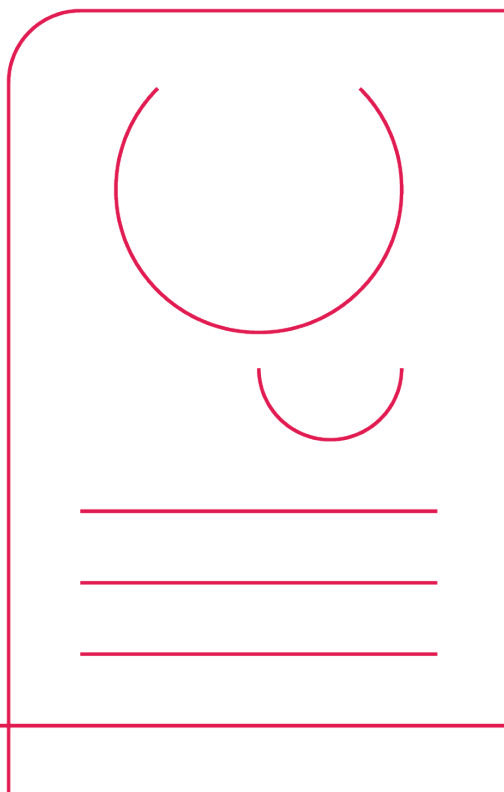


October / 2019

Principles for the implementation of genomic medicine



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Principles for the implementation of genomic medicine

Genomics is a rapidly advancing field and these overarching principles set out the basis on which the Academy of Medical Royal Colleges (the Academy) believes genomic medicine in patient care and population health should be implemented and delivered.

These implementation principles should be read in conjunction with the Academy's March 2019, **Genomic medicine in the NHS** statement and other documents linked within these principles.

The implementation principles below reference the 10 principles from the March 2019 Genomic medicine in the NHS statement to maximise benefit and minimise harm.

1. Equitable access for the population for tests with **proven clinical utility** (see Principle 1: Equity; and Principle 10: Setting priorities to support primary providers):

- Consistent commissioning of appropriate investigations in all areas
- Clinical pathways of delivery for standardised patient care for testing and management.

2. Safety and quality of test accuracy, interpretation and utilisation (see Principle 2: Evidence-based medicine — Diagnostic testing and Genomic screening, Principle 3: Safety and Principle 8: Quality and appropriateness. See also Annex 1 Patient safety for genomics)

- Tests should be requested based on sound evidence of clinical benefit
- Recognition of the difference between 'variant' and 'diagnosis' with appropriate contextualisation
- Quality assurance of test accuracy — methodology and results — repeat or verify through recognised confirmatory data
- Develop secure genomics incident reporting systems.

3. The development of clinical pathways to provide best use of current resources and standardised safe care (see Principle 2: Evidence-based medicine, Principle 3: Safety, Principle 5: Research and Annex 2 Network development to support mainstream Clinical pathways for medical genomics) including:

- Evidence to inform which elements of the genome are included in any given test in the Test Directory (which genes and/or individual variants should be included in a test for a

particular clinical presentation/disease]

- Patient selection criteria for particular tests in the Test Directory (identifying which genomic tests are appropriate for a given clinical indication) and at what stage they should be deployed
- Consistent strategies for the evaluation of variants including designating test and result complexity to determine when results can safely be returned to appropriately skilled teams through high throughput generic routes and when they require specialist input, MDT discussion or bespoke, specialist evaluation
- Pathways for unexpected / additional findings through various routes, including those sourced out with direct clinical indications.

4. Priority for the **clinical service** with adequate clinical time assigned within job plans for patient discussion, selection of appropriate testing and delivery of test results, participation in relevant research and the associated training and continuing professional development (see Principle 2: Evidence-based medicine and Principle 5: Research)

- Direct patient care, MDT and wider family interactions.

5. Transparency and communication for the public and patients regarding consent, testing and the limitations of tests (see Principle 4: Consent and Principle 6: Patient & Public Engagement. See also Annex 1 Patient safety for genomics paper and *Guidance on the use of genetic and genomic information in the clinic*.¹)

- Implications and limitations of tests for individual and their families – education and patient-friendly documentation
- Integration of the ethical aspects of genomic medicine
- Awareness of data usage and possibilities regarding current and future care
- Role of personal data and research in the development of genomic medicine
- Affordability of tests transparent to clinicians and the public.

