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Genomics in mainstream clinical pathways

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1. Why mainstreaming matters

Key points

- **Advances in technologies make the mainstreaming of genomics across clinical specialties a distinct possibility**
- **To be clinically effective, truly equitable and efficient, mainstreaming requires an understanding of how and where genomic testing fits into current clinical pathways and how clinicians would use it**

The term 'mainstreaming' was first used in 2003 by the Secretary of State for Health in the context of the genetics white paper *Our Inheritance, Our Future* when he argued that genomics must move from the narrow confines of clinical genetics to applications available in every clinic and specialty across the health system from tertiary to primary care. Since then, the advance in technologies has proceeded at pace to now, where the cost and speed of sequencing and our understanding of the utility of testing makes this a distinct possibility. This is reflected in the CMO's Annual Report 2016 *Generation Genome* whilst Genomics England has, through the 100,000 Genomes Project, established the principle that whole genome sequencing and high quality interpretation can be done at scale within a health system.

The next step to transform health services by the routine integration of genomic testing into clinical care is an ambitious move. This involves further development of the processes and clinical pathways put in place by NHS England as part of the 100,000 Genomes Project.

To be clinically effective, truly equitable and efficient, requires an understanding of how and where genomic testing fits into current clinical pathways and how relevant clinicians would use it to help their patients achieve better outcomes. Ultimately, this mainstreaming must go beyond the bounds of teaching hospitals and of enthusiastic champions and leaders of genomics within the various specialties. The question is: how can all NHS clinical specialists be enabled to easily access genomics for their patients?

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2. About the workshop

Key points

- **PHG Foundation has identified two points within the evolving genomic medicine pathway critical to eventual delivery of an equitable, efficient and effective system**
- **The workshop was organised to promote the necessary engagement between senior clinicians from a wide range of specialities, experts in clinical genetics and the clinical genomic science community to encourage dialogue between the different disciplines**
- **Our aim with this report is to highlight the changes essential to widening access to genomic medicine**

2.1 Purpose

Beyond education and infrastructure

Until now much of the discussion on mainstreaming genomic medicine within the UK health system has focused on education of the clinical professional workforce and the development of infrastructure for testing. Workforce development has focused on increasing genomic literacy and necessary skills, such as taking a family history and obtaining informed consent for genomic tests, in a wider range of existing and future health professionals. In the development of infrastructure there is a move towards centralisation of genomic testing to enable more efficient use of existing resources, and potentially to widen access to genomic testing.

Against this general backdrop, the PHG Foundation has identified two points within the evolving genomic medicine pathway that both clinical genomic scientists and specialists from mainstream areas of medicine believe will be critical to eventual delivery of an equitable, efficient and effective system.

The first is the interface between the clinician and the laboratory at the point of referral. This encompasses the dialogues, actions and information systems involved in empowering the clinician to identify which patients require genomic testing, to identify the appropriate genomic test to offer their patient and to enable the clinician to capture the clinical information (phenotyping) necessary for an effective referral, all within the constraints of an increasingly time and resource pressured out- and in-patient environment.

The second interface is between the laboratory undertaking the genomic analysis and the clinician, who will receive the result of the genomic test, discuss it with their patient and make clinical decisions based upon it. This encompasses the potential need for iterative dialogue between the referring clinician and the laboratory during the interpretation of a genomic test, availability of clinical genetics specialists to enhance the interpretation of genomic analyses for patients being seen in mainstream specialities, and delivery of a final report that it is readily understandable to clinical specialists and enables them to act appropriately and safely upon its findings.

Promoting interdisciplinary dialogue

The traditional model of test referral, interpretation and reporting within clinical genetic services has depended on a close and collaborative working relationship between the clinical geneticist, genetic counsellor and clinical scientists. Optimising these processes for the delivery of genomic medicine in mainstream specialties and in much greater volume requires the engagement of a far wider group of stakeholders.

A workshop was organised by the PHG Foundation to promote such engagement by bringing together senior clinicians from a wide range of specialities and locations with experts in clinical genetics and the clinical genomic science community (see appendix for details). Mainstream specialists included some who had extensive prior experience of delivering genomic testing to their patients, and others who had very little. Our aim was to encourage dialogue and to improve mutual understanding between the different disciplines. By sharing and comparing the widely varying experiences of participants we hoped to identify key outstanding challenges and existing examples of best practice that may support the advancement of genomics within the NHS.

2.2 Workshop approach

The workshop, held in London on 29 March 2017, was divided into three phases:

- **Phase one -** an opening series of plenary presentations, in which mainstream clinicians experienced in genomic testing and laboratory genetic scientists experienced in providing genomic tests to the mainstream specialties shared case examples and provided broader insights and opinions on how effective genomic testing services could be delivered
- **Phase two -** two parallel, cross-disciplinary breakout discussions in which each group considered a series of questions relating firstly to the referral interface, and secondly to the interpretation and reporting interface
- **Phase three -** a synthesis and plenary discussion to identify emerging areas of consensus and areas where further consideration would be required for effective implementation

2.3 This report

This report summarises and analyses the findings of the workshop, presenting them to the wider community of policy makers, system leaders and frontline professionals involved in delivering mainstream genomic medicine.

Our aim is for these findings to stimulate action and to enable the changes to current clinical practice, local service configurations and national policy direction that the participants identify as being essential for the success of this critical endeavour.

Throughout the report we refer to clinical specialists who are in specialties other than clinical genetics, collectively as 'mainstream' specialists. However, we acknowledge this is an extremely heterogeneous group, comprising all specialties outside clinical genetics and that these clinicians are all accredited specialists within their own clinical area.

> Our aim is to stimulate action and to enable the changes to current clinical practice, local service configurations and national policy direction that the participants identify as being essential for the success of mainstreaming genomic medicine

3. Getting the right test for the right patient

Key points

- **Innovative models of service development and delivery were discussed, with the aim of identifying best practices for widening access to genomic testing. The model of universal access is likely to have an important impact**
- **It is desirable to reach an accurate genomic diagnosis as early in the patient's journey through the healthcare system as possible**
- **Criteria to decide which patients should be tested vary widely as do views as to which clinicians should be able to order these tests. The pros and cons of different models were discussed**
- **In the UK particularly, there is confusion as to which tests should be ordered for which disease**
- **The effectiveness of genome analysis relies heavily on clinical and phenotypic information, yet this information is not always adequately captured**

3.1 Introduction

The drive for the mainstreaming of genomic medicine services within the NHS is to enable all patients for whom clinical genomic analysis may be beneficial for their care to access it in a timely fashion, regardless of location or their route through the health system. Participants explored in depth the current characteristics of referral pathways for genomic testing within mainstream specialties, and identified where current practices posed challenges to the effective ascertainment of patients in need of testing and to ensuring appropriate test referrals were then made.

