10 *Advances in laboratory medicine*

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Introduction

Advances in laboratory medicine are happening at an uneven rate. On the one hand there has been a rapid expansion in innovative rapid molecular diagnostic techniques, but on the other hand translation into clinical impact has often been slow. Pathology services in many parts of Europe are undergoing modernization and reform but in some places this can be slow and patchy.

In this chapter, the terms pathology and laboratory medicine are used as synonyms to indicate cellular pathology, microbiology, virology, chemical pathology, immunology and haematology, molecular pathology, genetics and histocompatibility, and other laboratory-based medical specialties. As important as it is diverse, pathology is poised to become a key medical specialty, central to the development of stratified

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and personalized medicine, but it needs to overcome several challenges, not least the huge increase in complexity of tests, demand for digital data, the expectation of ever-reducing test costs, and shortages of trained staff. These issues as they impact upon European pathology are outlined with some specific national case studies.

The points below illustrate some of the emerging trends:

- **An unprecedented velocity of technological advance.** Pathology services will continue to lead the transformation of medical care through, for example, genomics, proteomics, tandem mass spectrometry, and microarrays. These advances will have significant impact not only in the delivery of diagnostic and therapeutic services, but also in the workflow and ethos of patient care. Advances in technology, however, come at increased costs to organizations and health care consumers.
- **Self-testing and near-patient testing will proliferate.** In parallel with advances in large-scale technology within laboratories there will be a proliferation in self-testing and single use devices to perform pathology tests outside the laboratory. The accuracy and reliability of these devices need to be vigorously examined, and capturing and storing the data generated by these devices might be problematic. There is a need to coordinate results from self-testing and point-of-care devices with the results from formal laboratories. The increased use of "wearable IT" with a health care purpose will raise expectations for seamless transmission of information to and from patients, and primary and secondary care providers, including pathologists. However, these devices, part of the "Internet of things", raise concerns about data security, including both unauthorized access and commercial exploitation by software providers. Resolution of the confidentiality, privacy and security concerns will be led by patient or consumer demand.
- **Increasing collaboration and partnership is key.** Greater interdisciplinary contact within medical specialties and subspecialties and between organizations is an inevitable consequence of the requirement to ensure high quality. For example, an integrated diagnostic service between pathologists and radiologists could speed up diagnoses, increase accuracy, and improve patient outcomes. Ensuring that pathology services are adjacent to clinical teams will be important to minimize risks to patients, but there is a need to understand better the options for remote working arising from videoconferencing and telepathology so that the right balance is

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achieved between clinical adjacencies, reducing unnecessary specimen transport, and achieving economies of scale.

- **Digital pathology is a disruptive technology.** This development has great potential to make pathologists' working lives more efficient, facilitate intra- and inter-departmental consultations, improve the efficiency and documentation of research, and enhance education and training. However, the adoption of digital pathology requires resolution of some longstanding issues. The time taken to scan slides, the significant storage required for the images, the capital cost of slide scanners and the variable costs associated with storage space, and sufficient data security will all need to be addressed as a priority.
- **The laboratory is a translational environment.** For example, as clinical genomics moves from research to a routine diagnostic, prognostic and predictive method, this presents numerous challenges in terms of sample processing, quality control, and service developments in management and reporting. The knowledge base of pathologists trained and experienced in traditional methods will be tested by the need to provide and interpret the new reports. It is difficult for established pathologists, mostly based in traditional laboratories that do not provide the new tests, to add interpretation of these new tests to their repertoire. This may well require a new approach to learning which can integrate knowledge of clinical genomics into everyday practice. The implementation of new technologies tends to follow the Gartner Hype Cycle (Figure 10.1).

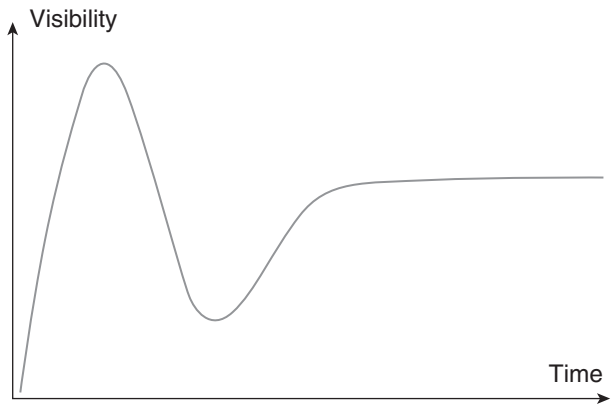

Figure 10.1 Gartner Hype Cycle

Source: Gartner, 2015

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What do these advances mean for the role of the hospital in the future?

Laboratory medicine is the bridge between analysis and interpretation of clinical data and care delivery. Pathologists order, conduct, and interpret the results of hundreds of individual tests to support clinical decisions that enable good patient care. The laboratory's role as a centre of diagnostics within the hospital of the future, however, may need to be redefined in the light of pressures for cost efficiencies, greater effectiveness and improved performance, and the impact of emerging technologies.

A common theme in European pathology is the quest for greater efficiency. In this respect, laboratories have looked towards increased automation to improve productivity and meet increased demand. Automation of the laboratory can lead to better task integration and quicker turnaround times. The argument follows that patients benefit as quicker clinical decisions can be made with the potential to shorten hospital stays.

Across Europe the modern laboratory environment is increasingly being organized to create networks based on large consolidated centres (hubs) and smaller local testing centres (spokes). A key driver for service reconfiguration has been cost pressures. In some countries laboratories face a bleak ultimatum: restructure or lose all your work. The key question, as Lord Carter put it in his Review of NHS Pathology Services in England (Carter et al., 2008), "What is the right level of consolidation?"

