NHS
Cheshire and Merseyside

Clinical Commissioning Policy

Monogenic Diabetes Testing

Category 1 Intervention - Not routinely commissioned -

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Purpose	This document is part of a suite of policies that the Integrated Care Board (ICB) uses to drive its commissioning of healthcare. Each policy in that suite is a separate public document in its own right but will be applied with reference to other policies in that suite.
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1. Introduction

1.1 This policy relates to the commissioning of interventions which optimise clinical effectiveness and represent value for money.

1.2 This document is part of a suite of policies which the Integrated Care Board (ICB) uses to drive its commissioning of healthcare. Each policy is a separate public document but should be considered alongside all the other policies in the suite as well as the core principles outlined in Appendix 1.

1.3 At the time of publication, the evidence presented per procedure/treatment was the most current available.

2. Purpose

2.1 This policy aims to ensure a common set of criteria for treatments and procedures across the region. This is intended to reduce variation of access to NHS services in different areas and allow fair and equitable treatment for all patients.

3. Policy statement

3.1 The ICB does not routinely commission monogenic diabetes testing**.**

3.2 Monogenic diabetes testing for adults and children is routinely commissioned by **NHS England** only if the criteria, as determined by the Exeter Genomics Laboratory (the national testing centre), are satisfied.

3.3 These criteria are constantly being developed and so clinicians should refer to this website regularly. The criteria can be accessed using the following link: https://www.diabetesgenes.org/tests-for-diabetes-subtypes/guidelines-for-genetic-testing-in-mody/

4. Exclusions

4.1 None

5. Rationale

5.1 The national scheme for testing is run by the Exeter genomics laboratory and funded by NHS England.

5.2 Tests outside the scheme are not permitted because of the complex nature of the condition and the indications for testing.

6. Underpinning evidence

6.1 Monogenic Diabetes of the Young (MODY) is a term first used in the 70s and it describes an inheritable diabetes which is distinct from the usual diabetes types 1 or 2. It typically presents before the age of 25 years and the genetic basis for its existence was subsequently recognised in the 90s.[1] To date, mutations have been found in at least 14 different genes. [2] The prevalence of MODY has been estimated at between 1% – 2% of all patients with diabetes. [1]

6.2 In 2008, one author suggested that the term MODY is outdated because the condition is not a single entity. The different genetic subtypes differ in terms of age of onset, pattern of hypoglycaemia, responses to treatment and associated extra pancreatic manifestations. Further, the use of "maturity" in MODY implies a resemblance to type 2 diabetes (previously known as maturity onset diabetes) and this is a misnomer because the two conditions are different. The correct monogenic names (see later) of the different forms of young-onset diabetes should be used.[3] Despite this, the word "MODY" has persisted over the last 10 years.

6.3 The principal genetic types include the enzyme Glucokinase (GCK), Hepatocyte Nuclear Factor 1α (HNF1A) and Hepatocyte Nuclear Factor 4α (HNF4A) and these account for 32% (GCK), 52% (HNF1A) and 10% (HNF4A) of all MODY cases.[1] Clinically, patients present with a strong family history of diabetes of any type, onset of diabetes occurring in the 2nd to 5th decade, insulin independence, absence of features of insulin resistance and absence of beta-cell autoimmunity.

6.4 From a practical point of view, identification of the genetic subtype could have important consequences for those patients who are currently being treated (erroneously) for types 1 or 2 diabetes. For example, HNF1A patients are extremely sensitive to the hypoglycaemic effects of the oral sulphonylureas. Patients in this group previously misdiagnosed with type 1 diabetes may be able to discontinue insulin and treated with a sulphonylurea without the risk of ketoacidosis. This switch is possible even after 20 years previous treatment with insulin. In addition, individuals with GCK, owing to their mild hyperglycaemia and absence of long-term microvascular complications, may require no treatment at all, with the exception of pregnancy when insulin might be required. Similarly, HNF4A patients may also respond to low-dose sulphonylureas. [4]

6.5 Unsurprisingly, the diagnosis is often delayed, and, in the UK, this average delay is 13 years from original "diabetes" diagnosis to establishing a more definitive genetic diagnosis. It has been estimated that greater than 80% of all MODY cases in the UK are currently misdiagnosed as type 1 or 2 diabetes.[1] However, it is recognised that genetic testing is too expensive for indiscriminate use in all patients with diabetes. [1] Best practice guidelines recommend genetic testing the people who match specific clinical criteria i.e. diabetes presenting before the age of 25 years, strong family history of diabetes and evidence of insulin independence. It is also recognised that these criteria are still not perfect.

