Current and Best Practices of Genetic Testing for Maturity Onset Diabetes of the Young: Views of Professional Experts

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Abstract
Aims: Currently, many patients with maturity onset diabetes of the young (MODY) are undiagnosed or misdiagnosed with type 1 or 2 diabetes. This study aims to assess professional experts’ views on factors which may influence the current practice of genetic testing for MODY and to explore next steps toward best practice. Methods: Twelve semistructured interviews were conducted with professional experts. These experts included physicians with potential or actual experience with genetic testing for MODY, representatives of (para)medical professional associations and a staff member of a diabetes patients’ organization. Results: Participants differed in their valuation of genetic testing for MODY. While most considered the test useful, not all were convinced of its clinical utility. Other factors mentioned to influence current practice were: (perceived lack of) possibilities for treatment and prevention, patients’ perspectives and perceived barriers, such as costs and a lack of knowledge and awareness. Participants agreed that guidelines would be helpful to facilitate expedient testing. Conclusions: This study identified next steps that should be taken to improve genetic diagnosis and care for patients with MODY. Besides the development of a consensus guideline, other suggestions included more education of healthcare professionals, a clearer allocation of responsibilities with regard to genetic testing for MODY and further research.

Introduction
Maturity onset diabetes of the young (MODY) is the most common monogenic subtype of diabetes that is characterized by an early-onset of diabetes, no requirement for insulin at diagnosis, and no signs of autoimmunity or insulin resistance [1]. MODY is inherited in an autosomal dominant manner. It is a clinically heterogeneous group of disorders caused by β-cell dysfunction. It is estimated that MODY accounts for up to 1.8% of patients with diabetes [2]. Mutations in 13 genes are known to cause MODY; the most prevalent are HNF1A, GCK and HNF4A [3, 4]. The MODY subtypes differ in age of onset of diabetes, the pattern of hyperglycemia, response to treatment, and associated extrapancreatic manifestations [5]. As compared to type 2 diabetes, the clinical
symptoms present often at a relatively young age in patients without overweight, who have a positive family history. As compared to type 1 diabetes, progression may be less severe, and the required dosage of insulin low.

Many patients with MODY are currently undiagnosed or misdiagnosed with type 1 or 2 diabetes mellitus [4]. In The Netherlands, for example, it was estimated that there should be ∼20,000 MODY patients [6]; however, until 2012, only 502 HNF1A, GCK and HNF4A patients were genetically diagnosed [7], and it is unknown how many patients were clinically diagnosed. A large number of patients have not been tested, even though genetic identification of MODY may have several benefits. Genetic confirmation of a MODY diagnosis, and thereby defining the subtype, may guide therapy choice and have implications for the anticipation of complications [8, 9]. For example, patients with HNF1A MODY are particularly sensitive to treatment with sulfonylurea derivatives (SUs) and are at risk of developing microvascular complications [8, 10]. SUs are oral medications, so insulin injections may not be needed, which is a clear benefit from the patient perspective. Patients with GCK MODY often do not need medication, but lifestyle advice instead. It is a very mild type of diabetes. In pregnancy however, the patients need close monitoring to avoid complications such as infantile macrosomia. Family members may also benefit from genetic testing; they can be offered presymptomatic testing to confirm or exclude genetic predisposition, and those with a mutation can be offered monitoring strategies [5]. Genetic testing for MODY also has disadvantages, including relatively high costs of testing, possible psychosocial impact of positive test results and potential insurance-related issues [9, 10]. Cost-effectiveness is, however, likely in selected populations [11].

