

## **Exemplar clinical pathways for a stratified approach to diabetes**

Summary of a meeting held on 8 December 2015 by the Academy of Medical Sciences, and supported by NHS England.

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## Contents

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Summary	4
Background	6
Introduction to a stratified approach	8
Exemplar clinical pathways for a stratified approach to diabetes	12
Conclusions and next steps	20
Appendix I Programme	21
Appendix II Delegate list	22
Appendix III Draft clinical pathways for stratification of diabetes	23

## Summary

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On 8 December 2015, the Academy of Medical Sciences, supported by NHS England, held a roundtable looking at '*Exemplar clinical pathways for a stratified approach to diabetes*'. The roundtable brought together key stakeholders from across the healthcare sector including academia, NHS, industry and research funders to map out high-level clinical pathways for stratification of diabetes, also addressing the challenges to implementation and the practical steps required to put these pathways into practice.

Stratified medicine offers a valuable opportunity to enhance patient care whilst delivering efficiencies across the healthcare system by drawing on genomics, informatics and related scientific advances. Diabetes is well positioned to act as an exemplar for a stratified approach as much of the necessary scientific rationale and associated tools for stratification have already been established; accordingly, this roundtable focused on monogenic diabetes which accounts for 2-3% of diabetes diagnosed <30 years of age, and where the clinical pathways are not yet well defined or widely adopted in clinical practice. Thus clinical implementation, rather than scientific knowledge, poses the main barrier to adoption, and the following areas were highlighted as key to overcoming this for successful implementation of a stratified approach to diabetes in the NHS:

- A **national approach to the commissioning of tests** and clinical pathways to ensure equity of access across the country including by resolving funding issues for diagnostic tests.
- Adopting a **systematic approach to stratifying patients** with **standardisation of tests** and thresholds, and utilising risk calculators amongst other tools.
- **Patient empowerment** to provide the pull for this approach into the healthcare system and to create a participatory environment where **patients are better engaged and supported** in disease management. There is also a need for a clear narrative from both patients and clinicians to fully communicate the impact of these clinical pathways for patients with diabetes.
- **Validating and communicating the economic argument** for implementation of a stratified approach in diabetes, not only underlining the cost-savings but also drawing attention to clinical effectiveness and the full impact of a diagnosis for patients. This is accompanied by a need to re-consider the type of evidence required to assess cost-effectiveness of stratified medicines due to the restricted patient populations.
- **Building capability, capacity and engagement** across the healthcare sector and in particular, training healthcare professionals to improve clinical detection and ensure that the patient enters the correct pathway. It was recognised as essential to engage clinical leaders and to establish local champions to expedite dissemination of the stratified approach across the country. **Decision support tools** will act as a pillar for this education, such as risk calculators and NICE guidance.
- A general **shift in mindset** from recognising two types of diabetes to accepting the presence of many diabetes subtypes, which can be partly achieved through the steps outline above.
- Finally, the importance of **recognising this as an evolving process**, where the approach can be trialled and refined in test beds before rolling out across the NHS. Areas that were identified as needing to continuously progress during implementation

include refinement of diagnostic tests and development of risk stratification models to improve applicability to different ethnic groups.

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 diabetes are fully integrated into the healthcare system.

## Background

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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.<sup>1</sup> 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.<sup>2,3,4</sup>

In recent years, both 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.<sup>2,5</sup> 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.<sup>6</sup> 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.<sup>4</sup>

Stratification in diabetes is a valuable exemplar for other disease areas as much of the science around patient subtypes has been discovered and the associated diagnostic tests already developed, providing the tools to establish such an approach in the NHS. The stratified clinical pathways for diabetes potentially demonstrate huge patient benefit and cost-savings, which, when combined with the learnings from implementing such an approach, will help to facilitate adoption of stratification in other disease areas. Therefore this roundtable explored the key factors required for implementation of a stratified approach to diabetes, as well as the barriers that need to be overcome to start on the journey towards fully integrating stratified medicine in the NHS. The meeting focused on monogenic diabetes which accounts for 2-3% of patients diagnosed with diabetes at <30 years of age and is an area where the clinical pathways are not yet widely implemented. Delegates specifically looked at pathways for maturity-onset diabetes of the young

<sup>1</sup> 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.

<sup>2</sup> Academy of Medical Sciences (2013). *Realising the potential of stratified medicine*. <https://www.acmedsci.ac.uk/viewFile/51e915f9f09fb.pdf>

<sup>3</sup> 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](http://www.abpi.org.uk/our-work/library/medical-disease/Documents/stratified_med_nhs.pdf)

<sup>4</sup> NHS England Board paper (2015). *Personalised medicine strategy*. <http://www.england.nhs.uk/wp-content/uploads/2015/09/item5-board-29-09-15.pdf>

<sup>5</sup> Academy of Medical Sciences (2007). *Optimizing stratified medicines R&D: addressing scientific and economic issues*. <https://www.acmedsci.ac.uk/viewFile/publicationDownloads/120151486883.pdf>

<sup>6</sup> Academy of Medical Sciences (2015). *Stratified, personalised or P4 medicine*. <http://www.acmedsci.ac.uk/viewFile/564091e072d41.pdf>

(MODY) and neonatal diabetes, also including the clinical pathway for gestational diabetes where one subtype of MODY is most commonly identified during routine antenatal screening. The draft clinical pathways for MODY, neonatal diabetes and gestational diabetes can be found in Appendix III.

## Introduction to a stratified approach

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Professor Sir John Tooke FMedSci introduced the roundtable meeting. He acknowledged the challenges faced in establishing a new model such as stratified medicine in the NHS, which will require a practical and systematic approach to ensure that it is fully embedded in the healthcare system. He noted that diabetes presents an exemplar area for stratified medicine as the science is well defined and in this instance, often accompanied by lower economic costs.

### **Developing NHS England's personalised medicine strategy**

*Professor Sue Hill OBE, 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.<sup>7</sup> 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.

#### ***Moving to a personalised medicine approach***

Professor Hill argued that the adoption of personalised medicine offers a move away from the 'one size fits all' approach to a new model that will improve the delivery of patient-centred care through utilising advances in diagnostic tests, genomic technologies, molecular pathways, data analytics and real-time monitoring. She asserted that an 'evolution of the NHS' is required to embed this new model.