6.6 More recent publications have built on these criteria for genetic testing and now include metabolic profiling, pancreatic antibodies and C-peptide which seem to be better selection tools than those used previously. [5] In addition, good candidates for genetic testing also include nonobese subjects with hypoglycaemia. [2] Despite this, improving the uptake of genetic testing by defining who should be tested is an area of active research. It seems that defining the high risk groups in adults with diabetes is more difficult (than children), but online decision aids may assist clinicians in selecting whom to refer for testing.

6.7 In the UK, the Monogenic Diabetes and Molecular Genetics Teams at the University of Exeter Medical School and Royal Devon and Exeter NHS Foundation Trust run a website (diabetesgenes.org) which aims to provide information for patients and professionals on genetic types of diabetes. The website includes the MODY probability calculator which is used to screen patients ahead of genetic testing. The calculator uses information such as the patient's sex, insulin treatment, BMI and HbA1c to come up with the probability as to whether genetic testing is appropriate. Few studies have been conducted which examined the validity of this screening tool.

6.8 In 2016, an American study compared the utility of the Exeter MODY probability calculator to their Unit's in-house computer system using local clinical criteria. There were marginal differences in sensitivity and specificity. [6]

6.9 Two other studies also recorded the sensitivity of the calculator to be 56% – 77% and specificities of 60% – 65% [7,8] In other words, for patients who are truly positive, the calculator has a false negative rate of approximately 25% – 50% (i.e. it would fail to pick up nearly half of the truly positive cases) and in the case of patients who are truly negative, nearly 1/3 would be categorised as false positives. In addition, a Polish study showed that 10% of known GCK MODY cases and 36% of known HNF1α MODY cases achieved low risk scores according to the calculator. [9]

6.10 Unfortunately, the situation becomes even more complex when one considers other biomarkers in addition to criteria used by the MODY calculator. For example, type 1 diabetes is generally held to be an autoimmune disease. Measurement of islet autoantibodies is frequently used to differentiate between MODY and type 1 diabetes, being zero in the former and high in the latter. A very recent study recorded 6.3% islet autoantibody positivity in MODY patients which, therefore, challenges the use of autoantibodies as a universal negative marker of MODY.[10]

6.11 With such a high prevalence of all forms of diabetes in the population (approximately 6%), commissioners will be anxious that whole population screening for MODY would be very costly. Interestingly, a recent health economics evaluation found that using clinical characteristics (such as the MODY calculator) or biomarkers were estimated to save approximately £100 – £200 per person with diabetes over a lifetime compared with no testing. [11] The authors assumed the cost of the genetics test to be £100 – £450 depending on the specific gene and acknowledged the results were limited because of the small number of individuals and also uncertainty around the estimates of some of the long-term costs. The authors also stated that if their assumed costs of the genetic test were significantly higher, it would be unclear whether there would be a financial benefit. In fact, the most up-to-date cost of the Exeter genetic test, as cited on the website is £650.

6.12 Data on the uptake of genetic testing have been made available from the national testing laboratory in Exeter (personal communication – Kevin Colclough, Principal Clinical Scientist). For all patients living in Cheshire, a total of 70 probands have been referred since 2000 when the service first began. Of these, 21 patients were diagnosed with MODY (a positivity rate of 30%). More recently, for the 3 years commencing in 2017, 12 probands were referred, of whom 4(33%) were positive for MODY. This indicates a low uptake in activity and suggests that the MODY calculator incorrectly identifies nearly two thirds of patients deemed suitable for genetic testing.

