Molecular pathology of solid tumours: some practical suggestions for translating research into clinical practice

I P M Tomlinson, M Ilyas

Abstract
“Molecular pathology” can be broadly defined as the use of genetic data, in addition to the standard pathological parameters, to optimise diagnosis and to indicate treatment and prognosis. The benefit to be gained from the exploitation of molecular techniques to provide additional information to aid patient management is potentially vast. Currently, molecular pathology is rarely used in clinical practice, although it is anticipated that it will eventually become a part of routine practice. However, incorporating molecular techniques into routine practice will not be straightforward because there are several issues to be resolved. Following on from a symposium held at the Royal College of Pathologists to discuss some of these issues, the establishment of a committee of molecular pathology is proposed to plan and coordinate the introduction of molecular pathology into routine clinical practice. (J Clin Pathol: Mol Pathol 2001;54:203–205)

Keywords: molecular pathology; routine clinical practice; molecular markers; committee of molecular pathology

The first draft sequence of the human genome was completed last year and was a major conceptual milestone in a revolution that is changing the way medicine is practised. It is universally accepted that many diseases have some genetic component that affects the way the disease is manifest, even when there are other obvious aetiological factors. Thus, polymorphic germline variants will be discovered that influence the risk of the development of disease, the response to treatment, and the prognosis. The behaviour of a tumour is predicated upon germline variants and the mutations that gave rise to that tumour. The full range of somatic mutations within tumours will be discovered and the most important mutations for tumour behaviour will be determined. The impact of this revolution will be felt keenly within the field of pathology because the work of a pathologist involves screening for disease, diagnosis of disease, and the production of data that influence management and prognosis.

Testing for germline determinants of disease is currently the responsibility of the clinical geneticist. With few exceptions, genetic testing within the National Health System (NHS) is limited to Mendelian diseases, although testing for lower penetrance variants may become more widespread as these are identified. Testing for somatic mutations is performed very rarely, although some histopathology and cytogenetics laboratories perform limited tests—for example, for specific rearrangements in lymphomas. Other non-germline molecular tests are performed—for example, on infecting microorganisms.

The current limited use of genetic data is the result, in part, of the cost of establishing molecular techniques and our comparatively poor understanding of the nature of many diseases. However, germline testing will come to include predisposition genes for complex diseases, optimisation of treatment (including pharmacogenetics), and prediction of prognosis as our understanding of complex genetic disorders increases. Similarly, the number of molecular tumour markers that can be used reliably in clinical practice is likely to increase considerably over the next 10 years as good quality studies with sufficient statistical power begin to emerge. The cost of the technologies is continually falling and will eventually become affordable to all.

For the patient with cancer, some form of integrated genetic testing is likely to be the norm. For example, although almost all cervical carcinomas are associated with human papillomavirus (HPV), not all patients who are exposed to HPV will develop cervical carcinoma. The reasons for discrepancies in the natural history of HPV infection may lie partly in the subtype of virus to which the patient is exposed. In addition, there may be inherited factors that make certain individuals susceptible to neoplastic progression after exposure to HPV. Conversely, the development of most malignancies is dependent on somatically acquired mutations. The behaviour and characteristics of the tumour depend on the mutations that led to its emergence. The response to
treatment will depend both on the mutations in the
tumour and on germline factors, such as
drug metabolism.
Although the above examples are related to
the development of neoplasia, it is likely that
every aspect of patient management will be
improved by the appropriate use of genetic
information. Thus, the identification of pa-
tients particularly at risk for disease (as
exemplified above) will improve screening
strategies; histological and cytological diagno-
sis will be refined by data that include the pat-
tern of key mutations in a tumour or the
pattern of cytokine expression in an inflamma-
tory lesion; knowledge of the genetic basis of a
disease will in turn allow more specific
targeting of treatment to the cause rather than
the symptoms of the disease; and genetic
data will allow improved prognostication and
will be used to monitor the efficacy of
treatment and monitor disease recurrence.
Once it is accepted that genetic information
will improve patient management, the medical
profession has an obligation to try to obtain
that information. This then raises two key
questions:
(1) How to ascertain which of the data are
going to be of value?
(2) How to distribute and perform the extra
work that is generated?
These points were debated with some vigour
at a symposium of the Royal College of
Pathologists held on 24 February 2000 and
entitled “The molecular genetics of solid
tumours: translating research into clinical
practice”.