6. Adequate **IT systems and personnel** that work with the clinical and laboratory systems to deliver the demand (see Principle 7: IT & connectivity)

- Secure and effective across and between regions
- Able to cope with changes of patient wishes for research purposes i.e. redact data or annotate the record.

7. Training for the current and future workforce (see Principle 9: Training resources)

- Ongoing education of all healthcare professionals re: genomic testing, treatments and infrastructure of genomic services
- Future workforce training — including new and expanding roles.



8. Investment in a core **workforce with expertise in genomics** (clinical geneticists, genomic counsellors, clinical scientists, bioinformaticians) in order to deliver, develop and evaluate emerging tests and services and facilitate knowledge transfer (see Principle 2: Evidence-based medicine, Principle 3: Safety and Principle 9: Training resources)

— Workforce planning around service needs — current and future.

1. A report of the Joint Committee on Genomics in Medicine (RCP, RCPATH, BSGM) [3rd edition 2019] *Consent and confidentiality in genomic medicine. Guidance on the use of genetic and genomic information in the clinic*

Annex 1

Patient safety for Genomics

Prof JE Martin, Royal College of Pathologists
September 2019

The genomic era is here, but how are we dealing with the challenges of genomic patient safety?

Rapid expansion of genomic testing is happening. NHS genomic hubs are up and running. Direct to consumer testing enables people to question ancestry, disease risk, and what vitamin supplements they should take, based on genome.

There is a perception in healthcare and the public, that genomic tests are 'the answer'. Serious safety issues related to genomic testing and practice are occasional and exceptional, but real, but there is increasing evidence of more widespread concerns. So, what do we need to know about them and what issues do they raise? In particular, what do we do next?

No test process is infallible. Errors happen in sample collection, laboratory handling, laboratory hardware, software, interpretation and understanding of reports by clinicians.¹ Potentially dangerous therapies, especially in cancer, are being used based on a single test result. At least one patient has come to harm through treatment based on a single erroneous genomic result.

External quality assurance helps with monitoring and laboratory performance improvement, but 100% accuracy is a goal, not a reality. Some of the reference sample variance between centres is startling.^{1,4,5} Do patients and their healthcare professionals understand how reliable these tests are? Do they cross check the result before taking important therapeutic decisions?

Errors and bias are found in reference literature and genetics databases. Some arose due to failure to appreciate the extent of variation in genomes (4-5 million variants each) and are corrected as resources such as gnomAD expand, others through not appreciating the importance of ethnicity. This has caused real problems. Families were told they had a risk for cardiomyopathy, based on a predominantly white population database, when the variant is common, and non-risk bearing in their non-white background.²

Another area of concern is diagnosis. 'Diagnosis' is used to describe both variant classification and an expert clinical evaluation that a given variant is a full explanation for the features seen. Many pathogenic (or likely pathogenic) variants show incomplete penetrance (only some of those with them will develop disease) and age-dependent penetrance (disease that emerges later in life). Accurate molecular genetic diagnosis requires integration of an approved evaluation of the variant³ and expert clinical assessment as to whether it explains the patient's clinical features in full, in part, or not at all. While automated analysis can undoubtedly improve variant interpretation, biological complexity in genotype translation to phenotype means that caution is needed.³ Variant reports should not be used in isolation for clinical management.

In cancer genomics, variant pathogenicity must also be in the context of clinical actionability.³ Integrated reporting, including histological assessment is also critical for validation and assessing actionability. However, this is dynamic, and variants are likely to be reclassified over time, with results that may need subsequent re-evaluation.

Other technical issues exist: tumour-derived DNA is often limited, requiring PCR amplification, with introduction of artificial alterations. In haematological malignancies, getting uncontaminated germline samples can be challenging, again with impact on interpretation.

Different methods may over or under call pathogenic variants. Patients are coming to ask for treatment with a direct to consumer SNP based test result. Even when referred to a geneticist, they need counselling and reassurance when the 'harmful' variant cannot be validated by sequencing - who do they believe?

So what needs to happen?

