
 - The trial took 3 years to recruit about 60 patients while the incidence in the UK is about 250 per year (HMRN data). It is very likely that many patients with BL are currently not recognised. This condition is very successfully treated with intensive chemotherapy but not with CHOP-R, the standard treatment of diffuse large B-cell lymphoma.
34. The specific cause of this problem is the fact that Burkitt Lymphoma cannot be reliably diagnosed by morphology and requires systematic use of extended immunophenotyping and Fluorescent in-situ Hybridisation (FISH) investigations. Morphology is no longer a gold standard; though an important starting point, it must be complemented by other studies.
35. A similar situation pertains in a number of other types of haematological malignancies. These conditions will only be recognised reliably if a diagnostic pathway designed to sensitively detect them is applied systematically to all specimens in appropriate setting. This particularly applies to rare, low-frequency tumours
36. Finally, the assessment of prognosis is an increasing component of the workload of laboratories engaged in the diagnosis of leukaemia and lymphoma. This includes the identification of prognostic markers at the time the patient presents and the use of monitoring through therapy. This is a highly complex area involving the integration of multiple forms of investigation which should ideally be combined into a single assessment of outcome. The same considerations apply to the assessment of prognosis and response as for primary diagnosis. Clinically important decisions depend on accurate monitoring during the course of therapy.

¹¹ Graham M Mead, Sharon L Barrans, Wendi Qian et al, A prospective clinicopathological study of dose modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial), Blood, doi:10.1182/blood-2008-03-145128 <http://bloodjournal.hematologylibrary.org/content/early/2008/07/08/blood-2008-03-145128.full.pdf>

Commissioning for quality

37. In order to ensure quality service are provided, commissioners should:
- ensure that providers have the necessary size, structures, organisation, laboratories, integrated diagnostic SOP's and IT systems.
 - require Networks to audit compliance of referral patterns from clinical units to ensure that samples are being referred to the network board nominated centre,
 - commission only from Diagnostic Centres with integrated diagnostic procedures as set out in this guidance,
 - measure the proportion of diagnostic and monitoring samples referred to the specialist centre,
 - measure time from biopsy to final report from SIHMDS laboratory and time from biopsy to point of referral to SIHMDS.

Cost Effectiveness.

38. The traditional approach to the diagnosis of leukaemia and lymphoma is duplicatory and often ineffective. If there is no integrated diagnostic pathway samples are often sent to multiple laboratories specialising in individual techniques. As a matter of routine, each laboratory carries out its own series of investigations based on clinical referral information and an, as yet, unconfirmed diagnosis. The data produced may be irrelevant to the clinical problem or duplicate information produced in another laboratory. There are three key examples that illustrate this problem:
- The demonstration of genetic abnormalities. This is a central element in the diagnosis of leukaemia and lymphoma. There are many techniques available to demonstrate individual abnormalities and these are often done in different laboratories. In an integrated diagnostic laboratory the most appropriate technique for a particular clinical situation can be selected and unnecessary duplication avoided. This is particularly important in the case of metaphase cytogenetics and other very high cost techniques. In Leeds, implementation of audit data reduced the use of conventional metaphase cytogenetics by 60%. For many of these specimens there was no indication for any genetic investigation while for others, a simpler more targeted technique was used in the diagnostic pathway.
 - Reporting of Bone Marrow Specimens. It is common practice in the UK for the bone marrow aspirate, bone marrow trephine biopsy and flow cytometry to be investigated and reported separately in different departments. Each of these components is required for the final diagnosis and examining each separately is wasteful in time and resources and is clinically ineffective. It has been suggested that reporting a trephine biopsy in isolation requires up to 45 minutes of an histopathologist's time and usually results in immunocytochemical investigations (draft RCPATH workload guidelines www.rcpath.org). An additional 15mins of a consultant haematologist time would be spent separately reporting the aspirate. Reporting the trephine and aspirate together, with flow cytometry data available, reduces the time taken to an average of 15-30mins. The

availability of flow cytometry results at the time of reporting greatly reduces the need for immunocytochemistry to around 10% of cases. Even in centres with a small workload this is a very significant cost improvement.

