Molecular Pathology - UK

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Honorary Consultant Pathologist, NHS Greater Glasgow & Clyde
Perspective

• In Glasgow, Scotland, UK
• Various roles involving molecular pathology (MP):
  – Lead for Glasgow Molecular Pathology Node, in network of six Nodes funded by Medical Research Council (MRC)
  – Previously Chair of Cellular & Molecular Pathology (CM-Path) initiative of National Cancer Research Institute (NCRI)
  – Previously local lead for Glasgow for Cancer Research UK (CRUK) Stratified Medicine Programme (SMP) Phases 1 & early 2
• But this is personal perspective/ understanding – errors are my own!
• Selected key references/weblinks
  http://cmpath.ncri.org.uk/
  https://www.gla.ac.uk/colleges/mvls/node/mrcepsrcmolecularpathologynetwork/
  https://www.cancerresearchuk.org/funding-for-researchers/how-we-deliver-research/our-research-partnerships/stratified-medicine-programme
What does molecular pathology “include”?

• Perspective: Evolved as clinical discipline from application of genetics to tumours therefore including aspects of medical (germline) genetics, focused on somatic haemato-lymphoid tumours & somatic solid tumours, with original tests mainly DNA-based

• For (local) **clinical** practice currently,
  – “Molecular pathology” includes somatic haemato-lymphoid and solid tumours, with DNA and some RNA testing i.e. MP based on nucleic acid testing
  – Most protein-based testing especially by IHC not “called” MP but may be linked e.g. ER/PR, HER2 by IHC, immuno-oncology (PD-1, PD-L1) etc
Who performs molecular pathology?

• Provision has varied by location across lab medicine specialties/depts of genetics, molecular diagnostics and/or cellular pathology, and joint working of those

• Staffing
  – Technical: scientific and technical staff
  – Reporting: mainly clinical scientists, including bioinformatics expertise
  – Interpretative and integration: variable, mostly clinical scientists, sometimes medically-trained pathologists, latter particularly involved in correlation with pathology reporting (or inclusion and integration of molecular information therein) and multi-disciplinary team (MDT) discussion
How is MP done?

- Has depended on what testing being done and where, therefore mix including Sanger, FISH, PCR, pyrosequencing, NGS panel...
- Includes diagnostic and theragnostic purposes
- Exemplar: (Older) Excel sheet of Molecular Pathology testing in Scotland as of 2013

### Molecular Pathology Testing in Scotland

<table>
<thead>
<tr>
<th>Number</th>
<th>Tests</th>
<th>Description of test</th>
<th>Aberdeen</th>
<th>Dumbarton</th>
<th>Glasgow</th>
<th>Edinburgh</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>test</td>
<td>no</td>
<td>test</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>ALK</td>
<td>FISH</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>113a</td>
<td>ALK</td>
<td>FISH</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>114</td>
<td>EGFR mutation</td>
<td>FISH</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>115</td>
<td>MET FISH in lung cancer</td>
<td>FISH</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>116</td>
<td>RET FISH in lung cancer</td>
<td>FISH</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>117</td>
<td>RET FISH in lung cancer</td>
<td>FISH</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 118    | KRAS mutation | FISH                | X        | X         | in development | X
| 119    | BRAF mutation | FISH                | X        | X         | in development | X

### Disease Colorectal

- KRAS mutation | FISH | X | X | in development | X
- EGFR | FISH | X | X | in development | X
- BRAF mutation | FISH | X | X | in development | X

### Disease Gastrointestinal

- ECD | FISH | X | X | Part of a clinical trial
- FGFR | FISH | X | | Part of a clinical trial
- PIK3CA in colorectal and gynaecological | FISH | X | | Part of a clinical trial
- BRAF | FISH | X | X | Part of a clinical trial
- MET FISH in colorectal and gynaecological | FISH | X | | Part of a clinical trial
| | | | | |
| | | | | |

[https://www.nsd.scot.nhs.uk/services/specserv/molpath.html](https://www.nsd.scot.nhs.uk/services/specserv/molpath.html) 2013 Excel sheet
Covered by social security/medical assurance? #1

• Yes. About 10% of UK GDP is spent on health. Most is spent in the public sector, where healthcare is provided by the National Health Service (NHS). NHS aims to provide services that are comprehensive, universal and free at the point of delivery. NHS funding comes from taxation.