It is not entirely clear why so few MODY patients have been identified. It is possible that healthcare professionals feel the disadvantages of testing outweigh the benefits. Another possibility is that MODY patients are not recognized as such by physicians, who may not be aware of the clinical criteria for genetic testing for MODY. Some resources were developed to assist physicians in their decision to test for MODY, such as practical guidelines related to the provision of genetic testing [12] and a MODY calculator to assess the probability that a particular patient has MODY, based on several clinical characteristics, including age at diagnosis, BMI, HbA1c level, treatment (with insulin or oral hypoglycaemic agents), and whether a parent also has diabetes [13]. Various practice guidelines exist for MODY, such as the European Molecular Genetics Quality Network (EMQN) Best Practice Guidelines [14], the Clinical Practice Consensus Guidelines by the International Society for Pediatric and Adolescent Diabetes [15], and a guideline on counseling patients [12]. However, none of these guidelines alone provide comprehensive information on testing criteria, clinical implications for management, predictive genetic testing, and genetic counseling. It is also unclear if healthcare professionals are aware of these resources and guidelines and whether they are currently being used.

In general, despite the growing number of genetic discoveries, few of these are translated from genomics to evidence-based practice [16]. This may also be the case for MODY; the relatively low number of genetic tests that are requested suggests that their use is not yet fully integrated in healthcare. To understand the lack of translation of genetic testing for MODY into healthcare application, it is important to understand the perspectives of the (potential) requesters of the tests and other healthcare professionals involved. During 2 national multidisciplinary expert meetings in The Netherlands (‘Diabetes and Genetics – from knowledge to application’ in 2007 in Utrecht and the Dutch Health Care Insurance Board’s meeting ‘Diabetes Mellitus’ in 2008 in Leiden), genetic testing for MODY was discussed. In these meetings, participants expressed a need for research into the development of a guideline, and a need for dissemination and implementation research. Since the use of genetic testing for MODY does not seem to be limited by policy or by the availability of the test, the lack of translation of the test into clinical practice may have to do with the potential requesters of the test. This study, thus, aimed to assess Dutch professional experts’ views on factors which may influence the current practice of genetic testing for MODY and to explore the next steps toward best practice. By exploring attitudes, needs, practical barriers and facilitators, this study can aid in the development and implementation of a consensus guideline for genetic testing for MODY in The Netherlands.

Materials and Methods

Study Design and Participants
The study was approved by the Medical Ethics Committee of the VU University Medical Center in Amsterdam. A qualitative study design was used, as this is considered most suitable for the exploration of stakeholders’ perspectives [17]. Semistructured interviews with Dutch professional experts were conducted to explore their views. Participants were purposely recruited to include a range of healthcare professions with potential or actual experience with requesting genetic testing for MODY. Since 2001, genetic testing for MODY in The Netherlands has been provided primarily by the Laboratory for Diagnostic Genome Analyses at the Department of Clinical Genetics at Leiden University Hospital. Ini-
Initially, 8 physicians who had requested genetic testing for MODY were selected from the database of the Laboratory for Diagnostic Genome Analyses. The selection was based on achieving variety in how long the physician had been requesting the test (experienced requesters: requests since 2003 and at least up to 2009; recent requesters: first request in 2009 or 2010). The selection was also intended to achieve variety in the medical setting in which the requesters worked (primary, secondary or tertiary care). In addition, participants were sought from the staff or boards of organizations potentially concerned with MODY. Potential participants were also identified from a list of people who had taken part in workshops prior to the start of the project (‘Diabetes and Genetics – from knowledge to application’, 2007 and the Dutch Healthcare Insurance Board meeting ‘Diabetes Mellitus’, 2008) and, subsequently, by snow-ball method. In total, 27 potential participants received an invitation by mail, explaining the purpose of the study. Twelve professional experts agreed to participate; those who declined or did not respond were clinicians (13) or representatives of medical professional organizations (2). Those who declined gave several reasons, including lack of time, not interested in the topic, and no longer requesting the test. The participants were endocrinologists, internists, clinical geneticists, a vascular specialist, a pediatrician, a general practitioner, a representative of a diabetes patient organization, and representatives of a diabetes nurses association and of an internist association. Physicians from regional hospitals, as well as academic hospitals, were interviewed. Most of the participants (n = 9) were male; participant characteristics are shown in Table 1.