- Investigation of Lymph Node Biopsies. Most lymph node biopsies are sent in fixative to Histopathology departments. This precludes the use of flow cytometry and compromises molecular investigations even although these tests may be available in other departments of the same institution. Flow cytometry and molecular studies considerably enhance the quality of diagnosis of nodal lymphoid malignancies by providing a tumour specific phenotype and fast and reliable detection of clonal B-cell populations. The use of modern multi-parameter flow techniques allow much more reliable definition of cellular population compared to a conventional approach based on morphology and immunocytochemistry. This approach is commonplace in other developed countries but not in the UK. As well as improved diagnosis, the reporting time is reduced because flow cytometry is carried out in parallel with the histology processing and the results are available when the tissue sections are examined. A turnaround time of 2-3 days is readily possible.
39. These three examples represent a major component of haematopathology workload and demonstrate the savings that are possible in an integrated model as opposed to separate laboratories based on individual techniques.
 40. A fundamental weakness of this traditional approach is that the onus is placed on the clinician or the MDT to bring together these disparate and sometimes highly complex pieces of information. In most cases the individuals concerned do not have the experience and competence to do this to the quality level required. This issue was raised as a matter of concern in the Carter Report¹²
 41. These problems of effectiveness can be overcome in a fully integrated laboratory and it would be expected that significant savings would also be made by eliminating duplication. However, a fully effective diagnostic integrated haematopathology service requires considerable investment in specialist staff and equipment (listed below) and this places constraints on the minimum workload that is consistent with cost-effective operation. In this context, the benchmarks for cost-effective operation should mean providing the enhanced service at unit costs equal to or less than existing services based on multiple laboratories. This is a complex calculation but is achievable where a laboratory serves a population of at least 2 million (this will be refined in the light of further economic evaluation currently being undertaken).

¹² Department of Health, Report of the review of NHS pathology services in England, Chaired by Lord Carter of Coles, An independent review for the Department of Health, 2006
http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4137607.pdf

42. The change is in setting the systems around the country so that all hospitals providing a haematological malignant clinical service are part of a diagnostic network. A centralised specialist testing also provides in-built quality assurance that is inherent in the processes of integrated testing, not just in integrating a final report. Centralised laboratories will have the critical mass to fund the capital expenditure needed for an evolving service and support the translational research that allows rapid technological implementation.
43. The clarification provided by the IOG is not about the morphology skills of haematologists (which we encourage them to maintain) but is about the proper development of an integrated diagnostic process of specialist testing which is core to the NICE guidance.
44. If there are haematologists or haemato-morphologists who have a specialist interest or a mainly Haem-Onc laboratory role they could be incorporated into the provision of services centrally and will have the advantage of being exposed to a wider range of diagnostic technologies and clinical material.

Technical and Organisational Developments

45. Diagnostic techniques and basic concepts of disease have entered a phase of rapid evolution. This has been driven by an impressive expansion in knowledge which has, in turn, been the result of very high levels of investment in research by government, charities and the commercial sector. These developments promise very significant benefits to patients. Structures within the NHS should be specifically designed to facilitate the introduction of these techniques into clinical practice.
46. In haemato-oncology the benefit to patients includes improved certainty and accuracy of diagnosis, the use of minimally invasive techniques, improved assessment of prognosis, risk stratification and the effective use of new targeted therapies. The service described in this document is particularly suited to the introduction of the new generation of diagnostic techniques through the flexible use of skilled staff and the use of structured diagnostic pathways. Where services are fragmented and uncoordinated introduction of new technologies and concepts may be very difficult, not least because of the problems of transferring staff and resource between traditional departments and institutions. This has been clearly demonstrated in the evolution of many services. Underpinning these technical changes is a need for laboratories to have a sufficient critical mass to undertake diagnostic research or translational research, service development and training of scientific and medical staff.

The Need for Accurate Data

47. The national datasets for leukaemia and lymphoma are extremely poor and this has been highlighted by Eurocare¹³ and others. Publishing data on incidence and outcome for all leukaemia and lymphoma patients (current

¹³ <http://www.eurocare.it/>

practice in the UK) is effectively meaningless and expensive. The main problems in this area are poor ascertainment because primary data reside in multiple laboratories and clinical databases and there is a lack of standardised approach to diagnosis. The ability to provide high ascertainment and detailed datasets that can be used for analysing outcome and service performance is a major benefit of network-based integrated laboratories that extend beyond the direct patient pathway (see www.hmrn.org). Ascertainment of new cases, as well as follow-up, is required to derive incidence and prevalence and outcome data and in line with the National Cancer Intelligence Network initiatives.

