A CONCEPTUAL DESIGN FOR GENETIC INFORMATION EXCHANGE CODING STANDARDS IN TÜRKİYE

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF INFORMATICS OF
MIDDLE EAST TECHNICAL UNIVERSITY

BY

AYHAN SERKAN ŞIK

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
MEDICAL INFORMATICS

JULY 2023

Approval of the thesis:

A CONCEPTUAL DESIGN FOR GENETIC INFORMATION EXCHANGE CODING STANDARDS IN TÜRKİYE

Submitted by AYHAN SERKAN ŞIK in partial fulfillment of the requirements for the degree of **Doctor of Philosophy in Health Informatics Department, Middle East Technical University** by,

Prof. Dr. Banu Günel Kılıç
Dean, **Graduate School of Informatics** _____

Assoc. Prof. Dr. Yeşim Aydın Son
Head of Department, **Health Informatics** _____

Assoc. Prof. Dr. Yeşim Aydın Son
Supervisor, **Health Informatics Dept., METU** _____

Assoc. Prof. Dr. Ergin Soysal
Co-Supervisor, **School of Biomedical Informatics,**
The University of Texas Health Science Center at Houston _____

Examining Committee Members:

Prof. Dr. Seher Nur Sülkü
Econometrics Dept., Ankara Hacı Bayram Veli University _____

Assoc. Prof. Dr. Yeşim Aydın Son
Health Informatics Dept., METU _____

Assist. Prof. Dr. Aybar Can Acar
Health Informatics Dept., METU _____

Prof. Dr. Tolga Can
Computer Science Dept., Colorado School of Mines _____

Assist. Prof. Dr. Arsev Umur Aydınoğlu
Science and Technology Policies Dept., METU _____

Date: **24.07.2023**

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last name : Ayhan Serkan ŞIK

Signature : _____

ABSTRACT

A CONCEPTUAL DESIGN FOR GENETIC INFORMATION EXCHANGE CODING STANDARDS IN TÜRKİYE

ŞIK, Ayhan Serkan

Ph.D., Department of Health Informatics

Supervisor: Assoc. Prof. Dr. Yeşim AYDIN SON

July 2023, 211 pages

Genomics-based technologies emerged and adapted to clinical diagnosis in the last decade. Worldwide, these test results are reported in unstructured and free text format. Moreover, the Ministry of Health Türkiye even provides a mandatory paper-based report template for hematologic hereditary disease records. The National Health Information Systems – Türkiye (NHIS-T), namely SağlıkNET, is based on ICD-10 (International Classification of Diseases) and does not contain codes for genetic tests and diseases. As a result, due to the lack of standardisation, most genetic and genomic tests cannot be coded in EHR, hindering meaningful exchange. On the other hand, Health Level 7 Fast Health Interoperability Resources (HL7 FHIR) affirms a promising role subject to enabling terminologies and ontologies related to genetic testing. In this dissertation, we developed a conceptual design for genetic information exchange coding standards for NHIS-T infrastructure to integrate genetic test reporting using the proposed standards. Our goal is to set an interoperable solution for integrating genomic data at the national level.

Keywords: Genetic Information Exchange, Conceptual Design, Qualitative Research, Precision Medicine, Electronic Health Records of Türkiye: Turkish National Health Information System

ÖZ

TÜRKİYE'DEKİ GENETİK BİLGİ DEĞİŞİMİ KODLAMA STANDARTLARI İÇİN KAVRAMSAL BİR TASARIM

ŞIK, Ayhan Serkan

Doktora, Sağlık Bilişimi Bölümü

Tez Yöneticisi: Doç. Dr. Yeşim AYDIN SON

Temmuz 2023, 211 sayfa

Son on yılda artan genom bilimine dayalı teknolojiler, klinik teşhise uyarlanmaya başlandı. Dünya çapında, bu test sonuçları yapılandırılmamış ve serbest metin formatında rapor edilmektedir. Ayrıca, Türkiye Cumhuriyeti Sağlık Bakanlığı, hematolojik kalıtsal hastalık kayıtları için zorunlu bir kağıt tabanlı rapor şablonu bile sağlamaktadır. Türkiye Ulusal Sağlık Bilgi Sistemi olan SağlıkNET, genetik testler ve hastalıklar için kodlar içermeyen ICD-10'a (Uluslararası Hastalık Sınıflandırması) dayalıdır. Sonuç olarak, standardizasyon eksikliği nedeniyle, çoğu genetik ve genomik test SağlıkNET'te kodlanamamaktadır. Ortaya çıkan bu süreç, anlamlı genetik alışverişini engeller. Öte yandan, HL7 FHIR, genetik testlerle ilgili standart terminolojileri ve ontolojileri etkinleştirmeye dair umut verici bir rol üstlenmiştir. Bu tezde geçerli standartları kullanarak SağlıkNET alt yapısına genetik test ve sonuçlarını entegre eden, genetik bilgi değişim kodlama standardına kavramsal bir tasarımı ortaya koymayı amaçladık. Hedefimiz, ulusal seviyede, sağlık kayıtlarına girilen genomik verinin birlikte çalışabilir şekilde olmasını sağlayan bir çözüm oluşturmaktır.

Anahtar Sözcükler: Genetik Bilgi Değişimi, Kavramsal Tasarım, Nitel Araştırma, Hassas Tıp, Türk Elektronik Sağlık Kaydı: Türkiye Ulusal Sağlık Bilgi Sistemi

Solely To My Family

ACKNOWLEDGMENTS

At the very outset, I wish to dedicate this dissertation to my beloved Mother, Nuriye BENLİ. Her constant encouragement throughout my extended education and life has been unwavering. Mom... I am deeply grateful.

To my sisters Seda and Seray and my cherished nephew Elifnaz... Your boundless support and firm presence mean the world to me. I love you all deeply and am immensely grateful for everything.

I consider myself fortunate to have crossed paths with my Supervisor, Assoc. Prof. Dr. Yeşim AYDIN SON, and Co-Supervisor, Assist. Prof. Dr. Ergin SOYSAL. Every one of us is confident that this dissertation would not have reached its completion without their boundless support, valuable feedback, limitless availability for questions and answers, and solid patience. I extend my heartfelt gratitude and deep appreciation to them for their enduring dedication and assistance.

I would like to convey my deepest thanks to Assoc. Prof. Dr. Arsev Umur AYDINOĞLU for his invaluable guidance throughout the qualitative research phase of this dissertation. I will forever remember his meticulous "line by line" and "thematically coded" support. Additionally, I extend my acknowledgement to the anonymous interviewees whose insights have paved the way for this dissertation.

I extend my sincere thanks and blessings to my thesis committee members: Assist. Prof. Dr. Aybar Can ACAR, Prof. Dr. Tolga CAN, and Prof. Dr. Seher Nur SÜLKÜ. Your invaluable support and insightful contributions have greatly enriched my study and thoughts. Thank you for your guidance and encouragement.

I would like to take a moment to offer a special tribute here. I want to express my heartfelt gratitude to Prof. Dr. Neşe YALABIK, the Founding Director of METU Informatics Institute. Your presence and unwavering support have played an instrumental role in shaping my academic journey, and I owe my status as a graduate in Health Informatics to you. May you rest in peace.

I also want to extend my sincere appreciation to Prof. Dr. Nazife Baykal. The establishment of the Department of Medical Informatics would not have been possible

without your tireless dedication and hard work. I am deeply grateful for every contribution you made along our path.

My dear friends, Dr. Beste MİMAROĞLU ALTINAY, Dr. Kübra NARCI and Onur ERDOĞAN. Meeting each one of you has been a great pleasure for me. Your collaboration has consistently provided me with the support and comfort needed to overcome the challenges along this journey. My heartfelt gratitude goes out to all of you. Thank you.

Lastly, I extend my deepest appreciation to my esteemed colleague Assoc. Prof. Dr. Pınar AYYILDIZ. Your continuous inspiration, guidance, time management, and support have been invaluable. This dissertation would not have come to fruition, completed, and bound without your influence. Thank you immensely for everything.

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LIST OF ABBREVIATIONS

ACA	Affordable Care Act
ACMG	American College of Medical Genetics
API	Application Programming Interface
ATC	Anatomical Therapeutic Chemical Classification System
CI-B	Continuous Integration Build
CDA	Clinical Document Architecture
CDSS	Clinical Decision Support Systems
CG WG	Clinical Genomics Workgroup
CPT	Current Procedural Terminology
CSER	Clinical Exploratory Research
EHR	Electronic Health Record
eMERGE	Electronic Medical Records and Genomics
FAIR	Findable, Accessible, Interoperable, And Reusable
FHIR	Fast Health Interoperability Resources
GDPR	General Data Protection Regulation
GINA	Genetic Information Non-discrimination Act
GR IG	Genetic Reporting Implementation Guideline
GWAS	Genome Wide Association Studies
HCPCS	Healthcare Common Procedure Coding System
HCRS	Health Coding Reference Server
HIC	Health Implementation Communiqué
HIPAA	Health Insurance Portability and Accountability Act
HIS	Health Information System
HL7	Health Level Seven
HLA	Human Leucocyte Antigen
ICD-10	International classification of Diseases version 10
ICD-O	International Classification of Diseases Oncology
IG	Implementation Guide
ISCN	International System for Human Cytogenomic Nomenclature
KVKK	Kişisel Verileri Koruma Kanunu
LOINC	Logical Observation Identifiers Names and Codes

LPPD	Turkish Law on the Protection of Personal Data
MED	Medical Enforcement Declaration
MHDS	Minimum Health Data Set
MI	Medical Informatics
MoH	The Republic of Türkiye, Ministry of Health
MSVS	Minimum Sağlık Veri Seti
NHDD	National Health Data Dictionary
NHIS-T	National Health Information Systems – Türkiye
NIH	National Institute of Health
OMIM	Online Mendelian Inheritance in Man
PACS	Picture Archiving and Communication Systems
PGx	Pharmacogenomics
REST	REpresentational State Transfer
SGK	Sosyal Güvenlik Kurumu
SKRS	Sağlık Kodlama Referans Sunucusu
SMART	Substitutable Medical Applications and Reusable Technologies
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terminology
SSI	Social Security Institution
SSIEM	Society For the Study of Inborn Errors of Metabolism
STU	Standard Trial Use
SUT	Sağlık Uygulama Tebliği
USVS	Ulusal Sağlık Veri Sözlüğü
VCF	Variant Calling Format
VEM	Veri Modeli

CHAPTER 1

INTRODUCTION

From birth to death, an individual's medical status is documented under various headings, including welfare, diseases, medications, laboratory tests, and vaccinations. In conjunction with the advance of information technologies, for more than 60 years, documentation has been handled through Electronic Health Records (EHR) [1]. Successful progress in decision support systems for public health by combining records from individuals [2]. Constructive public health and precision medicine achievements can be accomplished by adopting EHR standards based on structured data. Besides, standards provide interoperable and accessible recordings among the actors of medical information.

Following the advances in molecular genetics and genomic technologies, a tremendous amount of molecular data is being produced. Genetic tests and biomarkers for different diseases are increasing daily [3]. Considering precision medicine, interoperable genetic test result reporting is indispensable. The ticket for interoperability is embracing standardised medical records among shareholders (personal/machinery).

The National Health Information System of Türkiye is known as SağlıkNET. SağlıkNET is EHR of Türkiye. International standards translated into Turkish language and officially in use cannot manage genetic data in a standardised manner. Codes in effect, are mainly focused on diseases. For reimbursement, a few genetic tests are coded locally in an idiosyncratic way. Recently, in April 2022, gene names associated with diseases were provided in the Health Code Reference Server (HCRS) of Türkiye. A total of 20.493 genes are provided but not explicitly stated in the National Health Data Dictionary (NHDD) of Türkiye. In conclusion, with full intent to achieve an interoperable health record, implications in Türkiye for genetically oriented diseases and genetic tests do not obey any standards or structured data format. In this dissertation, we targeted to provide a conceptual framework for a meaningful and information exchange capable electronic health information system, benefitting international standards for genetic test result reporting.

1.1 Background

The Republic of Türkiye, Ministry of Health Türkiye (MoH) declared Health Transformation Programme in December 2003 [4]. Besides organisational transformation, MoH aimed to increase the quality of life of Turkish citizens and collect medical data created by healthcare providers under a structured and electronic format beneath its custody. The MoH controls expenses and tracks national health using some Clinical Decision Support Systems (CDSS). Concurrently, transformation concluded interoperability, i.e., any test or imaging request/result, treatment, and diagnosis performed in one hospital could easily be shared and observed in other healthcare centres or the MoH.

However, for genetic test results in Türkiye, there is no established regulation on sharing or storing them in an internationally accepted and standardised manner. The existing rules for various genetically related tests or diseases do not cover the findable, accessible, interoperable, and reusable (FAIR) requirements of genetic data.

Simultaneously, the available software standard tools for medical data management in Türkiye cannot handle structured genomic data representation. Healthcare experts establish various tools to cope with the genetic test result representation. Consequently, variations in the tools and products hinder interoperability.

1.2 Motivation

Worldwide, there is no systemic research on evaluating the current status of genetic testing and requirements for reporting. Only one study about the United States of America (USA) was published [5], [6]. So, we have initiated our study by collecting the opinions and thoughts of area experts on genetic testing result representation, revealing the expectations of the experts in Türkiye.

Since the Health Transformation Phase in Türkiye, there has been no further study about the coverage of the transformation in genetic testing and precision medicine. A focus group study to probe the experts' thoughts about the regulations on the health information systems, data security, privacy, and confidentiality in Türkiye was recently published in December 2022 [7].

Also, there is no comparative study about reimbursement of medical expenses in Türkiye concerning counterparts worldwide. Reimbursement procedures in some European countries and the USA are well explained in the literature [8]–[10].

The technical barriers of the software standard tools drive us to propose different software standards for the conceptual model. The implications of the proposed standard have positive feedback and promotion among organisations [11].

1.3 Contributions of this dissertation

In this dissertation,

- We assessed the readiness of Turkish health information systems for genetic/genomic test reporting under the rules and regulations in charge. As an initial output of this dissertation, our review article was published in Health Policy Journal.

- With the increase in genetic data output, there is a clear need to understand the specialists' daily routines and policy expectations. Based on the global endeavours on translating genomic research from bench to bedside, we lay the groundwork for future work on the technical and regulatory arrangements anticipated by policymakers in Türkiye.

- While comparing reimbursement methodologies, we lay down the genetic testing reimbursement policy and blockages on the structured representation of genetic testing in EHR and reimbursement.

- We provided an insight into a conceptual model for standardised genetic/genomic information exchange capable Electronic Health Records for Türkiye.

1.4 Organization of this dissertation

We present this dissertation under six Chapters: Introduction, Literature Review, Materials and Methods, Results, Discussion, and Conclusion.

In the first Chapter, Introduction, we provide a summary of the research, stated the motivation behind the study, and put forward the contributions of this dissertation.

For the Second Chapter, Literature Review, we present the materials on supporting tools for healthcare information exchange in Türkiye, qualitative research on experts' opinions on genetic testing, ethical and legal assessment of genetic testing in the world, reimbursement constraints, and enabling tools on genetic information exchange available in the literature.

In the Third Chapter, Materials and Methods, we explain the data collection and data generation methodologies with theoretical backgrounds where available.

On behalf of the Fourth Chapter, Results, we lay down the status of genetic testing in Türkiye with several dimensions: legislation, standardised representation, reimbursement, experts' opinions and thoughts, comparison of the findings with the global counterparts, and a conceptual model for interoperable genetic information exchange by Electronic Health Records.

The fifth section, titled "Discussion," aims to recap the dissertation's contributions in evaluating genetic testing legislation, documenting practices related to testing, sharing

information, reimbursement aspects, and the anticipations of genetic testing specialists at the Ministry of Health. Moreover, the chapter delves into the suggested theoretical framework for sharing genetic testing information, considering the tools currently operational within Turkey's Electronic Health Record system.

Finally, in the Sixth Chapter, Conclusion, we synopsise the contributions of this dissertation on genetic testing information exchange capable systems and policy potentials.

CHAPTER 2

LITERATURE REVIEW

This chapter presents a literature review under four separate research topics about the content of the dissertation. First, we go through the "Health Transformation Programme" and reveal the reforms it brought to healthcare information technologies in Türkiye. The review also puts forward the efforts to overcome technical and ethical impediments that emanated following the burden of genetic data created. For the second part, we revealed the genetic testing reimbursement methodology and constraints in Türkiye. Meanwhile, we described the concept of a benefit catalogue for reimbursement, which is utilised in most European countries. On behalf of the third topic, present the literature review on experts' opinions on genetic testing representation. In the last part, we review genetic information exchange capable initiatives and methodologies.

2.1 Assessing the Readiness of Turkish Health Information System and Legislations for Genomic Patient Data Integration Under the Projection of Global Counterparts

This section of the dissertation is arranged in parallel with our manuscript published in the Health Policy Journal in February 2021 [12].

Genomic science and associated implementations bring about new requirements that necessitate unique clinical practices, i.e., precision medicine, oncogenetics, pharmacogenetics, etc. [13]–[18]. For the final diagnosis in clinical practice, targeted sequencing, and thanks to their reliability and efficiency in variant detection and decreasing cost, Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) are widely utilised [13], [19]. A transparent policy on EHR is highly required to establish meaningful exchange among authorised genetic data accessor parties. The policy subtitles are data standards, storage, privacy, and legislation [12].

Since the first use of EHR, the clinical utility has been boosted with Clinical Decision Support Systems (CDSS), which promotes the secondary usage of medical data. In the era of precision medicine, interoperable, ethics guided, governmentally and legislatively supported, and genome-enabled EHR is a prerequisite [12], [17], [20]–[32].

The United States Congress signed the Health Information Technology for Economic and Clinical Health Act (HITECH) in 2009. The HITECH promoted meaningful use

of EHR [12], [33]. Contrarily, the secondary use and privacy of genomic data by virtue of meaningful use of genome-enabled EHR are reviewed in several studies [3], [11], [14], [15], [27], [34]–[38].

In 2014, two groups, Clinical Sequencing Exploratory Research (CSER) and Electronic Medical Records and Genomics (eMERGE), joined to probe the representation of genetic information in EHR. Their observation concluded that the meaningful use of EHR in genomic data is still missing and observed the ongoing use of PDFs, e-mail, or instant messaging tools [12], [36]. By 2020, National Health Service (NHS) clinical genetic services will be completely paperless [25], [26], [39].

Health Level 7 (HL7) is a globally adopted and well-established communication standard for medical data exchange among data partners [40]. Efforts to integrate and exchange genomic data with HL7 are unfavourable [11], [14]. HL7 v3, A Domain Analysis Model, Clinical Genomics, Release 1, was released in July 2018 and is retired today [41]. To the authors' knowledge, no centre or government implemented the Clinical Genomics release for HL7 v3 [12].

Fast Health Interoperability Resources (FHIR) is a new model enabling interoperability developed by HL7 community members (HL7, 2022). Within the United Kingdom and the United States, FHIR is supported for genomic data exchange [22], [43]–[45]. While integrating and interpreting the genetic data with EHR, phenotypic data should be combined in a standardised manner. The minimum data requirements definition and implementation of ontology-based terminology, i.e., Systematized Nomenclature of Medicine (SNOMED) are still under progress using FHIR [14], [17], [22], [23], [46]–[49].

Considering EHR's capacity, managing the storage requirements of genetic testing data inside EHR is not feasible. Depending on the clinical utility requirements of genetic data and precision medicine, a separate data storage field is expected [19], [28], [36], [37], [46], [50].

Besides standardised, structured representation and genome-enabled EHR, the way to achieve a meaningful use of genetic data, extensive cohort studies should be performed for a successful clinical implementation of genetic testing [13], [25], [34], and the results should be stored with genome/phenome relation [12]. Biobank linked EHR, genomic medicine projects, and the Global Alliance for Genomics and Health (GA4GH) beacon project are some of the relevant initiatives [17], [20], [21], [51]–[54].

Genetically related diseases and procedures are determined to take preventive actions to encompass precision medicine. Focus areas and candidates are planned by countries and initiatives [13], [52], [55]–[59].

Due to the unique nature of genetic data, governments, organisations, and multinational agencies set rules on genomic data exchange. The efforts are grouped as data protection, human rights, consent, sharing genetic testing information with the patient (return of results), and related policies to be followed [38]. A detailed review and comparison of the American College of Medical Genetics (ACMG), Health

Insurance Portability and Accountability Act (HIPAA), Genetic Information Non-discrimination Act (GINA), Affordable Care Act (ACA), General Data Protection Regulation (GDPR), and Turkish Law on the Protection of Personal Data (LPPD) are provided in our manuscript [12].

To achieve competency with global practices, by December 2003, the Ministry of Health, Türkiye (MoH) declared the Health Transformation Programme ("Sağlıkta Dönüşüm Programı," 2003). Putting in a nutshell, besides organisational transforms, the Programme's aim is to increase the quality of life of Turkish citizens while gathering medical data produced by all stages (primary, secondary, and tertiary) of healthcare givers in a single place named MoH, in a coded, structured, and electronic format. (We supply a detailed definition of those stages in the following Chapters of this dissertation). This enabled the MoH to control expenses and track national health using some Clinical Decision Support Systems (CDSS). At the same time, transformation guided through interoperability means that a test request/result, imaging request/result, treatment and diagnosis performed in one hospital can easily be shared and observed in other healthcare centres [12]. Like other countries [60], Türkiye also benefits from the International Classification of Diseases version 10 (ICD-10) for disease coding, prescription tracking, and billing [12], [61].

Türkiye has established a personal mobile health record system (Personal Health Record – PHR) named e-Nabız. Personal genetic data is not transferred, displayed, or stored in e-Nabız (except for the positive or negative COVID-19 PCR diagnostic test result) [12].

In Türkiye, genetic/genomic tests can be ordered in four different ways [12]:

1. Through EHR of hospitals,

2. Referral of specific cases to research centres of the hospital (not over EHR),

3. Through personal application to private laboratories (with or without clinical request),

4. Forensic Medicine Institutions request upon a court decision.

As an aid to diagnosis and for the secondary use of genetic data, Türkiye's centres retrieve and store the allele frequencies and common mutations specific to the Turkish population as in-house data [12]. Countries started to establish methods for infrastructure, clinical cohorts (for cancer, diabetes, rare, infectious, and neurological diseases), population-based cohorts, pathogen projects, and drug discovery [18]. By September 2019, Türkiye had completed the Turkish Genome Project's pilot phase for 100 genomes [62]. A genomic map of the Turkish population is expected to be available to genetic experts and help perform targeted genetic testing depending on the clinicians' phenotypic information. To the authors' knowledge, none of the biobanks established in Türkiye is linked to the EHRs, and no EHR is integrated with CDSS experiencing its facilities [12].

Employing a legal basis, Türkiye has clarified the collection of health data from laboratories with various rules and regulations, depending on the laboratory's speciality. The rules and regulations also cover the administrative structure, operational details, and minimum requirements for any specialised laboratory's architectural design [12].

In April 2016, Türkiye enacted the Law on the Protection of Personal Data (LPPD) [63]. In terms of definitions of personal data of unique nature, it complies with GDPR [12]. As per the European Commission's Türkiye 2018 Report, no objections were raised regarding the aspects of the LPPD that pertain to the handling of personal data [64]. On the other hand, Turkish academicians expect comprehensive expressions and clarifications for other cited regulations at LPPD (Gürsel, 2016; Öztunay, 2019). Chronologically, compared to EU Directive 95/46/EC, which was annulled and replaced by GDPR in 2018, Türkiye is the first country to include biometric and genetic data as personal data of unique nature and set rules for processing [65]. Turkish parliamentary members and non-governmental organisations have concerns, and there are active legal cases against the LPPD [65].

2.2 Health Expense Reimbursement in Türkiye and Global Counterparts

In Türkiye, the "Republic of Türkiye, the Social Security Institution (SSI)" is the primary healthcare insurer. Turkish citizens are registered under General Medicare Insurance coverage, and healthcare is provided without considering their previous or existing illnesses (Republic of Türkiye Social Security Institution, 2016; Şık et al., 2021). Please refer to our paper for details [12]. Healthcare expenditure is dependent on Health Implication Communiqué (HIC) – in some published documents and webpages, it is also named Medical Enforcement Declaration (MED) – in Turkish: Sağlık Uygulama Tebliği (SUT). In this dissertation, HIC is preferred.

The Turkish government reimburses the cost of non-elective healthcare expenditures. The genetic testing costs are covered only when the patient and the healthcare centre are registered with the SSI. The requested healthcare procedure shall be coded in the HIC [67]. The exact reimbursement conditions apply for the medication with a partial cost share [12],

1. The prescription should have a relevant ICD-10 diagnosis code prepared by the clinician, possessing a diagnosis-related medical profession, and

2. The medication must be included in the coverage list of the SSI.

HIC is used to standardise reimbursement where the codes only provide procedural descriptions for genetic tests. A single procedure code covers multiple tests. The HIC codes and coverage conditions are updated ad hoc depending on the government reimbursement policy [12].

For reimbursement through SSI, clinicians and genetic testing laboratories must use the ICD-10, the HIC, and the LOINC observation codes in their request and result reports (MoH Türkiye, 2016; LOINC Kullanımı, 2014). For private insurance

coverage, ICD-10 coding is sufficient. It's important to highlight that the ICD-10 classification doesn't cover most rare diseases [70]. Many of these rare diseases are hereditary [55]. Among approximately 7000 rare diseases, only 500 have a specific code in ICD-10 [71]. Analogously, the US healthcare system uses ICD-10-CM, a clinical modification for diagnosis codes, and Current Procedural Terminology (CPT) codes for billing. CPT can define less than 200 codes for genetic tests for reimbursement [72].

