TIGAR™
Personalized Medicine in Diabetes

Frequently asked questions by Physicians

This information is solely for use by an appropriately qualified health care professional. This manual is meant to be used as a supplementary aid for a clinician. As a health care professional, you are encouraged to use this information in conjunction with other information relevant to you. It should not be solely relied upon, it may contain errors.

IR2DX TIGAR™ Report

Frequently Asked Questions

What is the TIGAR™ Report?

The TIGAR™ Report is an analytical report that provides a personalized approach to optimize therapy for your diabetes patient. Our clinical decision support system matches the patient's underlying biological pathway test results to specific anti-diabetic drug classes' mechanisms and effects. Thus the information in the TIGAR™ Report allows you to make better informed therapy decisions for your patients. Using TIGAR™ with other information about the patient, a physician can guide treatment for any stage of Type 2 diabetes, from prediabetes to late stage. Our proprietary web based algorithm includes over 13,000 specific treatment possibilities based on marker levels from each of seven markers and the patient's stage of disease or treatment. The name TIGAR™ stands for 'Treatment Integration and Guidance Analysis Reporting'.

What tests are necessary for the TIGAR™ Report?

The following test results are required for a TIGAR™ Report:

hsCRP - an inflammation marker associated with cardiovascular risk and beta-cell stress. It's often elevated in patients with diabetes and prediabetes. CRP is unique among our markers in that it is not only associated with poor metabolic control likely related to inflammation, but also cardiovascular/cerebral risks, even when an elevated CRP is the only abnormal marker, as elucidated in the large rosuvastatin JUPITOR study.

Adiponectin - a well-recognized marker for visceral fat tissue activity and insulin resistance. Patients with low adiponectin levels not only point to poor metabolic control related to the items listed above, but also higher risk of other sequelae like cardiovascular risks.

Intact proinsulin, insulin and C-peptide – these three markers of beta-cell activity allow you to ascertain the complete picture of beta-cell function. Beta-cell abnormalities are very useful in understanding both the state of beta-cell function, and the stage of disease. A high value points to stress on insulin producing cells in the pancreas, with a degree of elevation that relates to disease stage. A very low value points to beta-cell exhaustion and the need to add exogenous insulin to the treatment regimen. In addition, proinsulin has been studied in numerous clinical trials and is highly specific for insulin resistance and cardiovascular risk.

HbA1c – a measurement to assess average blood glucose status over approximately the prior three-month timeframe. The value of HbA1c is well established, used in over 100 million patients globally each year in both prediabetic at risk patients and those with active type 2 diabetes. This marker correlates well with other markers in TIGAR report. Levels often correlate with stage and disease status. However, numerous IR2Dx studies and results from other independent drug studies have demonstrated that this important marker often does not distinguish between the degree of glucose control and the other underlying conditions and risks associated with diabetes and prediabetes.

eGFR - an estimated Glomerular filtration rate to gauge kidney function. This measurement is used to determine whether certain drugs may be contraindicated, or need to have a particular dose adjustment due to impaired renal status. Most of the widely-used diabetes medications can be used in patients with no, mild or even moderate renal impairment, but the list of medications is very limited in more severe, renal impairment to end stage renal disease (ESRD) or on dialysis. Those approved for use in such patients almost always require downward dose adjustments.

Stage of disease or therapy – the ordering physician must indicate the patient's stage of disease or treatment on the requisition.

How was TIGAR developed and this particular group of markers selected for analysis?

The TIGAR algorithm is a proprietary algorithm resting on complex decision trees and clinical interpretation rules. It matches patient biochemistry showing underlying pathway function with drug mechanisms and effects at the class level for anti-diabetic agents. The TIGAR™ algorithm rests on four foundations. 1) Comparative marker research was done over 5 years to select the best drug response markers. Most of this is unpublished. 2) Prospective pharmaceutical clinical studies were done, comparing the marker and HbA1c responses between drugs, which validated the utility of the markers. Almost all of this is published. 3) Third party literature on the markers and the drugs supplements the first two. All of this is published. 4) Clinical judgment and interpretation rules for the report content rests on the medical judgment and consensus of our internationally renowned AACE advisors (American Association of Clinical Endocrinologists), and other prominent physicians and experts in diabetes. This is all unpublished. The algorithm has embedded in it the marker determined drug selection steps of the AACE patient management algorithm, and incorporates some trade secrets.

The markers were selected following a review of over 800 potential protein biomarkers, chosen so that current expression of key metabolic pathways could be evaluated. Comparison studies were done of sensitivity/specificity/drug response. Then candidates were evaluated for suitability as a routine test against several development criteria, including 1) Ease of collection; 2) Storage stability; 3) Biological variability; 4) Response to drugs; 5) Response to improvement of metabolic regulation; 6) Pathway assessment accuracy; 7) Complementary information; 8) Well defined markers (function and characterization); and 9) Established reference methods.