Disease burden and drug efficacy and development are the major drivers behind adoption of a stratified approach, complemented by advances in genome sequencing and the emergence of 'multi-omics' which have been catalysed by the 100K Genomes Project. Professor Hill also noted the opportunities presented by the next generation of 'omics' such as new biomarkers and metabolomics, and proposed that these innovations are brought to the forefront of healthcare. For example, a patient's susceptibility could be characterised using genomics to address the large number of hospital admissions associated with adverse drug reactions.

In addition to these genomic and other 'omic tools, the integration of big data and informatics is essential to achieving adoption of personalised medicine. The wealth of data from diagnostics, and scientific and other interventions, needs to be fully utilised to facilitate the clinical characterisation required to deliver personalised medicine. Professor Hill stressed that these rich datasets can also drive basic research and therapy development when combined with new analytical techniques. For example, integrated datasets are already used in oncology to stratify patients at a molecular level, with selection of therapies based on this molecular profile.

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

The patient must be at the centre of this approach and there is the potential that in the future, an individual could undergo genome sequencing at birth to produce a stratified profile which would enable more effective healthcare and help to direct lifestyle choices. Professor Hill aspired to a comprehensively linked diagnostics picture for each patient, requiring integration of clinical services and a move away from organisation of services by organ specialities to a '*whole body approach*'. However, current variation in the commissioning of diagnostics and adoption of NICE-recommended diagnostics, and the complexity of clinical pathways and the commissioning structure, are barriers to implementing this vision. There is a need to create a responsive and agile commissioning framework to tackle this confused commissioning system for diagnostics.

The 13 NHS Genomic Medicine Centres (GMCs) are expected to create a legacy of infrastructure involving multidisciplinary working, standardisation of lab protocols and practice, common datasets and standards and developments in analytic techniques. NHS England will utilise this pioneering network structure and new ways of working across geographies to inform its future work in this area.

### ***Developing an approach to personalised medicine***

NHS England is considering four areas in its approach to personalised medicine: infrastructure; the clinical change model; technology and innovation; and policy and system alignment. Underpinning these themes is engagement with all stakeholders including patients and the public, and NHS England has held events with regional healthcare leaders to ensure that the planning is grounded and focused. This stakeholder has identified broad support for personalised medicine; however, there are challenges to be overcome such as commissioning barriers, the evidence base, information silos, affordability and a need for cultural narrative.

### **Stratifying the treatment of diabetes**

*Professor Andrew Hattersley FRS FMedSci, Professor of Molecular Medicine and Consultant Physician, University of Exeter*

Professor Hattersley commenced by emphasising that the stratification of diabetes is a model based on old technology, where most of the concepts and science were discovered 15-20 years ago but are still not yet implemented effectively. He highlighted that a stratified approach is already applied in cancer using clearly defined subgroups, however, it is difficult to use cancer pathways as exemplars as they differ significantly from non-cancer disease areas. Whereas current cancer treatment is based on histological and molecular subtypes, diabetes management does not generally involve further investigation into the specific aetiology beyond initial diagnosis of hyperglycaemia, with patients often continuing with interventions that they do not respond to. Conversely, he noted that the major monogenic diabetes subtypes and their specific interventions were identified over a decade ago, reiterating that clinical implementation is the barrier to uptake of stratified medicine in diabetes rather than limitations of the science itself. Professor Hattersley then proceeded to outline the most common types of monogenic diabetes as described below: neonatal diabetes and MODY.

### **Neonatal diabetes**

Neonatal diabetes is a subtype of monogenic diabetes that presents in children <6 months old with approximately 50% of cases caused by a potassium channel ( $K_{ATP}$ ) mutation. Professor Hattersley explained that this subtype can be distinguished from type 1 diabetes (T1D) which does not occur at <6 months. Neonatal diabetes is diagnosed through genetic testing and those with the  $K_{ATP}$  mutation respond to treatment with sulphonylureas, relieving patients from potential dependence on insulin injections through misdiagnosis. Professor Hattersley confirmed that 90% of patients with a mutation in the Kir6.2 subunit of the  $K_{ATP}$  channel can stop insulin completely when taking sulphonylureas, demonstrating the impact of this diagnosis for a patient with diabetes.<sup>8</sup>

### **MODY**

MODY is another, more common, form of monogenic diabetes. One genetic subtype is caused by a glucokinase (GCK) mutation which explains >60% of persistent paediatric incidental hyperglycaemia in the UK and has a population prevalence of 1 in 1000 Caucasians.<sup>9</sup> Professor Hattersley explained that GCK-MODY patients have a higher fasting blood glucose which is regulated around a stable set point and so patients are often misdiagnosed with T1D or type 2 diabetes (T2D). GCK-MODY is also often identified during routine antenatal screening and misdiagnosed as gestational diabetes. GCK-MODY patients do not respond to therapy and will not benefit from treatment, however, he emphasised the importance of a diagnosis to prevent potentially lifelong inappropriate treatment.

Professor Hattersley noted that the MODY genetic subtype will determine the clinical prognosis and treatment response for the patient. Therefore diagnosis and management requires genetic testing with subsequent treatment using specific therapies, and, as well as the significant patient benefit, this can have economic advantages. In GCK-MODY, no treatment is required so stopping therapy reduces costs and improves quality of care. The most common forms of MODY are caused by mutations in the transcription factors HNF1A and HNF4A and will benefit from treatment with relatively cheap sulphonylureas, which can often replace insulin and are four times more effective than metformin for these patients.

### **Detection and diagnosis of monogenic diabetes**

Monogenic diabetes accounts for 2-3% of children and adults diagnosed with diabetes at <30 years and currently 80-90% of monogenic diabetes remains undiagnosed in the UK.<sup>10</sup> Even for patients who have received a diagnosis of monogenic diabetes through genetic testing in the Exeter laboratory, it has taken, on average, 12 years between diagnosis of diabetes and referral for genetic testing. Professor Hattersley recommended further education of clinical staff to enhance detection, such as training specialist monogenic diabetes nurses or the participation of healthcare professionals on training

<sup>8</sup> Pearson E, *et al.* (2006). *Switching from insulin to oral sulphonylureas in patients with diabetes due to Kir6.2 mutations.* NEJM **355(5)**, 467-477.

<sup>9</sup> Chakera A, *et al.* (2014). *The 0.1% of the population with glucokinase monogenic diabetes can be recognized by clinical characteristics in pregnancy: the Atlantic diabetes in pregnancy cohort.* Diabetes care **37**, 1230-1236.