Participants also shared their experiences of innovative models of service development and delivery within their locality, with the aim of identifying best practices that could be adapted and adopted across the NHS to enable more equitable access to genomic testing.

3.2 Referral for testing

Identifying patients who need testing

Given the inherent rarity of many clinical conditions with an underlying genomic basis, the primary task facing mainstream clinicians of identifying which of their patients require genomic testing is often not straightforward. Early and appropriate ascertainment for genomic testing can be confounded by primary or secondary care physicians being presented with a complex mix of non-specific clinical features that are then explored by a range of clinical specialties (leading to the well-recognised phenomenon of the 'diagnostic odyssey').

Even where the clinical phenotype is well defined, if it is common and being managed in mainstream care the possibility of an underlying genomic cause may simply not be considered by the clinician managing the patient. Thus, for example, the nephrologist should be alert to the possibility of Alport syndrome in the patient with end stage renal disease of unknown aetiology. Suspicion should be strengthened by a family history of renal disease and by hearing loss or ocular abnormalities, although the nephrologist would not necessarily be expected to have the expertise or equipment to make a detailed eye and ear examination outside of their main clinical area.

Participants agreed that it is desirable to reach an accurate genomic diagnosis as early in the patient's journey through the healthcare system as possible. For rare phenotypes where the likelihood of an underlying causal genomic abnormality is high, such as congenital cataracts, it was argued that there is a case for testing all patients upon their first presentation to the relevant specialist (in this case, a paediatric ophthalmologist). However, where the phenotype is more common e.g. end stage renal disease, it was clear that a different approach, potentially with a higher threshold, might be required, including focusing on those patients for whom the aetiology of disease remains unknown despite having undergone the current standard investigations.

Regardless of the prevalence of the condition, there was wide acknowledgement of the importance of mainstream clinicians taking a family history as a way of detecting cases that may be more likely to have a genetic aetiology.

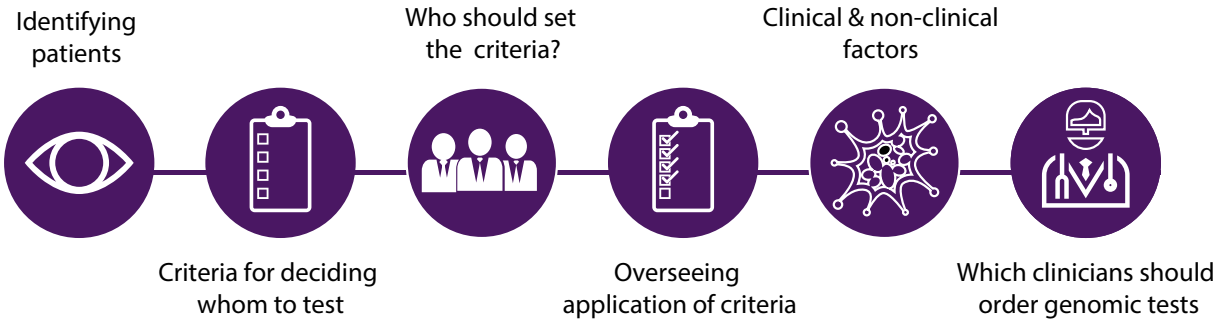
Criteria for deciding whom to test

Current approaches to defining criteria to determine which patients should receive a genomic test vary widely. However, it was widely acknowledged that such criteria would become more important as the potential pool of referring clinicians widens, in order to ensure that test referrals are clinically appropriate, that resource constraints are managed and inequities in test access are minimised.

When considering criteria to guide the use of clinical genomic testing, fundamental questions arose:

- Who should set them?
- Who should support/ensure appropriate application of any criteria?
- What clinical and non-clinical factors need to be taken into account in setting test criteria?
- Which clinicians should order genomic tests?

Referral for testing - questions to address



Who should set the criteria?

Different models were explored including:

Criteria established by (or on behalf of) national bodies

In some cases these already exist; for example, UKGTN criteria have been developed to guide the appropriate use of testing for rare inherited diseases (ukgtn.nhs.uk/find-a-test/testing-criteria/). In other cases, it was proposed that national professional bodies or subgroups could work together to agree best practice guidelines for testing in specified clinical scenarios e.g. ophthalmologists could agree that as a national 'policy' all children presenting with congenital cataracts should receive a genomic test to facilitate diagnosis. Such an approach facilitates a consistent use of testing, and is most likely to have been developed with appropriate (often scarce) highly specialist clinical and scientific input.

Criteria established within local health economies

This is a common model currently in use. In some settings, clinical geneticists and/or laboratory clinical genetic scientists worked in collaboration with clinicians from mainstream specialties to develop a set of agreed criteria under which such testing could be offered by the mainstream clinicians. This model allows for an element of local context with regard to funding arrangements, variation in local clinical pathways, and even the preferences of individual clinicians to be taken into account. However, they are in most cases still grounded in nationally agreed criteria where these existed.

Decision to test outside formal criteria

Often individual mainstream clinicians using their own judgement and expertise may make a decision on referral for a genetic test. In many cases, particularly where mainstream clinicians do not have access to local laboratory or clinical genetics expertise, a decision to offer testing will be taken on an individual level using clinical judgement, essentially on an ad hoc basis. It was clear from the meeting that, even where national criteria for testing for some conditions are available, many clinicians are unaware of them and use their own criteria, developed either individually or 'in house' amongst a group of local specialists seeing patients with the same or similar conditions.

Whilst this approach frees the clinician to take greater account of individual patient circumstances, it may be less desirable from a patient perspective, particularly where, in the absence of external guidelines, mainstream clinicians may lack the awareness, knowledge or confidence to offer testing where it might be appropriate. This approach may also place a greater burden on the test providers (the laboratories) to 'gate keep' referrals for tests. This challenge is discussed below.

Many clinicians are unaware of them and use their own criteria, developed either individually or 'in house' amongst a group of local specialists seeing patients with the same or similar conditions

In the specialist area (and thus outside mainstream provision), individual clinical geneticists do make the decision to test based on their own judgement or expertise. This is to be expected and is likely to be where the disease is extremely rare or syndromic, or where the wider circumstances, possibly related to familial impact, make it particularly important to achieve a molecular diagnosis.

Who should support/ensure appropriate application of any criteria?

Given the varying level of expertise in genomics of mainstream specialist clinicians, and the multi-system phenotypic complexity of at least a proportion of the patients who they will be managing, it is reasonable to expect that not all referrals for genomic testing made by such clinicians will be appropriate. Indeed, inappropriate referrals – particularly at the early stages of any attempt to mainstream test provision – were frequently noted within the workshop as a challenge to ensuring clinically effective care for patients, and cost effective use of scarce resources.