2.3 Experts' Thoughts and Opinions About Genetic Test Representation

Ensuing immense measures of genetic data and their proven success in diagnosis, clinicians were faced with requesting and using these test results without integrating them into their clinical practice [73]. To mitigate the errors in test ordering decisions or interpreting the genetic test results, the experts concentrated on achieving adaptable report templates and conducted qualitative studies [73].

Regarding the experts' opinion on the current status of genetic testing representation and exchange, to our knowledge, there are only two studies related to the US. The authors probed the interoperability standards and gathered experts' benefits, challenges, and motivations about genetic data exchange standards [5], [6].

2.4 Genome Enabling Technologies for Electronic Health Records

Information-rich genetic test results exhibit a significant role in clinical diagnosis and drug prescription. Gene-disease association and PGx studies require a well-established clinics-genetics association. To set CDSS, organisations provided some efforts utilising websites [11], [36], [74]–[76] or clinicians utilise PubMed literature [34].

Depending on the unique nature of genetic data, patient privacy is considered while developing such systems [75].

Under its well-known format, EHR cannot handle genetic data like standard medical data. Differentiative characteristics of genetic data compared to medical data and candidate technical desiderata for genetic test management are presented by Masys et al. [77].

Another study, presenting a conceptual model of genomic data for precision medicine, discriminates the levels of utility of genetic data in research and clinics [15]. According to the proposed model, the vast amount of "omic data" can be translated to patient care using the well-known "Data, Information, Knowledge, Wisdom" pyramid approach. Clinically actionable "omic data" should be extracted and inserted into EHR in a structured and interoperable manner.

For EHR, the widely adopted medical data exchange standard is HL7v3. Initially, the attempts to integrate and exchange genetic data took place with this standard.

A method was offered by [78] as a general architecture of their system based on the GO-WELL concept. It is developed based on the requirements and facts of the Turkish e-health system. Clinical data from healthcare providers and genomic data from genomic laboratories are transferred to SağlıkNET EHR repositories utilising HL7 v3 and Clinical Document Architecture (CDA) R2. Later, clinical, genomic, and enviro-behavioural data ultimately emerged and interpreted for the end user. Knowledge management tools need to be proposed and interfaced to represent those data. The requirement for this proposal can be ensured using a standardised and structured representation of data obtained on laboratory benches, healthcare centres, and self-tracking/environmental monitoring. The main idea is the meaningful use of all types of medical data; to that end, standardisation is the main asset.

On the other hand, together with clinically actionable information, raw genetic test results should be stored for further evaluation. A solution for this requirement was discussed during the Electronic Medical Records and Genomics (eMERGE) project [79]. A system like Picture Archiving and Communication Systems (PACS) used in radiology can be employed as an ancillary system for genomic data storage. Together with an ancillary system, it was discussed in eMERGE that the raw genomic data should be supported with multiple external knowledge sources like some standards and ontologies to implement data storage.

Another solution is to use cloud technology. Data can be presented in the cloud, but again, there is a requirement to implement standards to store those data. GA4GH – Global Alliance for Genomics and Health brought various stakeholders and worked on standardised genetic data storage in the cloud [11].

eMERGE initiative put forward more tangible outputs about integrating genetic tests into EHR. Under the sponsorship of The National Human Genome Research Institute [50], eMERGE developed methods and best practices for utilisation of the EHR for genomic research. eMERGE network started with five sites in 2007 (Phase I), expanded to nine locations in 2012 (Phase II), and 13 sites in 2015 (Phase III). Topics they deal with and related workgroups per each phase, together with the previous, are provided in Table 1.

Table 1: eMERGE project phase contents.

Phase-I:	Consent and Community Consultation Workgroup
	Genomics Workgroup
	Informatics Workgroup
Phase-II	EHR Integration
	Return of Results
	eMERGE PGx
	Consent, Education, Regulation, and Consultation (Replaced with Consent and Community Consultation Workgroup)
	Phenotyping (Replaced with Informatics Workgroup)
	Paediatrics
	EHR Integration
Phase-III:	Clinical Variant Annotation Workgroup
	Outcomes Workgroup

eMERGE utilises EHR as a tool for genomic research. Every research site within the eMERGE Network has its own DNA repository. By the beginning of Phase II, the contributing sites can extract phenotypic data from EHR. The primary goal of the eMERGE network is to combine DNA biorepositories with the EHRs' longitudinal phenotypic data [50]. They studied existing EHR to extract phenotypes by software tools. According to the phenotypes, they performed Genome Wide Association Studies (GWAS) and explored ethical, legal, and social issues associated with GWASs sharing via EHR.

The primary challenge encountered during the eMERGE Phase-I was related to data integration. Despite utilising the same genotyping platform, various genotyping facilities faced difficulties when attempting to combine their data [50]. Sample relatedness, population stratification across sites, inconsistencies in strand orientation and site-specific batch effects can be listed as the pitfalls of Phase-I.

During Phase-II, the primary objective of eMERGE was to extensively investigate the potential advantages of incorporating EHR data. This aimed to identify connections between genotypes and phenotypes, ultimately leading to the integration of genotype information into the EHR system. [50]. PGx was introduced in Phase-II. PGx is a method that is generally used in personal medicine. Before prescribing a drug, clinicians know the patient's genomics and evaluate those data for possible patient risk.

Following the achievements in Phase-I, eMERGE network extended its attention to pilot studies for implementing genomic medicine through EHR [28]. A genotype imputation pipeline was implemented to generate a single and homogeneous data set for all individuals to generate a single and homogeneous data set for all individuals genotyped across the network so that the phenotype and genomic data can be amassed across all eMERGE sites.

Another organisation is Clinical Exploratory Research (CSER). Gathering 21 institutions, CSER is also supported by the National Institute of Health (NIH). It aims to explore the use of genomic sequence data in the care of patients [80] under the concept of

- Generation of genomic sequence data,
- Interpretation and translation of data for the physician,
- Communication with the patient.

There are three project teams per site,

1. Practice,
2. Lab,
3. ELSI (ethical, legal, and social implications)

Lab project teams deal with sequencing and reporting of genome-scale results to clinicians/EHR and how to present the relevant information in the EHR in the best way.

At the same time, CSER aimed at the cross-site collaboration of genetic information for integration and CDSS into the EHR.

In the Spring of 2014, CSER and eMERGE working groups joined to explore the representation of genetic information in the EHR. The objectives of the collaboration are:

- Description of clinical genetic data representation in each CSER and eMERGE site.
- Consensus about the most important and feasible improvements in the clinical representation of genetic data.
- Publish a manuscript on the current state and ideal future state.
- Influence EHR providers and policymakers to improve the presentation of clinical genetic information in EHRs.

Two working groups conducted a multiphase, iterative process involving working group discussions and two surveys [36]. They observed that,

- There is heterogeneity while entering or documenting genetic information in EHR.
- The primary data sources are laboratories and clinician notes.

This publication states that the consortia noted the necessity of developing interoperable systems to receive and disseminate genomic information.

The consortia worked in two phases. In phase one, they defined the types of genetic information that should be displayed on EHR and assessed the location and format of genetic information by semi-structured phone calls. Later, they conducted surveys according to phone call results. In phase two, they identified the recommendations for improving the display of genetic information in EHR. They prioritised recommendations for practical usage and genetic information display in EHR according to the results they obtained in phase one.

In the end, the results they obtained can be summarised as:

- Genetic information has many overlapping use cases and applies to many clinical solutions. The consortia working groups agreed on a list of categories for genetic information,
    - Disease defining/diagnostic.
    - Risk actionable.
    - Low Risk, not actionable, theoretically actionable.
    - Significant chromosomal changes and cytogenetic test results.
    - Pharmacogenomics.
    - Carrier recessive.
    - Somatic/tumour genetics.
    - Incidental.
    - Variants of uncertain significance (VUS).
    - Uninterpreted Variants.
    - New-born Screening.
    - Sensitive Genetic Information.

The interviewed centres noted the genetic information areas that exist or do not in their own EHR.

- Critical characteristics of current practice, like sources of genetic information and reporting style, are documented.
- Recommendations for EHR improvement were listed with 20 distinct items. Some top ones are (with more than 50% of respondents):
    - Develop effective CDSS for genetic results that are medically actionable.
    - Develop a decision-support knowledge base to recommend appropriate action.
    - Develop an alert system.
    - Develop an alert system for PGx.
    - Develop effective CDS for genetic results that are diagnostic/disease-defining.
    - Provide mechanisms for EHRs to access external CDS knowledge bases and rule engines.

A key feature for genetic reporting and EHR integration that was clarified by the end of this analysis is the need to link genetic information to disease-specific knowledge bases:

- Linking variants to annotation-oriented knowledge bases that can effectively describe the variant in terms of clinical use.
- Expected function (activating, inactivating, unknown).
- Classification, and,
- Origin.

To sum up, the results obtained at the end of this consortia,

- They observed that some sites report genetic information in PDFs while others apply structured data.

- It is critically essential that EHR with genetic information will maximise the value of the system.

- Clinicians should be well-educated to utilise genetic information.

- Medically actionable incidental findings are becoming much more critical with the advances in whole genome sequencing.

- Integrating genomic test results with EHR should not be limited to academic institutions; it should be applied widely in all clinical areas.

- EHR providers should be aware of the genomic studies and get ready.

- Financial barriers and competing priorities for the integration with EHR should be overcome.

In 2012, HL7 developed FHIR. FHIR is a next-generation standards framework. It combines the best features of HL7's v2, v3, and CDA while leveraging the latest web applications ("Summary - FHIR v1.0.2," 2015).

HL7 FHIR is notably preferred for its exceptional suitability, attributed to its straightforward implementation process, an abundance of implementation libraries, and comprehensible specifications.

In their article (Alterovitz et al., 2015), Alterovitz et al. shed light on the facilitating properties of FHIR. They mentioned the requirement of combining clinico-genomic data standards for the genomic variant data coming from different sequencing systems. Those different genomic data systems (sequencing systems) offer different Application Protocol Interface (APIs) for data storage in the cloud. Some of them are:

- Illumina Inc.
- GenoSpace
- LLC

- Seven Bridges

Global Alliance for Genomics and Health (GA4GH) brought various stakeholders rather than a proprietary API controlled by a single company [11] - including Substitutable Medical Applications and Reusable Technologies (SMART) on FHIR Genomics. GA4GH also focused on the communication of genomic information in the cloud. An example of transmission of variants was demonstrated between the EHRs of Partners HealthCare and Intermountain Healthcare. It was observed that genomic information might not be suitable for the message format used by HL7 v3 [11].

Alterovitz et al. [11] recommends creating an abstraction layer above specific file formats due to the following advantages:

1. Although DNA sequencing technologies and data types stored in those sequences are subject to change, gene and variant data will be utilised in clinical applications.
2. APIs that are mapped to sequencing files may contain unnecessary/unused details. Conflicting vendor applications may cause trouble or the valuable missing data of doctors, researchers, and developers. Maybe it is hard to define such standards in a constantly developing area, but it is better to start from a point.
3. API should be connected to a standards organisation. EHR vendors, doctors, and government can have more meaningful and valuable data with this.
4. API should extensively cover genomics information with other clinical data for clinical care, subsequent outcomes analysis, and discovery research. With this approach, the benefits of genetic tests would be more utilised by insurance companies, the government, and healthcare services.

SMART on FHIR combines FHIR-compliant clinical data access from EHR systems with web standards to launch web and mobile apps from a user's EHR session [11]. It specifies genomic variant data resource definitions to support the development of clinical-genomic apps.

- Data can be from EHR or a separate sequencing system.
- The critical effort for the data provider is to implement a SMART on the FHIR Genomics data adaptor.

Using the large set of existing technologies on top, SMART on FHIR Genomics specification adopted:

- SNOMED-CT (Systemized Nomenclature of Medicine, Clinical Terms) for diseases and qualifier values,
- The Human Genome Variation Society Mutnomen Syntax for mutation names and locations,
- Consensus Coding Sequence representation for genomic regions, and
- The Human Genome Organization Gene Nomenclature Committee (HGNC, or HUGO) symbols and identifiers for common gene names.

SMART on FHIR genomics developed FHIR's formal mechanism [11].

- For source extension to handle multiple types of clinical genomics data, including wrappers for genomic data files,
- Messaging services for genomic lab results, and
- Document services for interpretative genomic reports.

Obeying the FHIR protocol, three new FHIR resource and extension definitions for variant data are:

1. **The Sequence Resource:** to show the genetic information of the patient.
2. **The SequencingLab extension:** to define sequencing technology while producing the sequence – GA4GH data repositories were utilised.
3. **The GeneticObservation extension:** to define the relationship between phenotype and genotype.

As a result, creating "omics" data standards was problematic [11]. They have tested their solution by prototyping adaptors for Illumina, 23andMe, and the Vanderbilt Research Derivative. Their genomic data specification has been tested and found to be capable of supporting high-functioning clinic-genomics apps. Creating prototype adaptors with familiar genomics data sources has verified the feasibility of their endeavour.

Table 2 lists the proposed resources and extensions of (Alterovitz et al., 2015).

Table 2: Description of the additional FHIR-compatible specifications (a. Sequence resource, b. SequencingLab extension to the FHIR Procedure resource, c. GeneticObservation extension to the FHIR Observation resource) defined by the SMART on FHIR Genomics API [11].

Field Name	Field Type	Cardinality	Description
a. Sequence			
GenomeBuild	String	1	Assembly of the Sequence
Type	String	1	Type of the sequence (Protein, DNA, RNA), SNOMED-CT
Quantity	Quantity	0.. 1	Quantity of the sequence
ReferenceSeq (Reference Allele)	String	0.. 1	Reference of the sequence (IUPAC format)
ObservedSeq (Observed Allele)	String	1	Read string for the sequence (IUPAC format)
CIGAR	String	0.. 1	CIGAR string for the sequence
Source.Sample (GenomicSourceClass)	Code	0.. 1	Source of the sequence. The genomic class of the variant: Germline, Somatic, or Prenatal. Associated with LOINC answer list: 48002-0.
Source.Lab	SequencingLab	0.. 1	Laboratory source of the sequence
Chromosome	String	1	Chromosome of the sequence. The chromosome containing the genetic finding values should be 1-23, X, Y, mito, viral, bacteria.
StartPosition (GenomicStart)	Integer	1	Start of the sequence
EndPosition (GenomicStop)	Integer	1	End of the sequence
Species	CodeableConcept	1	Species identifier (NCBI taxonomy)
PatientID	Patient	1	Genetic laboratory's patient identification for this sequence
b. SequencingLab			
Genetics Laboratory	Organization	1	Sequence Laboratory organisation
Repository	Uri	1	Repository for this laboratory (GA4GH type)
DatasetId	String	1	Dataset identification of a laboratory folder containing multiple sequences

Table 2 (Continued)

c. GeneticObservation			
AssessedCondition	Condition	1	Condition described by this observation
SourceSeq	Sequence	0.. *	Sequence resource linked to this observation
DNASequenceVariation	String	0.. *	HGVS nomenclature for cDNA variant
GeneId	CodeableConcept	0.. *	HGNC identifier and symbol
VariantTranscript ReferenceSequenceId	CodeableConcept	0.. *	cDNA reference sequence identifier either RefSeq or ENSEMBL
DNASequenceVariationType	CodeableConcept	0.. *	Classification of variant change using LOINC Answer List values 48019-4 or Sequence Ontology values
DNARegionName	String	0.. *	Gene region containing the variant, e,g, Exon 19
ProteinReference SequenceId	CodeableConcept	0.. *	Protein reference sequence identifier either RefSeq or ENSEMBL
AminoAcidChange	String	0.. *	HGVS nomenclature for amino acid change
AminoAcidChangeType	CodeableConcept	0.. *	Classification of variant change using LOINC Answer List values 48019-4 or Sequence Ontology values
VariationId	CodeableConcept	0.. *	Variant identifier in ClinVar, dbSNP, or COSMIC
AlleleName	String	0.. *	Common name for variant for display purposes
AllelicState	CodeableConcept	0.. *	Level of occurrence of the DNA variation in relation to the genomic context. LOINC answer list: LOINC 53034-5
Subject	Patient	1	Genetic laboratory's patient identification for this sequence
Specimen	Specimen	1	Specimen source of data
Interpretation	CodeableConcept	0.. *	Interpretation of the effect of this observation. Uses "Observation Interpretation Codes" value set of FHIR.
Comment	String	0.. *	Comments on this variant

By the conclusion of Phase-III, the eMERGE consortium accomplished the structured and standardised representation of genetic test information, enabling the exchange of genomic data among EHRs in XML format. However, the consortium chose to pursue a more advanced approach to integration, opting to embrace HL7 FHIR as a fresh HL7 standard. This marked the commencement of Phase-IV. During this phase, they integrated their workflow using HL7 FHIR and contributed to developing the FHIR Genomic Implementation Guide for Pharmacogenomics [81].

In their implementation process, they extracted data elements from sample genetic testing records and skilfully mapped them to the existing FHIR resources and profiles

[81]. When data elements were without direct mappings, they generated extensions and conveyed this information to FHIR developers. Their efforts led to an enrichment of the artifacts within the FHIR Genomic Implementation Guide.

In Türkiye, to provide an international interpretation and track expenses for clinical and laboratory observations, MoH finished the translation of LOINC to Turkish. Mapping of LOINC – HIC was published in (MoH Türkiye, 2016). Users can define HIC definitions for microbiological and tissue typing laboratory procedures in a structural and standardised manner rather than idiosyncratic codes of HIC.

NOTE: In Türkiye, HIC changes in an ad hoc manner. After the changes in HIC, the reference link webpage or LOINC-HIC map may temporarily be unavailable. During the preparation of this dissertation, the map was temporarily unavailable. In Figure 1, I have added a screenshot of the first mapping. The HIC code in the screenshot is annulled as of December 2021.

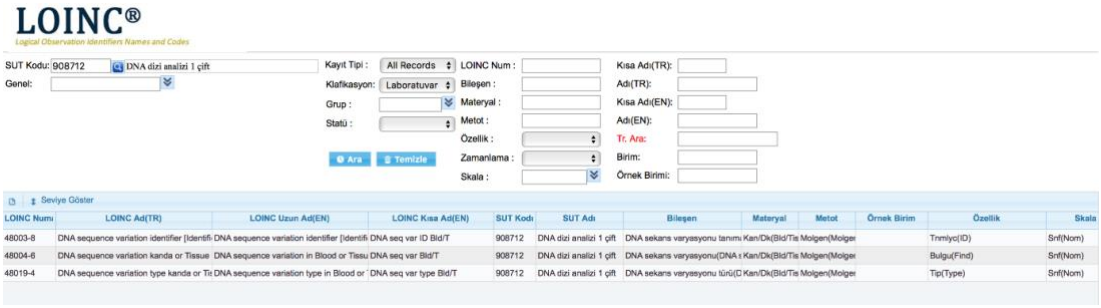

Figure 1: MoH, LOINC Translation and MED Mapping. A sample for HIC Code: "908712, DNA Dizi analizi 1 çift" and corresponding LOINC Codes.

Another initiative held by MoH is the "Hospital Information System Minimum Data Model" (VEM: Veri Modeli). In 2015, v1.0 and v1.1 were published, and the recent model VEM2.0 was announced in 2020. This is a guideline for Health Information System (HIS) developers. It is aimed to provide a sustainable and standardised model for HIS developers and vendors during data submission and transfer [82]. As a result, when a healthcare centre switches to a different vendor for their Health Information System (HIS), using a standardised data structure ensures that the risk of data loss during data migration is minimised, potentially even eliminated.

It is important to note that, depending on the requirements, the data elements and fields are updated by the MoH ad hoc.

Under the Minimum Data Model (VEM), examination data groups have "LOINC_CODE" fields. Existing examination data groups under VEM2.0 are:

- VEM_TETKIK
- VEM_TETKIK_CIHAZ_ESLEME
- VEM_TETKIK_NUMUNE

- VEM_TETKIK_PARAMETRE
- VEM_TETKIK_REFERANS_ARALIK
- VEM_TETKIK_SONUC

In Appendix A, for the purpose of example view, we provide the Data Information Model for VEM_TETKİK.

This dissertation will take the advantage of qualitative analysis. In the view of qualitative analysis, the sources employed to propose the research problem of this dissertation are technical and non-technical literature and from personal and professional experience in hospital information systems (Strauss & Corbin, 2008).

As a summary of the above literature review,

- In her dissertation (Heras, 2012) studied FISH test coding and integration with LOINC.
- Also, the eMERGE, CSER, and SAGE-CARE projects (“Sage Care,” 2015; B. H. Shirts et al., 2015) reveal the lack of standardised presentation and storage of genetic test results in HIS.
- Hoffmann (Hoffman, 2007) mentioned the critical steps for integrating genome-enabled electronic medical records.

Within the framework of identifying research problems through qualitative analysis [83], considering the existing literature and the situation in Türkiye, a significant research gap emerges around the question of "How can standardised, exchangeable, and reusable storage and presentation of genomic tests be achieved?"

Based on my observations, mainly from my involvement in hospital projects, I've noticed that genetic test results often do not find their proper place within healthcare facilities' Hospital Information Systems (HIS). This gap raises pertinent questions about integrating genomic data into clinical workflows and the necessity for a systematic solution to ensure efficient and meaningful storage, exchange, and presentation of genetic test information. This research problem resonates with my experiences and points toward the broader challenge of harmonising genomic data within healthcare systems.

CHAPTER 3

MATERIALS AND METHODS

3.1 Data Generation for the Genetic Testing Status Assessment and Reimbursement Review and Genetic Testing Information Exchange Enabling Technologies

For this part of the dissertation, we probed the literature on the enforcing statutory constraints for Türkiye and global counterparts to establish a comparison. Most of the literature related to Türkiye is published in Turkish. In case available, we cited original English literature for Türkiye. In this dissertation, we translated all Turkish material into English. To collect data for SağlıkNET and e-Nabız, we used the MoH website. For the reimbursement part, we used the websites of SSI, Republic of Türkiye Ministry of Labour and Social Security.

In Türkiye, laboratories apart from the hospitals are authorised to operate under specific legislations. Additionally, reimbursement of their service depends on distinct constraints. Either governmental or private, they are called "specialised laboratories". We picked governmental and private hospitals and specialised laboratories relevant to genetic testing and reviewed the rules and regulations for each. We evaluated the Law on the Protection of Personal Data (LPPD) for genetic and health-related articles and sub-articles. We performed searches on the National Library of Medicine, Google, and Google Scholar to project the results with the global literature. We aimed to find the answers for global counterparts. The search strings used are EHR/PHR and genetic testing, genetic test representation standards in EHR, EHR/PHR and privacy, genetic privacy, Sağlık Uygulama Tebliği (HIC), benefit catalogue, and genetic testing reimbursement.

For the genetic information exchange, we reviewed the technical infrastructure of SağlıkNET and covered the enabling technologies and standards in action. To sort out how genetic testing results are integrated to EHR, we accomplished Google Scholar search using the following keywords: Integrating genetic tests into EHR, genome enabled EHR, Sağlıkta Dönüşüm, HL7 Genomics, FHIR, FHIR Genomics, Standardisation and Genetics, Ulusal Sağlık Veri Sözlüğü, Veri Modeli, LOINC Türkiye.

We conducted semi-structured interviews to sort out the enabling tools for genetic testing information exchange, opinions, and daily routines of the genetic testing experts in Türkiye. From the interview data, we extracted themes using qualitative study methods.

3.1.1 Background and Reflections on the Dissertation

In literature for qualitative studies, deriving concepts and interacting deeply with raw data is called Grounded Theory" [84]. Embedded meanings in data can be extracted with detail, which is equivalent to being "grounded" [85]. We used open coding and an inductive approach to define the concepts and themes that will support the proposed research topic of this section of the dissertation.

Concepts would provide the basics of any subject with typical constructions and give us a shared understanding [83]. The experts' daily routine, in-depth experience, and thoughts in the research area must be discovered and assessed to define the concepts. To determine the basics of the status of genetic testing in Türkiye, we conducted semi-structured interviews with genetic specialists, clinicians, and genetic counsellors. We aimed to understand the current situation in hospitals and laboratories in Türkiye about genetic test result recording. During the interviews, we included all healthcare actors performing genetic tests. The interviewees' workplaces are hospitals and genetic testing laboratories spanning government, private and university.

In qualitative research, interviewing is the most common method of data collection [86]. In his book, Patton noted three alternatives for collecting qualitative data through open-ended interviews [85]:

- The informal conversational interview
- The general interview guide approach, and
- The standardised open-ended interview

In this dissertation, to collect data, we used the third alternative. Interviews were flexible, standardised, open-ended, and focused on people's experiences rather than general beliefs and opinions.

To conduct the research, the methodological approach is the research question. The research question triggers the researcher to envision the study area from the interviewee's perspective. It defines the boundaries of the qualitative analysis study, and the researcher gets relevant experiences and answers from the interviewees. It is mainly exploratory and hypothesis-generating [83]. The research question of this study was more focused on the information we wanted to retrieve so as not to have broad and non-relevant approaches and answers from the interviewee. Our previous experience and literature survey about the research problem provided us to set our research question as concept achieving and making connections between concepts. A literature survey was not a driving force in managing interviewees during interviews; instead, it was a driving force in defining interviewees' key competencies [83].

The research question of this study is: 'How do genetic testing experts manage genetic testing concerning storage, reporting, privacy, pedigree, sharing (including the third parties), and standardised data representation under the requirements of governmental rules and regulations?'

We prepared a set of interview questions following the semi-structured interview guidelines. The questions were designed to understand a genetic testing lab's daily routine in data storage and representation. The scope of the questions was not broad and focused on the interviewee's experience and daily practice in the clinic or laboratory. Hence, the answers are not scattered and not beyond the aims of this study. Ultimately, we revealed the differences and similarities among the clinics, laboratories, and institutes.

Each interviewee was interviewed with the same questions in the defined order. Thus, the variations in the data the differences among interviewees may create will be guarded [85].