<sup>10</sup> Shields B, *et al.* (2010). *Maturity-onset diabetes of the young (MODY): how many cases are we missing?* Diabetologia **53(12)**, 2504-2508.

courses such as the monogenic diabetes course at Exeter. He also emphasised the importance of adopting a systematic approach to identifying patients who need testing, improving genetic and non-genetic tests and ensuring equity of access across the country.

Nevertheless, diagnosing MODY is difficult with no single criteria or absolute cut off. To address this, researchers at the University of Exeter have developed the MODY probability calculator which determines an overall risk factor for MODY from simple clinical factors and family history.<sup>11</sup> The calculator, which is also incorporated into the 'Diabetes Diagnostics' phone app, assesses the risk of monogenic diabetes compared to T1D and T2D and gives a probability of MODY for an individual. This allows the most appropriate patients to be selected for genetic testing by supporting clinicians to make a decision on whom to refer for testing. Professor Hattersley noted that an awareness of the clinical pathways for monogenic diabetes will still be important when using the tool as they are not currently referenced in NICE guidance nor part of formal diagnostic pathways.

Autoantibody tests provide a useful non-genetic approach to exclude MODY and improve diagnosis in insulin-treated patients. Professor Hattersley described the 'Better Diabetes Diagnosis' project in Sweden where systematic antibody testing at diabetes diagnosis led to a 55% pick up rate on monogenic diabetes when introduced across the country.<sup>12</sup> However, there are also limitations of these tests and similarly to the probability calculator, antibody tests are not 100% sensitive, nor are they specific for T1D. The University of Exeter is currently developing a 'one tube test' to improve the diagnostic process, where only a single blood tube will be required for testing antibodies, C-peptide and DNA.

Professor Hattersley concluded that despite being a complicated area, a stratified approach to MODY is highly important with new tools available to support implementation such as advances in DNA sequencing technology which allow a single test to be used for all known genetic subtypes.<sup>13</sup> Therefore a national systematic approach is now critical for patients to be able to truly benefit from the clinical advances in monogenic diabetes.

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<sup>11</sup> The MODY probability calculator can be found on the diabetesgenes website via the link below, as well as on the 'Diabetes Diagnostics phone app': <http://www.diabetesgenes.org/content/mody-probability-calculator>

<sup>12</sup> Further information on the Better Diabetes Diagnosis project in Sweden can be found here: <http://www.ludc.med.lu.se/research-units/diabetes-and-celiac-disease/research-projects/better-diabetes-diagnosis/>

<sup>13</sup> Ellard S, *et al.* (2013). *Improved genetic testing for monogenic diabetes using targeted next-generation sequencing.* *Diabetologia* **56(9)**, 1958-1963.

## Exemplar clinical pathways for a stratified approach to diabetes

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During the discussion sessions, participants addressed each clinical pathway in turn, mapping out the pathways at a high level, discussing the barriers to implementation and then exploring the practical steps required to put these pathways into practice. Delegates considered the economic case for implementation; the commissioning and funding framework for diagnostics; adoption of a systematic approach; raising awareness; and building capacity and capability amongst other areas. An outline of the proposed clinical pathways for MODY, neonatal and gestational diabetes can be found in Appendix III.

It was agreed by all delegates that a national strategy must be founded on a patient-centric, systematic and pragmatic approach, with local ownership and clear incentives to facilitate uptake of, and access to, these pathways. It was acknowledged that this approach and the associated steps outlined below will need to be '*a work in progress*' with the models adapted as they are implemented.

Over the course of the discussions, a wider barrier to the adoption of a stratified approach was identified: the need to shift the mindset from recognising all diabetes patients as being either T1D or T2D, to recognising the range of monogenic diabetes subtypes. There was also widespread consensus that it is essential to tailor this stratification for all populations and in particular, different ethnic groups where the prevalence may differ.

### **A systematic approach to stratification**

Delegates considered how to introduce a systematic approach to stratification of patients alongside the rationale behind doing this and the potential impact of misdiagnosis. For example, one delegate questioned whether disease management is significantly changed with the proposed MODY clinical pathway. They explained that children often dislike insulin, with some stopping insulin for months at a time, and the GCK-MODY patients without complications from temporarily stopping insulin are then noticed by clinicians and steered onto the right pathway. Conversely, it was argued that such a non-standardised approach would only capture a minority of patients and there is huge patient benefit in a diagnosis by potentially avoiding unnecessary lifelong treatment with insulin. In particular, one delegate emphasised the impact of misdiagnosis of HNF1A/4A-MODY if NICE guidance was followed, as treatment – particularly first line – with sulphonylureas would be unlikely when following NICE guidance. However, these patients would actually significantly benefit from treatment with this drug class as opposed to the conventional first line treatment for type 2 diabetes, metformin. In general, it was noted that NICE guidelines for diabetes can be confusing with numerous drug classes and different lines of treatment available.

### ***Risk stratifying MODY patients***

Case finding and identification of patients is a challenge and the MODY probability calculator could remedy this by stratifying and thus facilitating selection of patients based

on risk.<sup>14</sup> Delegates suggested that the probability calculator could be embedded into GP computer systems to prompt GPs to complete the questionnaire as part of a decision support system that then recommends tests to define the clinical diagnosis at a molecular level. The calculator could be relatively easily integrated given that there are only three main providers of GP systems and it was proposed to trial it in one of the systems first, where patients above a threshold risk of MODY using the calculator should be offered genetic testing. For insulin treated patients, a likelihood of MODY >12.5% would prompt antibody testing and if this gives a negative result, genetic testing. In non-insulin treated patients a threshold of >20% should be applied; the evidence supporting these thresholds would need to be reviewed on a regular basis. In general, delegates proposed that diagnosis of MODY should start at <30 years as patients rarely present older than this. This approach could be used as an exemplar for other therapy areas and would also facilitate data collection for research and public health analysis.

Delegates voiced concerns about the applicability of the calculator to different ethnicities as it is less robust for ethnicities other than Caucasian due to a lack of samples from these populations. To start addressing this issue, there is an ongoing Imperial College London study collecting data on South Asian populations that can be later incorporated into the tool, and one in eight of MODY tests is now carried out for non-Caucasian populations.<sup>15</sup> A larger project looking at MODY in different populations may be required, combined with data from initiatives such as the 100K Genomes Project. Personalisation and its associated tools must serve the entire UK population and so it was agreed that the current limitations of the model should be recognised and the barrier to modelling in all ethnicities must be overcome.

