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AstraZeneca  Pfizer  The Catalyst Club

And our associated partners

Oracle  Roche  University of Oxford  Bristol-Myers Squibb  Public Health England
In 2011, the Cancer Research UK (CRUK) Stratified Medicine Programme set out to work in collaboration with a number of hospitals and genetics laboratories to tackle the challenges in delivering large scale, molecular testing in cancer within the NHS. We hoped to demonstrate the feasibility of the approach as well as support research into Stratified Medicine, ultimately aiming to improve access to targeted treatments for patients.

Commissioning something of this scale and complexity was always going to be a challenging endeavour. Partnership and collaboration have been central to the Programme for delivering its goals. We worked closely with our pharmaceutical partners, Pfizer and AstraZeneca, and the Department of Health to shape the initial plans and, later with clinical and research teams across our network of hospitals and labs to implement them. We joined forces with different industry partners such as Illumina and Oracle to develop the technology needed to support the Programme, and teamed up with the Cancer Registry Eastern Office to establish the infrastructure for clinical data collection. As the Programme developed, its scope broadened to include collaborations with Roche and Bristol-Myers Squibb to support recruitment to their trials for tumours with rare genetic mutations.

It was the willingness and hard work of our collaborative network of 26 hospitals and 3 diagnostic labs that really made the first stage a huge success. Without this network of over 200 enthusiastic and dedicated individuals, the Programme could not exist. This multidisciplinary approach has been vital in tackling the complexities and challenges we encountered.

This booklet illustrates the complexities of delivering a collaborative, national model of molecular testing and the approaches and solutions developed to overcome them, providing insight into what needs to be accomplished in the NHS to truly support a Stratified Medicine approach.
The ability to classify cancers according to their genetic make-up holds huge potential in delivering effective, personalised therapies that target specific pathways and mutations. However, the delivery of these treatments requires adaptation of the patient pathway to include molecular testing for specific mutations and this presents challenges in the accessibility of tumour samples and ensuring the quality and timeliness of results.

In 2010, a handful of these treatments were already available in clinical care but, with more on the horizon, it became clear that in the near future, tumours would not just require single molecular tests but analysis for broad panels of genetic markers. This would call for a coordinated, nationwide system for molecular testing in cancer.

With the aim of understanding what such a system would entail, CRUK set up The Stratified Medicine Programme; a multi-site model that would demonstrate just how large scale testing could be achieved within the NHS, while driving forward research into targeted therapies by creating a centralised data repository of molecular and associated clinical data.

Based at eight CRUK Experimental Cancer Medicine Centres (ECMCs) and incorporating 26 referring hospitals, the clinical hubs gained consent from patients diagnosed with the most common tumour types (breast, lung, prostate, ovarian, colorectal cancer and advanced malignant melanoma) for the use of their samples and data in research. Slides or scrolls of formalin-fixed, paraffin-embedded (FFPE) tumour material and matching blood were then sent to one of three Clinical Pathology Accredited (CPA, now UK Assessment Service, UKAS) molecular diagnostic labs, or technology hubs.

In total, 10 genes were selected for analysis and arranged into panels of 4 or 5 for each tumour type. Initially, the laboratories employed a combination of established processes such as direct (Sanger) sequencing, pyrosequencing and Single Strand Conformational Analysis (SSCA) but, towards the end of the pilot study, a Next Generation Sequencing (NGS) panel was developed and cross-validated. The molecular results were returned to the referring clinical hub electronically through a secure online server.

This molecular data was combined with patient clinical data (diagnostic, treatment and outcomes) based on the new Cancer Outcomes and Services Dataset (COSD) requirements and uploads regularly provided to the National Cancer Registry, Eastern Office in Cambridge. A research interface is developed at the University of Oxford in partnership with Oracle will allow the anonymized data to be viewed and interrogated by the external research community.

Key to the success of the Programme was maintaining a flexible framework that allowed the sites to adapt their existing processes. This would not only make the Programme more durable but would give the participating hospitals and labs an opportunity to review and improve their local processes, providing valuable insight into how to embed it into the NHS.
By June 2013, 9010 patient samples had been sent for genetic testing and over 40,000 genetic tests completed. Patient support for this approach and type of programme was consistently high and is demonstrated by the 10,750 patients that consented to participate. By November 2013, over 8,000 patient records had been stored in a central data repository with access planned for researchers in 2014.