An inappropriate referral may be one made where the underlying cause of the disease is unlikely to be genetic, where a genetic disease is suspected but the wrong test is ordered, or where prior assessment by a clinical geneticist may be required due to the complexity of the patient phenotype or circumstances. There are three main approaches to so-called 'gate-keeping' of referral:

- **A clinical geneticist in a joint clinic -** where mainstream specialties have established inherited disease clinics e.g. an inherited cardiac disease clinic, or in specialist clinics in which a proportion of their patients are likely to be considered for genomic testing, they may engage a clinical geneticist to be available during clinic sessions to advise on whether testing is appropriate for individual patients. This approach is common where a mainstream specialty is in the early stages of establishing genomic testing and feels they benefit from the support and educational impact of having a clinical geneticist on hand.

  Alternatively, a patient who is identified as potentially needing genetic testing is referred to a sub-specialist who may either be dual-accredited as a clinical geneticist, or have been trained to a level that enables them to act in lieu of clinical genetics as a 'gatekeeper' for their specialty. The training of sub-specialists can thus help to reduce the burden on clinical genetics.

- **The pre-test MDT meeting -** some genetics laboratories arrange pre-test MDT meetings, where referrals for testing from mainstream clinicians (particularly for expensive and complex tests such as WES or WGS) are discussed with the input of a clinical geneticist before being processed by the laboratory. This provides an opportunity for an alternative testing strategy to be considered if required, and for the clinical geneticist to suggest onward referral to the clinical genetics service or to reject the referral outright (although this is rare).

- **The clinical scientists in the laboratory receiving the test -** it is common for laboratories to receive test referrals from mainstream clinicians without the mediation of a clinical genetics opinion either in a clinic or a MDT setting. Depending on the accuracy and completeness of phenotypic information contained within the referral, the laboratory will themselves make an assessment of whether the request conforms to published criteria (where they exist). They may contact the referring clinician for clarification and can then, if needed, either propose an alternative testing strategy (based on their own clinical scientific expertise) or reject the referral altogether with an appropriate explanation.

What clinical and non-clinical factors need to be taken into account in setting test criteria?

The key details of the testing criteria or eligibility criteria for genomic testing are generated from the clinical pathway in which the test is going to be used. The purpose of developing the criteria needs to be clear. Often these are developed to ensure specific test performance, including expected benefits, for patient safety reasons or to manage healthcare costs.

Criteria details can be generated through the evaluation process for a new test. Key aspects include:

- Characteristic clinical features of the condition
- Definition of the target population for the test
- Prevalence of the condition in the target population
- Clinical context in which the test is to be used
- Clinical utility of the test

In addition, criteria can be developed that outline the level of expected expertise for diagnosing and managing certain clinical conditions that would be required for clinical referrers to access certain tests.

The clinical criteria should be the minimum required to define the target population and enable test use. In certain cases, these can be very specific with well-defined clinical features and test results, or alternatively, the clinical features can be less specific to enable testing of a target population with considerable clinical heterogeneity.

Which clinicians should order genomic tests?

Together, the application of testing criteria and some level of expert-led gatekeeping offer a safety net for both the patient and health system that ought to enable clinicians from mainstream specialties to refer their patients for genomic testing. However, in practice, views vary widely on precisely who should have access to what can be expensive and complex tests that, under some circumstances, have profound implications for patients and their families.

Restrictions on access to genomic testing may be justified on the grounds of patient safety, to ensure that patients are not harmed by the inappropriate use of genomic testing, and on the grounds of health system efficiency, to ensure that scarce resources are not wasted on inappropriate use of an expensive investigation. Models used include:

- **Training dependent 'restricted access' -** the genomic medicine service at Liverpool Women's Hospital has been mainstreaming their genomic testing services for over 10 years, and has developed a model that aims to maximise the number of clinicians (who are not clinical geneticists) who can order tests, by providing training on how to order the right test, how to consent the patient and how to understand the test report. This has taken place through workshops, the provision of joint clinics with clinical geneticists and other peer-to-peer interactions.

  Clinicians who have participated in the appropriate local training are then added to a register of 'approved' referrers held by the genomic laboratory, who assess all incoming referrals for clinical appropriateness. Clinicians who have not undertaken the necessary training are not excluded from ordering tests, but their referrals may be subject to a great degree of scrutiny and they will be offered the opportunity to participate in future training sessions.

  Similar to the Liverpool approach, other leading genomic medicine centres have made agreements with mainstream specialities within their local health economies as to the extent of their capabilities to order genomic testing. These approaches often include limiting referral for certain more complex tests to consultant level clinicians, or requiring a patient to be seen in a joint clinic with a clinical geneticist prior to referral.

- **Guideline enabled 'universal access' -** while these approaches aim to minimise the burden on the laboratories of having to scrutinise incoming referrals, they all operate on the assumption that not all mainstream specialists should, without further training, be considered qualified to undertake genomic testing for their patients. This was not a universally accepted premise. Indeed alternative arguments were advanced at the workshop that, given the provision of appropriate guidelines and criteria, all specialist clinicians should be able to order such a test where they believe their patient could benefit. This might involve a list of clinical features that would always be indications for testing. Maximising the pool of clinicians who can refer for a genomic test should, in theory, widen patient access and shorten the time to diagnosis by eliminating the need for additional referrals to sub-specialists or clinical geneticists who might be considered better qualified to make the referral.

This broader access approach is, however, predicated on the need for far greater standardisation of the approach to genomic testing i.e. the provision of a standardised testing panel of genes for specified clinical presentations so that the referring clinician does not need to understand or even be aware of the genomic architecture of the disease they are investigating. It would also require the provision and adherence to more standardised guidelines and criteria for when to test, so the clinician can have confidence they are following expert-assessed best practice. While all of these are achievable, the broad access approach poses a significant challenge to the system when considering how the results of the genomic test are managed.

It was clear from the discussion that the vast majority of clinicians, even those at consultant level, would not consider themselves qualified or competent to interpret the results of a genomic test as currently provided by the clinical laboratories.

It was clear from the discussion that the vast majority of clinicians, even those at consultant level, would not consider themselves qualified or competent to interpret the results of a genomic test as currently provided by the clinical laboratories. Thus, even if it is possible to provide simplified guidelines and test referral processes that enable any specialist clinician to recognise when a test is warranted and to know what test to order, the level of genomic knowledge and clinical experience required to use the results appropriately is not as obviously reducible to such a standardised approach. The challenges of improving the return of results are discussed further below.

The model of universal access is likely to have an important impact. Appropriately implemented, it will lead to an increased volume of testing and increased numbers of diagnoses, often of relatively rare diseases, that will require referral into the agreed relevant pathways within the system. A level of previously unmet diagnostic need will be unmasked leading to demands on the specialist system that must be catered for. There may also be a perceived reduction in efficiency of testing as the diagnostic yield for individual tests is likely to be reduced, albeit that this may be mitigated through increased efficiencies elsewhere in the diagnostic or treatment pathways for this group of patients.

