Exemplar clinical pathways for a stratified approach to cardiovascular disease

Summary report of a meeting held on 17 March 2016 by the Academy of Medical Sciences, and supported by NHS England.

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This document reflects the views of participants expressed at the meeting and does not necessarily represent the views of all participants or of the Academy of Medical Sciences or NHS England. For further information, please contact Liberty Dixon, Policy Officer at the Academy of Medical Sciences (liberty.dixon@acmedsci.ac.uk, 020 3141 3222).

All web references were accessed in March 2016.

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Summary

The Academy of Medical Sciences, supported by NHS England, held a roundtable on 17 March 2016 to explore '*Exemplar clinical pathways for a stratified approach to cardiovascular disease'*. This meeting aimed to build upon the findings of the previous roundtable centred on the adoption of stratification in diabetes, and to discuss different aspects of the clinical pathways for cardiovascular disease including commissioning, awareness, education and training, and health economics.

The meeting brought together participants from across the healthcare sector to consider the drivers for adoption of a stratified approach, barriers to implementation and next steps to addressing these challenges. Familial hypercholesterolaemia is a relatively common inherited disorder, where, despite featuring in NICE guidance, there is limited access to relevant diagnostics and considerable variation in patient management across England. Genetic testing and cascade testing are effective methods to identify and confirm patients and affected relatives, facilitating early diagnosis and prevention of heart disease. Similarly, the clinical pathways for inherited cardiac conditions hypertrophic cardiomyopathy and long QT syndrome benefit from genetic and subsequent cascade testing processes, but are still not yet widely adopted in the UK. All three diseases can lead to serious consequences including heart disease and sudden cardiac death, and so there are tangible benefits to implementing a stratified approach to these patient pathways.

Participants identified several common themes that are essential to ensuring effective, country-wide adoption of the stratified clinical pathways:

- **Review and alignment of commissioning processes** whether in Clinical Commissioning Groups or specialised commissioning, to ensure equity of access and streamlined clinical pathways for adoption by overcoming issues such as funding for tests.
- **Integration of clinical services** across the end-to-end patient pathway, enabling efficient knowledge transfer and effective referral processes.
- **Implementing a systematic approach** to identifying patients both retrospectively and prospectively, and for stratification of patients along the clinical pathway.
- **Building capability** through clinical education by embedding the care pathways into specialist and non-specialist training, and **developing capacity** through additional, focused resources such as trained genetic nurses.
- **Raising awareness** with both clinicians and patients to facilitate entry onto the right clinical pathway as early as possible, and overcoming clinician and public negative perceptions which may impede patient management.
- Developing and **communicating clear messages on the economic benefits**, and wider advantages, of the clinical pathways and working to shift the mindset from short term financial goals to a more holistic view of long term financial and health gains.
- Establishing **standardisation and consistency of genetic testing processes,** supported by further education and knowledge sharing platforms.

This report reflects the views of the participants at the meeting and will feed into NHS England's and the Academy's work on stratified medicine. The suggested next steps for

implementation should be considered by all stakeholders to ensure that the stratified pathways for cardiovascular disease are fully integrated into the healthcare system.

Background

Stratified medicine offers a wealth of opportunities for the healthcare sector, potentially enabling patients to benefit from more targeted treatments while delivering efficiencies across the healthcare system.[1] It represents a move away from a 'one size fits all' treatment approach to one which better manages patient health on a more personalised level using emergent approaches in areas such as diagnostic tests, 'omics' technologies, molecular pathways and data analytics. This presents a powerful opportunity to better target therapies to achieve the best outcomes in the management and prevention of disease.[2,3,4]

In recent years, the Academy of Medical Sciences has played an active role in supporting the implementation of stratified approaches in the NHS. The Academy identified key barriers to implementation in its 2007 report and given the slow progress in overcoming these issues, a working group report on '*Realising the potential of stratified medicine'* was published in 2013, making recommendations to address challenges around infrastructure, development of companion diagnostics, regulation, collaboration and pricing and reimbursement.[2,5] Most recently in May 2015, the Academy held a FORUM symposium to explore progress against some of these challenges, and this highlighted the continued need for the health system to evolve in order to keep pace with technological innovation and the new approaches to healthcare that this enables.[6] To date, NHS England's main focus in this area has been on the NHS contribution to the 100K Genomes Project and embedding genomic technologies in clinical care pathways. It recognises the need to locate this initiative within a broader strategy for personalised medicine and is therefore in the process of developing its approach to personalised medicine.[4]

Building on the previous roundtable looking at a stratified approach in diabetes, this meeting aimed to consider exemplar clinical pathways for a stratified approach to cardiovascular disease and specifically, familial hypercholesterolaemia (FH) and the inherited cardiac conditions hypertrophic cardiomyopathy (HCM) and long QT syndrome (LQTS). These areas offer useful exemplars for the wider field of cardiovascular disease as they are well characterised at a molecular level, with the diagnostic tests and proposed clinical pathways for stratification already established. As these patients face potentially serious consequences, there is significant patient and system benefit to be derived from accurate, early diagnosis, which could prevent cardiac disease or even death. However, there are still barriers remaining to uptake and adoption of a stratified approach in these areas. Therefore this roundtable aimed to explore these challenges further and identify

[1] It should be noted that in this report, the terms 'stratified', 'personalised' and 'precision' medicine are used according to the speakers and delegates and confer the same meaning.
[2] Academy of Medical Sciences (2013). *Realising the potential of stratified medicine.* https://www.acmedsci.ac.uk/viewFile/51e915f9f09fb.pdf
[3] Association of the British Pharmaceutical Industry (2014). *Stratified medicine in the NHS.* http://www.abpi.org.uk/our-work/library/medical-disease/Documents/stratified_med_nhs.pdf
[4] NHS England Board paper (2015). *Personalised medicine strategy*. http://www.england.nhs.uk/wp-content/uploads/2015/09/item5-board-29-09-15.pdf
[5] Academy of Medical Sciences (2007). *Optimizing stratified medicines R&D: addressing scientific and economic issues.* https://www.acmedsci.ac.uk/viewFile/publicationDownloads/120151486883.pdf
[6] Academy of Medical Sciences (2015). *Stratified, personalised or P4 medicine*. http://www.acmedsci.ac.uk/viewFile/564091e072d41.pdf

ways to overcome these to achieve country-wide adoption of the clinical pathways, as part of the implementation of a broader personalised medicine approach across the NHS.

Introduction to a stratified approach

Introducing NHS England's Personalised Medicine Strategy

Professor Sue Hill, Chief Scientific Officer, NHS England

Professor Sue Hill opened with an overview of NHS England's current work programme on personalised medicine, which was approved in September 2015.[7] Genomics lies at the core of the approach, which will incorporate legacies from the 100K Genomes Project. Aligned to the Five Year Forward View and NHS priorities, an approach to personalised medicine is being developed which will aim to facilitate and improve prevention and prediction of disease, earlier and more precise diagnosis, and more targeted interventions and diagnostics.

In the long term, NHS England envisions that every patient will receive personalised care based on a comprehensive understanding of the cause of disease and the end-to-end patient pathway from initial presentation to secondary, or perhaps tertiary, care. This may build upon genomic information to better target interventions alongside employing emergent approaches such as other 'multi-omics' – for example proteomics and metabolomics – together with the use of data analytics and machine learning. Professor Hill stressed that this will advance the delivery of patient-centred care and support efficiencies across the healthcare system.