Another driver for change is the desire to reduce variation of diagnostic tests across countries both in test investigation costs and the over/under-requesting of tests. The United Kingdom Atlas of Variation, for example, shows that cancer patients who received an early-stage diagnosis – a critical factor in treatment outcome – ranged from 22.7% to 60.8% between the United Kingdom's best- and worst-performing areas (Public Health England, 2015).

Major advances in diagnostic laboratory medicine may be disruptive, as technical advances have the potential to provide a more efficient and cost-effective pathology service. For example, molecular diagnostic technologies are being utilized in a wide range of medical specialties including genetics, infectious disease, oncology and haematology. Their advantages have been well documented and allow for the simultaneous sequencing of many millions of individual DNA molecules. Using this technology, pathologists and researchers are provided with increased

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sensitivity and specificity for the detection of abnormal DNA in solid tissues and body fluids, as well as a wide range of metabolites and signalling molecules and immune system responses to drug therapies. Technological innovation in pathology appears to be accelerating the paradigm shift to precision or stratified medicine, an approach that takes into account individual variability in genes, environment, and lifestyle for each person.

A plethora of other technological advances are impacting on the pathology laboratory, including liquid and gas chromatography and plasma mass spectrometry, conventional and next-generation sequencing, point-of-care testing (POCT) and "lab-on-chip" devices prompted by miniaturization of molecular assay steps, biochips and microfluidics, and digital pathology systems which allow the scanning, imaging, and storage of histological slide data for analysis by pathologists.

The adoption of these emerging technologies across Europe, however, is varied and this is a fundamental challenge for pathology. The impact of new technologies on the hospital in the future will be difficult to predict but tough to ignore in terms of investment decisions. Technology has provided pathology with a unifying narrative and the vision of the laboratory as an aggregate of preventative, diagnostic, predictive, prognostic, and interpretative roles will become key to the development of the future hospital.

Some of the reasons for varied adoption or "technology diffusion" include: length of time the technology has been available; a hospital's culture of embracing innovation (e.g. a large teaching hospital may find it easier to adopt new technologies because a translational research culture pervades); at national level there could be incentives and a supportive infrastructure to speed up the rate of adoption – or conversely nothing at all; it could be that some hospitals are simply better at measuring the impact of technology adoption in terms of patient health outcomes; in the case of POCT diagnostics, it is often the case that costs are accrued in a different area from the gains. The Review on Antimicrobial Resistance (2015) provides an example where a primary care facility may invest in a diagnostic device that could reduce the number of hospital admissions. While this is desirable, the costs saved are not only hard to quantify, but the money saved might not be passed on to the facility even though it has paid for the test.

Pathology departments are increasingly presented with opportunities to form translational research networks within hospitals, universities and

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biomedical research centres, and with industry. Several laboratories do not have the organizational resilience to translate research technologies to a clinical environment. In turn, this may prompt the need for new workforce capabilities aligned to the most desired patient outcomes within each European country.

As an endpoint, there is growing evidence to support the emergence of "population health systems" as a means of meeting future health care needs. A population health system is defined by the American-based Institute for Healthcare Improvement (2015) as a framework for improving patient experience, improving the health of populations, and reducing the costs of health care. Approaches to population health have long been enshrined in many tax-financed health care systems, forming the basis of the purchaser/provider split in the United Kingdom, Italy and some other countries since the 1990s, and in Scandinavian countries where health care is organized by local government, but are now gaining increased traction in other parts of Europe, as identified by the United Kingdom King's Fund (Alderwick, Ham & Buck, 2015). The Kaiser Permanente model in America is often seen as a prime innovator in this regard. Making the shift towards effective population health commissioning will require collaboration across a range of sectors and wider communities and may intensify further change for the pathology laboratory in the hospital of the future.

Box 10.1 Case Study – Genomics England and the 100 000 Genomes Project

Context

- Whole genome sequencing technology is sufficiently advanced to rapidly provide vast amounts of information on the nature of diseases and predisposing factors.
- The technology is likely to impact on the delivery of a wide range of health care services, from inherited diseases, through infections, to cancer.

Challenges

- By 2017 to sequence 100 000 genomes from NHS patients with rare diseases (and their families) and those with cancer.
- To link genome sequences with high quality clinical and pathological information.

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Box 10.1 (cont.)

- To accelerate the availability and uptake of advanced genomic practice into the NHS through better diagnostics, devices, and treatments.
- To improve public understanding and support for genomic medicine.

Responses

- Genomics England Limited created to drive the project, to inform training, and to develop partnerships with industry.
- Eleven Genomics Medicine Centres created in 2014/15 with the remit to deliver against a specification and under strict performance management.

Achievements to date

- Detailed protocols with research standards for the identification and recruitment of patients and families, sample collection and processing, and the validation of results and feedback of information to participants.
- NHS Genomic Medicine Centres have developed local partnerships with the public, patients, and a range of local NHS organizations and universities.
- Laboratory processes underpinned by an external quality assurance scheme.
- The information technology required to support this complex process has been developed and implemented locally so that data collection is efficient and comprehensive. Data are transmitted securely to a central data hub.
- Recruitment of patients and families to the rare diseases pathway started in April 2015.
- Recruitment of patients to the cancer pathway began in September 2015.
- Genomics England Clinical Interpretation Partnerships have been created as topic-specific groups of clinicians and researchers from universities and the NHS to analyse the data from the project. These will be integral to helping front-line clinicians and pathologists formulate the genomic data useful for managing patients in the context of personalized medicine.

Source: Written by Tim Helliwell with information from Genomics England, 2015

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Where does pathology sit within wider hospital activity?

