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Evaluation of Human Body Temperature Measurements with Infrared Thermography in the Ear Region

Kulak Bölgesinde İnfrared Termografi ile İnsan Vücut Sıcaklığı Ölçümlerinin Değerlendirilmesi

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ABSTRACT

Objective: Estimating body temperature using infrared thermography (IRT) varies in terms of measurement sites and the applied procedures. The main aim of this article is to explore the use of IRT in order to perform accurate remote human body temperature measurements using the ear region since the human ear canal is one of the most thermally closed places to external influences.

Methods: An observational clinical study was conducted involving 50 subjects in which forehead and tympanic body temperatures were measured by non-contact infrared thermometers as references, as well as capturing frontal and sagittal thermal images. Statistical analysis was performed on the gathered data samples and regression functions were determined for IRT measurements obtained from multiple sites against non-contact infrared thermometer references.

Results: We found a low agreement between forehead and tympanic non-contact infrared thermometer measurements (root-mean-square 0.79 °C). We also observed that the linear regression of tympanic non-contact infrared thermometer on sagittal IRT measurements from the right ear region provided the best results, with the clinical bias of 0.04 °C and 0.19 °C root-mean square.

Conclusion: We presented that real body temperature can be estimated accurately from sagittal face thermal images, especially from the rectangular region surrounding the human ear.

Keywords: Body temperature, fever screening, infrared thermography, regression analysis, tympanic temperature

ÖZ

Amaç: İnfrared termografi (IRT) kullanarak vücut sıcaklığını tahmin etmek, ölçüm yerleri ve uygulanan prosedürler açısından farklılık gösterir. Bu makalenin temel amacı, insan kulak kanalının dış etkilere termal olarak en kapalı yerlerden biri olması nedeniyle, kulak bölgesini kullanarak uzaktan insan vücut sıcaklığı ölçümleri yapmak için IRT kullanımını araştırmaktır.

Yöntemler: Alın ve timpanik vücut sıcaklıklarının referans olarak temassız infrared termometreler ile ölçüldüğü ve frontal ve sagital termal görüntülerin yakalandığı 50 hasta içeren bir gözlemsel klinik çalışma yürütülmüştür. Toplanan veri örnekleri üzerinde istatistiksel analiz yapılmış ve temassız infrared termometre referanslarına karşı birden fazla yerden elde edilen IRT ölçümleri için regresyon fonksiyonları belirlenmiştir.

Bulgular: Alın ve timpanik temassız infrared termometre ölçümleri arasında düşük bir uyum bulunmuştur (karekök ortalama kare 0,79 °C). Ayrıca, sağ kulak bölgesi sagittal IRT ölçümlerinde timpanik temassız infrared termometrenin doğrusal regresyonunun 0,04 °C ve 0,19 °C karekök ortalama kare klinik sapma ile en iyi sonuçları sağladığı gözlemlemiştir.

Sonuç: Gerçek vücut sıcaklığının, özellikle insan kulağını çevreleyen dikdörtgen bölgeden, sagittal yüz termal görüntüleri kullanılarak doğru bir şekilde tahmin edilebileceği sunulmuştur.

Anahtar Kelimeler: Vücut sıcaklığı, ateş taraması, infrared termografi, regresyon analizi, timpanik sıcaklık

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INTRODUCTION

Measurements of the vital signs provide the most important indicators of the state of the human body functions. In the field of medicine, vital signs are monitored and evaluated at the prioritization (triage), diagnosis and follow-up stages. There are four primary vital signs: pulse rate (heartbeat), respiratory rate, blood pressure and body temperature.

The main methods for human core body temperature measurement are divided into invasive and non-invasive approaches (1). The invasive approaches, mostly applied in healthcare organizations, are the most reliable ones. The invasive measurements can be performed on several sites: rectal, pulmonary artery and by swallowable temperature sensors. Non-invasive methods consist of sublingual measurement (mouth), intra-ear measurement (tympanic) and axilla (armpit) measurements.

The use of invasive and contact methods in public places is impractical and unsuitable from a hygienic point of view. Therefore, non-contact methods, which are usually based on non-contact infrared thermometers (NCITs) and infrared thermal cameras have become popular for fever screening, especially during epidemics of infectious diseases that prioritized body temperature as one of the symptoms; severe acute respiratory syndrome, H1N1, Ebola and coronavirus disease-2019 (2-5).

Infrared thermography (IRT) can be defined as the acquisition and evaluation of thermal images by using filtered lenses and infrared-sensitive bolometers. Unlike non-contact thermometers, a two-dimensional array of thermal measurements is obtained by IRT. This also creates an opportunity for the detection of certain points on the human face, allowing detailed evaluation of temperatures. An important point to note is that only outer skin temperature can be measured with IRT. If it is desired to obtain the internal body temperatures instead of just making a comparison, the skin temperature values should be transferred to references which is called conversion.

Several studies have pointed out that IRTs are not accurate for fever screening (6-9). Although recommendations for the assessment of accurate fever screening and implementation details of IRTs are presented in IEC 80601-2-59:2017 and ISO/TR 13154:2017 (10,11) standards, the processes for assessing measurement accuracy are still controversial.

There have been many studies performed on the NCIT measurement location. Bijur et al. (12) found that tympanic temperatures were more precise than temporal thermometry, with a sensitivity of 68.3% to detect a rectal temperature equivalent of 38 °C. Similarly, Fong et al. (13) had an experiment with a total of 1576 visitors to Singapore General Hospital and recorded temperatures from three different sites (i.e., temporal, forehead and tympanic) and the results demonstrated that temporal and forehead temperature readings were generally lower than those of tympanic temperature readings, and hence may not detect patients with fever. Goggins et al. (14) also concluded that the tympanic temperature was the least impacted by environmental temperature than forehead thermometers including an IRT. Mah et al. (15) compared several commercially available thermometers (including an IRT camera) with a gold standard thermometer and concluded that not all temperature monitoring techniques are equal, and suggested that tympanic thermometers are the most accurate commercially available system for the regular measurement of body temperature.

Several prior studies have investigated the relationship between oral and tympanic temperatures with core temperature and found that these sites are well-correlated candidates for core temperature (16,17). Several other studies have also proposed that the tympanic temperature is closer to the body's core temperature than forehead temperature and provides the most accurate measurements (18-21).

The inner canthi are thought to be ideal locations for non-contact temperature measurement. Inner canthi are typically the warmest regions on the face and have the highest correlation with the core body temperature due to internal carotid artery perfusion (22-24). Previous IRT studies targeting the human ear are fewer than studies focusing on frontal face thermal images. Muniz et al. (25) investigated the ear canal together with the forehead and the corner of the eye. Limpabandhu et al. (26) examined ear and temple regions together with the eyes and nose. Putrino et al. (27) found out that ears and inner canthi areas can be used as an alternative to forehead digital thermometer measurements using a thermal camera connected to a mobile device.

Several conversion approaches have been studied in past IRT research. Švantner et al. (6) examined several conversion techniques, including constant offset and normalization to approximate the reference armpit thermometer values. Limpabandhu et al. (26) used a linear regression model to successfully convert IRT values to those of an Food and Drug Administration-approved thermometer. Wang et al. (22) compared several regression models to convert IRT values to a reference oral temperature and found out that the inner canthi or facial maximum measurements provided the highest accuracy. Similarly, Sun et al. (2) converted facial IRT skin temperature to axillary temperature using linear regression.

The main aim of this study is to explore the use of infrared thermal imaging in order to perform accurate remote human

body temperature measurements from the ear region. We assumed that targeting the ear region in IRT procedure would be much more effective, since the ear canal is one of the most thermally closed places to external influences and is not affected by the use of glasses and medical masks.

MATERIALS AND METHODS

We conducted an observational clinical research including 50 patients in İzmir Tınaztepe University Galen Medical Hospital from March to September 2021. The clinical research, which was a part of the project "Development of Artificial Intelligence-supported Software that Remotely Evaluates Human Body Temperature and Performs High Accuracy Measurements with Thermal Cameras", was approved by İzmir Tınaztepe University Health Sciences Scientific Research and Publication Ethics Committee (protocol code: TUBAYEK: 002, date: 10.03.2021). Written informed consent was obtained from all subjects.

Environmental Conditions

The clinical study was conducted between March and September 2021. The examination room did not have air flow or any window openings. The examination room had no radiant heat sources, and the climate controller was set to keep the room temperature constant between 21-22 °C. Before each measurement, the room temperature and relative humidity measurements were recorded using a thermometer (MEDISANA HG100 Digital Thermo Hygrometer).

Based on the standard (11), the ideal environmental temperature and relative humidity intervals should be 20-24 °C and 10-50% respectively. In our study, most of the measurements were performed in the ideal room temperature interval. The room temperature mode value was 22 °C. We only had two room temperature samples (25 °C) outside the ideal interval. We also had 11 relative humidity values above the upper interval limit of 50%.

Experimental Setup and Temperature Measurement Procedure

Volunteers for the clinical research were kept calm for 15 minutes and then taken to the imaging room. In addition, the patients did not drink any hot/cold beverages within 30 minutes and did not smoke. The people were not allowed to wear any excessive clothing or head covers (e.g., headbands and bandanas). The test area of the forehead was clean, dry and not blocked during measurements.

We used an infrared thermal camera with an uncooled microbolometer sensitive to the long-wave infrared band (T540, Teledyne FLIR LLC., USA). We set its emissivity parameter to 0.98, as described in IEC 80601-2-59:2017 standard (10). We used Thermoval Duo Scan (Heidenheim, Germany) for forehead temperature measurement and Braun ThermoScan 6026 NCIT for tympanic temperature measurement. In their product specification documents, Thermoval declares its measurement accuracy as (±0.2 °C) in the 35.5-42.0 °C interval, similarly, ThermoScan declares its temperature accuracy as (±0.2 °C) in the temperature range 36.0-39.0 °C. These NCIT device accuracy values conform to the standard (28) about IR thermometers. There was no blackbody calibration device available.

The measurement procedure applied to all subjects was as follows:

1. At first, the subject's medical mask was removed.
2. Subject waited 30 seconds, in order to eliminate sudden temperature changes caused by the removal of the medical mask.
3. NCIT value from the middle of the forehead and tympanic region was measured.
4. The first frontal face thermal image was captured by the thermal camera.
5. A sagittal right and left head images were captured by the thermal camera.
6. The second frontal face thermal image was captured by the thermal camera.

All thermal camera images were taken from a distance of 1.0 meters against a non-reflectant wall. The time interval between consecutive thermal image captures was approximately 30 seconds. Therefore, the second frontal thermal image was captured approximately 60 seconds after the first one.

Demographics

The subject group consisted of 21 (42%) males and 29 (58%) females. Subjects were between the ages of 21 and 88. The mean age value is 66.72 and the standard deviation (SD) value is 14.04.

Manual Analysis of Thermal Images

All thermal images were manually analyzed using FLIR Tools software package (Teledyne FLIR LLC., USA). Measurement shapes were inserted on the thermal images and the thermal statistics were obtained. These measurement sites in frontal and sagittal (lateral) views are illustrated in (Figure 1a).

The variables (acronyms) that describe the frontal thermal image, the manual measurement area and statistics are presented in (Table 1). Similarly, the statistics for the measurement geometries presented in (Figure 1b) are obtained with corresponding variables for the sagittal thermal images (Table 2).