6.13 The National Institute for health and care excellence (NICE) in its guidance for types 1 & 2 diabetes in children (NG 18) recommends that genetic testing should be performed if atypical disease behaviour, clinical characteristics or a family history suggest monogenic diabetes.[12] In the full guideline, NICE noted that genetic testing is the gold standard for identifying monogenic forms of diabetes and is the only method which can confirm the suspicion of monogenic diabetes. Interestingly, NICE also recommends that C-peptide or autoantibody titres shouldn't be measured at initial presentation to distinguish between types 1 & 2 diabetes. However, measurement of C-peptide may be appropriate after initial presentation to distinguish between the various types of diabetes, and this is because C-peptide concentrations have better discriminative value the longer the interval between initial presentation and the test. According to NHS England's manual for prescribed specialised services (2018/19), NHS England commission services for rare forms of diabetes in children such as MODY.

6.14 In its guidance on type I diabetes in adults (NG 17), NICE recommend measurement of C-peptide and/or autoantibody titres in adults who present with some atypical features of diabetes and specifically when there is clinical suspicion of monogenic diabetes. [13] The recommendation further suggests that these measurements might guide the use of genetic testing. However, NICE do not specify how these tests should be used in practice and also state that genetic testing *per se* was outside the scope of the guideline. The complexity of these tests is underlined because antibody tests have the greatest positive predictive value within the first year of diagnosis, whilst C-peptide has a higher predictive value with an increasing time from presentation of diabetes. One of the research recommendations asks whether these diagnostic tests are useful for defining type 1 diabetes and if so, what is the optimal time when they should be measured.

6.15 **Summary**

a. The term monogenic diabetes of the young (MODY) is outdated because although this genetic condition will be present at birth, it may not be manifested until adulthood. “Monogenic diabetes” is preferred and there are at least 14 different genes.
b. The clinical significance of identifying this atypical form of diabetes may be important in some individuals who potentially could switch from insulin to oral hypoglycaemics or may require no anti-diabetes drugs at all.
c. There is some concern about widespread testing of all diabetics (approximately 6% of the total population) at a cost of £650 per test.
d. Targeted screening is therefore appropriate and currently this uses the MODY calculator developed by the monogenic diabetes team in Exeter.
e. However, although the uptake for testing is low (12 tests over the last 3 years), two thirds of potential individuals identified by the current system tested negative.
f. Identification of people suitable for screening is highly complex and involves the interplay of many factors which include:- currently type 1 or type 2 diabetes, insulin therapy, age of diabetes diagnosis, current age, BMI, HbA1c, family history of diabetes, time-dependent C-peptide level, time-dependent autoimmune antibody titres and presence/absence of ketones.
g. There are limited data on the cost effectiveness of widespread, targeted genetic testing. However, based on the current list price of the Exeter genetic test, such targeted genetic testing is unlikely to be cost-effective.
h. None of the neighbouring CCGs have a policy for genetic testing for monogenic diabetes.

6.16 Following the CPDIG meeting when this paper was first presented, it has subsequently transpired that genetic testing for monogenic diabetes is funded by NHS England for both adults and children, but referrals must satisfy the inclusion criteria as laid down by the Exeter Genomics Laboratory (the NHS’s national testing centre).

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7. Force

7.1 This policy remains in force until it is superseded by a revised policy or by mandatory NICE guidance or other national directive relating to this intervention, or to alternative treatments for the same condition.

8. Coding

8.1 Not generally available

9. Monitoring And Review

9.1 This policy may be subject to continued monitoring using a mix of the following approaches:
- Prior approval process
- Post activity monitoring through routine data
- Post activity monitoring through case note audits

9.2 This policy will be kept under regular review, to ensure that it reflects developments in the evidence base regarding effectiveness and value.

10. Quality and Equality Analysis

10.1 Quality and Equality Impact Analyses have been undertaken for this policy at the time of its review.

Appendix 1 - Core Objectives and Principles

Objectives

The main objective for having healthcare commissioning policies is to ensure that:

- Patients receive appropriate health treatments
- Treatments with no or a very limited evidence base are not used; and
- Treatments with minimal health gain are restricted.

Principles

This policy aims to ensure a common set of criteria for treatments and procedures across the region. This is intended to reduce variation of access to NHS services in different areas and allow fair and equitable treatment for all patients.