1. Confirm results. When considering any potentially harmful therapy or procedure based on a genomic result, make sure that you have repeated the test, or have excellent confirmatory data.
2. Quality assurance data needs to be transparent and linked to robust and rapid quality improvement, to reduce variation. Look at the data from 'as a patient would I trust this result' and 'how can we get this right', not 'well, we're getting better'.
3. Implement systems to collect and collate technical, system and human errors. National incident reporting systems need to collect and collate genomic incident data from across all disciplines.
4. Learn from events. Errors that can lead to harm, are nowhere better understood than in transfusion. The Serious Hazards of Transfusion system, with the MHRA, is the best example of patient safety reporting and feedback into daily practice. Haemovigilance data has led to a two sample rule that might well be applicable in genomics.
5. Improve databases to include more population groups. Expand services, and research programmes, with this in mind.
6. Improve genomic testing literacy. Everyone needs to understand not just what the tests are, but also their risks, benefits and potential uncertainties.

Safety must be built in to genomic services. Reporting, surveillance and robust quality improvement must ensure that results are correct and valid, before use, and we all need to appreciate the limitations of this exciting technology.

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Annex 2

Network development to support mainstream clinical pathways in medical genomics

NHS England has undertaken an ambitious and far-reaching reorganisation of genomic medicine services including the development of a **National Genomic Medicine Service [GMS], comprising a series of regional Genomic Medicine Centres [GMC] aligned to seven Genomic Laboratory Hubs [GLH].**

The changes are aimed at improving the personalisation of clinical care, increasing access to genomic testing and ensuring greater equity of access. The process will, in the fullness of time, allow broader testing for both common and rare diseases, greater use of genomic tests to characterise cancer subtypes in order to focus therapeutic choices and increasing use of pharmacogenomic testing to prescribe appropriately and monitor drug response. The changes reflect a radical step towards the delivery of individualised care. The first steps concentrate on diagnosis of rare diseases and the management of cancers.

Delivery of genomic medicine will require integration of the GMS into the distributed delivery structures across the breadth of healthcare — so-called ‘mainstreaming’ of genomic medicine. This will require the development of new clinical management and systems based delivery pathways and the creation of processes for multidisciplinary working. This will also need the acquisition of new skills and recognition of the resources — including clinical and laboratory time — if it is to be a success. Furthermore, these processes will require oversight and management to ensure that novel methodologies for testing are introduced in a safe and appropriate manner.

The aim of this document is to propose a framework for implementation of genomic medicine across primary, secondary and tertiary care to the optimal benefit of our patients. It reflects the need to provide lifelong multidisciplinary and multi-specialty care to patients at hereditary risk of both rare and common diseases. We propose this would be delivered through national and regional networks - which link specialist care and clinical interventions to patients at all stages of their pathway.

This paper we will outline the proposed:

- 1) Overall structure of clinical genomic networks
- 2) Specialist Rare Disease Genomic Networks
- 3) Specialist Cancer Genomic Networks.

The proposed overall structure of clinical genomic networks

The roll out of genomic medicine will be dependent on newly formed or existing, updated clinical networks. These will be specialty / disease dependent (Figure 1) to optimise and share the clinical and scientific genetic experience of the specialist while relying on the current knowledge and direct clinical input of the non-specialist geneticist (but clinical specialist – e.g. cardiologist, ophthalmologist etc.).

This model would enable:

- Identification and recognition of those able to request tests
- MDT participation
- Training structures
- Assessment of needs for funding
- Assessment of geographical and patient need

i. Requesting tests within clinical networks

Within the first and current iteration of the test directory, clinical specialities eligible for ordering particular tests are specified [e.g. Clinical genetics, Dermatology, Breast Surgeons]. Further detail will need to evolve locally or across disease areas regarding the particular attributes of seniority, sub-specialty or expertise by which those eligible to order tests are further defined.

ii. Reporting within clinical networks

Clarity of reporting will be key in the context of an expanded clinical workforce. Reports should recognise clearly actionable mutations that relate to the clinical (phenotype) request and provide appropriate information for the referrer regarding relevance of the result. Networks should be structured in such a way that the integrated report that is developed through the MDT structure and mechanisms are in place to automatically trigger appropriate onward referral for those patients who require further genetic / specialist input. **Clear pathways for onward management should be developed via specialist coordination of the network, rather than reliance upon proactive referral by the generalist [i.e. directly triggered by laboratory].**