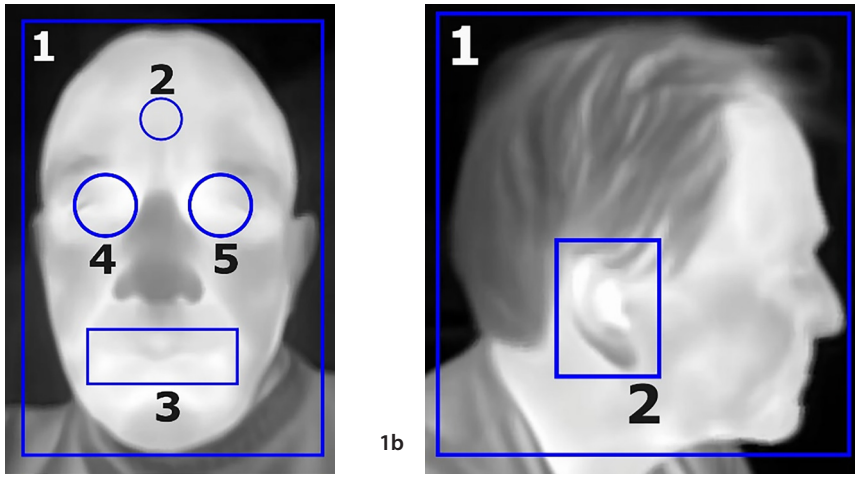


Figure 1. Thermal image measurement sites (a) Frontal, (1) frontal face region, (2) circular area in the forehead, (3) mouth region, (4,5) right and left canthus regions. (b) Sagittal, (1) sagittal face region, (2) ear region. Photos are of authors

Table 1. The variables and corresponding definitions of frontal thermal image reading areas (suffix_X represents the first and the second captured thermal image, by the number 1 or 2)

Variable	Explanation
T_FC_IRT_X	Maximum temperature reading from the rectangle enclosing the frontal face region.
T_FO_IRT_X	Temperature reading from the spot in the forehead.
T_MO_IRT_X	Maximum temperature reading from the rectangle enclosing the mouth region.
T_CR_IRT_X	Maximum temperature reading from the circle enclosing the right canthus region.
T_CL_IRT_X	Maximum temperature reading from the circle enclosing the left canthus region.
T_CM_IRT_X	Maximum of T_CR_IRT_X and T_CL_IRT_X.

T: Temperature, IRT: Infrared thermography, FC: Frontal face region, FO: Forehead region, MO: Mouth region, CR: Canthus right region, CL: Canthus left region, CM: Maximum of right and left canhtus regions

Table 2. The variables and corresponding definitions of sagittal thermal image reading areas (suffix_X represents the first and the second captured thermal image, by the number 1 or 2)

Variable	Explanation
T_FSR_IRT_X	Maximum temperature reading from the rectangle enclosing the right sagittal face region.
T_FSL_IRT_X	Maximum temperature reading from the rectangle enclosing the left sagittal face region.
T_ER_IRT_X	Maximum temperature reading from the rectangle enclosing the right ear region.
T_EL_IRT_X	Maximum temperature reading from the circle enclosing the left ear region.

T: Temperature, IRT: Infrared thermography, FSR: Right sagittal face region, FSL: Left sagittal face region, ER: Right ear, EL: Left ear

Statistical Analysis

Measurement Accuracy Assessment Metrics

In order to compare the measurements obtained from either NCIT or IRT devices to assess their body temperature measurement accuracy, we have used the following metrics: the Pearson correlation coefficient, the clinical bias, the SD of the bias samples and the root-mean-square (RMS) difference.

The Pearson correlation coefficient (r-value) is the most common way of measuring a linear correlation. It is a number between -1.0 and 1.0 that measures the strength and direction of the relationship between two sets of data. It is the ratio between the covariance of two variables and the product of their SDs, so it is essentially a normalized measurement of the covariance.

Basically, the clinical bias between variables a and b is obtained by $\frac{1}{N}\Sigma(a-b)$ where N is the number of samples. For simplicity, we depicted the mean and the SD of bias samples by μ_{Δ} and σ_{Δ} respectively. These metrics are defined in standards (28,29). The RMS value of two variables is obtained by $(\frac{1}{N}\Sigma(a-b)^2)^{(1/2)}$ where N represents the number of samples.

Regression Methods to Predict Body Temperatures

In this study, we wanted to reveal if we could approximate NCIT body temperatures by applying a regression analysis to other variables. We wanted to measure how well we could model the relationship between following variable pairs (independent input vs predicted output):

1. T_FO_NCIT vs T_TY_NCIT.
2. Facial IRT variables vs T_FO_NCIT.
3. Sagittal IRT variables vs T_TY_NCIT.

In order to determine the regression function to approximate the target samples, the data samples were divided into random training and test sets in proportions of 70% and 30%, respectively. With the training samples, the regression functions that best performed the prediction were determined, and the performances were calculated on the test set. For simplicity, we depicted the predicted samples with the superscript character * on the target variable. For example, the regression of T_TY_NCIT on T_FSR_IRT means that T_FSR_IRT is the independent input variable to which a regression function is applied and T_TY_NCIT* is the predicted T_TY_NCIT samples.

RESULTS

Comparison of Forehead and Tympanic NCIT Measurements

The mean and SD pairs of tympanic and forehead NCIT measurements are (36.64, 0.20) and (35.94, 0.39) respectively. In addition, the r-value between them is calculated as 0.31. The bias statistics, μ_Δ, σ_Δ and RMS values are (-0.69, 0.38) and 0.79 respectively. The density curves and Bland-Altman plot of the tympanic and forehead NCIT measurements are presented in Figure 2a, 2b. It is observed that with increasing mean temperature values, the difference between forehead and tympanic NCIT measurements tends to decrease.

The box plots of the NCIT measurements are presented in (Figure 3). It is observed that:

1. Tympanic NCIT measurements are higher than all other parameters with the lowest temperature variance,
2. Forehead NCIT measurements are significantly lower than tympanic NCIT measurements.

Analysis of Frontal IRT Measurements

The box plots of the first and the second (delayed) frontal IRT measurements are presented in (Figure 3). Looking at these box plots, it is observed that:

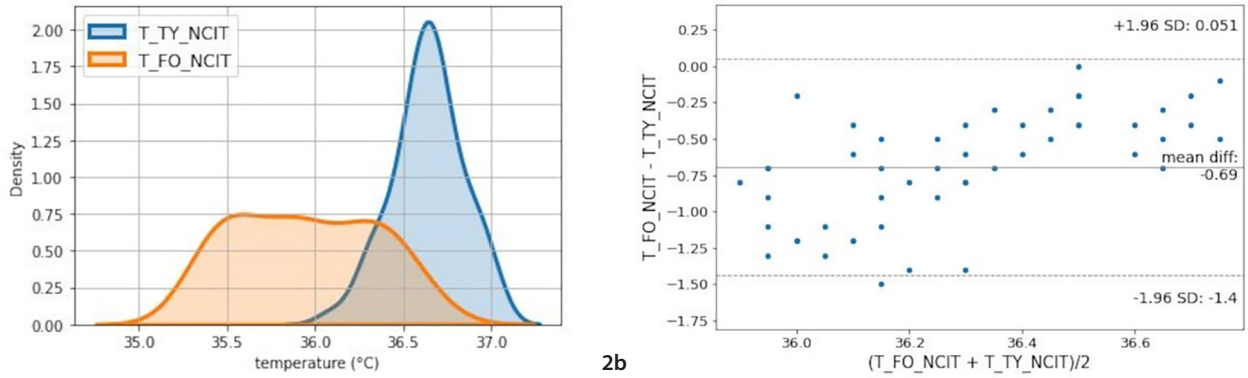
1. The forehead IRT values are lower than the rest of their frontal IRT measurements.
2. The forehead IRT temperatures have the highest SD.
3. The second frontal IRT measurements are lower than the first.

The temperature drop of the second measurements can be interpreted as a result of medical mask removal. Note that, most of the values were decreased after the medical masks were removed.

Analysis of Sagittal IRT Measurements

Box plots for the sagittal thermal camera readings are presented in (Figure 4). In the first two box plots (red colored), NCIT measurements are presented in order to provide comparison. Looking at the box plots, it is observed that:

1. The tympanic NCIT measurements are higher than all other parameters with the lowest temperature variance.
2. The forehead NCIT measurement distribution is more similar to sagittal IRT measurements than to sagittal NCIT.



2a 2b

Figure 2. Forehead and tympanic NCIT measurement comparison (a, b). Forehead and tympanic NCIT measurement density curves (a), Bland-Altman plot of forehead and tympanic NCIT measurements, i.e., means vs differences (b)

T: Temperature, TY: Tympanic region, FO: Forehead region, NCIT: Non-contact infrared thermometer, SD: Standard deviation

It is noted that the r-values between the sagittal face and the ear readings [i.e., T_FSR_IRT vs T_right ear (ER)_IRT and T_ left sagittal face region (FSL)_IRT vs T_left ear (EL)_IRT] are very high. With the exception of two pairs, all the right and left ear measurement samples remain within the limits of agreement.

Correlations of Frontal vs Sagittal IRT Measurements

It is found that each sagittal IRT parameter has maximum correlation with one of the second canthus IRT measurements. By comparing these, it can be stated that the r-values increased with the second frontal thermal images. This increase can be interpreted as a result of the removal of medical masks. In both comparisons, the maximum temperatures the left sagittal face have a higher correlation with other frontal sites.

Analysis of NCIT vs IRT Measurements

It is observed that the correlation between forehead NCIT and forehead IRT measurements (i.e., T_FO_NCIT vs T_FO_IRT) are relatively lower than the r-values for the other variables. Overall, the minimum bias SD is 0.61 °C, therefore, the forehead NCIT and the frontal IRT values do not have clinical agreement.

Similarly, the minimum σ_{Δ} between tympanic NCIT and sagittal IRT measurements is 0.50 °C, therefore, the tympanic NCIT and the frontal IRT values do not have clinical agreement. It is also observed that the correlation between tympanic NCIT and sagittal IRT measurements is relatively higher than that of forehead NCIT.