Although questions were prepared beforehand, with the careful and precise wordings of the questions, and being reflective during interviews, the collected data are still open-ended since the interviewees reflected thoughts and insights with their wordings in the answers. Meanwhile, the standardised open-ended interview approach makes data analysis easier since each interviewee's answer can be located to the same question.

According to Patton, six kinds of questions can be asked to the participants in a qualitative interview [85]:

1. Experience and Behaviour Questions
2. Opinion and Values Questions
3. Feeling Questions
4. Knowledge Questions
5. Sensory Questions
6. Background/Demographic Questions

With our interview questions, the interviewees could present their opinions, feelings, recommendations, and knowledge about integrating genetic tests into EHR and their existing applications and experiences for genetic testing registry and storage.

There is a difference between qualitative and quantitative research regarding sampling and the number of samples. In quantitative research, to be in the confidence level of 95%, a population of 100 people requires 80 samples for generalisation, where 500 requires 217, and 1000 requires 270 people etc. [85].

In contrast, for qualitative research, small samples, even one (N, sample number =1) selected purposefully, would be enough to represent the population if it is focused in depth. In purposeful sampling, one can obtain the main eminent facts by selecting an "information-rich" case. This issue is also well confirmed by Bent Flyvbjerg as an "information-oriented sample selection" [87]. There is no rule to define the number of samples in qualitative research. The saturation of information from the interviews can

define the number of samples. In our research, we conducted interviews with 13 experts.

According to Patton, there are 15 strategies to purposefully select information-rich interviewees plus one combination of those 15, which makes 16 [85]. In this study, we followed the purposeful sampling and snowball (or chain) sampling methodologies. The snowball sampling strategy is used to locate participants in critical cases/duties. The rich information they possess is the key concept, and they recommend other information-rich participants. In their book, King & Horrocks [86] noted that there may exist a bias in snowball sampling methodology since the interviewee may recommend another interviewee who holds a similar idea or shares the same view about a phenomenon. On the contrary, they [86] also noted the cases where the above argument does not fit. Some research areas can be specific, and participants in the field can hardly be accessed. In our research case, the number of specialists working on genetic testing and genetic data storage and registry is too low. That is why the participants are key personnel in this field, and we need to reach them using snowball sampling methodology. On the other hand, because of the current interviews, all participants have different thoughts, approaches and database methodologies in their institutes, laboratories, and hospitals.

At the end of the interviews, the conversations were transcribed verbatim by someone, not from our research area. This is a required transcription methodology in a qualitative study if the research aims to analyse the interviewee's experience and thoughts [86]. According to [86], if the researcher transcribes, the researcher will become more familiar with the data. However, transcribing the interviews to another person made us gain time and selecting this person from a non-relevant area directed us to check the transcriptions from the beginning. So, the first data analysis was to check the complete transcription by listening to the conversation.

During the analysis of the interviews to analyse the existing status of genetic test data management in Türkiye, concepts will be revealed through the answers to the questionnaire designed. Concepts are words that stand for groups or classes of objects, events, and actions that share some significant common property(ies), though the property(ies) can vary in dimension [83].

The raw data (the whole interview) are coded to derive concepts. Coding describes “Deriving and developing concepts from data [83]”. Codes are the names given to concepts. The concepts will give a detailed attitude to the genetic data regarding acquisition, storage, standardisation, and governmental regulations for reimbursement. It is good to note here that, as [84] noted, “even the most accurate facts change, the concept itself will not change”. Defining the concepts would reveal the ever-lasting requirements of genetic test data management.

The grounding concepts retrieved from the interview data will construct the scientific basis of our analysis. As the research advances, the concepts will be confirmed considering the current body of literature. The interview data will be organised using concepts.

The strategies used during coding are called analytic tools. Analytic tools are “thinking techniques used by analysts to facilitate the coding process” [83].

During the qualitative data analysis, the repeating items/words in the interviews are generally the concept candidates. The interviewee repeats or emphasises some words/concepts more intensely in the content. During the analysis of the qualitative data content, the sensitivity of the participant within the context of my research in the interview will be reduced [85].

In the first stage of the qualitative analysis of interviews, defining concepts in the transcriptions are inductive. Possible concepts emerge with the interaction of data. After inductively defining concepts, deductive analysis reveals the proposed theory during the thesis study.

The genetic specialists' key phrases, terms, and practices were extracted from the verbatim transcriptions. This is the inductive analysis [85]. They are indigenous concepts and practices. This type of analysis is called emic analysis, where the interviewee's feelings, thoughts, and views are studied. This is also called “in vivo coding” [88].

Along with the indigenous concepts retrieved from the raw interviews, sensitising concepts will be defined based on the researcher’s perception of the study. The researcher brings these concepts to the data via their research questions, which evolve from literature searches and previous professions. The concepts aid the researcher in finding the direction where they must look and develop a general sense of reference [85]. Patton notes, “Concepts are never a substitute for direct experience with the descriptive data. What people say, and the descriptions of events observed remain the essence of qualitative inquiry” [85]. With the enlightenment and in parallel with this phrase, we are not in the position to direct or drive the analysis in our research study. We use concepts to present the current practice of the genetic test registry in Türkiye and reveal how to internationally standardise the test registry into the EHR to present them to doctors and patients meaningfully. In this way, the system can reuse genetic data for lifelong implementation and follow-up [34].

The first step of analysing the interviews is developing a manageable classification or coding scheme [85]. The interview data will define the codes, categorisations, classifications, and labelling of the primary patterns. The researcher can determine what is significant from the view of the interviewees. The first reading through the data mainly aims to reveal the coding categories and the classification system, and the next reading is the start-up. After reading the verbatim transcript, we labelled the relevant phrases to the relevant codes.

After defining the concepts in the interviews, the statements collected will become more significant, the relations between the concepts will be revealed, and the research findings will move beyond conceptual ordering through theory [85].

In this study, with the aid of interviews, we find out the hidden details and interpret the view of the experts about genetic testing recordings by making comparisons,

asking questions about the concepts we retrieve and putting forward their answers to exhibit their properties and significance.

The qualitative analysis of the interviews helps us become more competent in our research area. We built the theory using the concepts in the interview data. The codes, which eventually define the concepts, categories, properties, and relationships, are defined by coding, a conceptual mode of analysis [83], [85].

Later in the analysis, the concepts may be combined into a common notion. Within this notion, they may have similarities and differences. So that concepts can be clustered into basic-level and high-level concepts.

Basic-level concepts provide details for the higher-level concepts [83]. To explain high-level concepts, low-level concepts are used. Determining low-level concepts and keeping them in the research helps us integrate data. High-level concepts would be easily grasped, and the research would be more descriptive and data-rich. Details in the research data would not be missed [83].

3.1.2 Evaluation Of the Results and Significance

By its nature, qualitative analysis cannot show the significance of its results as quantitative analysis. Qualitative analyses are evaluated by their substantive significance [85]. The questions that the analyst should address are:

- How solid, coherent, and consistent is the evidence supporting the findings?
- To what extent and in what ways do the findings increase and deepen understanding of the phenomenon studied?
- To what degree do the results align with existing understanding?
- To what extent are the findings useful for some intended purpose?

At the end of the research study, the experts evaluate the proposed solution.

The theory directs us to the necessity of genetic data management standards.

3.1.3 Data Generation Through Semi-Structured Interviews

We conducted semi-structured interviews with 13 key informants from nine health organisations. We utilised qualitative research methods to identify the existing status of genetic testing and the demands of the specialists. Before the interview, each interviewee was informed about the research and signed the ‘Informed Consent Form’. One of the interviewees was out of Türkiye during the interview period and was informed about the ‘Informed Consent Form’ via e-mail. Appendix B provides the interview questions in Turkish and English, prior information documents, and Informed Consent Forms.

We prepared the questionnaire by following the guidelines of the semi-structured qualitative interview. The interview aimed to find the answers to ‘How medical care providers manage genetic testing concerning storage, reporting, privacy, pedigree,

sharing (including the third parties), and standardised data representation under the requirements of governmental rules and regulations?' Additionally, we inquired and discussed whether the centres have any digitalisation attempts to manage genetic test data. During the interview, the participants presented their workflow in their centres, such as how genetic test requests are ordered and how they represent and disseminate the test results to the clinicians and patients.

The interviewees are experts with past or present managerial roles within a genetic testing laboratory. They hold educational qualifications in molecular biology or medicine and professional training in medical genetics. Moreover, they have expertise in genetic test recording software as a user or manager. We used purposeful sampling to select the initial participant since a limited number of experts with the said criteria are present in Türkiye. The rest of the participants were recruited using snowball sampling methodology as it provided two significant benefits:

1. To locate participants in critical cases/duties,

2. The aim is to build a trusting rapport with participants by mentioning the referencing interviewees [86]. This is particularly crucial given that the research question pertains directly to governmental matters and is highly specific.

We continued interviews until we achieved information saturation from the participants. Towards the end of the study, the interviewees provided similar replies as the previously interviewed ones, supporting that few experts with desired qualifications are present in Türkiye and all are experiencing the same regulations.

The interview order and referencing scheme for snowball methodology are depicted in Figure 2, and Table 3 shows the employment information of the interviewees. Experts 14 and 15 were not from the field of research; we did not interview them, but they directed us to critical participants. Interviewee number 1 is the initial contact point, recruited by purposeful sampling.

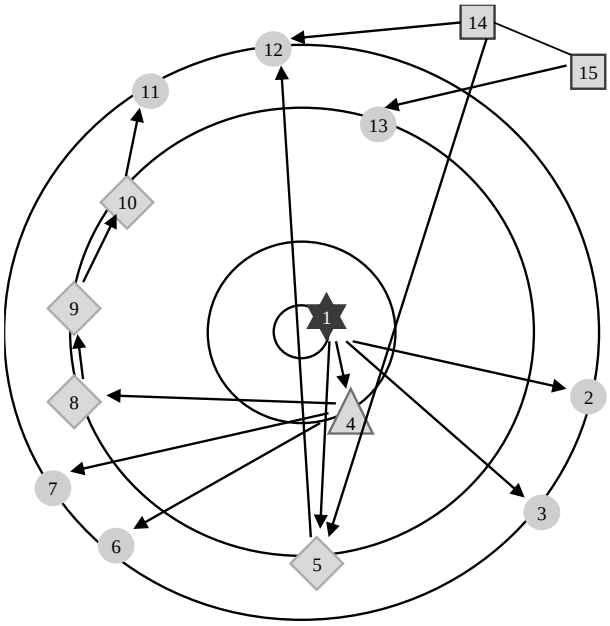

Figure 2: Initial Purposeful Sampling and Snowball Sampling Methodology to Recruit Key Interviewees. Legend: Star – Initial interviewee, Triangle – Interviewee who recommended more than two experts, Diamond – Interviewee who recommended one or previously interviewed expert, Circle – Interviewee who did not recommend any or recommended the previously interviewed participant, Square – External expert.

Table 3: Recruited Key Information Rich Informants for Semi-Structured Interviews via Purposeful and Snowball Sampling Methodology. Laboratories are classified as in-house (government, private or university hospitals), private laboratories, laboratories run by private companies on behalf of the government due to service procurement, or private Genetic Diseases Assessment Centres (GDAC) licensed to serve the government.

Participant Workplace	**Total Number**	**Workplace Category**	
		Government	**Private**
Faculty of Medicine	8	5	3
Laboratory	5	2	3
Total	13	7	6

We conducted interviews in Turkish. Twelve out of 13 were face-to-face, and one was via Skype since the participant was not in Türkiye. The interview questions were administered in the same order. We scheduled meetings depending on the interviewee's availability and conducted the interviews in their offices.

To state briefly, we can group our interview guide into four sets of questions:

1. How do you handle genetic test records in your centre? Do you apply any standards for storing/archiving your data? Additionally, while reporting results to the patient, do you adhere to any established criteria, and if so, what are those?

2. What kind of data (raw, analysis result, patient report) and how long do you store/archive about the genetic/genomic tested patient? Do you have any inconveniences and concerns about it, and if yes, what are they?

3. What are your thoughts about pedigree?

4. Can you criticise pedigree and genetic test records concerning privacy? Do you have any reservations? If yes, what are they? In your opinion, how can we protect privacy? How should we inform individuals about their test results?

Ten out of 13 participants agreed to be audio-recorded; three participants did not want their interviews to be audio-recorded; thus, we took extensive notes during their interviews. On average, the interviews lasted 45 minutes. The shortest was 23 minutes, and the longest one was 72 minutes. We could ask every question we have in the interview guide and receive answers. The time limitation due to workload, narrative style of the interviewee, and open-ended structure of the interviews caused the variation in the duration of the interviews. All data presented in this study are anonymised. The results are organised according to the interviewee's workplace category: 1) governmental or private, 2) hospital, laboratory centre, or university.

All interviews were transcribed verbatim [86]. We received professional services for the transcription of the audio-recorded interview data. We analysed interview data using MAXQDA software [89]. We performed line-by-line coding of the interviews with investigator triangulation to ensure the quality and credibility of the qualitative inquiry. We determined codes, in-vivo codes, and concept candidates during the analysis. Interviewee responses quoted in the manuscript are translated from Turkish. The analysis of the interview data revealed the concepts of the existing status of genetic test data management in Türkiye.

3.2 Ethics Clearance

To conduct semi-structured interviews with area experts, we obtained the approval of the "Middle East Technical University (METU) Human Subjects Ethics Committee," Approval Number: 28620816/012. Each interviewee was requested to sign the 'Informed Consent Form' before the interview. Appendix C provides the approval letter of the Middle East Technical University (METU) Human Subjects Ethics Committee.

3.3 Information Handling and Interoperability for Medical Data

Medical care and continuity are not a single-handed process. Instead, it involves communication among care providers, individuals who fall short of care and continuity, any equipment contributing to healthcare, and the financing body. It is better to call this type of multi-contributed communication, which includes transferring information from one partner to another as “information exchange”.

Considering the well-known “Data-Information-Knowledge” pyramid used in informatics science, each contributor generates tremendous amounts of data and can solely communicate individually at the “Data Level” of the pyramid.

The information level of the pyramid represents a “meaningful content changing in time”. To orchestrate the communication of contributors and sustain actionable information, we should maintain interoperability. The exchange of information includes interoperability at technical (syntactic), semantic and clinical layers (Figure 3).

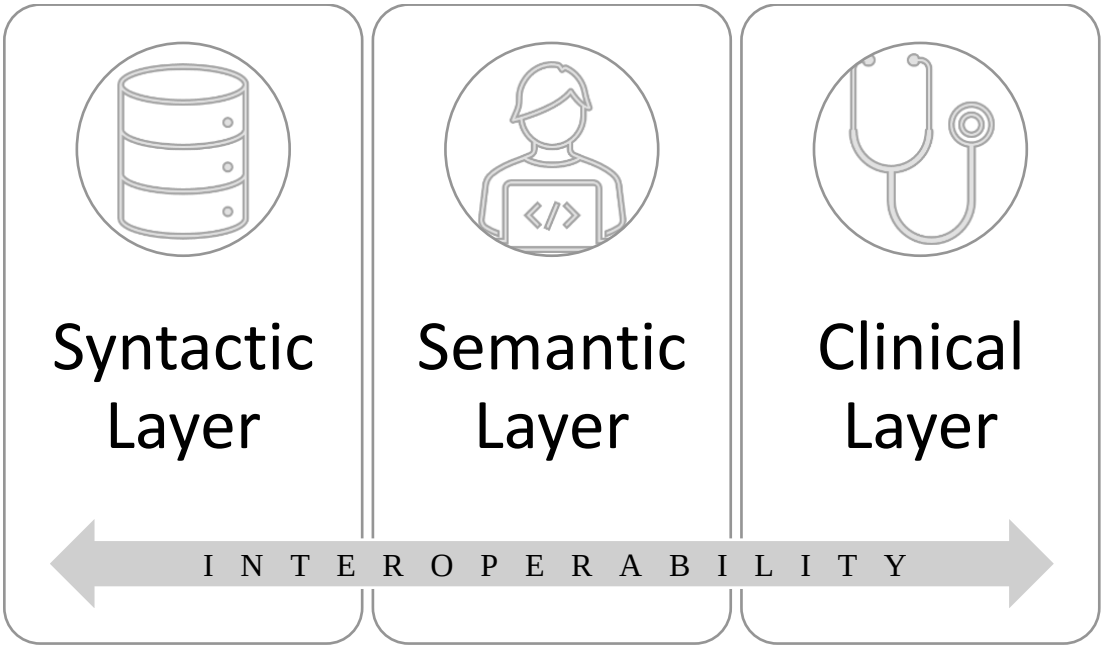

Figure 3: Information Exchange in Syntactic, Semantic and Clinical Layers

The definitions of layers of interoperability [90], [91] are in Table 4.

Table 4: Definition of Interoperability Layers

Syntactic Layer	refers to the exchange of data
Semantic Layer	refers to the ability of information shared by systems to be understood with least human interference/perturbation
Clinical Layer	refers to process or workflow management with the successful integration of advice and alerts into data presentation and workflows and/or the deployment of resources in keeping with a plan or protocol (often computer-based)

At the syntactic layer, the structure of the message is defined, but the meaning is not. Syntactic interoperability allows different systems to send and receive data in different formats, i.e., transfer of health information structured in the form of HL7 v2 messaging standards capable system to HL7 v3 capable system. If there is no syntactic layer of interoperability, data exchange is impossible. Semantic interoperability reduces the effectiveness of human decision-making on the information exchange between systems while establishing the data exchanged to have the same meaning. Clinical interoperability is concerned with the interoperability of the workflow.

At the information level of the pyramid, there is not only a change in the content of the single contributor but also an information exchange among the contributors. Two information contributors need one link or interface for communication. Considering N contributors, the number of interfaces is given in Equation (3.1):

$$Number\ of\ interfaces = \binom{N}{2} = \frac{N\ x\ (N-1)}{2} \tag{3.1}$$

Managing the "change and exchange" requires some constraints, which we call standards. The standards contribute to achieving FAIR use of medical information for machines and individuals: Findable, Accessible, Interoperable, Reusable. Electronic Health Records benefit from the standard representation of medical data and propound its success through facilitating information technologies. Succeeding standard representation for contributors drops the number of interfaces stated in Equation (3.1) to one (Figure 4).

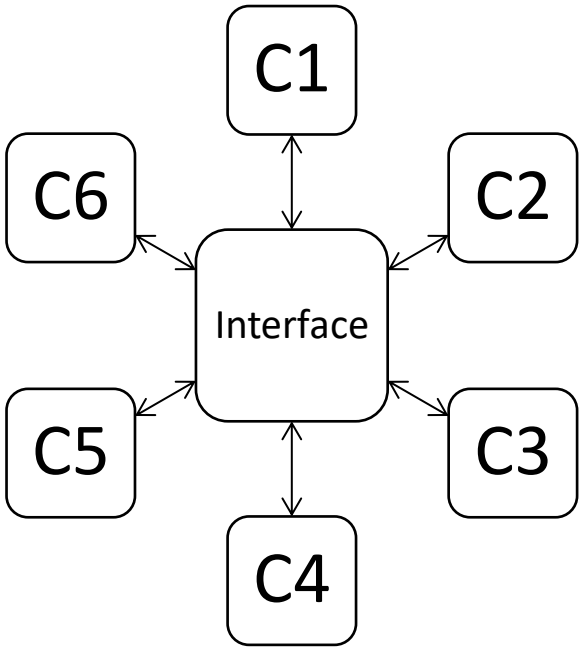

Figure 4 An example depicting information exchange through a single interface (Six contributors: C1 to C6)

Although the term “meaningful use” of medical data is initially aimed at the financial improvement of health expenses [92], caregivers benefit from FAIR use within the context of precision medicine. Thanks to the vast amount of genetic data produced, the meaningful use of genetic testing results paved the way for precision medicine.

Considering the complexity induced due to the increasing amount of medical data and the contributors, while designing an EHR, we need to implement the following to prevent errors in the system and break the reluctancy of the users [91]:

- Keep minimum time to read and understand the concepts.
- Consider the level of domain knowledge for each contributor.
- Length of the specifications.
- Keep a minimum the number of options and the way of statement.
- Keep a minimum the number of implementations.

We set up models to ease complexity, prevent errors, and describe the system. Whilst exhibiting rules and modes of interoperability, models grant to define the system as it is now and how we want it to be [91]., In the modelling stage, interoperability standards and the process lifecycle are stated.

For the models in the interoperability standards, the standards development organisations implemented syntax-independent specifications for digital health data. Three types of specifications and their example for the medical informatics field are in Table 5.

Table 5: Models in Interoperability Standards

Specification	Definition	Example
A Single Domain-wide Model	Referred to as a reference model	• HL7 v3/RIM • ISO 13606 Reference Model • FHIR Resource Definitions
Technology-Independent	Constraint on the domain-wide model	• HL7 v3/RMIM • CDA Templates • FHIR Profiles and Archetypes
Implementable Message	Mappings from technology-independent message specifications into the selected syntax	• XML • JSON • RDF Turtle

For the lifecycle, we follow scope and objectives, process analysis and design: “as is” and “to be”, and conceptual design and specification. Details are provided in Table 6

Table 6: Lifecycle of Modelling

Scope and Objectives	• What is included and excluded from the project?
	• Define constraints such as the standards used.
	• Define SMART goals:
	  o Specific
	  o Measurable
	  o Attainable
	  o Relevant to needs
	  o Time bounded

Process Analysis	• State the situation (as is) • Show the proposal (to be) • Storyboards • Use cases
Conceptual Design and Specification	• Model of the "to be" system • It does not define the software to be used • It is a level between the developers and the users for a clear understanding

3.4.1 Major Standards in Health Information Exchange

According to the International Organization for Standardization (ISO), a standard is a document that provides requirements, specifications, guidelines, or characteristics that can be used consistently to ensure that materials, products, processes, and services fit their intended purpose. Standards are developed through a consensus-based process involving experts from relevant fields, industry representatives, and other stakeholders.

In Health Information Exchange, standards define the formats, protocols, and vocabulary for exchanging health information between healthcare systems and providers. Unless otherwise stated, the implementers voluntarily comply with the standards. The substantial standards in medical informatics (MI) and their key areas are in Table 7.

Table 7: Major standards in medical informatics

Standard Name	**Key Area**
ISO TC 215	International standardisation for MI
CEN TC 251	International standardisation for MI originated from the European Committee for Standardization (CEN)
HL7	For clinical and administrative data
DICOM	Digital Imaging and Communications in Medicine: Provide standards for medical images
ICD	International Classification of Diseases: Diagnosis
LOINC	Logical Observation Identifiers Names and Codes: Provides codes for observation names
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms: Concepts and procedures
IHE	Integrating the Healthcare Enterprise: develops profiles for specific use cases
OpenEHR	Focuses on elements of the EHR architecture in technology independent manner

3.4.2 Coding and Classification

It is well known that computers can only interpret coded data, not the string. Pertaining to this information, two distinct but related concepts in healthcare and information management, namely “coding and classification”, should be noticeably utilised to represent clinical information.

Coding involves assigning specific codes to represent individual medical concepts or items, while classification involves categorising and organising related concepts into groups or categories based on common characteristics. Coding provides the means to represent and identify specific information, while classification provides the framework for organising and structuring medical knowledge.

The choice of which classification system to use is generally determined by the payment agencies in Türkiye, the Ministry of Labor and Social Security, in conjunction with the Ministry of Health. Their choice, ICD, does not encompass the needs of the doctors since it does not cover terms in a precise and unambiguous manner. On the majority, while creating a semantic interoperability problem, they also sacrifice the medical record's truthfulness and completeness.

For example, to put forward the insufficiency of ICD on semantic interoperability, we can consider [91] an “injury causing closed spiral fracture of the shaft of the right tibia with fractured fibula after an accident” (

Table 8).

Table 8: Insufficiency of ICD on semantic interoperability

CASE			
injury causing a closed spiral fracture of the shaft of the right tibia with a fractured fibula after an accident			
No	**ICD-10 DISPLAY TERM**	**ICD-10 CODE**	**CODING**
1	***Injury***, poisoning and certain other ***consequences of external cause***	S00-T98	~~**injury causing**~~ a closed spiral fracture of the shaft of the right tibia with a fractured fibula ~~**after an accident**~~
2	Injuries to the ***knee and lower leg***	S80-S98	**-*/*-** closed spiral fracture of the shaft of the right tibia with a fractured fibula **-*/*-**
3	***Fracture*** of lower leg, including ankle	S82	**-*/*-** closed spiral ~~**fracture of**~~ the shaft of the right tibia with a fractured fibula **-*/*-**
4	Fracture of ***shaft of tibia*** (with or without mention of fracture of fibula)	S82.2	**-*/*-** closed spiral **-*/*-** the ~~**shaft of**~~ the right ~~**tibia**~~ with a fractured fibula **-*/*-**
5	***Closed*** fracture of shaft of tibia	S82.2.1	**-*/*-** ~~**closed**~~ spiral **-*/*-** the **-*/*-** the right **-*/*-**with a fractured fibula **-*/*-**
6		S82.2.1	**-*/*-** **-*/*-** spiral **-*/*-** the **-*/*-** the right **-*/*-**with a fractured fibula **-*/*-**

In the first line, we can infer an injury due to an external accident. In the second line, thanks to the clues “tibia and fibula”, we can understand the case is related to the knee and lower leg. Consequently, we can infer a fracture for the case at the third line, but whether the fracture is from the tibia or fibula is still fuzzy according to the code syntax. In the fourth line, we can code the fracture belongs to the shaft of the tibia. The fibula is still open and cannot be coded yet. For the fifth line, we can infer that the fracture is closed. Finally, in the sixth row, we can say that ICD-10 cannot define the laterality of the leg (right or left), the type of the tibia fracture (simple, spiral, or compound), and how the fibula is affected.

