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An Evaluation of the 7K Medicine Model Established for Gentest Practice Using a Piloted Outcome Measurement Framework

A Mixed Methods Study Triangulating Biological Outcomes, Consultee Experience & Changes in Quality-of-Life

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1 Summary

Introduction & Contextual Background

Noncommunicable diseases (NCDs) are accountable for the majority of global deaths; however, healthcare systems and the population wide approaches initiated in response, have been ineffective at tackling such pressures. A novel 7K Medicine Model implemented by Gentest Institute, combats such phenomenon by using personalised and preventative techniques to target and prevent NCD development. However, due to the complexities associated with evaluating personalized medicine interventions, its effectiveness is yet to be comprehensively determined. Garton (2020) initiated such a study by developing and piloting an outcome measurement framework to identify patterns in biological trends over time. However, study limitations including: small sample sizes, low validity, limited arrays of contextual factors and the focus on one aspect of Gentest's outcomes emphasises the need for further research. Therefore, this study will investigate the research question: 'To what extent can Gentest's 7K Medicine Model be evaluated based upon the piloted outcome measurement framework and desired program impacts?'

Methodology

A mixed methods approach using a concurrent embedded design, emphasising quantitative data analysis was used to triangulate three outcome and impact dimensions to initiate Gentest's program evaluation. The first relates to further evaluating biological outcomes by modelling NCD biomarker trends using linear mixed effect regression models. The influence of numerous contextual factors on biomarker-NCD risk status were explored and iterated through workshops, whereby inclusion criteria were applied during their analysis. The second outcome; consultee experience, was investigated through surveys and supplemented with semi-structured interviews. The results were categorized into each of Gentest's operational domains to explore quality of care and areas in need of improvement. Finally, changes in consultee quality-of-life (QoL) before and after consultees Gentest report interpretation was analysed. A survey was again used to collect comparison data whereby paired t-tests and Wilcoxon signed rank tests were used to make statistical inferences.

Results

Several main biological outcome patterns were identified which relate to the at-risk group (8/15; p-values<0.05), males (9/14; p-values<0.05), younger adults (7/15; P-values>&< 0.05) and those enrolled for less than one year (14/15; p-values< & >0.05) to improve biomarkers at a significantly more rapid rate when compared to comparison groups. Interestingly living in Istanbul had a negative effect whereby 11/15 (p-values>0.05) biomarkers had worse outcomes. The second program outcome; consultee experience, resulted in the analysis of 43 survey responses and four semi-structured interviews. Results indicate positive experiences in all program domains, whereby a good explanation

of health risks, respectability of needs, increased health knowledge, professionalism and staff approachability were themes identified. Quantitative results highlight several aspects in need of improvement and relate to the clarification of health concerns, increased involvement in regimen development and more personal and detailed exercise recommendations. To triangulate the results, QoL impact analysis indicated that the mean rating of sexual life decreased for those who had their report interpretation after June 2020 and the median rating of enjoyment of life increased for those who had their report interpretation before June 2020, p-values<0.05.

Conclusions
This study further developed, expanded and piloted an outcome measurement framework to evaluate the 7K Medicine Model implemented by Gentest Institute. The different patterns identified per contextual variable can be used to validate priorities and promote policy changes; including, the closer monitoring of highlighted groups or the implementation of techniques to maintain motivation levels. Consultee's appreciation of Gentest's professionalism, flexibility and staff approachability were emphasized; however, certain areas of the program were identified to need minor levels of improvement. Such adaptations may be implemented to enhance patient-physician relationships, consultee adherence and thus Gentest's success. Further research is needed in all domains, especially changes in QoL as two significant but inconsistent results were obtained which may be confounded by the impact of COVID-19. Gentest may implement the developed survey for routine data collection, expand upon the dataset and investigate additional contextual and confounding factors. This will enable the continuous monitoring and evaluation; using sufficient sample sizes, to increase Gentest's effectiveness, quality and further improve program delivery. As a result, the 7K Medicine Model may be effectively implemented into primary healthcare systems and used to tackle the global surge in NCDs.

2 Introduction

The prevalence of chronic, non-communicable diseases (NCDs) is rapidly increasing, whereby they contribute towards 71% of all global deaths (WHO, 2018a). Their genetic predispositions are intensified through the interaction of cumulative risk factors; including, physical inactivity, unhealthy diets and substance abuse (Konstsevaya et al., 2018). Due to the global ageing population, such phenomenon is enhanced, causing healthcare costs to soar and economic productivity to diminish (Beaglehole, 2011a; Montecino-Rodriguez et al., 2013). Despite these concerns, current healthcare systems are designed to target acute diseases in need of episodic care. Consequently, many NCDs are symptomatically diagnosed, indicating the later, irreversible stages of the disease (Mills & Ranson, 2012). A prime example follows the case of Turkey whereby such pressures are intensified. The

Ministry of Health implemented a Health Transformation Program (HTP); a population wide approach, to combat low life expectancy, huge catastrophic spending and fragmented healthcare governance (Acemoglu & Ucer, 2015; WHO et al., 2011). However, political shifts deviated such efforts and consequently NCDs contribute towards 87% of all country deaths, despite the annual 24.5 billion Turkish Lira spent on their treatment (Konstsevaya et al., 2018). As a result, a heavy burden is placed on Turkish workforce productivity due to disability and premature death (Baris et al., 2011; Konstsevaya et al., 2018). This highlights the inefficiency of current healthcare systems and emphasizes the need for effective global action.

In contrast to population wide approaches, the rapidly advancing field of personalized and preventative medicine uses multidisciplinary techniques to address the emerging challenge imposed by NCDs (Chan & Ginsburg, 2011). Whilst its definition is largely debated, this study adopts a holistic conceptualisation, whereby unique clinical, genomic and lifestyle information is used to inform and direct treatment programs to extend and improve quality-of-life (Cesuroglu, 2016; Chan & Ginsburg, 2011; Garton, 2020). Such techniques have been associated with improved health outcomes and cost rationalization; however, highly coordinated and multidisciplinary responses requiring large initial costs over prolonged periods of time are needed for their widespread implementation (Epstein & Teagarden, 2010; Hasanzad et al., 2019; Nolte et al., 2008; Pritchard et al., 2017).

Despite such barriers, Gentest Institute; an emerging practice based in Istanbul, adopts personalized and preventative techniques in an innovative 7K Medicine Model to target and avert NCD development (Cesuroglu et al., 2009). Additionally, The Public Health Genomics European Network identified this as the 'best practice model' in 2008 (Cesuroglu et al., 2009). Personal health risk profiles and comprehensive lifestyle plans to monitor and prevent NCD risk development are provided to Gentest's 'consultees', based on elaborate lifestyle questionnaires, laboratory and body measurements (Cesuroglu et al., 2009). Whilst these techniques are adopted, it is challenging to determine the effectiveness of such interventions due to small study samples, individual variation and lengthy follow-up periods needed to determine health outcomes (Misra et al., 2019; Sedda et al., 2019).

Possible evaluation study designs may include the assessment of the short to long term changes; referred to as outcomes and impacts, directed by the program's operations (Belcher & Palenberg, 2018). Garton (2020) recognised this by developing and piloting an outcome measurement framework for Gentest practice to evaluate consultee biological outcomes. The realist evaluation was adopted to

account for complex system dynamics, whereby the question *'what works for whom, in what circumstances and in what respects, and how'* was continuously posed (Pawson & Tilley, 1997, pg. 2). This enabled relevant stakeholders to be centralized throughout the process, permitting the influence of individual and contextual factors to be acknowledged (Gilmore et al., 2019). However, study limitations concerning: small sample sizes, limited arrays of contextual factors and the focus on one outcome, emphasises the need for additional research to expand and further develop Garton's (2020) framework.

This study will therefore answer the following research question: *'To what extent can Gentest's 7K Medicine Model be evaluated based upon the piloted outcome measurement framework and desired program impacts?'*. By posing this question, several outcome and impact indicators will be evaluated to validate the effectiveness of Gentest's preventative and personalised techniques. The study's findings can inform future policy and contribute towards Gentest's program improvement to further decrease NCD risk development. Moreover, this will enable an effective and efficient implementation of the 7K Medicine Model into primary healthcare systems and used to tackle the global surge in NCDs.

3 Contextual Background

To gain further insight into Gentest Institute as a personalized and preventative healthcare service in Turkey, a detailed overview of their operations is discussed, in addition to the recent developments of Garton's (2020) study.

3.1 Gentest Institute & The 7K Medicine Model

Developed and initiated by the GENAR Institute for Public Health and Genomics Research in Ankara, Gentest Institute is one of the only healthcare services in Turkey that acknowledges and acts upon the widespread threat of NCDs (Cesuroglu, 2009; Gentest, 2021). Directed by Dr. Serdar Savaş, Gentest encompasses a range of disciplines including: biotechnology, genetics, nutrigenetics, personalized medicine, pharmacogenetics and behavioral sciences which are intertwined to initiate behavior change and manage health according to individual's priorities (Cesuroglu et al., 2009). To achieve this, a personalized and preventative approach is adopted through a 7K Medicine Model (see **BOX 1**.) aimed at tackling individual NCD risks through lifestyle modifications (Cesuroglu, 2009; Cesuroglu, 2016).

BOX 1. The 7K Medicine Model

A detailed outline of the 7K's translated from Turkish that constitute the 7K Medicine Model implemented by Gentest.

1. **Kişiye özel (Personalized):** Represented by a shift from a 'one size fits all' towards a 'personalized' approach in medicine, whereby extensive biological, anthropometric, lifestyle and genomic data are used as health determinants

2. **Kestirimci (Predictive):** Predicting personal risk developments will enable the targeted prevention of NCDs.

3. **Koruyucu (Preventive):** Personalized and preventative measures are developed in response to risk profiles which include dietary, exercise and medication actions as necessary

4. **Kapsamli (Comprehensive):** Current medicine must comprehensively account for holistic systems consisting of macro and microbiota.

5. **Keskin (Precise):** Precision medicine accounts for technological advancements whereby granular measurements, in combination with personal information increase the accuracy of health interventions.

6. **Kanıta dayalı (Evidence based):** Deviating from the conventional meaning of the term 'evidence based', this model centers all assessments and interventions on the findings ('evidence') from specific individuals.

7. **katılımcı (Participatory):** To prevent information asymmetry, the patient is actively involved in all aspects of their monitoring, prevention and treatment cascade following close guidance and support of health professionals.

**This description is used across several parallel research studies for Gentest practice. Information was obtained from Cesuroglu et al. (2016) and supplemented with information gathered from private conversations with Gentest employees*

Implementing the 7K Model, each consultee must follow a series of standardized processes which aim to collect, asses, interpret and monitor: proxy biomarkers, anthropometrics and lifestyle characteristics to ensure good health and prevent NCD development. A brief outline of Gentest's operational cascade is presented in **BOX 2.**

BOX 2. Gentest's Operational Cascade

1. **Information & Data Collection: 1st appointment**
   Each consultee is provided with a clarification of what Gentest entails. The most suitable package is chosen in consultation with the physician and is based upon the individual's priorities and personal characteristics. Consent forms are signed and the individual becomes a Gentest consultee.

2. **Assessment Stage: 2nd appointment**
   Elaborate measurements and lifestyle assessments are performed using questionnaires, blood and urine samples, body measurements and bioelectrical impedance. The vast array of information is used to establish recommendations on maximum and minimum intake levels of macro-and micro-nutrients. All data is collected and analysed by Gentest Institute to produce an extensive health report for the individual.

3. **Report Interpretation: 3rd appointment**
   The consultee is taken through the report with the Gentest physician and dietician. The report entails individual risks of the most common chronic complex diseases established through risk algorithms and based upon risk factors disclosed in various epidemiological studies. The consultee is presented with three types of risks: the estimated risk using the consultee's current data, the average risk for a peer (based on sex and age) and the estimated risk when following Gentest's lifestyle and medical follow-up plan. To enable interpretation, the risks are visualized in a series of colour-coded graphs, which are expected to emphasize personal vulnerability and increase motivation. A lifestyle plan including: nutrition, exercise, supplements, medication regimens and medical follow-up is outlined as an optimum program scheme for achieving and maintaining the consultees personal goals.

4. **Counselling & Follow-up**
   After the report interpretation, consultees can actively participate in the program by taking up follow-up meetings and engaging in one-to-one support via WhatsApp with the physician and dietician. Continual appointments can be made to track the individuals progress and make regimen adaptations as needed.

**This description is used across several parallel research studies for Gentest practice obtained from Cesuroglu et al. (2016) and supplemented with information gathered from private conversations with Gentest employees.*

Due to Turkeys healthcare system, lack of patient referral chains, and the normalization of out-of-pocket health expenditure (17.5% of total healthcare expenditure in 2018), Gentest remains a private service, available to those who can afford the associated expenses (Acemoglu & Ucer, 2015). Gentest strives to combat NCDs, through the implementation of its 7K Medicine Model into primary healthcare systems of various countries, beginning with Turkey (Gentest, 2021). To ensure its effective and efficient expansion, the program's influence on consultee outcomes and impacts must be evaluated.

3.2 The Initiation of Gentest's Program Evaluation: Garton's (2020) Outcome Measurement Framework

Garton (2020) developed and piloted an outcome measurement framework to evaluate biological outcomes by modelling trends in NCD surrogate biomarkers over days since ones' first Gentest encounter. Such components were identified based on their ability to ascertain NCD risk development and data availability (HbAc1, homocysteine, magnesium, selenium, total HDL: cholesterol ratio, triglyceride, vitamin B12, vitamin D, hs-CRP, BMI, body fat %, waist: height ratio & diastolic blood pressure). The differences in biomarker trends for at-risk and not at-risk consultees were investigated using linear mixed effects regression models (MER). Furthermore, Garton was able to incorporate the contextual influences of sex and educational status on biomarker outcomes by adopting the realist evaluation (Garton, 2020).

The results indicated that the at-risk population and male consultees attained better outcomes; however, inconsistent findings were observed for educational status. Despite these results, confounding variables, small sample sizes and low statistical power of many MERs may have impeded the study's validity (Garton, 2020). This emphasises the need to further investigate biomarker outcomes across follow-up periods, whilst taking into account additional confounding and contextual factors. Garton provided suggestions for future research and highlighted that risk factors such as: smoking status, pre-existing conditions, place and country of residence and family adherence to Gentest may influence biological outcomes.

3.3 The Implication of COVID-19 on Gentest's Operations

The context in which this research was conducted has also been impacted by the COVID-19 pandemic. Gentest's consultations switched to online discussions and home kits were delivered to consultees to assess biomarker levels. The governmental restrictions resulted in regimen adaptation, of which exercise plans were most severely affected. A significant downsizing of the inflow of new consultees and Gentest's staff also occurred; whereby only the head physician and director, research & development coordinator, head dietician and IT specialist remained in April 2021 (Gentest, 2021). Consequently, Garton's recommendations have not yet been implemented; however, such research will enable Gentest to efficiently expand and revert back to their normal practices with an added dimension of precision.

4 Theoretical Background & Conceptual Model

The theoretical concepts used throughout this study reflects Gentest's holistic approach to program implementation. A multi-dimensional conceptual model is derived using Garton's (2020) initiative which superimposed the realist evaluation onto the logical framework (log-frame).