Validation of the marker selection was done in prospective pharmaceutical studies. Classification, drug response, and consistency across major anti-diabetic classes were assessed. We then evaluated the set of markers in over 40 published pharmaceutical clinical trials, totalling more than 14,000 patients with metabolic syndrome or diabetes with various drug regimens. These pharmaceutical clinical trials were randomized, controlled clinical settings ranging from prediabetes and early stage Type 2 diabetes patients on oral therapy (first line medications such as metformin or sulfonylureas), to late stage patients on insulin, and even in end stage renal disease. The studies demonstrated that the IR2Dx TIGAR™ markers correlated better metabolic control with certain drugs or drug combinations to well-accepted surrogate markers like LDL/HDL ratios, intima media thickness of the arterial wall and current standard markers like HbA1c or FPG. In some studies, results were shown to be independent of blood glucose levels, which can lag behind the IR2Dx TIGAR™ diagnostic metabolic markers by months or even years. This is important because macrovascular and microvascular deterioration, such as atherosclerosis, retinopathy, deterioration of renal function, or peripheral neuropathy, is often independent of glucose status.

The final steps involved derivation of the rules of the algorithms, development of clinical interpretation/content rules with our Medical Director and advisors, and development of our reports, portal software and database. Expert review and improvement of our content rules and database is an ongoing process.

What evidence do you have in the clinical setting for using this personalized approach to guide therapy?

The TIGAR approach has been used by physicians for patients in all stages if disease. The company has numerous studies in patients ranging from prediabetic patients with either cardiovascular or cardiovascular and diabetes risk to type 2 diabetes patients on first line therapy compared between two different drug regimens, those on multiple drugs with or without insulin injections and even patients with ERSD on dialysis. We have published studies in over 14,000 patients in 40 published papers, a compendium not matched by any other diagnostic or physician algorithm. Numerous trials with newer diabetes medications now include some of our biomarkers in their Phase III or IV post market clinical studies, bringing the total clinical data base to around 25,000 patients. We have a number of these published outcome studies in our list of references along with the actual full papers or abstracts.

When should I run TIGAR™ for my diabetes patient?

You should run TIGAR any time you desire additional information to optimize treatment for your patient. If your diabetes patient has an unsatisfactory outcome to date based on current therapy, your patient is a good candidate for the IR2Dx TIGAR™ clinical decision support tool. The TIGAR™ analytical report can help you understand the nature of the patient's disease and aid in selection of a more effective, truly individualized therapy. The TIGAR™ Report can also aid in the initial selection of therapy for a patient. If the underlying markers are clearly abnormal, a follow up with TIGAR is appropriate two to three months later, until the right drug regimen brings the patient under good control. Semi-annual or annual repeat testing thereafter is helpful for monitoring therapy response, as the patient's condition changes over time.

How do I interpret the results and information on the Report?

The TIGAR™ Report displays the marker results along with a gradient chart showing degree of normal/ abnormal values. Based on the specific pattern of results, the report provides an interpretation which allows you to understand the condition of the underlying disease of your patient. A summary of the recommended anti-diabetic drug classes most appropriate to optimize therapy for your patient follows the interpretation. Information in the report suggests appropriate drug regimens to use in a priority order, and is adjusted for those with renal impairment. The TIGAR Report will provide a personalized therapy approach and assist you in better therapy decisions for your patient, whether using mono, dual or triple drug treatments. To optimize therapy for your patient, it may be possible to eliminate one or more currently used drug classes, as well as optimize the dosage of current medications, based on marker values for the underlying metabolic markers and patient compliance and tolerability.

How does the TIGAR™ Report complement my current clinical practice for patients with diabetes?

Blood glucose levels have served as the gold standard of treatment success for the past fifty years, with the only major movement over the past ten years being a shift to using HbA1c, in lieu of fasting plasma glucose. The HbA1c test provides a better overall view of the patient's glucose levels over the previous three months. Blood glucose and HbA1c levels tend to vastly underestimate the degeneration of the patient's underlying metabolic control. The TIGAR markers provide a much clearer picture of the drivers of metabolic control - systemic inflammation, beta-cell function and visceral fat tissue function. When all three of these functions are measured together, they elucidate whether or not your patient's current treatment regimen is reducing the risk of disease progression, and its associated macrovascular and microvascular side effects.

With so many factors to consider in choosing anti-diabetic agents for your patient, it may be difficult to sort out the complexity in choosing the optimal drug therapy for your patient for both glucose control and disease management. The TIGAR clinical decision support tool assists you in sorting through this complexity and determining better drug treatments for your patient. This gives your patient the peace of mind that you have provided the best drug combination to augment their dietary and physical activity, and it also contributes to their higher overall quality of life. Better drugs have been shown to lower overall medical costs even in the first year of therapy[1], reflecting better patient health.