• UK made up of four nations: England, Wales, Scotland & Northern Ireland. NHS healthcare operates independently in each, accountable to relevant government.

• Unified healthcare with unique patient identifiers provides benefits for healthcare organisation, planning & research

https://en.wikipedia.org/wiki/National_Health_Service
How is MP organized in each country?

- **Delivery arrangements for MP in each UK nation, 2016**
  - England: Molecular pathology tests are completed by specialist laboratories across the country through a ‘hub and spoke’ model.
  - Scotland: Nationally commissioned and provided in four labs/centres
  - Wales: All tests are currently completed by one laboratory – the All Wales Medical Genetics Service in Cardiff.
  - Northern Ireland: Most MP tests completed at the specialist centre of excellence lab in Belfast. Some tests sent to England for completion.

- With rest of pathology, MP moving over long-term towards lab amalgamation, federation (“hub & spoke”) & pathology networks for service sharing/standardisation

Pathology networks https://improvement.nhs.uk/documents/3240/Pathology_state_of_the_nation_sep2018_IQ.pdf
MP Organisation example

- Scotland, National Genetics Laboratory Management Structure
  - Diagnostics Steering Group reports on its recommendations for investment in diagnostic laboratory genetics / molecular pathology services, to National Specialist Services Committee and above
  - (National commissioning)

https://www.nsd.scot.nhs.uk/services/specserv/molpath.html
Covered by social security/medical assurance? #2

- Yes, MP funded by NHS, historically with national commissioning in Scotland & local/regional elsewhere
- Private healthcare in minority in UK but geographical variation, more in England
- Existing “standard-of-care” molecular tests generally covered by NHS funding – but challenge with new tests and recommendations….
- Different/additional testing e.g. by patient request would usually have to be funded privately; occasionally “special cases” can be made

https://www.nsd.scot.nhs.uk/services/specserv/molpath.html
“Standard-of-care”?...Clinical guidelines, standards and datasets

• National/UK guidelines on clinical care and management:
  – **NICE** (National Institute for Health & Care, Clinical, Excellence); SIGN (Scottish Intercollegiate Guideline Network)
  – May include pathology including MP. Personal: adding MP different to “just” adding another IHC biomarker

• Royal College of Pathologists (**RCPPath**) datasets and tissue pathways for cancer pathology include relevant MP

• Guidelines don’t mandate funding for tests (unlike treatment), so resourcing may not match recommendation
  – e.g. MSI/ MMR/ Lynch syndrome testing – evolving just now

[Links]
https://www.nice.org.uk/guidance
How much does an EGFR and an NGS (< 20 kb) test cost?

• Exemplar from Glasgow
  – “Stand-alone” EGFR test not now done
  – The cost per NGS test for EGFR (delivered as a lung panel rather a single NGS test) is £151.50 per patient – 170 Euros

• Exemplar “routine” MP testing just now:
  – Breast: (ER, PR) HER2, Oncotype Dx
  – Lung: EGFR, RAS, ALK1, ROS1
  – Colorectal: KRAS, NRAS, BRAF, MSI/MMR
  – Sarcoma and lymphoma: range of tests, overall still involve a lot of cytogenetics/ FISH
Is MP results part of pathology report?