4.1 The Logical Framework

The log-frame has proved to be an effective project planning and management tool; with wide applications throughout various contexts (Chang, 2015; Crawford & Bryce, 2003). The framework provides an overall project vision through the determination of goals and objectives using a structured hierarchal chain of cause-and-effect linkages. These constitute: (1) the desired inputs; resources needed for program functioning, (2) activities; functions required to make use of the resources, (3) outputs; direct products of program activities, (4) outcomes; secondary changes imposed by the program, and (5) impact; the program's wider influences and long-term effects (Baccarini, 1999; Couillard et al., 2009; Roduner, 2008). This was adopted to create a clear vision of Gentest's operations and to facilitate the identification of elements that may affect the program outcomes and impact, Gentest's operations mapped out onto the log-frame is provided in **appendix B**.

4.2 The Realist Evaluation

Pawson & Tilley (1997) emphasize that complex interventions; composed of numerous interacting components, cannot be studied in isolation or be constant in nature. This promoted the development of the realist evaluation which assumes that programs are embedded in social systems (Pawson & Tilley, 1997). Using this notion, complex interventions are perceived as part of 'open systems', whereby the effect of external influences is recognised, through the question *"what works for whom, under what circumstances and how?"* (Pawson & Tilley, 1997, pg. 2). This proves to be highly beneficial when evaluating personalized services, as the individual and their interacting surroundings are acknowledged. The concepts of 'Mechanism'; how the intervention brings about its intended effects, 'Context'; the conditions in which programs are introduced and their subsequent influence on its operations, and 'Outcome Pattern'; the varying results due to differences in the activation of mechanisms (CMO) are defined to describe how interventions function under particular circumstances. As a result, both their intended and unintended effects are identified (Pawson & Tilley, 1997). By adopting this perspective, a comprehensive evaluation tool can be produced to oversee Gentest operations, accounting for system dynamics, consultee involvement and intra-system power relations.

4.3 The Superimposition of The Realist Evaluation onto a Logical Framework (Garton, 2020)

It has been suggested that the use of layered theories enables a comprehensive description of system dynamics and can assist in understanding multiple causation (Westhorp, 2012). Using this notion, various elements of causation may contribute towards the emergence of outcome patterns. As this phenomenon is widely apparent throughout Gentest's operations, a conceptual model accounting for individual differences, contextual elements and program flexibility would provide great insight into Gentest's system dynamics. This was achieved by Garton (2020) who superimposed the 'CMO' of the realist evaluation onto the logical framework. Subsequent adaptations recognised the influence of externalities on each component of Gentest's operations, **figure 1.**

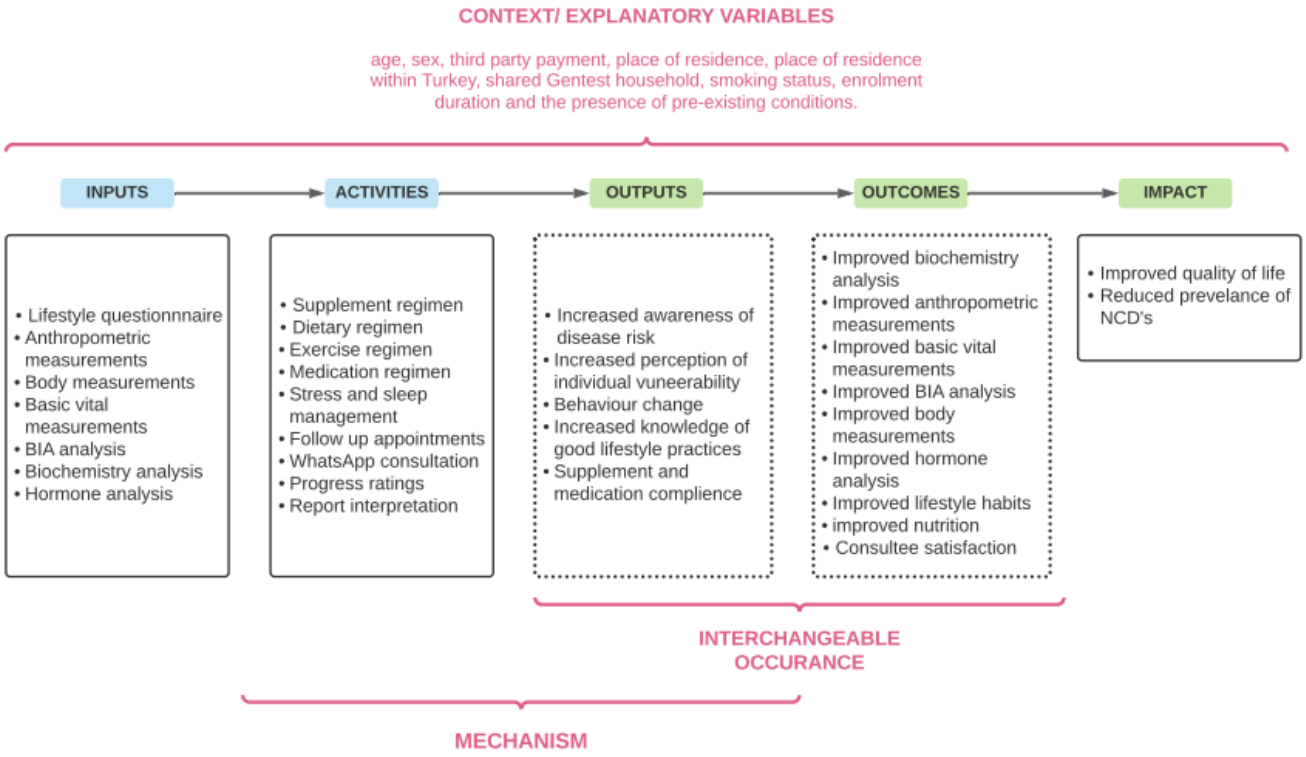


Figure 1. The Superimposition of the Realist Evaluation onto the Logical Framework, Adapted for the Purpose of this Research.

This conceptual model is an extension of the log-frame and depicts different components extracted from **appendix B**, representing the resources, tools and goals most relevant for Gentest's success. This hierarchical model conceptualizes each stage of their operations, adding a layer of complexity, as the realist evaluation is used to acknowledge the influence of contextual and explanatory factors on all components.

In accordance with the realist evaluation; 'mechanisms' link activities to the program outputs, representing how consultees use the available resources to produce immediate changes. This can differ between each consultee based upon the interaction of contextual elements and the chosen activity. As a result, the combination of these processes contributes towards 'mixed outcome patterns', represented by different rates of biological and behavioural improvements. Furthermore, the simultaneous onset of outputs and outcomes can lead to their interchangeable occurrence and thus the inability of their distinction (Pawson & Tilley 1997). In this study, the outcomes have been determined as biological and habitual changes in risk factors due to increased awareness of disease risk and the perception of individual venerability. An additional outcome relates to consultee satisfaction, an integral indicator used to assess the quality of healthcare services as the gap between consultee expectations and reality is explored (Assefa, 2011; Prakash, 2010). Such attributes may lead to wider influences on one's physical, mental, and social well-being, defined as quality-of-life (QoL) by the WHO (WHO, 1997). This is captured within the conceptual model as the primary aim of NCD treatment is to reduce the impact of disease and enhance QoL (Carr et al., 2001).

By using this holistic conceptual model to answer the central research question; a step towards evaluating Gentest as a personalized and preventative program is achieved. This can contribute towards improving the 7K Medicine Model, enhancing its effectiveness and consultee value in regard to its initiative in targeting and preventing NCD development. As numerous outcome and impact indicators are outlined, this study will further evaluate biological outcomes, consultee experience and changes in quality-of-life. These have been selected based on previous research, time limitations and research feasibility, leading to the derivation of several sub-research questions.

5 Sub-research Questions

a. How do contextual variables affect biomarker improvement for at-risk and not-at-risk consultees across follow-up periods?

. **Contextual variables**: age, sex, country of residence, place of residence, shared Gentest household[1], smoking status, enrolment duration, the influence of COVID-19 and the presence of pre-existing metabolically dysfunctional conditions.

. **Biomarkers:** lab results (HbAc1, homocysteine, magnesium, selenium, testosterone, total HDL: cholesterol ratio, triglyceride, vitamin B12, vitamin D, hs-CRP), body measurements (BMI, body fat %, weighted skeletal muscle mass index, waist: height ratio) and anthropometrics (diastolic blood pressure).

[1] Multiple members of a family, or a couple, may come to Gentest together and obtain personalized regimens which they follow simultaneously.

b. Which aspects of program delivery do consultees value and desire improvement in?

c. How does consultees quality-of-life change after adhering to Gentest?

6 Methodology

A mixed method approach using a concurrent embedded design was adopted as it is widely used throughout healthcare research and facilitates enriched understandings of complex phenomena (O'reilly & Parker, 2013; Molina-Azorin, 2016; Regnault et al., 2018). This study emphasises quantitative analysis to identify trends in biological outcomes. Furthering Gentest's evaluation, consultees Gentest experience and changes in QoL are analysed using surveys and semi-structured interviews. These domains are triangulated to further develop and expand Garton's (2020) outcome measurement framework.

6.1 Identifying Trends in Biological Outcomes: A Biomarker Analysis

Trends in biological outcomes are identified by assessing the influence of contextual factors on NCD surrogate biomarkers using MERs and supplementary workshops.

6.1.1 Study Population

A nested retrospective longitudinal design was adopted to enable the use of pre-existing and new consultee' service data, resultantly maximising the sample size (Caruana et al., 2015). This was used to expand Garton's (2020) dataset, whereby data obtained from new consultees and follow-up measurements to March 2021 were incorporated. Each consultee had to meet the following inclusion criteria: (1) had a minimum of one follow-up session to enable the MERs account for individual trends and (2) were above the age of 18 to prevent developmental effects on biomarker outcomes (Goldman et al., 2011; Pinheiro & Bates, 2000).

6.1.2 Data Processing & Analysis

Biomarker and demographic data were manually extracted from KEAP; an online platform used to store consultee files, due to the non-standardization of data formats. Data processing was conducted using Python 3.9 (64-bit) whereby pandas, matplotlib and statsmodels were primarily used (Van Rossum & Drake, 1995). This was chosen due to its easy-to-read code, versatile features and extensive supporting libraries that enable flexibility and recognise Turkish characters (Moore, 2015). All pre-existing conditions were filtered to include only those associated with metabolic dysfunctions: prediabetes, diabetes I & II, hypocholesterolemia, hypertension, cancers and hypertriglyceridemia, to minimize variation in MERs (Iwen et al., 2013; Seyfried et al., 2014). Data points were then categorized into before and after March 2020 to investigate the effect of COVID-19 (WHO, 2020). The majority of

contextual/ explanatory variables were then converted into dummy variables, apart from age ('Elderly, 65+ years', 'Middle-Aged, 36- 64 years' & 'Young Adults, 18-35 years) and enrolment duration ('Longer 5+ years', 'Medium 1-5 years' & 'Short <1 year') to enable MER computation. Each contextual factor was then assessed for multicollinearity using Chi square tests, Point-biserial correlation coefficients and Pearson's correlation coefficients, to prevent obscure outputs and unstable p-values (Gonzalez-Chica et al., 2015; O'Hagan, & McCabe, 1975; Vatcheva et al., 2016). Risk groups were differentiated using pre-determined risk thresholds validated by Gentest's head physician, **appendix A.** Outliers were identified and removed using descriptive statistics to prevent skewed results (Osborne & Overbay, 2004). Three further questions were then formulated to answer sub-research question A, see in **table 1.**

Table 1. Linear Mixed Effect Regression Model Research Questions

Questions Answered Through Linear Mixed Effect Model Analysis
A. Do at-risk consultees have differences in _*biomarker*_ outcomes compared to those not-at-risk?
B. Are there differences in _*biomarker*_ outcomes for not-at risk consultees who engage in a selected _*explanatory variable*_ and those who do not?
C. Are there differences in _*biomarker*_ outcomes for at-risk consultees who engage in a selected _*explanatory variable*_ and those who do not?

MERs were chosen as they overcome the challenges of irregular time intervals and missing data imposed by longitudinal designs (Garcia & Marder, 2017). Furthermore, they can recognise individual influences by defining cluster specific trends over time (Garcia & Marder, 2017). This infers that MERs compile the progression of each consultee's biomarkers to display the dataset's average outcome patterns. Additionally, contextual factors can be modelled as fixed effects to create another dimension, whilst maintaining individuality (Garcia & Marder, 2017). As panel data was analysed, time in years since consultee baseline measurement was used.

Preliminary results were discussed in three workshops held with various stakeholders including: Gentest's head physician and director, research & development (R & D) coordinator, the head dietician, IT specialist and co-researchers. Perspectives on consultee behavior and program dynamics were shared to facilitate enriched MER interpretations. This resulted in defining inclusion criteria to identify the most significant, valid and interesting MERs, **table 2.**

Table 2. The MER Inclusion Criteria

Inclusion Criteria	Explanation/ Examples
1. No underlying confounders	Inability to account for interacting factors e.g.: a) Gentest's continual improvement of service delivery b) The influence of the COVID-19 pandemic c) The age-related deterioration of biomarker levels
2. Sufficient sample sizes	If samples are <49 consultees, resultant statistical power is <0.8 (standard acceptance level), increasing the incidence of a type II error & decreasing validity (Kim, 2016).
3. Useful results	Can Gentest use the MER outputs to optimize their service delivery in relation to biomarker priorities and health outcomes.

6.2 *Survey Design & Procedure:* Consultees Gentest Experience and Quality-of-Life

To investigate consultees Gentest experience and their wider impacts on QoL, a survey was co-created and translated into Turkish. Ensuring contextualization, comprehensibility and time efficiency the survey was piloted on 10 consultees, after which a minor feedback and adaptation moment was completed (n=8 respondents). Google Forms was used as the administering platform due to its user-friendly initiative, easy distribution, accessibility and delivery methods (Melno, 2018). Consultees were given a period of three weeks to complete the final survey, whereby two reminder emails and one WhatsApp message were sent to increase the response rate.

6.2.1 Study Population

The sample consisted of consultees who had their report interpretation since January 2020 to ensure they experienced the full Gentest process, to enable QoL comparisons and to obtain a large enough sample size to produce valid results. A total of 105 consultees were asked to complete the survey, of which 10 pilot respondents were systematically selected by Gentest's head dietician based on their good relations to increase response rates.

6.2.2 Dimension 1: Gentest Experience

The conceptual framework identifies consultee satisfaction as one of Gentest's outcomes; however, due to criticism directed at the inefficiency and low validity of such survey scales, a focus is placed on consultee experiences and program development (Collins & O'Cathain, 2003). The EUROPEP Instrument, developed by the EQuiP Task Force for patient satisfaction was used to formulate questions as it has been internationally validated and administered across 33 medical practices in Turkey (Dagdeviren, & Akturk, 2004; Grol et al., 2000). The questions were translated into Turkish, contextualised and adapted to cover aspects surrounding consultees report interpretation,

communication and follow-up engagement, regimen adherence and overall experience. A resultant 18 questions were rated on a 4-point improvement scale. The results were analysed through the categorization of questions relating to the different domains of Gentest's operations (**BOX 2**.), whereby cluster bar charts were created using Python 3.9 (64-bit).

*6.2.2.1 Dimension **1**: Gentest Experience- Supplementary Semi-Structured Interviews*

To provide depth to the quantitative results, semi-structured interviews were conducted in parallel to the survey. Interview guides complementing the survey questions were used to direct the interviews which took place over Zoom for approximately 30 minutes. A total of four consultees were randomly selected from a larger list used for different research purposes, based on availability and the time-frame of this research. This was due to data saturation, the limited number of English-speaking consultees and Gentest's translation capacity. The broader sample of included a mix of genders, those with a minimum of one follow-up assessment, had good relations with Gentest and were able to speak English. The final sample had a mean age of 45 years ± 15.1 SD, and a higher proportion of males (n=3).