In medical informatics, coding systems provide standardised codes to represent medical concepts. At the same time, terminologies offer more comprehensive vocabularies and structured information to describe clinical entities and support accurate representation, communication, and medical data analysis. Consequently, some phrases [91] encountered during this dissertation and EHR designs are in Table 9.

Table 9: Most encountered terms in EHR designs

Coding Systems	
Concept:	Clinical meanings that do not change
Coding Scheme: (i.e., Table 8, line 1)	Each concept code originates from a coding scheme. A coding scheme defines a set of concept codes, which are unique within the namespace of the coding scheme and are globally unique when coupled with the name of the coding scheme itself.
Display Term:	Human readable term. In some cases, more than one display term may be provided for the same concept to cover proper synonyms, i.e., translations into different languages. One display term is usually designated as the preferred term.
Relationship:	Concepts may be related to other concepts via a relationship.
Value Set:	A set of values that are allowed for a particular data item.
Identifiers:	Computer systems need unique identifiers for people, things, places, and codes.
Terminologies	
Terminology:	A set of concepts designated by terms belonging to a unique domain of knowledge or subject field.
Reference Terminology:	A terminology in which every concept designation has a formal, machine-usable definition supporting data aggregation and retrieval.
Terminology Binding:	The process of specifying in archetypes and templates what codes belong in which fields. It establishes links between elements of a terminology such as SNOMED and an information model [93].

The EHR users await three basic properties [91] from any coding and classification system:

1. A classification representing cases and payment, i.e., DRG, CPT, HIC

2. A classification system for diagnosis and procedures to monitor, track and audit clinical activities, i.e., ICD.

3. A clinical terminology used for patient care.

3.4.3. Medical informatics, information exchange tools

As put forward in Table 7, for information exchange at clinical and administrative levels, HL7 is a globally adopted standard. Since the first use of HL7 in 1987, several versions are in charge. In Türkiye, HL7v3 is employed [12].

HL7 v2 is based on messaging in response to trigger events, i.e., admission, discharge, and transfer (ADT). The message types are general acknowledgement, ADT, order, observation, and result unsolicited messages. HL7 v3 RIM is based on an object-oriented model. It defines a standard reference model for all HL7 v3 messages and provides a framework for consistently representing clinical and administrative data.

Compared to HL7 v2, HL7 v3 RIM differs in message structure, design approach, vocabulary usage, and implementation complexity. HL7 v2 is more widely implemented and flexible, i.e., local code sets and message customisation are generously allowed. While bringing easy implementation, flexibility concludes to a well-known jibe [91], proof of data integration hindering: "When you have seen one implementation of v2, you have seen one implementation; each one is different".

HL7 v3 RIM focuses on semantic interoperability and standardisation. Compared to HL7 v2, they provide a standardised and consistent way to represent healthcare information, allowing for better integration and exchange of data across different systems by representing health data as a set of interconnected classes and relationships. Thanks to RIM, pre-defined attribute sets are defined for each class; these are the only ones allowed in HL7 messages. These classes are Act, Act Relationship, Participation, Role, Role Link, and Entity [91]. Each has its specific data type. HL7 v3 RIM promotes standardised vocabularies like SNOMED CT, LOINC, etc. HL7 v3 allows more triggering events while satisfying little optionality, concluding rigorous standardisation.

The most widely adopted application of HL7 v3 is the Clinical Document Architecture (CDA) [91]. CDA is aimed at information exchange in the form of documents. Some “Clinical Documents” are pdf, image, audio, and video. Document analogy sheds light on comparing the differences between database and documentation. Hence, CDA manages to create human-readable and machine-processable outputs. Whenever a machine cannot process the codes, humans can interpret the clinical information

included in the CDA. CDA documents are created using Extensible Markup Language (XML). They include a header and a body section:

- The header contains metadata about the document, such as patient demographics, authorship information, and where/when/for what reason it is created. The metadata is used in document registers and databases to classify, find, and retrieve documents.

- The body section contains human-readable and structured data content (machine-processable) about the patient's health status, medications, procedures, and other relevant data.

HL7 FHIR

Instead of dealing with the burden of core HL7 messaging standards and syntax rules, the consistency disadvantage of HL7 v2, and the complexity disadvantage of HL7 v3, the HL7 community created a new way of information exchange methodology using modern web standards and "REpresentational State Transfer" capable Application Programming Interface (RESTful API). The information exchange parties do not bother with the counter party's interface, program, system, or data storage methodologies. The exchange is conducted over Uniform Resource Locators (URLs) and hypertexts (i.e., HTML, XML, JSON). Semantic interoperability is achieved by representing medical care and continuity data using external terminologies and codes referencing their specific URLs. Fast Healthcare Interoperability Resources (FHIR) is the recent information exchange standard. The characterisation of each word in the standard name is in Table 10. FHIR is a freely available standard. Implementers do not need to register or pay for any standards organisations to be able to use the specifications.

Table 10: The FHIR Standard

The FHIR Standard		
F	Fast	Indicates the quick implementation of the proposed system
H	Healthcare	The core focus of the standard
I	Interoperability	The principal aim of the standard
R	Resources	Atomic piece of information exchange

FHIR uses REST as the basis for data exchange in its API. While API allows the computer program to access the features of the data of a different program or system, REST defines categories of data to exchange data [94], [95]. Those data categories are the 'Resources' at the heart of the new standard.

FHIR considers all healthcare-related data as a collection of independent resources that can be downloaded and used. The philosophy behind FHIR is to create a set of

Resources that, individually or in combination, satisfy the most common use cases [96].

Resources are discrete data concepts, i.e., Patient, Practitioner, Encounter, Medication, Diagnostic Report, etc [97]. In the recent version of FHIR R5, there are 157 [98] resources. Resources have defined meanings in the FHIR Specifications. They have known locations at any server (internal or external) addressed at URLs. The meaning and content of the Resources do not change after an exchange between the systems. Instead of defining a vast concept that may describe everything, the FHIR implementers provided an atomic piece of implementable elements, which anyone can easily understand what it is used for [97].

Resources can reference other resources. For example, while constructing the Diagnostic Report Resource, the implementers refer to the Patient resource to describe the patient, to the Specimen resource to express the type and collection time of the specimen, or to the Encounter resource to prompt the healthcare event when the test is ordered for that Diagnostic Report, etc. (Figure 5). On the specifications page of any given resource, there is a list of other resources referenced by that specific resource.

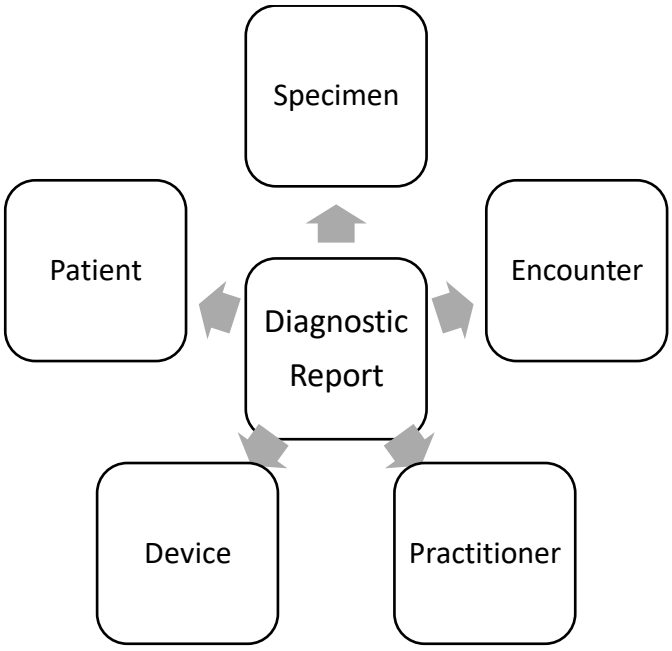

Figure 5: Resources can reference other resources.

To implement specific use cases, FHIR has created Profiles. Profiles encompass all the required extensions and resources that are essential for implementing or defining a particular use case. Use cases have their own content-specific terminological data groups. These data groups are called ValueSets. The interoperability – syntactic, semantic, and clinical (i.e., workflow), is backed by Profiles using messages, documents, REST API, and services (e.g., decision support services). Interoperability isn't attained solely through utilising FHIR; it's accomplished through adopting shared profiles. This eliminates the necessity for transformation, as the same profiles are used,

leading to seamless compatibility. Exchanging information in the computer era requires a minimum, almost no human interaction. Since the data should be machine-readable, interoperability measures should work appropriately for the computers to understand the exact meaning just as human perception. Computer systems need specific descriptions and definitions for the data concept to understand and exchange that data concept with the same meaning. The specific descriptions and definitions of a computer data concept are called the Clinical Information Model. The Clinical Information Model covers the rules, relationships, and vocabulary or terminology binding to describe the data concepts. FHIR profiles create the relationship between the data elements in the particular use case or data concept. Assuming we consider a FHIR profile for a Diagnostic Report, which might be a laboratory result, an imaging study, or an anatomic pathology report, they have some common elements summarised in Table 11.

Table 11: Elements in common for a Diagnostic Report Profile

FHIR Profile	Elements in Common
Diagnostic Report	Name of the Diagnostic Report Resource
	Patient Resource
	Practitioner Resource
	Encounter Resource (where the diagnostic report took place)
	Condition Resource: The reason the diagnostic report is created

Those details of the profile should exist and to specify the details of this FHIR Profile, there are two basic concepts:

1. Terminology or vocabulary binding: the values that the elements must have in an implementation. Those values – which aggregately form Value Sets, are fetched from one or more code systems or terminology servers staying on a specific URL (no need to upload code information for each implementation in each terminology server).

2. FHIR Extensions: FHIR was designed to be more implementable and less complex. A rule of 80:20 (focus on a common scenario) was considered while defining Resources [91]. The 80% of the resource specifications cover only the content that is needed by 80% of the systems worldwide. Implementers are not expected to differentiate a Resource more than 20%. However, since each local requirement and specific definition could lead to that percentage, the issue is handled by Extensions. FHIR Extensions cannot stand alone; they extend a FHIR Resource.

Finally, a FHIR Implementation Guide Resource is created, also residing at a specific URL. An implementer can validate the use case with this Resource. Rules for a specific

use case, including human readable documentation and examples for that implementation guide is provided in this resource.

Figure 6 provides a snapshot of a portion of the DiagnosticReport resource (HL7 International, 2023a). This is a sample FHIR Data Model. The standard interface is just a regular web page, where implementers may use the links for detailed information about the information in the resource or hover their mouse over to fetch the information pop-up window. The model element types are grouped in columns: Name, Flags, Cardinality, Type, Description & Constraints.

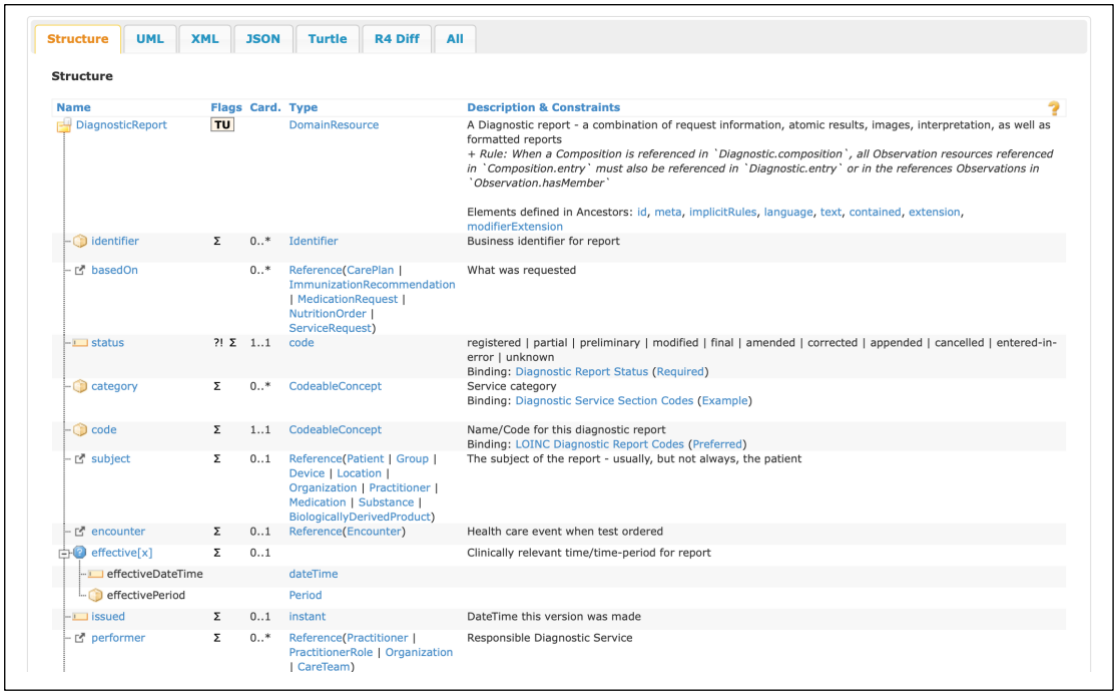

Figure 6: DiagnosticReport resource

Each element has a name, data type, and cardinality. Cardinality represents the existence constraints of any data element, i.e.,

- 0..1: data between zero and one, it is optional
- 0..*: it is again optional, but the maximum is unlimited
- 1..1: there should be only one value for that data

The actual instance of a resource can be split into four sections (Figure 7): Metadata, Extensions, Narrative, and Body, where those instances are exchanged between systems.

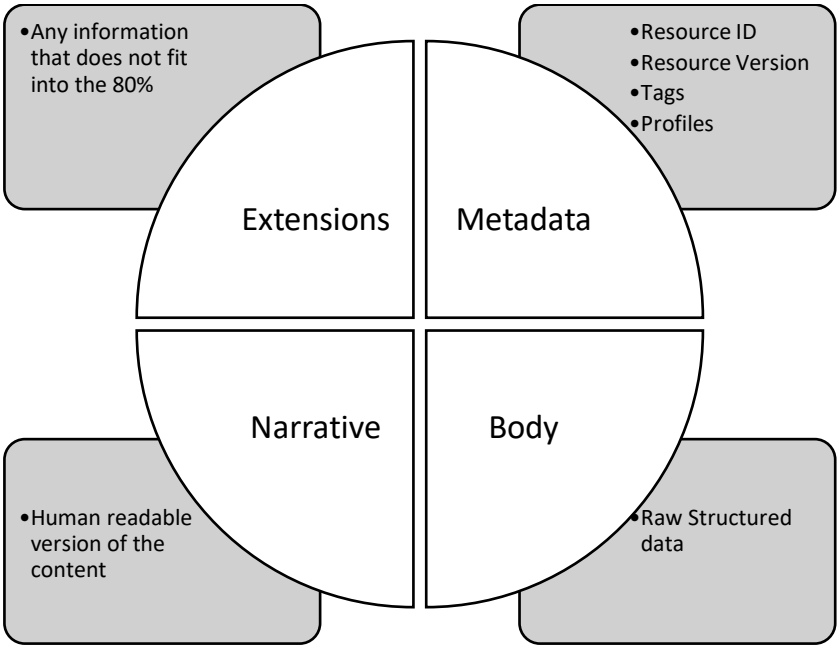

Figure 7 FHIR Data Model for Resource

FHIR defines three encodings: XML, JSON, and RDF/Turtle. A sample Patient Resource in XML encoding is in Figure 8.

```
<Patient xmlns="http://hl7.org/fhir">
  <id value="glossy"/>
  <meta>
    <lastUpdated value="2014-11-13T11:41:00+11:00"/>
  </meta>
  <text>
    <status value="generated"/>
    <div xmlns="http://www.w3.org/1999/xhtml">
      <p>Henry Levin the 7th</p>
      <p>MRN: 123456. Male, 24-Sept 1932</p>
    </div>
  </text>
  <extension url="http://example.org/StructureDefinition/trials">
    <valueCode value="renal"/>
  </extension>
  <identifier>
    <use value="usual"/>
    <type>
      <coding>
        <system value="http://hl7.org/fhir/v2/0203"/>
        <code value="MR"/>
      </coding>
    </type>
    <system value="http://www.goodhealth.org/identifiers/mrn"/>
    <value value="123456"/>
  </identifier>
  <active value="true"/>
  <name>
    <family value="Levin"/>
    <given value="Henry"/>
    <suffix value="The 7th"/>
  </name>
  <gender value="male"/>
  <birthDate value="1932-09-24"/>
  <careProvider>
    <reference value="Organization/2"/>
    <display value="Good Health Clinic"/>
  </careProvider>
</Patient>
```

Figure 8: FHIR Patient Resource in XML Encoding

The last point of FHIR that needs to be mentioned for the introduction part for FHIR of this dissertation is “Slicing”. Slicing provides functional flexibility for representing real-world data in FHIR while demonstrating them using resources or data types with repeating elements. The implementers can group these elements depending on their nature and content. For example,

- a patient has different identifying numbers inside a hospital during an encounter, i.e., National ID Number, Hospital ID Number, Encounter ID Number (in Turkish: Protokol No)
- a patient may have more than one address,
- an observation for vital sign measurements of a patient may have multiple components, i.e., Blood Pressure has two different values: systolic and diastolic.

Implementers reflect slicing guidelines for Patient and Observation resources while implementing these multiple component data elements, i.e., different Identifier

Numbers for different purposes, multiple addresses under the address data element, and two components for the observed blood pressure value.

CHAPTER 4

RESULTS

This dissertation focuses on an examination of the present state of genetic and genomic testing within Türkiye. It delves into the applicable rules, regulations, and the capacity for exchanging information in this field. The outcomes assisted in proposing a conceptual model for integrating genetic/genomic testing with SağlıkNET.

Initially, we reviewed the governmental rules and regulations in effect. Later, we conducted semi-structured interviews with 13 key informant experts recruited using purposeful sampling and snowball sampling methodologies among hospitals and government and private sector laboratories. Verbatim transcriptions of interview data were analysed using qualitative research methods with MAXQDA software. The Research Question is: 'How do genetic testing experts manage genetic testing concerning storage, reporting, privacy, pedigree, sharing (including the third parties), and standardised data representation under the requirements of governmental rules and regulations?'

We noticed vague legislation; thus, an interoperable genetic/genomic information exchange structure is crucial for EHRs in Türkiye. The findings allow us to propose genetic/genomic data exchange capable EHR at the national level. We divided this chapter into four categories:

1. Healthcare Interoperability Tools, Legislations and Data Privacy in Türkiye About Genetic Testing and a Comparison with Global Best Practices
    i. Healthcare Interoperability Tools in Türkiye
    ii. Legislations in Türkiye Concerning Genetic Testing
    iii. Genetic Data Privacy in Türkiye
2. Genetic Testing Reimbursement in Türkiye
3. Qualitative Analysis of Interview Results
4. A Conceptual Model for Genetic Information Exchange in Türkiye

4.1 Healthcare Interoperability Tools, Legislations and Data Privacy in Türkiye About Genetic Testing and a Comparison with Global Best Practices

4.1.1 Healthcare Interoperability Tools in Türkiye

SağlıkNET has a centralised architecture, the messaging infrastructure is based on HL7 v3, and the communication protocol is web services [99]. National data standards were adopted to be international, and the data elements to be accordingly standardised are defined in National Health Data Dictionary/Ulusal Sağlık Veri Sözlüğü (NHDD/USVS) [100]. Data definition and format, defined in (NHDD/USVS), enables the information systems used at health institutions to use it as a reference. NHDD/USVS allows shareholders to share the exact meaning of data and use them for the same purpose [99]. The data groups used for data collection are called Minimum Health Data Sets/Minimum Sağlık Veri Setleri (MHDS/MSVS) and are formed from the NHDD. MHDS define the data sets that emerge when presenting a particular service. MHDS is being used for the National Decision Support System to determine the health policies of MoH. MoH also defined Health Coding Reference Server/Sağlık Kodlama Referans Sunucusu (HCRS/SKRS). HCRS aims to provide all healthcare providers with standard coding/classification system [99]. Some of the international coding systems are ICD-10, International Classification of Diseases Oncology (ICD-O), Anatomical Therapeutic Chemical Classification System (ATC) to define medications and drugs, and Logical Observation Identifiers Names and Codes (LOINC).

In Türkiye, the main point to set an EHR in a healthcare institution is obeying NHDD. We must ask whether NHDD has room for genetic data, tests, or disease. Until today, MoH has published four versions of NHDD ("Ulusal Sağlık Veri Sözlüğü," 2014), namely USVS 1.0, USVS 1.1, USVS 2.0, and USVS 2.2. The latest version, USVS 2.2, was published on the 7th of May 2014. USVS 1.0 and 1.1 have 46 Minimum Health Data Sets (MHDS), USVS 2.0 has 65, and USVS 2.2 has 66. MHDS has a structure that can be revised and updated, and a commission is in charge.

Among 66 MHDS, there is no definition for genetic tests and diseases. Cancer MHDS and Stem Cell MHDS are two expected data sets that may have room for genetic test data, but they weren't defined to have. The cancer data set and Stem Cell data set have the following elements, as shown in Table 12. Two more data sets are in use: Cancer Follow-Up MHDS and Stem Cell Transplantation Follow-Up MHDS, which also don't contain any genetic data element. Since NHDD is a list that Electronic Health Record software developers should obey in their products at a minimum level, we can easily say that genetic test results are still not in a structured format.

Table 12: Cancer and Stem Cell MHDSs [*]: Surveillance, Epidemiology, and End Results Program

Cancer MHDS Data Elements	**Stem Cell Transplantation Notification MHDS Data Elements**
• Initial Diagnosis	• Transplantation Type
• Place of the Tumour	• Source of the Stem Cell
• Diagnosis Method	• Reason of Waiting Before Transplantation
• Histological Type	
• SEER[*] Summary Stage	
• Laterality	
• Occupation and Cancer	

For a general overview to understand genetic tests and result sharing in Türkiye, we should concentrate on SağlıkNET. It is mainly based on ICD. Currently, version 10 is used. ICD-10 is a standard which codes diseases. Other international standard organisations behind SağlıkNET are ICD-O to define morphology and topography for oncology (contains codes for oncologic diseases, not genomic data related to oncology), ATC to define medications and drugs, and LOINC to mainly define the laboratory tests. With the addition of LOINC recently, genetic tests can be implemented on SağlıkNET. But as their names are on, none besides LOINC have standards/codes for genetic test results and procedures. LOINC is translated to Turkish, mapped to HIC, and added to the existing HCRS. Figure 9 depicts the structure of the National Health Information System of Türkiye.

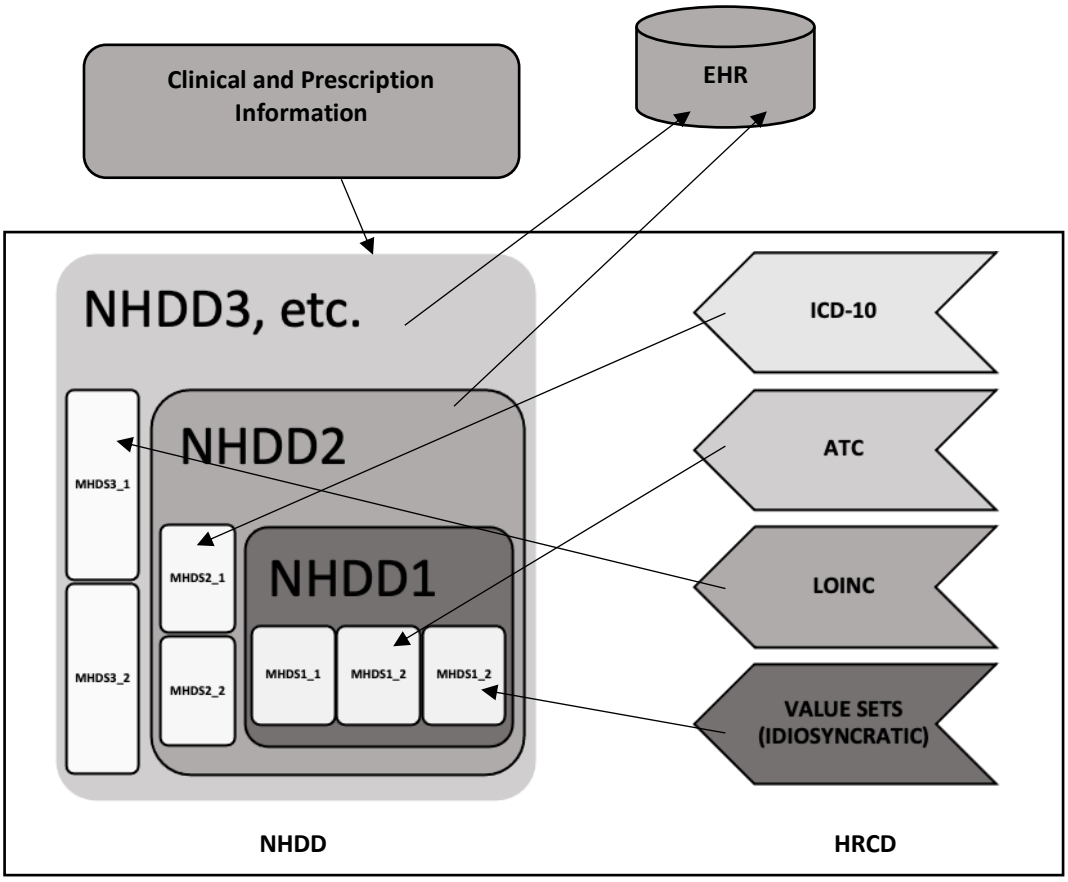

Figure 9: Structure of NIHS-T: Registration of patient, diagnosis, test requests, prescription information, and other clinical findings coded according to the available terminologies and codes included in HCRD and stored in EHR.

On the other hand, reimbursement in SağlıkNET is based on HIC codes. Those codes are idiosyncratic. They are not international and are valid only in Türkiye. In each separate declaration (sometimes annually, sometimes more than once per year), some codes are removed, or some more additions/revisions are performed.