Table 1. Characteristics of interviewed healthcare professionals

| Participant No. | Profession                                      | Years since first test was requested | Number of tests requested | Organization type             |
|-----------------|-------------------------------------------------|--------------------------------------|---------------------------|-------------------------------|
| 1               | Internist-endocrinologist                       | 9                                    | >20                       | Regional hospital             |
| 2               | Vascular specialist                             | 7                                    | 5                         | Regional hospital             |
| 3               | Endocrinologist                                | 10                                   | 30–40                     | Academic hospital             |
| 4               | Internist                                      | 7–8                                  | 10                        | Academic hospital             |
| 5               | Pediatrician-endocrinologist                   | 7                                    | 10–20                     | Academic hospital             |
| 6               | Clinical geneticist                            | 3–7                                  | 1                         | Academic hospital             |
| 7               | Clinical geneticist                            | 11                                   | 5–10                      | Academic hospital             |
| 8               | Pediatrician                                   | 14                                   | 80–90                     | National diabetes treatment center |
| 9               | General practitioner specialized in diabetes    | 9                                    | 2                         | Primary care                  |
| 10              | Representative diabetes section Dutch Internists association | 8                                    | 1                         | Professional association      |
| 11              | Representative Dutch Diabetes Nurses association | N/A                                   | N/A                       | Professional association      |
| 12              | Representative Dutch Diabetes patient organization | N/A                                   | N/A                       | Patient organization          |

*At the time of the interview. N/A = Not applicable.

The interviews were conducted by 2 researchers (S.W. and A.B.). They took place at the respondents’ workplace or by telephone. Participants gave informed consent and permission to make an audio recording, before the start of the interview.

Data Preparation and Analyses

The interviews were recorded and transcribed verbatim. Subsequently, conventional content analysis [18] was done using Atlas.ti version 5.2. Open coding was done by reading the transcripts and marking the text. Six interviews were coded independently by 2 researchers for validation of coding; the other 6 interviews were coded by one researcher only. Connections between the codes were identified and grouped into categories. Within these categories, text fragments with the same code were compared to detect differences and similarities and then grouped into the main themes. Codes, categories and themes were discussed, and the differences were resolved by discussion between A.Z. and S.W. In case of disagreements, a third researcher was consulted (L.H.). In the results section, quotations were translated from Dutch to illustrate the themes.

Results

Most participants in this study were familiar with genetic testing for MODY, and could explain the rationale as to why MODY testing might be of help for patients and family members. The participants generally supported genetic testing for MODY, although most healthcare professionals did not routinely order genetic testing. With regard to participants’ views of the current practice of genetic testing for MODY and factors that influence current practice, several themes emerged: (1) perceived influence of a MODY diagnosis on the treatment plan, (2) possibilities for prevention, (3) patients’ perspectives, and (4) perceived barriers.
In fact, according to one of the participants, this ‘trial and error’ approach is the path most general practitioners currently take. These physicians may consider regulation to be more important than the exact diagnosis and may not be aware of other aspects of MODY, such as the consequences for children:

Yes, there are many GPs who say: ‘We are just going to start treatment because it’s probably a MODY.’ So there is still a lot to be gained there. […] I don’t think the average GP will think or feel the need to say ‘Because of offspring, etcetera, etcetera it may be wise to find out which type of MODY and which mutation[,] I don’t think that that awareness exists in GP practices. (P9, GP specialized in diabetes)

Possibilities for Prevention in MODY Patients
Several other factors were mentioned as influential in current practice with regard to genetic testing for MODY. One factor was whether participants believed that it is possible to delay the onset of MODY. One participant was convinced that modifying an unhealthy lifestyle would be beneficial in postponing the onset of diabetes symptoms in MODY patients:

But yes, when someone has a body mass index of 29, doesn’t move at all and smokes, I would say, well there are three things you can do. Of course you have a predisposition, of course I think you will get it eventually, but you don’t know how old you’ll be. By intervening with what you should do yourself [adopting a healthy lifestyle], you might gain 10 years without illness, without diabetes. That’s well worth it. (P4, internist)