The interviews were recorded, anonymised, transcribed and coded using a pre-defined codebook, whereby Atlas.ti Windows was primarily used based on its user-friendly nature and ability to easily group, add and assign codes across several transcripts (Barry, 1998; Hwang, 2008). If new codes arose, they were added to the code book and thus a hybrid of deductive and inductive coding was adopted. This technique was chosen due to the structured nature of the questions discussed and overall clear aim of the research (Fereday & Muir-Cochrane, 2006). The codes were then categorized and grouped to identify major themes and triangulated with the quantitative survey results.

6.2.3 Dimension 2: Quality-of-Life

The same survey was used to investigate changes in QoL before and after consultees report interpretation. Questions were selected based upon the QoL statements of Gentest's initial information sheet and ascertained by the WHOQOL-BREF, resulting in 13 questions (WHO, 2004). The same 10-point rating scale was adopted to enable their direct comparison. The results were categorized into groups who had their report interpretation before and after June 2020 to minimize the influence of external effects and prevent response shifts (Allison et al., 1997; Blome & Augustin, 2015). Statistical analysis was used to test the alternative hypothesis that the true mean/median difference in changes of QoL will not be equal to zero after adhering to Gentest. Whereby Python 3.9 (64-bit; pandas, pingouin and scipy packages) was used to calculate paired t-test or Wilcoxon's signed rank test depending on the assumption criteria. Additionally, Cohen's D was used to determine the relative strength of the change in QoL, based upon small (0.2), medium (0.5) and large (0.8) effect sizes (Cohen, 1988; Lakens, 2013).

6.3 Ethical Considerations

This research was conducted under the extension of the ethical approval obtained from Üsküdar University Ethics Committee initiated on 29 February 2020, extended on 26 March 2021. The ethical considerations followed the principles of the World Medical Association Declaration of Helsinki per Üsküdar University Policy and concerned the responsible use of protected health information and the ethical involvement of Gentest employee' and consultee' participants through surveys and semi-structured interviews.

All consultees had given consent for their data to be used for research purposes of Gentest Institute. During the processing of the results, each consultee's identity was anonymised through the assignment of personals ID's and all anonymised data files were securely stored on Gentest's OneDrive. This was conducted in accordance with the General Data Protection Regulation (GDPR) and Turkey's law on the protection of personal data, data privacy and responsibility (Personal Data Protection Authority, 2016). Each survey respondent had their data confidentiality and anonymization guaranteed during the analysis and interpretation of all results. Written and verbal consent was obtained from all consultees who took part in the semi-structured interviews, whereby recordings were deleted and transcripts anonymised. Information transparency was ascertained throughout the study.

7 Results

The most significant biomarker patterns, consultees Gentest experience and the statistical analysis of changes in quality-of-life are presented and triangulated to further develop Garton's (2020) outcome measurement framework

7.1 Identifying Trends in Biological Outcomes: A Biomarker Analysis

The final dataset consisted of 185 individuals, including 95 new consultees and 74 additional data points. Differences in sex, date of data collection, place and country of residence, smoking status and a shared Gentest household were observed, **table 3.** Multicollinearity was identified between place and country of residence and place of residence and smoking (P-value<0.05). All explanatory variables were therefore assessed in separate models to prevent undesirable effects on their statistical significance (Allen, 1997).

Table 3. The Proportion of Individuals Within Each Contextual/ Explanatory Variable (n= 185)

Contextual/ Explanatory Variable	Observations, n (%)
Mean Age of Males vs Females	M 57.9: F 55.5
Males	104 (56)
Turkish Residents	165 (89)
Istanbul Residents	123 (66)
Smokers	39 (21)
With Pre-existing Metabolic Conditions	94 (51)
Shared Gentest Household	37 (25)
Data Points After March 2020	264 (21.6)

A total of 420 MER models were analyzed using each possible variable combination, of which 75 models met the inclusion criteria. **Figure 2**., presents the most significant patterns identified per explanatory/ contextual variable to answer questions A, B & C (**table 1.**). The sample size (n), slope of the mean trajectory (β, rate of change per year) and significance (p) at $\alpha <= 0.05$ are provided for each outcome. Significant trends are visualized through dashed lines and blue β values indicate significant gradients. Supplementary material regarding comparative values for each outcome and the reasons for variable exclusion is provided in **Appendix C**. and **D.**, respectively.

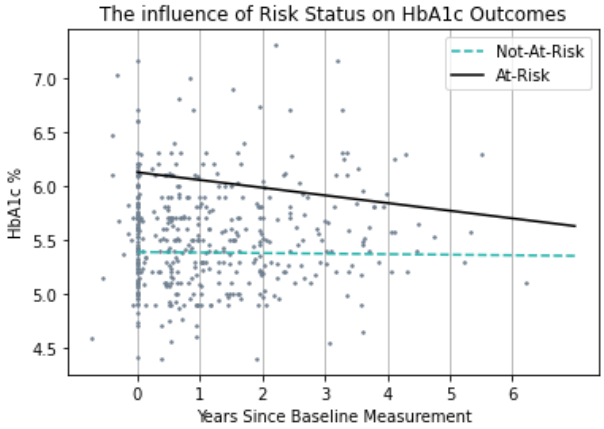
7.1.1 *Risk Status*

The at-risk group improved at a more rapid rate than those not at-risk (p-values<0.05), in 8/15 outcomes: total HDL: cholesterol ratio, triglyceride, hs-CRP, vitamin B12, BMI, body fat, waist: height ratio and diastolic blood pressure. The remaining biomarkers; excluding testosterone, followed the same trend (p-values>0.05). The not at-risk group worsened in 8/15 outcomes, whereby six had relatively small gradients (β <1), leaving body fat% (p-values<0.05) and weighted skeletal muscle index (wSMI; p-values>0.05) with the highest rates of change.

Risk Status: Comparable to Garton's (2020) Results

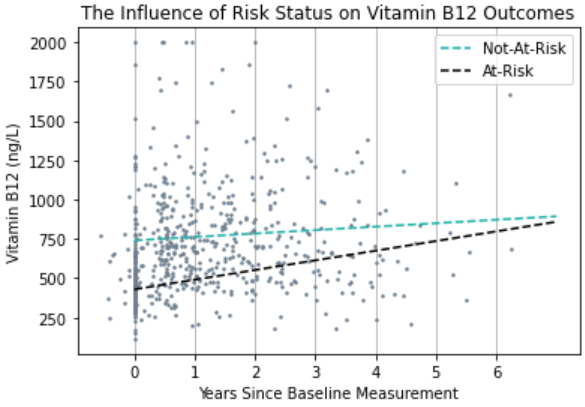
*N: not-at-risk, R: at-risk

HbA1c (>6%)



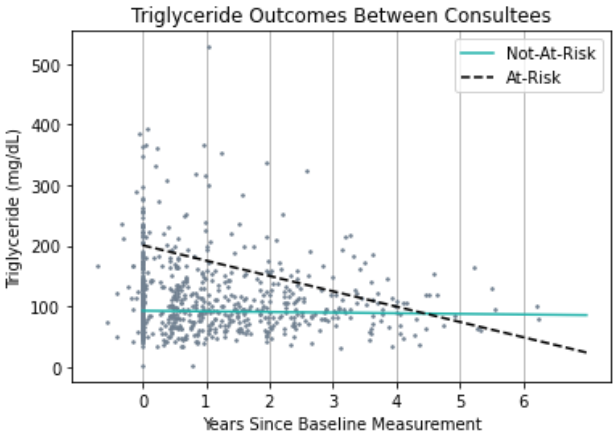
n = 134, β = N: *-0.005**, R*: -0.071**

Vitamin B12 (<400 ng/L)



n= 177, β = N:*21.867**, R:*61.427**

Triglyceride (>150 mg/dL)



n= 182, β = N: -1.034, R: *-25.281**

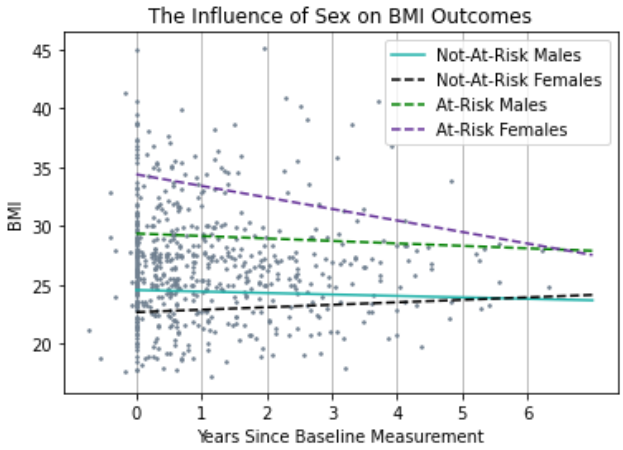
Body Fat % (M:>20% / F:>24%)

n= 357, β = N: *1.861**, R*: -1.385**

Sex: Comparable to Garton's (2020) Results

*M: Male, F: Female

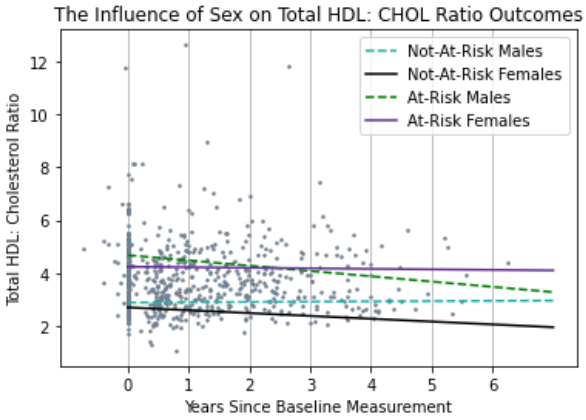
BMI (F: >28/F50:>30/M: >25/M50: >28)



nN = 88, β = M: -0.12, F: *-0.981**

nR = 78, β = RM: *-0.21**, RF: *-0.981**

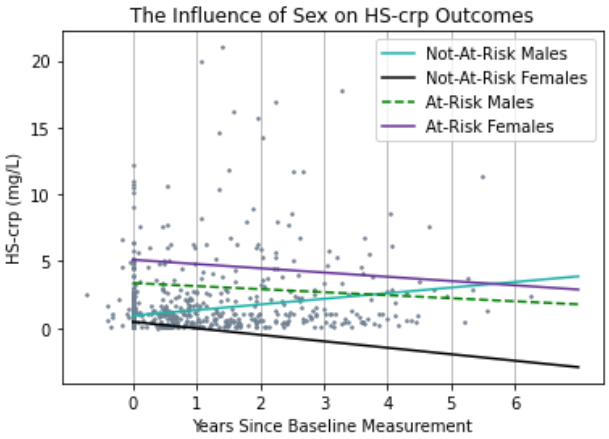
Total HDL: Cholesterol Ratio (>3.5)



nN= 65, β = M:*0.104**, F: -0.107**

nR = 107, β = RM: *-0.2**, RF: -0.02

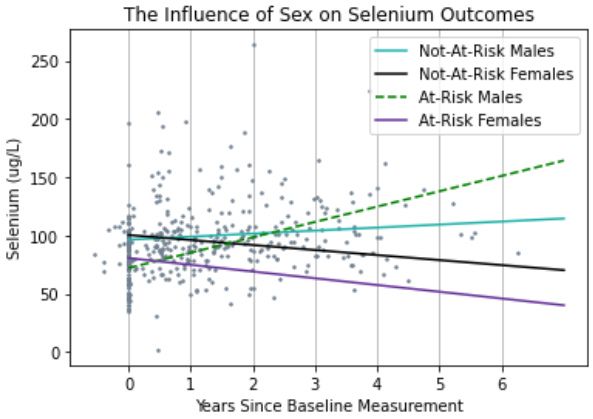
HS-CRP (>2 mg/L)



nN = 114, β = M: *0.42**, F: *-0.227**

nR = 55, β = RM: *-0.227**, RF: -0.318

Selenium (<80ug/L)



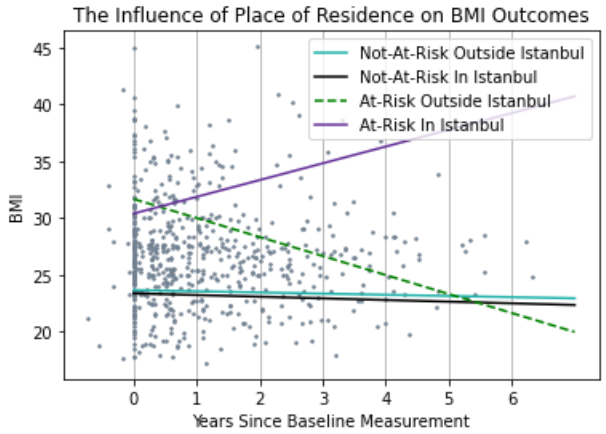
nN = 84, β = M:2.596**, F: -4.307

nR = 73, β = RM:*13.181*, RF: -5.785

Place of Residence

*O: Outside Istanbul, I: Istanbul

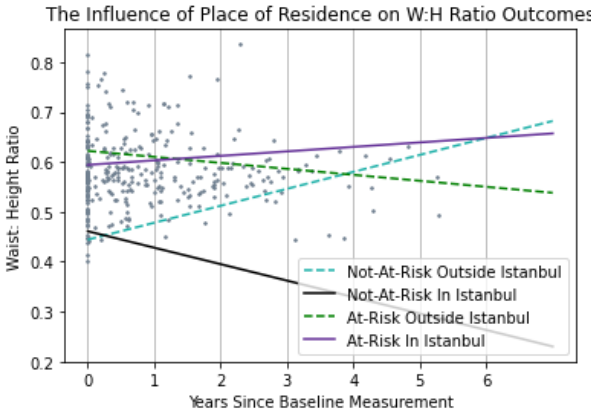
BMI (F: >28/F50:>30/M: >25/M50: >28)



nN = 79, β = O: -0.21, I: -0.416

nR = 73, β = RO: *-1.676**, RI: *1.476**

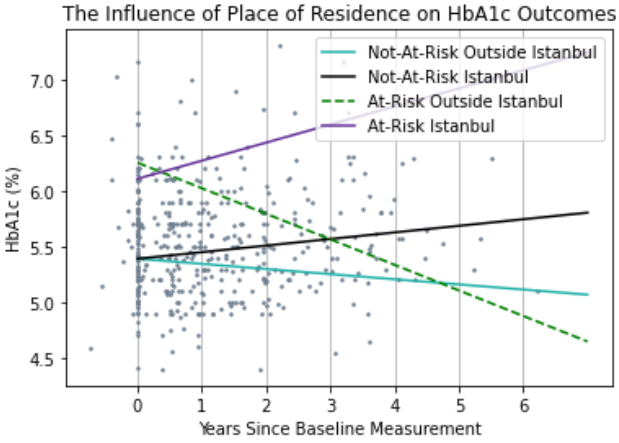
Waist: Height Ratio (>0.5)



nN = 12, β = O:*0.034**, I: *-0.033**

Rn = 96, β = RO: *-0.012**, RI: 0.0 09

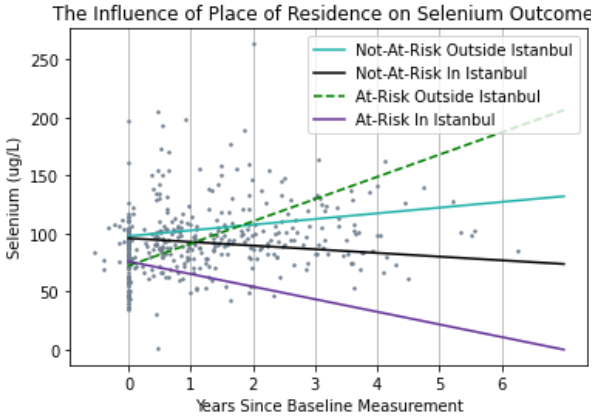
HbA1c (>6%)



nN = 107, β = O: -0.046, I:0.059

nR = 27, β = RO: *-0.229** RI: 0.162

Selenium (<80 ug/L)