Pathology is the largest diagnostic service in hospitals as measured by the number of requests it responds to annually, in expenditure, and in the proportion of clinical decisions it affects. For example, in the United Kingdom over 50% of biochemical tests are related to chronic disease management and pathology is involved in 70% of all diagnoses made in the NHS (Right Care, 2011). Pathology is part of the clinical governance of public hospitals and the wider health system, playing an important role in monitoring and managing disease, infectious agents, and public health.

The development of subspecialties in pathology is well developed to meet the needs of patients: cytopathology, dermatopathology, chemical pathology, haematology, medical microbiology, virology, endocrine pathology, forensic pathology, immunology, cytogenetics, blood transfusion, neuropathology, ophthalmic pathology, to name but a few. However, these subspecialties are not uniform across Europe.

Depending on the urgency of tests, pathology investigations can take place in what are often termed "hot" or "cold" laboratories. Hot laboratories process pathology tests requiring a fast turnaround and clinical support. Cold laboratories process less-urgent high volumes of routine tests. Because there is less urgency to receive the results of these tests, cold laboratories can be located further away from the patient. As the technical complexity of test methods increases, so does the complexity of reporting.

Pathology services are closely integrated with other clinical services, to support patient care by providing information and expertise to facilitate diagnosis and treatment decision-making. This is particularly true with cancer, a disease process whose complexity is increasingly recognized, with a detailed understanding of the pathological characteristics essential for targeted treatment. The complex pathway undertaken by what might appear superficially to be the simple process of taking a tissue biopsy is set out graphically in an illustrated web page: http://www.journeyofatissuebiopsy.com

Adjacency to clinical teams is important if pathology is to be integrated as a valued "companion diagnostic" and to move away from having a passive service role to taking on an active one. Adjacency to molecular diagnostic centres will also become important in order to benefit from genomic (gene expression), proteomic (protein expression)

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and metabolomic (metabolite profile) data and to hasten the shift to personalized medicine.

Pathologists are core members of MDTs and provide essential inputs for patient management. Laboratories are used to working across primary and secondary care organizations and will often serve several secondary and tertiary care providers. Providers of pathology services in public hospitals also play a leading role in the education and training of pathologists, clinical scientists and researchers. They are increasingly required to provide specialist input for translational research including involvement with clinical trials and evaluation of new technologies.

The wider and extended role of pathology is demonstrated by the range of other clinical services provided, which includes:

- specialist information and advice to health care professionals in primary and secondary care as well as public health
- mandatory surveillance of disease
- infection prevention and control
- guidance and advice, quality assurance and support for POCT in a range of hospital settings (e.g. outpatient clinics)
- specialist advice on blood transfusion
- mortuary services, including post-mortem examinations.

Box 10.2 Case Study – a national framework for quality assurance in cellular pathology

The Irish National Cancer Control Programme

Context

- Irish population = 4.5 million.
- 23 000 new cases of cancer annually.
- 7500 cancer-related deaths annually.

Challenges

- Projected doubling of new cases by 2020.
- High-profile cancer misdiagnosis cases in 2007 and 2008.
- National histopathology workload increasing each year.

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Box 10.2 (cont.)

- No formal measures to assure the public that pathologists practise to the highest international standards.
- No national standards or benchmarks for key aspects of diagnostic service.

Responses

- Development of a National Quality Improvement Programme within each Irish pathology department to review performance routinely and drive improvement against intelligent targets.
- Programme initiated in 2008 with strong collaborative commitment from Irish Health Service Executive Quality Improvement, Service Management and Information and Communication Technology Divisions, National Cancer Control Programme, Independent Hospitals Association of Ireland, Department of Health and Faculty of Pathology, Royal College of Physicians of Ireland.

Achievements to date

- A unique national programme across: 27 public and 7 private laboratories; 8 different laboratory information systems; and small and large hospitals with different levels of resourcing.
- Robust clinical governance including monitoring and key indicator reviews.
- Development of a central repository National Quality Assurance Intelligence System for Histopathology.
- Collection of national data for histopathology which has never before collected on this scale.
- Confidence in the data to understand in real time workload and extent of quality activities.
- Ability to set national targets based on accurate and locally owned data.

Source: Swan, 2015

How does pathology link with services located outside the hospital?

The interface between pathology and services located outside the hospital is well established but may not be well understood. The health

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care services based outside hospitals are described as primary and community care sectors, which lie between self-care and hospital care. Hospital pathology has a long history of working with outside services (i.e. primary care doctor practices and health clinics).

In Europe primary care differs considerably and several categories of organization exist. Meads (2009) provides a valuable typology of primary care organizations in Europe. To add to the complexity, European countries will have different arrangements for registration with a primary care doctor or GP. This may be financially encouraged, compulsory, voluntary or free.

Pathology is a touch point across the patient's lifecycle from pre-natal to post-mortem. The diagram below illustrates where pathology sits regarding screening, diagnostic, and monitoring functions.

Laboratories are often located in or near hospitals to meet demand for a 24/7 service. Many hospital departments are highly pathology-dependent and need to respond rapidly to the clinical needs of busy emergency medicine departments and intensive care units. This means that extensive networks of transport, IT and management links between laboratories have evolved outside the hospital to provide quick turn-around times for tests and equitable access to services over defined geographical areas.