48. The points summarised above demonstrate the benefits of integrated laboratories with effective diagnostic pathways. These anticipated benefits are now much broader and with potentially greater impact across the whole patient pathway than was originally envisaged in the Improving Outcomes Guidance.

Key components and processes

49. The provision of an integrated diagnostic service, as set out above, is most easily achieved in a single laboratory with a full complement of specialist staff and equipment. However, it is possible, although much more difficult, to design a compliant service based around multiple laboratories each providing a component of the service. Irrespective of how the service is structured there a number of essential components as set out in the following paragraphs.

Organisation

50. This should include:
 - The service should have clearly defined organisational structures including an identified person responsible for the operation of the service, including the design of the diagnostic pathway, the use of resources and standards of reporting. The service lead should be a member of the Network Site Specific Group.
 - Managerial and financial responsibility should rest with a single Trust/organisation. A business planning process should be in place to ensure that diagnostic and therapeutic developments are co-ordinated.
 - There should be a central reception point for all specimens even if some tests are performed at a different location
 - There should be a full range of protocols covering sample handling, the diagnostic pathways, compilation of reports and relationships with users.
 - An IT system regulating the diagnostic pathway, compilation of reports and communication with users should be in place. This can be a commercially available system or one produced in-house.
 - The service should be formally accredited by CPA either as a standalone department or as part of haematology.
 - Reporting of diagnoses sub-typed by the WHO leukaemia/lymphoma classification.

51. To ensure appropriate clinical governance of this service, commissioners should expect that responsibilities of the Cancer Network Board and the Network Site Specific Groups are set out as suggested in Annexe A

Diagnostic Pathways and Technologies:

52. The diagnostic pathways and protocols that are agreed with networks form part of the network guidelines and should be accessible to users.

The key diagnostic technologies are:

- Cytomorphology
- Histology/Immunocytochemistry
- Immunophenotyping by cytometry
- Cytogenetics and FISH
- Molecular genetics - Polymerase Chain Reaction based techniques for detection of clonality, chromosomal translocations, mutations and chimerism studies

53. It is important to realise that these technologies each include a very wide range of options within each category and that many centres in the UK use methods and equipment that could be considered as obsolete (e.g. two colour flow cytometry - probably >50%). The specification of range of acceptable techniques needs to be regularly reviewed. The need for specialist staff is also a critical consideration.

54. Multiple new technologies are becoming available for routine use. These include advanced multicolour flow cytometry, gene expression profiling, whole genome copy number analysis and high throughput sequencing. These will have a substantial impact on the nature of the future services provided to patients. These technologies are capital intensive but with potential for savings in staff and recurrent costs. If implemented in centres with a high workload then there is potential to contain or reduce overall unit costs. To realise these savings, obsolete methods of investigation will need to be discarded, again emphasising the need for integrated diagnostic pathways rather than the current ad hoc approach found in many areas. Diagnostic centres need sufficient capacity to fund, develop, evaluate and implement these new technologies.

Components of the Specialist Integrated Haematological Malignancy Diagnostic Services.

55. With the recent improvements in diagnostic pathways and technologies described above the specialist integrated haematological malignancy diagnostic services (SIHMDS) should ideally comprise the following:
- There should be a single lead for the service who should be a consultant pathologist, consultant haematologist or clinical scientist with equivalent professional status.