Challenges in test selection

Having established that their patient requires a genomic test, the mainstream clinician is currently confronted with the challenge of determining which test is the most appropriate one to order given the clinical presentation. For certain conditions where only one or a small number of well understood genes are known to underlie a specific clinical phenotype e.g. the *CFTR* gene for cystic fibrosis or the Huntington gene for Huntington's disease, this process is straightforward. However, more often clinicians are faced with significant diagnostic uncertainty – their patient has a phenotype or symptoms attributable to multiple different underlying genetic causes – and in these cases, current best practice would be to order a panel test covering the range of genes currently known to be associated with certain phenotypes or diseases.

These panel tests can greatly simplify test ordering for mainstream clinicians, in that they remove the requirement for the clinician to know which specific genes to request for each patient. On the other hand they can cause confusion. In the UK this confusion has arisen from the provision across multiple laboratories of gene panel tests, each covering the same clinical indications e.g. inherited cardiac arrhythmias, but offering a varying set of genes to be tested. In these circumstances a clinician is faced with the dilemma of not knowing which panel test is the most appropriate and more likely to provide a diagnosis for their patient.

Alternatively, a clinician may be faced with a patient with multiple phenotypes, each of which aligns with a different panel test; for example, a patient with both ataxia and epilepsy could be tested using either an ataxia panel or an epilepsy panel, but it is not immediately clear without further reading and research (which is often undertaken outside of the clinic appointment time) whether either panel includes genes in which mutations would cause the more complex syndrome they observe in their patient.

Information capture during the referral process

The effectiveness of clinical genomic analysis depends as heavily on the availability of clinical/phenotypic 'data' as it does on the generation of accurate genomic data about the patient. This presents significant challenges to the mainstream deployment of genomic testing as much of the clinical and phenotypic information required to interpret a genomic test and produce a clinically meaningful report is not typically captured in the course of a 'standard' clinic appointment with a specialist.

For example, taking an accurate and complete family history, including drawing a family tree, which is necessary to determine the likely pattern of inheritance and to establish the prior likelihood of the disorder being inherited, is not a widely practiced skill in mainstream specialist medical practice. As well as family history, there may be a requirement for additional (deeper) phenotypic information than is usually gathered as part of a standard clinical assessment. This may extend to additional investigation or even referral to a sub-specialist. More challenging may be the concern that a clinician who is a specialist in one field might need to recognise and record potentially subtle abnormalities in organ systems that they do not normally examine, but which form an important part of an underlying syndrome with a genomic basis.

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Current inadequacies in the capture of clinical and phenotypic data are frequently raised as a challenge by the laboratory scientists receiving referrals from mainstream clinicians. Where referrals are still made with generic paper forms, as occurs in the majority of services, it is common to receive very sparse clinical details, or requests simply for a 'gene screen'. This has driven some laboratories to produce more detailed requests for phenotypic information and to require all parts of the form to be completed before testing of a sample will be undertaken.

A solution proposed to the challenge of obtaining the required phenotypic information at the time of referral is the use of digital phenotyping and family history tools that feed into electronic referral systems. This approach has been used successfully in large scale research programmes such as Deciphering Developmental Disorders (DDD) project and 100,000 Genomes Project, and has some significant advantages. These include:

- Standardisation: the ability to provide standardised and limited nomenclature (important for consistent laboratory interpretation) through the use of 'drop down' boxes from which clinicians select relevant phenotypes
- Decision support: the ability to add 'logic' to the referral form, so that inclusion of one phenotype generates a prompt to the clinician to record a focused subset of phenotypes known to be relevant in that particular context
- Ease of use: in principle, the ability to transfer information directly from electronic patient records where these exist. However, electronic referral systems are far from a panacea. Discussions within the workshop emphasised that the vast majority of patient data in the NHS remains paper-based

In all these models significant clinician time and effort must still be expended to obtain and extract the relevant data, particularly where phenotypic information from multiple specialties is required. Given the limited time (10-15 minutes) allocated to a standard specialist clinic appointment, it is frequently not possible for clinicians to capture and record in an electronic (or paper) system the depth and breadth of information that may ultimately be required to achieve a diagnosis for their patient.

This limitation has led many genomic laboratories to informally begin to deploy so-called 'reverse phenotyping' strategies. These laboratories accept referrals with relatively minimal accompanying clinical and phenotypic information and, on the basis of the initial results of their genomic analysis of the patient, seek more specific additional phenotypic information from the clinician to clarify the significance of potentially clinically meaningful findings. This strategy has the significant advantage of only requiring additional clinical effort when the prior probability of it contributing significantly to a positive diagnosis is high.

Alternatively, where the patient information is available electronically, access could be granted to clinical scientists within the laboratory undertaking the genomic analysis to allow them to extract any additional clinical information required to complete the interpretation and reporting processes. However, this functionality is currently rarely available within the NHS and laboratories rely on MDT co-ordinators or individual clinical scientists to contact (by phone, email, or in person) the relevant clinician to obtain additional information for interpretation.

4. Getting the correct result

Key points

- **Given our dynamic and sometimes limited state of knowledge relating to interpretation, reporting processes will need to evolve**
- **Genomic sequencing is increasing the complexity of interpretation of genetic test results and therefore increasing the necessary skill level**
- **Some cases will require the involvement of a multidisciplinary team**
- **Integrating phenotypic information is key to the interpretation of genomic variants. However, referrals from mainstream clinicians do not always include adequate information**

4.1 Introduction

Interpretation and reporting of wider genomic testing (Whole Genome Sequencing (WGS) and Whole Exome Sequencing (WES)) can be more complex than other forms of laboratory diagnostics as it needs to take into account:

- The clinical phenotype
- The decisions that the referring clinician needs to make

The way in which it is undertaken will also be influenced by the knowledge and skills of the referring clinician, the clinical area involved and organisational locations of the referrer, the genetic service and the laboratory.

Given our dynamic and sometimes limited state of knowledge relating to interpretation, the question to be addressed is how reporting processes can evolve to meet the needs of a wider set of more mainstream referring physicians and their patients. These physicians usually:

- Are less expert in genomics
- See fewer cases of a specific condition
- Have less time to spend on individual cases
- Are less likely to have close professional relationships with genetics services

Nevertheless, it is important that these services can be made to work for them and their patients in order to extend access to genomic testing.

4.2 Levels of interpretation and reporting

There are two steps of interpretation and reporting: a gene level or molecular report followed by the phenotypic contextualisation of the variant, that may be an MDT based fully integrated analysis in which the molecular finding is correlated with the phenotype.