Capitalising on the data revolution

The exponential growth in clinical data, including from the 100K Genomes Project, must be fully utilised and integrated in routine care. With the gradual shift from genotyping to full sequencing, NHS England is exploring the number of whole genome sequences that should be procured for clinical care from 2018/19 onwards. To enable maximum clinical and research utility, further developments in informatics and data in the NHS are therefore required.

Professor Hill emphasised that a mechanism is needed for ensuring that emergent technologies are fully adopted at scale and pace within the NHS, underpinned by a flexible and responsive commissioning system. A fit-for-purpose infrastructure is critical to this, allowing the breadth of data to be captured for the integrated clinical picture required for personalised medicine. These data provide the opportunity to tackle various issues such as adverse drug reactions and ineffective treatment regimes, enabling more effective use of the current NHS spend of £8 billion on diagnostics and £13 billion on drugs. She stressed that NHS England will continue to drive better use of clinical data for practice, research capabilities and partnerships with industry.

Delivering the personalised medicine vision

Personalised medicine will help to accelerate the move from a 'one size fits all' approach with services arranged by organ speciality, limited use of innovative markers and underutilised data, to a new taxonomy of medicine with both an individual and holistic approach to care, tailored therapies and integrated clinical services. Essential to achieving

[7] NHS England Board paper (2015). *Personalised medicine strategy*. http://www.england.nhs.uk/wp-content/uploads/2015/09/item5-board-29-09-15.pdf

success is engaging the raft of healthcare professionals involved, which will require system and leadership changes in clinical care as well as recognising the participatory role that patients and the public will need to play.

The 13 NHS Genomic Medicine Centres (GMCs) established as part of the 100K Genomes Project, work across defined geographies and comprise a lead organisation for contracting purposes and partnership agreements with other local hospital Trusts. This country-wide network approach is helping to build the NHS infrastructure needed for personalised medicine as well as driving up standards, streamlining pathways and industrialising processes. It is also informing the need, in part, to re-design increasingly complex commissioning pathways to overcome the multiple commissioning options and variation in approaches.

To date, NHS England has engaged regional leaders on its strategic approach, including clinicians, commissioners, academics and patient representatives. Surfacing from these interactions is a shared ambition for a bold five year programme for personalised medicine, and Professor Hill emphasised that this is recognised as transformational for the NHS, requiring multiple system partners to coordinate delivery. There are challenges to be overcome to achieve this including commissioning barriers, information silos and affordability. Finally, she concluded that it is essential to improve all diagnostic services, and not only genomics, which will rely on a responsive commissioning framework founded on a clear economic case for new models of care.

A national approach to familial hypercholesterolaemia

Professor Huon Gray, National Clinical Director for Heart Disease, NHS England

Professor Huon Gray urged participants to reflect upon the significant contribution of high cholesterol towards the global burden of disease. As the seventh largest risk factor contributing to burden of disease, cholesterol levels are critical from a wider population perspective.[8]

The Department of Health's Cardiovascular Disease Outcomes Strategy raised the importance of FH and inherited cardiac conditions in the NHS, and the Five Year Forward View drew attention to prevention of disease including cardiovascular disease where modulating cholesterol is imperative to achieving prevention.[9] Professor Gray proposed that cholesterol and FH should be paid greater attention considering that there are 240K FH patients in the UK (at the maximum estimated prevalence), compared with the high awareness of the estimated 25K type 1 diabetes patients under 25 years of age.

Despite concluding that FH cascade testing and treatment programmes are both clinically and cost-effective, Professor Gray highlighted that the 2008 NICE guideline for FH is still

[8] Murray C *et al* (2013). *UK health performance: findings of the Global Burden of Disease Study 2010.* Lancet, **381 (9871)**, 997-1020

[9] Department of Health (2013). *Cardiovascular Disease Outcomes Strategy: Improving outcomes for people with or at risk of cardiovascular disease.* https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/217118/9387-2900853-CVD-Outcomes_web1.pdf

not widely implemented, with similar levels of low awareness for the 2013 Quality Standard. Today, the cost-effectiveness is even further improved by the reduced cost of statins and increased known prevalence of FH, so much so that it is estimated that current care pathways cost less than half of the original NICE estimate.[10]

Challenges to adoption of a stratified approach

Professor Gray considered the key barriers to implementation of the NICE endorsed approach, which include focusing on short term costs of the clinical pathway rather than long term gains. In addition, the commissioning process for FH and hypercholesterolaemia is poorly understood and impeded by the absence of FH within Clinical Commissioning Group (CCG) business plans (the high prevalence places FH within CCG budgets) as well as by the need for change in the whole system approach to service provision. Underpinning these barriers are challenges around mindset with perceptions that cholesterol at 7.5mmol/l is too 'common' and so should not be highlighted in primary care. He also proposed that FH is sometimes misinterpreted as a specialist area and therefore not managed appropriately in primary care.

Professor Gray stressed that data collection across the clinical pathway will be critical for implementation, from suspected cases to treatment, spanning the many disciplines involved such as lipidology and genetics, and also to enable an assessment of the implementation of the pathways in clinical practice. To date, there has been notable progress such as funding of licenses for the PASS FH database by HEART-UK, availability and refinement of genetic testing, and establishment of FH nurses in lipid clinics.[11] However, much of the progress is supported by temporary, finite funding and once this ends, the costs will need to be picked up by others including CCGs to ensure sustainability.

The genetics of familial hypercholesterolaemia

Professor Steve Humphries FMedSci, Director of the Centre for Cardiovascular Genetics, University College London

Professor Steve Humphries provided an overview of FH, a relatively common disease with an estimated UK prevalence of between 1 in 250 to 1 in 500, but underdiagnosed with less than 10% of predicted patients known. Diagnosis is based on the UK Simon Broome FH register for patients with cholesterol >7.5mmol/l in adults and >6.7mmol/l in children, and other factors including a history of high cholesterol. FH patients are at high risk of heart disease, with 50% male patients having a myocardial infarction by 50 years of age, and 60% of women by 60 years of age. However, intervention with statins – more aggressively than for other high cholesterol patients – is highly effective and gives treated patients the same life expectancy as the general population. Given that it is an autosomal dominant disorder where inheritance of only one affected gene copy from one parent can result in FH, cascade testing (subsequent genetic testing of family members to identify affected relatives) is a highly effective system of identifying FH patients.

[10] Pears R *et al* (2014). *The reduced cost of providing a nationally recognised service for familial hypercholesterolaemia*. Open Heart, **1**

[11] As discussed later, PASS is the database used in Wales for management of FH patients.

The genetic basis of FH

Professor Humphries explored the aetiology of FH which arises from the accumulation of cholesterol in the blood, predominantly caused by mutations in genes coding for one of three proteins: the LDL receptor which is the most common cause; ApoB; and PCSK9 which is the least prevalent cause. Genetic testing is used to confirm a mutation and until recently this was expensive and time consuming, but this has since been overcome by next generation sequencing methods which are more rapid at lower cost. Professor Humphries noted that the cost is not likely to decrease further as it now mainly comprises the costs of staff needed to administer these tests.