- They should have agreed a list of responsibilities with the cancer lead clinician of the trust and should have agreed specified time for the role in their job plan with the cancer lead clinician and their relevant line manager. The responsibilities would include:
 - Scientific and Clinical Direction of the Service
 - Development of diagnostic protocols
 - Liaison with service users
 - Ensuring quality standards are met.
- There should be a single reception point for all specimens sent to the service, even if some tests are performed at a different location.
- There should be facilities and equipment for the provision of the following investigational modalities:
 - Cytomorphology
 - Histology/Immunocytochemistry
 - Immunophenotyping by flow cytometry
 - Cytogenetics/FISH
 - Molecular genetics
- The service should provide the investigations needed for the diagnosis of haematological malignancy using *systematic and integrated methodology*. The key components of this are:
 - Working to protocols agreed with the haemato-oncology NSSG.
 - The use of multiple investigational modalities to confirm a given patient's diagnosis, so that the results of one modality may be used to corroborate those of another, thus providing a degree of internal QA to the process.
 - The ability to make choices between investigations and redirect the investigational pathway if necessary during the diagnostic process, depending on results so far.
- The service should also provide the investigations needed for prognostics, minimal residual disease monitoring and follow up protocols using the same systematic, integrated principles specified above.
- There should be a quality assurance system for the investigational process consisting at least, of:
 - An audit trail showing the pathway followed by each sample.
 - Participation in all relevant and current NEQAS schemes.
- The investigation of a given case should result in a *final integrated report*, which means it should fulfil the following key requirements:
 - It should be compiled entirely within the SIHMDS.
 - It should summarise the results of all investigations performed, contain interpretative comments and a final diagnosis using the categories and terminology of the current WHO classification for haematological malignancy.
 - It should be authorised by a single pathologist, one of a group within the SIHMDS, authorised for this by the service lead.
- The report should be produced within a time limit agreed between the SIHMDS and the NSSG.
- There should be a single IT system for the SIHMDS which covers the investigational pathways, report generation, diagnostic coding and communication of results with users and which meets the following minimum specification:

- It records patients' demographics and clinical details on reception.
- It records specimen types and tracks them to the laboratories to which they have been sent and through the tests they have been sent for.
- It allows choices between tests and redirection of the pathway during the diagnostic process, depending on results so far, and can track this process.
- It can show all test results of a case on the same screen.
- Interpretative comments on and review of all results can take place on the same occasion to allow final authorisation of a report by a single pathologist.
- Authorisation of reports by designated personnel only, is made possible by password protection of the system.
- It is linked to all subsections of the SIHMDS.
- It allows users to obtain reports electronically.
- It records diagnoses using the categories and terminology of the current WHO classification of haematological malignancy.

A template service specification for an integrated haematological malignancy diagnostic service can be found in Annexe B.

Interface with Clinical Haemato-oncology.

56. The specialist diagnostic laboratory should be fully integrated with the clinical services and must be able to provide support to multi-disciplinary teams within the network. There should be clearly identifiable contacts for discussion of clinical problems and defined mechanisms for ensuring consultation with users on the organisation and performance of the service.

Training/Research and Development.

57. The institution should have sufficient resources to undertake research, technology and service development. The SIHMDS must be able to provide appropriate resources for teaching and training medical and technical staff on rotation from the host organisation and from other network hospitals.
58. Diagnostic training will be delivered in centres, as is increasingly occurring, and has the advantage of exposing the trainees to flow cytometry, cytogenetics, FISH and molecular genetics to which many were previously not exposed. As with the diagnosticians, they will also see a far greater number of specimens, a greater variety and greater exposure to the rare cases from a larger catchment population with access to increasingly specialist technologies for investigation.
59. Centralisation of laboratories for leukaemias as well as lymphomas makes best use of scarce staff and expensive technologies. Diagnosis is now rarely made on morphology alone and treatment rarely commences without the specialist tests which increasingly define the subtypes of disease and direct therapy, follow-up and MRD monitoring. It is believed that by emphasising the importance of integrated reporting and its close relationship to treatment will

strengthen the links between clinical and laboratory training and practice for the trainee haematologist.

Summary

60. Commissioners can ensure that significant quality improvements are gained by commissioning against this service model. Commissioners need to ensure that they commission correct diagnoses and pathology services that can demonstrate that diagnoses are correct by following a systematic protocol for investigation and reporting. Financial savings are also possible both from improved efficiency of the diagnostic process and from reduction in error. These financial gains are only achievable by centralised services where the effects of relatively high fixed costs are offset by a high workload and correspondingly low unit costs. Experience in several centres has shown that services can be provided by a centralised facility serving more than one network whilst maintaining a high level of integration with clinical services. This is fully consistent with the approach outlined in the Carter Report and more recently in the NHS Confederation document 'Dealing with the Downturn'¹⁴.
61. The IOG model was consulted on with the first NICE guidance 8 years ago and uncoordinated diagnostics remains a problem. Although the purpose of the document is to provide some practical advice, it is not the intention to revisit the fundamental principles underlying the original recommendations. The document is designed to clarify the original IOG as recent technological advances, increasing capital costs and the scarcity of skilled staff make it even more important that the recommendations are rapidly enacted.

¹⁴ NHS Confederation, Dealing with the downturn: the greatest ever leadership challenge for the NHS? NHS Confederation, 2009 http://www.nhsconfed.org/Publications/Documents/Dealing_with_the_downturn.pdf

Responsibilities of the Cancer Network Board on behalf of commissioners.