Findings of the symposium
Speakers presented talks of three types: (1)
molecular methodology; (2) examples of mo-
lecular markers of tumour behaviour in re-
search; and (3) mechanisms of undertaking
molecular testing of tumours in practice.
The speakers reached a broad consensus as
follows:
(1) Methods for molecular testing of tumours
are well established.
(2) Equipment for molecular testing exists in
NHS genetics laboratories, but some invest-
ment in new equipment may be necessary.
(3) A major step in successful molecular testing
of tumours will be obtaining and preparing
tumour samples; the mindsets of both clini-
cians and pathologists need to be changed to
allow the collection of such material.
(4) Fresh frozen tumour samples are preferable
to archival samples as long as the origin of the
former can be determined.
(5) Molecular testing of tumours is likely to be
of limited use in the near future, but of consid-
erable use in the medium/long term, for which
planning should start now.
(6) For all genes, molecular testing should be
assessed against alternative techniques, such as
immunohistochemistry.
(7) Molecular testing should be regarded as a
means of complementing rather than replacing
current methods.
(8) A means must be found of integrating the
expertise of histopathology, haematology, and

genetics laboratories in the NHS (for example,
to provide rational treatment based on a
patient’s own genotype and that of his/her
tumour).
The focus of the meeting was the role of
molecular pathology in neoplastic disease,
although it was generally acknowledged that
the role of molecular pathology will extend
beyond that. It was proposed that a committee
for molecular pathology be established by the
Royal College of Pathologists to investigate the
two questions raised above and the various
issues arising from the meeting.

Details of the proposed committee for
molecular pathology

AIMS
The aim of the committee would be: (1) to
provide a framework for the introduction of
molecular diagnosis into routine medical prac-
tice and (2) to provide guidelines for the estab-
lishment of national standards in molecular
diagnosis.

TERMS OF REFERENCE
Guidelines on the use of molecular markers
One of the concerns expressed at the meeting
was that, apart from screening for a small
number of diseases, and the use of gene
rearrangement studies in haematological
malignancies, genetic information has thus far
offered little in the way of disease diagnosis and
patient management. Many diagnostic and
prognostic markers have not proved to add
more to histological diagnosis and careful stag-
ing. There is a risk that technology will be used
simply because it is available. The committee
will look into mechanisms of providing guide-
lines on the use of molecular data. One
possibility is the establishment of a pathology
equivalent of the National Institute of Clinical
Excellence (NICE), which will be responsible
for assessing published data and recommend-
ing optimal use of molecular resources. The
committee will look into the potential structure
and remit of such a body, and will liaise with
other appropriate bodies (for example, the
Clinical Molecular Genetics Society).

Location of work using combined expertise of
different laboratory services
The impact of molecular diagnosis will be felt in
all specialties. It is wholly impractical, given the
scarcity of resources, that each department will
develop its own diagnostic unit. Sharing of
expertise and resources is much more appropri-
ate and the committee will look into models
whereby this could occur. Because the require-
ments of departments will differ, the committee
will assess how such units would be structured,
to provide as broad a range of technologies as
possible, and the methods of quality assurance
with regard to each of the techniques. The com-
mittee will also look into the funding and
administration of such units given the multiplicit-
y of potential users. Discussions would be held
with appropriate college representatives from
the disciplines involved (histopathology, molecular genetics, cytogenetics, haematology, biochemistry) and external bodies (such as clinical pharmacologists).

Postgraduate training
Although training in molecular biology is an integral part of the training of laboratory geneticists, there is no training requirement for this in the other branches of pathology. The committee will look into the desirability of integrating some training in molecular biology in the various pathology disciplines.

Facilitating research
Another concern raised at the meeting was the shortage of high quality material for conducting research studies. In addition, the small size of many studies lowers the overall quality of data. It is proposed that the remit of the committee will be broad enough to look into ways of facilitating research studies through the exchange of materials and the establishment of multicentre collaborative studies under the auspices of the college.
Molecular pathology of solid tumours: some practical suggestions for translating research into clinical practice

I P M Tomlinson and M Ilyas

Mol Path 2001 54: 203-205
doi: 10.1136/mp.54.4.203

Updated information and services can be found at:
http://mp.bmj.com/content/54/4/203

These include:

References
This article cites 9 articles, 1 of which you can access for free at:
http://mp.bmj.com/content/54/4/203#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/