- Varies by centre, test and subspecialty (e.g. neuropath)
  - MP results may be standalone MP report
  - MP results may be incorporated within pathology report, long-standing exemplar is integrated haematolymphoid reporting of Haematological Malignancy Diagnostic Service (HDMS) in Leeds
  - Or both, with standalone MP report & pathology cross-reference
  - Forms part of subsequent MDT discussion

- Considerations of integrated reporting
  - Royal College of Pathologists (RCPath) – Standards published
  - Association for Clinical Genomic Science (ACGS)


The Association for Clinical Genomic Science (ACGS)  https://www.acgs.uk.com/  http://hmds.info/
What about accreditation according to ISO 15189 standard?

- Yes, via UK Accreditation Service (UKAS), Medical Laboratory accreditation (ISO 15189)

Guidance for laboratories performing molecular pathology for cancer patient. Ian A Cree, Zandra Deans & colleagues for the European Society of Pathology Task Force on Quality Assurance in Molecular Pathology and the Royal College of Pathologists
Quality assurance (QA) and standardisation

- For laboratory medicine offered via NEQAS (National External QA Service)
  - Director of UK NEQAS for MP is Zandra (Sandi) Deans, Consultant Clinical Scientist
  - For individual tests and also controls
  - NEQAS is international

Results of the UK NEQAS for Molecular Genetics reference sample analysis. Susan D Richman and colleagues. https://jcp.bmj.com/content/71/11/989
How pathologists are trained for MP? #1

• Pathologists
  – Medical graduates; post-graduate training in pathology according to (5-year) curriculum & assessment set by Royal College of Pathologists (RCPath), with training provided by NHS within local/regional pathology departments
  – MP component is increasing, recent addition of two-week MP module; curriculum in review linked to wider medical changes

• Clinical scientists
  – Scientific graduates, Masters or PhD, trained in clinical science in NHS; MP training in evolution, various routes e.g. custom-designed programme in Scotland, and RCPath curriculum for clinical scientists in MP

Curriculum for Specialty Training in Histopathology 2015

Clinical Scientists undertaking Higher Specialist Scientific Training (HSST) in Molecular Pathology
Involvement with molecular pathology

- Survey of UK pathology consultants’ attitudes towards academic and molecular pathology – 274 replies on MP
- 84% use molecular pathology in their diagnostic work
- Of these, half feel they use it ‘a lot’
- 19% are involved in the delivery of molecular pathology services
Training in molecular pathology

- Survey of UK pathology consultants’ attitudes towards academic and molecular pathology – 274 replies on MP
- 53% have had no training in molecular pathology

- Through research activities
- Through involvement establishing the local molecular service
- Through interacting with the scientists that produce the reports
- Learnt ‘on the job’
- Self-directed reading/attending courses
How pathologists are trained for MP? #2

- Additional MP training offered via optional courses from single days up to Masters courses and beyond, provided by mix of pathology and healthcare organisations, Universities, including RCPath, PathSoc, NHS Health Education England, US TRiG (Rich Haspel), CM-Path, Barts/QMUL, Belfast, Leeds, Southampton and more

- Molecular Pathology Nodes funded by MRC/EPSRC 2015-2019, aiming to build MP capacity and expertise
  - Edinburgh, Glasgow, Leicester, Manchester, Newcastle, Nottingham, each offers new Masters-level training and outline course structure and contents (curriculum) are online

Information about the Masters-level training provided by each Node: https://www.gla.ac.uk/colleges/mvls/node/training/node-sponsoredtrainingopportunities/
How pathologists are trained for MP? #3

Time for change: a new training programme for morpho-molecular pathologists?