Sometimes the interpretation of findings is relatively simple. For example, if the laboratory finds a variant that it is used to seeing or has found before and it fits the referral phenotype, then the scientist can sign the report and it can go straight back to the referring clinician. The referring clinician may sometimes be involved in test interpretation before the report is written and signed out.

The requirements of interpretation are shifting as we move away from panels of a relatively few, well-understood genes to genomic testing which increases the number of variants likely to be found and the potential for misinterpretation of a variant as disease-causing when it is not. Interpretation is increasingly complex, making it particularly important that it is undertaken by experts with the experience, resources and time to undertake the necessary evidence review.

4.3 Involving an MDT

> “MDTs are often a jumping-off point for further analysis, initiation of further tests to ‘firm up’ diagnosis”

It was noted that some cases will require wider, multidisciplinary consideration before a report can be issued. The purposes of the MDT were described as being for variant classification (the ‘genomic MDT’) or for diagnosis/management. These different purposes may be reflected in the type of MDT undertaken: the genomic MDT would be more laboratory driven, whereas the diagnosis/management MDT would be driven more around the specialty needs and the clinical decisions to be taken– (for example, in cardiology or neurology).

MDTs described in the workshop varied in their configuration and mode of operation, but essentially their role was said to be that of bringing together the clinical and any investigatory findings with the molecular findings for the purpose of providing an interpretation of results – an integrated diagnosis. The MDT sometimes may suggest expanded analyses or request further clinical information or investigations that would help with the assessment of the molecular findings. In other cases they provide an opportunity for discussion before result giving.

Specialist involvement on MDTs varies between services, depending in some cases on the referring mainstream clinician and also on their level of expertise. In other cases, the involvement of the referring clinician was found to change over time, starting with specialists who are genomics experts but evolving to include those with less genomics expertise. To start with the process had specialist cardiologists in MDTs, but now non-specialists bring cases to MDTs too.

The MDT is likely to include a range of professionals – laboratory scientists, geneticists and sometimes the relevant clinical specialists. The actual referring clinicians may also be involved, although this was not always possible or practical.

There is a general realisation that the more phenotypic work gets done upfront, and particularly before the MDT, the easier the downstream interpretation will be

MDTs have evolved a number of different processes, including physical face-to-face meetings, and virtual meetings by telephone or email. Sometimes these processes are iterative, with further information being requested from the referring physician. This may be done in person where the physician is from the same hospital, but is also undertaken by phone and email. One service had a coordinator, whose role was to gather the further phenotypic information from referring physicians for use in the MDT. There is a general realisation that the more phenotypic work gets done upfront, and particularly before the MDT, the easier the downstream interpretation will be.

Given the number of different professionals involved and the detailed evidence to be considered, such meetings can be time consuming. Indeed, the face-to-face meeting time was characteristically backed up by detailed research for each patient, which we were informed may be up to two hours for each patient. Mechanisms in place to streamline them included:

- A pre MDT consideration, where a virtual consideration of findings can take place with decision of whether the case needs to go to a full MDT
- Collecting a number of cases from one specialty for discussion
- Various arrangements such as phone-in or virtual MDTs

Despite being fairly resource intensive, there were positive wider outcomes of MDTs. As well as contributing to better patient care, they help to develop clinical engagement for the approach and provide a useful educational tool. The impression was that mainstream clinicians can benefit very quickly from this involvement.

4.4 Which cases are discussed in MDTs?

> “Cases discussed at the MDT are ones that require clinicians, clinical phenotype information, family history, counselling, VUs – i.e. cases where an integrated opinion is required”

Genomic MDTS are common where multiple potentially pathogenic variants are found (in large panels /WES/WGS), of which none entirely fit the clinical picture and a decision has to be taken concerning how to classify them and whether or not to report them. This would be done in consultation with the referring clinician or another expert clinician, in order to consider whether one or more of the variants were more plausible explanations for the phenotype, or whether additional phenotypic information could bring clarity.

Other cases that might go for MDT discussion are typically those where variants of unknown significance (VUS) have been found, and where further investigations or phenotyping or even molecular analysis may be required. Some of these were described as ‘hot 3’ class of variants: where there is insufficient evidence for significant clinical action but further action is necessary (mandated), such as further investigations, phenotyping and nuanced communication to the patient. It was noted that these results are very difficult to communicate by written report.

4.5 Incorporating phenotypic information

Acquiring and integrating the necessary phenotypic information is key to the interpretation of information on genomic variants. However, when referrals are coming from mainstream clinicians this is problematic for a number of reasons including inadequacy of the referral process.

Quite often, ‘to resolve the maybes’ the laboratory has to look for further information. Whilst it was sometimes possible to do this by looking back through patient notes, these were described as characteristically ‘massive piles of paper’ and not often electronic, making the work extremely cumbersome. Frequently the laboratory has to go back to the referring clinician, which in many ways was considered preferable as, in general, it was thought that there is no substitute for speaking to the clinician who has seen or knows the patient.

The implication of this need to gather further information is that, although mainstream clinicians are not expected to have a deep understanding of genetics, they must be able to participate in a dialogue as part of interpretation.

Collecting phenotypic information could be expedited by:

- Electronic referrals with mandatory fields (coming soon)
- Incorporation of HPO terminology in referral AND analytical approach
- Laboratory access to full patient records - this is very useful for the laboratory

There are tools available to capture phenotypic data for example Gen-O, a web-based tool that enables mainstream clinicians to access genomic information in the care of their patients. It is iPad friendly and allows interaction with patients during a secondary care appointment. Gen-O standardises patient phenotype capture, provides secure integrated viewing of images, genomics and phenotypes, and enables virtual MDTs.

5. The genetic report

Key points

- **It was reported that in the vast majority of cases, the laboratory report goes directly back to the referring clinician without any input from other specialist physicians via an MDT**
- **There are real concerns that mainstreaming genomics will involve clinicians with little understanding of this rapidly developing field and limited practical experience of how they should use it**
- **There should be no expectation that mainstream clinicians will be able to interpret the technical details of the report. It is highly likely that clinicians will need support from clinical scientists and this should be part of the testing service**
- **Going foward, reports should be consistent and standardised**

5.1 Requirements for the referring clinician

> "I feel worried for my colleagues who are sending off these tests - with little genomics experience"

The referring clinician wants to know:

- Are the reported gene variants responsible for the patient phenotype (a definite yes)? If not, what more does the laboratory need to know to interpret this?
- What do I do next? Are further investigations indicated e.g. exome sequencing, further phenotyping or referral to another specialist such as a clinical geneticist?