However, others did not believe prevention of diabetes for someone with MODY (e.g. asymptomatic family members) is possible:

But when I think about … What’s important when actively offering cascade screening? Yes, it’s about, is prevention useful? Is it harmful to wait for symptoms? Etcetera, etcetera. That’s not the case here, as far as I know. (P6, clinical geneticist)

Participants’ perceptions of the risk of complications was also mentioned as a factor influencing their consideration to test. Some thought testing was important for the anticipation of complications, for example, in pregnancy. On the other hand, others considered this less relevant, as they felt that MODY patients have relatively few complications anyway.

Patients’ Perspectives
Another factor which may influence the decision to test for MODY is the perspective of the patient. Several participants stated that patients generally like to know whether or not they have MODY. According to these
participants, patients are glad to have an explanation, as they often already believe they are different from other diabetes patients. Participants mentioned that patients may consider MODY less stigmatizing than type 2 diabetes, which they feel carries the implication of its being one’s own fault. However, it was also mentioned that people may fear the possibility that a positive test could have consequences for their insurance or mortgage, and, therefore, patients decide against getting tested.

Perceived Barriers in Genetic Testing for MODY
Participants mentioned several (potential) barriers to requesting a genetic test for MODY. One such barrier was the cost of genetic testing (which is paid for by insurance companies in The Netherlands). This was mentioned as a reason to be selective in testing:

Of course there’s a negative financial aspect [of broad testing], you think, yes I could do that, but if the test comes back negative 10 times, that would be very inconvenient. (P4, internist)

Another important barrier mentioned was the lack of knowledge and awareness among healthcare professionals; MODY may simply not be thought of as a diagnosis. Several participants stated a ‘default assumption’ may exist among physicians, where they think it is either type 1 or type 2 diabetes mellitus, causing misdiagnosis:

I think it’s a disadvantage that some internist-endocrinologists, who, when it is not type 1, in some patients it immediately becomes type 2. Even when those patients are not overweight, they don’t look further. (P5, pediatrician-endocrinologist)

Next Steps toward Best Practice
Regarding next steps toward best practice for genetic testing for MODY, 4 additional themes emerged: (1) guideline requirements, (2) an allocation of responsibilities, (3) education and information needs, and (4) the need for more evidence.

Guideline Requirements
Participants mentioned several steps that could be taken toward best practice. The majority thought a guideline would be helpful. Although the participants differed in their opinions on whether the test is useful, and whether it is currently requested too often or too rarely, they all agreed that the implementation of a guideline could aid in more expedient testing, thus, preventing over- as well as undertesting. Participants stated several requirements for a guideline for genetic testing for MODY: it should be concrete, practical and evidence-based, and should be linked to treatment advice. It was also suggested that the guideline be integrated in an existing guideline on diabetes care, instead of developing a separate one.

Allocation of Responsibilities
Participants had different suggestions who should initiate the implementation of a guideline. Most agreed it should be a collaboration among several organizations, including the Dutch College of General Practitioners, the Dutch Internists’ Association and the Diabetes Federation (an umbrella organization including a charity as well as professional and patient interest groups). Additional suggestions for organizations that should collaborate were associations of other health professionals such as pediatricians, clinical geneticists and diabetes nurses, and the Dutch diabetes patients’ organization.

Regarding the roles of different healthcare professionals in genetic testing for MODY, all participants reported that requesting genetic tests for MODY should be left to specialists and not GPs, who should refer patients. The specialists who were mentioned as suitable requesters of the test were internists (specialized in diabetes), pediatricians (specialized in diabetes) and clinical geneticists. One participant suggested that diabetes nurses could play an important role in the implementation of a guideline for MODY, as they could utilize it in daily practice:

Research shows, and I also see in practice, that nurses are of course very good at following guidelines. Physicians may sometimes act more by the seat of their pants, you know, the clinical eye, intuition. While nurses would, I think, if you would explain why it’s important to ask about family history and characteristics of MODY, I would imagine they could really apply it [a guideline] in daily practice. (P11, representative of the Diabetes Nurses association)

Some participants wondered whether family members should be informed and if so, whose responsibility this should be: the treating physician’s, the clinical geneticist’s or the patient’s responsibility.

