OPTITHERA™ Genetic Health Risk Test Report to Healthcare Providers

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. The OPTITHERA™ report includes brief descriptions of the genetic risk of your patient to diabetes-related complications. This report identifies the specific resource materials upon which the information presented is based, and that may be helpful to you for preventing diabetic complications of your patient. The report does not represent medical diagnosis but is a "decision-aid tool" based on a set of carefully collected genetic and clinical data in the OPTITHERA database.

RATIONALE BEHIND THIS TEST

Diabetes is one of the most challenging health problems of the 21st century touching every country and people of all origins. People with diabetes have an increased risk of developing multisystem complications, resulting from the interaction between genetic predisposition, the environment and lifestyle.

Microvascular complications include nephropathy, neuropathy, and retinopathy. Macrovascular complications include cardiovascular diseases (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 aims to select effective 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 clinical signs appear.

Our test is intended for a person diagnosed with T2D who wants to know his/her 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.

OPTITHERA™ Genetic Health Risk test estimates the level of risk of a person to develop T2D-related complications, before clinical signs appear. OPTITHERA provides an easy-to-read report based on the genomic profile and a few personal characteristics of a patient with T2D. OPTITHERA™ Genetic Health Risk test is a "decision-aid tool" that health professionals can use in support of their own medical judgment to manage their patients with T2D.

Personalized Report for Genetic Health 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 **Genetic Health Risk REPORT**

MAIN COMPLICATIONS	GENETIC RISK CATEGORY (from 1 to 5)
NEPHROPATHY: Albuminuria	**MEDIUM (2.0)**
Decline of glomerular filtration	**HIGH (3.0)**
MYOCARDIAL INFARCTION	**HIGH (3.6)**
STROKE	**LOW (1.2)**
HEART FAILURE	**HIGH (4.2)**
GLOBAL Risk for T2D-related complications is	**HIGH** 

HOW SHOULD YOU INTERPRET THIS TEST?

For clarity and simplicity, the 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 the genetic profile of your patient 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 next 5 to 10 years of follow-up. 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 patient's global genetic risk falls within the HIGH-risk category of individuals with T2D, suggesting that he/she may be at increased risk of developing nephropathy (3-times more at risk to have rapid decline of 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, in the context of a high genetic risk individual, intensification of medical treatment and early intervention planning should be considered at your discretion for this patient.

If genetic risk is high: Since higher prevention rates are most attainable in individuals with high risk [2], you are encouraged to assess early 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 genetic risk is medium: As individuals with diabetes have increased risk of micro-and macrovascular diseases compared to those without diabetes, you should increase surveillance and consider patient's global environment, concomitant diseases, family history, physical activity and adjust medication accordingly.

If 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 the least likely to benefit from intensive combined blood pressure and blood glucose therapy [5]. Continue to follow local therapeutic guidelines, promote and guide patient's self-management and consider unnecessary medication side effects and expenses to your patient and society.

References of results with intensive therapies are included below.

TECHNICAL DETAILS

OPTITHERA' test assess the genetic risk of developing T2D-related complications based on the following factors: Sex, age at diagnosis of T2D, diabetes duration, ethnicity [3] and genomic profile [4] of each subject. OPTITHERA™ Polygenic Risk Score (PRS) 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 in the multinational ADVANCE clinical trial and ADVANCE-ON observational follow-up study, 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 largest 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.

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 the 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 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 OPTITHERA™ Test

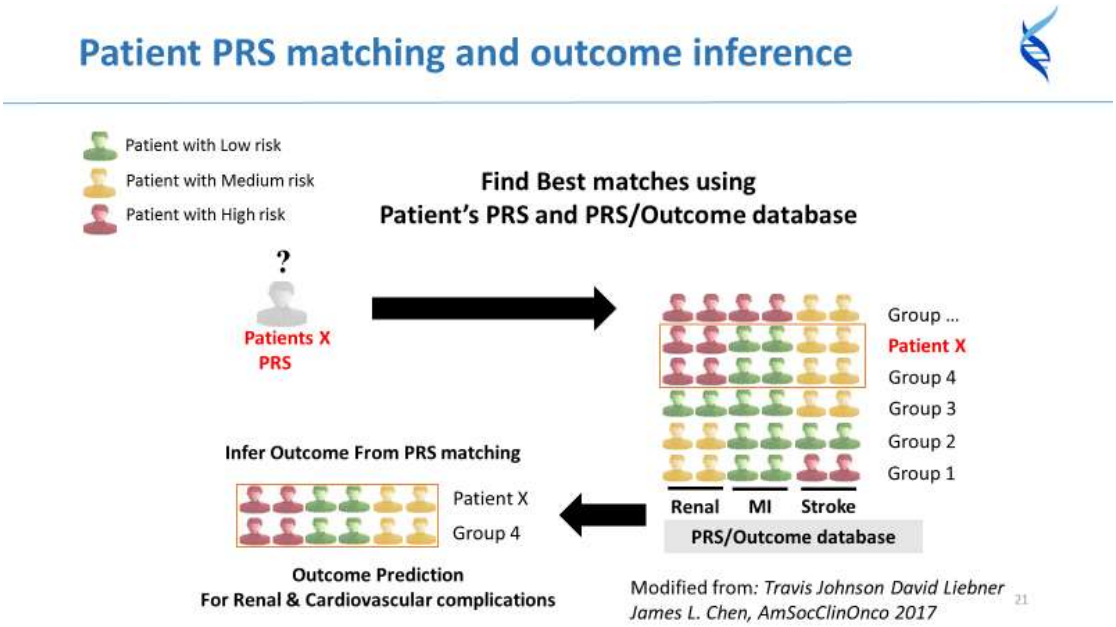
Common diseases, including type 2 diabetes and its complications, are multifactorial and **polygenic diseases,** meaning that many genes, environmental factors and lifestyle influence disease predisposition and development. Risk assessment for common diseases is a novel part of genetic testing that refers 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].

