

**STUDY PROTOCOL**

**Implementing a patient-centred care model to diagnosis of Maturity Onset Diabetes of the Young (MODY)**

Short Title:*Mainstreaming MODY genetic testing*

**St Vincent’s Hospital Sydney**

**Clinical Genomics & Department of Endocrinology**

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**Summary**

|  |  |
| --- | --- |
| **Study Title** | Implementing a patient-centred care model to diagnosis of Maturity Onset Diabetes of the Young (MODY) |
|  | (Short title: Mainstreaming MODY genetic testing) |
| **Objectives** | Primary aim: To explore the feasibility of a novel genetic mainstreaming care model, including comfort levels and support needs of physicians, as well as the associated psychosocial stress of patients  Secondary aim: To develop local clinical guidelines and criteria for MODY genetic testing |
| **Study design** | Mixed design - observational/qualitative and quantitative components |
| **Planned sample size** | 70 participants |
| **Selection criteria** | Adult patients aged 16 years and over; and  Australian citizens with fluency in English; and  Diagnosed with either Type 1 or Type 2 diabetes less than 6 months prior to recruitment, who fulfil specific criteria as specified in *Eligibility Criteria (Section 4)* |
| **Study procedures** | The study involves systematically screening patients attending Diabetes Clinic against an *Eligibility Criteria*, to identify those who fulfil the criteria for MODY genetic testing. Those fulfilling the criteria will be enrolled in the study, and genetic testing will be arranged by their Endocrinologist at point-of-care in the Diabetes Clinic. Samples will be collected and forwarded to Exeter Laboratory in UK for clinical MODY genetic testing. Results will be given by their treating Endocrinologist. Those tested positive for MODY will be referred to the St Vincent’s Clinical Genomics for genetic counselling and follow-up of familial implications as per routine clinical care.  Participant psychosocial stress associated with testing will be evaluated through a validated questionnaire prior to undergoing testing, and again after result disclosure. Clinician comfort levels and support needs will be explored via a face-to-face or virtual interview at the completion of study. |
| **Statistical considerations** | Sample size calculation not applicable as this is predominantly a qualitative study |
| **Study duration** | 12-18 months |

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# BACKGROUND

## Disease Background\*

Maturity Onset Diabetes of the Young (MODY) is the most common genetic form of diabetes ([1](#_ENREF_1)), affecting up to 4% of all diabetes cases ([2](#_ENREF_2), [3](#_ENREF_3)). Currently, there are at least 14 genes implicated in MODY ([4](#_ENREF_4)), the accurate diagnosis of which requires molecular genetic testing due to their indistinguishable clinical features that are often shared with non-genetic forms of diabetes. Consequently, MODY is commonly misdiagnosed as type 1 or type 2 diabetes, due in large to the limited access to genetic testing until recent years. The accurate diagnosis of MODY is important, as either no treatment is required (MODY2) or patients respond better to oral sulfonylureas, rather than insulin (MODY3) ([1](#_ENREF_1)). MODY testing therefore allows tailored drug treatment thence improved glycaemic control leading to fewer complications; furthermore, it avoids unnecessary treatment such as insulin and its potential adverse effects. More recently, routine genetic screening for MODY has been shown to be cost-effective in a paediatric diabetes cohort ([5](#_ENREF_5)).

The diagnosis of MODY requires molecular genetic testing. Current routine clinical care recommends that genetic testing be offered to patients with suspected MODY.

## Rationale for Performing the Study\*

## Currently, genetic testing is recommended to be undertaken by genetics professionals (e.g. clinical geneticists, genetic counsellors) following appropriate counselling. This approach requires an additional referral to a genetics clinic which often has a long waiting list. This research explores the feasibility of “mainstreaming” genetic testing for MODY by allowing genetic testing to be arranged by non-genetics professionals and in this case to be arranged by Endocrinologists in their usual routine clinical setting. The advantage of mainstreaming is that it can be done at point of care, as a one-stop shop, for the patients, rather than having them referred to a genetics unit.