Commissioning decisions by ICB Commissioners are made in accordance with the commissioning principles set out as follows:

- Commissioners require clear evidence of clinical effectiveness before NHS resources are invested in the treatment.
- Commissioners require clear evidence of cost effectiveness before NHS resources are invested in the treatment.
- Commissioners will consider the extent to which the individual or patient group will gain a benefit from the treatment.
- Commissioners will balance the needs of an individual patient against the benefit which could be gained by alternative investment possibilities to meet the needs of the community.
- Commissioners will consider all relevant national standards and consider all proper and authoritative guidance.
- Where a treatment is approved Commissioners will respect patient choice as to where a treatment is delivered, in accordance with the 'NHS Choice' framework.
- Commissioning decisions will give 'due regard' to promote equality and uphold human rights. Decision making will follow robust procedures to ensure that decisions are fair and are made within legislative frameworks.

Core Eligibility Criteria

There are a number of circumstances where a patient may meet a 'core eligibility criterion' which means they are eligible to be referred for the procedures and treatments listed, regardless of whether they meet the criteria; or the procedure or treatment is not routinely commissioned.

These core clinical eligibility criteria are as follows:

- Any patient who needs 'urgent' treatment will always be treated.
- All NICE Technology Appraisals Guidance (TAG), for patients that meet all the eligible criteria listed in a NICE TAG will receive treatment.
- In cancer care (including but not limited to skin, head and neck, breast and sarcoma) any lesion that has features suspicious of malignancy, must be referred to an appropriate specialist for urgent assessment under the 2-week rule.
- NOTE: Funding for all solid and haematological cancers are now the responsibility of NHS England.
- Reconstructive surgery post cancer or trauma including burns.
- Congenital deformities: Operations on congenital anomalies of the face and skull are usually routinely commissioned by the NHS. Some conditions are considered highly specialised and are commissioned in the UK through the National Specialised Commissioning Advisory Group (NSCAG). As the incidence of some cranio-facial congenital anomalies is small and the treatment complex, specialised teams, working in designated centres and subject to national audit, should carry out such procedures.
- Tissue degenerative conditions requiring reconstruction and/or restoring function e.g. leg ulcers, dehisced surgical wounds, necrotising fasciitis.
- For patients wishing to undergo Gender reassignment, this is the responsibility of NHS England and patients should be referred to a Gender Identity Clinic (GIC) as outlined in the Interim NHS England Gender Dysphoria Protocol and Guideline 2013/14.

Cosmetic Surgery

Cosmetic surgery is often carried out to change a person's appearance to achieve what a person perceives to be a more desirable look.

Cosmetic surgery/treatments are regarded as procedures of low clinical priority and therefore not routinely commissioned by the ICB Commissioner.

A summary of Cosmetic Surgery is provided by NHS Choices. Weblink:
http://www.nhs.uk/conditions/Cosmetic-surgery/Pages/Introduction.aspx and
http://www.nhs.uk/Conditions/Cosmetic-surgery/Pages/Procedures.aspx

Diagnostic Procedures

Diagnostic procedures to be performed with the sole purpose of determining whether or not a restricted procedure is feasible should not be carried out unless the eligibility criteria are met, or approval has been given by the ICB or GP (as set out in the approval process of the patients responsible ICB) or as agreed by the IFR Panel as a clinically exceptional case.

Where a General Practitioner/Optometrist/Dentist requests only an opinion the patient should not be placed on a waiting list or treated, but the opinion given and the patient returned to the care of the General Practitioner/Optometrist/Dentist, in order for them to make a decision on future treatment.

Clinical Trials

The ICB will not fund continuation of treatment commenced as part of a clinical trial. This is in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and the Declaration of Helsinki which stipulates that the responsibility for ensuring a clear exit strategy from a trial, and that those benefiting from treatment will have ongoing access to it, lies with those conducting the trial. This responsibility lies with the trial initiators indefinitely.

Clinical Exceptionality

If any patients are excluded from this policy, for whatever reason, the clinician has the option to make an application for clinical exceptionality. However, the clinician must make a robust case to the Panel to confirm their patient is distinct from all the other patients who might be excluded from the designated policy.

The ICB will consider clinical exceptions to this policy in accordance with the Individual Funding Request (IFR) Governance Framework consisting of: IFR Decision Making Policy; and IFR Management Policy.