David A Moore,1 Caroline A Young,2 Hayley T Morris,3 Karin A Oien,3 Jessica L Lee,4 J Louise Jones,5 Manuel Salto-Tellez5

ABSTRACT
The evolution of cellular pathology as a specialty has always been driven by technological developments and the clinical relevance of incorporating novel investigations into diagnostic practice. In recent years, the molecular characterisation of cancer has become of crucial relevance in patient treatment both for predictive testing and subclassification of certain tumours. Much of this has become possible due to the availability of next-generation sequencing technologies and the whole-genome sequencing of tumours is now being rolled out into clinical practice in England via the 100,000 Genome Project. The effective integration of cellular pathology reporting and genomic characterisation is crucial to ensure the morphological and genomic

for the development of pathology as both a clinical discipline and a modern science. In the late 19th and early 20th centuries, teachers in morbid anatomy were found in medical schools throughout Europe representing the early 'academic pathologists'. Meanwhile, the clinical practice of 'surgical pathology' was beginning to be performed by physicians and surgeons who used microscopic findings for clinical diagnosis. By the mid-20th century, these roles were consolidated as histopathology became recognised as a medical diagnostic discipline in its own right, one based on light microscopy, and with a strong academic ethos.13 Many names have been applied to the discipline of identifying the shape and form of cells and their spatial arrangement in molecular diagnostics and precision medicine are now a reality. With the roll-out of the 100,000 Genomes Project, one of the most
cells. For example, lymphomas (Sick-Bian et al, 2008), sarcomas

How many MP tests are performed in a year?

- Exemplar:
  - Somatic Programme, NHSGGC
  - Workload approx. 4000 somatic (not haemato-lymphoid) reports/samples for 2.7 million population
  - Equates to 100,000 reports/samples for UK 66 million population
Is local Ministry of Health involved in the promotion/development of MP?

• Yes
  – National level consideration, planning and national/regional/district commissioning/funding and organisation of delivery
  – Increasing laboratory amalgamation and networking
  – Promotion often linked to research & development initiatives funded by government-related agencies or charities – often act as “vanguard” e.g.
    • CRUK SMP, MRC MP Nodes
    • 100K Genomes projects - Genomics England Limited and devolved nation programmes Scottish Genomes Project
    • (Similar initiatives now underway in digital pathology & AI)

https://www.genomicsengland.co.uk/about-genomics-england/
Scottish Science Advisory Council Informing the Future of Genomic Medicine in Scotland
What does the 100,000 Genomes Project mean for histopathologists?

J Louise Jones
Centre for Tumour Biology
Barts Cancer Institute
Lead for Molecular Pathology, Genomics England

Pathological Society of Great Britain and BDIAP
Leeds 2019
Genomics England

• Genomics England, with the consent of participants and the support of the public, is creating a lasting legacy for patients, the NHS and the UK economy, through the sequencing of 100,000 genomes.

• Genomics England was set up to deliver the 100,000 Genomes Project.

• This flagship project is sequencing 100,000 whole genomes from NHS patients with rare diseases, and their families, as well as patients with common cancers.
Pathology and Genomics

• Sample handling
  – Fresh tissue
  – ‘Genomic friendly’ biopsies

• Assessing tumour burden

• Integrated reporting and GTAB (Genomic Tumour Advisory Board)