There is also the wider reach of pathology services and diagnostic products into local populations. "Smart pathology" is emerging in the

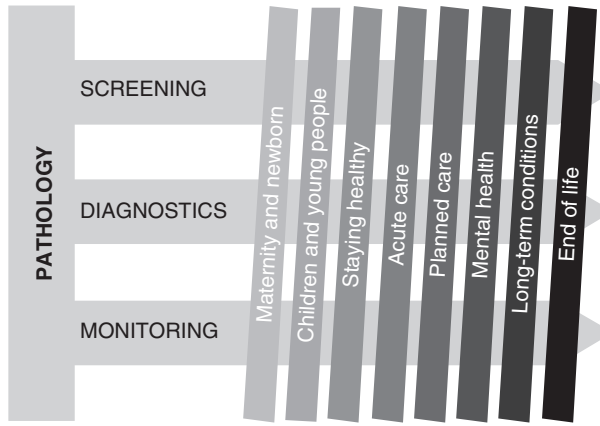

Figure 10.2 Pathology touch points

Source: NHS England National Pathology Programme, 2014

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form of new-generation POCT devices. The availability and use of these have steadily increased in Europe. They have been used in primary care, diabetic and sexual health clinics, and care homes for over 40 years, but are now being assimilated into high street retail outlets as well as the home. The rapid test turnaround time provided by POCT potentially allows for accelerated identification and classification of patients into high-risk and low-risk groups (Larsson, Greig-Pylypczuk & Huisman, 2015). There are, however, regulatory and quality assurance challenges which need to be overcome. The proliferation of so many additional users and devices in operation make the maintenance of acceptable quality levels problematic (St John & Price, 2014).

The future relationship between hospital pathology and primary care needs to be shaped by value expectations and whether value of service can be demonstrated through improved patient outcomes and managed costs. Insights could also be gleaned as to how a laboratory could better manage demand on its services and how this might benefit the local health community. Some examples could include the use of data for comparing testing rates to emergency admissions, number of tests requested, length of hospital stay, and cost of emergency readmissions for relevant conditions.

An example of this type of work was the INvestigation of ThE Root Causes of Excessive RepliCatE Pathology Testing (INTERCEPT) study, which involved over 115 000 patients from North Staffordshire, England, and aimed to reduce the burden of unnecessary pathology requesting. It used HbA1c testing (a test for monitoring blood sugar control in people with diabetes) as a model by assessing adherence to national guidelines and recommendations for retesting intervals. Results from the study found over half of key blood test requests from doctors for patients with diabetes were inappropriate and that guidance on monitoring diabetes patients was not being followed by the majority of primary care and hospital doctors. Further work by this research team found major incentives to establish systems that provided timely HbA1c tests in terms of fewer diabetes-related emergency admissions per 1000 patients, fewer hospital bed days, and reduced costs of emergency admissions for diabetes-related illnesses (Driskell et al., 2012).

The key message for health commissioners and policy-makers is that primary care engagement with pathology professionals and wider use of this type of data can change requesting behaviour and produce better patient outcomes.

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The pathology workforce

Pathology is a combination of medically trained pathologists, clinical scientists and biomedical scientists together with essential support from staff occupying a wide range of laboratory roles. Each European country uses different pathology specialty taxonomies. The European Union of Medical Specialists identifies 43 specialist sections, with the sections relevant to pathology including clinical genetics, infectious diseases, laboratory medicine, medical biopathology, medical microbiology, and pathology. The workforce is therefore extensive and heterogeneous in its composition.

Across Europe demand for diagnostic services continues to rise year on year both in terms of the number of samples and the increasing complexity of test requests. This puts considerable pressure on the workforce as the emergence of new tests steadily drives up case volume. Europe's ageing population and the increased incidence of cancer, chronic diseases, and other co-morbidities continue to add pressure.

Advances made in molecular-based diagnostics offer new approaches and the number of variants generated that have as yet unknown medical significance will require clinical interpretative support. Since the time of Hippocrates all medicine has been "personalized" at the point of diagnosis and treatment, but genomics and molecular-based diagnostics bring the potential for personalized prevention strategies based on the inherent likelihood of future disease for each individual. Also these new technologies will require the monitoring of the effects of ever more complex individually tailored drug treatments. Technologies that are part of molecular diagnostics are far reaching and rapidly being developed for genetic testing, infectious diseases testing, blood screening, oncology testing, cardiovascular testing, and others. Continued growth is expected. It is anticipated that a constant stream of test kits for the newest molecular targets will become commercially available requiring pathology staff to expand their understanding of these techniques to provide the services and interpret the results. Far from being replaced by new technology, it seems likely that demand for most "traditional" pathology tests will increase due to increased uptake of molecular-based diagnostics. This must be borne in mind when considering workforce requirements.

Pathologists now perform complex investigations to determine the phenotype, prognosis and likely response to treatment of a variety of diseases. The potential clinical significance of these data frequently cannot be encompassed in simple reports but require detailed interpretation and

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simultaneous communication to clinicians and to patients in order that appropriate management strategies might be formulated, agreed, and reviewed as response to treatment becomes apparent. There will be a need for pathologists to provide more interpretative and advisory services directly to patients as they obtain the right to access their own results directly. Pathologists increasingly find themselves making significant and important contributions as to how diagnostic testing can improve the whole patient pathway. This may include guidance, explanation, and interpretation provided to other health care professionals less able to deal with the complexity of modern diagnostic medicine.

Chemical pathologists, as a direct consequence of the increasing prevalence of diabetes, obesity, and lipid disorders, are pivotally involved in the provision of direct specialist patient care. This will inevitably lead to more involvement in community provision of pathology services and the support of patients to reduce morbidity. As microbiologists, haematologists, and biochemists become more clinically involved in providing direct patient-facing care, they have less time available to provide traditional laboratory oversight. The oversight of laboratory services is intrinsically linked to the quality of the service provided and to patient outcomes and so the importance of external quality assurance monitoring will increase.

The increasing use and dependency on POCT will continue to expand, not just in primary and secondary care, but also in the high street and in patients' homes. There will be vital input required from pathology professionals to ensure that the technical aspects of such POCT is carried out to an adequate quality-assured standard in the correct clinical context.

Pathologists make significant contributions to research, both directly via their own research activity, but also by providing essential and important collaboration and diagnostic support to many other studies and trials. However, a worrying trend in some European countries is the demise of clinical research roles in pathology.