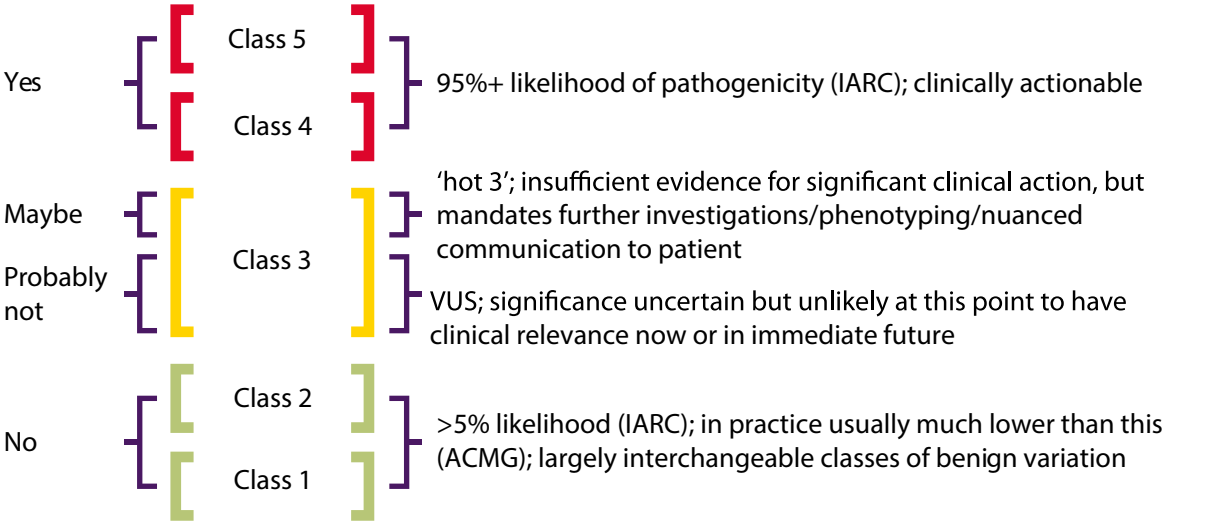
The problem when considering mainstreaming genomics is that the expanded pool of clinicians who will be encouraged to refer patients for testing currently have little understanding of this rapidly developing field of medicine and limited practical experience of how they should use it for their clinical decision-making. There are real concerns amongst those more specialist in the area that test results will be misinterpreted, with obvious risks to patient safety for the individual and relatives

Examples of misinterpretation were given e.g. a variant in *BRCA1* (noted at the bottom of the form) was reported back to the patient as a mutation when no mutation was detected.

5.2 Reporting variants: classification of variants

> “The big problem in mainstreaming is that clinicians see a variant in the gene that goes with the disease they are thinking about and they assume it is pathogenic. No type of classification will change that, unless it is headlined what is/isn't actionable. But we still need other ways of capturing/reporting the VUS as these may be picked up by other laboratories later with further evidence of pathogenicity ”

Standard practice is for laboratories to classify variants into 5 classes:



(Image from Leeds Genetics Laboratory)

Many of the clinicians supported the idea that having five groups was not helpful and that three would be enough. The word 'pathogenic' here was not helpful and some laboratories talk of 'clinically actionable' rather than 'pathogenic'. It was generally thought that the clinical report ought to explain the results and required actions in standard terms. However, as a counter to this, clinical scientists noted that the five classes were helpful in signifying the degree of certainty that could or should be attached to the result.

Depending on the clinical decisions that may be made on the basis of such results, this expressed level of uncertainty could be critical.

5.3 Variants of uncertain significance

In general, it was thought that laboratories should be discouraged from reporting back VUSs in most cases, as these will only be of use to the clinical scientists or clinical geneticists. Where they are included, it should be stated on the report that any VUSs returned are not actionable variants.

Examples of approaches to VUS:

- Exeter approach to diabetes: In diabetes they don't report VUSs from a panel unless they think there is something that could be done to resolve them
- Class 3 variants are not reported but are available on request. In the body of report, it is stated that nothing has been found that is actionable

However, even if not reported back to the mainstream clinician, VUSs cannot be ignored - in the hands of clinical genetics expert, they may provide an answer to a clinical question. With respect to providing future information, it is important that VUSs are logged for later review as appropriate. In this case, there needs to be a pathway for revisiting these. As an example, in Liverpool, this is done via a file note:

> … come back in 2-3 years to consider if tech/knowledge warrants re-analysis. Patients never discharged, always under review

5.4 Inclusion of technical details about the test

> "If it came back as a 'we don't know but that's because the coverage is less than 100%', then fine, but I still want guidance on what I should do now"

Workshop participants thought that technical details about the test (e.g. how the test was done, what genes were covered and to what depth) should be accessible in some way, although they will not be needed by most mainstream clinicians. There should be no expectation that mainstream clinicians will be able to interpret the technical details of the report. However, other laboratories may need access to the technical details for a variety of reasons, such as for testing of relatives.

> "Clinicians do not need to know how the test was done"

5.5 Further referral to clinical genetics

For some patients with positive results onward referral will be recommended to clinical genetics. These may include syndromic patients, complex cases or cases where cascade testing or reproductive counselling may be required. In such cases, the recommendation for further referral should be clearly stated on the report.

5.6 Recommendations for reports

> "Generating a lot of genomic results but not being able to commit to what is actionable – may undermine the process of doing genetic testing in first place"

Many different styles and contents of reports were described in the workshop. One of the most important findings of participants was that, going forward, reports should be consistent and standardised.

> "Would not want all cases to go through an MDT, but we do need confidence as to what is a pathogenic variant, to be able to implement cascading"

Important features of reports for referring mainstream physicians were noted as:

- Reports need to be consistent and understandable by patients as well as by their physicians. It would be helpful if both the language and the format of reports were standardised
- Reports need to be simple, stating whether or not any finding is clinically actionable. They should include the conclusions of the MDT. To enhance simplicity, it was suggested that the simple clinical findings and actionability could be on the front of the report and all other findings and information on the reverse
- The evidence for the interpretation should not be included but should be accessible, for example via a weblink
- Technical details should not be included but should be accessible from the report, as an appendix or via a web link
- Where further referral to clinical genetics is recommended, this should be clearly stated on the report
- Reports should include supporting educational material for the receiving clinician and for the patient

5.7 Formal standards for reporting

In the light of the discussion above regarding the nature of clinical reports, participants reflected on the formal standards for reporting.

Participants were clear that reports should be standardised. In general terms, there should be consistency between laboratories on what and how to report. Although some standards will be generic, the detail may need to be adapted for different diseases. In terms of content, for example, if two centres are providing reports on the same gene, they should communicate and decide how they will report.

Balancing levels of detail is also a challenge. Expectations of EQA and accreditation bodies to include considerable detail are currently at odds with the discussion above outlining that the level of detail desirable will depend on the audience.

The BSGM and associated body ACGS are currently working on Best Practice Guidance with respect to the detail in reports and, as part of the 100,000 Genomes Project, the Validation and Reporting work streams are considering what is appropriate to include in genomic reports. This is of particular importance since the area has been identified as carrying the greatest risk for the NHS with regard to litigation. If a report is issued and the clinician acts on it, but in an uninformed way, this will not be a defence. Clearer signposting of sections and their clinical significance could improve clarity.