Aside from successfully demonstrating the feasibility of such a programme, the pilot study yielded various other benefits through:

- Establishing a multi-professional, collaborative network comprising representatives from the fields of oncology, histopathology, surgery, biomedical science, clinical informatics, molecular genetics and cytogenetics.
- Screening and recruitment of patients to international, commercially sponsored clinical studies.
- Contributing to enhanced bio-banking and informatics facilities at NHS sites through the use of electronic test requesting and reporting using structured XML (extensible mark-up language) format and transfer via a dedicated, secure FTP (file transfer protocol).
- Creating a tumour type-based external quality assurance scheme administered through UK NEQAS (National External Quality Assurance Scheme).
- Embedding targeted Next Generation Sequencing (NGS) technologies into clinical practice.
The Programme has been a learning process for all those involved, highlighting a number of important issues relevant to future wider adoption, the resolution of which we want to tackle through our list of recommendations. These fall under the four broad areas of Consent, Sample Preparation, Data and Genetic Testing and are discussed in detail in the following pages.

**PATIENTS & CONSENT**

**Alleviating Patient Concerns**
An education campaign for public and healthcare staff about genomic medicine to ensure accurate knowledge underlies every individual decision.

**Standardised research consent**
Innovative methods for acquiring prospective and enduring patient consent for research use of tissue in routine NHS practice, based on national ethical standards for consent and information forms.

**PATHOLOGY**

**National pathology standards**
Establishment of agreed standards in molecular pathology led by a relevant authority such as the Royal College of Pathologists. Standards should be set:
- Optimum sample requirements
- Tissue fixation and processing factors
- Nomenclature and reporting terminology
- Configuration of efficient workflows in NHS histopathology departments

**Guidelines on macrodissection**
Expert consensus should be reached on the circumstances and setting in which tissue macrodissection is required prior to mutation analysis.

**Communicating clinical results**
Integration of molecular data with histopathological data, provided as a timely, comprehensive report for clinical decision making.
**DATA**

**Interoperability of data systems**

**Immediate**: Address the inability of NHS systems to obtain crucial pathology data required for patient management and COSD by replacing text reports with consistently coded data items and reports.

**Long term**: Develop an integrated electronic patient record with full interoperability between the systems in use in different clinical areas.

**Consistent data recording**

Dedicated resources for collecting of high-quality, complete data from routine clinical care. Current modernisation provides the ideal opportunity.

**Up-to-date coding systems**

Clear data standards and provision of a detailed specification with central mapping and cleansing of data for uniformity.

**UK-wide data solutions**

The Departments of Health for England, Scotland and Wales should agree cross-border solutions to allow capture of UK-wide data on national cohorts.

**Modernisation of data exchange**

Implementation of electronic test requesting and reporting to provide a fast, standardized, secure, scalable and cost-effective means of communication.

**Communicating clinical results**

Integration of molecular data with histopathological data, provided as a timely, comprehensive report for clinical decision making.

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**TESTING**

**Overcoming poor DNA quality**

NGS panels will need to be developed to allow successful analysis of small amounts of fragmented DNA available from clinical samples.

**Clinically relevant turnaround times**

Turnaround times may be made achievable through improved sequencing technology and test multiplexing.

In the meantime, prioritisation of results for clinical care, trial eligibility and research could prevent delays for patients.

**Validating new technology**

Sample sharing between researchers for future cross-validation of assays using new technology.

**Improving interpretation**

A regularly updated and rigorously curated online reference resource for recording and reporting genetic abnormalities.

**Improving patient treatment**

Develop the UK clinical trials portfolio and facilitate identification of clinical trials across multiple tumour types with eligibility determined by the presence of a particular genetic abnormality.

**Budgeting for the future**

The cost of increasingly important molecular testing should be budgeted for by the NHS Commissioning Board at a national level.