Scientific and medical staffing levels in pathology services are declining in most countries and a detailed analysis of the workforce crisis in the United Kingdom in relation to cancer services is highlighted in a Nuffield Trust report (Imison, Castle-Clarke & Watson, 2016) and in a Cancer Research UK review (Bainbridge et al., 2016). One possible solution is improved training and broader roles for scientific staff traditionally not involved in detailed microscopic cancer diagnosis, as illustrated in the case study in Box 10.3.

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Box 10.3 Case Study – extending the roles of scientists in cellular pathology

Biomedical Scientist Histopathology Reporting Pilot in the United Kingdom

Context.

- Clinical scientists are an accepted facet of clinical provision in some pathology disciplines.
- In 2011 the NHS Information Centre found only 17 consultant clinical scientists in cytology and histopathology in the United Kingdom.
- Some extended roles for scientists already exist in cytology, macroscopic dissection, and molecular pathology.
- There is no formal clinical scientist training programme in cellular pathology.

Challenges

- Projected increase in new cases of cancer.
- Increased quality-assurance scrutiny and national key performance indicators.
- Inability to fill consultant vacancies in many parts of the country.
- Large backlogs of patients' biopsies and resections awaiting reporting or being outsourced.
- Career opportunities limited for scientists in cellular pathology.
- Predicted reduction in demand for cervical cytology as a primary screening modality.

Responses

- Development of an RCPath-led nationwide pilot of new ways of working in cellular pathology.
- Participants trained to report cellular pathology in clinical context.
- High volume, low complexity and low litigation areas of practice initially chosen to prove concept.
- Pilot participants recruited in 2012, 2013 and 2014.
- Curriculum and assessment tools developed with RCPath approval and strong collaboration with the Institute of Biomedical Scientists.

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Box 10.3 (cont.)

Achievements to date

- An innovative national training programme across 37 NHS hospitals.
- Robust educational standards and clinical assessments.
- New Conjoint Board established with the Institute of Biomedical Science to move the pilot onto a permanent footing.

For the future hospital

- Expansion of areas of reporting practice planned with the introduction of new curricula and training programmes.
- Expansion of the recruitment into cellular pathology reporting to wider health care scientist population.
- Formal clinical scientist training programme in cellular pathology.

Source: Liebmann et al., 2015

Barriers to optimal pathology services

Barriers impeding the delivery of an efficient and effective pathology service include those related to service configuration, demand management, workforce, finance, quality, attitude, IT, and innovation adoption. These are discussed in turn.

Service configuration barriers

In some European countries there are too many laboratories carrying out specialist tests on too small a scale. Reconfiguration can be seen as a way to optimize pathology and to attain economies. However, consolidation, such as joint ventures and mergers, must be compliant with national and European competition law, which can constrain reorganization, as well as the undesirability of creating commercial monopolies that can lead to higher costs, worse performance, and reduced innovation.

The impetus for transformation can be slowed or blocked because pathology is not high enough on hospitals' priority lists. Many hospitals are evaluating options to develop new models of care within social,

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community, primary, and secondary care and this may push pathology modernization further down the chain of importance.

Demand management barriers

Most laboratories across Europe have experienced significant increases in workload year on year and the capacity of a service to manage demand is stretched, especially without a commensurate rise in staffing levels. Workload, measured in terms of crude sample numbers or test requests, is increasing and this probably belies actual workload because greater sophistication of diagnosis is now needed.

For example, increasing numbers of cases now require consensus reporting and referral for specialist opinion, demonstrating increasing sophistication of diagnostic processes and an increasingly risk-averse culture. Equally, more objective assessments are now required, whether it is a lead to provide reproducible assessments that determine patient treatment (e.g. quantitative immuno-histo-chemistry results which act as a threshold for breast cancer oncotherapy).

Where pathology is excluded from strategic planning processes and investment decisions, there is a risk that there will be unexpected, unplanned, and unfunded demands on those pathology services in the future.

Increased expectations will contribute to demand pressures in the following areas: providing ongoing clinical advice to doctors in training and primary care doctors, direct interpretative and advisory liaison work with patients who can access their test results directly, and provision of direct specialist outpatient care in diabetes, obesity, lipid disorders, and metabolic diseases.

Medical microbiology has seen an increased requirement for ward-based consultation with patients with suspected or proven infection, as a means to facilitate earlier discharge from hospital. Increasing antimicrobial resistance has placed greater emphasis on antimicrobial stewardship, with pathologists working alongside pharmacists specializing in antimicrobials.

There is a need for payment systems to take account of these rapid changes, with regular revisions that recognize new ways of delivering care. The regular reviews of the system for paying providers in Germany offers such an example.

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Workforce barriers

Wider training issues, such as the trend in some countries to expand general medical training before specialization, could lead to a shorter time for pathologists to acquire specialist competencies. Recruitment to particular pathology specialties has been problematic. Outsourcing tests or using locum staff may alleviate workload but this only represents a short-term and expensive solution. There is uncertain capability to undertake some emerging techniques and technologies. The ability of pathologists, for example, to understand the disease phenotype (the detailed characteristics of the patient) is essential for interpretation of the current explosion in "-omics" data, i.e. genomics, proteomics, metabolomics, and transcriptomics.

Financial barriers

Traditionally, diagnostic tests in pathology have seemed cheaper than, for example, the costs of imaging. However, with many pathology services increasing their repertoire to include molecular testing, costs are increasing. A test costing €1000 could be perceived as being expensive but this has to be seen in context, such as whether the test is used to determine the use of a drug treatment which may cost more than 10 times as much. Unfortunately there can be a focus on the unit cost of pathology rather than looking more holistically at the "downstream" value for money that pathology contributes to the whole health care economy.