A genetic mainstreaming model has been successfully trialled in oncology care to guide breast/ovarian cancer management. Leveraging Next Generation Sequencing technology, MODY represents an ideal non-cancer disease model for genomic mainstreaming, as its point-of-care diagnosis will guide tailored management in those newly diagnosed with diabetes.

# STUDY OBJECTIVES\*

## Primary Objective\*

To explore the feasibility of a novel approach to diagnosis and management of MODY via a mainstreaming care model, including comfort levels and support needs of physicians, as well as the associated psychosocial stress of patients. The altered approach includes: (1) routinely implementing genetic testing to allow accurate diagnosis of MODY and (2) handing the responsibility of genetic testing to non-genetics professionals (i.e. endocrinologists) at point of care.

## Secondary objective

To develop clinical guidelines and clinical criteria for MODY genetic testing

# STUDY Design\*

## Design\*

Mixed methodology with observational/qualitative and quantitative methods.

## Study Groups

Single arm of patients who were diagnosed with either Type 1 or Type 2 diabetes.

Endocrinologists involved in the care of the patient participants.

## number of participants\*

Expected total number of patient participants to be recruited: 70

Expected number of Endocrinologists: 10

## number of SITES

Single Site Study

All participants will be recruited from the Diabetes Clinic and the Department of Endocrinology at St Vincent’s Hospital Sydney

## duration

Expected study duration: 18 months (1 July 2019 – 1 January 2021)

Expected duration of the recruitment phase: first 6-8 months

# Participant section / PATIENT ELIGIBILITY CRITERIA

## PATIENT Inclusion Criteria\*

* Adult patients aged ≥18 years
* Diagnosed with either Type 1 or Type 2 Diabetes, and who meets the following *additional* criteria:

|  |  |
| --- | --- |
| Type 1 Diabetes Mellitus (MODY3 to be excluded) | Type 2 Diabetes Mellitus (MODY2 to be excluded) |
| * Negative Antibodies   AND at least one of:   * Positive Family History * Positive C-peptide | Patient must satisfy *both* of the following:   * BMI <27   AND   * Age of onset <50 years old |

* Understands written English
* Willingness to give written informed consent, and willingness to participate in and comply with the study
* Willingness to undergo MODY genetic testing, after informed consent

## PATIENT Exclusion Criteria\*

* Patient who had previously undergone MODY genetic testing
* Patient who has a known family history of MODY diagnosed through genetic testing

# STUDY Outline\*

## Study Flow Chart

## 

Positive

Negative

## Investigation plan

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | List Interventions | Routine Clinic Visit 1  (Enrolment) | Routine Clinic Visit 2 | At completion of study |
| PATIENT PARTICIPANTS | Inclusion / Exclusion criteria | ✓ |  |  |
|  | Informed Consent | ✓ |  |  |
|  | Demographic & clinical data collection | ✓ |  |  |
|  | Standard of care Blood sample collection for diagnostic genetic testing | ✓ |  |  |
|  | Diagnostic genetic test result disclosure |  | ✓ |  |
|  | Psychosocial Questionnaire | ✓ | ✓ |  |
| CLINICIAN PARTICIPANTS | Face-to-face interview |  |  | ✓ |

**Methodology**

The study will comprise of 2 study visits and these will both be scheduled around the participant’s routine clinical visits to reduce participant burden

**Clinic Visit 1 (Enrolment visit)**

Blood samples will be collected by a qualified phlebotomist at St Vincent’s Hospital or an appropriate laboratory local to the participant and handled accordingly. A blood sample will be collected after informed consent has been signed and the participant has been allocated a study ID. After blood collection the participant will fill out the questionnaire at clinic with assistance if needed form the SC. If the visit is being conducted virtually the SC will fill out the questionnaires over the phone with the participant. This visit will take 1-2 hours.

**Clinic Visit 2**

Clinical MODY testing results will be returned to participants at their next routine Diabetes Clinic Visit (in person or virtual) by their treating Endocrinologist who will manage them accordingly as per routine clinical care. They will then complete the questionnaire with the SC at the clinic visit or virtually. This visit will take 1-2 hours. Those tested positive for MODY will be referred to the St Vincent’s Clinical Genomics for routine clinical care including follow-up on the familial implications and assistance with informing relatives of positive MODY results. This visit can be organise virtually if the participant wishes.