**Maintaining quality**

Membership and participation of molecular genetics and histopathology laboratories in appropriate UK-approved external quality assurance schemes e.g. UK NEQAS.
Patient support for the Stratified Medicine Programme has been uniformly and consistently high, with 96% of the patients approached giving consent for their tumour samples to be used in the Programme. The reasons for declining to participate varied from an information overload on the day to not understanding the nature of the genetic testing, things we are working to tackle in future.

At the start of the Programme, a great deal of effort was invested in understanding the patient pathways and when it is appropriate to approach patients at what is a difficult time for them. At one site, over 20 different possible ovarian cancer patient pathways were identified. The Programme then allowed the hospitals to tailor their approaches according to their findings, which gave rise to innovative processes to maximise patient acceptance, such as the use of electronic consent forms, sending information prior to meeting the patient in clinics and sending thank you letters following participation.

Close collaboration between research and clinical teams to find the right time to approach the patient was important. Some sites opted to approach patients after diagnosis which was a more efficient use of staff time and avoided recruitment of patients later found to be ineligible, while others chose to consent pre-diagnosis, ensuring that all potentially eligible patients were given the opportunity to participate.

Key to the success of Stratified Medicine in the UK is the effective integration of the genetic testing consent into routine practice and, although a Programme-specific consent form was ethically approved for use, many of the hubs chose to adapt local consent forms used for existing bio-bank activity. Full integration into NHS consent forms for surgical procedures was achieved at two of the clinical hubs yet, inconsistency of approach between Regional Ethical Committees meant that this approach was rejected in other locations. The disparity highlights the need for standardisation of the approach that ethics committees across the UK have towards consent, especially in light of the general willingness of patients to donate tissue to research.
In order to avoid conflicting with local needs for tumour material, instead of blocks, only FFPE material left over after diagnostic procedures was collected for the Programme. Challenges have included a lack of resources and delays in retrieving archived blocks from referring sites. However, most hubs successfully embedded the Programme into routine procedure through a combination of engagement with pathologists and streamlined processes.

Examples of small process changes that have had a big impact on delivery have included reporting the best block for testing, sending lists of consented patients to pathology departments in advance of specimen receipt and establishing effective working relationships between bio-bank staff and pathologists. Different approaches have also been adopted for integrating molecular information with pathology data and how this is presented in the pathology report and, eventually, the patient record.

The Programme has highlighted the potential impact that sample preparation has on the quality of the DNA and therefore the success of subsequent genetic analysis. There is currently little evidence to demonstrate how sample handling factors affect DNA quality but examples in the Programme have shown that variation in practice, like the cleaning fluid used on microtome blades or the type and timing of fixatives, can have an impact. There is also variation in tissue economy, of vital importance in small biopsy samples, for example whether intervening sections cut between levels are discarded or kept for future work such as immunohistochemistry or mutation analysis.

The successful implementation of stratified cancer medicine in the UK will depend on a review and adaptation of practices in pathology laboratories to accommodate the requirements of molecular pathology. This will necessitate the development of standards for preparing samples to maximise the quality and quantity of DNA that can be extracted, updated guidelines for block retrieval and inter-departmental transfer, and changes in workflow configuration within pathology labs.

We are already working with the Department of Health and Royal College of Pathologists to address these issues and create an environment conducive to Stratified Medicine in the UK. Through the Programme we have developed a network of pathology labs that are already engaged with these areas and we will be working with them in the second stage of the Programme to provide further evidence to inform optimum standards, with a particular focus on lung cancer.
An IT solution was needed that would capture standardised genetic information from cancer patients, link it to existing NHS clinical data and retain it in a secure database to which members of the research community could have controlled access. Importantly, the system had to be scalable to ultimately incorporate millions of patient records.

To allow standardised and timely exchange of genetic information between staff at clinical and technology hubs, an electronic request and reporting system was set up using XML messaging and a secure FTP server, often with direct entry into the electronic patient record. Once running, it provided a secure, scalable and cost-effective means of communication between different organisations that has been endorsed by both clinical and technology hubs as an approach that should be adopted by the NHS.