When HIC is examined as a support for genetic test coding standards, we can observe that the existing idiosyncratic codes solely define genetic testing procedures, not the test or method itself. In other words, it doesn't list the name of the genetic test or the name of the gene to be analysed. It is based on the reimbursement of the methodology conducted for the test. The same methodology can define several different genetic tests. MoH's reimbursement regulation applied by SSI via idiosyncratic codes cannot define structured data information for genetic tests in SağlıkNET.

4.1.2 Legislations in Türkiye Concerning Genetic Testing

There is no specific regulation or code about sharing or storing genetic test results in an internationally accepted, interoperable, and standardised manner in Türkiye. According to literature [12], six different rules and regulations on laboratories may relate to medical genetics.

1. Medical Laboratories Regulation [101]
2. Regulation on Genetic Disease Diagnosis Centres [102]
3. Guidance on Tissue Typing Laboratory [103]
4. Hemoglobinopathy Control Program and Diagnosis and Therapy Centres Regulation [104]
5. Regulation on Centres for Early Detection and Screening of Cancer [105]
6. Regulation on Notification of Cancer and Centres for Cancer Registry [106]

The Medical Laboratories Regulation [101] is executed as the broadest one since it regulates all laboratories in action [12]. It addresses the need for routine data transfer to MoH in a defined paper-based format to statistically collocate the medical data following the Public Sanitary Regulation [107]. The regulation also points to archiving paper-based data for at least 30 years. If the laboratory can define and apply administrative and technical precautions for the security and privacy of electronic medical data, the requirement for paper-based archiving could be dismissed. Per the Electronic Signature Regulation [108], electronically signed medical data are accepted as official data as long as their backup and archives are provided.

The "Regulation on Genetic Disease Diagnosis Centres" establishes administrative, architectural, and essential equipment prerequisites for genetic testing centres. It does not enforce standardised representation for genetic test result reports [12].

Another paper-based, at the same time, sometimes stored in a separate electronic database procedure is Tissue Typing Laboratory test results: Human Leucocyte Antigen (HLA). MoH controls tissue Typing Laboratories; their data must be stored in a database separate from EHR. Tissue Typing data are unstructured and don't have international data standards. In the electronic version [109] of this paper-based form, laboratory personnel are required to enter HIC codes and names of the equipment used during the test.

Another example is "Hemoglobinopathy Control Program as One of the Hereditary Diseases and Its Diagnosis and Therapy Centre Regulation" [104]. In item 10, Registration System and Notification, it is stated that "to be a basis for constructing a database to follow, control and prevent hemoglobinopathy, constituting a registry system and notification that track patients, carriers and actions performed in every stage is a must. The registries in every stage should be sent to the Directorate monthly and sent to the MoH quarterly via a form prepared by the Science Board"—none of

the items of this regulation state about the terminology or standards-based coding of hereditary findings.

Cancer is one of the diseases that can be genetically diagnosed and followed for prognosis. In "Regulation of Early Detection and Screening Centres for Cancer" [105], case registration is stated to be done in separate patient files and archived in the centre, which makes it challenging to integrate them with electronic health records of a patient. This regulation still forces paper-based recording.

In the National Health Data Dictionary [100], some axes of this cancer notification form are kept in EHR software as a "must" field. This is not as detailed as the paper-based "Cancer Registry Information Form" [110]. Additionally, the previous version of this form, which is currently removed from the Public Community Health Institution Department of Cancer [111] web page, and the recent one [110] have different idiosyncratic codes.

National Cancer Control Plan [112] noted that CanReg software is in charge of storing and registering cancer case data [113]. CanReg software, which utilises ICD-O for coding, is produced by the International Agency for Research on Cancer in collaboration with IACR and is free to members of the Association [114]. The Republic of Türkiye is a member of the association. This software doesn't contain any genetic test information for cancer registries.

According to the Regulation for Cancer Notification and Cancer Registry Centres [106], cancer notification is a must for health institutions (notifiable diseases) and electronic records of those "Cancer Data" should be kept for 20 years in an electronic database [12]. Those forms do not contain genetic testing or genetic/genomic information for cancer data.

4.1.3 Genetic Data Privacy in Türkiye

SağlıkNET and e-Nabız are two central systems that track and store the individual's health data. A recent bylaw about the protecting personal health records mandates both systems [115]. e-Nabız is an online platform where Turkish citizens and health professionals can access and share health data (Ministry of Health Türkiye, 2016a, 2016b). The MoH holds the health data, and the individual can control their privacy to give temporary or full access rights to clinicians or medical centres in an opt-in or opt-out fashion. Since e-Nabız does not display genetic test data, this review study will not provide information about the genetic data privacy concern of e-Nabız.

In April 2016, the Law on the Protection of Personal Data (LPPD) became effective [63]. Article 6 (1) of LPPD itemise personal data of a unique nature. Here, the health and genetic data are deemed personal data of a unique nature as separate titles. Article 6 (2) prohibits processing personal data of a unique nature without the data subject's explicit consent. Nevertheless, Article 6 (3) constitutes two dilemmas about the privacy of genetic data: "All personal data listed in Article 6 (1), excluding health and sexual life, may be processed without the data subject's explicit consent in the cases determined by law."

i. the need for explicit consent for genetic data is not emphasised in health data [63],

ii. the law that determining the cases is not precisely attributed [118], [119].

In a focus group study [7], experts stated two reservations about blurred discrimination between health and genetic data:

i. Genetic data and health data are two different personal data types and cannot be processed without explicit consent.

ii. Differentiating these two types of data may constitute a problem for the reimbursement of genetic testing costs: If the genetic data is excluded from the health data, the government may deny genetic testing costs from their reimbursement program in the future.

According to a recent Turkish Grand National Assembly, Planning and Budget Commission decision on July 16, 2019 [120], a revision request on the Law on SSI articles related to personal data is accepted and sent to vote in the general assembly. So, upon request, SSI is subjected to share personal health data with the MoH Türkiye to protect public health or operation of preventive medicine, medical diagnosis, treatment, and nursing services, monitor the compliance and expediency of healthcare services provided, and their financing planning and management. This recent revision allows personal health data to be processed contrarily to the LPPD articles without seeking the individual's explicit consent, which realises the reservations of the experts interviewed in the focus group study [7].

Based on personal communications, genetic testing experts assessed the privacy of genetic data under five titles:

1. Privacy and security within EHR,
2. Privacy issues for DNA biobanks,
3. Genetic information share with the third parties,
4. Privacy during reporting results (information share) to the patient,
5. Privacy within a pedigree and right to not to know.

While the experts strongly recommend not to share the genetic information of a patient and a pedigree member with the third parties, unanimously, they exemplified a counter case with the following reservation:

"If an individual's genetic predisposition may harm other people in the society, sharing genetic/genomic test results with the third parties should be deeply evaluated under ethical concerns."

As stated in the LPPD, experts are concerned about the patient's privacy and their pedigree. Without the consent of the pedigree member, the pedigree should not be shared or processed. When requested, pedigree members should be removed from the study. If the privacy of any pedigree member is not appreciated, it might lead to a legal case. Experts noted that, during pedigree studies, a relative who gave informed consent and approval for the genetic testing might not want to learn the genetic predisposition to any disease that they are not aware of yet, known as the "right to not to know." Although ethically arguable, sharing observation of an actionable incidental finding may benefit the patient. Against the privacy policy, experts stated that they prefer to inform to save a life. The extent of information to be shared is another difficulty, where experts anticipate a decision and a regulation from the MoH Türkiye. In August 1988, Türkiye enacted Regulation on Patient Rights [121]. This regulation covers the right to know, the right to not to know, and the right of clinicians about not to share clinical conditions with patients who may have possible psychological counter effects. Nevertheless, the reporting of the incidental genetic findings is not defined. While establishing related regulations, governmental and non-governmental organisations should cooperate to increase the public's risk perception.

The status of Turkish health information systems for integrating genetic/genomic patient data compared to global best practices are listed in Table 13 alphabetically. The findings of other countries are provided as related references.

Table 13: Status of Turkish health information systems for integrating genetic/genomic patient data compared to global best practices in alphabetical order

Genome Enabled Interoperable Messaging Standards (FHIR)	
Türkiye	None
Global Practices	In the US: [22], [24] In the UK: [23], [25], [26], Finland [122], Austria [123]
Cohort studies for genomic medicine	
Türkiye	Turkish Genome Project [17], [62]
Global Practices	Details provided in [17]
Data Nomenclature for Genetic and Variant Data (HGNC and HGVS)	
Türkiye	None
Global Practices	In the US:[22]; In the UK: [23], [124]; In Dutch [125], Published Suggestions: [91], [126]
EHR integrated biobank	
Türkiye	None
Global Practices	Details provided in [51]
Electronic Genomic Data Exchange	
Türkiye	Not available. SSI request full paper-based output of genetic test results for reimbursement
Global Practices	In the UK: [39]
Full Implementation of LOINC	
Türkiye	Only reimbursed procedures are translated into Turkish by MoH and implemented NHIS-T.
Global Practices	Originally published in English, also translated into 13 languages.[127]

Table 13 (Continued)

Genome Enabled Interoperable Messaging Standards (FHIR)	
Türkiye	None
Global Practices	In the US: [22], [24] In the UK: [23], [25], [26], Finland [122], Austria [123]
Legislations on the return of results	
Türkiye	None
Global Practices	The detailed study provided in [38]
Minimum genetic data set	
Türkiye	None
Global Practices	In France: [128] GA4GH: [48]
Ontology-based terminology for the phenotype (i.e., SNOMED)	
Türkiye	None
Global Practices	In the US: [22], In the UK: [23], in Norway: [49]
Privacy legislations on genetic data	
Türkiye	Personal Data Protection Law (PDPL) [63]
Global Practices	Details provided in [54]

4.2 Genetic Testing Reimbursement in Türkiye

Our manuscript [12] details Turkish General Medicare Insurance coverage and reimbursement constraints. HIC explicitly defines both the entitlements of the insured person and the duties and obligations of the purchasing organisation SSI, a branch of the Ministry of Labor and Social Security.

Pertaining to HIC, MoH grouped health service providers into four, and among them, tiered health care facilities into three: primary, secondary, and tertiary [129].

HIC itemises constraints and acts for reimbursement and transactions under four Annexes:

1. Healthcare provider types, hospital types and levels, general rules, and document templates

2. Therapy

3. Medical Equipment

4. Pharmaceuticals

Annexes explicitly describe the transactions (benefit catalogues). Each transaction has a unique idiosyncratic code, definition, and score. A commission in charge updates transactions several times a year, deemed necessary, i.e., addition, deletion, and code and score updates. Depending on governmental policy and regulations, SSI insurer shares a percentage of some of the transactions out of pocket (OOP) in direct payments or cost-sharing [130].

The list of genetic/genomic test transactions under reimbursement coverage is in "Annex 2/B, List of Transactions per Service" (Appendix D). Reimbursement is conditional upon attaching a paper-based detailed report on test steps and testing equipment's result printouts to the invoice (HIC, Annex 1). Please note that we provided complementary details for reimbursement and prepared a comprehensive decision flowchart for genetic testing reimbursement in Appendix E.

Cost is equal to the multiplication of the score and a unit price that the Government of Türkiye announces in Turkish Liras per fiscal year.

For genetic/genomic tests, the annulled communiqué dated 13.12.2021 contained 77 transactions (benefit catalogue) under three groups. Merely one is targeted gene (FMF/MEFV) mutation analysis; the remaining 76 are genetic/genomic testing procedures. Although test panels and actual costs bear no similarity, a single procedure covers more than one genetic test under identical coding and reimbursement scores.

Starting from the HIC dated 08.02.2022, the commission regrouped the genetic/genomic test catalogue into five. From now on, Annex 2/B resides a total of 229 transactions, including more targeted gene tests (Appendix D). On the other hand, this improvement concluded an utter change in the idiosyncratic coding scheme for

genetic/genomic test reimbursement. Table 14 provides an illustrative dissimilarity, executed on reimbursement and coding for two selected sample genetic tests: BRCA1 and BRCA2 mutation tests for hereditary breast cancer and CTFR mutation test for cystic fibrosis diagnosis. It is underpinned that experts are to use new codes for reimbursement.

Table 14: After the change in HIC, the dissimilarity in codes, transaction names and scores for two selected genetic tests.

Genetic Test	HIC Version	Transaction		
		Code	Name	Score
BRCA1/ BRCA2	**Annulled**	908717	DNA Sequence Analysis, 21 and more reaction	2.244,51
CTFR				
BRCA1/ BRCA2	**Recent**	G100580	Hereditary Breast/Ovarian Cancer (BRCA1 & BRCA2 Gene Sequence Analysis)	1.259,19
CTFR		G101120	Cystic Fibrosis (CTFR Gene Sequence Analysis)	842,25

Appendix D provides annulled and recent HIC Annex 2/B. Consecutively, it presents sample panel test lists according to annulled HIC transactions. The target audience can determine that the same transaction code of reimbursement covers numerous genetic test panels or tests.

4.3 Qualitative Analysis of Interview Results

In this part of the dissertation, we explored the perspectives and policy recommendations of medical professionals in Türkiye regarding the existing status of genetic/genomic testing under the requirements of governmental rules and regulations following the health transformation program in the Republic of Türkiye. We conducted semi-structured interviews with 13 key informant medical genetics specialists from nine health organisations, recruited through purposeful and snowball samplings among government and private hospitals and laboratories, covering all domain stakeholders. Qualitative analysis of the interview data outlines the existing status of genetic testing in Türkiye, spanning initial test requests through reporting from the experts' perspectives and their expectations from policymakers.

Overall, eight themes emerged, which we categorised as a pipeline of Input-System-Output (Figure 10):

1. Standards in use,
2. Ordering,
3. Pedigree,
4. Management of the raw data,
5. Customised software along with the paper-based detailed record,
6. Reporting,
7. Information exchange with the patient, and
8. Information exchange with the third parties

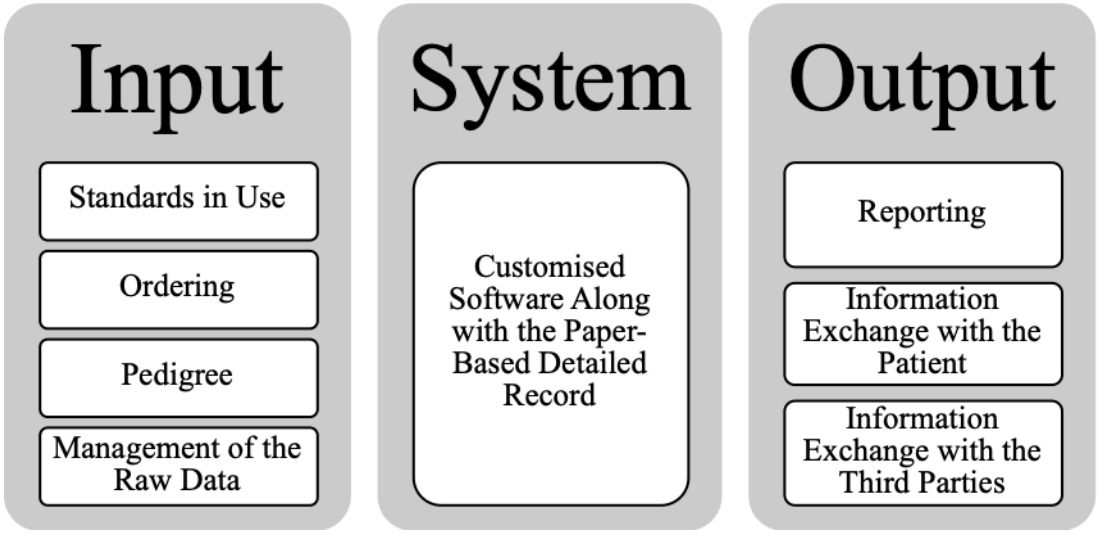

Figure 10: Eight Themes that Emerged Regarding the Current Status of Genetic/Genomic Testing in Türkiye Categorised as a Pipeline: Input-System-Output.

According to the workflow and interview data, when any health insurance authority (government or private) reimburses a test, the genetic test request is accompanied by an ICD-10 diagnosis code. Genetic test orderings are executed in several ways, depending on the requesting entity. Experts genuinely benefit from pedigrees while ordering and analysing the tests and finalising the diagnosis. The genetic testing centre predominantly manually prepares pedigrees; only a few centres and experts utilise digital tools. Every centre has a particular approach to storing and managing genetic test data results. However, for reimbursement, they obey the rules of government and private insurance requirements. Some centres utilise customised software, and paper-based records, boosting their data integrity and consistency. At the end of testing, genomic information can be shared with different actors: with the clinician, directly with the patient, and with third parties.

The findings and expectations from the policymakers extracted as themes are below:

4.3.1 Standards in Use

When HIC is discussed as a support for genetic test coding standards, the consensus of the interviewees is that the existing idiosyncratic codes solely define reimbursement for genetic testing procedures, not the gene name, test, or method. One procedure code covers several genetic tests. MoH's reimbursement regulation applied over SSI via idiosyncratic codes cannot define structured information exchange for genetic tests in SağlıkNET.

An expert from a government laboratory centre gave an example for the BRCA1 gene, setting forth the incapability of HIC as a genetic test coding standard:

> "According to MED, for reimbursement we cannot directly codify BRCA1 test, the experts should select – 24 pairs or more – option."

Depending on the reimbursement policy of the government, HIC is subject to change (additions or deletions) in an ad-hoc manner. If the test procedure is not listed (coded) in the HIC, it is not reimbursed; the patient should pay the charge for the test from the pocket. An expert in a government university exemplified the modifications and inadequacies in HIC:

> "For diagnosis, we utilise ICD-10 as an international standard. Moreover, for metabolic diseases, we use the coding of the Society for the Study of Inborn Errors of Metabolism (SSIEM). It is a disease code. ICD-10 is more general, but SSIEM covers metabolic diseases in more detail. At the end of the analysis, we report the disease name, the ICD-10 code of the disease, and the name of the gene that the mutation observed. Using HIC as a genetic/genomic test coding standard has no meaning. The procedures coded in HIC cover almost all the genetic tests. Moreover, it is changing from time to time. Two cases as an example are:
>
> - Previously, ArrayCGH and microarrays were not coded under HIC, but now they are.
>
> - Instead of testing 200 or 300 genes responsible for epileptic encephalopathy, we prefer to use WES, but it is not reimbursed (as of February 2016) since it is not listed under HIC. The patient affords the cost."

Some centres have initiatives to use other standards along with the existing ones to code the genetic tests they conduct or to code their diagnosis more broadly. OrphaNet, SSIEM, OMIM, ISCN, and FASTQ are reported by interviewees. Online Mendelian Inheritance in Man (OMIM) is a standard to define genes in the human genome [131]. SSIEM and OrphaNet [132], [133] have extensive codes for rare diseases compared to ICD-10. International System for Human Cytogenomic Nomenclature (ISCN) [134] is an international standard to describe human chromosomes and abnormalities. FASTQ [135] is a text-based format representing biological sequences. Those centres are mainly the ones that benefit from dedicated software and hardware solutions. Indeed, while codes and regulations may not mandate the utilisation of dedicated software for managing genetic tests, it's crucial to acknowledge that experts in the field are aware of the limitations inherent in the current standards employed to define genetic tests. This recognition of insufficiencies underscores the need for improved standards and solutions that can more effectively address the complexities of genetic testing and ensure accurate and comprehensive management of genetic data. While not obligatory, the use of dedicated software could potentially aid in overcoming these challenges and contribute to better management and utilisation of genetic test information within the healthcare landscape. One of the experts who are using in-house developed software said about their test reports:

> "Along with the obligatory ones, we use SSIEM and the name of the gene that the mutation is observed for metabolic diseases. Using HIC as a genetic/genomic test coding standard has no meaning."

A manager in a government laboratory explained that they are using different standards together with the obligatory ones due to their previous education discipline. He notes the importance of genetic test coding is not considered by MoH yet:

> "We use ICD-10 and OMIM in our reports. For our Fluorescence in situ Hybridization (FISH) reports, we utilise ISCN standards. Except for ICD-10, all other standards that we use for reporting are not mandatory by governmental rules and regulations."

One of the centres in a private university hospital is adopting its genetic test results in line with GA4GH. They are a collaborator of this organisation in Türkiye. GA4GH is a promising organisation working on "enabling the genomic data exchange":

> "As for the structural representation of genetic test results, we utilise GA4GH. We are included in this project and try to achieve an interoperable solution for sharing genetic/genomic test results."

ICD contains gender and age-specific disease codes. In hereditary diseases, pedigree members, irrespective of gender, should be tested. In case any member cannot be correctly coded due to existing insufficient gender-specific code, in order to reimburse or store the case in their records, doctors diagnose that member with an irrelevant ICD code, which results in a wrong disease classification and statistics community-wide. An expert from a private university noted that:

> Gender Case:
>
> "During the hereditary test of habitual abortion for a woman, we cannot request "habitual abortion test" for diagnosis of a man using ICD because of gender-specific insufficiency. To conduct a test on a man; we diagnose man as 'unidentified chromosomal anomaly'".
>
> Age Case:
>
> "To diagnose a child with a translocation carrier property, to test parents in the pedigree, the doctor should code 'congenital anomaly' or related clinical history."

A private genetic testing laboratory is more enthusiastic. It is working on utilising standards and finding a better-standardised representation of their genetic test results in their in-house developed software. The doctor said:

> "We have participated in translating the genetic testing part of LOINC for MoH. We have observed some drawbacks of LOINC for the representation of genetic tests in a standardised manner. Moreover, we have translated OrphaNET to use in our centre's software. We have managed to generate an automatic test list. It is more comprehensive and useful. We are planning to represent OrphaNET solution to the ministry."

There is a lack and demand to express an accepted standardisation to define genetic tests. Centres use different standards, which is a major drawback in achieving interoperability in EHRs. HIC cannot be a solution to define genetic tests in a structured way. Moreover, besides not containing genetic test codes, ICD-10 has drawbacks that would result in wrong statistical distributions.

4.3.2 Ordering

According to interviews, in Türkiye, genetic/genomic tests are requested in four different ways:

- Through EHR of hospitals
- Some special/specific cases to research centres of hospitals (not over EHR)
- By personal application to private laboratories
- Through Forensic Medicine upon court decision

All those different requests produce the reports in a way that obeys the governmental regulations and codes.

4.3.3 Pedigree

Unanimously, interviewees mentioned the significance of pedigree. It is very advantageous during family tracking and diagnosing a patient. The clinicians or genetic counsellors draw pedigrees by hand or use third-party software outside SağlıkNET or centres' EHR. This is not satisfactory for the clinicians. Especially hand-drawn pedigrees might have missing points. A reason behind this is the lack of importance given by the clinicians or assistants to the pedigree; another reason is the lack of time. So many cases reported by the interviewees about incidental diagnosis of the asymptomatic pedigree members having a predisposition to genetic disease. The centres with in-house developed software for their genetic/genomic test result storage scan and store their pedigrees digitally. They also keep them in the paper-based records. There is a common requirement for a useful software for pedigree. The need for a comprehensive education background and training in drawing, implementing, and interpreting pedigree is notably mentioned. None of the centres' EHRs includes software for pedigree. Contrarily, the experts are eager to utilise pedigree software when embedded in EHR. Instead, they use third-party software. The notations from government and private university hospital interviewees about pedigree are:

> "Pedigree is so crucial for geneticists, genetic counsellors, and clinicians. It demonstrates which test to apply, the transformation model of the test applied, and the bioinformatics way to follow. In the market, there is software that draws pedigree with a simple drag-and-drop property. Such software should be embedded in EHRs and SağlıkNET."

> "To be able to examine any relevant potential diseases pertaining to patients of different profiles as well as the offspring of pregnant individuals and alike, we

fulfil pedigree in a detailed fashion. Monitoring sporadic cases and carrier individuals is crucial to tracking disease occurrences and repetition patterns. This practice allows for a better understanding of the frequency and distribution of diseases within a population and aids in identifying potential trends or clusters. It is especially important for prenatal diagnosis. In our centre, we keep our pedigree in digital format and use Cyrillic software."

"Even though we are a genetics department, I can hardly get my assistants to draw a pedigree. It is a necessity for us. Clinicians should be good at pedigree drawing. Cyrillic and Progeny are the well-known software. There are some challenges in pedigree. If you observe a variant in a relative via pedigree, that relative may not give you consent to be analysed. So, you should enter the evaluation of that case anonymously, without name data. Those issues require extra workload for pedigree. . Using the informed consent mechanism during your study would be best. All local files are more detailed than the ones sent for EHR."

"In our centre, we hand draw our pedigree. But if I find or if somebody embeds a user-friendly software to keep our data in a reliable, digitised, and durable format, I will immediately use it."

"Pedigree is a sine qua non for us, and it would be better to have pedigree together with a test request from the referring clinician side. But it is so hard to satisfy it. During my career, there have been many cases where we caught a mutation during pedigree. The individual is unaware of the genetic predisposition to that disease."

"We diagnose nearly all rare diseases with the support of pedigree. This process involves utilising both hand-drawn pedigree charts (created with pen and paper) as well as digital pedigree tools. These methods help understand and visualise the inheritance patterns and familial relationships that significantly identify and diagnose rare genetic conditions. Paper-based ones are scanned and stored in digital means. We plan to get rid of paper-based storage within one year. In means of privacy, there are so many cases that we remove a pedigree member from our study. If not, there are too many stories, including divorce or family-wide problems. We always obtain informed consent before pedigree."

Another expert from a government university hospital explained the privacy of pedigree information with applicable legal basis and additionally emphasized how to approach some important cases with extra medical support:

"Pedigree information is private to individuals and cannot be shared without consent. It is also defined in KVKK. Nobody has a right to access and disseminate an individual's genetic information, even to a pedigree member. Maybe the pedigree member will not want to learn their genetic predisposition, or the patient may not want to inform their family members. But there are some

> important cases like Huntington. Risk perception of the public should be increased, and those tests should be performed with psychological support."