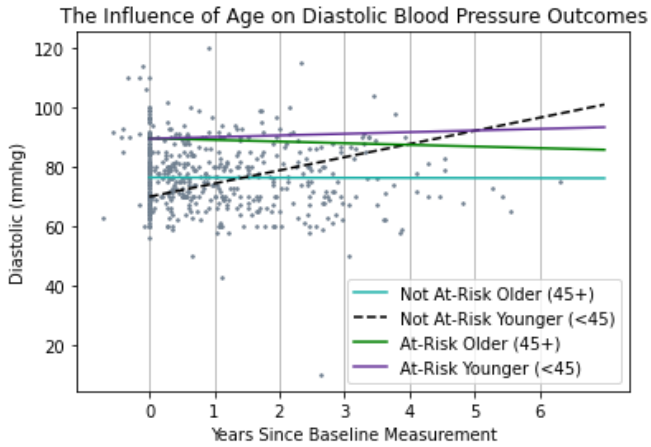
nN = 78, β = O:4.904, I: -3.175

nR = 68, β = RO:*19.168**, RI: -10.866**

Age

*E: 65+, M: 36-64 years, Y: 18-35 years/ excl. Diastolic blood pressure: O: 45+, Y: <45

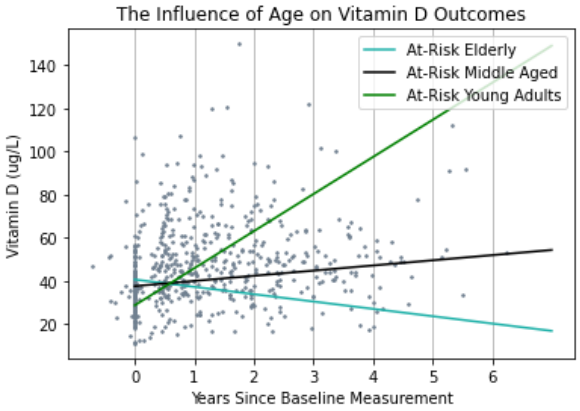
Diastolic Blood pressure (>80/ 50+ >90mmgh)



nN = 136, β = O: -0.994, *Y:4.434**

nR= 39, β = RO: -0.553 RY:0.553

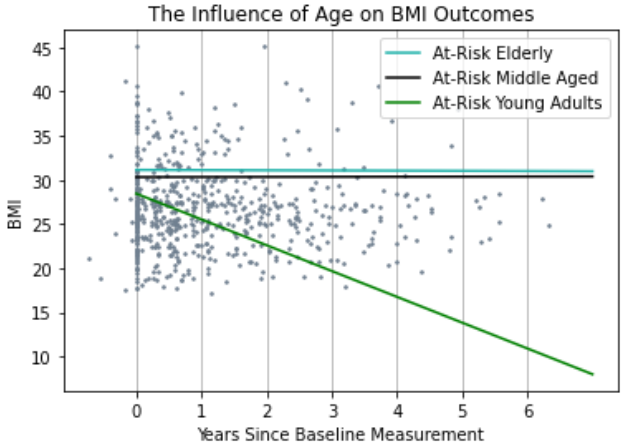
Vitamin D (<40 ug/L)



nR = 86, β = RE: -3.399, RM: 2.39

RY: 17.181

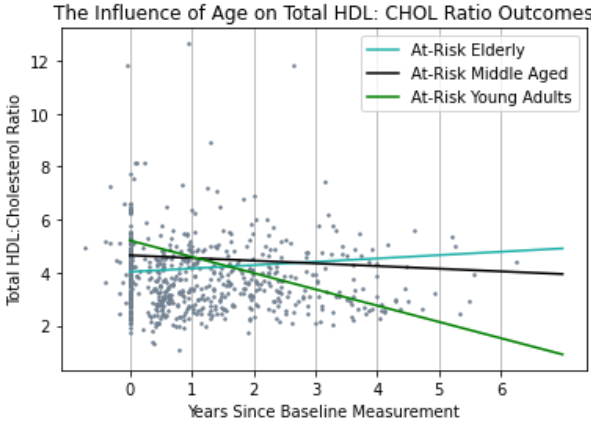
BMI (F: >28/F50:>30/M: >25/M50: >28)



nR = 63, β = RE: -0.022, RM: 0.011

RY: -2.924

Total HDL: Cholesterol Ratio (>3.5)



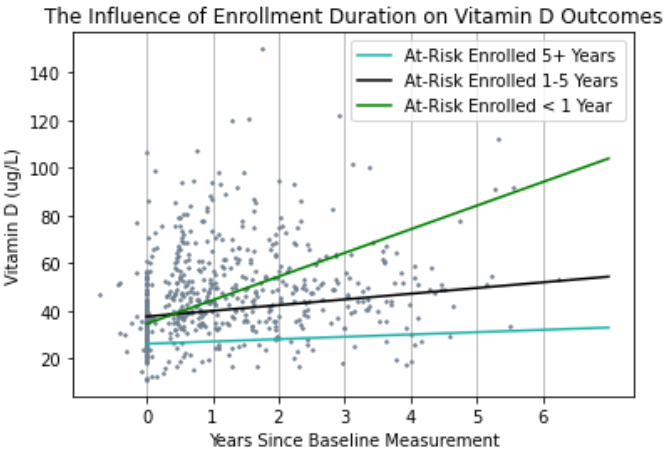
nR = 110, β = RE:0.126, RM: -0.101

RY: -0.614

Enrollment Duration

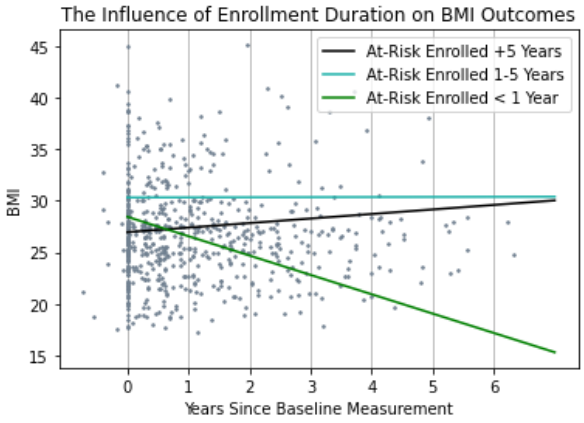
*L: 5+ years, M: 1-5 years, S: <1 year

Vitamin D (<40 ug/L)



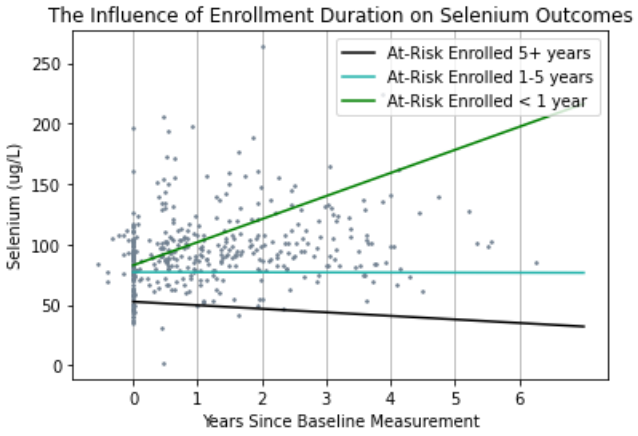
nR = 86, β = RL: 0.974, RM: 2.39
RS: 9.905

BMI (F: >28/F50:>30/M: >25/M50: >28)



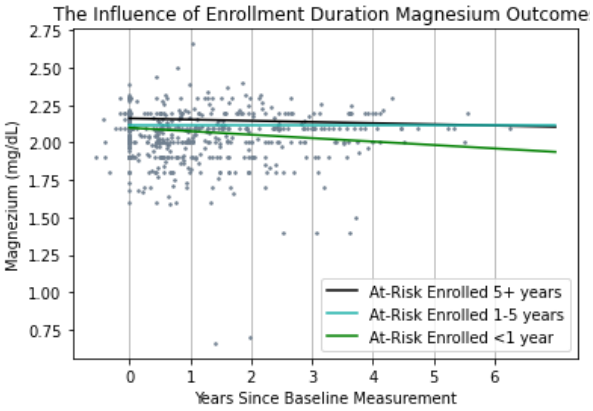
nR = 63, β = RL: 0.44, RM: 0.011
RS: -1.879

Selenium (<80 ug/L)



nR = 74, β = RL: -2.934 RM: -0.075
RS: 19.1

Magnesium (>2 mg/dL)



nR = 128, β = RL: -0.008 RM: 0
RS: -0.023

Figure 2. Visualizations of the most significant & Interesting Outcome Patterns

Number of consultees: n, at-risk consultees: R, not at-risk consultees: N. Dashed lines represent significant trends and blue β indicates significant gradients. Significant β values are identified by * under 5% significance (α= 0.05) and ** significance under 10% (α= 0.1).

7.1.2 *Sex*

Males had more outcomes with p-values<0.05 (9/14 excl. testosterone) when compared to females (1/14: BMI, p-values<0.05), and only worsened for body fat% and wSMI (p-values>0.05). Males improved at a more rapid rate for total HDL: cholesterol ratio and triglyceride, whereas females did

better in hs-CRP, magnesium and BMI. At-risk females performed worse in 6/15 outcomes: HbA1c, homocysteine, selenium, vitamin B12, vitamin D and diastolic blood pressure (p-values>0.05).

7.1.3 Place of Residence

Living in Istanbul elicited negative impacts on biomarker outcomes; 11/15 worsened for those at-risk who live in Istanbul (p-values>0.05). This excludes homocysteine, magnesium and vitamin B12 which improved (p-values>0.05). Contrastingly, those at-risk not living in Istanbul improved in 14/15 biomarkers (9 p-values<0.05), whereby magnesium was the only one to worsen (p-values> 0.05). The not at-risk group followed the same pattern; however, differences were observed for hs-CRP, BMI, waist: height ratio and magnesium.

7.1.4 Age

At-risk young adults improved at a much faster rate in 7/15 outcomes (BMI, body fat%, total HDL: cholesterol ratio, hs-CRP, magnesium & vitamin D; P-values> & < 0.05) when compared to the other at-risk age groups. The at-risk middle age group performed better in triglyceride (p-values>0.05), whereas the at-risk elderly rapidly improved in vitamin B12 (p-values< & >0.05) and testosterone (p-values< & >0.05). Interestingly, the latter group performed worse in homocysteine (P-values>0.05) and selenium (P-values>0.05). No pattern could be identified for those not at-risk due to inconsistent results, however the not at-risk younger age group had worse outcomes for diastolic blood pressure (P-values<0.05). No consultees from the younger age group were at risk for HbA1c, magnesium and selenium.

7.1.5 Enrolment Duration

Those at-risk enrolled for <1 year saw faster improvements in 14/15 outcomes (excl. triglyceride) and had p-values of< & >0.05. Interestingly, those at-risk, enrolled for 5+ years had much worse outcomes for total testosterone and hs-CRP (p-values< & >0.05). Not at-risk consultees had 6/15 relatively stable outcomes: HbA1c, total HDL: cholesterol ratio, HS-CRP, magnesium, vitamin D and waist: height ratio (p-values< & >0.05).

7.2 *An In-depth Analysis of Consultees Gentest Experience:* The Triangulation of Qualitative & Quantitative Data

Respondents (n=43) included a similar number of males (n=22 [51%]) and females (n= 21 [48%]), who communicated positive Gentest experiences, in parallel to the semi-structured interviews. The pilot study was combined with the respondents to create a sample of 51 consultees. Less than 30% of the sample indicated that Gentest would benefit from minor improvements in their report interpretation

for each of the specified items, **figure 3**. Only 1.9% (n=1) wanted Gentest to fully develop their ability to clarify concerns during the session.

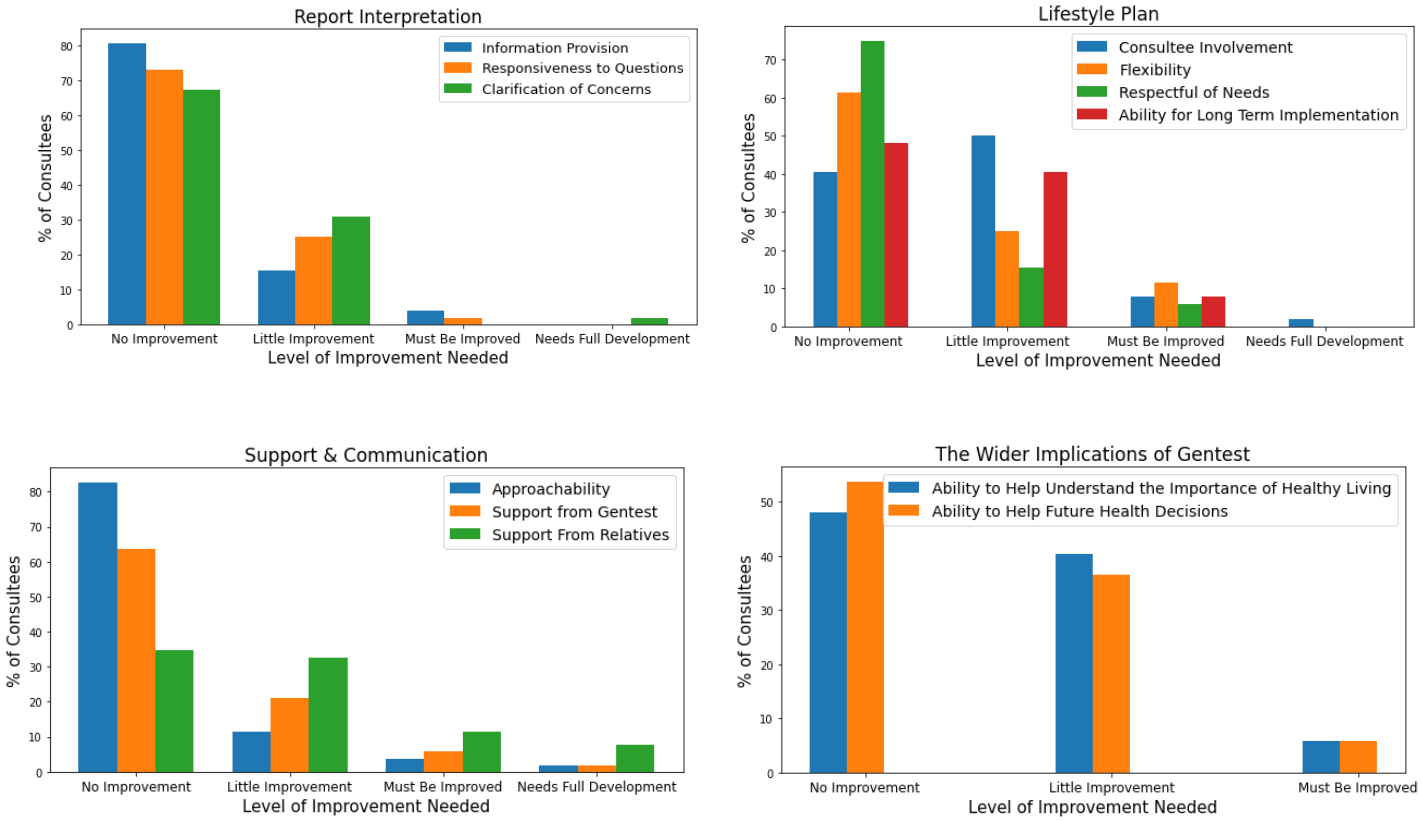


Figure 3. The Quantitative Survey Results Categorized by Each of Gentest's Operations and Their Wider Influences

The major themes identified from the semi-structured interviews support these outcomes as they relate to Gentest's 'great explanation of health risks' and consultee concerns towards them being 'overwhelming'. This may represent the different desires for program improvement within this stage of Gentest's operations.