#### ***Autoantibody tests as another stratification tool***

Delegates agreed that antibody testing should be included as the first line of investigation for MODY following risk assessment, then moving to confirmatory genetic testing if there is a negative result. Again, it was suggested that this test should be carried out for every diagnosis of diabetes at <30 years. It was also noted that antibody testing for different ethnicities is reasonably accurate.

At present, there is disparity in the quality of antibody tests where assays between different centres are not comparable due to a lack of standards and the multitude of assays available including historical in-house tests. The tests are strengthened by using more antibodies, however, one delegate noted that many services still only offer one or two antibodies despite 90-95% successful diagnosis when using three (GAD65, IA2, ZnT8 are used at Exeter) and a marginal cost of a few pounds. Delegates agreed that antibody testing should be limited to laboratories offering the most appropriate repertoire of tests based on current evidence, and there should be a uniform and reproducible approach including standardisation of methodologies and appropriate population based thresholds.

<sup>14</sup> It should be noted that the Diabetes Diagnostics app incorporates the MODY probability calculator into a wider set of measures which will calculate probability of all types of diabetes.

<sup>15</sup> Information on the MYDIABETES trial can be found here: <https://clinicaltrials.gov/ct2/show/NCT02082132>

***Systematic blood glucose testing to identify neonatal diabetes***

Early diagnosis of neonatal diabetes is paramount to prevent prolonged hyperglycaemia arising from delayed diagnosis, which may have potentially severe consequences of lifelong difficulties such as neurological damage and dependency on care.  $K_{ATP}$  mutations are expressed in the brain so the earlier the infant receives sulphonylureas for neonatal diabetes, the better the neurological function outcome. Undiagnosed children will fall very ill by six months and there is often a delay in diagnosis due to the non-specificity of the symptoms of hyperglycaemia. Thus there was consensus that blood glucose must be tested early to accelerate genetic testing and rapid treatment with sulphonylureas if required.

It was concluded that a systematic approach is required to identify infants with neonatal diabetes, avoiding unrecognised hyperglycaemia, and it was agreed that the best option would be to test blood glucose in all infants. Ideally, it would be tested at birth as part of a newborn screening process whilst recognising the difficulties around cut offs and managing false positives. Delegates acknowledged that Public Health England may be required to establish a screening process although it was suggested that implementation of this approach may be faster through the NHS. An additional blood spot to test blood glucose could be used as part of the NHS heel prick tests for infants at five days old, however, more research is required to first establish the accuracy and cost-effectiveness of a newborn screening strategy. One delegate asked if the neonatal test could be conducted as part of a panel for monogenic diabetes but this would prove ineffective as with the exception of GCK-MODY, MODY does not present this early.

***Stratification of gestational diabetes***

GCK-MODY patients are often identified with raised fasting blood glucose during routine antenatal care, and can be selected for genetic testing utilising clinical criteria (BMI <25 and blood glucose  $\geq 5.5$ mmol/L) to stratify them amongst the majority of suspected gestational diabetes patients who will not require a genetic test. If a mother has GCK-MODY then it is useful to know if the fetus has inherited the mutation, as a fetus without a GCK mutation may require the mother to receive insulin to combat exposure to maternal hyperglycaemia which results in fetal hyperinsulinaemia, causing increased growth and other adverse effects. An ultrasound scan is currently used for this diagnosis and if the fetus is a 'normal' size then it is assumed to have the mutation and the mother is not treated. The mother should enter the MODY clinical pathway after birth, however, there is often an issue with failure to follow up after pregnancy. The University of Exeter is currently developing a non-invasive maternal blood test as a more accurate replacement for ultrasound scans to determine fetal GCK genotype.

Opportunities to incorporate GCK-MODY genetic testing into the broader maternal pathway were noted, as a variety of tests are already included in the pathway such as those for pre-eclampsia. One delegate identified the potential benefit from incorporating other stratified approaches at this part of the lifecourse, and so this exemplar could be built upon to integrate other testing elements.

It was agreed that there is a need for a more sophisticated risk stratification tool for GCK-MODY amongst pregnant women rather than – as one delegate described it – the

relatively 'crude' BMI and fasting blood glucose tests. The MODY probability calculator could be modified for this target population if improved for different ethnicities as suggested earlier. Identification of high risk patients is further complicated by the tendency for larger numbers of slim individuals with high fasting blood glucose to be found in the high prevalence populations.

#### **Suggested next steps for implementation of a systematic approach to stratification:**

- Standardising the diabetes diagnostics pathways and incorporation of the different monogenic diabetes pathways into NICE guidelines.

##### *MODY*

- Establishing the cut off age for MODY diagnosis at <30 years of age.
- Securing funding to pilot the integration of the MODY probability calculator into one of the three GP IT systems.
- Refinement of the MODY probability model for different ethnicities through further research.
- Agreeing national standards and thresholds for pancreatic autoantibody testing in laboratories.

##### *Neonatal diabetes*

- Consider introducing a systematic newborn screening programme for blood glucose, possibly as part of the NHS heel prick test for infants at five days old.

##### *Gestational diabetes*

- Developing a risk stratification tool for pregnant women which integrates clinical and biochemical data to identify patients for MODY-GCK genetic testing.

### **Funding of diagnostic tests**

Delegates were in agreement that there are urgent issues around the funding for genetic tests in England. The genetic tests for MODY and neonatal diabetes carried out at Exeter have been approved by the UK Genetic Testing Network (UKGTN) but according to participants, difficulties have been encountered where the funding for these tests from specialised commissioning has not reached diabetes centres or GP practices. This has contributed towards the confusion around where the funding for the tests should originate from and difficulties with reimbursement, and so a fit-for-purpose funding framework is required to ensure country-wide access to the tests.

Additionally, concerns were raised around further funding for the 'bottoming costs' such as the blood tests to obtain the samples for genetic testing, even if the direct test costs are covered. However, it was countered that these should be managed by including them within the overall costs for other services such as the blood service rather than requiring separate funding. One delegate also observed that if more equitable access to genetic testing was achieved, higher numbers of tests would be carried out and so the cost per test would decrease and the cost-effectiveness would increase.

NHS England highlighted that it shortly intends to procure genetic testing with a designated specialist national service for diagnostics where budget will be allocated to a service for providing access across the whole of England.