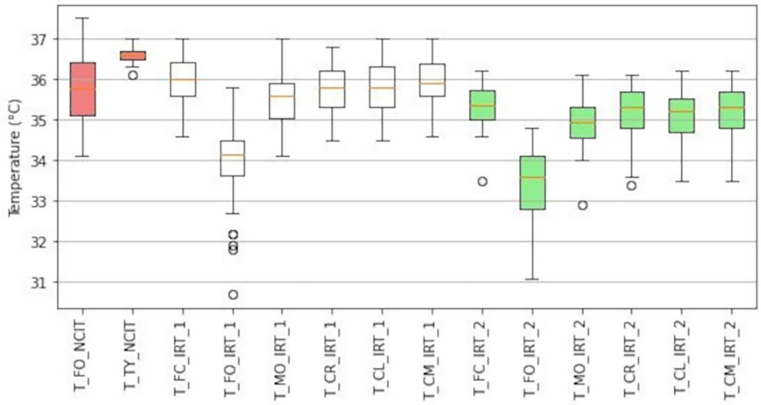


Figure 3. Box plots for NCIT and frontal thermal camera readings. NCIT measurements are presented in red color, the first frontal readings are presented in white and the second (delayed) frontal readings are presented in green color

NCIT: Non-contact infrared thermometer, IRT: Infrared thermography, T: Temperature, TY: Tympanic region, FC: Frontal face region, FO: Forehead region, MO: Mouth region, CR: Canthus right region, CL: Canthus left region, CM: Maximum of right and left canhtus regions

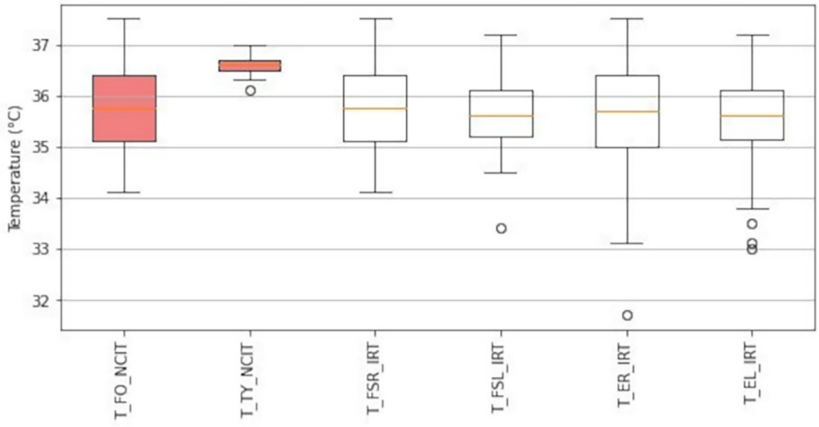


Figure 4. Box plots for NCIT and sagittal thermal camera measurements. NCIT measurements are presented in red color

NCIT: Non-contact infrared thermometer, T: Temperature, FO: Forehead region, TY: Tympanic region, FSR: Right sagittal face region, FSL: Left sagittal face region, ER: Right ear, EL: Left ear

Regression Analysis Results

In this section, the regression analysis results of each NCIT variable on each one of the IRT variables and the analysis of each NCIT variable on another NCIT variable are explained. As a result of this study, we concluded that the first, second and third-order polynomial regression results were very close to each other. This implies that the relationship between these variables are approximately linear. For simplicity, we only presented linear regression solutions.

Regression of Tympanic NCIT on Forehead NCIT

The linear regression function to model the relationship between forehead and tympanic NCIT samples was determined by the line equation (in °C units):

$T\_TY\_NCIT^{*} = 0.13 * T\_FO\_NCIT + 32.01$ (1).

The resultant prediction bias statistics is calculated as (0.04, 0.18).

Regression of NCIT Temperatures on Frontal IRT

In frontal and sagittal sections, each IRT variable was selected as an independent variable against the corresponding NCIT measurements in that plane and corresponding regression functions were calculated. It is important to note that the bias statistics and the RMS values for T_TY_NCIT predictions are lower than those of the T_FO_NCIT. This means that we can predict tympanic NCIT measurements from frontal IRT measurements with satisfactory agreement, despite the limitations in predicting frontal NCITs from frontal IRTs.

Regression of Tympanic NCIT on Sagittal IRT

The scatter plot and resultant regression line converting the input variable T_FSR_IRT to the predicted variable $T\_TY\_NCIT^{*}$ is depicted in (Figure 5). This scatter plot and regression line are shown as an example: other regression line results relating to other variables are not presented to make this article easier to read.

The resultant clinical accuracy metrics to model the relationship between the sagittal IRT variables and $T\_TY\_NCIT^{*}$ are presented in (Table 3). The results indicate that there are significant clinical accuracy and agreement between NCIT measurements. This means that we can predict tympanic NCITs from sagittal IRT measurements (by using separate linear conversion functions for each) and can use them in clinical practice interchangeably.

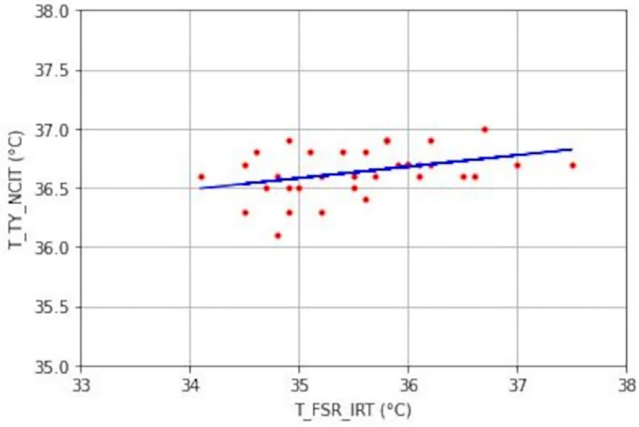


Figure 5. Regression line of tympanic NCIT measurements on sagittal right face IRT measurements

NCIT: Non-contact infrared thermometer, IRT: Infrared thermography, T: Temperature, TY: Tympanic region, FSR: Right sagittal face region

Table 3. The regression error list for each sagittal IRT input variable, to predict tympanic NCIT samples (i.e., $T\_TY\_NCIT^{*}$)

	T_FSR_IRT	T_FSL_IRT	T_ER_IRT	T_EL_IRT
μ_{Δ}	0.07	0.06	0.04	0.05
σ_{Δ}	0.18	0.18	0.19	0.19
RMS	0.19	0.19	0.19	0.20

T: Temperature, TY: Tympanic region, NCIT: Non-contact infrared thermometer, IRT: Infrared thermography, FSR: Right sagittal face region, FSL: Left sagittal face region, ER: Right ear, EL: Left ear, RMS: Root-mean-square

DISCUSSION

Using the information gathered in our clinical study, we evaluated the clinical accuracy of the IRTs with respect to reference forehead and tympanic NCITs. The measurements obtained from different NCITs are also compared to each other to assess the degree of agreement. Finally, the linear regression functions were determined to estimate approximate body temperatures from the IRT skin temperatures.

Clinical Study Limitations

The study group has a mean age of 66.72, despite having the younger samples this is an elderly figure. The age interval may affect the IRT measurements (30). In the future, an extended clinical study including a more balanced population of various age groups may also be conducted.

In this study, the first thermal images were captured 30 seconds after the medical masks were removed. After 60 seconds following the first thermal images, the second images were captured. This sequence was designed to quantify the thermal effect caused by taking off medical masks. It may be considered to continue with a third frontal IRT capture after some delay to minimize any adverse effects of the medical masks.

Comparison of Forehead NCIT with Tympanic NCIT

It is observed that the forehead and tympanic NCIT measurements have high differences. The mean and SD of tympanic and forehead NCIT measurements are (36.64 °C, 0.20 °C) and (35.94 °C, 0.39 °C) respectively. The reason why tympanic NCIT measurements have a lower SD, might be that the tympanic temperature was found to be the most consistent regardless of the environmental temperature (13,14,15,19).. Besides, each forehead measurement is lower than the corresponding tympanic sample. This result agrees with the results obtained in (19,21,22). In addition, there is another study resulting with a fixed offset between forehead and tympanic NCITs (19) which contradicts our results.

These differences imply that, without any manipulation, our two NCIT devices are not consistent with real body temperatures. This result may be caused by the fact that skin temperature at different sites tends to be sensitive to environmental factors (31). It is also common for various NCIT thermometers display inconsistent measurements (15).

IRT Analysis in Frontal Face

In the frontal face, it is determined that the maximum facial temperature is strongly correlated with canthus and mouth region IRT measurements, in that order. This finding is similar to previous studies (22,23).

We also revealed that the forehead IRT values are lower than and less correlated with the rest of their frontal IRT samples. These results are consistent with (22,27,31) and may be caused by the fact that the skin temperature at the forehead site tends to be sensitive to environmental factors.

IRT Analysis in Sagittal Face

In the sagittal face, the hottest point is almost always spotted in the ear region, on both the right and left sides. The right and the left ear IRT temperatures are highly correlated (r=0.72). Although the bias mean is being very low (μ_{Δ}=-0.09 °C), σ_{Δ} value is 0.53 °C and RMS value is 0.55 °C. Therefore, they cannot be used in clinical practice.

Effects on IRT After Putting off Medical Mask

The dynamics of thermal inhomogeneities induced by increased concentrations of carbon dioxide in the exhaled air was captured (32). We thought that these inhomogeneities would also affect our frontal IRT measurements.

We observed that the mean value of all frontal IRT measurements at a specific site decreased by the time after the medical mask was removed. The SD values stay almost at the same level. As an example, the mean of the maximum of both canthus IRT temperature values decreases by 0.63 °C and the SD changes only around -0.01 °C. We considered that these temperature changes were caused by the disappearance of the negative effects by time and reaching local thermal stability after the removal of the masks.

Regression

The corresponding NCIT and IRT measurements in our study are inconsistent regarding clinical accuracy (6,7,22,23,26). This concluded that IRT sensors are more feasible than invasive sensors but should not be the same as those used for measuring core body temperatures (25).

To achieve consistent measurements as in conversion studies, we determined the regression functions to model the relationship between dependent and independent variables (2,22) and after the conversion, we re-evaluated the clinical accuracy. Limpabandhu et al. (26) performed a similar study to ours, which includes capturing IR images in the temple plane. They recorded core body temperatures by using a contact forehead temperature monitoring system and determined that accurate core body temperature prediction could be provided using the linear regression model.

Regression of Tympanic NCIT on Forehead NCIT

While the majority of studies analyze IRT temperatures against those obtained by thermometers, there are also studies that analyze NCIT values comparatively (15,26). In addition to IRT

vs NCIT comparisons, we also compared forehead against tympanic NCIT measurements. Assuming that each output of these devices is a function of actual core body temperature, we predicted that the fundamental relationship between them could be determined.

We found out that there is a divergence between forehead and tympanic NCIT measurements. The linear regression (1) converts forehead NCIT measurements to tympanic NCIT estimates and produces quite accurate clinical measurements. The resultant bias statistics are (0.04 °C, 0.18 °C) and RMS is 0.19 °C. The forehead temperature becomes an estimate for the tympanic temperature in clinical accuracy after the conversion.

Regression of NCITs on IRTs

The IRT variables in our dataset have correlations to be considered high to each other, but the bias statistics and RMS values imply that there are major deviations from NCIT references. As a result of this IRT vs NCIT deviation, it is clear that we have to convert the samples from an IRT site to NCIT references, if we want to make a proper body temperature measurement approximation by a thermal camera.

Our regression studies have shown us that when we apply a conversion to sagittal IRT measurements (i.e., ear region), the most accurate tympanic NCIT measurement predictions can be provided. Similarly, Limpabandhu et al. (26) found out that the temple and nose regions were identified as optimal IRT inputs as long as contact forehead thermometer measurements were set as reference.

Naturally, the regression performances of frontal NCIT on frontal IRTs and the regression of tympanic NCIT on frontal IRTs were different. Frontal IRT to tympanic NCIT conversion resulted in better bias statistics and RMS. It produced the outputs that were much more within the acceptable limit. It has a minimum bias mean of 0.04 °C (SD 0.22 °C) and 0.22 °C RMS.

Wang et al. (22) have tried various regression techniques to impute clinical oral temperatures from several frontal IRT sites. Their selected promising results are much better than our regression results. The major reason for this is considered to be the higher variance and different density curve of our forehead thermometer measurements, as shown in (Figure 2a).

Sun et al. (2) calculated the linear regression function of axillar NCIT temperature on IRT facial skin temperature as $y=0.43 x + 22.57$, whereas we calculated the conversion of forehead NCIT on facial IRT as $y=0.08 x + 32.88$. These two regression functions are quite dissimilar to each other. The main reason may be the use of different NCIT measurement sites, i.e., axilla vs forehead. Also, thermal cameras and thermometers used in both studies were different. These results emphasized that each experiment should recalculate its own conversion (calibration) functions with regard to the devices, subject types, measurement sites, environment setup etc.