Great explanation of Health Risks

"(...) but in a gentle way you know it's uh, so you do understand the seriousness of what's going on [health risk interpretation]"

"Like he has perfectly designed charts and diagrams that he explains everything over [health risks]"

Overwhelming

"(…) If you see [in the report], you know two red triangles…oh my God, am I gonna die?"

Survey data (**figure 2**.) indicated satisfaction with the respectability of needs (75%) in relation to lifestyle plan development. An increased involvement in the creation of regimens (50%) and improvements in long-term implementation (52%) were desired. Less than 11.5% wanted more elaborate developments for each item analyzed. Furthermore, the rates of regimen implementation were assessed; **figure 4**., whereby tobacco (35%) and alcohol (19%) recommendations had the lowest rates of adherence. Interestingly, exercise plans received the lowest proportion of 'always implementing' (11.3%) but relatively high ratings for both 'partially' and 'mostly' implementing (39.6% each). Moreover, nutritional supplements (39.6%), medication (34%) and probiotic (28.3%) regimens received the most ratings for 'always implementing'. Qualitative data fortified these results as positive themes regarding their realistic and flexible nature were illustrated.

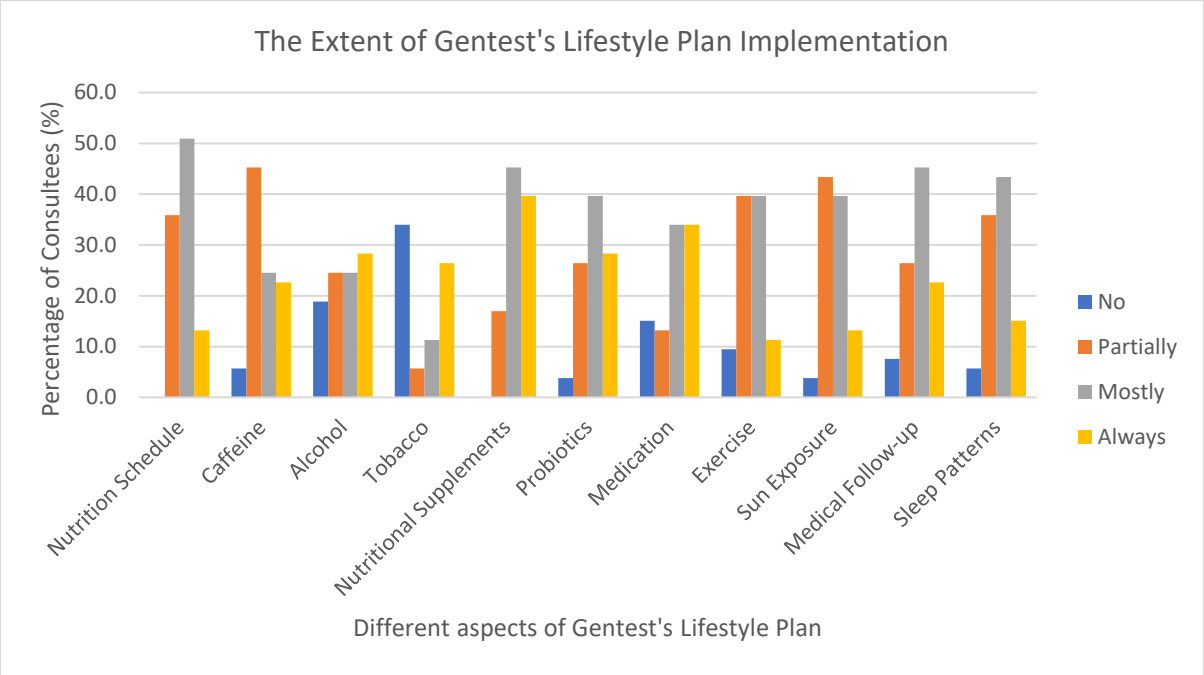


Figure 4. Quantitative Survey Results for the Degree of Lifestyle Plan Implementation

Contrastingly, concerns were raised regarding the quantity and costs of supplements and medication. This may however support the quantitative results of long term-implementation, **figure 3**. Additional qualitative inferences related to exercise regimens, which were described as 'easy to follow' but depended on the consultee, their subsequent Gentest package and resultant priorities. Indications towards the need for a more personalized approach towards the frequency and intensity of recommended exercise were also noted.

Diet

"I really like that uh, diet is on four months. It was like they were in several steps."

"I tell her [Gentest's dietician] what's is difficult for me, she tried to find a solution to go around it. That's what I really like about that [Nutrition Schedule]."

Supplements & Medication

"(…) recommended [Gentest] that I should use a number of vitamins, but then I discussed this with my physician and when we look at my diet, I think I'm already getting all those vitamins anyway, and I didn't need supplements for that."

"I mean I'm 38 years old and I'm using that much medicine that's I really don't like, but I think it's necessary at that point (…)"

Exercise

"The ones that advised me were beautiful [exercise plans] but I think I do more than that one"

"And he [Gentest's physician] told me you have to do a 10-minute cardio before you work out (…)"

In relation to support and communication, Gentest staff had the majority vote for their great approachability (82.7%) and support system (63.5%; **figure 3**.). However, 7.7% of consultees wanted major improvements in the support received from relatives. Qualitative themes reinforced these results as Gentest's effective communication and follow-up techniques were described.

"They [Gentest] reply back to me straight away or maybe the next day (…)"

"I think if there wasn't any more rigorous follow up it, whatever it will be my own fault, not theirs"

Improved knowledge on health decisions were categorized within the survey (**figure 3**, wider implications of Gentest); however, a similar number of respondents indicated their satisfaction and desire for minor improvements across both knowledge domains. This is interesting as interviewees expressed their gratitude in relation to increased knowledge, and highlighted Gentest as their main source of health information. Additional outcomes related to weight loss and overall feeling better.

Wider Implications of Gentest

"I get all the answers I need [from Gentest] so I don't look anywhere"

"So, the knowledge is there, the attitude is there, so I have to practice now."

"I lost 12 kilos in five months, which is without any exercise mind you (…)"

In general, positive experiences in relation to the staff, Gentest's professionalism and program appreciation were portrayed.

Professionalism & Staff

"I have been treated extremely nicely. People are very professional"

"(...) you know that he [Gentest's head physician] knows his stuff. That is important, and that's what I get (…)"

Inclusivity & Personalization

"So, in this program [Gentest] It is just like you have an ID. You have a personality"

"I feel much more comfortable and like I'm being taken care of"

Program Appreciation

"Yeah, there's a significant difference between before Gentest and after"

"(…) it is [Gentest] what I need"

Despite these encouraging outcomes, several recommendations regarding Gentest's service delivery were discussed. Interesting suggestions included the need for more personal comparisons during the report interpretation, connection links to family physicians, an overview of the regimen timelines and an online review section for consultees to share their experiences. Supporting Quotes can be found in **Appendix E.**

7.3 Impact: Changes in Quality-of-Life

A total of 37 survey respondents, including those from the pilot study provided data comparable to their respective QoL ratings acquired during their initial lifestyle assessments. Each QoL item met the assumptions of the paired t-test apart from 'often feel general pain', enjoyment of life', 'often depressed', 'private life' and 'general life' which did not follow normal distribution and thus analysed using the non-parametric Wilcoxon signed rank test. The results are presented in **table 4.,** and enables comparisons between consultees who had their report interpretation before (Group 1; n= 11, 20% of respondents, mean follow-up period = 40.5 months, SD ± 2.8) and after June 2020 (Group 2; n=26, 70% of respondents, mean follow-up period = 21.0 months, SD ± 5.4).

Table 4. Statistical Analysis of Changes in Quality-of-Life

WHOQOL categorization	Item	Group	Mean	df	Paired T-test/ Wilcoxon Signed Rank Test	p-value (Two-tailed)	95% CI	Cohen's D
Physical Health	Ability to Fall Asleep	1	8.0	10	-1.30	0.22	-0.98-0.26	0.39
		2	7.2	23	0.08	0.93	-0.98- 1.06	0.019
	Quality of Sleep	1	7.3	10	1.85	0.09	-0.2- 2.2	0.69
		2	6.9	22	0.45	0.66	-0.63 - 0.97	0.09
	Often Feel Under Stress	1	5.2	10	-0.43	0.67	-2.79- 1.88	0.18
		2	5.9	22	-0.10	0.33	-2.01 - 0.71	0.27
	Often Feel General Pain	1	4.1	-	W: 18	0.55	-	-
		2	4.0	-	W: 112.5	0.65	-	-
	Enjoyment of life	1	8.2	-	W:35	0.07*	-	-
		2	7.5	-	W:103	0.38	-	-
	Working Life	1	7.5	9	-1.62	0.14	-1.2 - 0.2	0.31
		2	7.1	19	0.78	0.44	-0.5 - 1.1	0.16
Psychological health	Motivation to Work	1	8.0	10	-1.30	0.22	-0.98 - 0.26	0.39
		2	7.7	22	0.25	0.79	-0.61 - 0.79	0.05
	Ability to Concentrate	1	7.3	10	1.85	0.09	-0.2 - 2.2	0.69
		2	7.1	23	1.66	0.11	-0.14 - 1.31	0.33
	Often Depressed	1	3.7	-	W: 26	0.36	-	-
		2	4.2	-	W:131.5	0.16	-	-
	Often Anxious	1	4.0	10	-0.919	0.37	-1.87 - 0.78	0.25
		2	5.4	23	-0.69	0.49	-1.66 - 0.82	0.17
Social/ Environmental Health	Sexual Life	1	6.4	9	-0.52	0.63	1.61 - 1.01	0.11
		2	5.3	16	-2.55	0.02*	1.61 - 1.01	0.55
	Private Life	1	7.9	-	W: 20	0.42	-	-
		2	7.5	-	W:99.5	0.27	-	-
General Life		1	8.2	-	W: 12	0.13	-	-
		2	8.0	-	W:88	0.62	-	-

*Indicates 5% significance (α= 0.05), W represents items analysed using the Wilcoxon signed rank test. Each item has been categorised based upon the subgroups identified by the WHOQOL group (1998). Group 1 refers to respondents who had their report interpretation prior June 2020 and group 2 are those and after/ including June 2020.

Positive t-values were present across both time periods for 'quality of sleep' and 'ability to concentrate', which continued in group 2 with 'ability to fall asleep', working life' and 'motivation to work' (p-values>0.05). Group (2) 'sexual life' and group (1) 'enjoyment of life' were the only items with p-values<0.05. Group 1 had the largest Cohen's D values for 'ability to concentrate' (0.69) and 'enjoyment of life' (0.69), whereby 'sexual life' (0.55) had the highest in group 2. Upon further analysis the mean change in rating for 'sexual life' was 1.96 and when divided between the categories (1): -0.46 & (2): -1.11

Open-ended questions enabled consultees to comment on their QoL. Thirteen responses were recorded whereby the majority (n=6) mentioned the impact of COVID-19 negatively influencing different domains of one's lifestyle. Such instances included 'reduced movement' and 'limited private

life'. Positive aspects of Gentest were also provided whereby consultees felt 'more conscious' and 'physically feeling good', **Appendix F**.

8 Discussion

Gentest's effectiveness and program quality are evaluated through the exploration of biological outcome patterns, personal consultee experiences and changes in quality-of-life.

8.1 Biological Outcome Patterns: A Biomarker Analysis

Throughout this analysis biological outcome patterns have been identified based on the influence of contextual/ explanatory factors on Gentest's operations as illustrated by the conceptual model.

8.1.1 *Risk Status:* A Comparison to Garton's (2020) Findings

Answering question, A, **table 1.,** the at-risk group experienced more rapid improvements in the majority of the biomarkers (14/15); of which eight were significant, when compared to those not at-risk and is reciprocated by Garton's (2020) findings. Stakeholder discussions highlighted the different priorities between such groups whereby those at-risk focus on improving whereas those not-at risk focus on maintaining biomarker levels. This is observed in numerous cases and portrayed by triglyceride and HbA1c in **figure 2**. Additionally, the results reflect Gentest's priorities in preventing sudden illnesses (e.g., stroke) as they closely monitor HbA1c, total HDL: cholesterol ratio, homocysteine, vitamin B12 and vitamin D outcomes, all of which improved at a more rapid rate. Contradicting results between studies were identified for hs-CRP and may be attributed to Garton's small sample size and low statistical power (Cohen, 1992; Garton 2020). Finally, body fat % has significantly worse outcomes for those not-at risk (β>1). Waist: height ratio and BMI outcomes reflected this as they worsened but at a lower rate. This may suggest a low adherence to respective regimens for those not at-risk, highlighting the need for further research to identify possible undermining factors.

8.1.2 *Sex:* A Comparison to Garton's (2020) Findings

Males had more statistically significant results and improved in more outcomes when compared to females which is consistent with Garton's (2020) findings. Gender differences in Gentest package choice may explain these results as men usually opt for extensive analysis and women choose the more basic packages. Consequently, women undergo less measurements which may be represented through smaller sample sizes and less significant results. Additionally, women's average age was 55.5 years which may infer their post-menopausal state as literature from Eastern Turkey suggests spontaneous menopause occurs around 47.4 years (SD ± 3.7) (Pirincci, 2016). The menopausal

fluctuations in hypothalamic and pituitary hormones may thus provide further explanations for the lack in significant results as these influence numerous processes across the body (Dalal, & Agarwal, 2015).

Interestingly, both studies highlighted better BMI outcomes for at-risk women. Possible explanations may relate to their higher starting BMI which is suggested to promote rapid weight loss (Barte et al., 2014). However, Garton (2020) hypothesised that this may be due to their unilateral focus on weight loss, but a qualitative case study indicated that weight loss was ranked the 5th when females were asked for their motivation for coming to Gentest. The results of this study raise speculation towards these inferences and support Garton's initial hypothesis. When compared to body fat % and wSMI outcomes, minor differences were observed between males and females which were not statistically significant. Due to changes in Gentest's policy regarding biometrical impendence analysis (BIA) which took place in 2017, comparisons of body fat% and wSMI could not be conducted prior to this date. Therefore, small samples sizes were used which questioned the validity of their MER outputs (Faber, & Fonseca, 2014).