**Data Collection**

Patient participant’s demographic and clinical data will be collected by the SC at the time of enrolment. The clinical data collected include phenotypic data (age at diagnosis of diabetes, history of diabetes-related complications, treatment history, biochemical results, BMI, waist circumference, presence/absence of renal/pancreatic anomalies), and family history of diabetes.

Data will be kept confidentially in a secured database hosted at the St Vincent’s Clinical Genomics at St Vincent’s Hospital. A copy of the *MODY Database* is attached (also outlined in section 12: other study documents

Potential psychosocial stress associated with this testing approach will be evaluated quantitatively through a Psychosocial Questionnaire, combining two validated questionnaires (6, 7), electronically via SurveyMonkey, at two time points: at time of enrolment (pre-test) and after result disclosure (post-test). A copy of the MODY Psychosocial Questionnaire is attached (also outlined in section 12: other study documents).

**Sample Collection**

As per standard of care the Endocrinologist will consent that participant to genetic testing, using the NSW Health Genomic Testing Consent Form (Section 12), one blood samples will be collected for DNA extraction at SydPath as per NATA-accredited protocol.

**Standard of care sample**

The SC will coordinate for one aliquot of DNA per patient to be batch-shipped to an accredited clinical laboratory, Exeter Clinical Laboratory in the UK, for clinical MODY genetic testing, using local NATA-accredited (or ISO-15189 accredited) methodology for testing. Any leftover sample will be stored for future unknown research related to MODY until the end of the study when it will be destroyed as per laboratory policy.

**Physician interviews**

At the completion of recruitment and the completion of result disclosure, all St Vincent’s Endocrinologists (N ≈ 10 who attends Diabetes Clinic) involved in the care of patient participants will be invited for a 30-minute face-to-face semi-structured interview with the SC. The interview aims to explore the comfort levels and support needs of non-genetics specialists in offering and discussing genetic testing with their patients. Thematic and descriptive analysis will be used to represent the findings. A copy of the *Physician Interview* questions is attached (Section 12). In order to retain the anonymity of the participating Endocrinologist’s, their identifiable details will be permanently de-identified and forwarded to the St Vincent’s Clinical Genomics at St Vincent’s Hospital for analysis.

Data Collection

Data collected from Physician Interview in the form of hard copies will be locked in the filing cabinet in the office of the Principal Investigator in the St Vincent’s Clinical Genomics located on 97 Boundary Street Darlinghurst NSW 2010.

Outcome Measures

The outcome measures include:

* For primary objective: To explore the feasibility of a novel approach to diagnosis and management of MODY via a mainstreaming care model, including comfort levels and support needs of physicians, as well as the associated psychosocial stress of patients. Physician comfort levels and support needs will be qualitatively measured via a face-to-face interview with open-ended questions. Patient psychosocial stress will be measured quantitatively by two validated scales: the Satisfaction With Decision (SWD) Scale ([7](#_ENREF_7)), and the Genetic Counselling Outcome Scale ([6](#_ENREF_6)).
* For secondary objective: The performance of MODY Eligibility Criteria will be measured by (1) the percentage of MODY-positive cases out of total number of participants tested; and compared against (2) the MODY Probability Calculator Score (<https://www.diabetesgenes.org/mody-probability-calculator/>) ([8](#_ENREF_8)). Knowledge gained from these measures will be used to develop clinical guidelines and refine clinical criteria for MODY testing.

## COVID Virtual care clinic

Due to the global effect of COVID 19, the protocol needs to adhere to the ever-changing environment and adhere to social distancing rules to ensure the protection of staff and participants.