If untreated, FH can result in coronary artery disease and Professor Humphries explained that PCSK9 mutation patients have the highest cholesterol levels and so are most at risk. FH is treated with statins which enable a 30% reduction in cholesterol. The mutation often dictates treatment response, with ApoB mutation patients responding most favourably. Patients with PCSK9 mutations have the highest cholesterol levels following treatment, although these patients still greatly benefit from statins. Therefore several pharmaceutical companies have developed monoclonal antibodies targeting the PCSK9 protein to further reduce cholesterol – these have recently received NICE approval for use in a limited subgroup of patients with raised cholesterol.

The NICE guideline for FH was published in 2008 and made two key recommendations: that all patients should be offered a genetic test; and that cascade testing for families should be initiated. Identifying the mutation in a family is key to enabling cascade testing which can lead to efficient prevention of cardiovascular complications in family members through early statin therapy.

The economic argument

A monogenic cause of FH is found in ~40% patients. For those without an FH mutation, a large proportion of elevated cholesterol can be attributed to polygenic hypercholesterolaemia where each genetic variant can incrementally raise cholesterol to produce an overall level that imitates monogenic FH.[12] Professor Humphries argued that cascade testing should only be initiated for monogenic FH patients. For the other patients, who often have fewer than 30% affected relatives, it was proposed that further investigation should be carried out instead, as health economics modelling indicates that focusing cascade testing on monogenic FH patients delivers tangible, cost-effective benefits. Expense is saved through managing polygenic patients in primary care rather than referral to an expensive tertiary centre, whereas there is a strong imperative to manage monogenic FH patients in tertiary care as they are more severely affected by a higher cholesterol burden from birth and resulting risk of coronary artery disease.[13] In the future, this approach would also facilitate identification of those mutations with a higher risk of coronary artery disease, for application of targeted drugs such as PCSK9 inhibitors.

[12] Talmud P *et al* (2013). *Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study.* Lancet, **381(9874)**, 1293-1301

[13] Futema M *et al* (2015). *Refinement of variant selection for the LDL cholesterol genetic risk score in the diagnosis of the polygenic form of clinical familial hypercholesterolaemia and replication in samples from 6 countries.* Clin Chem, **61(1)**, 231-238

In conclusion, Professor Humphries stressed that stratification of those with a clinical diagnosis of FH into high risk monogenic and lower risk polygenic will have an important impact on guidelines and should be addressed by NICE, which currently recommends cascade testing for all FH diagnoses. This proposed approach, including selectivity around tertiary centre referrals, will ultimately further improve the cost-effectiveness of the overall FH clinical pathway combined with efficient genetic and cascade testing processes.

A stratified approach to inherited cardiac conditions

Professor Hugh Watkins FMedSci, Professor of Cardiovascular Medicine, University of Oxford

Professor Hugh Watkins highlighted that inherited cardiac conditions (ICCs) are not especially rare, indeed affecting 150-200K patients in the UK with population prevalences of: 1 in 500 for HCM; 1-2 in 5000 for LQTS; 1 in 5000 for Marfan syndrome. He stressed that despite the prevalence, these conditions are sufficiently uncommon that population screening would be ineffective given the complicated and costly diagnostic tests and interventions. The conditions are often discovered later in life and are generally managed in tertiary care as they can carry potentially serious implications such as sudden cardiac death. They are mostly autosomal dominant and highly variable with no single causative gene, but are well characterised at a genetic level which permits effective stratification and cascade testing.

The benefits of genetic testing

Professor Watkins pointed out that 40-60% of HCM is caused by mutations in the genes coding for sarcomere proteins, with the remaining cases due to other monogenic disease gene mutations and non-genetic causes. The latter 'sarcomere negative' cases often correlate with better prognosis and lower likelihood of family recurrence, and so are approached differently in the clinic. Genetic testing facilitates stratification through confirmatory diagnosis and prediction of patient outcomes, whilst also offering the opportunity to identify other diseases such as Fabry and Danon. Gene-specific stratification of LQTS also helps steer treatment strategy as certain mutations can inform patient management by predicting patient outcomes and treatment response. He drew attention to the minimal benefit – and even possible harm – of large gene panels for HCM, and advocated a cautious approach which is cognisant of the less favourable signal-to-noise ratio and false positives generated by larger gene panels. At present, the Oxford genetics laboratory pilot project indicates a 16 gene panel for HCM as optimal.

Professor Watkins confirmed that genetic testing for ICCs is predominantly useful for cascade testing as a confirmed mutation is a highly effective tool for screening families, and those with preclinical mutations can only be identified through genetic testing. He reiterated the importance of using a genetic approach in combination with clinical tools as these will help to capture the numerous private genetic variants that are found in ICCs. Over the next five to ten years, Professor Watkins envisioned the likely development of targeted treatments predicated on genetic defect, but noted that it is still important to embed genetic testing now to support patient management and cascade testing processes.

Guidance for, and challenges to, adoption

There are no NICE guidelines for ICCs, however, the European Society of Cardiology has established pan-European guidelines for these disease areas and in particular, recommends genetic and cascade testing for HCM and LQTS patients as a key part of the clinical pathways.[14] This approach is also recommended by other expert sources including the NHS Cardiac National Service Framework and the Association of Inherited Cardiac Conditions (AICC). A barrier to implementation is variable uptake of this approach and Professor Watkins estimated that the proportion of ICC programmes with clinical diagnosis in a centre ranges from 10-90%, often depending on whether this is a small provider in control of their 'send away' budget or a large commissioning body where the test is not supported.

Professor Watkins discussed the other obstacles to uptake including a lack of awareness in the public and primary care such as reluctance from clinicians to impose a diagnosis on a 'well' person, which could be overcome with training on good patient counselling and the benefits of diagnosis. Additionally, cascade testing amplifies workload and requires extensive counselling, forming part of the challenges to adoption as even with demonstration of cost-effectiveness and wider economic benefits, new finance is still required to implement the pathways. Finally, he pointed out the overwhelming need to foster better engagement throughout the healthcare system, leading to a joined up-approach across different centres.

[14] European Society of Cardiology (2014). *2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy*. Eur Heart Journal, **35**, 2733-2779

Adopting a stratified approach to familial hypercholesterolaemia

Participants discussed various aspects of the clinical pathways for stratification of FH including building capacity and capability, raising patient and clinician awareness, strategies for systematic identification of patients, integration of services along the patient pathway and the economic rationale for implementation. It was noted that although the roundtable focused on a particular risk group for cholesterol, reducing population levels of cholesterol is also important for public health.

Building capacity and capability

Participants emphasised that it is crucial to develop capabilities within the healthcare system to support all healthcare professionals involved in the FH clinical pathway, alongside raising general levels of awareness of FH and genetic testing with clinicians and the wider public. There is a need to shift the mindset of how patients are managed and how they engage with their treatment and developments in awareness, capability and capacity should help to achieve this.

Embedding FH pathways into clinical education

Delegates highlighted the need to integrate FH pathways into clinical training, not only to support an understanding of the pathway but also to propagate a mindset where FH patients are treated as if they already have heart disease, as the high cholesterol from birth places patients at significant risk of coronary artery disease.

