OPTITHERA™ Genetic Health Risk Test Report to Patients

For Type2 Diabetes (T2D)-Related Cardiovascular and Renal Complications

(Sample Report)

The information presented in this report is based on the proprietary OPTITHERA™ database and algorithm as well as curated literature in the field of Type 2 diabetes (T2D) clinical and genetic knowledge. This is an overview of your personal OPTITHERA™ report. It provides brief descriptions of your genetic risk and your diabetes-related conditions. More detailed information will be sent to your healthcare provider. This report identifies the specific resource materials upon which the information presented is based, and that may be of assistance to your healthcare provider to whom this report is primarily addressed. The report does not represent medical diagnosis but a "decision-aid tool" addressed to your healthcare provider, based on a set of carefully collected genetic and clinical data in the OPTITHERA's database.

RATIONALE BEHIND THIS TEST

Diabetes is one of the most challenging health problems of the 21st century touching every country and all types of people. T**ype 2 diabetes** accounts for **90**% of **diabetes cases** and typically develops during adulthood. It is caused by insufficient insulin production in your pancreas, or by resistance of the cells to the insulin produced. People with diabetes have an increased risk of developing serious complications implicating blood vessels in their body, resulting from the interaction between genetic predisposition, the environment and lifestyle.

Microvascular complications related to small blood vessels, include kidney disease (nephropathy), nervous system damage (neuropathy) and eye disease (retinopathy). Macrovascular complications related to any large blood vessels including cardiovascular disease (myocardial infarction, heart failure), cerebrovascular disease (stroke) and peripheral vascular disease, particularly in lower limbs.

Diabetes doubles the risk of cardiovascular diseases. Diabetes and hypertension or a combination of both are responsible for 80% of cases of end-stage kidney disease.

MANY OF DIABETES-RELATED COMPLICATIONS ARE PREVENTABLE!

Complications in patients with diabetes are frequently detected when damage is already occurring. Prediction of risk prior to development of these diabetes-related complications is helping select effective use of measures to prevent, delay or attenuate these complications. Accordingly, genetic information, with which one is born, offers a way to make early detection of risk before symptoms appear.

OPTITHERA's test is intended to a person diagnosed with type 2 diabetes (T2D) who wants to know his/her level of risk of developing T2D-related microvascular or macrovascular

complications in following years or to have the information for his/her children since T2D and its complications have strong link to family history and lineage.

As healthcare providers continually seek out ways to improve the care of their patients, OPTITHERA™ Genetic Health Risk test estimates the level of risk of a person to develop T2D-related complications, before clinical signs appear. OPTITHERA provides you this easy-to-read report based on your genomic profile, and a few personal characteristics to be shared with your healthcare provider. This aims to help you better understand and participate actively in your own health care with your health professional.

Personalized Report for Risk Estimate of T2D-Related Complications

- Created for ID Number Bar Code

PATIENT PROFILE	SPECIMEN INFORMATION	Healthcare Provider
Patient PIN: **Age:** 62 **Gender:** Female **Ethnicity:** European ancestry **Age at diagnosis of T2D:** 60 y/o **Hypertension:** Yes	**Source:** buccal swab **Accession ID:** OPTI 10102 **Test ID:** PRS10102 **Collected:** Jan 16, 2020 **Received:** Jan 20, 2020 **Reported:** Feb 1, 2020 **Report Version:** Final **Test:** Test Report For Type2 Diabetes (T2D)-Related Cardiovascular and Renal Complications	**Name: XXX** **Credentials**: Endocrinologist **PIN:** OPTI A102 **Institution:** Clinic Angus, Montreal, QC, Canada

PIN **YOUR PERSONAL TEST REPORT**

MAIN COMPLICATIONS	GENETIC RISK CATEGORY (from 1 to 5)
NEPHROPATHY: Albumin in urine	MEDIUM (2.0)
Kidney filtration (eGFR) decline	HIGH (3.0)
MYOCARDIAL INFARCTION (heart attack)	HIGH (3.6)
STROKE (cerebrovascular accident)	NORMAL (1.2)
HEART FAILURE	HIGH (4.2)
GLOBAL Risk for T2D-related complications is HIGH	

HOW SHOULD I INTERPRET MY TEST?

For clarity and simplicity, your risk for each of the above-mentioned complications is color-coded. The Polygenic Risk Score (PRS) is derived from the OPTITHERA™ proprietary algorithm that compares your genetic profile to that of thousands of individuals with T2D classified in the OPTITHERA's database whether they developed or not a specific T2D-related complication during 5 to 10 years of follow-up. Your sex, age, genetically determined-ethnicity, age at onset of diabetes are also considered in the risk assessment. The risk estimate is optimized for a period of five years. [1]

Your global genetic risk falls in the HIGH-risk category of individuals with T2D, suggesting that you may be at increased risk of developing nephropathy (3-times more at risk to have rapid decline of renal function (eGFR), 3.6-fold more risk of myocardial infarction and/or 4.2 fold more risk of heart failure than reference patients with T2D.

The recent clinical evidence from medical literature suggests that the highest benefits of intensive treatment and prevention are for individuals in the high genetic risk category [2]

Notice: In light of these results, OPTITHERA considers that medical management and intervention planning should be left to the discretion of your healthcare provider and interpreted in the context of a high genetic risk individual.

DISCUSS YOUR RESULTS WITH YOUR PHYSICIAN

If your genetic risk is high: Since higher prevention rates are most attainable in individuals with high risk [2], your physician should assess earlier preventive measures, in the form of intensification of medical treatment and lifestyle modifications to prevent, delay or attenuate T2D-related renal or cardiovascular complications.