### **Neonatal diabetes**

The Wellcome Trust is currently funding the  $K_{ATP}$  genetic testing worldwide through a five year research funding programme at the University of Exeter.<sup>16</sup> It was agreed by delegates that this test must be nationally funded to ensure equity of access and sustainability.

### **Suggested next steps for implementation of a fit-for-purpose funding framework:**

- Creation of a national funding structure for diabetes diagnostic services to ensure sustainability and equity of access.

## **Building capability, capacity and engagement**

Delegates described the '*powerful message*' for clinicians around getting the diagnosis right to mitigate the notable consequences of misdiagnosis such as a lifelong pathway of inappropriate treatment. It was also identified as important to engage the 209 Clinical Commissioning Groups (CCGs) and key individuals from these to disseminate the stratified approach to local areas.

Education and training of clinicians is required to ensure that a patient enters the right pathway, as well as helping to communicate *why* they are utilising the different tools for stratification. One participant emphasised that the diagnostic pathway cannot rely on skilled diabetologists seeing every patient as they could not cover the entire population; therefore it is important to consider the education needed at all steps of the patient journey and not simply at consultation with a specialist. For example, the University of Exeter has developed a Massive Open Online Course aimed at a general audience, which could be adapted to produce a tailored version for GPs.<sup>17</sup> The development of educational modules should involve the medical Royal Colleges, and Health Education England who could include the new pathways within its Genomics Education Programme.<sup>18</sup> Despite the need for training, in some cases this should remain at a relatively high level, as rolling out a stratified model across primary and secondary care cannot rely on an in-depth understanding of the biological rationale across all disciplines. An exemplar-based approach was suggested by delegates where training for this approach is first introduced for diabetes and then applied to other therapeutic areas based on initial learnings.

Delegates suggested that understanding of, and compliance with, the diagnostics processes would be reinforced if diabetes was a registrable disease and clinicians were obliged to fulfil certain functions to treat patients; this would also build a database for

<sup>16</sup> This research funding was allocated to Professor Andrew Hattersley FMedSci and Professor Sian Ellard for 2012-2019.

<sup>17</sup> Further information on the course 'Genomic medicine: transforming patient care in diabetes' can be found here: <https://www.futurelearn.com/courses/diabetes-genomic-medicine>

<sup>18</sup> <https://www.genomicseducation.hee.nhs.uk/>

further research. However, one delegate argued that this is already in place with GP registers and Quality Outcome Framework (QOF) points for T1D and T2D diagnoses/treatment.

The importance of empowering patients was highlighted and patient education can be built on current information streams such as patient information leaflets and clinical consultations. A participatory environment with patients will provide the pull for the healthcare system to adopt a stratified approach and NHS England is organising national discussions with patient groups in 2016 to drive this demand. It was noted that as part of the genetic testing service provided at Exeter, information about the genetic subtype and its implications is provided in addition to the genetics report which supports both the patient and clinician.

### ***MODY***

Delegates anticipated the need for specially trained 'genetic diabetes nurses' and a more general focus on training diabetes specialist nurses (DSNs) who are the most likely point of primary care for diabetes patients within the MODY age range.

### ***Neonatal and gestational diabetes***

Neonatal paediatricians require training to support provisional diagnoses of neonatal diabetes based on clinical presentation. It was suggested that clinicians tend to contact a local specialist if a child <6 months old presents diabetic symptoms in a District General Hospital, which helps to facilitate a monogenic diabetes diagnosis. Nevertheless, a certain level of education is still beneficial for non-specialists to prevent any patients from being missed. The training approach suggested earlier for DSNs could also be extended to midwives and paediatricians to create local champions.

### **Suggested next steps for implementation of an education and engagement strategy:**

- Engaging CCGs and clinical leaders around the proposed stratified approach to diabetes.
- Producing detailed educational courses for specialists and including the monogenic diabetes pathways in routine clinical education.
- Creation of high level educational courses/information for other clinicians (including GPs, paediatricians, nurses and midwives) that address the relevant diabetes pathways. The medical Royal Colleges and Health Education England should be involved in designing this training.
- Establishing local champions for each of the diabetes pathways (e.g. genetic diabetes nurses).
- General patient engagement to raise awareness of this approach.
- Incorporating information on the diabetes subtypes and diagnosis pathways into patient education (such as through patient information leaflets).

## The health economics of stratification

There is confidence that the proposed stratified approach for diabetes is cost-saving. This is reflected by the health economics modelling carried out by the University of Exeter which explored different scenarios for how this approach could be rolled out; the cost-effectiveness of testing all against testing none; the current pick up rate for monogenic diabetes in patients; and other factors.<sup>19</sup> The models did not include clinical effectiveness, the patient benefit derived from a patient stopping insulin or the theoretical benefits of changing treatment; these factors were excluded as it is difficult to demonstrate improvement, however, this could be justified as a cost-saving intervention simply from changing medication. In addition, as a model is increasingly personalised it is easier to demonstrate clinical effectiveness in the target population. It was agreed that health economics modelling should include these quality of life variables and also take into account the economic case for co-diagnoses as monogenic diabetes is hereditary.

### **Cost-effectiveness modelling**

Nevertheless, there were challenges in demonstrating that this model is cost-effective, and one delegate noted that stratification is '*not a perfect process*' with misclassification affecting cost-effectiveness. A key issue faced in calculating cost-effectiveness is the insufficient patient numbers for a Randomised Controlled Trial (RCT) as with stratification the patient populations become increasingly small and so an RCT may no longer be practicable. Delegates therefore underlined that a change in mindset around the acceptable evidence for cost-effectiveness must be generated. Where possible, it was identified as important to demonstrate where approaches are cost-saving, and to communicate the balance between cost-savings and clinical outcomes.

### **MODY**

In addition to the positive impact on quality of life and disease management for patients, there is a strong economic argument for the MODY diagnostic pathways as treatment is often a cheaper sulphonylurea which is the most effective intervention (HNF1A/4A-MODY), or no intervention at all (GCK-MODY).

### **Neonatal diabetes**

As with HNF1A/4A-MODY, treatment with sulphonylureas for a patient with neonatal diabetes is cheaper and more effective than insulin. Despite being cost-saving at all stages of diagnosis, these savings are further maximised by diagnosis in the newborn. Delegates argued that implementing this pathway will have additional economic value by preventing potential lifelong dependency on care due to a missed diagnosis, and although the relative numbers are too small to calculate for health economics, the impact is clearly profound. One delegate estimated that a lifetime of care could cost a million pounds or more, whereas it is a 20 pence marginal cost for blood glucose screening. Therefore one patient diagnosed would likely pay for all neonatal blood glucose tests over a few years as the extra blood spot required for testing is inexpensive. These calculations support the argument for the proposed national neonatal screening programme.