The low pick up rate on cholesterol levels in primary care needs to be addressed. It was suggested that this could be overcome through raising awareness and fully conveying the benefits of early cholesterol measurements and associated diagnoses as, at present, GPs may be 'scared' by the relatively low cholesterol threshold for FH diagnosis. Training and continuous professional development should not only target healthcare professionals such as GPs but also practice nurses who are extensively involved in chronic disease management. Measurement of cholesterol in relation to heart disease was recently removed from the Quality and Outcomes Framework (QOF), which also reduced incentives for, and awareness of, measuring cholesterol for heart disease. Additionally, delegates expressed concern that FH is wrongly considered an area for specialists rather than primary care and so cholesterol measurements must be made common parlance of non-specialist clinical practice. Health Education England will play a role in this education by underpinning the exemplar pathways in NHS England's 'approach to personalised medicine' with educational interventions.

Finally, there was consensus that cardiovascular risk should be approached as a lifetime risk rather than the ten year risk calculated in line with NICE guidance. For example, when cholesterol is checked at a younger age, there will be fewer warning signs as these patients may not exhibit a 'phenotypic risk' but may have an underlying genetic risk which is not considered by the current ten year model. Therefore clinician perceptions of long and short term risk need to be re-configured and the JBS3 tool was upheld as an

exemplar by some delegates for calculating this lifetime risk.[15] It was noted that NICE are currently revising the clinical guidelines for FH and in particular, the sections on cascade testing, statin cost and lifetime risk.[16]

Changing patient and clinician perceptions

Delegates voiced concerns that there are deeply ingrained cultural barriers for both clinicians and the public that need to be tackled to ensure country-wide adoption of the pathways. These are influenced by negative publicity about statin use, overmedicalisation and genetic tests. The negative portrayal of statins in the media may dissuade patients from seeking treatment or taking prescribed treatments, as well as impacting clinician diagnosis decisions.[17] It was suggested that the Royal College of GPs could inform clinicians in these areas alongside providing information for the public. Making balanced, evidence based information available would be valuable for all stakeholders.

Raising patient awareness

An opportunity was identified to amplify messages around the benefits of genetic testing, particularly to support cascade testing. NHS England recently rolled out an awareness initiative via the 'NHS Health Check' programme, inviting members of the public for a vascular health check with their primary care service which includes measurement of cholesterol, however, the initiative has only had a 50% take up rate.[18] Diagnosing FH in younger generations was identified as a particular challenge, as this demographic is less inclined to use health checks and may not even register with primary care.[19]

The number of relatives participating in cascade testing is less than desired and on average only two relatives are tested per patient. Therefore delegates described a need for clear communications about the benefits of participation including the impact on life expectancy, to counteract the potential negative connotations of genetic testing as a *'doom laden prospect'*. It was suggested that the British Heart Foundation (BHF) could play a role in these communications. It was also asserted that the perceived benefits of available interventions are key in influencing uptake. For example, there is high uptake of BRCA gene testing for breast cancer because patients can take action to reduce the risk of the disease if they have the gene. In comparison, there is low uptake of Huntington's tests where there is little perceived benefit of knowing that you have the disease. It has also been shown that direct contact between clinicians and patient's relatives, as used by nurses in Wales, is far more effective than indirect contact where patients approach relatives themselves. Delegates noted that this choice is heavily influenced by the way is it communicated to the patient.

[15] http://www.jbs3risk.com/
[16] The advisory committee was being put together at the time of the meeting and the new guidelines were anticipated for publication in January 2017.
[17] This is being explored in the Academy project on how can we call best use evidence to judge the potential benefits and harms of medicines: http://www.acmedsci.ac.uk/policy/policy-projects/how-can-we-all-best-use-evidence/
[18] http://www.nhs.uk/Conditions/nhs-health-check/Pages/NHS-Health-Check.aspx
[19] http://www.local.gov.uk/documents/10180/6869714/L15-28+Health+check_10.pdf/d35d76ca-ec50-4ee0-8e32-b051f6eb9bf1

Suggested next steps for adoption of a stratified approach:

- Development of informative communications around genetic testing and statins for patients and relatives, such as patient information leaflets.
- Incorporating FH pathways into non-specialist clinical education.
- Approaching cardiovascular risk as a lifetime risk rather than a ten year risk, to be considered in all guidance including NICE guidelines.
- Embedding cholesterol measurements (in relation to heart disease) in primary care practice.

Systematic identification of patients

Delegates discussed methods for retrospectively identifying 'at risk' patients using current information silos, as well as establishing a systematic approach to stratification of all patients facilitated by decision support tools.

Identifying 'at risk' patients

Delegates advocated systematic identification of FH patients by dredging routine clinical data, providing an opportunity to utilise novel data mining tools. For example, FH patients could be identified retrospectively through the NHS Health Check using a cut off for cholesterol, and then prospectively with automatic referral of patients to an FH nurse when a cholesterol level above a threshold is inputted. This type of review could be initiated for all patient laboratory records to flag those with cholesterol >8.5mmol/l to GPs. Reference was made to the exemplar model adopted in Wales where LDL cholesterol >6.5mmol/l triggers email alerts for clinicians, prompting a review of patient details and possible referral for genetic testing. One delegate suggested that the systematic approach could be modelled on the Medway case study where FH patients were identified in primary care using an audit prompt for GPs. The prompt raised number of known patients from 1 in 750 to 1 in 450, with a further increase to 1 in 357 when introducing a dedicated nurse to review these patients.[20] These approaches also imitate the recently launched Healthier You: NHS Diabetes Prevention Programme which instigates direct referral onto a prevention programme based on certain measurements. Finally, delegates discussed the possibility of self referrals of patients, a mechanism featured in the service specifications for other inherited cardiac conditions.

Supporting clinical decision-making

The decision-support tools for FH could be integrated into the three primary care IT systems to identify high risk patients by interrogating primary care data, as has been done with increasing numbers of diagnostic templates.[21] Delegates discussed re-engineering the cholesterol screening process and suggested that systematic cholesterol checks could be instigated for all patients on registration in primary care, then stratifying patients for genetic testing, as well as an additional genetic test for infants with monogenic FH parents as part of the NHS heel prick test at five days old.

[20] HEART-UK (2014). *Systematically identifying familial hypercholesterolaemia in primary care.* https://heartuk.org.uk/files/uploads/09-14_HEART_UK_Medway_report.pdf

[21] A similar approach was proposed for systematic identification of monogenic diabetes patients in the report of the 2015 Academy and NHS England roundtable on *'Exemplar clinical pathways for a stratified approach to diabetes':* http://www.acmedsci.ac.uk/viewFile/57cfd3c90098c.pdf

Suggested next steps for adoption of a stratified approach:

- Reviewing and interrogating clinical data stores with an established cut off for cholesterol to identify potential FH patients.
- Integrating a tool into GP IT systems to create prompts around measuring cholesterol and to flag levels inputted above a certain threshold.

Integration of services

There was agreement that it is essential to better integrate healthcare services across the patient pathway, including primary care referrals and feedback between pathology and coroner services. Problems with lack of feedback from coroner services to the NHS, and cascading of results from pathology services, need to be tackled to ensure that patients are not missed. Delegates noted the need for more emphasis on the coroner's responsibility to notify the family and NHS of any findings. However, despite the significant room for improvement, it was acknowledged that over recent years there has been an increase in referral of sudden death cases from coroner services.