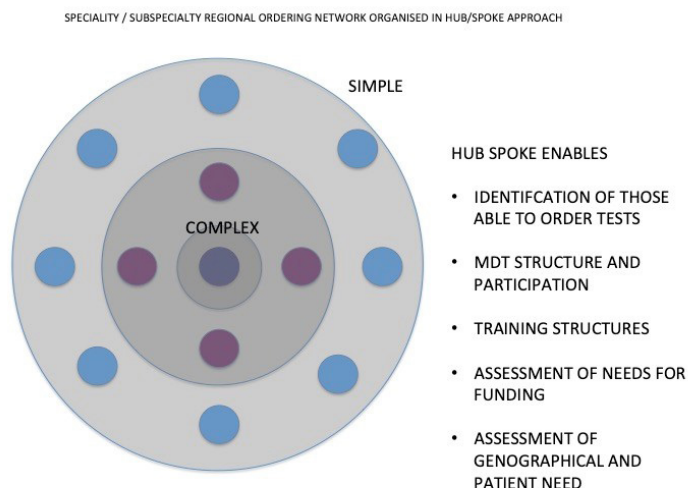
iii. Oversight of clinical networks

Effective governance of clinical implementation and resource utilisation would be critical. It would ensure that feedback and audit is provided within and across regions to ensure appropriate use of tests and outcomes to the benefit of our patients.

Effective IT would need to be upgraded to support these pathways.

Speciality-specific expertise will vary regionally so national guidelines from speciality-specific experts in genomics and sharing best practice within a specialist area is important. Having national expertise in specialty genetic topics at certain GLHs to augment the regional GLHs would enhance clinical decision making. It would also enhance opportunities for clinical quality improvement and facilitate academic activity.

Figure 1. Specialty/sub-specialty regional ordering network



iv. Communicating results to patients and families

Clinicians are usually comfortable undertaking investigations to confirm a suspected clinical suspicion. Many genomic requests and reports fall into this category ('Does the patient have Marfan syndrome?' confirmed by a clearly pathogenic variant in FBN1). Here delivering anticipated genomic diagnostic results to patients is likely to become part of a specialist skill set quickly. While genetic signposting is important — e.g. family cascade counselling — this can be offered after testing and delivery to the proband of results.

v. Identifying complex cases and reports

A key issue will be to ensure that, through the networks and the MDT structures, clinicians are provided with mechanisms to identify complex and unusual reports that need to be dealt with promptly and safely — but are not readily within the competence of the non-specialist. This should be facilitated at the level of the MDT (i.e. the 'complex' or unexpected 'actionable' or unexpected constitutional findings report should activate an immediate decision/pathway/referral). The patient should be aware of this arrangement as part of the consent process. There should be a communication structure to provide advice across this network that is automatically triggered and timely.

vi. Trainee participation

Clinician and scientist trainees from a broad range of backgrounds should participate in MDTs and other aspects of rare disease and cancer genomics network in order to facilitate workforce development and sustain the model long-term.

Where there is a contract to report whole genome sequencing (WGS) and additional findings (which will grow with time), it will be key to explicitly define what is the pathway for reporting and acting on those additional findings. For this reason, it is likely that WGS would be focused centrally for many conditions in the first instance. Similarly, careful thought should be given to the timing and re-analysis of genomic data, when this is to be initiated and by whom.