5.8 Support required for mainstream clinicians throughout interpretation and reporting

Genomic medicine is a very new developmental area for clinicians in mainstream practice. It cannot be expected that they will be able to adapt their practice immediately, even though they may have attended awareness raising events and short courses. They will need time within their clinical practice to acquire sufficient expertise and skills to be able to deliver safe, high quality genomic testing.

It is also likely that, even after that, they will need to be able to access appropriate clinical and laboratory scientific expertise and be supported by ongoing education and training. It was clear that those who would be expected to refer for genomic testing would require training in interpretation and what they may be expected to contribute to it. They would also need to understand what to expect in the clinical report, particularly the way in which it may support clinical decision-making.

However, even if upfront learning has been achieved, it was still considered highly likely that clinicians would need support from clinical scientists on receipt of the report and that this should be provided as part of the testing service.

6. A fully integrated referral and reporting service

Key points

- **The Leeds Teaching Hospitals NHS Trust provided an example of how a fully integrated MDT service could operate**

The capture of phenotypic data (including clinical assessment and specialist investigations) was undertaken as part of a specialist multidisciplinary service in the investigation of Genetic White Matter Disorders – Leukodystrophy and Leukoencephalopathy. This was offered in the context of a specialist teaching hospital/regional genetics laboratory (Leeds). The new format for a fully integrated MDT service operates as follows (see Appendix 8.2):

- Initial referral through usual pathway using UKGTN testing criteria (Genetics, Neurology)
- Clinical coordinator contacts referrer to arrange electronic capture of neuroradiological imaging & full clinical details
- Exome (Agilent Focused) set-up (~6-8 weeks processing)
- MDT (Genetic Scientist, Genetic Clinician, Paediatric Neurologist, Neuroradiologist)
- Preliminary discussion of phenotype & scans to determine differential diagnosis; virtual initial exome panel (six options) chosen
- Analysis of virtual panel; expansion to full 98-gene panel if negative
- Agnostic assessment of exome data to identify candidate variants in 2000+ gene list
- MDT discussion of potential candidates; scans re-assessed to determine likelihood of diagnosis
- Additional tests, research group and investigations initiated
- Final report written (lab-based; refers to MDT outputs)

This format includes many of the elements discussed above, with a key coordinator role to assemble information and a defined process that formalises the various stages and enables clinicians to access the service and be sure of high quality sequencing and interpretation, even though they may have limited expertise themselves.

7. Conclusions

Key points

- **Choosing which patients will benefit from genomic testing and making the right referral is a significant challenge in mainstream medicine**
- **It is unlikely that mainstream clinicians will have the knowledge to select the appropriate test in any level of detail**
- **There are serious questions about how the process of capturing phenotypic information can be made more effective and efficient**
- **Vital to effective referral is obtaining detailed consent for testing, which requires both training and time**

This PHG Foundation-led workshop brought together clinicians from a wide range of specialties to discuss the issues that will arise in the wider incorporation of genomic testing into clinical practice in mainstream specialties.

Identified in that workshop, and set out in this report, are some of the complexities and unresolved issues that must be addressed if genomic testing is to be more widely and equitably accessed through the health system.

Choosing which patients will benefit from genomic testing and making the right referral is critical, but remains a significant challenge in mainstream medicine. Equitable access means this must be supported by clear criteria, guidelines or standardised information of which the clinician must be aware. These must be sufficiently broad but backed up by gate-keeping mechanisms to ensure appropriate referral.

It is unlikely that mainstream clinicians will have the knowledge to select the appropriate test in any level of detail; indeed, selecting the most appropriate test - particularly where the patient has multiple phenotypes - can be difficult. It is probably therefore not realistic to expect mainstream clinicians to do this. However, as it can be confusing to have different laboratories using different test panels for the same or similar phenotypes, test panels should be standardised.

There is a question about who can order tests. Opinions varied depending on the service represented. Some felt that any consultant should be able to do this, others that ordering tests should be limited to a subset of specialists who have received additional training.

Further questions arise as to who should develop the criteria or guidelines that are used for test referrals. Various models apply, including the UKGTN testing criteria and those developed by local services such as the regional genetics service or professional bodies.

There are questions about who should ensure appropriate application of the guidance or criteria – whether this should be the local genetics service, or self-policing the use of tests within specialties through audit.

Once the decision has been made to refer for testing, it is important this process enables the achievement of the most clinically accurate interpretation possible and consequently the best possible outcomes for the patient. Getting the diagnosis wrong can be harmful to the patient and possibly also to their family members. Here, there is a balance of the skill and resources of the referring clinician as well as the time and support available through the health system.

Making the referral - conclusions

- Clinically meaningful and accurate genomic analysis requires a good phenotypic and clinical description of the patient
- Short clinic slots are not conducive to 'deep phenotyping', including taking an extensive family history
- Specialists tend to focus investigations on their own organ or system of interest (e.g. kidneys and nephrology) and may miss more disparate syndromic features
- Reliance on paper records makes collecting detailed patient information difficult and time consuming
- Referral forms need to guide and support, but not overburden the clinician with demands for information

There are therefore serious questions about how the process of capturing phenotypic information can be made more effective and efficient. Some options were discussed, including EPRs, logic models and reverse phenotyping, but overall the workshop concluded that this task must be addressed and supported explicitly with a framework for how it should happen and the necessary resources to support its implementation.

Another vital aspect of the process of referral is obtaining detailed consent for testing. This requires both training and time – two resources that are in short supply in mainstream clinics across the country. Some specialties and services operate by having specialised 'inherited disease' clinics, where specialists have received formal sub-speciality training in genomics. Such clinics are also often set up with clinical genetics input (for example through a genetic counsellor). However, it was reported that such sub-specialty clinics are not provided on an equitable basis across England.

Detailed phenotyping and consent processes both require adequate clinical time. This may be achievable where specialties characteristically have longer clinic appointments, but a different model will be necessary for specialties where much shorter clinic slots are the norm, such as ophthalmology.

Interpreting genomic test results - conclusions

Interpreting genomic test results and making the necessary clinical decisions is a complex task. Interpretation depends on the molecular findings, the clinical phenotype and the decision to be made. Even those mainstream clinicians who have had some specialist genomics training may struggle with this, and it is probably unrealistic to expect them to interpret results without considerable help from the clinical genetics services, except where such results are judged to be extremely straightforward.

- Wider genomic testing is now being undertaken, which tends to increase the number and diversity of abnormal variations that may be found and which will need interpretation
- There is potential for harm from a 'wrong diagnosis' when a clinician has erroneously interpreted a variant as disease-causing
- The harm may include the patient being tested and family members who may also wrongly be labelled with a disease-causing variant

The proportion of tests considered relatively simple to interpret compared to those judged to be more complex and requiring assistance may differ between specialties.