Creating a patient database to link up services

The PASS database is used as a patient register in Wales, and incorporates the functions required along the FH clinical pathway such as drawing and linking family pedigrees, template letters for cascade testing and electronic alerts for genetic testing laboratories. For example, the electronic alerts for laboratories enable use of a cheaper relative test rather than a full genetic test when a suspected patient from a known family enters the clinic, demonstrating the importance of linking services to create an integrated patient picture and the role of the database in enabling this. Lipid clinics treating patients in England are likely to be using lipid databases and not PASS so there is an opportunity for the latter database to be deployed.

Tackling variation in commissioning

Delegates considered the importance of coordinating cascade testing across the UK to ensure equity of access and to overcome difficulties with catchment areas for lipid clinics and testing of relatives outside of these geographical areas. Cascade testing is effectively implemented in the devolved administrations but not in England where there are challenges with variation in commissioning and in particular, long term funding. Cascade testing programmes with dedicated FH nurses are currently only funded in England through the BHF pilots and CCGs will be required to pick up the funding for these tests to ensure sustainability. Delegates highlighted the challenge posed by the unwillingness of local commissioners to fund genetic tests, even with the availability of BHF-funded nurses. Nevertheless, it was agreed that this is not an 'impossible' task as the process has already been implemented in some areas. After the completion of the cascade testing pilot, the BHF will evaluate the general resource requirements and cost-effectiveness to facilitate uptake in CCGs.

Suggested next steps for adoption of a stratified approach:

- Establishing a single FH patient database for use across England, possibly using the PASS database.
- Enhancing communications between coroner and pathology services and the NHS.
- Building a robust case for adoption of these pathways for CCGs, supported by the findings from the BHF pilot.
- Improving access to relevant genetic testing.

The economic case

It was confirmed that the number of relatives tested per suspected FH patient is much higher in Northern Ireland, Scotland and Wales than in England. Delegates stressed that cascade testing is more cost-effective with the more relatives that are tested, providing a robust argument for equity of implementation of cascade testing across the country. However, this is partially impeded through the 'out of area' issue described earlier where relatives in a different geographical area are not covered by the same lipid clinic.

NICE approved the FH pathway as cost-effective, and as outlined by Professor Gray, it is likely even more so now than when evaluated in 2008. Nevertheless, delegates argued that often healthcare professionals such as GPs are less interested in cost-effectiveness and more focused on short term costs and savings. Delegates described the culture of short termism in the healthcare system with a focus on balancing budgets within the financial year rather than a consideration of cost savings in the long term. Therefore cost, and not cost-effectiveness, is proving a key barrier that needs to be overcome to embed the FH pathways in clinical practice.

Stratification of patients to support economic viability

Delegates agreed that at present, there is a clear rationale for stratifying monogenic patients from polygenic patients for cascade testing and referral to tertiary centres, as is already done in Wales. Although there is a familial factor for polygenic patients, the risk of heart disease is significantly higher for monogenic FH patients because of the high cholesterol experienced from birth. It is also simpler and cheaper to only test the three core monogenic FH genes rather than testing for the polygenic genes where the test is more costly and requires specialist interpretation of the results. Therefore based on this knowledge, a pragmatic approach was endorsed by delegates where only monogenic patients are entered into cascade testing as a cost-effective solution that takes into account current resources. It was proposed that polygenic patients are then managed in primary care through normal treatment regimes rather than expensive follow-up in tertiary centres. Delegates were reminded that some of the information to support this is from a small pilot that needs to be expanded but at present, the data from this pilot and the approach adopted in Wales imply that this is an appropriate strategy.

Suggested next steps for adoption of a stratified approach:

- Propagating a culture change in clinical decision-making to focus on long term economic and wider benefits rather than short term cost savings, by clearly communicating the advantages of implementing the clinical pathways.

- Further information should be collected on the stratification of polygenic and monogenic FH patients along the clinical pathway. This stratification should also be considered by NICE once sufficient levels of data have been collated.

Adopting a stratified approach to inherited cardiac conditions

Delegates agreed that the exemplar clinical pathway for a stratified approach to ICCs should be based on the general pathway proposed by the AICC that can be found in Appendix III. Despite there being many similarities between the pathways and barriers to adoption for ICCs and FH, the key difference between the two disease areas is that ICCs are predominantly managed entirely in tertiary, rather than primary, care.

Delegates explored training and capacity including standards and consistency of genetic testing, as well as how to better integrate and coordinate services, re-designing the commissioning process and the economic rationale for such an approach. There was general emphasis on the need for a local approach for the ICC pathways, coordinated at a national level to ensure the equity of access that is so essential for these conditions, as outlined in the UK Strategy for Rare Diseases.[22]

Building capacity and capability

Delegates discussed the importance of embedding the stratified approach for ICCs into clinical education, and developing standards and protocols that will allow a consistent approach to implementation across the country. This support for healthcare professionals will help to tackle the potential issues with reduced confidence in starting patients on the ICC pathway where there is a risk of misdiagnosis, as interventions can be potentially life changing with a profound impact on lifestyle.

As identified in FH, there are also issues with patient and clinician awareness and perceptions which impede referral of relatives for cascade testing. Delegates described the uncertainty and sometimes negative perceptions about genomics which need to be countered by easily implemented exemplars of care with well understood benefits.

Developing standards and consistency for genetic testing

Standards for ICC genetic testing need to be developed, and the AICC is currently looking at developing quality markers for this. It was noted that tests such as the 16 gene panel for HCM have been approved by the UK Genetic Testing Network (UKGTN) for adoption by the commissioning system.

Delegates recognised that further specialist education is needed around feedback of genetic findings to patients. There must be a carefully considered, standardised approach to incidental findings during genetic testing and the model developed by Genomics England can be used as an exemplar where feedback is only provided on high probability, incidental findings that may impact health. Alongside standardisation, consistency of reporting is imperative, requiring agreed criteria and a coordinated approach to diagnosis linking in with physiological and pathological data. It was noted that data interpreters are often conservative when reporting pathogenicity of mutations but confidence can be built through further refinement of genetic tests to only use informative genes, also helping to

[22] Department of Health (2013). *The UK Strategy for Rare Diseases.* https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/260562/UK_Strategy_for_Rare_Diseases.pdf

reduce confounding incidental findings. Reporting is challenging as it is subjective for the interpreter and so it would be helpful to create a structure that aggregates expertise and evidence, such as that adopted by the University of Bristol where newly discovered variants are entered into the PASS database and discussions coordinated to confirm the result. It was emphasised that the data sharing platform that will be established by Genomics England will allow clinicians to view the totality of data and identify similar variants to build confidence in results and ensure consistency of reporting.

Integrating pathways into clinical education

There is a need to raise awareness of the ICC pathways in the clinical community as genetic information may direct patient management through stratification. For example, the gene mutation in LQTS will likely influence the intervention and there is also evidence for targeted treatment in other areas such as aortopathies where for Marfan syndrome, surgical decisions may be based on genotype. For ICCs, genotype often seems to predict outcome as well as directing treatment advice on triggers such as environment and exercise, and interventions such as implantable devices or β-blockers. One delegate highlighted the seemingly promising new LQTS treatments in development that are predicated on specific genotypes, although there are difficulties in amassing sufficient patient numbers for meaningful results. The challenge of proving effectiveness of stratified medicines in increasingly small patient populations is well documented and is discussed in the Academy's report *'Realising the potential of stratified medicine'*.[23]

Delegates identified possible ways forward to support clinical training including learning modules, made more attractive to healthcare professionals through badging as genomics, and potential decision support tools such as automated electrocardiograms with a QTc interval threshold which alerts GPs.