Establishing a transparent tariff for pathology tests could be beneficial, as is the case in many countries, such as Germany. Having tariff transparency would enable business cases for service transformation to be built up more easily.

Quality barriers

Many pre- and post-laboratory processes remain outside laboratory control, even though they impact significantly on the value of the service. End-to-end quality depends on others (e.g. requesting clinicians) over whom pathology has less control. The quality of the clinical pathology service will be impacted where there are areas of differential influence and control.

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Appropriate ordering and commissioning of relevant laboratory tests and having timely access to the tests and test results are central to the provision of quality care for patients and patient flows through the hospital system. There is considerable variability in awareness and understanding, which leads to suboptimal and inappropriate use.

ISO 15189 accreditation may have value in assessment of laboratory quality management systems but is highly expensive to maintain and is entirely focused on processes within the laboratory and not on the end-to-end pathology contribution to health care.

Attitudinal barriers

Van Krieken, President of the European Society of Pathology, identified a lack of collaboration between pathologists and other stakeholders such as the pharmaceutical sector. His idea is to move towards a system in which tests and drugs are integrated, so that payment for a drug includes all necessary testing (van Krieken, 2015).

It is frequently observed that pathologists themselves need to take on more of a clinical leadership role and move out of the shadows. Risk-averse over-requesting of tests can prevail due to perceived threats of medico-legal liability and a monetary incentive may exist for over-requesting in some systems.

If testing is perceived as a cost-free service as far as requestors are concerned, there is little incentive to avoid waste and duplication. The most effective method of managing demand and promoting new technology is to ensure appropriate recovery of cost to the laboratory budget from other clinical budgets.

IT barriers

Within many European countries a wide range of IT systems are in use and this creates problems of interoperability between service users and pathology. In radiology the Digital Imaging and Communications in Medicine (DICOM) standard has achieved a near-universal level of acceptance among medical imaging equipment vendors and health care IT organizations but such a standard does not yet exist in pathology.

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The lack of end-to-end IT connectivity in pathology limits the opportunity to achieve effective communications between laboratories and those ordering tests, as well as decision support, both of which minimize inappropriate or unnecessary repeat testing. There is a widely held perception that results data are not being fully leveraged by pathology service users and providers, and this is a key obstacle to cost and service improvement.

Innovation adoption barriers

At a national level delays in approval processes can constrain innovation. At a local level many test sites will be required by ISO 15189 to perform their own evaluation of a new test and duplicate many of the assurances already fulfilled by the test developer.

Aggressive national pathology cost saving plans may discourage adoption of new techniques. A complex cost–benefit relationship often underpins decisions to use new devices. Point-of-care devices are a good illustration and highlight how costs and benefits are often accrued in different areas. A primary care group may have funded a diagnostic device and reduced the need for patient hospital visits but may not receive the benefit of saving money for the health system because of opaque reimbursement mechanisms.

Investment in innovation for some pathology specialties has been limited. For example, many drug companies have no commercial interest in the development of rapid diagnostics for determining antibiotic sensitivity because of low commercial returns. The uptake and adoption of diagnostic tests across Europe shows significant variation. For example, C-reactive protein (CRP) tests have been used for some time in the Netherlands and Scandinavia to indicate whether an infection is bacterial or viral, and these countries have some of the lowest rates of prescribing antibiotics in Europe (Review on Antimicrobial Resistance, 2015).

In recent years there has been growing interest in using more accurate, efficient and reliable technologies such as mass spectrometry. Despite the important scientific advantages of such technologies, many clinical diagnostics services have continued to use traditional immunoassays, facing barriers such as the need for investment and expertise in mass spectrometry.

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The future of pathology

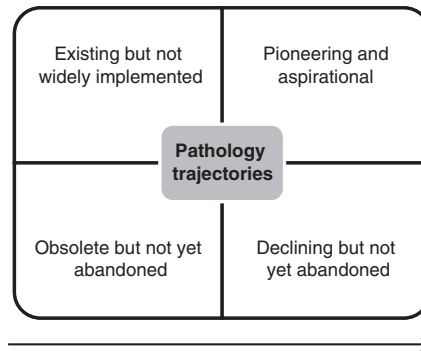

Figure 10.3 Quadrant highlighting pathology trajectories

Source: Authors' compilation

Obsolete but not yet abandoned

Obsolete ways of working include: laboratory standard operating procedures existing in isolation from patient pathways, single-handed pathologists, and old methods and out-of-date technologies.

Declining but not yet abandoned

Some aspects of hospital laboratory medicine are in decline but have not yet been abandoned. In some instances this is because there is a hope that the importance of these activities will be recognized. Notably, research capacity in pathology is in a steady decline and academic pathology is small scale and disjointed in all but a few major teaching centres where huge efforts are being made to keep up this aspect of the service.

In the United Kingdom there was such widespread concern about the loss of research capacity in 2015 that the National Cancer Research Institute, together with the ECMC Pathology Network Group, funded the Cellular Molecular Pathology initiative (CM-Path) – a five-year project which was awarded £635k. It aims to reinvigorate pathology research by building the change needed to support academic cellular molecular pathology. A report on the Experimental Cancer Medicine Centre Initiative (2015) gives more details.

Also, most pathology services are making great efforts to retain the interpretive and clinical advice aspects they provide, which is threatened by low-cost, dumbed-down "results-only services" which

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sacrifice patient-centred care and close working relationships between pathologists and clinical requestors. Importantly, hospital autopsies are in decline all over Europe (Box 10.4).

Box 10.4 Case Study – decline of consented autopsy following hospital death in Europe

Context

- Consented autopsy rates have fallen significantly in Europe over the past half century to the verge of extinction (Turnbull, Osborn & Nicholas, 2015).
- The benefits of autopsy are established and include: clinical audit, patient safety, public health in a time of global antibiotic resistance, epidemiology, research, education, improved mortality statistics, improved diagnostics, improved resource allocation, comfort and explanation to grieving families.
- The priority of the autopsy in modern health and social care is highlighted by the Francis report and in the United Kingdom will be crucial to the work of Medical Examiners of the Cause of Death due that was due to be implemented in England in 2018.