A partnership was set up with the National Cancer Registration - Eastern Office to collect and manage the flow of clinical information. They received regular uploads of a dataset of approx. 100 data items derived from the core items of COSD. The aim was to eventually automate these uploads, though different approaches were taken with varying levels of automated and manual resources.

The Programme partnered with Oracle and the University of Oxford to develop a research portal to allow characterisation and analysis of the Programme cohort to inform further research. Another programme aim is to demonstrate what research can be meaningfully conducted on routine NHS clinical data.

There were some local challenges in sourcing some data items which required close working between clinical and informatics team to improve the quality of recorded data, define clinically relevant information and obtain them from differing local systems. However, there were a few notable programme-wide issues that will have implications for national schemes collecting this type of data:

- Lack of resources in both dedicated staff and information technology.
- Difficulty sourcing data items discussed at Multi-Disciplinary Team (MDT) meetings e.g. performance status, Tumour Nodes Metastases (TNM) staging.
- Variation in coding standards (e.g. SNOMED) between trust teams and between trusts, requiring data mapping to standardise it.
- Lack of inter-operability between data systems used in pathology and other parts of the electronic patient record, requiring dedicated manual resources.
- Cross-border variation in data standards and information released under governance rules. This will impact the collection of UK-wide data on national cohorts for research and epidemiology purposes.
The Programme set the requirements that all the molecular results had to be delivered at a maximum cost of £300 per sample and with a target laboratory turnaround time of 15 days. Our three accredited labs, two regional genetics labs (Cardiff and Birmingham) and one research lab (ICR), were selected on their ability to meet these criteria. Each lab developed and optimised their own methods and approaches to run the analysis.

Successful analysis for all of the hubs depends on the quantity and quality of the DNA extracted from the sample being tested, which varied considerably between the samples collected by the Programme. The need for compromise was identified between obtaining faster turnaround times and achieving a meaningful result. Repeating a failed test may increase the chance of identifying an actionable mutation in a sample that otherwise wouldn’t have yielded a result but it increases turnaround times, and is more resource intensive. The Programme hopes to provide some evidence to show how repeat testing affects mutation frequency and guide how test failures are dealt with.

For results to be clinically relevant, interpretation and reporting needs to be standardised. Mutations in genes linked to NICE-approved therapies were better characterised and were therefore more straightforward to interpret, but establishing the possible clinical significance for more exploratory, research-based genes was more complex and extended turnaround times. Consensus had to be reached on what was classed as an actionable mutation, known polymorphism or unknown variant. Despite agreeing to use standardised, Human Genome Variation Society (HGVS) -approved nomenclature at the outset of the programme, later data analysis showed variation in how mutations were described e.g. use of one or three letter abbreviations to represent amino acids. Achieving the target turnaround times and cost constraints was a constant challenge using sequential, one-gene-at-a-time testing. The future of the Programme is a move towards widespread use of NGS that allows multiple genes to be tested in parallel for multiple samples. Validation of the technology has been successful but has shown the challenges in adapting this technology to degraded, FFPE-derived DNA. This required the development of techniques to minimise the number of unknown variants, bioinformatics analysis pipelines and development of standards for reporting e.g. classification of failures.
The next stage of the Stratified Medicine Programme, SMP2, will move towards bringing clinical benefits to patients through genetic stratification and support an area of unmet clinical need. We will be focusing on molecular screening of late stage lung cancer patients for targeted therapy clinical trials.

Over 2 years, we plan to screen between 4000 and 8000 patients for a broad range of genetic aberrations including mutations, amplifications and translocations. These will consist of both routinely investigated markers, as well as more speculative potential drug targets which will be linked to a landmark, multi-armed national matrix trial.

This trial will provide a framework to test targeted drugs on small cohorts of genetically stratified patients at a national level, with each arm corresponding to a different drug. Conducted under a single study protocol, it will be open to all ECMCs across the UK.

The existing SMP infrastructure will be aligned with the ambitious goals of SMP2 with the aim of opening the trial in June 2014. Our vision is that patients will obtain access to new and exploratory treatment and that, in the long-term, the trial will ensure the rapid development and availability of targeted drugs for future patients. For more information please contact stratifiedmedicine@cancer.org.uk
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