The regression of tympanic NCIT on sagittal IRTs gave slightly better results. It has the bias; 0.04 °C (SD 0.19 °C) and 0.20 °C RMS. The results of these regression methods showed us that one can accurately estimate the body temperature (obtained from the ear channel) from either frontal or sagittal sites on the thermal images.

The standard E1965-98:2016 document defines the maximum permissible errors; ±0.3 °C for skin IR thermometers and ±0.2 °C in the 36.0-39.0 °C range for ear canal IR thermometers (28). Assuming we had NCIT devices compatible with the standards, the converted NCIT values seem to go out of acceptable accuracy intervals. However, since IEC 80601-2-59: 2017 standard defines the maximum permissible errors; ±0.5 °C (in 34.0-39.0 °C range) for IRTs, the converted samples conform to this IRT standard (10).

CONCLUSION

In this study, a very low agreement was found between forehead and tympanic NCIT measurements. This may be due to the fact that the forehead area is more affected by environmental conditions, whereas the ear canal is relatively closed to external influences. When the IRT measurements were compared with each other, high correlations were determined.

It was also experienced that wearing a medical mask affected the IRT measurements, resulting in an overall increase. This result supports the condition that subjects should be kept waiting for a period of time after they were allowed to take off their masks. As a result, it is thought that it would be more accurate to make IRT measurements in the sagittal plane in cases where the negative effects of the medical mask are likely to be seen.

No clinical agreement was found between IRT and NCIT measurements. It was found that conversion should be performed to estimate body temperature. The clinical agreement was obtained when we estimated the NCIT values by linear regression using the input IRT measurements. The clinical agreement was slightly higher for sagittal plane measurements.

As a result, we showed that real body temperature can be accurately estimated from sagittal face thermal images, especially from the rectangular region surrounding the human ear. The fact that the ear area is more protected from

environmental conditions and does not have obstacles such as medical masks, hats and glasses, means that it should be used in manual use or in fully automated systems. In addition, it may be necessary to capture images with an installation in accordance with the standards and to calculate the conversion functions again for each device and environmental condition.

Ethics

Ethics Committee Approval: The clinical research, which was a part of the project "Development of Artificial Intelligence-supported Software that Remotely Evaluates Human Body Temperature and Performs High Accuracy Measurements with Thermal Cameras", was approved by İzmir Tınaztepe University Health Sciences Scientific Research and Publication Ethics Committee (protocol code: TUBAYEK: 002, date: 10.03.2021).

Informed Consent: Written informed consent was obtained from all subjects.

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Footnotes

Authorship Contributions

Surgical and Medical Practises: E.V., Concept: D.Ö., E.V., Design: D.Ö., E.V., Data Collection or Processing: D.Ö., E.V., Analysis or Interpretation: D.Ö., E.V., Literature Search: D.Ö., E.V., Writing: D.Ö.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Can ChatGPT be Used as a Drug Interaction Checker in Psychiatric Inpatients?

ChatGPT Psikiyatri Servisinde İlaç Etkileşimi Denetleyicisi Olarak Kullanılabilir mi?

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ABSTRACT

Objective: ChatGPT is a chatbot used in many fields. Recently, it has also been used in health science. The present study investigated the clinical usefulness of ChatGPT as a drug interaction checker in a psychiatric inpatient clinic.

Methods: This retrospective cross-sectional study was conducted at a psychiatric inpatient clinic in Hatay, Türkiye. Drug-drug interactions (DDIs) were analyzed using UpToDate and ChatGPT version 4.0 based on 126 psychiatric inpatient prescriptions collected between July and October 2024. The results were compared quantitatively, and Pearson correlation analysis was performed. Interaction mechanisms were evaluated using an interrater agreement test to assess accuracy and consistency.

Results: This study evaluates DDIs in a psychiatric inpatient clinic using ChatGPT version 4.0. ChatGPT identified 93% of DDIs, in 93% of the 126 prescriptions analyzed while UpToDate identified DDIs in 92%. UpToDate identified 1127 DDIs, categorized as follows: 57 (5.1%) B, 943 (83.6%) C, 120 (10.6%) D, and 7 (0.6%) X. ChatGPT detected 1694 DDIs, and 0 (0.0%) B, 1102 (65.0%) C, 584 (34.5%) D, and 8 (0.5%) X. ChatGPT demonstrated a weak correlation with UpToDate, and the mechanisms of interaction identified by the two tools were inconsistent.

Conclusion: Although ChatGPT demonstrates strong search capabilities and facilitates the comparison of multiple drug interactions, it still requires further improvement to be considered a reliable tool for drug interaction checking.

Keywords: ChatGPT, drug interactions, drug prescription, UpToDate

ÖZ

Amaç: ChatGPT, birçok alanda kullanılan bir sohbet robotudur. Son zamanlarda sağlık bilimlerinde de kullanılmaya başlanmıştır. Bu çalışma, psikiyatri servisinde ilaç etkileşimi denetleyicisi olarak ChatGPT'nin klinik yararını araştırmıştır.

Yöntemler: Bu retrospektif kesitsel çalışma, Türkiye'nin Hatay ilindeki bir psikiyatri yatan hasta kliniğinde gerçekleştirilmiştir. Temmuz-Ekim 2024 tarihleri arasında elde edilen 126 psikiyatri yatan hasta reçetesinde UpToDate ve ChatGPT 4.0 sürümü kullanılarak ilaç-ilaç etkileşimleri (İİE) analiz edilmiştir. Sonuçlar nicel olarak karşılaştırılmış ve Pearson korelasyon analizi yapılmıştır. Etkileşim mekanizmaları, doğruluk ve tutarlılığı değerlendirmek için bir değerleyici güvenebilirliği testi kullanılmıştır.

Bulgular: Bu çalışma, ChatGPT 4.0 sürümü kullanılarak bir psikiyatri yatan hasta kliniğinde İİE'yi değerlendirmektedir. ChatGPT analiz edilen 126 reçetenin %93'ünde İİE tespit ederken, UpToDate %92'sinde İİE tespit etmiştir. UpToDate aşağıdaki şekilde kategorize edilen 1127 İİE tespit etmiştir: 57 (%5,1) B, 943 (%83,6) C, 120 (%10,6) D ve 7 (%0,6) X. ChatGPT 1694 İİE tespit etmiş ve 0 (%0,0) B, 1102 (%65,0) C, 584 (%34,5) D ve 8 (%0,5) X grubu olarak sınıflandırılmıştır. ChatGPT, UpToDate ile zayıf bir korelasyon göstermiş ve ikisi tarafından tespit edilen etkileşim mekanizmaları tutarsız bulunmuştur.

Sonuç: ChatGPT güçlü arama yetenekleri sergilemekle birlikte çoklu ilaç etkileşimlerinin karşılaştırılmasını kolaylaştırmaktadır. Ancak, güvenilir bir ilaç etkileşimi denetleyicisi olarak kabul edilebilmesi için daha fazla iyileştirme gerektirmektedir.

Anahtar Kelimeler: ChatGPT, ilaç etkileşimleri, ilaç reçeteleme, UpToDate

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INTRODUCTION

ChatGPT is one of the large language models (LLMs) that enable searching, writing, and analyzing. It has gained popularity due to its wide range of applications. Students commonly use it to access basic information, engage in casual conversations, and receive academic assistance and tutoring in their daily lives (1). Moreover, it is being explored in the medical field, such as academic writing, student and patient learning (2), making a diagnosis (3), safe prescribing (4), drug discovery (5), and therapy management (6).

ChatGPT can generate patient handouts, assess their readability, and potentially supplement traditional research methods. Researchers have presented clinical scenarios to various LLMs, including ChatGPT, Gemini, Claude, and Llama, to evaluate their performance. They tested the models for dose checks, recommendations based on given pharmacogenetic information, drug-drug interactions (DDIs), and drug monitoring. LLMs showed limited performance in identifying dosing regimens and therapeutic drug monitoring. However, they evaluated potential drug interactions well and provided pharmacogenomic-based recommendations (6). In another study, ChatGPT demonstrated consistency in reporting adverse drug reactions and generating patient handouts but showed limitations in interpreting data for safe prescribing (4). It achieved a 79% success rate in responding to 264 questions posed by clinical pharmacists to assess its clinical usefulness (7). Additionally, ChatGPT 4.0 was tested on 39 patient management scenarios of varying complexity levels. Two clinical pharmacists evaluated the responses based on the criteria of drug interaction, contraindication, and alternative drug recommendation. The accuracy of ChatGPT was defined as over 70%, and in some cases, it discovered drug interactions that pharmacists did not mention. However, it consistently avoided recommending specific drug doses (8). In a separate study on geriatric patient management, ChatGPT was queried about polypharmacy which identified seven inappropriate drugs for geriatrics and suggested deprescribing measures.

ChatGPT correctly detected 5 out of 6 DDIs and 3 out of 8 drug-disease interactions. However, it it was unable to recognize an ineffective medication and fabricated two irrelevant drug-disease interactions (9). In another study, ChatGPT 4.0 was evaluated for its ability to analyze DDIs across 15 treatment regimens, successfully identifying 93% of all interactions. ChatGPT and the conventional method identified clinically significant DDIs as 86% and 53% of cases, respectively (10). Among the 40 drug interaction lists compiled from the literature, ChatGPT analyzed all and initially scored 39 out of 40. However, the final score was 20 out of 40. When the reason for each interaction was assessed, 17 were classified as conclusively true, 22 as inconclusive, and 10 as true (11). In a retrospective study, 120 patient prescriptions were randomly selected from a total of 3,360, and a pharmacist analyzed DDIs with Stockley's interaction checker. At the same time, a second, blinded researcher performed the same analysis using ChatGPT version 3.5. ChatGPT achieved only 24% of the detection rate compared to the pharmacist's results. The researchers suggested that using improved artificial intelligence (AI) programs, e.g., Bing, Bard, MedPalm, or ChatGPT 4.0, would be beneficial (12).

Recent studies have focused on real clinical samples and the latest versions of LLMs. In one such study, ChatGPT version 4.0 was used to analyze 301 discharge prescriptions, and its performance was compared with that of Micromedex. ChatGPT demonstrated high accuracy, achieving a 100% detection rate for DDIs. However, it demonstrated limited accuracy in describing the severity of DDIs (37.3%) and moderate accuracy in identifying their onset (65.2%) (13). With the introduction of ChatGPT version 4.0, several studies have compared its performance to version 3.5. One study evaluated diagnostic accuracy and reported an accuracy score of 0.86 for version 4.0, compared to 0.63 for version 3.5 (14). A survey assessing different chatbots for detecting DDIs involved 255 drug interaction scenarios analyzed by ChatGPT-3.5, ChatGPT-4, Microsoft Bing AI, and Google Bard and compared their sensitivity, specificity, and accuracy. They used Drugs.com and Micromedex as conventional drug interaction checkers. Microsoft Bing AI was the most sensitive, specific, and accurate among chatbots. ChatGPT-4 outperformed better than ChatGPT-3.5; different specificity and accuracy values were observed for pharmacologic groups of drugs. However, the study methodology did not cover rank or interaction mechanism-based analysis (15).

The aforementioned databases, such as Stockley's, Micromedex, Drugs.com, UpToDate and Medscape, are considered the standard for their drug interaction checkers. Among them, UpToDate is an evidence-based clinical database that provides current information supported by under Wolters Kluwer publication. UpToDate has achieved the highest scope score, reflecting its strong sensitivity in identifying and distinguishing drug interactions (16). In this study, we used the UpToDate drug interaction checker as the reference standard. This retrospective cross-sectional study aimed to evaluate the performance of ChatGPT in identifying DDIs and to compare its results with a validated clinical tool. A psychiatric inpatient clinic was selected as the study setting due to the high likelihood of polypharmacy and associated DDIs (17). The prescriptions from the clinic were analyzed

for DDIs using both the UpToDate drug interaction checker and ChatGPT version 4.0. The results from ChatGPT were compared with those from UpToDate in terms of accuracy and consistency to assess ChatGPT's potential as a drug interaction checker.