Workshop recommendation

Explicit consideration should be given in different specialties and services about whether referring clinicians should be involved in multidisciplinary team meetings, under what circumstances and how

Test reports can be confusing and hard to understand by those without genomics expertise or specific training.

The workshop concluded that:

- Reports should be simple and give straightforward information and clinical interpretation
- Reports should be standardised in terms of content, language and format
- Reports should not include evidence for interpretation nor technical details of the test, although this information should be available to clinicians should they wish to access it. However, we note that this may not align with ACGS requirements. Clear signposting within the report could improve clarity

Workshop recommendation

The referral report should be accompanied by educational information about the test and the condition that would be useful to professionals and the patient

8. Appendices

8.1 Workshop participants

Speakers

Ian Berry
Clinical Scientist, Leeds Genetics Laboratory, St James's University Hospital

Prof Graeme Black
Professor of Genetics and Ophthalmology and Strategic Director, Central Manchester University Hospitals and Manchester Centre for Genomic Medicine

Prof Angela Douglas
Scientific Director, Cheshire and Merseyside Regional Genetics Service

Prof John Sayer
Professor of Renal Medicine, Institute of Genetic Medicine, Newcastle University

Delegates

Dr William Bradlow
Cardiology Consultant, Queen Elizabeth Hospital Birmingham

Dr Manali Chitre
Consultant Paediatric Neurologist, Cambridge University Hospitals

Dr Amanda Churchill
Consultant Ophthalmologist, University Hospitals Bristol and Honorary Clinical Lecturer, University of Bristol

Prof Sian Ellard
Consultant Clinical Scientist, Royal Devon & Exeter NHS Foundation Trust

Dr Frances Elmslie
Consultant Clinical Geneticist, St George's Hospital

Georgina Hall
Consultant Genetic Counsellor, Manchester Centre for Genomic Medicine

Dr Luis Lopes
Consultant Cardiologist, and Honorary Senior Lecturer Barts Health Centre, Institute of Cardiovascular Science, UCL

Dr Ankit Mathur
Consultant Community Paediatrician and Clinical Director for Community Paediatric Medical Services, Suffolk Community Healthcare

Dr Fiona Macdonald
Scientific Adviser, UK Genetic Testing Network (UKGTN)

Dr Shehla Mohammed
Consultant in Clinical Genetics and Head of Service, and Honorary Senior Lecturer in Clinical Genetics, King's College Hospital and Guy's & St Thomas' NHS Foundation Trust

Prof Ruth Newbury-Ecob
Consultant in Clinical Genetics, University Hospitals Bristol

Dr Gerrard Phillips
Vice President of Education and Training, Royal College of Physicians

Dr Allison Streetly
Deputy National Lead, Healthcare Public Health, Public Health England

Dr Kate Tatton-Brown
Consultant in Clinical Genetics, St George's University Hospitals

Dr Claire Shovlin
Reader in Clinical and Molecular Medicine, Imperial College London

Prof Graham Taylor
Scientific Director, Clinical Genomics, ViaPath, Guy's & St Thomas' & King's College Hospitals

Dr Yvonne Wallis
Consultant Clinical Scientist, West Midlands Regional Genetics Laboratory (WMRGL)

Workshop secretariat

Dr Hilary Burton
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Dr Louise Gaynor
Policy Intern, PHG Foundation

Alison Hall
Head of Humanities, PHG Foundation

Dr Mark Kroese
Deputy Director, PHG Foundation

Dr Leila Luheshi
Head of Science, PHG Foundation

Dr Sobia Raza
Senior Policy Analyst (Data Science), PHG Foundation

8.2 An example of a fully integrated referral and reporting service

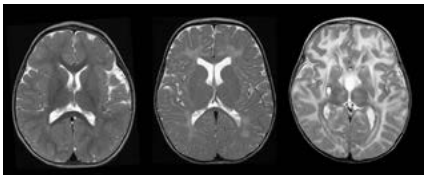
The Leeds Teaching Hospitals NHS
NHS Trust

Genetic White Matter Disorders - Leukodystrophy & Leukoencephalopathy

Focused exome analysis and MDT for white matter disorders

Multi-disciplinary Diagnostic Service for White Matter Disorders at the Leeds Teaching Hospitals NHS Trust

- Multi-disciplinary diagnostic service including specialist clinical and radiological assessment, plus molecular genetic diagnosis
- Phenotype-targeted analysis of up to 95 genes by next-generation sequencing
- All patient information and images reviewed at monthly MDT to determine the most appropriate diagnostic strategy and interpretation of results
- Flexible, exome-based analysis; Potential to expand analysis beyond this panel for patients with unusual presentations (on consultation)



Normal
Aged 16m

Hypomyelination
TUBB4A
Aged 20m

Dysmyelination
Alexanders disease
(*GFAP* mutation)
Aged 16m

Requirements

Blood (1-5mls preferably in EDTA), or extracted DNA, plus relevant imaging made available by IEP or equivalent imaging software

Turnaround

80 days

Price

£860 per sample (additional surcharges may apply for reanalysis)

Further Information

Email: leedsth-tr.dna@nhs.net *or* jh.livingston@nhs.net

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Leeds Genetics Laboratory

8.3 Workshop agenda

29 March

Wellcome Collection

Agenda

09:30	**Registration and coffee**
10:00	**Welcome and overview** *Dr Hilary Burton* Director, PHG Foundation
10:10	**Clinical pathways in genomic ophthalmology** *Prof Graeme Black* Professor of Genetics and Ophthalmology and Strategic Director, Central Manchester University Hospitals and Manchester Centre for Genomic Medicine
10:30	**Genetic investigations in familial renal disease - trials and triumphs** *Prof John Sayer* Professor of Renal Medicine, Institute of Genetic Medicine, Newcastle University
10:50	**Q&A**
11:00	**Break**
11:20	**How to successfully mainstream genomic testing into medical practice** *Prof Angela Douglas* Scientific Director, Cheshire and Merseyside Regional Genetics Service
11:40	**Mainstreaming genetic service in the Yorkshire & Humber GMC** *Ian Berry* Clinical Scientist, Leeds Genetics Laboratory, St James's University Hospital
12:00	**Q&A**
12:10	**Introduction to afternoon sessions** *Dr Leila Luheshi* Head of Science, PHG Foundation
12:15	**Breakout session - optimising the referral process**
13:15	**Lunch**
14:15	**Breakout session - optimising reporting results**
15:15	**Break**
15:30	**Present, refine and agree recommendations** *Dr Leila Luheshi*
16:15	**Summary & close** *Dr Hilary Burton*

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