How does the IR2Dx TIGAR™ algorithm differ from the American Association of Clinical Endocrinologists diabetes management guidelines?

The TIGAR algorithm supplements the AACE guidelines. The AACE diabetes management algorithm begins selection of treatment using four levels of HbA1c. Once the specific A1c level is identified, the algorithm provides a list of suitable anti-diabetic drug classes for a doctor to select treatment decisions based on mono, dual and triple therapy, which together encompass over 200 potential courses of therapy. However, these guidelines are not particularly easy for a physician to navigate between therapy groups, and among drug classes. Alternatively, the TIGAR™ algorithm provides much more focus, using over 13,000 specific classifications of individual condition as the basis for specific treatment options, and thus allows you to provide personalized treatment for your

diabetes patient. Both IR2Dx and AACE have developed tools to better facilitate treating your patient. Four of the leading authors of the AACE algorithm are clinical advisors to IR2Dx.

How often do I re-test using the TIGAR™ report and what will each new report reveal?

For a diabetes patient, we suggest that after a therapy change you retest the TIGAR™ markers every three months at the same time an HbA1c test is done, which is a running three month average of your patient's blood glucose levels. At a three month assessment, a new analysis will reveal whether or not the drug regimen changes resulted in improvements to the biomarkers in the panel, particularly, the non-glucose underlying metabolic markers. These demonstrate changes much earlier than glucose levels, and particularly HbA1c. If the TIGAR™ markers are not demonstrating marked improvement at three months, further changes will be necessary to find the right drug combination for your patient. With the TIGAR™ approach, you should be able to find the right drug combination much earlier than with glucose markers alone, and determine if it's clinically effective.

Once the patient is under good metabolic control, twice a year is sufficient for retesting. For a prediabetes patient, we suggest testing the TIGAR™ biomarkers once a year, or every other year if HbA1c and blood glucose levels are in normal ranges. If the HbA1c levels are in the grey zone i.e., 5.4% to 6.4%), and any of the three beta-cell markers are clearly elevated along with or without abnormal inflammation or visceral fat tissue marker, adiponectin), it is worth considering clinical intervention starting with a medically supervised dietary program and increased physical activity. Depending on the patient's other clinical risks like BMI, hypertension and coronary artery status, a more aggressive intervention with medications may be required if dietary and other lifestyle changes do not improve biomarker levels.

I have run the report once on one of my existing patients that has progressed on metformin. The information provided on the patient's condition confirms the poor control underlying the rising HbA1c levels and show that the patient requires a different drug regimen, but I find the list of recommended drugs fairly long and confusing?

The disease is complicated and the markers provide a precise picture of your patient's current metabolic health. The list of recommended drugs is ranked in order of preference for each individual. We work continually to make the report as concise as possible while continually updating the information on new medications; new clinical data etc., as we realize you have a very busy practice. We often list metformin first, as recommended by numerous authorities such as AACE and ADA. However, if you have a patient who has progressed despite the metformin therapy, often this patient will respond better to the addition of other drugs, rather than increasing the dose of metformin. The patient's report would indicate the best options for additional therapy given the patient's specific condition. Once you have been through the report two or three times, and know where the different types of information are located, the report is quite easy to navigate.

How do I order the TIGAR™ Report?

The TIGAR™ Report is available through your local medical representative at CIC-ALS Middle East SAL in Lebanon or Barcelona Medical Corporate in Egypt. Once the TIGAR™ biomarkers are run, the results are uploaded into the IR2Dx proprietary web portal, and the TIGAR™ Analytical Report is then generated, and sent to the partner laboratory. The report is then delivered directly to you. Test requisition forms are available by calling your local medical representative or our office. The tests used in the TIGAR™ analysis are reimbursed in part by most third party payers, including government entities, for patients being treated for diabetes.

Please call your local medical representative:

1. Gdovin J, Worley K, Louder A, Ward M, and Graham J. Retrospective Database Analysis of the Impact of Prior Authorization for Type 2 Diabetes Medications on Health Care Costs in a Medicare Advantage Prescription Drug Plan Population. *JMCP* June 2013; Vol. 19, No. 5: 374-384.
2. Hohberg C, Pfützner A, Forst T, Lübben G, Karagiannis E, Borchert M, & Schöndorf. Successful switch from insulin therapy to treatment with pioglitazone in type 2 diabetes patients with residual β-cell function: results from the PioSwitch Study. *Diabetes, Obesity and Metabolism*, 11, 2009, 464-471.

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