Training genetic nurses

Delegates observed that genetic nurses can greatly enhance service delivery and efficiency through supporting many activities along the clinical pathway such as collating family histories, coordination of processes and contacting relatives which reduces the time burden on other healthcare professionals. It was argued that commissioning must be fit-for-purpose to enable delivery of these pathways and that genetic nurses only offer a partial solution for ensuring implementation, however, they can act as the 'glue' to facilitate implementation of the pathways.

It was noted that introduction of genetic testing at some specialist centres was founded on the presence of genetic nurses and once an evidence base for this has been generated, the case can be made for this resource to the rest of the UK.

Suggested next steps for adoption of a stratified approach:

- Developing a set of reporting and consistency standards for genetic testing in collaboration with Genomic England's Genomic Mapping and Alignment Programme (GMAP).

[23] Academy of Medical Sciences (2013). *Realising the potential of stratified medicine.* https://www.acmedsci.ac.uk/viewFile/51e915f9f09fb.pdf

- Building an infrastructure/platform for sharing knowledge to support consistency of reporting.
- Introducing learning modules for different healthcare professionals on the ICC pathways through resources including the British Medical Journal and NHS Choices.
- Review and consider training of additional genetic nurses to support implementation.

Integration and coordination of services

Delegates advised that it is essential to better integrate care pathways and the healthcare professionals involved at each stage. They noted that the 100K Genomes Project will be valuable in supporting this through cultivating the mixed economy and integrated services which are needed for implementation of the ICC pathways.

It is important to link the different healthcare systems and the NHS Sustainability and Transformation Plans (STPs) will facilitate this through their aim to create a plan for joining up care in the community over the next five years. The plans will include priorities for prevention and in particular, cardiac secondary prevention, which could link in with stratified medicine and the ICC pathways. In addition, the 100K Genomes Project is developing an appropriate data sharing framework to support knowledge transfer across sites.[24]

Linking up coroner and pathology services to the wider healthcare system

Similarly to FH, problems are experienced with communication and feedback from coroner and pathology services. Delegates noted that in line with the Coroners and Justice Act 2009, cases in fields such as cardiac conditions are usually reported and referred by coroners to fulfil their commitment to the prevention of future deaths. However, delegates suggested that it may be perceived that there is no legal obligation to feed this information back to families, compounded by a lack of awareness, finances and time, which result in lack of feedback. It was noted that medical coroners generally understand the importance of feedback but that their non-clinical colleagues may feel that this does not lie within their responsibilities.

It was noted that there has been some progress here and coroners are starting to alert pathologists, who are in turn increasingly active in escalating this to clinicians. However, there are then referral issues caused by confusion around where molecular samples should be sent unless a cardiologist directly approaches the pathology service. St George's Medical School is undertaking a scheme to make samples available through a diagnostic laboratory, however, the only way to fund the test is if the families are made aware and arrive at the clinic themselves.

Establishing a joined up referral process

It was reiterated that direct referral to tertiary care is critical for ICCs, avoiding unnecessary delay and wasted resource through repeated tests in secondary care where there may not be the appropriate skillset. Counselling is an integral part of the tertiary

[24] http://www.genomicsengland.co.uk/genomics-england-selects-labkey-software-for-integrated-data-management-solution/

ICC service and is not available in primary or secondary care, nor are the necessary resources for collating a detailed family history. Therefore there is a need to instigate a shift away from normal referral processes and secondary care should be better engaged so that it can support, rather than unintentionally hinder, referrals. Issues are also encountered with primary care referral letters which are unlikely to contain essential information such as family history, and so delegates proposed to establish a standardised primary care referrals system.

Delegates also suggested that there may be a cultural barrier impeding referral from secondary care where cardiologists could perceive that referral to a specialist implies that they are non-specialists in their own field. This issue should be referred to the Royal Colleges and one delegate contemplated further accreditation for those who are this specialised within cardiology. CCGs could take responsibility for highlighting the widespread benefits of a streamlined referral process for patient care and resources.

Developing a database for patient management

At present, no single database is used to coordinate services and manage cascade testing for ICCs although commercially provided databases are used in individual universities. An opportunity was identified to customise the PASS database utilised in FH for ICCs, as the functionality will be very similar and widening the use of PASS would reduce its general cost. It was noted that NHS England and the Health and Social Care Information Centre are planning to compile genomic data into one data platform alongside other diagnostic information, with functionality to include all types of registry data and pedigree drawing tools. This will feed into the 100K Genomes Project and legacy plans but will not take place until at least 2018/19 so there will be a need to draw on existing systems to form this national approach.

Suggested next steps for adoption of a stratified approach:

- Improving coordination between coroner and pathology services and the wider healthcare community.
- Standardising the referral system for ICCs and considering the development of a single referral form for use in primary care.
- Investigating adaptation and use of the PASS database for ICC patient management.

Re-designing the commissioning process

A systematic approach to commissioning is required using a flexible system that delivers equitable access for patients. This includes the need for an efficient decommissioning process for those services that do not meet the required standards and service specification. It was agreed that this needs to be more rigorously implemented given the multitude of specialist centres which are offering diagnostic tests for ICCs. It was observed that family members will tend to travel to ensure treatment at the same specialist centre, potentially overcoming any issues associated with reducing the number of centres.

The decommissioning process is currently planned as part of NHS England's reprocurement of genetic laboratories. Delegates also noted the opportunity to drive a

systematic approach to the commissioning process through the STPs and NHS England's genomics management board which now has CCG input.

Funding for genetic tests

Despite falling under specialised commissioning, difficulties are encountered with access to funding for the genetic tests which lies between the Genetics Clinical Reference Group and the Cardiovascular Clinical Reference Group, causing confusion about which group is responsible for funding.[25] BHF will shortly roll out a cascade testing pilot in the UK with allocated resource similar to its FH pilot programme, but the BHF will not pay for genetic testing services. In the long term there is a common challenge around how commissioners can be persuaded that there is *value* in these services to continue the support. One delegate questioned why specialised commissioning has not acted further to implement a service specification in CCGs that was written three years ago, and suggested a top down approach to influence uptake.

Suggested next steps for adoption of a stratified approach:

- Establishing a comprehensive and consistent approach to the commissioning of relevant genetic tests, including the roles and responsibilities of funding bodies.
- Implementation of the decommissioning process to only select effective, high quality specialist centres.

Health economics of a stratified approach

It was agreed that when carrying out a detailed characterisation of a patient and their needs, it is important to understand the various tests that may be required. Therefore delegates strongly supported indicating these tests on the clinical pathways for ICCs to help clinicians to make informed decisions. However, they acknowledged the potential economic implications of this more comprehensive approach as full implementation of the clinical pathways and the guidance for tests could significantly increase expensive but necessary interventions such as the number of implantable cardioverter-defibrillators (ICDs) for treatment of ICCs.