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<sup>19</sup> Paper on health economics by Exeter University submitted for publication in 2016.

***Maximising the efficiency of the diagnostics process***

The University of Exeter is working to streamline the diagnostics process for monogenic diabetes by developing a 'one tube test'. This is a single blood vial which can be used for all relevant tests such as autoantibodies, C-peptide and gene panels, speeding up the diagnostic process whilst lowering sample and general costs. They also recommend that clinicians email completed request forms before the sample is dispatched so that tests can be pre-booked and started immediately when the sample is received; the child can then be placed onto the right treatment pathway as soon as possible and this maximises the efficiency of the diagnostics process.

**Suggested next steps for implementation based on health economics:**

- Trialling the proposed diabetes clinical pathways at test bed sites for a 'commissioning through evaluation' approach to address any early issues and confirm benefits of implementation including cost-savings.
- Provision of further information to commissioners on the health economics of implementing the various diabetes pathways.

## Conclusions and next steps

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Sir John Tooke FMedSci summarised the key points from the afternoon discussions and noted the general acceptance for the wider framework and pathways proposed. He highlighted the need for an iterative approach, with the model evolving over time as different issues and solutions arise. When considering the economic case for implementation of these pathways, Sir John emphasised that it is important to recognise that subsequent gains can be made downstream when patients are treated more precisely.

Sir John argued that the discussions indicated a need for national commissioning to ensure country-wide adoption of diagnostic tests, with standardisation of diagnostics and treatments and adaptation of NICE guidelines. One of the issues highlighted was the need to ensure that the model is applicable for all ethnicities, and he stressed the importance of clear communication around the current gaps in the evidence base for different populations. He also asserted that the incorporation of decision support tools into IT systems on GP desktops will be a key factor in ensuring the success of this approach.

Awareness can be raised through targeting clinical groups, and educating and training frontline clinicians, specialists, practice nurses and midwives. Sir John proposed that clinical leadership and local champions will be critical for widespread engagement and buy-in to the stratified approach to diabetes. There is an opportunity for communication through the media, and empowering patients themselves. He also stated the importance of involving families in the process and not just the patient, as the hereditary nature of monogenic diabetes may impact the wider family.

Sir John concluded that stratification in diabetes offers an opportunity to start on the pathway to adoption of stratified medicine across the NHS, and implementation of the proposed clinical pathways for diabetes in test beds will demonstrate the impact and benefits of such an approach. In a cash-constrained NHS, demonstrating the value of the approach in a manner that is not reliant on the introduction of expensive new drugs could aid the broader acceptance and adoption of stratified medicine.

## Appendix I Programme

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13.30-14.00	<b>Tea, coffee and refreshments</b>
14.00-14.05	<b>Welcome</b> Professor Sir John Tooke FMedSci (Chair), Former President, Academy of Medical Sciences
14.05-14.20	<b>Developing NHS England's personalised medicine strategy</b> <i>An introduction to NHS England's current work programme for personalised medicine, to include key findings of the recent AHSN meetings</i> Professor Sue Hill OBE, Chief Scientific Officer, NHS England
14.20-14.35	<b>Stratifying the treatment of diabetes</b> <i>An overview of current approaches to the stratification of diabetes, with particular emphasis on maturity onset diabetes of the young (MODY).</i> Professor Andrew Hattersley FRS FMedSci, Professor of Molecular Medicine and Consultant Physician, University of Exeter
<b>Developing an exemplar clinical pathway for the stratified treatment of diabetes, and key steps to implementing this pathway</b>	
14.35-16.00	<b>Discussion session 1</b> Discussion of (and revision as appropriate) a draft clinical pathway for the stratified diagnosis and treatment of type 1, type 2 and maturity-onset diabetes of the young (MODY), considering key risks and barriers to implementing this pathway. Identification of the key steps that would need to be taken to put the pathways discussed into practice.  A draft pathway – 'Pathway 1' – developed in discussion with Professor Hattersley and Professor Ellard, was circulated in advance of the meeting.
16.00-16.15	<b>Refreshment break</b>
16.15-17.30	<b>Discussion session 2</b> Discussion of (and revision as appropriate) two further pathways – 'Pathway 2' and 'Pathway 3' – for the stratified diagnosis and treatment of gestational and neonatal diabetes, again considering key risks and barriers and next steps for implementation.
17.30	<b>Close</b>

## Appendix II Delegate list

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**Professor Sir John Tooke FMedSci (Chair)**, Former President, Academy of Medical Sciences

**Professor Andrew Hattersley FRS FMedSci (Speaker)**, Professor of Molecular Medicine and Consultant Physician, University of Exeter

**Professor Sue Hill OBE (Speaker)**, Chief Scientific Officer, NHS England

**Dr Amanda Adler**, Consultant Physician, Addenbrooke's Hospital and Chair, Technology Appraisal Committee B, NICE

**Dr Fiona Carragher**, Deputy Chief Scientific Officer, NHS England

**Professor Sian Ellard**, Consultant Clinical Scientist and Head of Molecular Genetics, Royal Devon & Exeter NHS Foundation Trust

**Dr Tom Fowler**, Director of Public Health, Genomics England

**Dr Jane Fryer**, Medical Director for South London, NHS England

**Dr Henrietta Hughes**, Medical Director for North Central and East London, NHS England

**Professor Chris Hyde**, Professor of Public Health and Clinical Epidemiology, University of Exeter

**Dr Rahul Kapur**, Head of Medical Affairs, Novo Nordisk

**Dr Tim McDonald**, Principal Clinical Scientist, Royal Devon and Exeter NHS Foundation Trust

**Dr Claire Newland**, Programme Manager for Stratified Medicine and Molecular Pathology, Medical Research Council

**Professor Katharine Owen**, Associate Professor and Honorary Consultant, University of Oxford, and Diabetes Clinical Network Lead, Oxford Academic Health Science Network