* Participants will attend their standard of care appointment via telehealth with their physician. The study will be discussed, and the participant will be emailed the patient information and consent form to review.
* If deemed eligible participant will be consented to the study via verbal consent as per national statement (further information regarding consenting in section 5.5).
* NSW Health Genomic Testing Consent Form and pathology request form will be sent to participant who can go to their local collection centre to collect the standard of care blood sample for MODY testing
* Questionnaires will be emailed to the participant who will be asked to return these
* Data collection will occur over the phone and documented in the participant notes as per standard procedures
* Follow up appointment will occur virtually

## Study Procedure Risks\*

Potential risks associated with the current study for patient participants may arise mainly as a result of genetic testing:

* Patient psychosocial stress associated with either the genetic testing process or the genetic test results, or both. This is partially addressed by the study in its primary objective. In addition, this is potentially minimised by (a) the protocol of referrals to the Clinical Genomics for expert counselling for participants who tested positive for MODY; and (b) the staff at Clinical Genomics being available throughout the study period to provide support for all participants.
* Potential issues regarding risk-based insurance, such as life insurance and income protection. Whilst genetic testing will usually not affect such insurance for patient participants who are affected with illness (diabetes), it may affect the ability of their unaffected relatives in obtaining risk-based insurance. Insurance companies however may take into account of preventive interventions that an unaffected individual will undertake as a result of their personal/family history of a genetic disorder declared by genetic testing. Furthermore, from 1 July 2019, genetic testing will no longer impact on the ability of Australians taking up Life Insurance, as part of the Financial Services Council’s commitment to genetic inclusion.
* As blood samples will be collected for DNA extraction, there may be discomfort, or rare complications (such as haematoma or infection), associated with any blood draw.

## Recruitment and Screening\*

Recruitment and Screening

Participants will be identified via the Endocrinology clinics held at St Vincent’s Hospital. The Study coordinator (SC) will identify potential participants who are being seen by the Endocrinology team and review their medical records against the eligibility criteria. If a participant is deemed eligible by the SC they will refer to their treating Endocrinologist who will approach the participant in regards to participation in the study. Once the participant has reviewed the ICF and had time to discuss the study with family and GP if necessary they will be invited to attend clinic in person or virtually to consent as per ICH GCP. Participant’s clinical and demographic information will be collected by the SC into a MODY Database (Section 12: other study documents attached). The expected timeframe for recruitment is 6-8 months.

St Vincent’s Endocrinologists who attend the Diabetes Clinic (expected n ≈10) will be invited for a 30-minute face-to-face interview with the SC, at the completion of the patient recruitment.

## Informed Consent Process\*

Patient participants

Informed consent for participation will be obtained by the investigators and SC. The voluntary nature of research participation that will not impact on their professional relationship with care providers will be emphasised. Informed consent for MODY genetic testing will be obtained by participant’s Endocrinologist using the NSW Health Genetic/Genomic Testing Consent Form, as MODY genetic testing forms part of patient’s routine clinical care.

Physician Interview

At the completion of recruitment, all Endocrinologists (and Advanced Trainees) who routinely attend the St Vincent’s Hospital Diabetes Clinic will be invited verbally for a face-to-face interview. By agreeing to conduct the interview with the SC, the clinician gives their consent for participation. This will be documented in the paper format of *Physician Interview* document. The 30-minute interview will be conducted on the campus of St Vincent’s Hospital Sydney at mutually convenient time and location for both SC and the clinician.

Verbal Consent- COVID Virtual care

If the participant wishes to participate, the study visit will be conducted over the phone. By giving the study staff information over the phone, they are giving consent as per national Statements section 2.2.5 on implied consent. The participant must clearly and orally indicate that they consent to participation in the study. The verbal consent will be recorded in the participant's medical record. The decision whether to take part in the project will have no impact on their future care at St Vincent’s Hospital.

## Enrolment Procedure\*

The participant will be enrolled into the study after the informed consent process has been completed and the participant has met all inclusion criteria and none of the exclusion criteria. The participant will receive a study enrolment number and this will be documented in the participant’s medical record and on all study documents.

# TISSUE CoLLECTION

One blood sample is collected from a single venepuncture for DNA extraction, which is a mandatory component of the study. The DNA extracted will be used solely for the intended purpose of the study.