Delegates discussed the advantages of a genetic diagnosis for excluding other expensive tests such as costly monitoring tools repeated at regular intervals including cardiac MRI and exercise tests. Despite the advantages of implementing these stratified pathways, delegates highlighted the noticeable gap in the expected number of clinical cascades that should be implemented. Whilst it is hoped that this gap will be addressed, the additional cascades will require new funding from budgets, regardless of the long term cost savings and cost-effectiveness of such a strategy.

Delegates noted that effective implementation of direct referral will also be important to support the economic rationale for the ICC clinical pathways. As outlined earlier, tertiary care is the appropriate level for management of these patients and temporary management in secondary care through poor referral processes would simply waste time and resource with associated cost implications.

[25] A similar issue around access to funding for genetic tests was identified at the Academy's 2015 roundtable meeting on '*Exemplar clinical pathways for a stratified approach to diabetes*': http://www.acmedsci.ac.uk/viewFile/57cfd3c90098c.pdf

Suggested next steps for adoption of a stratified approach:

- Mapping of the clinical pathways (suggested AICC pathways) to specific tests that should be considered at each stage to support clinician decision-making.
- As for FH, propagating a culture change in clinical decision-making to focus on long term economic and wider benefits rather than short term cost savings, by clearly communicating the advantages of implementing the clinical pathways.

Conclusions and next steps

Several key themes emerged over the course of the day, centred around the overarching aims of driving adoption, improving equity of access and developing high quality, streamlined services. There were many commonalities between the discussions for FH and ICCs, reflecting some of the wider system challenges for stratified medicine, alongside more disease-specific barriers where the pathways can act as exemplars for other similar conditions. The first key step identified was engineering a change in commissioning behaviour through building a fit-for-purpose infrastructure to address challenges such as funding for tests and referral processes. This infrastructure needs to be supported through further training, education and awareness at all stages of the clinical pathways and better integrating services to create a joined up, efficient approach to patient care.

Participants explored different systematic approaches to patient identification and stratification as well as standardisation and consistency of services. Finally, it was agreed that the economic argument for implementation of such pathways needs to be further developed, alongside a shift in mindset from a short term view of financial implications to a long term view of wider economic benefit.

Appendix I Programme

12.30-13.00	**Lunch**
13.00-13.05	**Welcome** Professor Peter Weissberg FMedSci (Chair), Medical Director, British Heart Foundation
13.05-13.20	**Introducing NHS England's Personalised Medicine Strategy** Professor Sue Hill OBE, Chief Scientific Officer, NHS England
13.20-13.35	**Stratification of familial hypercholesterolaemia** *An overview of current approaches to the stratification of diabetes, with particular emphasis on maturity onset diabetes of the young (MODY).* Professor Steve Humphries FMedSci, Director, Centre for Cardiovascular Genetics, University College London
13.35-13.50	**A national approach to familial hypercholesterolaemia** *An overview of the current systems for familial hypercholesterolaemia and barriers to adoption* Professor Huon Gray, National Clinical Director for Heart Disease, NHS England
13.50-14.50	**Discussion session 1** Discussion of the high-level clinical pathway for the stratified diagnosis and treatment of familial hypercholesterolaemia, considering the key risks and barriers faced in implementing this pathway.
14.50-15.10	**Refreshment break**
15.10-15.30	**A stratified approach to inherited cardiac conditions** *An overview of certain inherited cardiac conditions and the current approaches to stratifying patients, focused on hypertrophic cardiomyopathy and long QT syndrome* Professor Hugh Watkins FMedSci, Professor of Cardiovascular Medicine, University of Oxford
15.30-17.10	**Discussion session 2** Discussion of the high-level clinical pathways for the stratified diagnosis and treatment of hypertrophic cardiomyopathy, long QT syndrome and Marfan syndrome, using the strategy for familial hypercholesterolaemia as an exemplar for these areas. Consideration of the key risks and barriers, and next steps for implementation.
17.10	**Close**

Appendix II Delegate list

Professor Peter Weissberg FMedSci (Chair), Medical Director, British Heart Foundation
Professor Sue Hill OBE (Speaker), Chief Scientific Officer, NHS England
Professor Huon Gray (Speaker), National Clinical Director for Heart Disease, NHS England
Professor Steve Humphries FMedSci (Speaker), Director, Centre for Cardiovascular Genetics, University College London
Professor Hugh Watkins FMedSci (Speaker), Professor of Cardiovascular Medicine, University of Oxford
Dr Elijah Behr, Reader in Cardiovascular Medicine and Honorary Consultant Cardiologist, St George's Medical School
Dr Paul Brennan, Clinical Director, Northern Genetics Service
Dr Fiona Carragher, Deputy Chief Scientific Officer, NHS England
Professor Mark Caulfield FMedSci, Professor of Clinical Pharmacology and Director of the William Harvey Research Institute, Queen Mary University of London
Ms Kate Haralambos, FH Researcher, Cardiff University
Dr Henrietta Hughes, Medical Director for North Central and East London, NHS England
Dr Matt Kearney, National Clinical Advisor – Equality and Health Inequalities, NHS England
Professor Gary McVeigh, Professor of Cardiovascular Medicine, Queens University Belfast and Chair of Technology Appraisal Committee D, National Institute for Health and Care Excellence
Dr Claire Newland, Programme Manager – Stratified Medicine and Molecular Pathology, Medical Research Council
Ms Jules Payne, Chief Executive Officer, Heart UK
Mr Robert Pears, Consultant in Public Health, Hampshire County Council
Dr Ian Sabir, Head of Medical Affairs for Diabetes and Metabolism, AstraZeneca
Professor Mary Seed, Honorary Consulting Physician, Imperial College Healthcare NHS Trust
Professor Mary Sheppard, Head of the Cardiovascular Pathology Unit, St George's Medical School
Dr Allison Streetly OBE, Deputy Director of Healthcare Public Health, Public Health England
Dr Frances Sutcliffe, Associate Director –Centre for Health Technology Assessment, National Institute for Health and Care Excellence
Dr Maggie Williams, Consultant Clinical Scientist, North Bristol NHS Trust

Secretariat
Ms Liberty Dixon, Policy Officer, Academy of Medical Sciences
Dr Rachel Quinn, Director of Medical Science Policy, Academy of Medical Sciences