**Dr Belinda Quinn**, Clinical Officer, Precision Medicine Catapult

**Dr Beverley Shields**, Senior Lecturer in Medical Statistics, University of Exeter

**Professor Adrian Towse**, Director, Office of Health Economics

**Professor Jonathan Valabhji**, National Clinical Director for Obesity and Diabetes, NHS England

**Dr John Williams**, Interim Executive Director, Academy of Medical Sciences

### Secretariat

**Ms Libby Dixon**, Policy Officer, Academy of Medical Sciences

**Ms Melissa Lennartz-Walker**, Policy Intern, Academy of Medical Sciences

### Observers

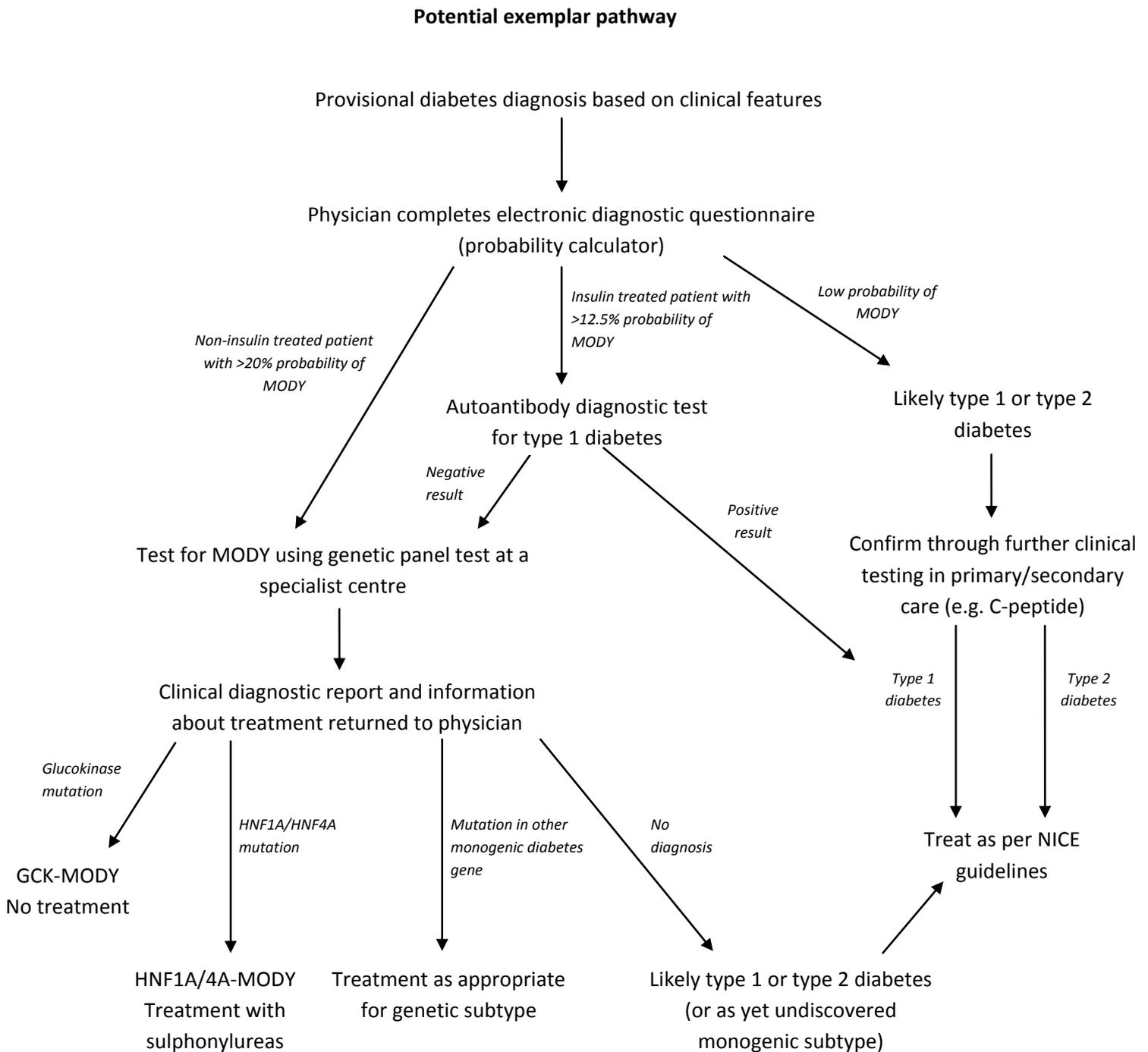
**Ms Sally Chapman**, Clinical and Scientific Policy and Strategy Lead, NHS England