Challenges

- The main reasons for the decline are: perceived difficulties in obtaining consent; a limited role given current diagnostics ("autopsy is pointless in modern medicine – we know the diagnosis"); and religious objection.
- In some countries legislation is thought to have had an impact on hospital autopsies, such as the Human Tissue Act in the United Kingdom.
- A change in attitude is required so that autopsy is considered an altruistic act similar to organ donation.

Responses

- Most religions contain no objection to autopsy and most families would consent to autopsy if appropriately asked.
- The number of diagnostic discrepancies would decline with an increase in autopsies.
- Diagnostic discrepancies may be due to co-morbidities or atypical clinical presentation.

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Box 10.4 (cont.)

- Despite technological progress, autopsy still has an important role in the assessment and improvement of the quality of surgical practice.

Achievements to date

- The European Critical Care Foundation (ECCF) held a conference in 2015 on the decline of the hospital autopsy to raise awareness among health care professionals.
- The idea to establish a pan-European anonymized autopsy database ("Europsy") was proposed at the ECCF meeting.

For the future hospital

- Autopsy should be offered to families across Europe upon the death of a relative to demonstrate willingness to discuss the patient's last episodes of care.
- Pathologists need to clarify and simplify the consent process to design a simple, yet effective, autopsy consent form.
- Alternative autopsies such as digital autopsies could be encouraged but their limitations should be understood and they are currently expensive and do not allow tissue to be obtained for in-depth diagnostic and research purposes.
- Medical research requires accurate causes of death. Autopsy should be used as a gold standard end-point for any deaths occurring in clinical trials.
- Specialist hospital professionals could be trained in consent, such as a pathology liaison nurse whose role would be to gain consent, to provide feedback to clinicians and to families, and to teach hospital staff about death.
- Teaching opportunities should be exploited so that students and junior doctors gain greater exposure to autopsy practice.

Source: Turnbull, Osborn & Nicholas, 2015

Existing but not widely implemented

Exciting new ways of providing pathology testing are not always implemented widely. For example, expansion of POCT and self-testing into the high street and homes has begun but in some instances is limited

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by patient acceptability (for a more detailed exposition see Larsson, Greig-Pylypczuk & Huisman, 2015). There are many other barriers to take-up of these devices, including the test devices themselves, patients' use of and interaction with the devices, providers' understanding of their uses, and the health systems in which they are used. Successful uptake usually requires integration of knowledge at these levels, which in turn can lead to trust and confidence.

The implementation of digital autopsies is limited by the diagnostic limitations of the technique. Standardization of units of measurement, reference ranges, coding and methods is required to enable results data to be of benefit in monitoring long-term conditions and in disease prevention, and implementation is limited by failure to implement national developments such as the National Laboratory Medicine Category in the United Kingdom.

Pioneering and aspirational

Some aspects of pathology service provision are envisioned but not yet in place. A key reason for this may be the traditionally slow rate of uptake of new technologies in pathology. The following technological innovations are discussed:

Wearables

Wearables are devices with sensors that monitor physiology. They can be integrated into devices such as smart phones, fitness bands, and clothing to track health and fitness. It is conceivable that these devices are able to generate self-monitored health data which could then be streamed directly into cloud-based data repositories or patient electronic health records. From here, general practitioners and hospital clinicians could access the data. However, several questions arise, including whether these devices are fit-for-purpose in bypassing an initial patient diagnosis and whether they can be used to triage a problem and direct the patient to relevant specialists. The accompanying growth of related apps could also facilitate transfer of data across different platforms and devices and lead to greater interoperability but it is too early to know whether patients would actually want this to happen. It also raises some regulatory issues as the devices would have to be cleared to use the same biomarkers which are used in clinical laboratory tests.

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The challenge for pathologists and laboratory managers is that if wearables become mainstream, strategies will need to be developed for data collection, understanding what utility these data will have and how to manage such data in conjunction with conventional laboratory test data.

Biosensor point-of-care devices

A biosensor is a compact analytical device that detects, records, and transmits information regarding a physiological change or process. The use of biosensors is well established in the management of chronic illnesses, such as blood glucose monitoring in diabetes and cholesterol monitoring in cardiovascular disorders. Biosensors have also shown potential for in vivo sensing of disease-specific biomarkers such as cancer. Here, sensors with nanoscale dimensions have been developed for effective diagnostics purposes (Hasan et al., 2014). Biosensors have many advantages: they are easy to use and yield fast results; there is no need to use labelled reagents; the cost per test ratio is low (although initial investment in the device is needed); and only a small sample is required. Challenges which need to be overcome focus predominantly on sensor accuracy and their minimum detectable levels. Additionally, it could be argued that some biosensors are "pseudo-portable" because their detection platform relies on bulky fluidic and detection systems.

Undoubtedly the next-generation whole-cell biosensors will see continued miniaturization of components, improved computing power, enhanced amplification capacity, and applications made further afield. The migration of some pathology tests from laboratories to point-of-care devices will continue and it is hoped that concerns about quality assurance and reliability, and their integration into a locally managed pathology network, will be fully addressed.