8.1.3 *Place of Residence:* Istanbul vs Other Areas

Living in Istanbul was associated with negative influences on biomarker trends for at-risk consultees which contrasts to significant improvements for those residing outside Istanbul. The high levels of stress experienced by Istanbul residents may cause them to deviate away from Gentest's recommendations, leading to worse outcomes (Park, & Lacocca, 2014). Additionally, Kara & Demirci (2010) identified that 61% of Istanbul residents do not participate in recreational activities due to constraints; including: a lack of time, financial issues, inadequate recreational areas and pollution. The resultant low levels of physical activity may offer suggestions for the rapid worsening of HbA1c, waist: height ratio and BMI. An additional hypothesis suggested by Gentest stakeholders may relate to higher levels of motivation amongst consultees who seek programs away from their usual place of residence. Whilst this is speculated, further research is warranted to establish valid claims and explore probable reasons for its emergence. It is important to acknowledge the small sample size of consultees living outside Istanbul (n=48) and the resultant influence on statistical power (<0.8) as this may impede the validity of results (Cohen, 1992).

8.1.4 Age

At-risk young adults (18-35 years) improved at a much faster rate for the majority of outcomes when compared to the older age groups. These results were partially significant whereby each value had only one p-value<0.05 (either baseline or trajectory). Such findings could represent the effect of age-

related declines in physical and mental capacity through the accumulation of cellular damage (WHO, 2018b). This predisposes individuals to a greater incidence of developing disease and therefore confounds the studied biomarkers. This was acknowledged during the analysis and efforts were directed to overcome this; however, small sample sizes resulted in invalid results, meriting further data collection. Despite the inconsistencies observed for those not at-risk, the younger age group performed significantly worse in diastolic blood pressure. This could be a result of two factors: (a) Gentest's prescription of antihypertensives to those above 40 years which emphasizes their observed controlled blood pressure or (b) the decrease in blood pressure with age due to the reduced elasticity of blood vessel walls (Mancia, & Grassi, 2002; Pinto, 2007).

8.1.5 Enrolment Duration

Consultees enrolled for less than one year improved at a much more rapid rate compared those enrolled for longer periods. The 'adherence challenge' may be used to explain such phenomenon as this suggests that the initial adherence to lifestyle interventions is usually encompassed by encouraging responses (Middleton et al., 2013). This may relate to ascertaining progress through follow-up, high motivation and compliance. However, this is frequently followed by disappointing results due to diminished devotion, and possibly include gains in self-confidence, high costs, sociocultural and psychological influences (Meichenbaum, & Turk, 1987; Middleton et al., 2013). As the longest enrolment was approximately seven years, it is important to consider the confounding effect of age, and must be accounted for in future research (WHO, 2018b).

8.2 *Consultees Gentest Experience:* The Triangulation of Qualitative & Quantitative Data

The conceptual model identifies consultee satisfaction as a program outcome due to its influence on various behaviours, including: adherence to recommendations, appointment consistency and uptake of professional advice (Akin & Erdogan, 2007; Bond & Thomas, 1992). The results indicate good experiences relating to items of the report interpretation and are supported by qualitative themes such as the good portrayal of health risks; however, some respondents perceived this to be 'overwhelming'. This may be represented by the highest level of minor improvement ratings observed for consultees wanting Gentest to advance their ability to clarify health concerns. Literature suggests this phenomenon is related to patient perceptions of how they are treated, and may hinder regimen adherence and treatment decisions (Moore et al., 2004). Therefore, attention should be paid to these domains to ensure the best possible patient-physician relationships to promote healthy behaviors.

Similar findings were obtained when analyzing consultee involvement and implementation of lifestyle plans; however, a higher proportion of improvement ratings were identified. Gentest emphasizes their

participatory nature to prevent information asymmetry commonly observed throughout healthcare systems (D'Cruz & Kini, 2007). Despite this, a desire for increased involvement in regimen creation was highlighted and may be attributed towards the cultural context whereby patient-physician relationships are usually hierarchical and encompassed with great respect (Dagdeviren, & Akturk, 2004). This is observed in Gentest's system dynamics and enhanced by the directors' political involvements. This may lead to a wariness in disrupting social norms and offer explanations for such occurrences. Studies have simultaneously observed that patient centred care contributes towards improved health outcomes, attributing them with an optimal investment value (Stuckey et al., 2015). Gentest acknowledges this and efforts continue to provide consultees with more control over their health choices, represented through the overall appreciation and gratitude of program flexibility.

Concerns towards the quantity and costs of supplements and medication plans were portrayed. Contrastingly, quantitative inferences indicate otherwise, as these regimens had the highest implementation rates (**figure 3.**). An explanation may relate to the minimal effort required to follow these plans; however, apprehensions towards their cost and access may arise as Gentest prescribes supplements not available in Turkey due to their greater health benefits. Furthermore, concerns towards the quantity prescribed may stem from a lack of knowledge and rationality surrounding medication use (Akici, et al., 2017; Basaran & Akici, 2012). These inferences may provide possible explanations towards the varying perceptions towards medication use. However, such findings may not be representable due to the small sample sizes which hinders their external validity.

Further results indicate that the majority of interviewees (n=3) stated they were already engaging in exercise. Interestingly, the respective plan received the lowest 'always' but high proportions of partial' and 'mostly' implementation rates, **figure 4.** Themes relating to their 'vagueness' and 'limited personalization' could justify such instances, indicating that consultees were unable to accurately follow such plans. The aforementioned barriers to recreational activity engagement in Istanbul could provide additional support to such inferences (Kara & Demirci, 2010). Despite the small sample sizes, these findings may promote program adaptations to increase regimen implementation, promoting positive results.

Gentest's support and communication methods received encouraging feedback which may be accredited by the flexibility and efficiency provided by WhatsApp, their primary communication platform. Literature identifies such instances as telemedicine is increasingly used between medical professionals and the public (Giordano et al., 2017). However, the necessary precautions for data

protection and correct ethical conduct must be overseen to facilitate the safety of such techniques (Giordano et al., 2017). Finally, the overall impressions and recommendations for service improvement were explored. Positive inferences related to the staff's professional, abundant knowledge and the inclusivity consultees felt within the whole program. The notion that increased knowledge and changing health behaviours lead to positive biological outcomes was identified throughout the data and is further captured by the conceptual model. This may enhance the validity of the study as such processes are iterated throughout.

8.3 Impact: Changes in Quality-of-Life

The conceptual model recognises the interplay between contextual factors, biological and behavioural outcomes to produce changes in one's QoL (Paterson et al., 2009). Consultees perceived their sexual life to worsen following their report interpretation after June 2020 whereby a statistically significant decrease of -0.46, $t(16) = 0.11$, $p < 0.05$, was observed, **table 4.** This contradicts Gentest's aim in positively influencing QoL; however, the effect of the COVID-19 pandemic on such results cannot be disregarded and is emphasised through the conceptual model. Recent literature infers that sexual activity reduced by a frequency of 4.4 times during the pandemic and may have arisen due to governmental restrictions and heightened levels of depression (Delcea et al., 2021; Özdin & Bayrak Özdin, 2020). The qualitative responses from the survey further supports this hypothesis as the limiting effect one one's private life and negative influences on their QoL (**Appendix F**) were portrayed in response to the pandemic. Despite these inferences, sexual activity is a phenomenon composed of different dimensions, therefore inherent difficulties are faced during its evaluation (Delcea et al., 2021).

The median rating of 'enjoyment of life' significantly improved; $W=35$, $p < 0.05$ (**table 4)**, for those who had their report interpretation before June 2020 and may represent Gentest's positive impacts. This is supported by the qualitative responses of the survey (**Appendix F**), whereby consultees expressed changes in an array of QoL items under the physical health domain; including 'enjoyment of life', defined by the WHOQOL group (1988). However, in relation to the conceptual model, contextual factors may impede this notion. Irrespectively, positive changes were observed despite the COVID-19 restrictions which began in March 2020 and enhances Gentest's initiatives (WHO, 2020). Small sample sizes may have resulted in the lack of statistically significant results and questions the internal and external validity of the study (Faber, & Fonseca, 2014). Data categorization was performed to strengthen such effects by decreasing the opportunity for additional external factors and response shifts to confound QoL associations (Alison et al., 1997; Blome, & Augustin, 2015). These results

provide Gentest with incentives to continue to collect comparable QoL data to explore their wider program impacts.

8.4 Strengths and Limitations

The use of MER models to evaluate biological outcomes enabled the recognition of individual differences in biomarker trends, acting to strengthen the validity of the identified patterns (Garcia & Marder, 2017). However, due to data standardization limitations and the low consultee inflow in 2020, Garton's (2020) sample size was merely doubled. This raises concerns towards sufficient statistical power of the MERs, whereby multiple models had values lower than the standard acceptance level of 0.8, decreasing their internal validity (Cohen, 1998). Moreover, the confounding effect of age may be represented in each of the models and thus must be accounted for in future research. Furthermore, Gentest's adapts regimens according to different priorities to promote changes in risk status. This was unaccounted for due to limited data availability; therefore, the biomarker trends may become invalid after a certain period of time. Future research may counteract this by incorporating the average at-risk time period and monitoring those not-at-risk to see if their risk status changes.

A limitation of the quantitative survey results, relate to non-response bias as only half the sample responded, despite the reminder messages, and therefore may be non-representative of all consultees due to a disproportionation of traits (Davern, 2013). To prevent this occurrence in the interviews, consultees who had good relations with Gentest were selected to enhance response rates; however, their good relations may have overemphasized the degree of positive outcomes. Despite this, the results provided insights into the concepts studied and can still be used to inform policy as degree of data saturation was obtained, promoting the internal validity irrespective of the small sample sizes (Saunders et al., 2018). Moreover, the rating scales may have been perceived differently; therefore, to minimize such effect, the same scales were used for QoL comparisons (Khadka et al., 2012). To combat these discrepancies for Gentest experience, semi-structured interviews were used to validate quantitative inferences as they are regarded as powerful tools in health service research to understand the beliefs and experiences of individuals (DeJonckheere, & Vaughn, 2019).

Finally, the widespread influences imposed by the COVID-19 pandemic on each dimension evaluated must be acknowledged. This study has attempted to incorporate such influences into its design, however, small sample sizes prevented valid conclusions from being drawn. This holds great promise for future research; especially for consultee experience, as comparisons between the adjusted and normal programs can be made.

9 Conclusion

This study further developed, expanded and piloted an outcome measurement framework to evaluate the 7K Medicine Model used for Gentest practice. By superimposing the realist evaluation onto the logical framework, the Gentest process was mapped to recognize the influence of individual and contextual factors on each operation. A mixed method approach using a concurrent embedded design was adopted to evaluate Gentest's effectiveness in relation to biological outcome patterns, consultee experience and changes in QoL. The results have ascertained Gentest's effectiveness in improving biological outcomes for at-risk consultees, emphasizing their directive in NCD prevention. Whilst exploring the influence of additional contextual factors, at-risk males, younger age groups and those enrolled for less than one year had better outcomes. Unexpectantly, consultees who lived in Istanbul had worse outcomes which raises speculation of the influence of demographical factors on outcome achievement. Comparing these results to Garton's (2020) study, the increased number of statistically significant results emphasizes the success of such investigation.

Further promising results were identified in relation to consultees' experience whereby Gentest's professionalism, flexibility and staff approachability were appraised, eliciting positive outcomes in relation to increased knowledge, weight loss and overall feeling better. Data triangulation identified program areas in need of improvement, including the desire for better health concern clarification and an increased involvement in regimen development with more detailed and personalized exercise plans. A focus on improving these aspects may enhance patient-physician relationships, prevent information asymmetry and increase patient centered care, resulting in improved regimen adherence and thus positive outcomes. To assess Gentest's wider impacts, changes in QoL were analyzed. A significant decrease in sexual life but significant improvements in enjoyment of life were observed. However, due to the lack of significant results in other QoL domains, low number of comparable results and interplay of confounding factors, valid claims cannot be stated.

This analysis has enabled Gentest to validate their priorities and ascertain their directive in reducing NCD risks. Investigating consultee experiences will enable Gentest to implement program adaptations to enhance program adherence and thus its success. Despite these inferences, the use of small sample sizes and the influence of the COVID-19 pandemic throughout each dimension studied questions the validity of such results. This emphasizes the need for further research, whereby larger sample sizes may be used to investigate the influence of additional contextual factors on biological outcomes, whilst accounting for the confounding effect of age. Examples include those which did not meet the inclusion criteria due to small sample sizes. Moreover, the survey may be further developed and used

to routinely collect data, expanding upon the dataset. This will enable the continuous monitoring and evaluation of the program to increase its quality and effectiveness and promote policy changes such as the closer monitoring of highlighted groups or the implementation techniques to maintain motivation levels. Such adjustments may act to effectively increase regimen adherence to promote positive program outcomes and impacts. This study has initiated a comprehensive evaluation for Gentest practice to enable the effective implementation of their 7K Medicine Model into primary healthcare systems to tackle the global surge in NCDs.

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11 Appendices

11.1 *Appendix* A: At-Risk Thresholds

The At-risk Thresholds Used for The Biomarker Analysis (Garton, 2020).

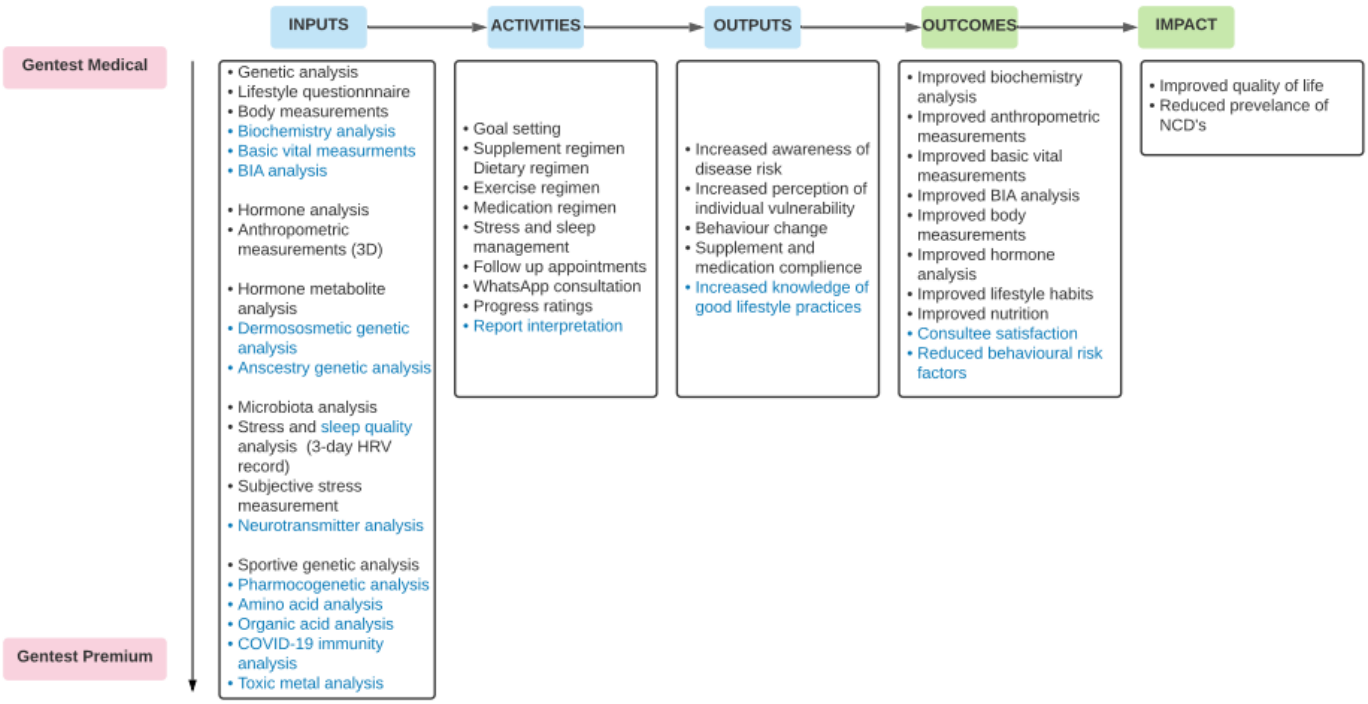
Outcome	Gentest Risk Threshold	Industry Standard Threshold	Alignment
HbA1c %	> 6	> 5.7 – 6.438	Similar
Triglyceride (mg/dL)	>150	> 150.39	Similar
Homocysteine (umol/L)	>8	>15.40	Similar
Magnesium (mg/dL)	>2	>2.341	Similar
Selenium (ug/L)	<80	<70	Similar
Vitamin B12 (ng/L)	<400	< 200 / 65+: < 300.43	Much Stricter
Vitamin D (ug/L)	<40	<30.44	Stricter
HS-CRP (mg/dL)	>2	>2.45	Similar
Total HDL: Cholesterol Ratio	>3.5	>5.46	Stricter
BMI	F: > 28 / F50: > 30 M: > 25 / M50: > 28	> 24.947	Less strict; adjusted for Turkish population specifically