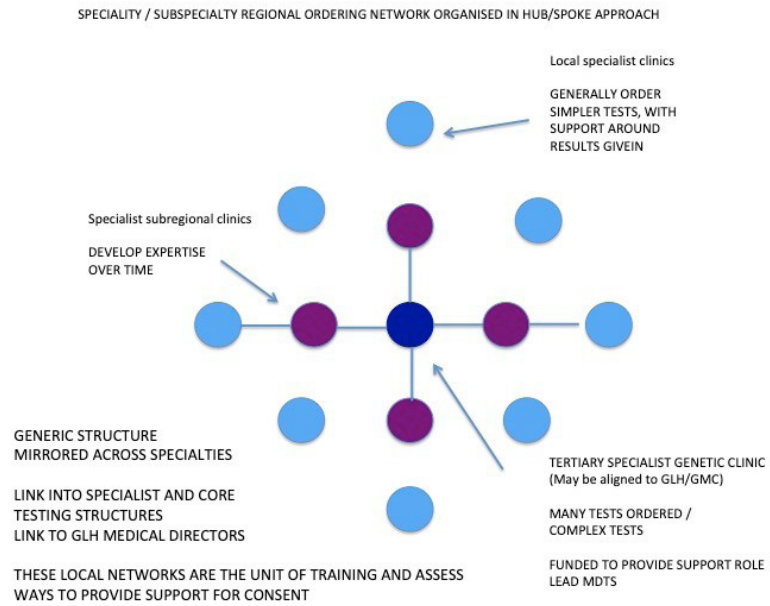
Development of Specialist Rare Disease Genomic Networks aligned to the GLH network

Specialty testing in rare disease will require close communication between clinicians and the GMS in order to promote understanding amongst mainstream clinicians of:

- **New funding structure**
- **Genomic Laboratory Hubs (GLH) network**
- **Genomic test directory including test eligibility criteria**
- **How to access advice from the Clinical Genetics service.**

For each given specialty, in particular early in the evolution of the new system, it will be necessary to identify the clinicians who will become the active workforce, delivering an increasing amount of the routine work that is envisaged in genomic medicine. Where possible it will be necessary to ensure that genomic tests are undertaken within existing care structures which will be delivered according to best practice guidelines. Such clinicians, who are responsible for managing and diagnosing the patients who require testing, will be trained in taking consent and will work closely with colleagues through genomic MDTs to ensure that testing is undertaken in a safe manner and those results given back appropriately (Figure 2).

Figure 2. Rare disease networks



Oversight of these groups of clinicians will be an important task. For this purpose it is proposed in each region **Specialty Specific Rare Disease Clinical Genomic Networks (CGN)**, will be developed and centred around every GLH that is delivering genomic tests. These would encompass all clinicians who may be involved in diagnosis and management of rare diseases and a group of specialty clinicians who support them in requesting and reporting genomic tests. It is likely that exemplars of such networks already exist (e.g. cardiac genetics and cancer genetics). Each clinical specialty will begin to develop and interact, through a CGN with the GLH infrastructure as well as with the Genomic Medicine Centres / Clinical Genetics centres. This interaction, supported by a lead clinician and a network coordinator, will be necessary to ensure that more patients in more regions are able to access genomic testing in a safe and standardised fashion.

The clinicians who are involved will:

- Require training in consent / test ordering. Such training would contain both
 - Generic (i.e. provided by GLH via HEE) and
 - Speciality-specific elements
- Work as a recognised network to ensure that testing was implemented widely and appropriately Interact with the GLH and regional genetics services to ensure that testing and reporting is undertaken in a safe manner
- Participate in regional MDT meetings to provide essential clinical and family history information and discuss variant interpretation and result reporting
- Ensure that regional access is sensitive to local patient need and is able to reach all parts of local populations
- Understand the implications of genomic testing — and where there is doubt, be able to access reliable assistance and information
- Understand the nature of genomic reports and be able to deliver these to all or specific patients according to the pathways which provide clear routes for referral and advice
- Understand when to refer patients for specialist advice from a Clinical Geneticist/Genetic Counsellor

Development of Rare Disease Clinical Genomic Networks

Regional CGNs will be set up to support specialist clinicians in understanding how to order a test and what to do with test results. The group will be trained about which pathway to send all patients including those with both straightforward and more complex tests /results. The Genomic MDT is likely to sit at the heart of the work of the networks, coordinating the reporting of patients and giving oversight and the ability to audit the return of results.

The networks would act as the unit of training for specialty clinicians. In order to develop such networks there needs to be support that would include:

- A Clinical network coordinator
- Recognition in job plans for clinical sessions for specialist clinicians
- Provision of facilities for multidisciplinary working — which may not be face to face
- Provision of training materials to ensure standardisation of approach.

At the current time such support — including funding — is not available and may sit outside of the GMS-funding envelope.