If your genetic risk is medium: As individuals with diabetes have increased risk of micro-and macrovascular diseases compared to those without diabetes, your physician should increase surveillance and consider your global environment, concomitant diseases, family history, physical activity and adjust your medication accordingly.

If your genetic risk is low: Although it is often assumed that all patients should receive treatment, considerations of cost, adverse side effects, development of resistance should be well-thought-out. Recent evidence showed that patients at low genetic risk are least likely to benefit from intensive combined blood pressure and blood glucose therapy [5]. Your physician should continue to follow local therapeutic guidelines and consider unnecessary medication side effects and expenses to you and society.

References of results with intensive therapies are included below.

TECHNICAL DETAILS

OPTITHERA' test provides a personal estimate of your genetic risk of developing T2D-related complications based on the following factors: your sex, current age, age at diagnosis of T2D, ethnicity [3] and your genomic profile [4]. OPTITHERA™ test is computed as the sum of 600 common genomic variants proven to be associated with diabetes complications and their risk factors in recent meta-analyses of genome-wide association studies (GWAS) that included over a million individuals. OPTITHERA™ test and algorithms have been developed using genomic and clinical data from participants with T2D in ADVANCE and ADVANCE-ON, carefully collected during a period of ten years [5]. Moreover, OPTITHERA™ predictive performance has been validated in four independent population-cohorts from Canada and Europe [1] including the large dataset of participants of the UK Biobank.

The level of genetic risk to develop complications (before any clinical manifestations) is calculated using the OPTITHERA's proprietary algorithm. The risk is optimized for a period of five years and calibrated for individuals of white racial group.

Disclaimer

OPTITHERA™ tests do not include all possible genetic variants or other factors related to these conditions. Other factors including lifestyle, environment and family history can also affect your risk of developing these complications. The phrases "data indicate" or "literature suggests" and the precautious phraseology such as "may", "could", and "should" in the "summary" fields of the report are meant to indicate logical links that could be made from publicly available literature in the field of clinical science or genomics. OPTITHERA undertakes no obligation to update this report except to the extent otherwise set forth in a separate agreement with the healthcare provider to whom this report is primarily addressed. OPTITHERA™ test does not diagnose T2D or any other health conditions. This report does not constitute a professional consultation. It is a "decision-aid tool" that health professionals can use in support of their own medical judgment and advices as to your treatment and/or lifestyle modifications.

NEED MORE INFORMATION?

If you or your healthcare provider have questions about your results, contact our genetic counsellor at 1-514-529-3374.

Test Results Reviewed & Approved by

Name:

Genetic Counsellor

SCIENTIFIC & TECHNICAL INFORMATION 

ABOUT THIS TEST

In **single-gene diseases** (monogenic diseases such as cystic fibrosis and Huntington disease), a mutation in just one gene of the whole genome is responsible for the disease. These diseases are usually rare as only carriers of the mutation will have the disease depending on its mode of inheritance.

Common diseases, including type 2 diabetes and its complications, are **polygenic diseases,** meaning that many genes and environmental factors influence disease predisposition and development. Risk assessment for common diseases is a novel part of genetic testing that refers to the probability (a polygenic risk score) of an individual carrying a specific disease-associated genomic profile, to have or not, the disease or its complications [6;7].

OPTITHERA™ Test Report is based on a Polygenic Risk Score (PRS) that estimates the level of risk of a person to develop a disease, or its complications based on the genomic profile of that person and other factors such as sex, age, ethnicity and age at onset of diabetes.

OPTITHERA™ Test is based on a PRS composed of 600 common variants (list can be provided upon request) in your genome, proven to be significantly associated with complications of type 2 diabetes or their risk factors, in studies including over a million subjects and reported in literature, tested by our team in ADVANCE, a large clinical trial of patients with diabetes from 20 countries in Europe, Asia and India, and then validated in four independent population-cohorts that included individuals from Québec, Canada and UK.

The level of risk to develop complications of diabetes (before any clinical manifestations appear) is calculated using the OPTITHERA's database of reference individuals with diabetes followed over 10 years with a clinical data collection of the highest quality (randomized control trial quality). The categorisation of risk with OPTITHERA™ Test uses artificial intelligence.

Clinical utility of the OPTITHERA™ Test has been demonstrated by nearly 50% reduction of cardiovascular death with intensive blood pressure and blood glucose control in patients with diabetes classified in the high-risk group category [1].

Recently, we have completed a health-economic evaluation, pondering the cost and benefits and demonstrated, using renal failure (leading to hemodialysis) as an important economic burden internationally, that application of OPTITHERA's test results in lowering health care expenditure while improving the number of healthy years lived [8].

LIMITATIONS

Predictive tests are based on probability with potential of false negative or false positive results. The clinical utility of OPTITHERA's tests is a balance between the severity of complications vs cost and side effects of intervention. In our reference cohort, the negative predictive value (meaning true negative) is more than 95% for people classified in the low-risk group meaning that less than 5% of patients with diabetes of the low-risk group developed a complication over five years.

In the high-risk group, the ratio of complications between the high-risk group and the remainder of individuals in the database, demonstrated more than 3-fold higher occurrence of most of complications during the five-year follow-up.

Furthermore, although OPTITHERA's test is well calibrated (predicted vs observed), a polygenic risk score (PRS) remains a probability that can be modified by environmental intervention including medication.

The risk is optimized for a period of five years and calibrated for individuals of European ancestry, South-Asian and African origins.

REFERENCES

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