Education and Information Needs
In addition to a guideline, some participants mentioned other steps that could be taken toward best practice. Among these steps was the education of healthcare professionals, specifically with the aim of raising awareness:

It’s also about PR, about making clear the disease exists, writing articles, mentioning it at conferences, at refresher courses. I think that is really necessary for MODY. (P8, pediatrician)

Another aspect of the current situation that could be improved is the information that is available for patients. While one participant’s organization did have informa-
tion flyers for patients, several did not. They stated that their patients complain about a lack of (Dutch) information material and attention for MODY by the Dutch diabetes patients’ organization.

Need for More Evidence
Further research was also mentioned as an important step. Specifically mentioned was research on treatment options for GCK patients for whom a healthy lifestyle is not sufficient to control diabetes symptoms. Moreover, participants felt more research was needed to assess whether the genetic test for MODY should be offered more often and to whom. For example, one participant wondered whether children should actually be tested. Another participant thought that next-generation sequencing will change the current practice and stated that this would first require further research and further development of this technique.

Discussion
This study assessed professional experts’ views on the possible factors that influence the current practice of genetic testing for MODY and explored next steps toward best practice. To our knowledge, no similar studies with regard to experts’ opinions on genetic testing for MODY have been conducted. Shepherd et al. [19] have published a case study in which the perspectives of the health professionals involved are described. However, that study focused on their experience with one particular case, rather than on their perspective on genetic testing for MODY in general.

Our participants differed in their valuation of genetic testing for MODY. While most considered the test useful, not all were convinced of its clinical utility. Participants, therefore, had different opinions on whether the test should be requested more often. A few participants doubted whether sufficient evidence is available that shows that a MODY diagnosis would influence the treatment plan, although others felt that it would. Suggestions for next steps toward best practice for genetic testing for MODY included evidence-based guidelines, a clearer allocation of responsibilities, professional education, and provision of information by patient organizations.

The available literature on this topic suggests that a diagnosis of MODY is indeed relevant to the treatment plan. Several studies found that patients with a mutation in HNF1A respond particularly well to treatment with SUs [8, 20, 21]. One study showed that in the UK, a genetic diagnosis of HNF1A alters treatment in clinical practice [22]. Although there is less evidence to support this, patients with a HNF4A mutation may also benefit from switching to treatment with SUs [23]. GCK patients may be able to discontinue pharmacological treatment altogether when diagnosed correctly [5].

In addition to consequences for treatment, some participants felt that a diagnosis of MODY may also have other benefits, such as the anticipation of complications. The MODY subtypes indeed differ in their risk for microvascular complications [24]. According to our participants, some physicians may feel that a MODY diagnosis is not all that important, as long as a patient has a good glycemic control. One of the participating physicians indeed stated that he takes this approach. This participant also felt that a genetic test may not be required to diagnose MODY, as a ‘trial and error’ approach can be taken with regard to treatment. To our knowledge, no studies have been conducted to assess how many MODY patients have been diagnosed without a genetic test. While there are studies estimating the number of undiagnosed MODY patients [4], it is not known how many MODY patients are indeed receiving suboptimal treatment due to the absence of a genetic diagnosis. Genetic testing would only alter the treatment in case of an incorrect diagnosis. The treatment would not differ if a correct clinical diagnosis of the MODY subtype is made without genetic testing.