At the centre of the network, the more specialised clinicians in genomics leading this work would begin to provide advice for patients across wide geographical regions. This should be part of their job plans and may, in time, become nationally / regionally, rather than locally, funded. Such clinicians would coordinate the networks and are likely to undertake the more complex aspects of genomics workload (e.g. undertake more of the WGS testing).

Some complex genomic tests should be requested in highly specialised clinics aligned to the GLH network while the more standard tests would be requested across these networks. Special consideration for dedicated support may apply to certain fields — for example, maternal-foetal medicine and paediatrics where genetic conditions are prevalent and where the number and complexity of actionable conditions is large and involves input from multiple specialists.

Structure of Rare Disease Clinical Genomic Networks

Clinical

- Highly specialist geneticists — provide specialist clinical input
- Organ or specialty specific specialists dealing with genomic medicine (e.g. cardiologists, oncologists, ophthalmologists)
- The majority of clinicians who are developing knowledge of genomics from primary through tertiary care
- Genomic/genetic counsellors
- Specialist nurses and midwives who are likely to take consent in many cases

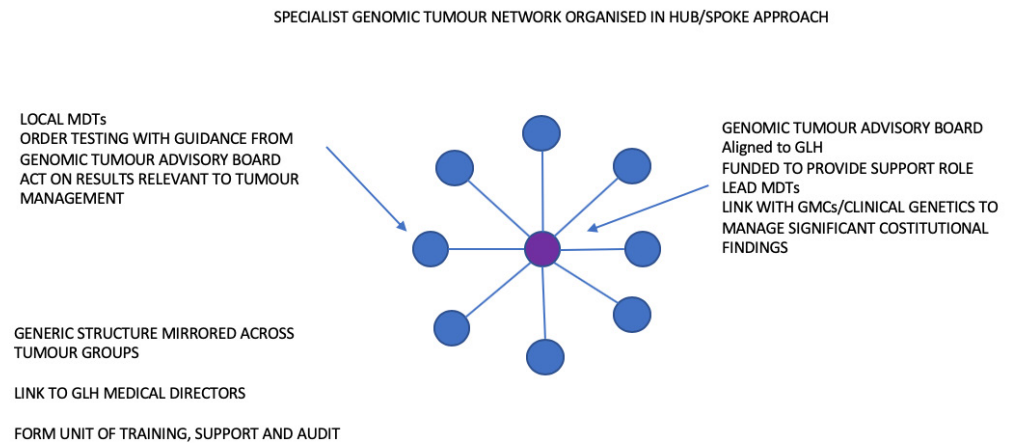
Laboratory

- Likely to include the leads for specialty testing across each GLH hub.

Development of Specialist Cancer Genomic Networks aligned to the GLH network

There will need to be closely coordinated communication between NHSE / the Academy, the Royal Colleges and the specialty associations to develop **Specialist Cancer Genomic Networks** (Figure 3) centred around Genomic Laboratory Hubs (GLH). It is essential to ensure that they can be implemented in a structured manner and be incorporated within established clinical care pathways. There will need to be an understanding of how each cancer pathology and clinical specialty group will begin to interact, on a broader level than is currently the case, with the GLH infrastructure as well as with the Genomic Medicine Centres / Clinical Genetics centres. This interaction will be necessary to ensure that more patients in more regions are able to access genomic testing.

Figure 3. Specialist genomic tumour network



Typically, for a given NHS trust/cancer service, there will be a weekly MDT at which all new and / or surgical cases are discussed. Attendance at such meetings is high, and time per patient allocated is low. It has widely been agreed that the weekly broad MDT is likely not the forum for lengthy deliberation of genomic results. Hence, there exists need for a model by which the distilled conclusions of discussions at the Genomics meeting [GTAB: tumour advisory board] can be fed into the weekly MDT. In particular, timing is critical, as the MDT is the forum for clinical management planning for surgery, chemo- and radio-therapy. Hence, the GTABs need to be sufficiently frequent so that their findings can be fed in a timely fashion into the respective weekly MDT.