MATERIALS AND METHODS

The retrospective cross-sectional study was performed in the psychiatric inpatient clinic of Hatay Mustafa Kemal University Tayfur Ata Sokmen Faculty of Medicine from July to October 2024, with the approval of the research Ethics Committees of Hatay Mustafa Kemal University Tayfur Ata Sokmen Faculty of Medicine (approval no: 26, date: 30.10.2024). As the study was retrospective in nature, patient consent was not required.

A clinical pharmacologist analyzed all prescriptions without exclusions for potential DDIs using the UpToDate drug interaction checker. Independently, a second researcher, blinded to the first analysis, evaluated the same prescriptions using ChatGPT (version 4.0). The results were compared quantitatively, correlation analysis was conducted, and interaction mechanisms were assessed using an interrater agreement test to increase precision. Data were stratified and analyzed according to patient age, sex, clinical indication, severity rankings of DDIs provided by UpToDate, and identified interaction mechanisms.

Prompt Adaptation

The analysis focused on determining ChatGPT's accuracy, consistency, and alignment with the risk categorizations provided by the UpToDate framework. The evaluation targeted specific interaction mechanisms such as central nervous system depression, QT prolongation, serotonin syndrome, and metabolic interference, ensuring a comprehensive assessment of clinical outcomes.

ChatGPT was first introduced to the UpToDate Risk Rating system to establish a consistent understanding of interaction categories. The system was explained using a series of prompts that defined the categories. The following prompt was used to ensure ChatGPT understood these categories:

- "These are the UpToDate risk rating categories: A means no known interaction; B means no action is needed; C means monitor therapy; D means consider therapy modification; and X means avoid combination. Do you understand?"

The study analyzed drug interactions after confirming that ChatGPT had accurately assimilated these definitions. The analysis was conducted in two phases. In the first phase, ChatGPT was prompted to analyze drug combinations using standardized queries, such as:

- "Analyze the interactions between (drug A), (drug B), and (drug C). Provide detailed descriptions, classify their severity using the predefined UpToDate categories, and justify your classification."

In addition to this primary prompt, supplementary prompts were used to enhance the depth of the analysis:

- "Describe the mechanisms of interaction between (drug A) and (drug B), and explain their clinical consequences."
- "Why would the interaction between (drug A) and (drug B) necessitate therapy modification or monitoring?"
- "Classify the interaction between (drug A), (drug B), and (drug C) using UpToDate risk rating categories, and explain the reasoning behind your classification."

These prompts ensured that ChatGPT provided structured outputs, including the interaction descriptions, risk classifications, and justifications for each classification. Responses were collected and organized into structured tables with columns for drug combinations, interaction descriptions, risk ratings, and justifications. The results from ChatGPT were compared directly with those from UpToDate to evaluate agreement, discrepancies, and potential gaps in ChatGPT's analysis. The findings were analyzed descriptively to assess the consistency and accuracy of ChatGPT's classifications compared to UpToDate. This comparison aimed to determine the extent to which ChatGPT could serve as a supplementary tool for identifying and classifying DDIs in clinical practice.

Statistical Analysis

Baseline characteristics and numerical comparisons were given as a mean and standard deviation or percentage (%). The Pearson correlation coefficient was used to test the accuracy of ChatGPT's ranking system (rank C and D). Cohen's Kappa analysis was used to evaluate the consistency of the drug interaction mechanisms. Microsoft Excel (2021) and GraphPad Prism (version 10, USA) were used for all calculations and analyses. A p-value below 0.05 is considered significant.

RESULTS

The study included 126 patient prescriptions, with 74 patients (59%) male. The mean age was 38.6±16.2 years, as presented in Table 1. The most common clinical indication was depression, observed in 52 cases (41%). The three most interacted drugs were olanzapine, quetiapine, and risperidone, as given in Table 2. A total of 552 medications were evaluated for potential DDIs. The analysis of DDIs identified by UpToDate and ChatGPT is presented in Table 3, including group-level results

and average DDIs per patient. UpToDate identified a total of 1.127 DDIs, with the following severity rank distribution: 57 (5.1%) classified as B, 943 (83.6%) as C, 120 (10.6%) as D, and 7 (0.6%) as X. This corresponds to an average of 8.9 DDIs per patient. In contrast, ChatGPT detected 1.694 DDIs, with the following distribution: 0 (0.0%) classified as B, 1,102 (65.0%) as C, 584 (34.5%) as D, and 8 (0.5%) as X. The average number of DDIs per patient was 13.4. ChatGPT identified a higher number of interactions than UpToDate, likely due to its ability to evaluate multiple drugs simultaneously and compare beyond two-drug combinations, unlike UpToDate. ChatGPT's internal ranking distribution for DDIs (separate from UpToDate's scale) was: 420 (98%) classified as X, 3 (0.7%) as D, and 6 (1.3%) as C. These values were not directly comparable with UpToDate's scoring system. To assess accuracy, the DDIs classified as C and D by ChatGPT were compared to UpToDate's corresponding ranks using Pearson correlation analysis. For rank C, a moderate and statistically significant correlation was found ($r=0.69$, $p<0.001$), as shown in Figure 1. For rank D, the correlation was weak and not statistically significant ($r=0.05$, $p=0.33$), as shown in Figure 2. The consistency of ChatGPT's identification of interaction mechanisms was also evaluated. As presented in Table 4, Cohen's Kappa coefficient was calculated as -0.475, indicating poor agreement and a lack of statistical significance.

Table 1. Baseline characteristics

Characteristics	Frequency n (%)
Gender	
Male	74 (59%)
Female	52 (41%)
Age (mean ± SD)	38.6±16.2
Indications	Depression 52 (41%) Bipolar disorder 32 (25%) Psychosis 30 (24%)

SD: Standard deviation

Table 2. The three most interacted drugs in UpToDate and ChatGPT

Number	UpToDate (total DDIs 1127)	ChatGPT (total DDIs 1694)
1	Olanzapine (332, 29%)	Olanzapine (231, 14%)
2	Quetiapine (217, 19%)	Quetiapine (188, 11%)
3	Risperidone (205, 18%)	Risperidone (185, 11%)

DDIs: Drug-drug interactions

DISCUSSION

The present study explores ChatGPT version 4.0's performance in detecting DDIs in the psychiatric inpatient clinic. In a similar study involving 511 patients, Lexicomp identified an average of 8.5±5.1 DDIs per patient (18). UpToDate found 8.9 DDIs per patient, while ChatGPT found 13.4. This finding aligns with the report by Roosan et al. (8) who observed that ChatGPT tends to detect more DDIs than conventional tools.

Several factors may explain this discrepancy. First, ChatGPT often counts overlapping mechanisms such as sedation and respiratory depression as separate interactions, whereas UpToDate typically merges them into a single entry. Second, side effects like weight gain, commonly associated with certain antidepressants, are listed as distinct interactions by ChatGPT, while UpToDate may either group them under a general advisory or omit them entirely. Lastly, ChatGPT occasionally assigns multiple interaction counts to a single mechanism. Similarly, Al-Ashwal et al. (15) reported that ChatGPT versions showed the highest rate of false-positive DDIs and the lowest accuracy and specificity among the LLMs evaluated. They explained this difference by noting that ChatGPT processes a vast amount of general information compared to the structured and curated content used in clinical databases such as Micromedex and Drugs.com (15).

UpToDate and ChatGPT revealed a significant correlation in identifying rank C DDIs (Figure 1) and failed to show a significant correlation for rank D interactions (Figure 2). When we examined the numbers in Table 3, ranks C and X appeared relatively compatible between the two tools. However, ChatGPT tends to identify DDIs as rank D, compared to UpToDate. ChatGPT identified more weight gain-related interactions and classified them as rank D. Secondly, ChatGPT tended to count more DDIs than were described in the interaction mechanisms. Additionally, as presented in Table 4, there was no agreement between the two platforms regarding

Table 3. Comparison of DDIs of UpToDate and ChatGPT

	Database / Rank	Total	B	C	D	X
UpToDate	(n, %)	1127 (100%)	57 (5.1%)	943 (83.6%)	120 (10.6%)	7 (0.6%)
	DDIs per patient (n)	8.9	0.4	7.5	0.9	0.05
ChatGPT	(n, %)	1694 (100%)	0 (0.0%)	1102 (65.0%)	584 (34.5%)	8 (0.5%)
	DDIs per patient (n)	13.4	0	8.7	4.6	0.06

DDIs: Drug-drug interactions

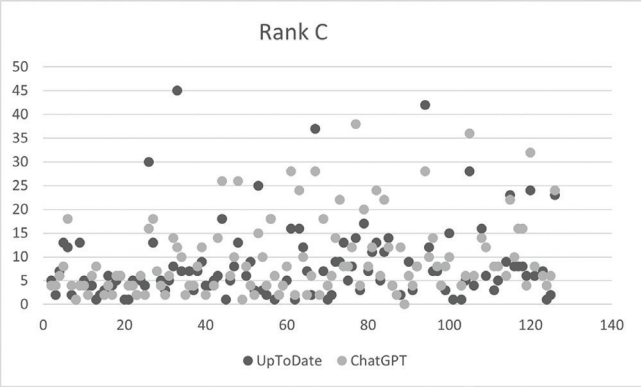

Figure 1. Pearson-correlation analysis of rank C DDIs UpToDate and ChatGPT [coefficient (r): 0.69, p=0.00]

DDIs: Drug-drug interactions

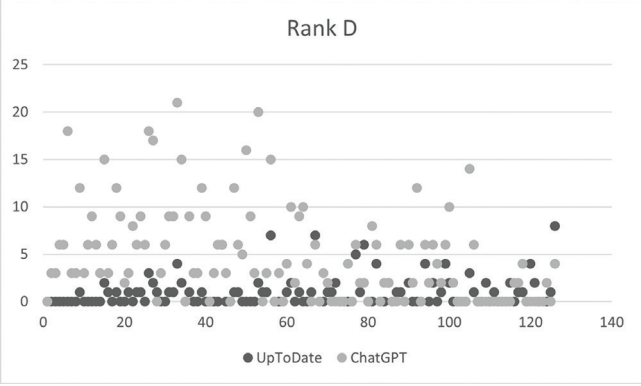

Figure 2. Pearson-correlation analysis of rank D DDIs UpToDate and ChatGPT [coefficient (r): 0.05, p=0.33]

DDIs: Drug-drug interactions

Table 4. Consistency of UpToDate and ChatGPT drug interaction mechanisms

		UpToDate	
		Agree	Disagree
ChatGPT	Agree	0.34684	0.294874
	Disagree	0.19365	0.164636

Weighted Cohen's Kappa analysis. Kappa <0: No agreement, Kappa =-0.475 [confidence interval (95%) = (-0.510 to -0.441)]

the underlying mechanisms of the DDIs. The most interacted drugs, which correlated with prescription numbers, are given in Table 2. When compared to interaction numbers UpToDate versus (vs.) ChatGPT: Olanzapine (332 vs. 231), Quetiapine (217 vs. 188), and Risperidone (205 vs. 185). ChatGPT missed some DDIs, and this result also addresses the inconsistency between UpToDate and ChatGPT.