Body Fat %	M: > 20%F: > 24%	M: > 23% W: > 28%48	Stricter
Waist: Height	>0.5	> 0,5549	Similar
Diastolic Blood Pressure (mmhg)	>80 50+>90	> 130/80.50	Similar
Total Testosterone (ng/dL)	M <300	<300 ng/dL	Same
Weighted Skeletal Muscle Index (%)	M < 34 / F < 25	M < 37.4 / F < 33.6	Stricter

**New additions include total testosterone and weighted skeletal muscle index. Industry standard total testosterone obtained from Elagizi, Köhler, and Lavie (2018) & weighted skeletal muscle index obtained from Bahat et al. (2019).*

11.2 Appendix B: Gentest's Operations Mapped onto the Log-frame

Gentest Operations Mapped onto the Log-frame (Garton, 2020)



*** Blue indicates adaptations to Garton's (2020) model.*

11.3 Appendix C: Comparative MER Outputs

The Linear Mixed Effect Regression Model Outputs: Answering Questions A, B & C (**Table 1.**)

Outcomes		**Explanatory variables**								
		COVID-19 **P: prior I: Including*	**Smoking** **S: smoking*	**Pre-existing MD Conditions** **MC: MD conditions*	**Sex** **M: Male F: Female*	**Place of residence** **O: outside Istanbul I: Istanbul*	**Country of Residence** **A: Abroad T: Turkey*	**Shared Gentest household** **F: Gentest Household*	**Age** **Elderly (65+) M: Middle Aged (36-64 years) Y: Young Adults (18-35 years)*	**Enrolment Duration** **L: Longer (5+ years) M: Middle (1-5 years) S: Shorter (<1 year)*
HbA1c (%)	n	P:152 I: 134	N:107 R:27	N: 138 R:20	N:107 R: 27	N: 107 R: 27	N: 107 R: singular Matrix	N: 107 R: 27	N: 134 R: 27	N: 134 R:27
	Baseline	PN:5.423* PR:6.111* IN: 5.387* IR:6.124	N: 5.413* S:5.297 RN: 6.180* RS:5.951	N: 5.326* MC:5.498* RN:6.097* RMC:6.178	M: 5.415* F: 5.35 RM:6.132* RF:6.108	O:5.391* I:5.391 RO:6.252* RI:6.108	A:5.422* T:5.384 RA: singular Matrix RT: singular Matrix	N:5.392* F:5.372 RN:6.208* RF:5.989	E:5.603* M:5.35* Y:5.206 RE:6.14 RM:5.126 RY: Singular Matrix	L: 5.471 M:5.35 S:5.34 RL: Singular Matrix RM:6.126 RS:6.187
	β/Coeff.	PN: -0.055* PR:0.048 IN: -0.005* IR: -0.071*	N: -0.004 S:0.005 RN: -0.086 * RS:0.024	N: -0.016 MC: -0.027 RN: -0.284 * RMC:0.081**	M: -0.021 F:0.041 RM: -0.042 RF:0.065	O: -0.046 I:0.059 RO: -0.229* RI:0.162	A: -0.053 T:0.052 RA: singular Matrix RT: singular Matrix	N: -0.015 F:0.037* RN: -0.122* RF:0.109**	E: -0.071** M:0.038 Y:0.186 RE:0.014 RM: -0.014 RY: Singular Matrix	L:0.036 M:0.038 S:0.105 RL: Singular Matrix RM: -0.014 RS: -0.35
Total HDL: Cholesterol Ratio	n	P: 151 I:178	N: 65 R:107	N:82 R:75	N: 65 R: 107	N: 57 R:100	N:48 R:84	N: 49 R:84	N: 68 R:110	N: 68 R: 110
	Baseline	PN:3.196* PR:4.658* IN:2.746* IR:4.517*	N:2.753* S:2.809 RN:4.383* RS: 4.981*	N:3.125* MC:3.171 RN:4.8*45 RMC:4.599	M:2.882* F:2.695 RM:4.675* RF:4.237*	O:2.777* I:2.783 RO:4.325* RI:4.617	A:2.854* T:2.774 RA:3.602* RT:4.553**	N:2.808* F:2.638 RN:4.599* RF: 4.25	E:2.69 M:2.793 Y:2.749 RE:4.031* RM:4.653* RY:5.213	L:2.978 M:2.793 S:2.831 RL:4.726 RM:4.653* RS:4.643
	β/Coeff.	N: -0.072 R: -0.001 IN:0.05 IR: -0.238*	N:0.064 S: -0.41 RN: -0.164* RS: -0.158	N: -0.081 MC:0.013 RN: -0.082 RMC: -0.055	M:0.104* F: -0.107** RM: -0.2* RF: -0.02	O: -0.058 I:0.103 RO: -0.338* RI:0.178	A:0.006 T: -0.009 RA: -0.000 RT:0.000	N: -0.004 F:0.010 RN: -0.16* RF:0.05	E: -0.08 M: -0.038 Y:0.118 RE:0.126 RM: -0.101 RY: -0.614	L:0.054 M: -0.038 S: -0.513 RL:0.051 RM: -0.101 RS: -1.654*
	n	P: 154 I:182	N: 125 R:53	N: 131 R: 30	N: 119 R:51	N: 114 R:49	N:97 R: 41	N:98 R:41	N:97 R:41	N:131 R: 53
	Baseline	PN:105.67* PR:218.479*	N:93.07* S:92.175	N:98.155* MC:110.773	M:95.588* F:90.221	O:88.066* I:95.448	A:95.127* T:93.174	N:95.308* F:83.193	E:87.16 M:94.86	L:87.889 M:94.332

Triglyceride (mg/dL)		IN:92.667* IR:200.643*	RN:190.218* RS:221.695**	RN:230.164 RMC:208.264*	RM:210.731* RF:179.932	RO:232.746* RI:197.476	RA:218* RT:207.255	RN:206.167* RF:208.687	Y:104.681 RE:179.961** RM:219.09 RY:198.555	S:98.987 RL: Singular Matrix RM:206.544 RS:195.022
	β/Coeff.	PN: -3.217 PR: -8.908 IN: -1.034 IR: -25.281*	N: -0.826 S: -3.126 RN: -24.217* RS: -4.117	N: -4.77 MC:0.042 RN: -11.033 RMC: -7.955	M: -0.904 F:0.167 RM: -22.723* RF: -13.914	O:1.367 I: -2.551 RO: -48.624* RI: 28.317	A: -3.217 T:3.228 RA: -0.334 RT:0.267	N: -0.870 F:3.248 RN: -27.312* RF:7.478	E: -2.75 M:3.542 Y: -32.695 RE:20.340 RM: -21.618 RY:37.654	L:3.295 M:2.188 S: -17.392 RL: Singular Matrix RM: -20.882** RS:0.308
HS-CRP (mg/L)	n	P: 148 I:175	N:114 R:55	N:105 R:50	N:114 R:55	N:109 R:54	N:91 R:44	N:94 R:44	N:91 R:44	N:91 R:44
	Baseline	PN:0.896* PR:3.843* IN:0.75* IR:4.18*	N:0.868* S:0.3323 RN:4.491* RS:3.376	N:1.078* MC:0.851 RN:2.99* RMC:4.286	M: 0.916* F:0.451 RM:3.354* RF:5.098*	N:0.818* I:0.709 RN:6.034* RI:3.652*	A:0.978 T:0.717 RA:5.001* RT:4.188	N:0.901* F:0.528 RN:4.214* RF:4.895	E:0.655 M:0.773 Y:0.526* RE:3.052 RM:4.754 RY:3.153	L: N/A M:0.773 S:1.206 RL:0.484 RM:4.754 RY:4.811
	β/Coeff.	PN:0.218 PR:0.315 IN:0.504* R: -0.856*	N:0.495* S:0.272 RN: -0.445** RS:0.147	N: -0.005 MC:0.435* RN:0.518 RMC: -0.419	M:0.42* F:0.484* RM: -0.227* RF: -0.318	N:0.195 I:0.411** RN: -0.901 RI:0.622	A:0.189 T:0.426 RA:0 RT: -0.002	N:0.293 F:0.833* RN: -0.551* RF: -1.748*	E:0.352 M: -0.348 Y: -0.88 RE:0.448 RM: -0.335 RY: -1.255	L:0.115 M: -0.348 S: -0.552 RL:1.304* RM: -0.335 RY: -3.253
Homocysteine (umol/L)	n	P: 149 I:177	N:18 R:153	N:36 R:121	N:18 R:153	N:18 R:139	N:17 R:115	N:17 R:116	N:17 R:115	N: 17 R:115
	Baseline	PN:8.726* PR:11.756* IN:7.401* IR:11.31*	N:7.432* S:7.388 RN:11.456* RS:11.29	N:7.787* MC:8.903 RN:11.397* RMC:11.963	M:7.36* F:7.554 RM:12.127* RF:10.222*	O:7.595* I:7.336 RO:10.55* RI:11.69	A:8.109* T:7.597 RA:12.636* RT:11.422	N:7.67* F:6.733 RN:11.464* RF:11.349	E: Singular Matrix M:7.408 Y:7.5 RE:11.917 RM:11.342 RY:10.878	L:3.617 M:7.408 S: Singular Matrix RL:10.678 RM:11.342 RS:10.92*
	β/Coeff.	PN: -0.531 PR: -0.029 IN:0.008 IR: -0.396	N:0.019 S:0.042 RN: -0.578* RS:0.33	N: -0.384 MC:0.08 RN: -0.518* RMC:0.042	M:0.226 F: -0.48 RM: -0.634* RF:0.432	O:0.238 I: -0.251 RO: -0.167 RI: -0.317	A: -3.105 T:3.314 RA: -0.002 RT:0.002	N: -0.061 F:0.0602 RN: -0.13 RF: -0.649**	L: Singular Matrix M: -5.042 Y:5.042 RE:0.578 RM: -0.619 RY: -0.141	L:1.03 M: -5.042 S: Singular Matrix RL:0.231 RM: -0.619 RS: -3.044
Total Testosterone (ng/dL)	n	P:73 I:87	N:69 R:17	N:74 R:9	N/A	N:65 R:16	N:13 R: Singular Matrix	N:55 R:13	N:70 R:17	N:70 R:17
	Baseline	PN:453.863* PR:177.692* IN:500.08* IR:249.547*	N:498.336* S:516.914 RN:245.243* RS:361.028?	N:547.633* MC:446.767* RN:180.724* RMC:202.762	N/A	O:498.495* I:502.129 RO:211.730* RI:279.093	A:614.443* T:493.159	N:489.343* F:590.539 RN:226.713* RF:280.27	E:538.798 M:474.646 Y:584.773 RE:206.885 RM:285.05 RY: -98.136**?	L:461.911 M:474.646 S:629.628** RL:288.897** RM:285.05 RS:115.709**
	β/Coeff.	PN:21.863**	N:28.428*	N:3.535	N/A	O:37.562	A:78.475**	N:41.153*	E:27.72	L: -45.310*

		PR: -14.996 IN:26.398** IR: -5.791	S: 3.721 RN:23.101 RS: -26.140	MC:39.438 RN:149.679 RMC: -136.417		I: -12.133 RO:76.068 RI: -86.928	T: -47.935	F: -58.839 RN: -9.419 RF:17.838	M: -25.021 Y: -16.351 RE:160.489* RM: -90.141* RY:108.861**	M: -25.021 S:230.044 RL:146.194* RM: -90.141* RS:231.818
Magnesium (mg/dL)	n	P:144 I:173	N:43 R:125	N:39 R:116	N:43 R:125	N:38 R:116	N: Singular Matrix R:98	N:32 R:99	N:32 R:98	N:45 R:128
	Baseline	PN:1.916* PR:2.102* IN:1.868* IR:2.107*	N:1.866* S:1.916 RN:1.098* RS:2.143**	N:1.869* MC:1.94 RN:2.094* RMC:2.102	M:1.86* F:1.885 RM:2.12* RF:2.092	O:1.858* I:1.89 RO:2.093* RI:2.108	RA:2.079* RT:2.107	N:1.884* F:1.833 RN:2.104* RF:2.109	E:1.85 M:1.883 Y: Singular Matrix RE:2.097 RM:2.11 RY:2.079	L:1.923 M:1.892 S:1.818 RL:2.162 RM:2.112 RS: 2.099
	β/Coeff.	PN: -0.012 PR: -0.002 IN:0.002 IR: -0.009	N: -0.004 S: -0.002 RN: -0.005 RS: -0.013	N:0.013 MC: -0.05* RN: -0.008 RMC: -0.002	M:0.007 F: -0.017 RM: -0.003 RF: -0.22	O: -0.66** I:0.072** RO:0.011 RI: -0.023	RA:0.011 RT: -0*	N: -0.003 F:0.005 RN: -0.001 RF: -0.024	E: -0.023 M:0.025 Y: Singular Matrix RE: -0.009 RM:0.008 RY: -0.027	L:0.04 M: -0.006 S: -2.02 RL: -0.008 RM:0 RS: -0.023
Selenium (ug/L)	n	P: Failed to converge I:161	N:84 R:73	N:99 R:49	N:84 R:73	N:78 R:68	N:166 R: Singular Matrix	N:66 R:59	N:87 R:74	N:87 R:74
	Baseline	IN:97.431* IR:75.45	N:99.113* S: 92.487 RN:77.347* RS:70.252	N:93.175* MC:94.062 RN:75.466* RMC:72.419	M:96.292* F: 100.303 RM:71.973* RF:80.51	O:97.906* I:96.062 RO:72.317* RI:76.055	A:99.919* T:95.495	N:95.959* F:95.243 RN:76.985* RF:73.798	E:101.585 M:96.323 Y:100.763 RE:75.007 RM:76.988 RY: Singular Matrix	L:90.506 M:96.323 S:99.544 RL:52.517 RM:76.988 RS:82.663 RS:19.1
	β/Coeff.	IN:1.304* IR: 9.93*	N:1.015 S:1.601 RN:10.386* RS: -7.095	N:5.671* MC: -1.277 RN:8.046* RMC: -4.975	M:2.596** F: -4.307 RM:13.181* RF: -5.785	O:4.904 I: -3.175 RO:19.168* RI: -10.862**	A:8.722** T: -6.235	N:2.497 F:1.458 RN:10.361* RF: -3.225	E: -5.379 M:5.639* Y: -5.017 RE: -4.272 RM: -0.075 RY: Singular Matrix	L:1.978 M:5.639* S: -0.399 RL: -2.934 RM: -0.075 RS:19.1
Vitamin B12 (ng/L)	n	P: 147 I: 177	N:116 R:56	N:132 R:25	N:116 R:56	N:104 R:53	N:89 R:44	N: 90 R:44	N:121 R:56	N:121 R:56
	Baseline	PN:685.319* PR:407.603* IN:740.346* IR:428.958*	N:751.126* S:762.748 RN:458.958* RS:419.584	N:682.039* MC:690.768 RN:346.506* RMC:465.693	M:742.815* F:769.671 RM:409.428* RF:503.524**	O:731.284* I:763.838 RO:433.326* RI:471.278	A:679.137* T:741.439 RA:367.553* RT:455.535	N:745.351* F:716.453 RN:455.562 RF:361.371	E:831.448 M:725.657 Y:864.19 RE:452.934 RM:457.426 RY:409.868	L:776.266 M:725.657 S:667.439 RL: -994.207?* RM:457.426 RS:464.936
	β/Coeff.	PN:56.525* PR: -16.666 IN:21.867*	N:31.213** S:6.343 RN:71.949*	N:40.531** MC:18.930 RN:67.367	M:33.843** F:0.308* RM:91.519	O:30.518 I:10.151 RO:69.326*	A:100.916 T: -51.140 RA:0.165	N:52.251* F: -4.972 RN:72.983*	E:25.858 M:35.146 Y: -66.388	L: -20.916 M:35.146 S:156.034