• The National Test Directory
### National Test Directory

<table>
<thead>
<tr>
<th>Clinical Indication</th>
<th>Setting</th>
<th>Test Scope</th>
<th>Target/Gene(s)</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-squamous non-small cell lung cancer</td>
<td>Prognostic/Predictive</td>
<td>Small variant detection</td>
<td>EGFR</td>
<td>Small panel</td>
</tr>
<tr>
<td>Non-squamous Non-Small Cell Lung Cancer</td>
<td>Prognostic/Predictive</td>
<td>n/a Small variant detection</td>
<td>n/a</td>
<td>Small panel</td>
</tr>
<tr>
<td>Non-squamous Non-Small Cell Lung Cancer</td>
<td>Prognostic/Predictive</td>
<td>Balanced rearrangement detection</td>
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<td>Balanced rearrangement detection</td>
<td>n/a</td>
<td>Small panel</td>
</tr>
<tr>
<td>Melanoma - primary melanomas at high risk of recurrence i.e. stage 2C / 3 / 4 (metastatic)</td>
<td>Prognostic/Predictive</td>
<td>Small variant detection</td>
<td>BRAF, KRAS for some</td>
<td>Small panel</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>Prognostic/Predictive</td>
<td>n/a Small variant detection</td>
<td>n/a</td>
<td>Small panel / large panel</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
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<td>n/a Small variant detection</td>
<td>n/a</td>
<td>Small panel / large panel</td>
</tr>
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<td>Oligodendroglioma</td>
<td>Prognostic/Predictive</td>
<td>Copy number variant detection to 1p19q codef</td>
<td>n/a</td>
<td>Large panel</td>
</tr>
<tr>
<td>Paediatric - Oligodendroglialoma</td>
<td>Prognostic/Predictive</td>
<td>n/a Copy number variant detection to 1p19q codef</td>
<td>n/a</td>
<td>Large panel</td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>Prognostic/Predictive</td>
<td>Small variant detection</td>
<td>BRAF</td>
<td>Small panel</td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>Prognostic/Predictive</td>
<td>Balanced rearrangement detection</td>
<td>BRAF-KIAA1549</td>
<td>Targeted mutation testing</td>
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<tr>
<td>Pilocytic astrocytoma</td>
<td>Prognostic/Predictive</td>
<td>Balanced rearrangement detection</td>
<td>BRAF-KIAA1549</td>
<td>Targeted mutation testing</td>
</tr>
<tr>
<td>Thyroid papillary carcinoma</td>
<td>Prognostic/Predictive</td>
<td>Small variant detection</td>
<td>BRAF, KRAS, NRAS, HRAS</td>
<td>Small panel</td>
</tr>
<tr>
<td>Thyroid anaplastic carcinoma</td>
<td>Prognostic/Predictive</td>
<td>Balanced rearrangement detection</td>
<td>RET/PTC</td>
<td>Small panel / large panel</td>
</tr>
</tbody>
</table>
Genomic Medicine Service

National Test Directory
- 300,000 Tests reviewed
- 25% upgraded to new technologies
- 22 categories of rare disease
- Cancer
  - 4 cancers planned for WGS
- Many more edge cases in cancer
- Annual Test Directory Review
- Pharmacogenetics from April 2019

Genomic Medicine Centres
- Providing care (continue till 2021)

National Laboratory Network
- Genomic Laboratory Hubs - 7 hubs doing single gene, panels, clinical exome

UK Genomics Knowledgebase
- Informatics architecture & data store

Whole Genome Sequencing Provider

Clinical Interpretation Pipeline

Workforce development
- Upskilling of existing staff

Industry/ academic/ international partnerships
- Supporting ongoing research & development through clinical care

500,000 whole genomes sequenced from the NHS in the next 5 years
- Offered consent for research
- Longitudinal Life Course
- Recall for research
- International researchers and industry

NHS Lead
Genomics England Lead
What about collaboration with commercial solutions…and pharmaceutical industries

- Clinical service delivery within NHS has tended to involved solutions offered “in-house”
  - Exceptions: Oncotype Dx; more?
  - May differ in private practice
- Increasing joint working with commercial providers to support clinical service
- Increasing collaboration with diagnostics and pharmaceutical industries, for clinical trials and diagnostics R&D; may help challenges of subsequent implementation in NHS
Are Liquid Biopsies part of MP practice?

• Not currently standard-of-case in solid tumours
• Used for some haematolymphoid applications e.g. minimal residual disease (MRD)
• Forefront of R&D!
Thank you! And welcome in 2020!

- Colleagues involved in:
  - Glasgow MP Node & Nodes Network
  - NCRI CM-Path
  - CRUK SMP
  - Laboratory medicine in Glasgow, Scotland, UK, Europe and internationally
  - Kindly sharing slides including Nicola Williams, Louise Jones and Scarlet Brockmoeller

- We look forward to welcoming you in 2020 to Glasgow, Scotland, UK!