Previous research has reported that version 3.5 has a low intra-rater agreement with pharmacists (12). In our study, version 4.0 also demonstrated inconsistency in this regard. Unfortunately, the study did not include a detailed analysis of the causes behind these discrepancies, which represents a limitation. One notable issue was that ChatGPT did not recognize the seizure-threshold-lowering effects of the drugs, a difference from UpToDate. This discrepancy may stem from UpToDate's access to a comprehensive range of proprietary scientific literature, whereas ChatGPT primarily relies on open-access sources.

Additionally, Medscape and Epocrates databases identified less interactions with biperiden (18). UpToDate reported a limited number of DDIs with biperiden, while ChatGPT reported a higher number and frequently classified them as rank D. Juhi et al. (11) also reported that although ChatGPT provided 22 accurate responses, these were ultimately considered inconclusive in their study. ChatGPT 4.0 demonstrated a sensitivity of 0.747, a specificity of 0.523, and an overall accuracy of 0.592 when compared to conventional drug interaction checkers (15).

A similar study reported that Micromedex identified 60.13% of DDIs from 301 discharge prescriptions, ChatGPT's accuracy achieved 100%, and guessed the onset (rapid, delayed, or not specified) of the interactions of 65.2%. However, it showed a weak performance in determining the severity of DDIs (37.3%) and could not document the relationship of DDIs (20.6%) (13). Another study investigated the pharmacology of drugs by comparing outputs from ChatGPT versions 3.5 and 4.0. The DrugBank database was used as a reference, with version 3.5 predicted 64.64% and version 4 predicted 64.33% of DDIs of some selected drugs (19). As a chatbot, ChatGPT lacks analytical depth and consistency. Several studies have indicated that its performance varies depending on the drug group. ChatGPT and the other LLMs showed different sensitivity, specificity, and accuracy scores according to drug type (15). For example, one study reported that ChatGPT failed to predict the properties of dequalinium, a large molecule compound (19). ChatGPT showed high accuracy (100%) and a weak sensitivity in determining the severity of DDIs (37.3%), which comprises respiratory system drugs 26.05%, and followed by several other pharmacological groups (13). Additionally, ChatGPT could analyze prescribed drugs such as haloperidol, chlorpromazine, and olanzapine and rank them X for QT prolongation. UpToDate identified interactions only in pairwise combinations, typically classifying them as rank C or D. This capability of ChatGPT to assess multi-drug interactions can provide clinicians with more comprehensive guidance and potentially save time in clinical decision-making. It is also important to predict the cumulative effect of concurrently administered drugs, particularly when they act as CYP3A4 substrates, inhibitors, or inducers, as these can significantly influence the pharmacokinetics and overall therapeutic outcome. While most conventional drug interaction checkers

assess interactions in pairwise combinations, Drugs.com and ChatGPT can evaluate multiple drug interactions simultaneously. After prompting ChatGPT with complex drug regimens, it provided detailed and ranked interaction data, offering valuable insights into potential risks associated with polypharmacy.

Study Limitations

This study has several limitations that warrant careful consideration. First, the retrospective cross-sectional design restricts the assessment of temporal consistency in ChatGPT's performance and limits conclusions about causality or clinical impact. Second, although we used standard comparison metrics such as Pearson correlation and Cohen's Kappa to evaluate the agreement between ChatGPT outputs and established references, the observed low concordance indicated fundamental discrepancies. Given this, we did not proceed with more advanced or outcome-focused statistical tests, as these would likely not yield meaningful additional insights at this stage of evaluation. The aim was to provide an initial benchmark of agreement between LLM outputs and UpToDate databases. Besides, medazepam was excluded from both lists due to its exclusion in the UpToDate drug interaction checker. Due to UpToDate's limitation to dual comparisons, ChatGPT was used to evaluate multiple drug interactions separately. Rank A, B, and X DDIs do not have sufficient data for correlation analysis.

CONCLUSION

ChatGPT demonstrates strong search capabilities, the ability to perform multiple drug interaction comparisons, and offers informative guidance, which may be beneficial in clinical settings and contribute to time efficiency. However, it still requires substantial improvement before it can be reliably used as a standalone drug interaction checker. This study focused on psychiatric medications; therefore, the findings may vary depending on the drug class involved.

Ethics

Ethics Committee Approval: The retrospective cross-sectional study was performed in the psychiatric inpatient clinic of Hatay Mustafa Kemal University Tayfur Ata Sokmen Faculty of Medicine from July to October 2024, with the approval of the Research Ethics Committees of Hatay Mustafa Kemal University Tayfur Ata Sokmen Faculty of Medicine (approval no: 26, date: 30.10.2024).

Informed Consent: As the study was retrospective in nature, patient consent was not required.

Footnotes

Authorship Contributions

Concept: E.B.G., Design: E.B.G., A.G., Data Collection or Processing: E.Y., Analysis or Interpretation: E.B.G., A.G., Literature Search: E.B.G., Writing: E.B.G., A.G., E.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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The Türkiye National Genome and Bioinformatics Project: An Overview

Türkiye Ulusal Genom ve Biyoinformatik Projesi: Genel Bir Bakış

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ABSTRACT

The Turkish National Genome and Bioinformatics Project is a large-scale initiative aimed at advancing genomic research and precision medicine in Türkiye. This project focuses on whole genome sequencing of diverse population samples, conforming to international standards and utilizing validated next-generation sequencing technologies. Genomic DNA extraction and sequencing are performed using automated high-throughput platforms to ensure accuracy and scalability.

The project, following the completion of the Türkiye Genome Project phase in 2018, continues with the COVID-19 Genome Project, covering healthy individuals, cancer, and undiagnosed diseases. As of March 2025, biological samples from a total of 2.500 individuals from the Turkish population have been collected, with half of the samples sequenced and secondary bioinformatics analyses completed. Variants and frequencies obtained from the sequenced cohorts have been systematically structured and are being shared securely through the Türkiye Genome Project data sharing portal. This portal allows researchers to analyze genetic data within ethical guidelines and facilitates the enhancement of global scientific collaborations.

By integrating big data analytics and advanced bioinformatics pipelines, the project enhances the understanding of population-specific genetic variations, disease associations, and potential therapeutic targets. This initiative marks a significant step toward the implementation of genomic medicine in Türkiye and strengthens the nation's contribution to global advancements in personalized healthcare and precision diagnostics.

Keywords: Genome project, Turkish genome, whole genome sequencing (WGS), next-generation sequencing (NGS)

ÖZ

Türkiye Ulusal Genom ve Biyoinformatik Projesi, Türkiye'de genom araştırmalarını ve tıbbi ilerlemeyi hedefleyen geniş ölçekli bir girişimdir. Proje, farklı kohortların tüm genom dizilemesi üzerine odaklanmakta olup uluslararası standartlara uygun şekilde doğrulanmış yeni nesil dizileme teknolojilerinden faydalanmaktadır. Genomik DNA izolasyonu ve dizileme süreçleri, doğruluk ve ölçeklenebilirliği sağlamak amacıyla otomatik yüksek verimli platformlar kullanılarak gerçekleştirilmektedir.

Proje; 2018 yılında tamamlanan Türkiye Genom Projesi fazını takiben, COVID-19 Genom Projesi, sağlıklı bireyler, kanser ve tanısız hastalıklar kapsamında devam etmektedir. Proje kapsamında Mart 2025 itibarıyla, Türkiye popülasyonuna ait toplamda 2,500 bireyin biyolojik örnekleri toplanmış olup toplam örneklemin yarısı dizilenmiş ve ikincil biyoinformatik analizleri tamamlanmıştır. Dizilenen kohortlardan elde edilen varyantlar ve frekansları, sistematik olarak yapılandırılmıştır ve güvenli bir şekilde Türkiye Genom Projesi veri paylaşım portalı aracılığıyla paylaşılmaktadır. Bu portal, etik kurallar çerçevesinde araştırmacıların genetik verileri analiz etmesine ve küresel düzeyde bilimsel iş birliklerini artırmasına olanak tanımaktadır.

Büyük veri analitiği ve ileri biyoinformatik altyapıları ile entegre edilen bu proje, popülasyona özgü genetik varyasyonların, hastalık ilişkilerinin ve potansiyel terapötik hedeflerin daha iyi anlaşılmasına katkı sağlayacaktır. Bu girişim, Türkiye'de genombilimin uygulanmasına yönelik önemli bir adım niteliğinde olup ülkenin kişiselleştirilmiş sağlık hizmetleri ve hassas tıp alanındaki küresel ilerlemelere katkısını güçlendirmektedir.

Anahtar Kelimeler: Genom projesi, Türkiye genomu, tüm genom dizileme (WGS), yeni-nesil dizileme (NGS)

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INTRODUCTION

The question that arose following the discovery of DNA in 1953 was whether the alignment of these consecutively arranged nucleotides could be sequenced. Fortunately, the sequencing of small DNA fragments commenced during the 1970s, facilitated by the advent of the Sanger sequencing technique. After small-scale sequencing such as bacteriophage genome, *Haemophilus influenzae* was the first organism to have its entire genome comprehensively sequenced (1). Following the success achieved in genome sequencing, attention subsequently shifted toward the sequencing of the human genome.

Genome projects have profound significance in various fields, particularly in medicine, agriculture, and environmental science. Currently, significant number of genome projects covering various regions and targets around the world have been completed or are ongoing (Table 1). The aims of these projects, which are programmed according to needs, can be summarized as advancing personalized medicine, improving healthcare, optimizing agricultural practices, and improving our understanding of biodiversity. From large-scale international initiatives such as the Human Genome Project (HGP) to more region-specific programs such as the Saudi Human Genome Program and the Turkish National Genome and Bioinformatics Project, each initiative contributes uniquely to the scientific community. These projects aim to gain valuable insights into genetic variation, disease mechanisms, and environmental interactions by mapping and sequencing genomes across different populations and species. Through these efforts, genomic research continues to shape the future of medicine, agriculture, and biodiversity conservation.

The HGP started in the 1990s. The first draft was released in 2001 (2) and completed in 2003 (3). The HGP provided a comprehensive map of the human genome, enabling breakthroughs in personalized medicine, gene therapy, and enhanced understanding of hereditary diseases (4). This project has also fostered global cooperation, making genomic data freely accessible to researchers worldwide, which is crucial for ongoing research and development (5).

Rare Disease Genome Projects

Among rare diseases, which are important public health problems, 10.000 different rare diseases have been identified to date, and it is known that they affect more than 300 million people worldwide (6). It has been observed that these diseases, which show a high rate of genetic transmission (approximately 80%), mostly emerge in childhood. It is understood that this rate increases especially in countries with a history of consanguineous marriage. The reason for this is known to be the increase in the prevalence of diseases with autosomal recessive transmission.

The rare disease genome projects aim to enhance the understanding and diagnosis of rare genetic disorders through advanced genomic technologies and collaborative efforts. These projects focus on identifying disease-causing genetic variants, improving diagnostic success rates, and addressing inequities in genomic research. They employ innovative bioinformatics strategies, variant prioritization methods, and large-scale data analysis to achieve these goals.

The Rare Genomes Project (USA) employs genome sequencing to identify causal variants, using computational models to prioritize variants based on quality scores, allele frequency, and phenotype. This approach has led to the discovery of novel diagnostic variants and disease-gene candidates (7). Another rare disease project is the Solve-RD project which is a major European initiative. This project has centralized and reanalyzed genetic datasets, identifying disease-causing variants in over 700 rare disease families. This project has developed new methods to detect unknown genetic variants and utilized long-read sequencing to diagnose previously undiagnosed families (8).