The promise of using POCT devices as an effective diagnostic in other contexts such as general practice is under review in many European countries. In the United Kingdom the National Institute for Health and Care Excellence (2014) issued draft guidance which recommended that GPs should consider using a POCT (CRP) to help decide whether patients presenting with mild pneumonia need antibiotics. A narrative review of primary care POCT and antibacterial use in respiratory tract infection was undertaken by Cooke et al. (2015). The researchers drew attention to a survey of Dutch general practitioners who reported that the most common POCTs currently used by family physicians were: blood glucose

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(96%); urine leucocytes or nitrite (96%); urine pregnancy (94%); haemoglobin (58%); and CRP (48%). The most commonly desired POCTs were: D-dimer (70%); troponin (65%); brain natriuretic peptide (BNP) (62%); chlamydia (60%); and International Normalized Ratio (INR) (54%). In terms of wider scalability for POCT devices, agreed protocols would have to be in place for data sharing across connected diagnostic networks within constituent countries as well as across Europe.

New technologies in pathology are sometimes heralded as game changers that will bring significant benefits to patients and providers alike. However, caution is needed over claims made by new technologies. The Theranos company is a case in point. Theranos was an American company founded in 2003 which successfully raised capital to streamline and standardize blood tests by creating a hand-held device using a few drops of blood obtained via a finger-stick "nanotainer" vial. It developed its own proprietary analyser to test blood samples. However, there were allegations against Theranos about discrepancies between a number of their specific blood tests when compared with traditional quality-assured methods. This resulted in a formal complaint to US regulators, which led to a finding that several clinical standards had been violated. A review of Theranos' systems, processes, and procedures resulted in Ms Holmes being charged by the Securities and Exchange Commission with widespread fraud, accusing her of exaggerating – even lying – about her technology while raising $700 million from investors said to include some of the world's richest people (*New York Times*, March and May 2018). There is a cautionary tale in the adoption of new technologies in pathology service. It is essential that the clinician is at the centre of technological adoption in the interests of patient safety and quality of care.

Conclusion

The tree of medicine diagram below provides a reminder of the centrality of pathology in medicine, as the trunk of the tree that links all aspects together is pathology.

Pathology in European hospitals is at a crossroads, with the future contingent on a willingness to address the barriers discussed in this chapter. There are many opportunities for pathologists to play a central clinical role. Despite operating under unrelenting fiscal constraints in some countries, pathology is entering into the "genome era" and pathologists must acquire and demonstrate visionary leadership.

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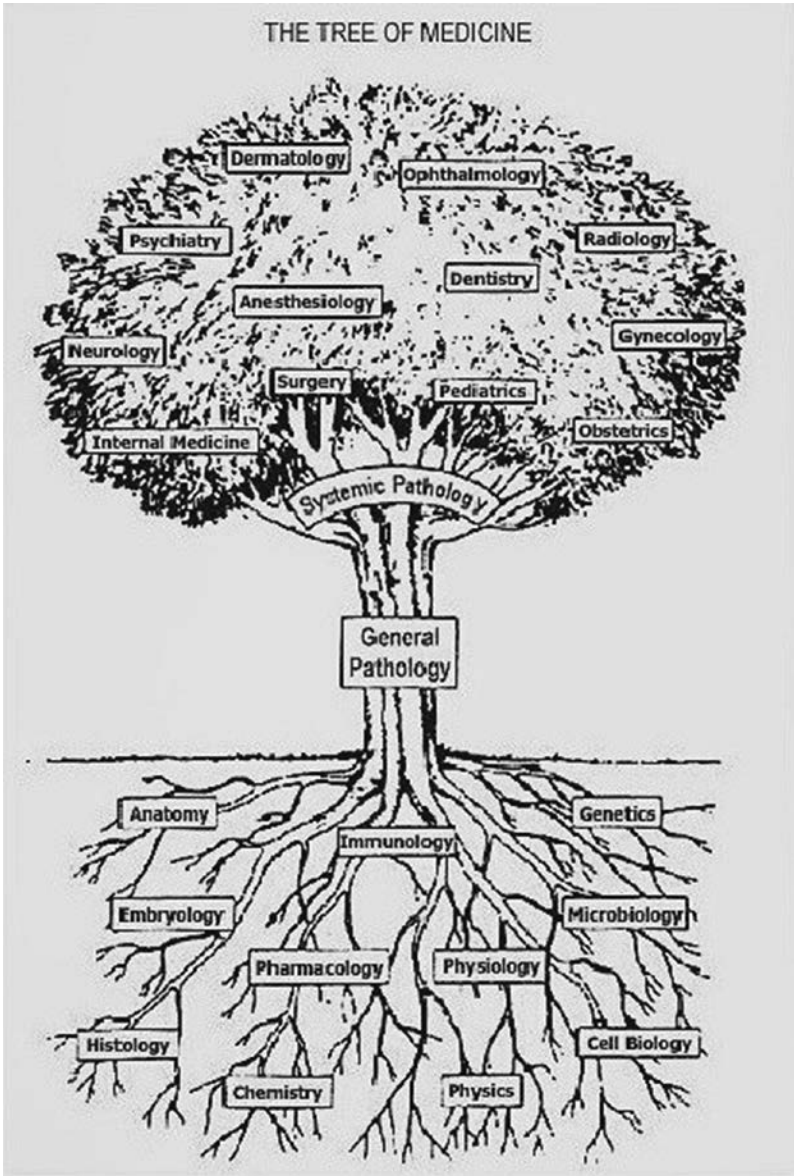

Figure 10.4 The tree of medicine (date of publication unknown)

Pathology services tend to be ignored by policy-makers and managers, and a key challenge will be to demonstrate how high quality pathology provision improves accuracy of diagnosis and effectiveness

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of monitoring or treatment, so creating better patient health outcomes. Quality in pathology reduces patient pathway costs as well as providing key health care data and impacting on all other health care interactions. The redesign of pathology so that it becomes part of an integrated patient pathway should be explored and communicated so that a clear demonstration of its value can be evidenced. This would enable pathology to be delivered where it is required while operating within an integrated quality framework (Myers, 2014).

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