The standard of care aliquot of DNA will be individually identifiable, and be used for MODY genetic testing in an accredited clinical laboratory, Exeter Clinical Laboratory in UK. Any remaining DNA at the completion of this testing will be stored in the Exeter Clinical Laboratory in accordance to its accreditation requirements and destroyed at the end of the study as per laboratory policy.

Privacy and confidentiality will be maintained as per clinical laboratory accreditation requirements and regulation, NSW Health policy on patient privacy and confidentiality, the Human Genetics Society of Australasia guideline on storage of genetic information, as well as the NHMRC guideline on ethical conduct in research ([9](#_ENREF_9)).

The current study does not involve the establishment of a tissue bank.

# SAFETY\*

Although it is unlikely that any serious untoward medical occurrence is expected as a result of participating in the current study, safety will be monitored by the SC, and by the Endocrinologists as part of their routine clinical care provision. In the unlikely event of a medical complication, immediate medical attention will be provided by their treating Endocrinologist during office hours, or the patient may be advised to attend a local Emergency Department for an initial assessment with ongoing follow-up provided by their Endocrinologist.

## Adverse Event Reporting\*

As the current study takes place within the participant’s routine clinical care setting, any adverse events arising during the study period will be reported as per St Vincent’s Hospital policy.

## Serious Adverse Event Reporting

As per stated in 7.1.

## Data Safety and Monitoring Board (DSMB)

A DSMB will not be convened for this study. It is not foreseen that there will be any safety concerns

## Early Termination

In the unlikely event that this study is terminated early, the Principal Investigator (or one of the Co-investigators if PI is unavailable) will notify the participants and the HREC in writing, and compile a final study report.

# OUTCOMES AND FUTURE PLANS

As outlined in Section 5.2, clinical MODY genetic testing results will be returned in a timely fashion, by Endocrinologist, to participant. The results from psychosocial questionnaires will not be returned to participants individually, but will be used to flag for intervention any significant psychological stress that may potentially arise as a result of genetic testing.

Data generated and analysed will be translated to new (or add to existing) knowledge and disseminated via peer-reviewed publications and conference presentations.

# STATISTICAL CONSIDERATIONS\*

A power calculation on sample size is not applicable for the current study as this is predominantly an observational/qualitative study.

For the quantitative measurement of psychosocial scales, comparison will be made between pre-test scores *versus* post-test scores, using the Paired t test. Any significant outliers, either as individual scores or as a significant difference between pre- and post-test scores for any individual participant, will be qualitatively described.

# CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY DOCUMENTS\*

Electronic data, including the MODY database (identifiable) and the psychosocial questionnaire (re-identifiable), will be securely stored in the hard-drive of the Principal Investigator, housed in the Clinical Genomics at St Vincent’s Hospital which can only be accessed by authorised personnel including the research team.

Paper documents, including signed Participant Consent Forms (identifiable) and Physician Interviews (non-identifiable), will be locked in a filing cabinet in the Principal Investigator’s office, in the Clinical Genomics at St Vincent’s Hospital, located on 97 Boundary Street Darlinghurst NSW 2010.

All data stored will be kept for a minimum of 15 years as per ICH GCP, from the date of publication, in accordance to the minimum recommended period for retention of research data stated in section 2.1.1 of the NHMRC Code for Responsible Conduct of Research ([10](#_ENREF_10)). After this period, electronic data will be permanently deleted, and paper documents will be securely shredded.

Participant MODY genetic test reports in paper format generated by the clinical laboratory will form part of their routine clinical care, and as such will be stored in their hospital medical records, for a duration in accordance to St Vincent’s Hospital Sydney medical record policy. A copy of their personal genetic test report will be made and returned to each participant for their own record keeping.

# Other study documents

Other study documents included with the submission:

* NSW Health approved ‘Consent: Genetic/Genomic Testing (For patients 14 years and above - not for Guardianship Act purposes)’ (in PDF format)

MODY Database (in Excel format)

MODY Psychosocial Questionnaire (in Word format)

Physician Interview questions (in Word format)

# RESOURCES

This study is kindly funded by the Curran Foundation Endowment Grant 2018/19.

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