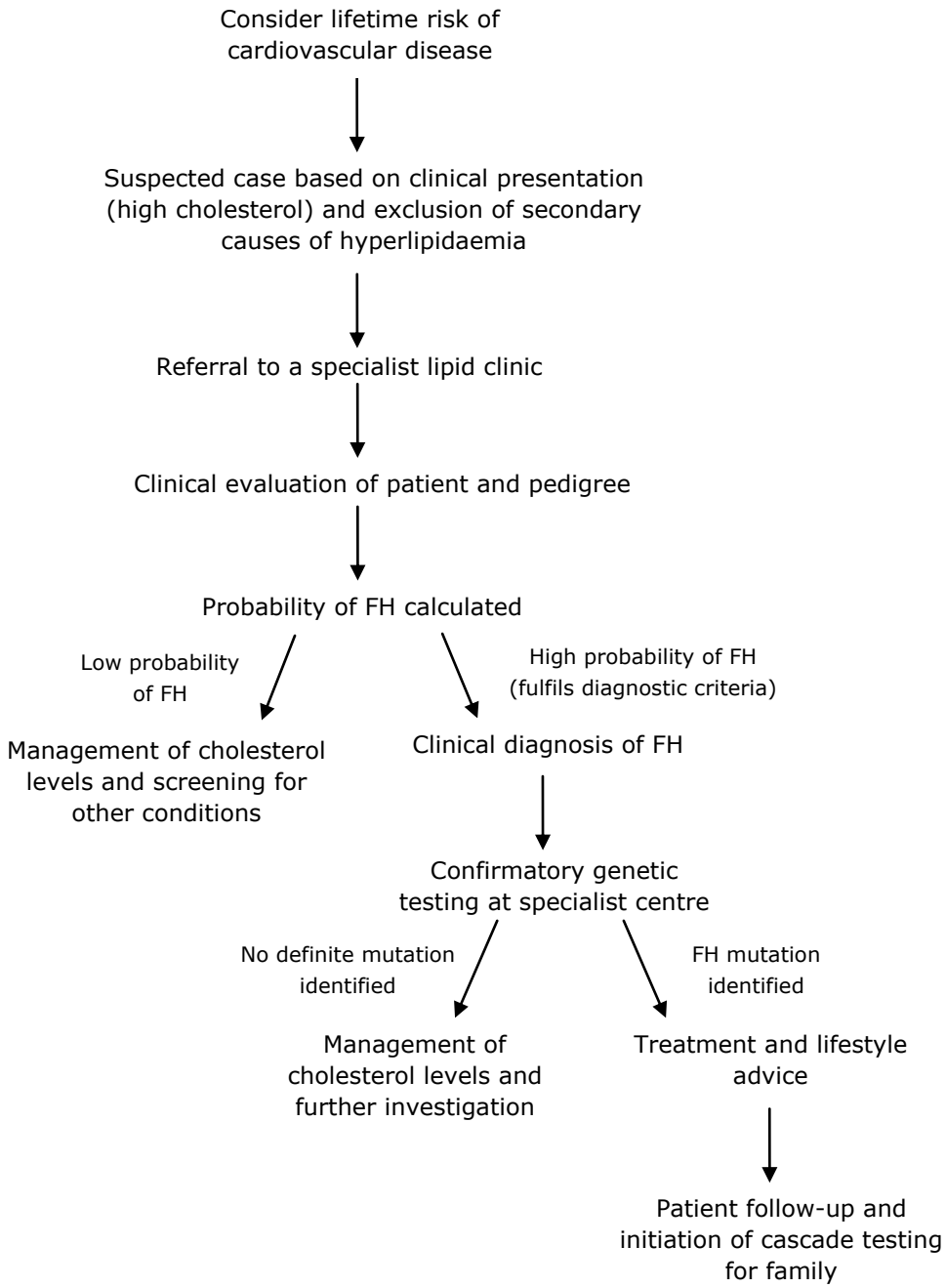
Observers
Ms Sally Chapman, Clinical and Scientific Policy and Strategy Lead, NHS England
Ms Deborah Williams, Programme Manager – Emerging Clinical and Scientific Policy, NHS England

Appendix III Clinical pathways

Familial hypercholesterolaemia

As adapted from NICE Guidance.[26]

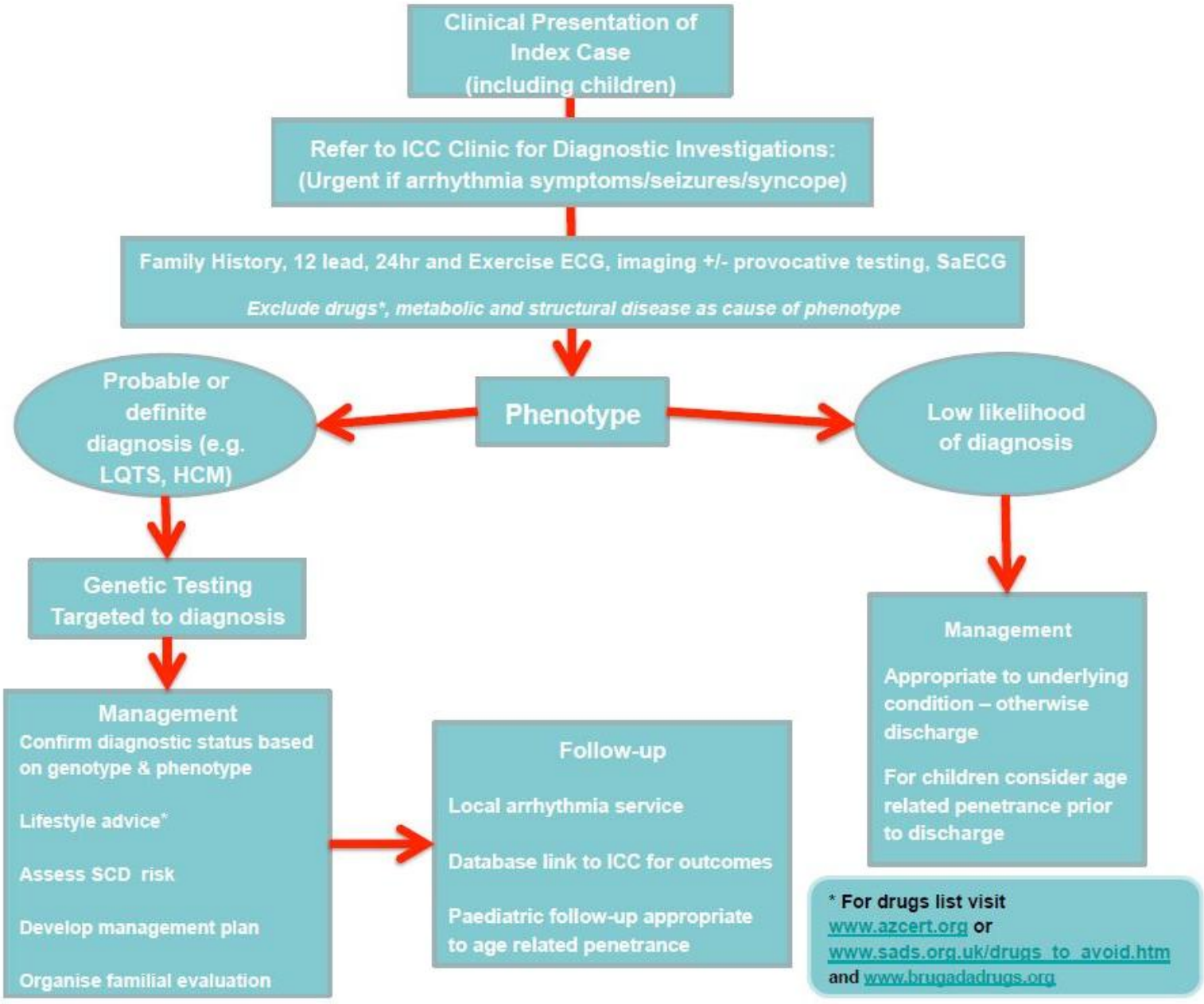
Potential exemplar pathway



[26] NICE (2008). *Familial Hypercholesterolaemia: identification and management.* NICE guidelines [CG71]. https://www.nice.org.uk/guidance/cg71

Inherited cardiac conditions

As taken from the AICC recommended pathways.[27]



[27] http://theaicc.org/?page_id=55

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