1. The cancer network board should agree a single named provider of specialist integrated haematological malignancy diagnostic services for the network (the SIHMDS) which fulfils the requirements specified in this guidance.
2. The agreement should specify which pathology laboratories in the network are part of the SIHMDS and which are not.
3. The agreement should specify a single named host trust as having overall managerial, operational and financial responsibility for the service.
4. The SIHMDS should cover a catchment population for the service of at least 2 million but there should be no new SIHMDS services set up as a result of this guidance, where none previously existed. In fulfilling this requirement the network may obtain this service from another network.
5. The simplest and the recommended configuration is for the whole of the service to be provided by one laboratory, but where it is agreed that more than one may contribute, then where a given laboratory is providing a certain investigational modality (*see 'components of the SIHMDS para. 5.3'*), it should be the only laboratory providing that modality for the whole service/catchment.
6. The agreement should specify the location and host organisation for each of the investigational modalities.
7. The network board should agree pathways with laboratories outside the SIHMDS to ensure that:
 - Specimens taken for a suspected diagnosis of haematological malignancy are transferred immediately to the reception point of the SIHMDS. The pathway should specify methods of sample handling and transport.
 - Specimens found to be suspicious of haematological malignancy during the course of the pathology investigation of a more general clinical problem, are transferred immediately to the reception point of the SIHMDS. The pathway should specify methods of sample handling and transport.

Responsibilities of the Network Site Specific Groups in providing clinical assurance to commissioners.

1. The Network Site Specific Groups (NSSG) should agree binding investigational protocols for the network with the SIHMDS and the MDTs which fulfil the following:
 - They should be aimed at disease categories and relevant presenting haematological clinical problems.
 - They should use multiple investigational modalities to confirm a given patient's diagnosis, so that the results of one modality may be used to corroborate those of another, thus providing a degree of internal QA to the process.
 - The option should be available to make choices between investigations and redirect the investigational pathway if necessary during the diagnostic process, depending on results so far.
 - They should include investigational protocols for prognostication, minimal residual disease monitoring and follow up using the principle of multimodality investigations where relevant.

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Template Service Specification (adapted from South West SHA specification)

OUTLINE REQUIREMENTS FOR AN INTEGRATED HAEMATOLOGICAL MALIGNANCY DIAGNOSTIC SERVICE

Objectives of an integrated haematological malignancy diagnostic service:

- Provide facilities to all haemato-oncology MDTs in one or more Cancer Network Areas for the rapid and accurate assessment of cellular morphology of blood samples in line with the quality level, outcomes and access criteria set out below;
- Provide network-wide access to accurate specialist services for immunophenotyping, molecular geneticbiology, and identification of cytogenetic abnormalities;
- Generate a single, comprehensive and electronic diagnostic report on samples;
- Achieve specified turnaround times from receipt of sample to delivery of report;
- Contribute to haematology audit, research, teaching and service development activities within the Network.

1 Quality level required

Prospective providers should demonstrate that they are able to meet the following general standards set locally. The service should be:

- Run by consultants with appropriate interest and experience in histopathology, cytomorphology, flow cytometry and cytogenetics and molecular diagnostics in haematological malignancies;
- Sited within a single facility with CPA accredited facilities
- Enrolled with the relevant National Quality Assurance schemes.
- Providing appropriate support for all the clinical MDT meetings within the Network;
- Providing a robust process of report validation including double reporting
- Have comprehensive diagnostic facilities and testing, including the following test repertoire:
 - * Cytogenetics (CG)
 - * Flow cytometry (FS)
 - * Fluorescent in-situ Hybridisation (FISH)
 - * Non-isotopic in situ hybridisation
 - * Molecular Diagnostics (MD)
 - * Standard morphology (M)
 - * Immuno-histochemistry (IH)

- * See <http://www.bcsghguidelines.com> for details on large range of investigations required
- Able to provide a web-based database and information site for all users;
- The cytogenetics and molecular genetics laboratories may be in another Network, provided they can comply with the reporting, outcomes and access standards of the networked service.