The OPTITHERA™ test 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, ethnicity, diabetes duration and age at onset of diabetes.

Diabetes increases the risk of serious and costly cardiovascular and renal complications. Prediction of risk prior to development of these complications is crucial to enable targeting individuals that could benefit from an early intervention. Current clinical risk prediction models are only applicable once clinical signs are present. Genetic information, with which one is born, offers a way to make early detection of risk. Genome-wide association studies (GWAS) identified multiple common variants associated with T2D, renal, cardiovascular diseases, and hypertension. Individually, these genetic variants account for only a small effect size but the combination of hundreds or thousands of them into polygenic risk scores (PRS) was recently introduced to predict individual risk of diseases including type 2 diabetes. Recent studies suggest that combining multi-PRS of related traits into a joint model could optimize its prediction performance. Because of their common risk factors, overlap in terms of pathogenic mechanisms and correlations among them, we combined 10 weighted PRS gathering genomic variants associated to cardiovascular and renal complications and their key risk factors into one logistic regression model, to predict micro- and macrovascular endpoints of T2D[1]. We first selected 598 SNPs within loci associated to 26 factors and outcomes of T2D obtained from summary statistics data of genome-wide and targeted genomic association studies conducted in hundreds of thousands of participants of European descent. We grouped the 598 SNPs into 10 wPRS that were then included as variables in the logistic regression model. The prediction performance of this PRS model was assessed by c-statistics using a target sample composed of 4,098 genotyped participants of European descent of the ADVANCE trial, extended to its post-trial follow-up, ADVANCE-ON for a total of nearly 10 years of observation. The predictors retained in the model were the ten PRS, the first principal component (PC1) of ancestry, sex, age at diagnosis, and diabetes duration. This PRS prediction model did not include any clinical or outcome data and was replicated in 17,604 individuals with T2D from the UK Biobank (UKBB) and three independent non-trial cohorts. It was used to identify individuals who benefited most (or not) from the intensive therapy administered in ADVANCE. The PRS model was then calibrated for other ethnic groups including South-Asian and African by controlling

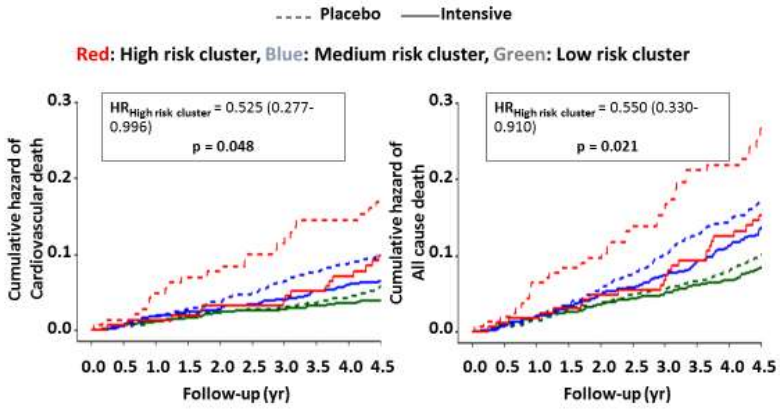
for genomic ancestry through principal component analysis (PCA) to address the effect of population stratification.

The level of risk to develop complications of diabetes (before any clinical manifestations) 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). Categorisation of risk with OPTITHERA test uses artificial intelligence.



Clinical utility of the PRS 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], while the intensification of therapy had no discernable effect in the low-risk group.
In conclusion, OPTITHERA's test identifies people with diabetes at low, medium and high risk of complications and improves targeting those at greater benefit from intensive therapy while avoiding unnecessary intensification in low-risk subjects.

Cumulative hazard plots of cardiovascular death and all cause death stratified by risk clusters in standard and intensive blood pressure treatment arm



A recent health-economic evaluation, pondering the cost and benefits of the OPTITHERA's test demonstrated, using renal failure (leading to hemodialysis) as an important economic burden worldwide, that application of OPTITHERA's test reduces healthcare expenditure while improving the number of quality years lived [8].

10-year time horizon	Albuminuria	test
Total QALYs	6.53	6.58
Incremental QALYs [a]		0.054
Total costs, $CA MoH perspective	$13,928	$11,582
Incremental total costs, $CA MoH perspective		-$2,346
Total costs, $CA Societal perspective	$15,070	$12,211
Incremental total costs, $CA Societal perspective		-$2,858
Incremental cost/QALY, $CA MoH perspective		Dominant
Incremental cost/QALY, $CA Societal perspective		Dominant

LIMITATIONS

Predictive tests such as OPTITHERA's tests are based on probability with potential of false negative or false positive results. The clinical utility of these 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 the test is well calibrated (predicted vs observed), a polygenic risk score (PRS) remains a probability that can be modified by environmental intervention including medication.

OPTITHERA's test is optimized for a period of five years and calibrated for individuals of European, South-Asian and African descents.

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