From the interviews, we can summarise the expectations and notifications by the experts about pedigree as follows:

- Hand drawn pedigrees are not feasible for the genetic experts since they might have missing points like:
  - The lack of importance given by the clinicians or assistants to the pedigree,
  - The lack of time to prepare them completely.
- There is a common requirement for detailed and user-friendly interface software for pedigree.
- The need for comprehensive education for drawing, implementation, and interpretation is importantly mentioned.
- None of the centres' EHR includes software for pedigree. Contrarily, the experts are eager to utilise pedigree software when embedded in EHR. Instead, they use third-party software.

Pedigree is also assessed in terms of ethical aspects among interviewees. They mentioned the necessity of informed consent of any pedigree member and the importance of privacy of the pedigree.

4.3.4 Management of Raw Data

Although codes and regulations in charge allow digital data storage under administrative and technical compliance, genetic/genomic testing centres keep their result report records and reimbursement-related outputs in paper-based format along with digital ones. Legislatively, according to HIC, presenting a paper-based output of geniting testing equipment is a constraint for reimbursement [129]. They do not want to face problems during reimbursement and possible judicial issues. They utilise archive rooms to keep their report copies and other test result-related printouts. The centres that do not have digital facilities do not store the whole raw test data.

One of the experts in a university research centre said that:

> "All those rooms are full of paper-based archives. When those rooms are filled, we must find an extra room. At one point, it will be impossible to keep those due to lack of space. All findings, clinical notes, and pedigree drawings are kept in those archives. There is no standardised and structural approach to store the genetic data."

Some centres with research facilities use their in-house developed software database for internal usage. The user of an in-house developed software said that:

> "Honestly speaking, we were using our in-house developed software to store our genetic test data even before we established integration with the EHR in our university once upon a time. We have no more integration with EHR due to security reservations expressed by the management. We store our genetic test data in paper-based and electronic format."

An expert from a private university hospital exemplified the importance of data storage to have support on legal issues.

> "Sometimes there may be legal cases. According to the chromosomal tests, an individual may be 46XX with a female genotype, but this diagnosis may be in court by the statement of the individual as she is male. At the trial, those printed image results would be proof and basis for the decision."

Some centres use digital media to store their raw genetic test results and reports digitally. They are aware of the importance of data backup. Centres with research facilities use their in-house developed software database for their internal usage to store data. Some others use cloud technology for their raw genetic data backup and retrieval and physical hard disc storage, but they have some reservations about cloud storage. The reservation depends on cost since they use well-known international cloud systems. An expert from a private university hospital mentioned that:

> "Along with paper-based storage, we keep our data in electronic format. There is an automatic backup system designed according to pre-defined time intervals. Moreover, we utilise cloud storage. Unfortunately, we have some reservations about cloud storage. The cloud system's access cost increases when you produce and store a high amount of data. We must pay unbelievable amounts for storage costs. In some way, we do not find cloud storage solution so feasible due to its cost."

Some of the government laboratories are managed and designed by private companies as a result of service procurement tender. Due to competitive bidding procedures, some of them provide electronic storage facilities for genetic test results for indefinite time, to comply with codes and regulations in charge [101]. At the same time, they keep their reports in paper-based format. The doctor in the centre expressed that:

> "Our centre stores our genetic test data in electronic and paper format. It is not a kind of dedicated software. I mean only storage. Electronic backup is offered in physical hard discs according to pre-defined time intervals. I think the best way is to store those data for a lifetime, but unfortunately, you cannot find a space for archiving and storage after a certain time. Besides, some of those stored data will no longer have any usage and can be deleted or removed."

An expert from a recently established government laboratory explained that they could store their raw genetic test data in portable hard disc drives and process their data using the spreadsheet. In parallel with the data protection laws of The Republic of Türkiye, the Ministry of Health is expected to provide a database and data storage facilities within the hospital they are mainly serving.

> "In our centre, we not only store but also actively support the retention of entire raw genetic data acquired as an outcome of the analysis process. This commitment to preserving the full genetic data is crucial for maintaining data integrity and facilitating potential future investigations or uses of the data. Currently, the hard disc drives are enough for our studies. Still, soon, we expect a dedicated storage area for our centre from the hospital side, which is under the laws and regulations of The Republic of Türkiye. Our future aim is totally different, and hence, to store that huge amount of data for our plans, we need storage resembling the medical image storage systems in the hospitals named PACS."

In summary genetic testing centres face challenges concerning the management of raw data, despite storing genetic test reports in paper-based formats. These challenges primarily revolve around limited available free space for data storage. Each centre is aware of the ease of digital means of the archive. The ones who do not have digital facilities do not store raw genetic test data. The experts want to store the raw genetic data, which requires professional data storage and management. Hence, they expect a cloud or PACS-like solution from the MoH with legal and ethical bases. Such expectation from the government mainly depends on the cost of the internationally available cloud storage solutions.

4.3.5 Customised software along with the paper-based detailed record

In 2007, Hoffman noted the attempts and usage of in-house developed software or software developed by niche-specific companies to store genetic and genomic information of the test results [34]. Analogously, some centres in Türkiye have established in-house developed software for their genetic test data storage. Those centres are either university hospitals (government and private) with the aim of research and stored data consistency or private laboratories with the aim of increased service quality to their respondents and establishing a proven solution for standardised genetic data storage to MoH during further discussions and requests from the government side. Consequently, one of the centres had a chance to integrate the in-house developed software with the EHR of the hospital by applying a patch. However, the integration was cancelled due to some barriers executed by the management side. The hospital managers did not want to underestimate the possible vulnerability of EHR to cyberattacks and did not want to take responsibility for this possibility. This is a show of reluctance and lack of common understanding. Some centres have purchased software that will help catalyse their workflow. Some have an LIS to keep track of their samples stored in Biobank. However, most use external hard drives to archive their digital raw genetic test data for future studies. The storage is not standardised through genetic test coding. The only existing common standard is the standardised output of the analysis equipment, depending on the brand.

Government hospitals, laboratories, and some private university hospitals do not have dedicatedly developed software for their genetic data storage besides existing EHR. Even equipment-based software for data storage is not utilised. An expert from a private university hospital stated that:

> "For the storage and representation of genetic test data, we do not have different software other than hospital EHR. We utilise hard disks only to store the images of the test results. We keep them for an indefinite time for further reference. We do not have any standards to keep those data. Our centre is under the reimbursement system of HIC, and we must obey governmental legislation. We keep our records in paper-based format."

A doctor from a government laboratory centre mentioned that:

> "Our centre doesn't have a separate dedicated genetic data storage and representation software. We must obey governmental legislation and HIC. We keep our records in paper-based formats. On the other hand, some of our genetic analysis equipment has built-in software to store genetic data. We don't use this software also."

One of the government university hospital testing centres had an opportunity to integrate their in-house developed software with the previous EHR brand of the hospital. They just retrieved demographic information and diagnosis of the patient from EHR to their database. With the change in management and EHR brand in use, their data integration was cancelled. After all, they only use it internally.

An interviewee noted that:

> "That department had an opportunity to retrieve demographic information from hospital EHR. Moreover, they have used different disease codes related to their department more detailed than ICD-10 named SSIEM. The advantage of SSIEM is the existing sub-codes that are more detailed than ICD-10. If ICD-10 has a related code, they use that one coherently. They had a chance to integrate those codes with the existing EHR. Also, they define some paper-based formats, scan their hand-written documents, and upload them to their in-house developed software database in a text-structured format using optical character recognition software (OCR). It is impossible to codify every finding. I think they are the only and best group that established in-house developed software together with the existing hospital EHR integration for genetic and genomic test results in Türkiye."

A specialist in the group benefiting from the software expressed the flexibility and ease of privacy and security applications they gained with the help of their software and the data consistency after EHR integration. They could group the allele frequencies and common mutations specific to the Turkish population, which aided them in conducting targeted genetic tests instead of analysing the whole genome. Moreover, he emphasised the consequences of cancelling the integration of in-house developed software and EHR:

> "In our centre, we analyse genes for many diseases and mutations. We point out the allele frequencies and common mutations specific to the Turkish population. Since some of those mutations are so specific for Türkiye, there is no need to analyse and scan all genes. By 2005, we were awarded and carried

> out a software development project from The Republic of Türkiye, State Planning Organisation (DPT). We could follow those issues and fulfil our requirements. We store the data of all our patients through that in-house developed database. With this software, for example, when a patient diagnosed with phenylketonuria is dispatched to our centre from clinics, we can list the patients with a similar diagnosis, their count, their geographical origin, and the ones with mutations with their frequency. It is independent of the hospital's EHR, and data belong to our centre. Later, we integrated our system with our hospital's existing EHR to eliminate data redundancy about patient demographic information between the two systems. Due to ethical, legal, and privacy issues, only authorised personnel could access our genetic/genomic testing results. It is possible to retrieve statistical results and comments via our software. Integrating the existing hospital EHR required a patch in the software and can be said to be a big project. It is possible to retrieve statistical results and comments via our software. Our software integration was cancelled due to the change in hospital management and EHR brand. This is evidence of the hospital management's reluctance and the possible security issues depending on the patches required. We returned to our legacy, paper-based system to acquire and store patient demographic information. Our system is still used in our internal network."

A private genetic laboratory owner reported that:

> "We have an in-house developed software to keep the records and track our patients. We utilise physical storage devices and cloud systems for data storage and backup. In future, our goal is to transition into a paperless laboratory within the next year. However, , due to prevailing governmental regulations, we must maintain and report our results in a paper-based format. We know the LOINC initiative of the Republic of Türkiye, MoH. We are involved in the process and participated in translating genetic tests from LOINC to Turkish. We had a chance to apply LOINC to our software. Moreover, we apply other international standards in our system. We get the necessary permissions from the standard organisations. Together with the results of the other standards, we will share our experience and report to MoH over Turkish Genetics Association."

Instead of in-house developed software, some centres have purchased software that allows them to barcode patient samples and prepare reports. This time, software companies may not take care of their sold product and do not tailor it according to the customer's needs.

> "The system we recently purchased is a barcode-enabled one, and we can analyse and prepare reports without entering patient information. Unfortunately, the company doesn't give qualified service, and we can no longer benefit from it."

A centre in a government university has established a DNA biobank laboratory and related LIS to store samples for further genetic testing follow-up. This centre uses its

in-house developed LIS software for sample tracking and the ownership and related access rights of that sample in a clinical manner. Other software they have established is for reporting. It has no integration with the EHR of the hospital.

> "We have a DNA biobank facility, settled by another centre in our hospital. We send and archive our DNA samples within that unit. DNA is isolated at that centre as genetic material, stored, and coded in terms of ownership. Central storage and archiving are better approaches than individual ones since this archive belongs to the organisation rather than the units. The biobank laboratory is based on diagnosis, and the centre has a well-defined and renowned DNA information form. This form and data storage have approval from the Ethics Committee of our hospital. Only the individual owner (depositor) or the referring doctor of the sample has access to the sample."

Considering the interview results, having in-house developed software dedicated to genetic test results in different centres is good. This would be good practice to observe possible different problems. On the other hand, it would be hard for them to integrate with the EHR of the hospital since they do not have any standardised approach. Moreover, different software and standards could create interoperability problems among health centres for genetic test storage and reporting. Security issues and management support are the other two things that should not be underestimated.

Furthermore, based on our interviews, we can explore and perceive distinctions between software created in-house and software that is acquired. If a centre has in-house developed software, they know how to develop or solve possible problems. If a centre buys software, they are connected to the vendor and get limited service, updates, and software tailoring according to their needs.

4.3.6 Reporting

Interviewees noted the lack of an existing standardised reporting style. If the centre and patient have a relation with SSI, to be reimbursed, they use HIC codes in their reimbursement-related documents to define the genetic testing procedure. There is no genetic/genomic test name standardisation in use. They use the ICD-10 code to define the disease to be consistent with the referral. Unanimously, the interviewees stressed that, at the end of the report, the genetic specialists should add a comment like:

> "This test is a diagnostic test for this gene or disease.".

This is necessary for reimbursement, further follow-ups and considering the next patients. Due to regulations, they should wet ink sign the reports. A specialist from a government university hospital said that:

> "Regrettably, we currently lack a standardised format for reporting. Our reports are similar to pathology reports, presenting analysis results and findings followed by subsequent comments. The report includes the patient information, diagnosis, tested material, DNA mutation, analysis results, and overall narrative comments."

Another expert in a different centre of the government university hospital noted that:

> "We don't give genetic consultancy. When we receive a test request, we perform our related analyses in a predefined time and send the results to the referring clinician in a certain format with a wet-ink signature. The only standard used is ICD-10. But our reporting format has a standard format (data entry fields)."

Since there is no standardised reporting, one of the centres likes to share diagnostic imaging reports. As a remark, in Türkiye, instead of printed film, diagnostic imaging results – which create the basis for the report – are shared with the patient with CD/DVD upon the patient's request. Likewise, a private university hospital provides the raw data of the genetic analysis via a memory stick. An expert from that centre noted that:

> "We deliver all our analysis results as a whole in a memory stick. More generally, they do not use the whole data. The main result is our written reports. But whole data is important for future analysis or consulting to other doctors/experts."

Genetic test experts expect a standard reporting format including coded areas as a general reporting approach. Some experts think sharing the data with the patient is necessary for future analysis or consulting. This may be useful to reduce extra test requests in future, which is beneficial to decrease unnecessary expenses.

4.3.7 Information exchange with the patient

Patients may reach their genetic test results before visiting their doctors. This is appraised as a problematic approach among experts due to ethical, psychological, and biased perceptual issues. Clinicians must be the patients' only point for genetic test result declaration. Additionally, in some specific cases and diagnosis interpretation, a psychiatrist or a family member's invitation is recommended for the patient's psychological conditions. To that end, interviewees noted the importance of background genetic/genomic information of referring clinicians. It is important to have a shared understanding among doctors. The referring clinician should be aware of the possible other rare diseases if the result is negative regarding diagnosis. A doctor from a university hospital said that:

> "I do not think sharing genetic test results directly with the patient or their relatives and family is good. The results may be misunderstood. We perform our analysis according to the diagnosis of the referring clinician. This analysis is defined according to the frequent mutations with more than 70% in the population. This is our routine approach. If that mutation analysis is negative, we report it as *'negative to this mutation'*. On the other hand, the mutation might exist in other genes with rare properties. If the patient is the first to get the report, s/he immediately thinks, ' My disease is not genetically related'. We face this numerously. At the same time, this is an ethical problem. Therefore, the referring clinician should share genetic test reports with the patient.

> Besides, the referring clinicians' genetic testing and report reading/interpretation background should be leveraged. We should speak the same language and educational level to inform the patient correctly."

The only way to protect result reports from patients' initial access is to share results digitally. While sharing a result with the patient, co-existence of any other family member is recommended. Some genetic test results may direct the patient to psychological problems that may lead to suicide. Some of the centres in England share genetic test results with family members. An expert from a private university hospital noted that:

> "There is a problem in Türkiye: Report is first accessed by the patient. This attitude should be prevented, and necessary actions should be taken immediately. After accessing the report, the patient may not go to the clinician, have psychological problems, and sometimes decide to use medication alone. The clinician should first access the report; the only convenient way to realise this is to transfer the report digitally. For example, in the UK, the patient has access to their genetic or genomic test report only after the approval of the clinician. Moreover, a relative is invited for the report presentation and consultation process. This prevents many psychological problems, including therapy decisions on its own and suicide."

The amount of information obtained through genetic analysis and its sharing with the patients, or their pedigree members is another point that needs clarification. Experts are expecting a governmental decision about it. Genetic/genomic test results are preferred to be shared as a whole result, but there is a reservation from the specialists. Some patients might not want to learn the existence of a genetic predisposition that is incidentally observed, other than the disease they are tested for. An expert from a government university said that:

> "Sharing the whole genetic or genomic analysis with a patient or pedigree member is an ethical problem. Would being informed about the personal genome be problematic? It may have both psychological counter-effects and advantageous consequences. We pay utmost attention to sharing the analysis results, but sharing the incidental findings is a problem for our side. We expect governmental regulations to be in charge and behave according to the rules."

Also, during pedigree studies, a relative with informed consent approval for testing might not want to learn the genetic predisposition to any disease that s/he is unaware of. These are the problematic areas that the MoH should decide and regulate. The specialists think they have no right to include any information in their report or EHR that a patient doesn't want to learn. Complementary notifications from two different interviewees in a government university hospital and a private laboratory are given correspondingly:

> "We should discuss the coverage of information to be inserted in the EHR. It should be handled in international dimensions. For example, during the analysis of a genetic disorder in other asymptomatic family members of

> pedigree, we request them to sign an informed consent. After an exome analysis, let's say that we have incidentally figured out a genetic predisposition to cancer – not our analysis aim. What shall we do in that case? Shall we inform the asymptomatic individual? Sometimes, a patient or individual doesn't want to be informed. On the other hand, this result should be in the reports. We write in our reports that – 'This genetic analysis is a diagnostic test'. With this approach, the clinicians would also be informed for further cases and request genetic/genomic tests accordingly."

> "We must present analysis data that is beneficial to the patient. Results that may divert the patient to depression should be shared with the consent of him/her. In our centre, we warn and tell patient or pedigree member about the possible findings and ask whether they want to learn those or not. Ethical limits start at that point. If there is no therapy for the possible predisposition, nothing differs between reporting and not reporting the analysis results. On the other hand, if information share would be beneficial, will increase the individual's quality of life and save the patients' life, then an approach with psychological therapy should take place. Another sample case is the analysis of a pedigree member that would save its or relatives life. If that pedigree member doesn't want to be informed about predisposition, we must behave family based. We declare the pedigree member about the importance of the test. We may break some ethical rules to save other relative's life. In advance we inform the pedigree member about the necessity of the results for the patient. If individual still doesn't want, we discard that member's test."

According to our interview results, there is a demand for experts from the MoH to set some regulations about the amount of information to be shared with the patients or pedigree members due to ethical and psychological concerns. Sometimes, the ethical rules might be broken to save an individual's life. For analysis reports, it is highly recommended to grant initial access to the clinicians before patients, which can be attained by digitally encrypted sharing of reports. It is highly expected from interviewees that clinicians' background information and interpretation of genetic test reports should be leveraged and taken to the same level with some initiatives from MoH to prevent misunderstandings and misdiagnosis.

4.3.8 Information exchange with the third parties

Collectively, the interviewees strictly recommended not sharing genetic information with third parties. The genetic information is private to the individual. Nobody has a right to share or access this information except in cases for individuals below 18 years old. Data protection from third-party access is also provided in e-Nabız. This is an ethical and privacy issue [12]. The discussion includes genetic/genomic test results and the pedigree information. An expert from a private university said that:

> "All over the world, any genetic/genomic test information and pedigree is accepted as private. It shouldn't be shared with third parties. Moreover, different personnel in the testing centres have different access rights. Even the

> analysts do not know any information about the owner of the sample to be tested – patient name, ID, etc."

A doctor from a private laboratory exemplified different dimensions for information sharing with third parties: Sometimes, information hiding may affect others' lives. He also agrees about not sharing genetic information with third parties, but he provided an example that covers ethical and preventive requirements,

> "Our laboratory also serves international companies under strict contractual rules. Some drug companies send us samples to be analysed. We do not share analysis results with those companies. In case of request, we remind them of our contract between. We only share the result with the patient's doctor in case of confirmed permission. Contrarily, some counter-cases require to be evaluated under ethical concerns. We conducted some pre-symptomatic tests, and incidentally, we found a genetic predisposition to a disease in a healthy person working in the public transportation sector. The mutation may be effective instantly, after a time or never. This should not be an obstacle to his job, but necessary precautions and routine controls should be made. In an unknown way, his employer –a third party, learned his test results and fired him. In one way of thinking, his illness can affect all the passengers he is with. In other words, his employee should not learn his genetic test results and should not make such a decision that is ruining his lifestyle. So, under the instruction of this and similar cases, genetic/genomic test results and sharing it with the third party should be deeply evaluated under ethical concerns. When an individual's genetic predisposition is incidentally observed that may affect other people's life, sharing it with the third party should be deeply evaluated under ethical concerns."

The government laboratory centre expert noted that most of the patient's health information is currently governed by The Republic of Türkiye. On the other hand, there are some private insurance companies and day by day, their number is increasing. Due to capitalist requirements, they do not want to cover any individual with a genetic predisposition to any mutation, or they will provide insurance at very high prices. Currently, the awareness in the public is not at a high level. Still, the expert strongly recommends not sharing genetic information with private insurance companies and other third party.

> "In my opinion, the most dangerous aspect of genetic test data sharing with third parties is that, in The Republic of Türkiye, the government takes in almost all healthcare provision. But as in most countries, we are evolving through the capitalist approach and our health service and health data will soon be provided and managed by private insurance companies. They do not want to cover insurance for individuals with genetic predisposition to any disease. Our citizens should be aware that data should not be shared with third parties, including insurance companies."

Any genetic test result conducted or reimbursed by any party should not be shared with third parties. There is a consensus among experts that the genetic information

should be kept private and secured by the governmental authorities. Public awareness about keeping their genetic data private should be provided and enhanced to preserve their rights. Even the bioinformatics experts conducting the tests should not be informed about the patient's demographic information other than their diagnosis, birthdate, and minimum phenotypic information, which may help their test method definition.

4.4 A Conceptual Model of Genetic Information Exchange in Türkiye

In this dissertation, we aim to present a conceptual model of genetic information exchange in Türkiye. Among the possible information exchange tools, the one that would be compatible with Türkiye is HL7 standards. For information exchange software tenders, MoH Türkiye accepts both HL7 v2.x and HL7 v3 capable systems [136].

Contrarily, there is no established genetic information exchange capable EHR in Türkiye. The reason behind this is well elaborated in Section 4.3 of this dissertation. Moreover, according to the literature, for the implementation of genetic information exchange, there are lacking features of HL7 v2.x and HL7 v3 [137]

A recent, well-established, proven solution for information exchange for medical data is HL7 FHIR. Structurally, as explained in Chapter 3.4.3.1, HL7 FHIR does not resemble its ancestors. It is based on web technologies, and it is freely available. Although FHIR is not yet declared as an official information exchange standard by MoH Türkiye, considering its proven success, we decided to use FHIR in our dissertation.

The base standards and guides of FHIR can be accessed through the FHIR home page [138]. In this dissertation, we provided the theoretical background of FHIR in Chapter 0.

In the fifth revision (R5) of HL7 FHIR, there are 157 resources. Among those, no specific resource is assigned for the implementation of genetic test reporting. Instead, the HL7 workgroup profiled the DiagnosticReport Resource as a GenomicsReport Profile and created a Genetic Reporting Implementation Guideline (GR IG) accordingly.

Under Level 4, Diagnostics Module, a set of Genomics Implementer Guidance are represented for Genomics in FHIR. To support precision medicine and enhance the semantic interoperability for genetic test information exchange, the Clinical Genomics Workgroup (CG WG) introduced three outputs (Table 15) for Genomics in FHIR [139].

Table 15: Genomics Implementer Guidance

Genomics Reporting Implementation Guide	Standardises the reporting of genomic variants, variant annotations, etc.
MolecularSequence Resource	A resource representing a nucleotide or protein polymer.
GenomicStudy Resource	A resource aiming at delineating relevant information of a genomic study.

The WG inserted an important notice for MolecularSequence Resource, stating that it was created before the Genomics Reporting Implementation Guide was developed. For that end, the developer's recommendation is to defer to GR IG in case of any contradiction during the implementation.

We can assess these three outputs as complementary to each. While GenomicStudy resource represents the details of the genomic analysis, MolecularSequence resource lays out the molecular sequence of the specimen analysed. At the end, Genomic Reporting Implementation Guide encapsulates the overall study.

- **Genomics Reporting Implementation Guide**

This guide focuses on the report data structures in which data should be present in the report and how it should be organised. It is important to mention that this implementation guide does not encompass the overall workflow; that said, it does not address how reports are requested, created, approved, routed, delivered, amended, etc. [140]. On the other hand, the resources utilised in the workflow, i.e., the DiagnosticReport or Observation, obey workflow patterns on their own by implementing the Event pattern of the Workflow module. While the guide focuses on genomic data reporting, it includes general information for genomics-related terms, variant reporting, pharmacogenomic reporting, somatic reporting, and histocompatibility reporting. The WG intended guide to be designed as:

- International in scope and use freely available terminologies.
- Avoid pre-coordinating the type of variant, medication, or other information into the Observation.code since it satisfies the leveraging of the industry standard terminologies for genomic information and avoids duplicating this information into observation coding systems such as LOINC.
- Maximising the use of resources that are in common use, i.e., Observation and DiagnosticReport.
- Minimising the use of FHIR extensions to prevent the risk of data loss during information exchange.

- Using separate observations for each independent analysis enhances the query success and data discoverability.

The GR IG presents five sections on declaring Genomic Reporting [141].

1. General Genomic Reporting
2. Variant Reporting
3. Pharmacogenomic Reporting
4. Somatic Reporting
5. Histocompatibility Reporting

The general genomic reporting encapsulates the preceding ones in the list, where the resources, profiles, or extensions in the FHIR can represent each. In particular, the genomics report includes and groups overall interpretations, genomic findings, genomic implications, region studied, other associated observations, recommended actions, and contextual resources.

FHIR Genomics IG has presented three abstract profiles (Table 16).

Table 16: Abstract profiles for Genomic Implementation Guide

Genomics Base	Base profile that defines characteristics shared by all genetic observations.
Genomics Finding	Properties common to genetic findings whose results are expressed as computable discrete elements (e.g., genotypes, haplotypes, variants, etc.).
Genomics Implication	Properties common to genomic implications are expressed as computable discrete elements.