Data related to rare diseases are also emerging from large-scale genome projects that do not directly focus on rare diseases. For instance, the 100.000 Genomes Project (100kGP) has applied an analytical gene burden framework to discover 88 novel rare disease-gene associations, potentially diagnosing 456 previously undiagnosed cases. This highlights the clinical impact of large-scale statistical approaches in discovery of novel variants that are responsible for rare diseases (9). Structural variants, including inversions, have been analyzed in 33.924 families, revealing their role in rare diseases and resolving complex diagnostic cases (10). Genome projects that have been conducted and are ongoing have shown that with a unified data infrastructure, collaborative data analysis, and long-term storage of genomic data, it becomes easier to improve diagnostic methods for undiagnosed patients and develop therapeutic drugs for rare diseases.

Cancer Genome Projects

Cancer genome projects, especially the 100kGP, have significantly advanced the understanding and application of WGS in oncology. The aim of 100kGP is to integrate genomic data into clinical practice to provide and develop more specific recommendations for cancer patients and develop treatment strategies. With the 100kGP, it was found that there were distinct pathogenic variants (PV) between European and non-European patients. In particular, 4.6% of South Asian patients

Table 1. Comprehensive overview of global human genome projects

Project name	Status	Objectives	Country	Websites
Human Genome Project	Completed (2003)	To map and sequence the entire human genome, providing foundational knowledge for genetic research and personalized medicine.	International	https://www.genome.gov/human-genome-project
Human Microbiome Project	Completed (2007-2016)	Study microbial communities and their health implications.	United States	https://hmpdacc.org/
1000 Genomes Project	Completed (2015)	To create a detailed catalog of human genetic variation by sequencing genomes from diverse global populations.	International	https://www.internationalgenome.org/
Cancer Genome Atlas	Completed (2006-2018)	Characterize genomic alterations in over 30 cancer types.	United States	https://portal.gdc.cancer.gov/
deCODE Genetics Project	Ongoing (since 1996)	Explore genetic variations and their implications for health.	Iceland	https://www.decode.com/
Canadian Genomics Enterprise	Ongoing (since 2000)	Support genomic research for advancements in health, agriculture, and environment.	Canada	https://genomecanada.ca/
Personal Genome Project China	Ongoing (since 2005)	To provide ethical alternatives for problematic human subject consent and to test novel technologies to collect data on genomes, environments and traits.	China	http://pgpchina.org/
UK Biobank	Ongoing (since 2006)	To compile extensive genetic, health, and lifestyle data to investigate disease determinants and promote personalized medicine.	United Kingdom	https://www.ukbiobank.ac.uk/
International Cancer Genome Consortium	Ongoing (since 2008)	Map genomic abnormalities in diverse cancer types.	Global	https://www.icgc-argo.org/
The African Genome Variation Project	Ongoing (since 2010)	Map genetic variation across African populations.	Africa	https://www.sanger.ac.uk/collaboration/african-genome-variation-project/
Tohoku Medical Megabank Project	Ongoing (since 2011)	To support personalized healthcare by analyzing genetic and environmental data from populations affected by the 2011 disaster.	Japan	https://www.megabank.tohoku.ac.jp/english/
IRDiRC	Ongoing (since 2011)	Promote global research collaboration for rare disease diagnosis and treatment.	Global	https://irdirc.org/
Saudi Human Genome Program	Ongoing (since 2013)	Map genetic mutations prevalent in the Saudi population.	Saudi Arabia	https://www.vision2030.gov.sa/en/explore/projects/the-saudi-genome-program
Genome Russia Project	Ongoing (since 2013)	Map genetic diversity among Russia's ethnic groups.	Russia	(-)
Genomics England	Ongoing (since 2013)	Sequence 100.000 genomes for rare diseases and cancer.	United Kingdom	https://www.genomicsengland.co.uk/
Korean Genome Project	Ongoing (since 2015)	To create a reference genome database for the Korean population to support precision medicine.	South Korea	https://kbds.re.kr/
China Precision Medicine Initiative	Ongoing (since 2016)	To sequence 10 million genomes to advance precision medicine tailored to the Chinese population.	China	(-)
GenomeAsia 100K	Ongoing (since 2016)	Sequence 100.000 genomes from diverse Asian populations.	Asia	https://www.genomeasia100k.org/
Australian Genomics Health Alliance	Ongoing (since 2016)	Integrate genomics into clinical practice for rare diseases and cancer.	Australia	https://www.australiangenomics.org.au/
Rare Genomes Project	Ongoing (since 2016)	Provide genome sequencing for individuals with undiagnosed rare diseases.	United States	https://raregenomes.org/

Table 1. Continued

Project name	Status	Objectives	Country	Websites
All of Us Research Program	Ongoing (since 2018)	To gather health data from over one million Americans to facilitate personalized medicine and health equity.	United States	https://allofus.nih.gov/
Türkiye National Genome and Bioinformatics Project	Ongoing (since 2018)	Analyze genetic diversity to understand diseases and develop personalized medicine strategies.	Türkiye	https://tgd.tuseb.gov.tr/en/
Earth BioGenome Project	Ongoing (since 2018)	Sequence genomes of all known eukaryotic species.	Global	https://www.earthbiogenome.org/
Solve-RD	Ongoing (since 2018)	Resolve diagnostic gaps for rare diseases using genomics.	Europe	https://solve-rd.eu/
Darwin Tree of Life Project	Ongoing (since 2019)	Sequence genomes of all eukaryotic species in the UK and Ireland.	United Kingdom	https://www.darwintreeoflife.org/
IndiGen Genome Project	Ongoing (since 2019)	Catalog genetic diversity to support personalized healthcare.	India	https://indigen.igib.in/

IRDiRC: International Rare Diseases Research Consortium

and 5.3% of African patients had PV, indicating the need for improved variant classification in various populations (11).

The use of whole genome sequencing (WGS) has enabled not only the detection of pathogenic variants related to lineage in cancer patients but also the implementation of personalized applications. In a study conducted by Leung et al. (12) it was shown that 59.2% of the participants received personalized clinical recommendations based on their genomic data. With the 100kGP, genomic data can be linked to understanding real health information to understand treatment outcomes and examine the long-term impact of genomic testing on patient care (13), enabling better survival rates analysis also allowing for patient-based clinical recommendations. Additionally, Shibata emphasizes the discovery of non-coding drivers and structural abnormalities through cancer genome sequencing, which may be surprising given their less understood role in cancer compared to coding regions (14).

Türkiye National Genome and Bioinformatics Project

The Türkiye National Genome and Bioinformatics Project has been established with the aim of elucidating molecular biological underpinnings of diseases that pose both significant social and economic burdens, including cancer, rare diseases, and coronavirus disease-2019. Additionally, comprehensive genome, transcriptome, and metagenome sequencing studies are being conducted with healthy volunteers to identify genomic variants specific to the Turkish population and to determine the frequencies of these variants.

The Türkiye National Genome and Bioinformatics Project adopts a vision parallel to large-scale genome initiatives conducted worldwide. For instance, the UK launched the 100kGP in 2013, aiming to sequence the entire genomes of 100.000 individuals. This project has been instrumental in uncovering the genetic basis of diseases, particularly rare diseases and cancer, achieving a diagnostic success rate of 25-35% for undiagnosed cases (15). Similarly, the United States' All of Us Research Program integrates personal health records with genomic information to advance personalized medicine approaches and has collected data from over one million volunteers (16). In Japan, the initiative on rare and undiagnosed diseases has developed a national model integrating genomic analysis for cases of rare diseases with undiagnosed conditions (17).

Rare diseases, identified as a global public health priority, are reported to occur more frequently in our country due to the high prevalence of consanguineous marriages (approximately 20-25%) (18). Therefore, the importance of conducting studies specific to our country, including analyses of variants unique to Türkiye, is increasingly recognized. Inspired by global examples, the Türkiye National Genome and Bioinformatics Project aims to increase diagnostic rates for rare diseases in Türkiye's population, characterized by its unique demographic and genetic structure. It also seeks to discover novel genetic variants and produces reliable, large-scale genomic data that contribute to international genomic research. Consequently, the project positions itself as a strategic initiative, providing a scientific foundation for advancing early diagnosis and the widespread implementation of personalized medicine within Türkiye's healthcare system.

In Türkiye, the diagnosis rate in the first 6 months was 69%, and almost 10% of the patients remained undiagnosed in terms of rare diseases (19). One of the most poignant aspects of undiagnosed rare diseases is their emergence during childhood. This high rate of undiagnosed cases underscores the necessity of incorporating national genome projects and

advanced genomic techniques into routine practices at a systemic level.

As emphasized within the 11th development plan of the Republic of Türkiye (2019-2023), which was published by the Presidency of the Republic of Türkiye in 2018, establishing a national genomic database for the early diagnosis and treatment of genetic diseases, as well as advancing personalized medicine applications, are among the primary priorities. Similarly, research projects focusing on rare diseases are being encouraged, and the development of biotechnological solutions is being targeted with the support of institutions such as the Health Institutes of Türkiye (TÜSEB) and the Scientific and Technological Research Council of Türkiye.

The Workflow of Türkiye Genome Project

WGS is a procedure that involves sequencing the DNA of collected samples while adhering to international standards, ensuring appropriate quality and depth in accordance with the principles of economic scale. This process is carried out using established and validated next-generation sequencing (NGS) technologies. The WGS process at the National Genome Center of Türkiye (TUGEM) encompasses the following key stages (Figure 1).

1. Accepting the Samples Taken According to the Project Acceptance Criteria at the Sequencing Center

Within the scope of the Türkiye National Genome and Bioinformatics Project, blood and tissue samples were collected from distinct cohorts during different phases of the study (Table 2). The peripheric blood samples were collected from patient groups and healthy volunteers at city hospitals, family health centers countrywide and General Directorate of Public Health of Türkiye. As of March 2025, biological samples (blood, tissue, serum, swab, etc.) have been collected from 2500 healthy volunteers and WGS process has been completed for a total of 1067 individuals from the Turkish population (Table 3).

2. Verifying the Quality of the Accepted Samples for Sequencing

Genomic DNA was isolated from blood and tissue samples using the QiaSymphony automation system (Qiagen), and the concentrations of the elutions were determined with Qubit Flex Fluorometer (Thermo Fisher) using Qubit dsDNA BR analysis kit (Invitrogen).

3. Conducting the Library Preparation (Wet Lab) Process by Using Robotic Technology

Illumina DNA PCR-Free Prep tagmentation beads and buffers, IDT for Illumina DNA/RNA UD indexes and Illumina DNA PCR-Free Prep purification beads and buffers kits were used for tagmentation, dual-index ligation and purification of the single stranded DNA libraries and this process was conducted using the Hamilton ML STAR automation system (Hamilton Company). Library quantification was carried out with Qubit Flex Fluorometer (Thermo Fisher Scientific) by Qubit ssDNA assay kit (Invitrogen).