2 Research and Development Quality Level

The integrated service should:

- Play a role in teaching and training of all medical and laboratory staff in the Network;
- Support the development of clinically relevant new investigations as required by the users;
- Actively engage in the evaluation and introduction of new diagnostic techniques into routine haematological practice;
- Have flexibility and ability to adopt new technologies as and when their value has been demonstrated;
- Help support clinical and epidemiological research in the field of haematological oncology within the Network;
- Promote and participate in research and development for the benefit of patients;
- Promote and participate in audit and quality assurance;
- Promote and participate in appropriate clinical trials.

3 Access and pathways

The integrated service should involve:

- A single request form and specimen reception;
- Provision of effective systems and protocols for collecting suitable fresh tissue samples and transporting them rapidly to specialist pathology facilities;
- Use of software designed to support precise identification of haematological malignancies, which generates worksheets and instructions on an appropriate sequence of diagnostic tests;
- Following agreed diagnostic pathways for a suspected diagnosis;
- Web-based IT data base system that is able to track samples through the diagnostic pathway, allow authorisation of reports by designated personnel and users to access results, offer users information, and provide direct billing; Password security for users is essential.
- Out of hours service provision including flow cytometry and morphology interpretation between 9am and 5pm on Saturdays, Sundays and Bank Holidays.

4 Outcome Measures

Outcome measures for the integrated service include:

- Single electronic report summarising all relevant results which:
 - * is authorised by a single designated pathologist or authorised jointly by more than one designated pathologist;
 - * incorporates the results of all the pathological diagnostic investigation techniques used in that patient's case (i.e. immunophenotyping, molecular genetics, cytogenetics and histological morphology);
 - * gives an overall integrated interpretation and diagnostic opinion based on all the results;
- Appropriate turnaround time from receipt for a Lymph Node Biopsy or Bone Marrow Aspirate and Trepine according to agreed protocols;
- Alerting the relevant MDT co-ordinator of a new diagnosis of haematological malignancy within 24 hours of confirmation by means of an automatic e-mail;
- Contributing to the achievement of new and existing cancer 31 and 62 day waiting time targets.

5 Exclusions

- Some specified tests will be provided out-of-area by regional or national reference centres. It will be the role of the network provider to manage relationships with these providers to ensure agreed national and network standards are met.

Glossary of Terms

Flow cytometry (FS): A technique for the detection of specific proteins expressed by cells using monoclonal antibodies labelled with fluorescent tags. Modern techniques allow the correlation of expression of multiple proteins on tumours cells. This is a core technique in the investigation of suspected leukaemia and lymphoma and in follow up after treatment. This is carried out on suspensions of cells in a liquid sample such as blood or bone marrow. Specimens or lymph node and other tissue can also be broken down into a form that can be analysed in this way.

Fluorescent in-situ Hybridisation (FISH): A technique for detection of abnormal chromosomes using DNA probes labelled with fluorescent tags, the probes bind to specific DNA sequences and this allows detection of many of the genetic abnormalities that distinguish individual types of cancer and predict prognosis.

Non-isotopic in situ hybridisation: similar to FISH but with probes labelled using tags that can be detected by conventional light microscopes.

Molecular Diagnostics (MD): Generic term for a wide range of diagnostic techniques based on the analysis of DNA or RNA.

Standard morphology (M)/ Cytomorphology : The examination of cells stained with various dyes in smears prepared from liquid samples by conventional microscopy.

Immuno-histochemistry (IH)/ Immunocytochemistry: A technique that combines conventional histology with the detection of specific proteins and other molecules expressed by the cells. This is based on monoclonal antibody probes labelled with a coloured dye. This technique is carried out on fixed tissue sections.

Histology/Morphology: The examination of tissue sections by conventional microscopy. Typically, this involves fixation of the sample in formalin and embedding the tissue in a supporting medium such as paraffin wax. This allows thin sections of tissue to be cut from the block.

Immunophenotyping (IP): The generic term for techniques that characterise cells using labelled monoclonal antibodies- see flow cytometry and immunocytochemistry.

Cytogenetics(Cy) : Generic term of for the investigation of structural chromosomal abnormalities- see also FISH

Molecular genetics: Generic term for the investigation of genetic abnormalities by molecular diagnostic techniques.

Abbreviations

SIHMDS

Specialist integrated haematological malignancy diagnostic services

NSSG

Network Site Specific Groups

NEQAS; The main UK quality assurance scheme for laboratory services. NEQAS runs quality assurance schemes that individually assess all the main diagnostic techniques described in this paper.

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