		IR:61.427*	RS:35.538	RMC: -6.756	RF: -28.781	RI:6.195	RT:0.028	RF:7.944	RE:47.407 RM: -51.095 RY: -23.279	RL:264.445* RM: -51.095 RS:392.748
Vitamin D (ug/L)	n	P: 147 I:174	N:56 R:114	N:96 R:59	N:56 R:114	N:52 R:103	N:44 R:86	N:45 R:86	N:44 R:86	N:44 R: 86
	Baseline	PN:44.511* PR:35.219* IN:52.17* IR:38.487*	N:52.454* S:50.268 RN:37.081* RS:42.319	N:46.977* MC:46.816 RN:32.784* RMC: 36.995	M:52.816* F:51.396 RM:38.945* RF:36.857	O:47.311* I:54.472** RO:34.998* RI:38.885	A:42.241* T:52.594 RA:37.926* RT:37.917	N:52.481* F:52.09 RN:38.513* RF:34.89	E:54.512 M:48.459 Y:61.164 RE:40.769 RM:37.724 RY:28.828	L:50.883 M:51.459 S:52.99 RL:26.284 RM:37.724 RS:34.688
	β/Coeff.	PN:5.849* PR: -3.191* IN:1.811** IR:2.418**	N:1.799 S: -0.139 RN:4.893* RS: -1.004	N:3.553* MC:1.115 RN:9.675* RMC: -7.703*	M:1.373 F:0.48 RM:5.073* RF: -0.878	O:2.13 I: -1.372 RO:6.764* RI: -1.784	A: -1.825 T:2.795 RA:0.012 RT:0.002	N:0.988 F: -0.374 RN:6.248* RN: -2.535	E: -3.766 M:3.186 Y:18.529 RE: -3.399 RM:2.39 RY:17.181	L:2.12 M:3.186 S:3.249 RL:0.974 RM:2.39 RS:9.905
BMI	n	P:148 I:171	N:88 R:78	N:86 R:65	N:88 R:78	N:79 R:73	N:65 R:63	N:66 R:63	N:65 R:63	N:65 R:63
	Baseline	PN:24.015* PR:30.739* IN:23.495* IR:30.234*	N:23.727* S:21.863* RN:31.162* RS:27.641*	N:22.814* MC:24.57* RN:30.053* RMC:30.735	M:24.537* F:22.656* RM:29.355* RF:34.393*	O:23.631* I:23.342 RO:31.67* RI:30.384	A:23.639* T:23.251 RA:31.087* RT:30.393	N:22.96* F:23.576 RN:30.371* RF:30.651	E:21.899* M:23.844* Y:20.952* RE:31.137 RM:30.318 RY:28.45	L:23.429 M:23.844* S:23.158 RL:26.956 RM:30.318 RS:28.441
	β/Coeff.	PN: -0.191* PR: -0.112 IN:0.024 IR: -0.365*	N:0.023 S: -0.234** RN: -0.393* RS:0.203	N:0.012 MC: -0.14 RN: -0.567* RMC:0.402	M: -0.12 F:0.21* RM: -0.21* RF: -0.981*	O: -0.103 I: -0.146 RO: -1.676* RI:1.478*	A: - 0.159 T:0.136 RA: -0.003 RT:0.00	N: -0.083 F:0.215 RN: -0.256** RF: -0.235	E: -0.118 M:0.084 Y:0.542 RE: -0.022 RM:0.011 RY: -2.924	L:0.0214 M:0.084 S: -2.096* RL:0.44 RM:0.011 RS: -1.879
Body Fat (%)	n	P:116 I:151	N:6 R:141	N: Singular Matrix R:137	N: Singular Matrix R:137	N: Singular Matrix R:131	N: Singular Matrix R:109	N:6 R:109	N:5 R:109	N:5 R: 109
	Baseline	PN:24.127* PR:33.288* IN:22.27* IR:33.65*	N:20.215* S:19.633 RN:33.66* RS:33.589	RN:32.301* RMC:35.198*	RM:33.427* RF:34.256	RO:34.93* RI:33.758	RA:34.852* RT:33.897	N:19.915* F:19.691 RN:33.584* RF:34.736	E: Singular Matrix M:20.423 Y:18 RE:33.787 RM:34.477 RY:26.67*	L: Singular Matrix M:20.423 S: Singular Matrix RL:33.553 RM:34.477 RS:33.958
	β/Coeff.	PN:1.793* PR: -1.467 IN:1.861* IR: -1.385*	N:2.379 S:0.246 RN:0.35 RS:0.647	RN:0.35 RMC:0.237	RM:0.461 RF:0.059	RO: -0.593 RI:1.265	RA: -0.002 RT:0.003	N:2.509* F:1.012 RN:0.652 RF: -0.831	E: Singular Matrix M: -2.032 Y:2.032 RE:0.543 RM: -0.871 RY: -0.623	L: Singular Matrix M: -2.032 S: Singular Matrix RL:0.411 RM: -0.871 RS: -2.305

Weighted Skeletal Muscle Index (%)	n	P:112 I:146	N: 4 R:141	N: 4 R:139	N: Failed to Converge R:141	N:3 R:133	N:3 R:112	N:3 R:113	N: Singular Matrix R:112	N: Singular Matrix R:142
	Baseline	PN:33.725* PR:23.016 IN: 33.511* IR: 22.855*	N:33.114 S:36 RN:21.784* RS:28.696*	N:24.902* MC:21.107 RN:24.902* RMC:21.107*	RM:25.553* RF:19.777*	O:27.305* I:42.828 RO:22.54* RI:23.001	A:27.305* T:42.828 RA:23.813* RT:23.268	N:32.264* F:53.517? RN:23.937* RF:21.587	RE:22.678 RM:23.455 RY:23.538	RL:23.41 RM:23.39 RS:22.13
	β/Coeff.	PN: -1.7114 PR:1.069 IN: -2.163 IR:1.974	N: -1.7114 R: -8.713 RN:0.102 RS: -1.86**	N:4.072 MC: -9.776 RN: -1.065 RMC:1.538	RM: -0.296 RF: -0.214	O:5.6 I: -12.831 RO:0.054 RI: -0.416	A:5.6 T: -12.831 RA:0 RT: -0.001	N: -3.582 F: -4.657 RN: -0.391 RF: -0.261	RE:0.118 RM: -0.037 RY: -1.416	RL: -0.027 RM: -0.518 RS:0.227
Waist: Height Ratio	N	P:119 I:120	N:15 R:102	N:12 R:92	N:15 R:102	N:12 R:96	N: Singular Matrix R:79	N:12 R:79	N:16 R:79	N:16 R:104
	Baseline	PN:0.459* PR:0.597* IN:0.46* IR: 0.599*	N:0.46* S:0.468 RN:0.614* RS:0.549*	N:0.457* MC:0.468 RN:0.591* RMC:0.601	M:0.464* F:0.457 RM:0.599* RF:0.6	O:0.444* I:0.461 RO:0.622* RI:0.594**	RA:0.609* RT:0.602	N:0.459* F:0.442 RN:0.601* RF:0.611	E: Singular Matrix M:0.464 Y:0.483 RE:0.603 RM:0.605 RY: Singular Matrix	L:0.457 M:0.464 S: Singular Matrix RL:0.554** RM:0.6 RS: Singular Matrix
	β/Coeff.	PN:0.005 PR: -0.008** IN:0.004 IR: -0.008	N:0.004 S: 0 RN: -0.006* RS:0.006	N:0.007* MC: -0.005 RN: -0.01* RMC:0.007	M:0.018 F: -0.014 RM: -0.004** RF: -0.004	O:0.034* I: -0.033* RO: -0.012* RI:0.009**	RA: -0* RT:0*	N:0.02** F: -0.018 RN: -0.003 RF: -0.004	E: Singular Matrix M: -0.002 Y: -0.033 RE: -0.004 RM:0003 RY: Singular Matrix	L: -0.012 M: -0.002 S: Singular matrix RL:0.013* RM:0.003 RS: Singular matrix
Diastolic Blood Pressure (mmgh)	N	P:150 I:175	N:133 R:39	N:119 R: Failed to Converge	N:132 R:39	N:119 R:37	N:100 R: Singular Matrix	N:101 R:32	N:136 R:39	N:136 R: 39
	Baseline	PN:75.428* PR:89.628* IN:75.397* IR:90.628*	N:75.851* S:73.448 RN:89.02* RS:92.248	N:75.02* MC:75.519	M:77.192* F:72.921* RM:90.824* RF:87.357	O:74.77* I:75.435 RO:90.351* RI:89.586	A:75.167* T:74.807	N:74.821* F:74.61 RN:90.951* RF:86.536	O:76.436* Y:69.974* RO:89.66 RY:89.512	L:75.908 S:73.7 RL: Failed to Converge RS:96.283*
	β/Coeff.	PN: -0.977** PR: -2.89* IN: -0.728 IR: -2.706*	N: -1.459* S:2.541* RN: -3.187* RS:3.421	N: -0.376 MC: -0.775	M: -0.776 F:0.034 RM: -3.244* RF:0.345	O: -1.816 I:1.308 RO: -7.933* RI:4.96	A:1.998 T: -2.876	N: -0.767 F: -0.317 RN: -3.505* RF:1.076	O: -0.994 Y:4.434* RO: -0.553 RY:0.553	L: -4.401** S:4.401** RL: Failed to Converge RS: -0.620

*Significant at α = <0.05 (5%) , **Significant α = <0.1 (10%), ? strange output (does not meet criteria) & singular matrices and the failure to converge resulted when sample sizes were too small to compute MERs

11.4 *Appendix D: Exclusion of Variables*

Validations for The Exclusion of Explanatory/Contextual Variables

Explanatory Variables	Reasons for Exclusion
The influence of COVID-19	**Confounding Variables** 1. COVID-19 occurred during the last year of Gentest service delivery, as Gentest is always modifying their service delivery the same year saw the most improved and precise measurements 2. COVID-19 restrictions affected different dimensions including effects on the individual and on Gentest's service delivery. Results in the inability to pinpoint which aspects influence biomarker outcomes 3. Decreased inflow of consultees resulted in less datapoints collected. This is not comparable with the previous years 4. Decreased number of staff resulted in Gentest having a limited capacity, this has also impacted their service delivery
Smoking	**Confounding Variables & Low Statistical Power** 1. This is based on if the consultees are smoking when they first come to Gentest. Some consultees stop smoking after their report interpretation (mainly prior to 2019) whilst others continue. There is no data on this so could not be accounted for and therefore affects the results. 2. Varying statistical power for different biomarkers. Only 39 people were smoking at their first Gentest encounter and therefore small sample sizes of smokers are included within the models.
The Influence of Pre-existing Metabolically Dysfunctional Conditions	**Confounding Variables** 1. Age is a confounder as the older you get; the more conditions arise (Prasad, Sung & Aggarwal, 2012). 80 consultees came to Gentest with pre-existing conditions whereby their mean age was 57.8. 20 consultees are below the age of 50 and 33 consultees are above the age of 60.
Country of Residence	**Statistical Power** 1. As Gentest is based in Turkey there is a limited number of people who use their services from abroad. A total of 20 consultees of the selected sample live abroad. Therefore, this is also represented within the models via low significance and statistical power (<0.8).
Shared Gentest Household	**Statistical Power** 1. A small number of consultees are adhering to Gentest with another family member (n= 37). This is therefore represented within the models and may explain the varying influence. Their validity is therefore questioned. However, Ackermann's theory of push and pull factors may also explain this (Ackermann, 2020).

Inclusion criteria is as follows (1) The presence of underlying confounding variables, (2) low statistical power (<0.8) and (3) utility of results.

11.5 Appendix E: Service Recommendations

The Recommendations for Service Improvement Suggested by Interviewed Consultees

Gentest's Operations	Recommendations	Supporting Quotes
Report Interpretation	**Need more personalized comparisons**	• "… but when you put it all together, how does that put me relative to people who have comparable genetic makeup and lifestyle? Am I of higher risk? Or lower risk when you aggregate them all in a way…Where do I stand? That kind of information may be more useful for people to take action." • "You have the risk profile but making sense of the data so to speak and relativizing it with the rest of the population who will be compatible to your age wise, weight wise, etc. That part I think is could be improved, otherwise, it's a fantastic report."
Support & Communication	**Connect to family physicians**	• "...you have all the genes and with regard homozygous and heterozygous etc. And how they are related to which these so those tables… that information could easily be related to the personal physician, family, physician of the patient and then make that connection for them to follow through with the patient..." • "...I think a big chunk of it could be followed through by the family physician and that connection will be important... maybe there could be some kind of a summary report part which will not compromise the confidentiality and the rights of Gentest that could be passed on by the patient to their family physician."
Lifestyle Plan	**Provie an overview of the lifestyle plan**	• "So if they are more clear about the days with about the meetings and how many days I should take that, it would be better for me for preparation"
Overall Experience	**Online Consultee review section**	• "It could be good on the online site to make a section for reviews of their like old and current patients saying how it would benefit them and make it obvious to people who want to take it so they will see it. "

11.6 Appendix F: Survey Comments on QoL

The Open-ended Responses Provided by Consultees When Commenting on Their Quality-of-Life.

Categories	Additional Quality of Life Responses
Positive Effects	• 'More conscious' • 'Physically feeling good' • 'A life without pain'

Influence of COVID-19	• 'The answers to some of the questions may have changed due to the pandemic ... my working hours have decreased by half ... rest hours have increased ... more time for myself has accelerated my adaptation to the program ... I experience the benefits of the program more clearly ... even the stress of loss of income can be tolerated.' • 'The possibility of movement has decreased with the effect of the pandemic.' • 'COVID -19 negatively affected the process' • 'Negative factors in QoL due to pandemic' • 'Unfortunately, the pandemic and the negative conditions in this period of my life in general cannot be an incentive to feel good...' • 'My private life is limited due to the pandemic'

The responses have been filtered to exclude more personal answers which relate to individual health conditions.