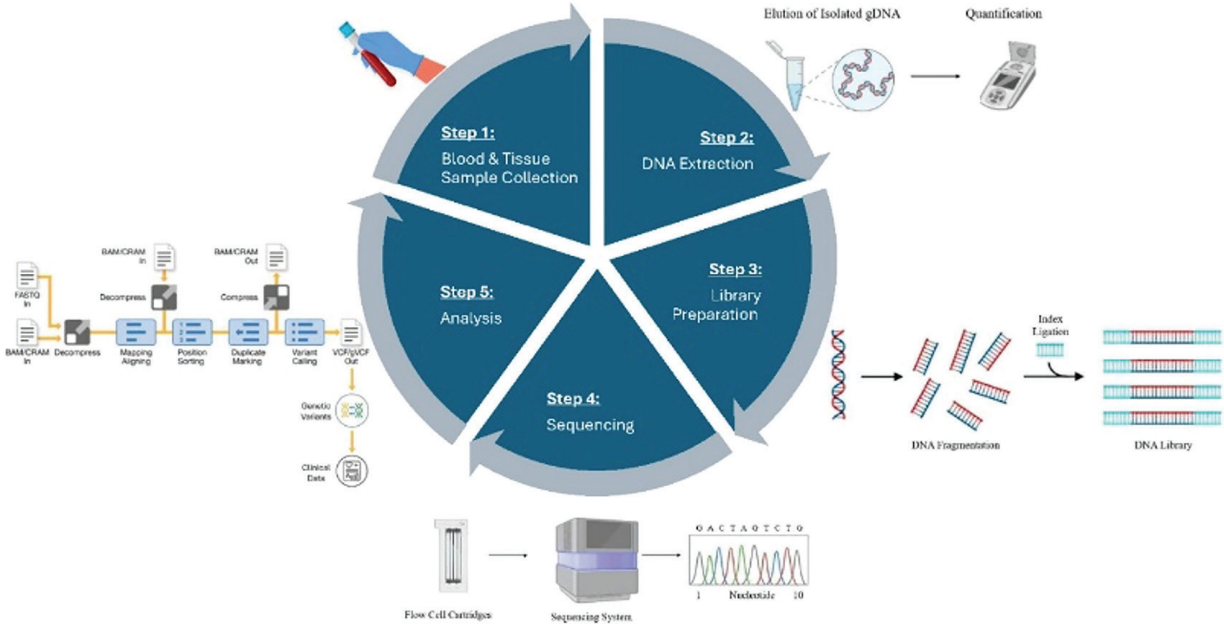

Figure 1. The workflow of WGS process at the TUGEM

WGS: Whole genome sequencing, TUGEM: National Genome Center of Türkiye

4. Sequencing the Prepared DNA Libraries by Using the Appropriate NGS System

Sequencing was performed using the S4 reagent kit v1.5 (300 cycles) on the NovaSeq 6000 sequencing system (Illumina) following the manufacturer's standard protocol, 151 base pair (bp) paired-end reads with an average insert size of approximately 450 bp were generated and an average coverage of 30x was targetted.

5. Processing Raw Sequencing Data and Secondary Bioinformatics Pipeline

Sequencing raw data obtained from TUGEM were recorded in data storage units operating on a local network and processed on the Illumina Dragen Bio-IT platform. Dragen DNA pipeline is used to perform bioinformatic analysis of the sequenced samples including mapping, aligning, QC check, sorting, small variant calling, copy number calling, and structural variant calling. DNA pipeline with Dragen targeted callers like HLA caller, star allele caller, HBA caller, RH caller, and LPA caller were also combined. Population-specific multi sample joint genotyping using genomic VCF files was assessed in healthy population. In rare diseases cohorts, pedigree based joint genotyping using trio data to better discover diseases related genomic variants, integrated with Dragen Expansion Hunter to identify disease related nucleotide repeats was determined.

To facilitate data accessibility, TÜSEB has developed the Türkiye Genome Data Sharing Portal, an intuitive online platform that allows researchers, clinicians, and patients to explore genomic data without requiring advanced bioinformatics expertise. The portal, accessible at https://tgd.tuseb.gov.tr provides interactive tools for genomic analysis, helping users visualize and query large-scale variant datasets in real time.

6. Storing the Obtained Raw Data in the Databank to be Analyzed with Backup

Efficient data storage and backup are essential for preserving the integrity of sequencing data. Raw sequencing data are securely stored in a local, internet-isolated data center, ensuring controlled access and data security. Redundant on-premises backup systems are implemented to prevent data loss and enable long-term retrieval. Adhering to standardized data management practices ensures the security, reproducibility, and scalability of large-scale genomic studies within a secure infrastructure.

Privacy and Data Security of Türkiye National Genome and Bioinformatics Project

Over the past decade, large-scale international consortia have leveraged NGS technologies to characterize the human genome, including its variations, dynamics, and associated pathologies. For example, the ongoing 100kGP, initiated by the British National Health Service, aims to sequence the genomes of 100.000 individuals within a clinical framework to establish a comprehensive population-scale genomic database with clinical annotations (20). The Cancer Genome Atlas research network has conducted extensive multi-omics analyses across major human cancer types, encompassing more than 11.000 patient samples (21).

Similarly, initiatives such as the Encyclopedia of DNA Elements and the Roadmap Epigenomics Project seek to construct high-resolution maps of chromatin organization and its variability. The 4D nucleome initiative further extends these efforts by investigating the spatiotemporal organization of the cellular nucleus in both physiological and pathological states.

The volume of data generated by these collaborative projects surpasses previous benchmarks by several orders of magnitude. Beyond large-scale consortia, an increasing number of smaller research initiatives are contributing to the accumulation of genomic data. For instance, the ArrayExpress database currently hosts over 10.000 records of research projects involving RNA sequencing data (22). Collectively, these datasets provide insights into the complex and heterogeneous nature of the human genome. In the future, the development of advanced computational approaches will be essential for structuring these vast datasets and integrating them with locally generated experimental data.

Table 2. Phases of Türkiye National Genome and Bioinformatics Project

Phase name	Status	Dates	Cohort
Pilot phase	Completed	2018-2019	Healthy volunteers
COVID-19 Genome Project	Completed	2022-2024	COVID-19 patients healthy volunteers
1000 Genomes Project	Ongoing	2024-	Healthy volunteers
Cancer Genome Project	Ongoing	2023-	Cancer patients
National Genome and Bioinformatics Project for Rare Diseases	Ongoing	2024-	Rare disease patients and their families
COVID-19: Coronavirus disease-2019			

Table 3. Current status in Türkiye National Genome and Bioinformatics Project

Donor type	Sample received	Sequenced
Healthy Turkish population	2500	1067
Cancer patients	77	67
Rare disease patients and family members	75	75

The potential for genomic datasets to enable individual identification has been previously demonstrated, underscoring the critical importance of privacy and confidentiality in genomic data management (23). In the case of the Türkiye National Genome and Bioinformatics Project, implementing stringent access controls and utilizing pseudonymization techniques, such as encoding individual metadata within barcodes, offer partial protection of subject identities. Furthermore, local system administrators, researchers and project staff are meticulously informed about data security principles and storage locations of sensitive data. TUGEM, located at the Aziz Sancar Research Center, Ankara, is protected 7/24 by fingerprint access and the individuals authorized to access are assigned by TÜSEB. All personnel are informed about the legally binding confidentiality of the patient data. Continuous security assessments are carried out to mitigate risks associated with potential data breaches and cyber threats. The closed circuit and fully-equipped technologic infrastructure enables the entire genome sequencing and data analysis of the Turkish population to be executed without the need for any patient sample or data output to leave the borders of TUGEM. The variant frequency data obtained in the Türkiye National Genome and Bioinformatics Project are accessible to researchers from all around the world via the "Türkiye Genome Project data sharing portal" (24).

Over the past ten years, most countries have made considerable investments in laboratory facilities, information technologies, and software infrastructure, leading to the widespread implementation of fundamental procedures at major genomic research centers worldwide. In the light of these technological achievements, in 2018, TÜSEB has undertaken the task of implementing the Türkiye Genome and Bioinformatics Project to analyze the molecular mechanisms of diseases, develop new diagnostic and therapeutic methods, and initiate individual-specific medicine studies within the scope of the tasks assigned to it in the 11th development plan. Accordingly, the TUGEM was included in the 2022 investment plan of the Presidency of the Republic of Türkiye, the Presidency of Strategy and Budget, and was established and put into operation within TÜSEB. Türkiye National Biobank, where biological samples obtained within the scope of the Türkiye National Genome and Bioinformatics Project is being stored, was established in 2020, and state of the art technological infrastructure have been allocated.

All types of donated biological samples are barcoded and labeled according to ISBT 128 standard (25). A donation identification number (DIN), which consists of the facility number, sample admission year, sample number, type and status, is appointed to the sample as soon as it is accepted. All biological samples are stored in Türkiye National Biobank with these labels which include a unique barcode and the DIN of the sample. This ensures the traceability for all types of biological samples and side-products related to the Türkiye National Genome and Bioinformatics Project, as well as the vigilance and surveillance tools to assist with data sharing and protection.

CONCLUSION

Despite significant advancements in the genomics field over the past three decades, the establishment of NGS data analysis workflows remains a complex challenge, particularly in core facility environments where computational infrastructure must accommodate the processing of data from thousands of samples annually. Although standardized protocols for fundamental data processing steps have emerged, numerous parameters still require optimization, imposing a substantial workload on researchers managing these pipelines.

TÜSEB continues to carry out research activities with high-level equipment using multiple methods, especially WGS. As the focus shifts from data acquisition to data utilization, there is an increasing demand for efficient data exploitation strategies. Global initiatives aiming to integrate genomic data from multiple sources necessitate substantial efforts in data organization and interconnectivity, yet these areas remain in their early developmental stages. Over the next decade, the integration of big data paradigms into genomic medicine is expected to drive substantial progress, ultimately enhancing medical outcomes such as developing diagnostic and therapeutic tools for cancer and rare diseases.

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Footnotes

Authorship Contributions

Concept: F.D.Ö.D., T.Ö., A.Ö., T.T., B.A., G.T.K., T.K.M., R.Y.Ö., Design: F.D.Ö.D., T.Ö., T.T., Data Collection or Processing: E.A., S.B.B., A.D., M.E., E.G.O., T.G., M.A.K., T.Ö., A.Ö., S.E.Ö., T.T., H.C.Ü., Analysis or Interpretation: F.D.Ö.D., E.A.,

S.B.B., A.D., M.E., E.G.O., T.G., M.A.K., T.Ö., A.Ö., S.E.Ö., T.T., H.C.Ü., Literature Search: F.D.Ö.D., E.A., S.B.B., A.D., M.E., E.G.O., T.G., M.A.K., T.Ö., A.Ö., S.E.Ö., T.T., B.A., G.T.K., T.K.M., H.C.Ü., R.Y.Ö., Writing: F.D.Ö.D., E.A., S.B.B., A.D., M.E., E.G.O., T.G., M.A.K., T.Ö., A.Ö., S.E.Ö., T.T., H.C.Ü.

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JHIT TÜRKİYE SAĞLIK ENSTİTÜLERİ BAŞKANLIĞI DERGİSİ
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Terzier C. An Overview of Graduate Studies on Health Policies in Turkey: A Bibliographic Review. J Health Inst Turk 2023;6(1):8-19.

This article has been retracted in accordance with the decision of the Editor-in-Chief. The reason for this retraction is that the manuscript was previously presented and published as congress material. Its publication in the journal subsequently raised the risk of being considered as duplicate publication. To maintain the integrity of the scientific record and to prevent any potential breach of publication ethics, the manuscript has been withdrawn.

Bu makale, Baş Editör'ün kararı doğrultusunda geri çekilmiştir. Geri çekilme gerekçesi, makalenin daha önce kongre materyali olarak sunulmuş ve yayımlanmış olmasıdır. Dergide yeniden yayımlanması, çalışmanın mükerrer yayın olarak değerlendirilme riskini doğurmuştur. Bilimsel kayıtların bütünlüğünü korumak ve olası yayın etiği ihlallerini önlemek amacıyla makale geri çekilmiştir.

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