These are profiles on resources or data types that describe patterns used by other profiles but cannot be instantiated directly [142]. The observation profiles are inherited from those abstract profiles in Figure 11 [141].

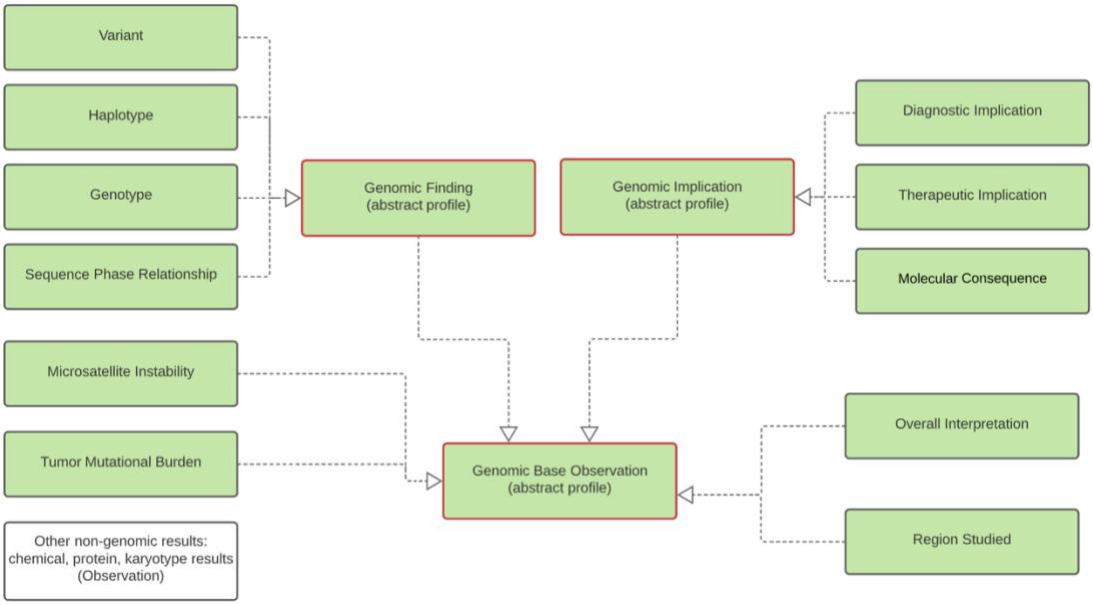

Figure 11: Genomic observations

- **MolecularSequence Resource**

MolecularSequence resource is created to cover molecular sequence representation to ensure semantic interoperability. The compact form of this resource [143] is in Figure 12.

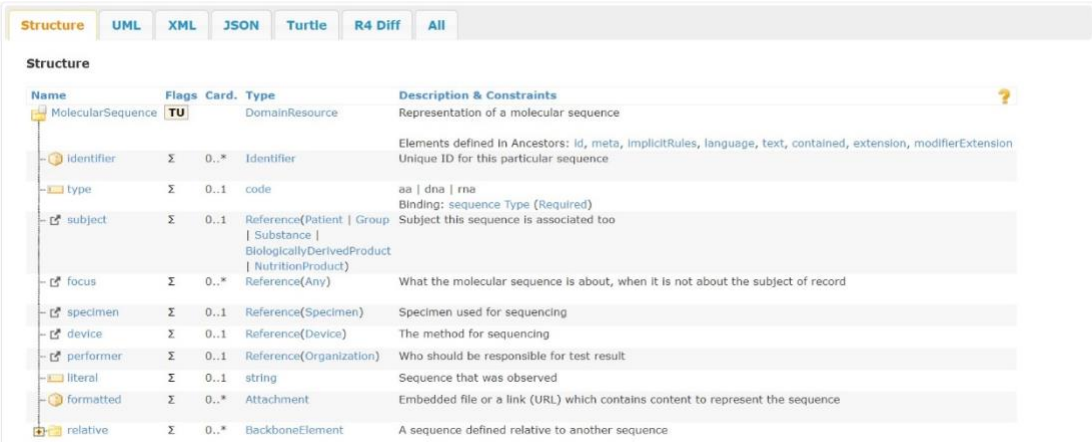

Figure 12: MolecularSequence Resource Elements, a compact screenshot.

- **GenomicStudy Resource**

GenomicStudy resource reflects the analysis process to represent genomic data. Corresponding elements (Figure 13) of this resource delineate the genomic analysis's reasons, purpose, and performers by adding metadata for the documentary [144]. Note that this resource also manages workflow within self-processes using elements basedOn, instantiatesCanonical, and instantiatesUri.

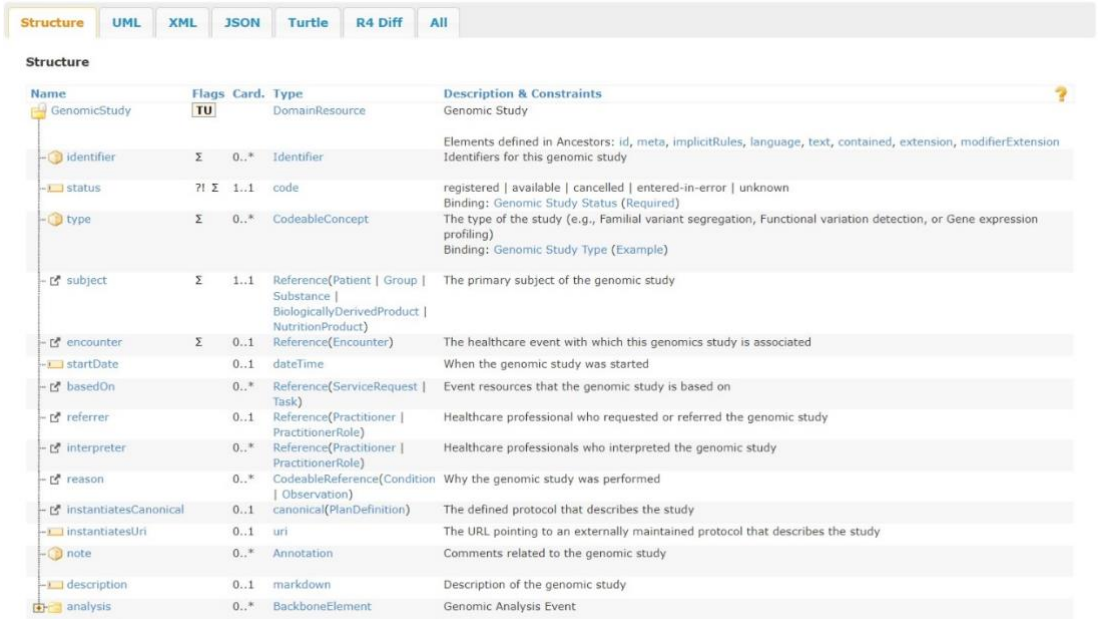

Figure 13: GenomicStudy Resource Elements a compact screenshot.

Considering these three outputs, our conceptual model should not be much more different than the Genomics Implementer Guidance. Obeying the 80:20 rule, we are only supposed to add profiles or extensions according to our utmost needs.

In summary, for genetic information exchange, we initially revealed the inadequacy of the existing health information system architecture in Türkiye. Briefly, due to the insufficiencies, we put forward according to the reviews and qualitative study for this dissertation, the reports are unstructured, not standard formatted, and different terminologies are used. We analysed four anonymised genetic test reports from three different genetic testing centres and the interview results to put forward a model. Ultimately, we proposed a conceptual model for genetic information exchange using HL7 FHIR.

4.4.1 A snapshot of the weaknesses

In view of the interview results and literature, the main blockages on the meaningful share of genetic test results in Türkiye are:

1. Inadequacy of health data exchange standards to represent genetic tests.
2. Lack of existing terminologies to represent clinical conditions and phenotypes.
3. Missing data elements within Minimum Health Data Sets (MHDS).
4. Lack of local value sets (Health Codes Reference Dictionary – HRCD codes) to define genetic test-related terminologies.

In the context of genetic test result representation standardisation, until 2022, MoH Türkiye did not attempt to translate or declare any international genetic testing terminology or nomenclature. As noted in previous chapters, there are only local codes for genetic testing procedures to track reimbursement. Surprisingly, as of 04.03.2022, MoH announced 20.493 genetic tests under HCRS. They used the gene names (symbols) from the HUGO Gene Nomenclature Committee. The list is embedded under HCRS, but the exact mapping to NHDD is unclear. In our opinion, rather than coding, the purpose of MoH is to track reimbursement to prevent unnecessary test repetition.

The Ministry of Health Türkiye has not translated any ontology-based terminologies (i.e., SNOMED-CT) into Turkish. We exemplified a sample benefit of ontology-based terminologies in

Table 8. Moreover, the non-comprehensiveness of the Turkish translation of Logical Observation Identifiers Names and Codes (LOINC) is deeply assessed in our review article [12] and further detailed in this dissertation's related parts.

4.4.2 The proposed solution

As we already extracted from the semi-structured interviews, in Türkiye, genetic tests are ordered in four different ways (Table 17) [12]:

Table 17: Genetic Testing Order Types

	Genetic Testing Order Types
1	Through EHR of hospitals
2	Referral of specific cases to research centres of the hospital (not over EHR)
3	Through personal application to private laboratories (with or without clinical request)
4	Through Forensic Medicine Institutions request upon a court decision

Notably, according to the interviewees, the path to prepare a genetic testing diagnosis report is figured out to be like the pathology reports: “Analysis results and findings, and later comments”.

At the very first step of our conceptual model, following the steps listed in Table 6, we completed the “as is” analysis of the four sample genetic test reports. Table 18 provides the report scenario verbally as a use case. The bold/underlined or the italic/underlined concepts will be a clue for FHIR resource mappings. The four reports are scanned, inserted and their enumerations are stated in Appendix F. For in-depth visualisations and explanations please refer to Appendix F.

Later we extracted the data field names of the sample genetic testing reports for three centres separately, and finally combined them in a single table. In Appendix F, we provided the details of this research process.

For the next step, we generated a genetic testing diagnostic report template (Table 19) encompassing all three different sample reports. This template will act as a basis for genetic test report in our conceptual model. We divided Table 19 into three separate fields, partitioned with bold and double split borders. The report header is at the top, the report body is in the middle, and the report footer is at the bottom.

Finally, we presented an enumerated the extracted concepts (Table 20) in the genetic testing diagnostic report use case, utilising the data elements and report content. Additionally, we mapped the concepts with template genetic test report data elements (Table 19).

Table 18: Use case scenario for the genetic testing reports

USE CASE SCENARIO
The **patient or proband** arrives at a **genetic testing centre** *based on* **request**[*]. The request is *attributed to* the **request/test intent (condition)** of the patient or proband. After gathering the patient/proband and **requester** *metadata*, the genetic testing related **specimen** is collected (either at the testing centre or the referral site). The test details, analysis panel and **observations**[**] accompanying the analysis are noted. The analysis **results** and **consultation reply** are given according to the request. The **secondary findings** are listed if the testing panel, or the test type enables such notification. The **recommendation** part also finds a place in the report. At the very end of the **diagnostic reports**, there is a **test disclaimer** section and the *metadata* for the **genetic testing centre**.
[*] The type of order/request is as stated in Table 17. In Report No: 2, this request originated from a personal intent, and in the remaining three, it is from a referral/consultation.
[**]Two reports (Report No: 3 and Report No: 4) are **Whole Exome Sequencing,** and the others are **targeted gene tests** using test panels.

Table 19: Template report and concept enumeration mapping (**M: Main Report Itself, EX: Extension**)

MERKEZ ADI			**1**
Hastanın Adı Soyadı	**2**	Rapor Tarihi	**M**
Hasta T.C. Kimlik No	**2**	Başvuru Tarihi	**M**
Dosya No	**2**	Gönderen Kurum	**5**
Bilgi İşlem No	**2**	Gönderen Doktor	**5**
Protokol No	**2**	Gönderen Adres/Tel/Faks	**5**
Cinsiyeti	**2**	Örnek Türü	**3**
YAŞI	**EX-1**	Doğum Tarihi	**2**
Örneği Gönderen Kurum	**5**	İstenilen Tetkik	**4**
Örneği Alan Kişi	**3**	Örneğin Geliş Tarihi	**3**
Örnek Alımı (Lokasyon)	**3**	Örnek Numarası	**3**
Testin Metodu	**7**	Çalışılan Genler	**17**
Referans Genom	**8**	Örneğin Analiz Tarihi	**M**
Çalışmayı Yapan	**9**		

Hastanın Başvuru Sebebi	**10**
Klinik Bulgular ve Endikasyon	**12, 13, 14, 15, 16, 17, 18, 19, 20**
Çalışmanın Özeti	**11**
Yorum	**21**
Çalışmanın Kalite Kontrol Tablosu	**22**

Sorumluluk Reddi	**24**
İstek Üzerine Yapılabilecek Diğer Testler	**25**

Table 20: Concept names and enumeration

No	Concept Name
1	Performing Laboratory
2	Patient
3	Specimen
4	Request/Test Intent
5	Ordering Identity
6	Name of the Test Performed
7	Test Method
8	Reference Genome
9	Performer
10	Reason of Request
11	Summary of the Test
12	Analysis Results
13	Overall Interpretation
14	Test Background
15	Clinical Interpretation
16	Identified Variant/Genotype
17	Gene Coverage (List of Variants Assayed)
18	Test Performed Methodology and References
19	Family History
20	Secondary Findings (ACMG Incidental Findings)
21	Recommendations
22	Quality Control Table of the Analysis
23	Results Interpreter
24	Test Disclaimer
25	Further Output Availability for the Test Upon Request
EX-1	Age

Although the sample reports do not contain “Age” and “Date of Birth” as data elements, in this template we added those data fields. The reason is, in the “condition assessed/case evaluation” part, the reports mention the age of the patient/proband. Other two reasons from the literature are:

- According to a focus group study in 2012, experts stated the importance of including patient age and date of birth data elements in a genomic report template [145].

- The sample anonymous reports in the literature have age as the data element of a report [146].

As the last step for the conceptual modelling, we lay down and match the concepts used in genetic test reporting. But first, we want to schematise the differences among the centres. The schematic representation of the sample reports is depicted in Appendix F. In the Appendix, initially we provided the use case summary for each report. Later, we matched the data fields and corresponding concepts of each report. As evident from Appendix F, the reports lack a consistent structure. The sample genetic testing reports are unstructured. To illustrate, the placement of concepts varies between different reports.

In Figure 14, we depicted the data field – concept match for the template report we generated at Table 19.

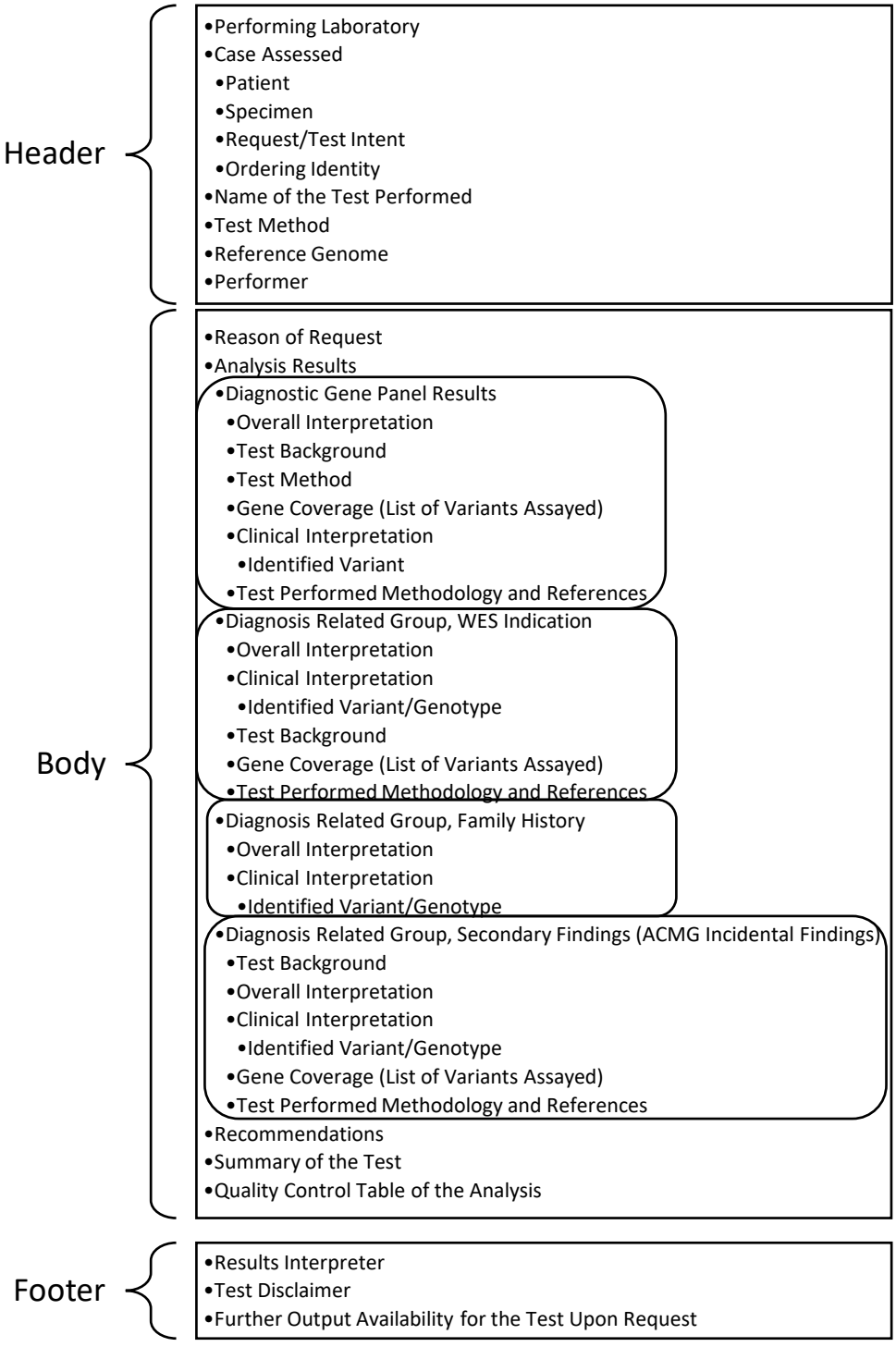

Figure 14: Concepts for the Report Template

In summary, considering the concept orientations for three different centres, we deduce the following:

1. The reports are unstructured, even for the two reports of the same centre.

2. There is no unique naming for the data elements.

- **Conceptual Model for the Report Template**

For this concluding step, we used our template model (Table 19). We analysed whether extracted concepts (Table 20) can be implemented using base FHIR resources. The mapped list will be artifacts for the Genetic Information Exchange Implementation Guide for Türkiye.

To better visualise the situation, we enumerate the concepts (Table 20) and insert the matching numbers into the template report (Table 19). At the last turn, we mapped the concept names with suitable FHIR Resources and FHIR Genomics Implementation Guide artifacts (Table 21). In case we cannot match, we need to generate a new extension.

In Figure 15, we depict the concept mapping with resources, profiles, and their relations. Observation resource resides in the analysis, and results are inserted as slice data elements Figure 16. The implementation guide provided extension artifacts in Figure 17. The Age extension is added as it was provided by [81].

Table 21: Final mapping

Concept Name	**FHIR Resource**	**Artifact Name** *(Artifact No)*
Report	DiagnosticReport	Genomics Report *(i)*
Performing Laboratory Requester Organisation	Organization	Organization *(ii)*
Patient	Patient	Patient *(iii)*
Specimen	Specimen	Specimen *(iv)*
Request/Test Intent	ServiceRequest	ServiceRequest *(v)*
Name of the Test Performed	PlanDefinition	PlanDefinition Resource *(vi)*
Test Background Test Performed Methodology and References	Extension	Related Artifact *(vii)*
Test Disclaimer Test Method Further Output Availability for the Test Upon Request	Extension	Annotation Code *(viii)*
Reference Genome	Observation	Genomics Finding Abstract Profile *(ix)* • component: reference-sequence-assembly
Performer	PractitionerRole	PractitionerRole *(x)*

Results Interpreter Ordering Identity	Practitioner	Practitioner *(xi)*
Reason of Request	Extension	Genomic Report Note (If there is a possibility of transporting the content of the note in a structured manner the usage of CodedAnnotation is forbidden and the corresponding data structures SHALL be used.) *(xii)* (Used as a component under DiagnosticReport)
	Extension	supportinginfo (Other information that may be relevant to this event) *(xiii)* (Used as a component under DiagnosticReport)
Summary of the Test	Observation	Genomics Base/Implication *(xiv)* • component: conclusion-string
Analysis Results	Observation	Observation *(xv)*
Overall Interpretation	Observation	OverallInterpretation *(xvi)*
Clinical Interpretation	Observation	Diagnostic Implication: *(xvii)* • component: clinical significance

Identified Variant/Genotype Quality Control Table of the Analysis	Observation	Variant *(xviii)*
Gene Coverage (List of Variants Assayed)	Observation	RegionStudied *(xix)* • component: gene-studied
Family History	FamilyMemberHistory	**None** • FamilyMemberHistoryForGeneticsAnalysis Profile *(xx)*
Secondary Findings (ACMG Incidental Findings)	Observation	secondaryFinding *(xxi)*
Recommendations	Task	Follow Up Recommendation *(xxii)*

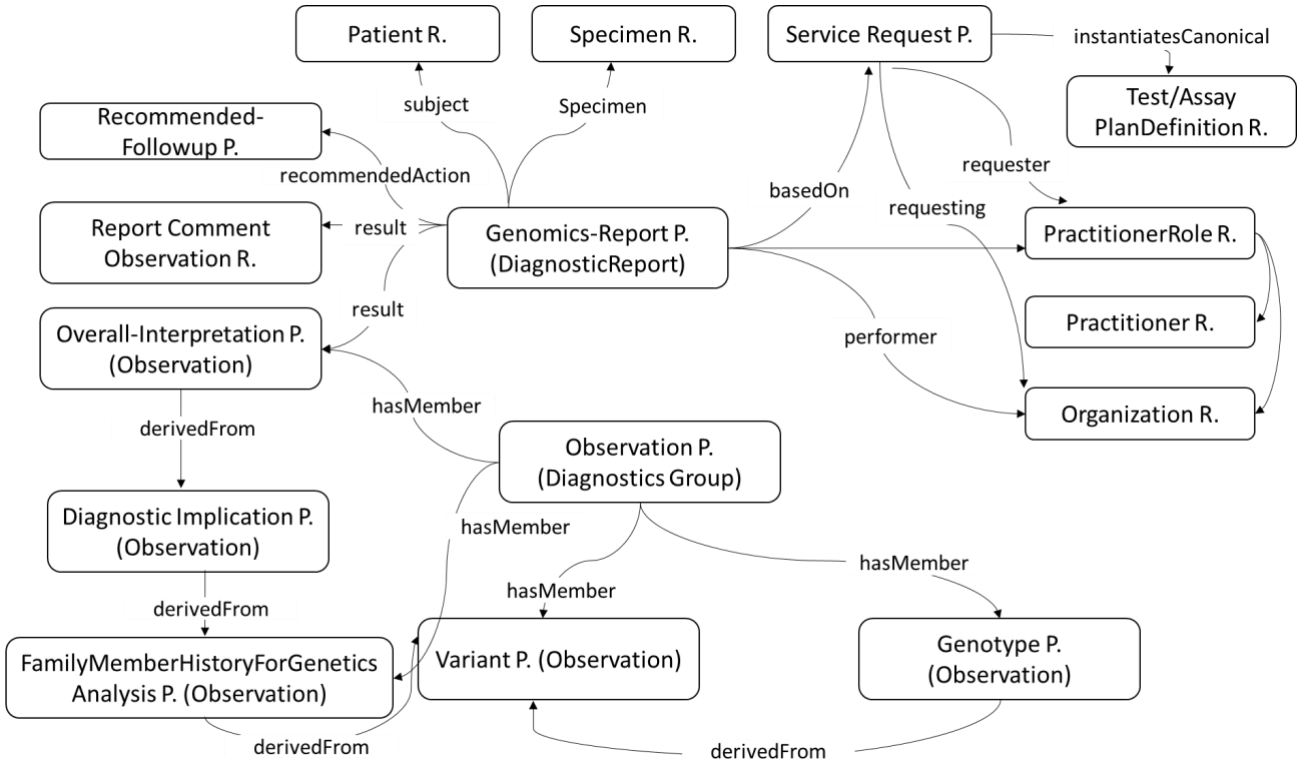

Figure 15: Artifact map and concept relations

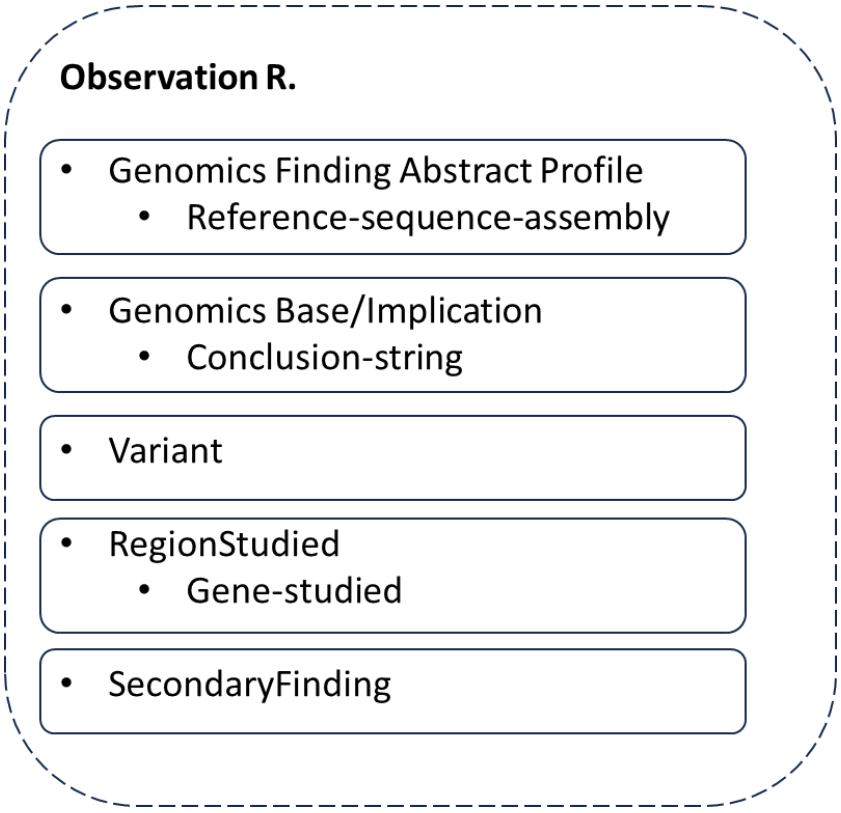

Figure 16: The slices under Observation resource

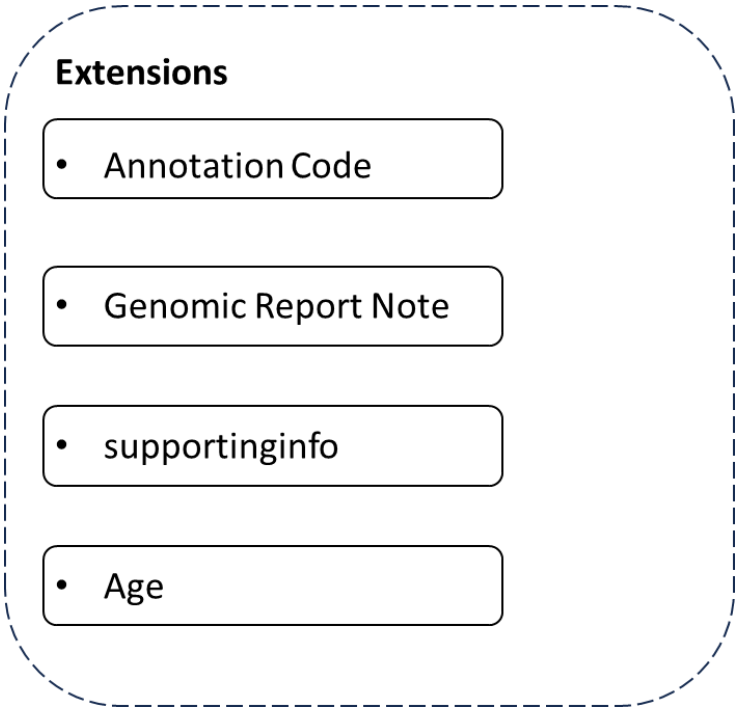

Figure 17: Extensions used in the conceptual model

- **Artifacts**

In this part, we elaborated and listed the data elements for the determined artifacts. We did not include the Observation artifact (number *(xv)*) since Observation Resource profiles are used in various artifacts and they are grouped under Observation Resource.