Our study found that several barriers may exist to requesting genetic testing for MODY. The cost of genetic testing was mentioned by some participants as a reason to limit testing. However, according to a recent international study, testing might be cost-effective. Analyses showed that genetic testing for GCK could potentially increase patients’ quality of life and reduce healthcare costs by avoiding unnecessary insulin treatment and follow-up care [25]. A simulation study was also conducted to assess the cost-effectiveness of genetic testing for MODY, which found that it may be cost-effective in selected populations based on contemporary incremental cost-effectiveness ratio thresholds in the US [11]. Further research is needed to assess whether genetic testing would be cost-effective in other healthcare systems as well. Another potential barrier to genetic testing for MODY was lack of knowledge and awareness among physicians. To our knowledge, there are currently no studies that substantiate this, although a deficiency of knowledge of genetics in general among healthcare providers and the need for further education has been reported [26–28].
The perspectives of the patients were also discussed during the interviews. Most participants stated that patients generally regard the test positively as they often feel they are different from other diabetes patients and are glad for an explanation. However, people may also believe that a positive test result may have negative consequences for their life insurance or mortgage and, therefore, decide against predictive testing. It is unclear if genetic discrimination of MODY patients actually occurs; no cases have been reported so far. It is known that fear of genetic discrimination is a common phenomenon in genetic testing, but often unfounded [29].

Regarding best practice, participants agreed that a comprehensive guideline would be helpful to facilitate more precise testing. Currently existing international guidelines for genetic testing for MODY do not provide all information in one concise guideline on testing criteria, clinical implications for management, predictive genetic testing, and genetic counseling [12, 14, 15]. It was suggested that a MODY guideline should be integrated in an existing guideline for diabetes; the recently published clinical utility card [30] could potentially be used to facilitate this. This would perhaps help in improving the awareness and knowledge among healthcare professionals who are currently not reached by the international guidelines. One participant suggested that diabetes nurses could play an important role. Such an approach was taken in a project in the UK, where experienced diabetes nurses were trained to become specialized in MODY. The 20-month evaluation of the project found that the awareness of MODY had been boosted and that the number of MODY diagnoses had increased [31]. Perhaps a similar approach could be used in The Netherlands, as participants stated that the awareness and knowledge among healthcare professionals should be increased, and better information provision for patients is needed. A lack of evidence was also mentioned as a barrier for genetic testing for MODY. Specifically mentioned were treatment options for GCK MODY and risk profiles to identify candidates for genetic testing. Such a risk profile has already been developed; the MODY calculator appears to discriminate well between MODY and type 1 and 2 diabetes and can be used to help select candidates for genetic testing for MODY. Further research is still needed to validate the model while implementing it in different settings and populations [13, 32].

This study has some limitations. The study had a small number of participants and does not comprise a representative sample. Rather, this study was intended to explore the views of a diverse spectrum of healthcare professionals and to derive illustrative inferences [33]. Another possible limitation of our study is that experts, who have more experience with genetic testing for MODY and a more positive attitude toward it, may have been more likely to participate. Most of the participants did have previous experience with requesting genetic testing for MODY. As a result, this study can only offer a limited account of the perspectives of healthcare professionals, who have less experience with genetic testing for MODY.

This study has determined many of the reasons for the current practice of genetic testing for MODY according to the healthcare professionals involved as well as identified next steps toward best practice. The results of this study indicate that healthcare professionals differ in their valuation of genetic testing for MODY. Not all were convinced of the test’s clinical utility, though most considered it useful, notably for treatment, and for the anticipation of complications and/or genetic advice. Other factors besides clinical utility that were reported to influence the current practice of genetic testing for MODY were patients’ perspectives and perceived barriers.

Several courses of action have been suggested to improve diagnosis and care for patients with MODY. Most importantly, the implementation of a guideline, which participants agreed would be helpful to facilitate more expedient testing. Additionally, other steps toward best practice for genetic testing for MODY were suggested, including the education of healthcare professionals and provision of information by patient organizations, a clear allocation of responsibilities (e.g. who should do what in the care team connected to genetic testing for MODY), and further research into treatment options, risk profiles to identify candidates for genetic testing and next-generation sequencing.

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