**Mr David Laszlo**, Director, David Laszlo Partnership

**Mr John Paul Maytum**, Special Adviser to the Chief Scientific Officer, NHS England

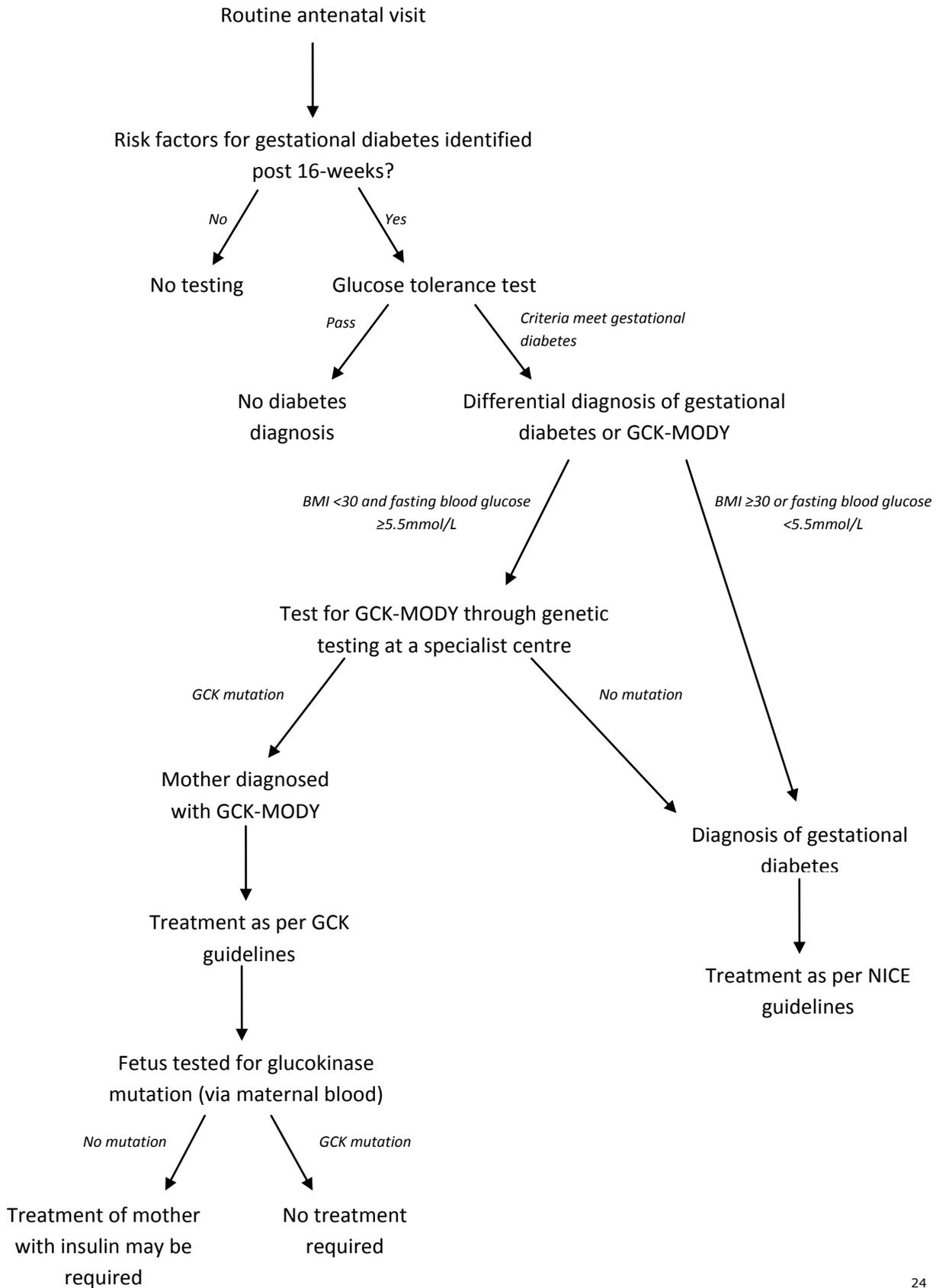
Appendix III Draft clinical pathways for stratification of diabetes

**Pathway 1: Maturity-onset diabetes of the young (MODY), type 1 diabetes and type 2 diabetes**



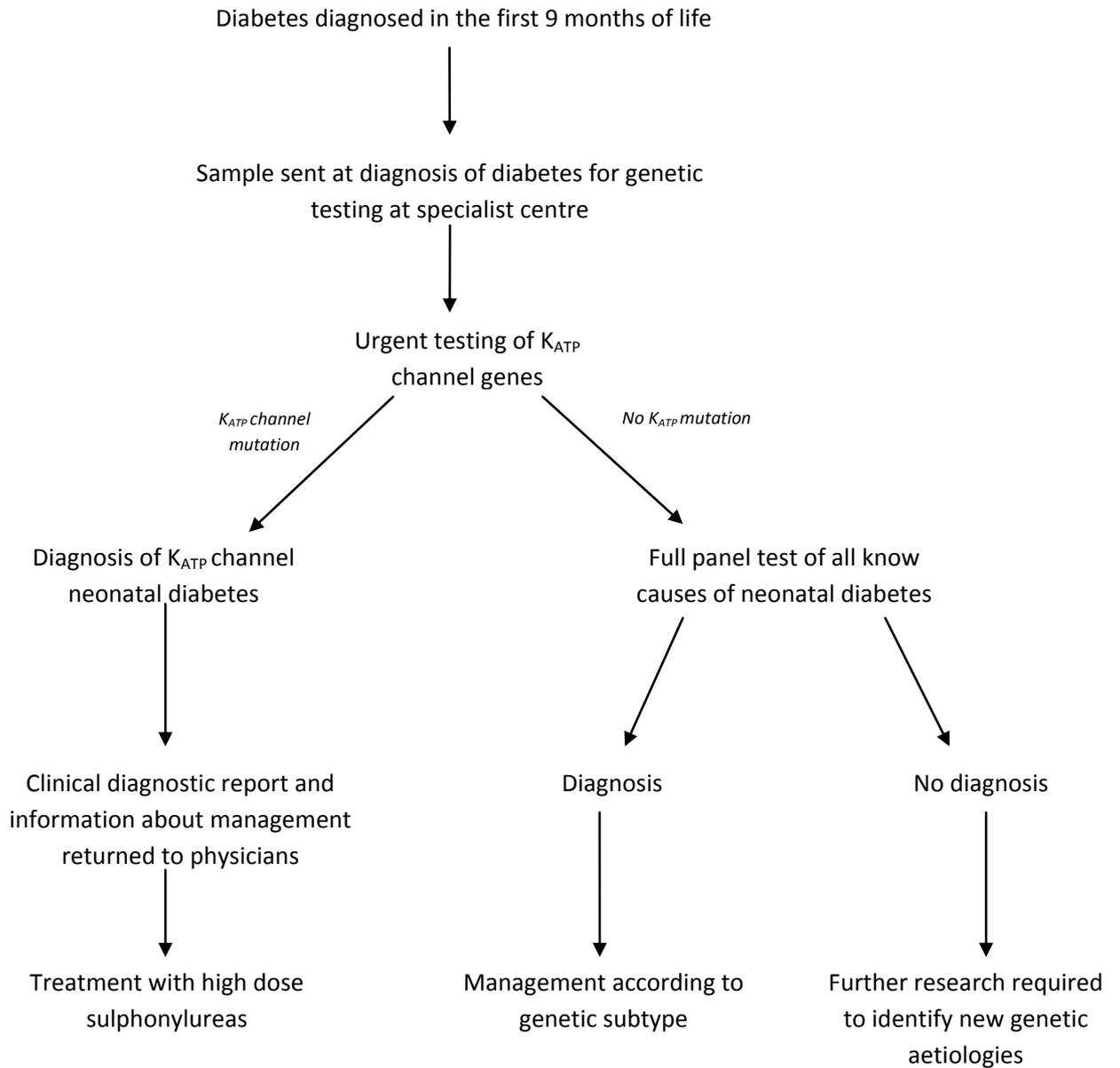
## Pathway 2: Gestational diabetes

### Potential exemplar pathway



**Pathway 3: Neonatal diabetes**

**Potential exemplar pathway**





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