For this reason, it is proposed that cancer groups develop **Specialist Genomic Tumour Networks** in each region, centred around a GLH. For each tumour group, this would encompass a genomic tumour advisory board [GTAB] which would include multidisciplinary clinicians, with oncologists playing a major role, pathologists, tumour specialists and others with a role in the clinical application of the results of genomic testing, in particular clinical trial enrolment. The GTAB would work with relevant cancer MDTs.

The role of the GTAB would include:

- Identifying which patients / tumours should undergo genomic tests
- Ensuring that actionable results are appropriately flagged to the treating MDT and clinicians and eligibility for approved therapies and/or trials is fully explored
- Providing an infrastructure for advice and support to the 'spoke'
- Longer-term multidisciplinary strategies for local service improvement, e.g. co-development of pathways by which tissue specimens collected are of optimal quality— this may include:
 - Improvement in collection, storage and preservation of fresh tissue samples, or
 - Evolution of better practices by which to mitigate the damage to nucleic acids and sequencing quality incurred on account of excessively long fixation in formalin.

Depending on the size of the **Specialist Genomic Tumour Networks** and the level of local expertise and engagement, GTABs, while ultimately tumour-type specific, may be oligo-tumour type or even Pan-Cancer in the initial stages.

Links with the Clinical Genetics services are essential to help interpret pathogenic constitutional variants identified during this testing. Administrative support and pathway coordinators will be required for service delivery.

Within each region every tumour specific MDT could therefore be identified and clinicians within it would:

- Require training in consent / test ordering. Such training would contain both generic- (i.e. provided by GLH via HEE) and speciality-specific elements
- Work as a network, supported by the regional GTAB, to ensure that testing was implemented widely and appropriately
- Interact through the regional GTAB with the GLH and regional genetics services to ensure that testing and reporting is undertaken in a safe manner
- Participate in regional MDT meetings to discuss testing criteria and result reporting
- Ensure that regional access is sensitive to local patient need and is able to reach all parts of local populations
- Understand the implications of genomic testing
- Understand the nature of genomic reports and deliver these to all or specific patients according to the pathways.

In summary, a regional Specialist Genomic Tumour Network will:

- Understand how and when to order a test
- Be trained and regularly updated in local tissue pathways to ensure acquisition of tissue samples appropriate for the required test type
- Understand what to do with test results
- Be trained and regularly updated to know through which pathway to send the patients who have actionable, or potentially actionable, results, in particular in regard of accessing NICE-approved drugs and or accessing clinical trials
- Be the unit of training and would require funding support from HEE and NHSE to ensure equity of approach. A training pack could be developed between NHSE and HEE to ensure that there was standardisation of approach to the development of such networks.

At the centre of the network, the clinicians leading the work of the networks through GTABs (likely working closely with each GLH hub) will provide support not only for the network but also for the wider group of clinicians. It is likely that this will need to be part of their job plans and may in time have to become nationally /regionally, rather than locally, funded. These clinicians will coordinate the networks and are likely to undertake the more complex aspects of genomics workload (e.g. identifying and flagging actionable results and incidental constitutional pathogenic variants).

Structure of Specialist Genomic Tumour Networks

Clinical

- Specialist geneticists — provide specialist clinical input
- Specialists dealing with specific tumour types (e.g. oncologists, surgeons)
- Specialist nurses might take consent in many cases.

Laboratory

- Likely to include the leads for specialty testing across each GLH hub.

Conclusions

Genetic diagnosis and the interpretation of genomic test results are a vital component of genomic medicine. However, to ensure its success the new genomics service must engage with frontline clinicians and disease specialists to ensure linked-up coordinated care for patients. We have identified rare disease and cancer pathway management as examples of how this structure may be developed and implemented in the NHS. There are many other important applications of genomic medicine e.g. other common diseases, pharmacogenomics, personalised care, etc., for which these models may be an exemplar of best clinical practice. In order to achieve this there needs to be adequate funding to deliver adequate training structures, multidisciplinary teams for rare and common disease pathways (with adequate IT and administrative support) and feedback from genomic testing to ensure implementation of the results in patient-specific care. There also needs to be formal links between primary, secondary and specialist/tertiary care with regional and national networks to support clinical decision making and continuity of care. At this time we have a unique opportunity and singular requirement to implement these genomics networks in the NHS to the benefit of our patients.

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