i. Genomic Report

Genomic Report is a profile derived from the Diagnostic Report resource. We directly took definitions from the FHIR specifications. The data elements that match our use case and their descriptions are listed in Table 22. In Türkiye, a requirement for reimbursement regarding genetic testing is the inclusion of the test image and the reimbursement request documents. In light of this, we want to stress the inclusion of the "media" data element from the basic DiagnosticReport resource during the implementation of the Genomics Report Resource Profile.

ii. Organisation

In Türkiye, the type of organisation is important. The reimbursement of a genetic test is determined according to the type of organisation, and it is represented via the “qualification” data element under the organisation resource. We provided the details of reimbursement constraints in the relevant chapter (Table 23).

iii. Patient Resource

For this artifact, we used the basic FHIR Patient resource. None of the FHIR-Core belonging to any country is used (Table 24). For the Türkiye case, we stated the importance of FHIR Türkiye Core in the discussion section.

iv. Specimen

In this context, we selected the pertinent data components that were evident in the sample reports (refer to Table 25). We intentionally excluded certain fundamental details from the Specimen resource data elements. Notably, the bodySite data element holds particular significance, and FHIR has incorporated the use of SNOMED-CT to define it. Understanding the bodySite where the specimen is collected is crucial, especially in genetic testing. It's worth mentioning that SNOMED-CT isn't currently utilised in Türkiye. To address this, we propose the adoption of SNOMED-CT as the official standard terminology in Türkiye, urging the relevant authorities to initiate the translation process.

v. Service Request

Every genetic test is performed based on a formal request. This request, encapsulated within the ServiceRequest resource, serves as the initiating event for generating the corresponding Observation resource (Table 26).

vi. Plan Definition

In crafting this artifact, we incorporated the data components found within the provided sample reports (Table 27). The PlanDefinition resource is employed to facilitate both clinical and non-clinical protocols essential to the genetic testing workflow.

vii. Related Artifact

It is an extension for representing documentation or ‘knowledge artifacts’ relevant to the base resource, such as citations, supporting evidence, documentation of processes, and caveats around testing methodology (Table 28). For example, in implementing genomic data, a "relatedArtifact" extension might be used to link a GeneticVariant resource to scientific publications, research studies, clinical guidelines, or other resources that provide further information about the specific genetic variant. This enhances the context and understanding of the variant's significance and implications. Similarly, a GenomicReport resource could use the "relatedArtifact" extension to link to pertinent clinical trial protocols, laboratory documentation, or other resources that contribute to the interpretation and utilisation of the genomic findings presented in the report.

viii. Annotation Code

An extension enabling insertion of test-disclaimer, test-methodology, and result-confirmation (Table 29).

ix. component:reference-sequence-assembly

This extension serves the purpose of representing the reference sequence assembly, with a particular focus on its application in WES tests. This allows for the inclusion of crucial information about the reference sequence assembly used in the genomic analysis, which is particularly relevant when dealing with WES data (Table 30).

x. Practitioner Role

This resource serves the purpose of depicting the diverse array of services that practitioners offer within specific organisational settings and designated locations. In Türkiye, including the "specialty" data element holds particular significance, as it aligns with the reimbursement criteria contingent upon the practitioner's role. Additionally, the "healthcareService" data element, which references the HealthcareService resource, further contributes to the reimbursement considerations by factoring in the specific services provided (Table 31).

xi. Practitioner

This resource establishes an individual with an official role in delivering healthcare or associated services. While we have incorporated the pertinent data elements from our sample reports, it's worth noting that, particularly in Türkiye, the "qualification" data element is of notable significance. This addition becomes crucial to ensure testing eligibility for reimbursement purposes (Table 32).

xii. Genomic Report Note Extension

This extension introduces encoded annotations within a report to encompass supplementary content (Table 33). If there exists an opportunity to convey the note's content in a structured format, the use of CodedAnnotation is prohibited, and instead, the prescribed data structures must be employed. This artifact is employed as a constituent element within the DiagnosticReport resource.

xiii. supportingInfo

This extension is utilised for the purpose of indicating the request's reason. It pertains to other resources within the patient record that could potentially hold relevance to the event at hand. The data sourced from these resources were either employed in generating the instance or supplied to aid in its interpretation. It's important to note that this extension should not be employed if more precise inline elements or extensions are available for the task (Table 34).

xiv. component: conclusion-string

The clinical conclusion and summary of the test are represented here (Table 35).

xv. Observation

This works as an encapsulating artifact, where as a resource, relevant artifacts are represented as slices or profiles. Therefore, we did not provide the resource data elements in tabular form as we provided in other artifacts in this section.

xvi. Overall Interpretation Profile

Provides a coarse overall interpretation of the genomic results reported (Table 36).

xvii. Diagnostic Implication Profile

This section provides guidance for genomic reporting of patient genetic implications regarding specific conditions (sometimes referred to as phenotypes) (Table 37).

xviii. Identified Variant/Genotype & Quality Control Table of the Analysis Profile

Variant Profile is derived from Observation resource. This profile allows a full description of the variant found using properties from a variety of testing approaches and allowing for a variety of descriptive mechanisms. If the laboratories populate the properties they know/observe, the population-related variant information would be more meaningful for precision medicine (Table 38).

An important point to highlight is the presence of the "Quality Control Table of the Analysis" in the sample reports. This tabular layout or guideline isn't currently in the FHIR Genomic Implementation Guide. We can use the “allelic-read-depth slice of the Variant profile for this representation. The sample report organises this aspect, which could be incorporated using FHIR Markdown data types. It's worth considering

sharing this observation with the FHIR developer team, possibly leading to creation of a new data field designed to depict the "Quality Control Table of the Analysis."

xix. Region Studied Profile

The Region Studied profile serves the purpose of confirming the specific regions that were examined during the conducted test(s). It's essential to note that the actual regions studied might deviate from the initially intended coverage areas, which could occur due to technical constraints during the test execution. This profile has the capability to offer this clarification in various formats—either as a list linked to individual genes or mutations, or as a textual portrayal describing the regions studied (Table 39).

xx. FamilyMemberHistoryForGeneticsAnalysis Profile

This profile includes data elements related to the information about the patient's relatives relevant to the patient (Table 40). It is mentioned but not included under Artifacts List in the FHIR Genomics Implementation Guide. We will notify the developers about the issue.

xxi. Secondary Finding Profile

Secondary findings are genetic test results that provide information about variants in a gene unrelated to the primary purpose for the testing, most often discovered when Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS) is performed. This extension should denote when a genetic finding is being shared as a secondary finding and ideally refer to a corresponding guideline or policy statement (Table 41).

xxii. Recommended Follow Up

This is a resource profile derived from Task resource. Its primary function is to outline the suggested actions or steps to be taken as a follow-up based on the task context (Table 42).

Table 22: GenomicsReport

Name	Card	Type	Description
DiagnosticReport	0..*	Diagnostic Report	A Diagnostic report – a combination of request information, atomic results,
Slices for extension	0..*	Extension	Extension **Slice:** Unordered, Open by value:url
coded-note	0..*	CodedAnnotation	Comments about the report that also contain a coded type **URL:** http://hl7.org/fhir/uv/genomics-
supporting-info	0..*	Reference(Resource)	Other information that may be relevant to this event.
Slices for category	1..*	CodeableConcept	Service category **Slice:** Unordered, Open by
category:Genetics	1..1	CodeableConcept	Slice category
coding	1..*	Coding	Code defined by a terminology system **Required Pattern:** At least the following
system	1..1	uri	Identity of the terminology system **Fixed Value:** http://terminology.hl7.org/CodeSystem/v2-0074
code	1..1	code	Symbol in syntax defined by the system **Fixed Value:** GE
effective[x]	0..1	dateTime	Clinically relevant time/time-period for report
slices for result	0..*	Reference(Observation)	Observations **Slice:** Unordered, Open by profile:resolve()
result:overall	0..1	Reference(Overall Interpretation)	Assessment of overall results

result:diagnostic-implication	0..*	Reference(Diagnostic Implication)	Diagnostic Implication
result:variant	0..*	Reference(Variant)	Variant
result:region-studied	0..*	Reference(Region Studied)	Region Studied
result:genotype	0..*	Reference(Genotype)	Genotype
result:haplotype	0..*	Reference(Haplotype)	Haplotype
media	1..1	BackboneElement	Key images or data associated with this report
comment	1..1	string	Comment about the image or data (e.g., explanation)
link	1..1	Reference (DocumentReference)	Reference to the image or data source

Table 23: Organisation

Name	Card.	Type	Description
Practitioner		DomainResource	A grouping of people or organizations with a common purpose
identifier	0..*	Identifier	Identifies this organization across multiple systems
type	0..*	CodeableConcept	Kind of organization Binding: Organisation Type
name	0..1	string	Name used for the organisation
contact	0..*	ExtendedContact Detailed	Official contact details or the organisation
partOf	0..*	Reference (Organization)	The organization of which this organization forms a part
qualification	0..*	BackboneElement	Qualifications, certifications, accreditations, licenses, training, etc pertaining to the provision of care
identifier	0..*	Identifier	An identifier for this qualification for the practitioner
code	1..1	CodeableConcept	Coded representation of the qualification
issuer	0..1	Reference (Organization)	Organisation that regulates and issues the qualification

Table 24: Patient

Name	Cardinality	Type	Description
Patient		DomainResource	Information about an individual receiving health care services
Slices for identifier	0..*	Identifier	Patient Identifier used to specify the individual **Slice:** Unordered
identifier: Republic of Türkiye Id No	0..*	Identifier	Patient Identifier set by Republic of Türkiye Id No
identifier: Healthcare centre, patient Id No	0..*	Identifier	Patient Identifier set by Healthcare organisation
identifier: Protocol Number	0..*	Identifier	Patient Identifier set by Healthcare organization (generally, this id is created using the encounter date/time combination, **i.e., effective[x] | 0..1 | dateTime | Clinically relevant time of encounter**
identifier: Information Technologies number	0..*	Identifier	Patient Identifier generated by IT unit (I think EHR generated id)
active	0..1	boolean	Whether this patient's record is in active use
name	0..*	HumanName	A name associated with the patient
gender	0..*	code	male | female | other | unknown Binding: AdministrativeGender (Required)
birthDate	0..1	date	The date of birth for the individual
extension: age	0..1	extension (age)	Age of the patient
url	1..1	uri	http://x.x.x
valueInteger	1..1	integer	Age value in integer

Table 25: Specimen

Name	Card.	Type	Description
Specimen		DomainResource	Sample for analysis
identifier	0..*	Identifier	External Identifier
accessionIdentifier	0..*	Identifier	Identifier assigned by the lab.
Type	0..1	CodeableConcept	Kind of material that forms the specimen. Binding:HL7 ValueSet specimenType
subject	0..1	Reference(Patient | Group | Device | BiologicallyDerived Product | Substance | Location)	Where the specimen came from patient(s), from a location, or sampling a substance, etc.
receivedTime	0..1	dateTime	The time when specimen is received by the testing laboratory
request	0..*	Reference(ServiceRequest)	Why the specimen was collected
feature	0..*	BackboneElement	The physical feature of a specimen
type	1..1	CodeableConcept	Highlighted feature Binding: SNOMED CT Body Structures
description	1..1	String	Information about the feature
collection	0..1	BackboneElement	Collection details
collector	0..1	Reference (Practitioner | PractitionerRole | Patient | RelatedPerson)	Who collected the specimen
collected[x]	0..1		Collection time
collectedDateTime		dateTime	
collectedPeriod		Period	
method	0..1	CodeableConcept	Technique used to perform collection Binding: FHIR Specimen Collection Method
bodySite	0..1	CodeableReference (BodyStructure)	Anatomical collection site Binding:SNOMED CT Body Structures)

Table 26: Service Request

Name	Card.	Type	Description
ServiceRequest		DomainResource	A request for a service to be performed
identifier	0..*	identifier	Identifiers assigned to this order
instantiatesCanonical	0..*	Canonical(ActivityDefinition PlanDefinition)	Instantiates FHIR protocol or definition
instantiatesUri	0..*	url	Instantiates external protocol or definition
basedOn	0..*	ServiceRequest (CarePlan | ServiceRequest | MedicationRequest)	What request fulfils
intent	1..1	code	proposal | plan | directive | order Binding: RequestIntent Category Codes
subject	1..1	Reference (Patient | Group | Location | Device)	Individual or Entity the service is ordered for
authoredOn	1..1	dateTime	Date request signed
requester	0..1	Reference (Practitioner | PractitionerRole | Organization | Patient | RelatedPerson | Device)	Who/what is requesting service
performerType	0..1	CodeableConcept	Performer role Binding: ParticipantRole
insurance	0..*	Reference (Coverage | ClaimResponse)	Associated insurance coverage
supportingInfo	0..*	CodeableReference (Any)	Additional clinical Information
specimen	0..*	Reference	Procedure samples

Table 27: Plan Definition

Name	Card.	Type	Description
PlanDefinition		DomainResource	The definition of a plan for a series of actions, independent of any specific patient or context
url	0..1	url	Canonical identifier for this plan definition, represented as a URI
identifier	0..*	identifier	Additional identifier for the PlanDefinition
name	0..1	string	Name for this plan definition (computer friendly)
title	0..1	string	Name for this plan definition (human friendly)
type	0..1	CodeableConcept	Order-set | clinical-protocol | eca-rule | workflow-definition Binding: Plan Definition Type
description	0..1	markdown	Natural language description of the plan definition

Table 28: Related Artifact Extension

Name	Card.	Type	Description
relatedArtifact	0..*	RelatedArtifact	Documentation or 'knowledge artifacts' relevant to the base resource such as citations, supporting evidence, documentation of processes, caveats around testing methodology.

Table 29: Annotation Code

Name	Card.	Type	Description
AnnotationCode	0..*	AnnotationCode	An extension enabling insertion of test-disclaimer, test-methodology, result-confirmation

Table 30: component:reference-sequence-assembly

Name	Card.	Type	Description
Reference-sequence-assembly	0..*	BackboneElement	Human Reference Sequence Assembly
code	1..1	CodeableConcept	LOINC: 62374-4
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system Fixed Value: 62374-4
value[x]	1..1	CodeableConcept	GRCh37 | GRCh38 | … **Binding:** LOINC Answer List LL1040-6

Table 31: Practitioner Role

Name	Card.	Type	Description
PractitionerRole		DomainResource	Roles/organisations the practitioner is associated with
identifier	0..*	Identifier	Identifiers for a role/location
practitioner	0..1	Reference(Practitioner)	Practitioner that provides services for the organisation
organization	0..1	Reference(Organization)	Organization where the roles are available
code	0..*	CodeableConcept	Roles which this practitioner may perform Binding: Practitioner
specialty	0..*	CodeableConcept	Specific Specialty of the practitioner Binding: Practice Setting Code Value Set
location	0..*	Reference(Location)	Location(s) where the practitioner provides care
healthcareService	0..*	Reference (HealthcareService)	Healthcare services provided for this role's Organisation/Location(s)

Table 32: Practitioner

Name	Card.	Type	Description
Practitioner		DomainResource	A person with a formal responsibility in the provisioning of healthcare or related services
identifier	0..*	Identifier	An identifier for the person as this agent
name	0..*	HumanName	The name associated with the practitioner
telecom	0..*	ContactPoint	A contact detail for the practitioner (that apply to all roles)
qualification	0..*	BackboneElement	Qualifications, certifications, accreditations, licenses, training, etc pertaining to the provision of care
identifier	0..*	Identifier	An identifier for this qualification for the practitioner
code	1..1	CodeableConcept	Coded representation of the qualification
issuer	0..1	Reference (Organization)	Organisation that regulates and issues the qualification

Table 33: Genomic Report Note Extension

Name	Card.	Type	Description
Genomic Report Note	0..*	Genomic Report Note	Genomic Report Note Adds codified notes to a report to capture additional content
url	1..1	uri	http:// xx
value[x]	0..1	CodedAnnotation	

Table 34: supporting-info Extension

Name	Card.	Type	Description
Supporting-info	0..*	Reference(Resource)	Other information that may be relevant to this event.

Table 35: component: conclusion-string

Name	Card.	Type	Description
conclusion-string	0..1	BackboneElement	Clinical conclusion
code		CodeableConcept	conclusion-string Binding: LOINC Codes: Codes identifying names of simple observations.
coding		Coding	Code defined by a terminology system
system		uri	Identity of the terminology system
code		code	Symbol in syntax defined by the system

Table 36: Overall Interpretation Profile

Name	Card.	Type	Description
Observation	0..*	GenomicsBase	Measurements and simple assertions
secondary-finding	0..1	CodeableConcept	Secondary findings are genetic test results that provide information about variants in a gene unrelated to the primary purpose for the testing, most often discovered when Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS) is performed. This extension should be used to denote when a genetic finding is being shared as a secondary finding, and ideally refer to a corresponding guideline or policy statement.
body-structure	0..1	Reference (BodyStructure)	Target anatomic location or structure
Slices for category	2..*	CodeableConcept	Classification of type of observation **Slice:** Unordered, Open by value:coding **Binding:** ObservationCategoryCodes (preferred): Codes for high level observation categories.
category:labCategory	1..1	CodeableConcept	Classification of type of observation
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
category:geCategory	1..1	CodeableConcept	Classification of type of observation

coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
code	1..1	CodeableConcept	51968-6 **Binding:** LOINC Codes (example): Codes identifying names of simple observations.
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	Positive | Negative | Inconclusive | Failure Binding: LOINC Answer List LL541-4 (preferred)
Slices for component	0..*	BackboneElement	Component results
component:All Slices			
code	1..1	CodeableConcept	Type of component observation
component:conclusion-string	0..1	BackboneElement	Clinical Conclusion
code	1..1	CodeableConcept	conclusion-string **Binding:** LOINC Codes (example): Codes identifying names of simple observations.
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system

Table 37: Diagnostic Implication

Name	Card.	Type	Description
Observation	0..*	GenomicImplication	Diagnostic Implication
Genomics-risk-assessment	0..*	Reference (Risk Assessment)	Genomics Risk Assessment
code	1..1	CodeableConcept	Diagnostic-implication
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
component: predicted-phenotype	0..*	BackboneElement	Predicted Phenotype
code	1..1	CodeableConcept	81259-4
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	Phenotype code, e.g., from SNOMED CT Clinical finding, ICD-10-CM chapters 1-18, or HPO. Multiple bindings accepted
component: mode-of-inheritance	0..1	BackboneElement	Mode of Inheritance
code	1..1	CodeableConcept	condition-inheritance
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	Autosomal dominant | Autosomal recessive | X-linked | … (more)
component:clinical-significance	0..1	BackboneElement	Clinical significance
code	1..1	CodeableConcept	53037-8

coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	Pathogenic | Likely pathogenic | Uncertain significance | Likely benign | Benign **Binding:** LOINC Answer List LL4034-6

Table 38: Variant Profile

Name	Card.	Type	Description
Observation	0..*	GenomicFinding	Variant
code	1..1	CodeableConcept	69548-6
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
Slices for value [x]	0..1	Quantity, CodeableConcept, string, boolean, integer, Range, Ratio, SampledData, time, dateTime, Period, markdown	Actual result **Slice:** Unordered
value[x]: valueCodeableConcept	0..1	CodeableConcept	Indeterminate | No call | Present | Absent **Binding:** LOINC Answer List LL1971-2
method	0..1	CodeableConcept	Sequencing | SNP array | PCR | Computational analysis | … **Binding:** LOINC Answer List LL4048-6
component: representative-coding-hgvs	0..1	BackboneElement	DNA change (c.HGVS)
code	1..1	CodeableConcept	48004-6
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	A valid HGVS-formatted ‘c.’ string, e.g., NM_005228.5:c.2369C<T **Binding:** Human Genome Variation Society (HGVS) Nomenclature

component: genomic-hgvs	0..1	BackboneElement	Genomic (gDNA) Change gHGVS
code	1..1	CodeableConcept	81290-9
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	A valid HGVS-formatted 'g.' string, e.g., NC_000016.9:g.2124200_ 2138612dup **Binding:** Human Genome Variation Society (HGVS) Nomenclature
component: cytogenomic-nomenclature	0..1	BackboneElement	Cytogenomic Nomenclature (ISCN)
code	1..1	CodeableConcept	81291-7
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	Actual component result **Binding:** not yet defined
component: genomic-ref-seq	0..1	BackboneElement	Genomic Reference Sequence
code	1..1	CodeableConcept	48013-7
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	Versioned genomic reference sequence identifier **Binding:** multiple bindings are acceptable (NCBI or LRG)

component: representative-transcript-ref-seq	0..1	BackboneElement	Reference Transcript
code	1..1	CodeableConcept	51958-7
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	Versioned transcript reference sequence identifier **Binding:** multiple bindings are acceptable (NCBI or LRG)
component: coding-change-type	0..1	BackboneElement	Coding DNA Change Type
code	1..1	CodeableConcept	48019-4
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	deletion | insertion | delins | SNV | copy_number_gain | copy_number_loss | … (many) **Binding:** DNA Change Type: Concepts in sequence ontology under SO:0002072
component: genomic-source-class	0..1	BackboneElement	Genomic Source Class
code	1..1	CodeableConcept	48002-0
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system

value[x]	1..1	CodeableConcept	Germline | Somatic | Fetal | Likely germline | Likely somatic | Likely fetal | Unknown genomic origin | De novo
component: sample-allelic-frequency	0..1	BackboneElement	Sample Allelic Frequency
code	1..1	CodeableConcept	81258-6
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	0..1	Quantity	Relative frequency in the sample
system	0..1	uri	System that defines coded unit form
component: allelic-read-depth	0..1	BackboneElement	Allelic Read Depth
code	1..1	CodeableConcept	82121-5
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	0..1	Quantity, markdown	Unfiltered count of supporting reads
component: allelic-state	0..1	BackboneElement	Allelic State
code	1..1	CodeableConcept	53034-5
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system

value[x]	0..1	CodeableConcept	Heteroplasmic | Homoplasmic | Homozygous | Heterozygous | Hemizygous **Binding:** LOINC Answer
component: variant-inheritance	0..1	BackboneElement	Variant Inheritance
code	1..1	CodeableConcept	variant-inheritance
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	Maternal | Paternal | Unknown **Binding:** Variant Inheritances (Extensible)
component: variation-code	0..1	BackboneElement	Variation Code
code	1..1	CodeableConcept	81252-9
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	ClinVar ID or similar **Binding:** Multiple bindings accepted
component: variant-confidence-status	0..1	BackboneElement	Variant Confidence Status
code	1..1	CodeableConcept	variant-confidence-status
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	0..1	CodeableConcept	High | Intermediate | Low **Binding:** Variant Confidence Status

Table 39: Region Studied

Name	Card.	Type	Description
Observation	0..*	GenomicsBase	Region Studied
code	1..1	CodeableConcept	53041-0
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
component: gene-studied	0..1	BackboneElement	Gene Studied
code	1..1	CodeableConcept	48018-6
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	The HGNC gene symbol is to be used as display text and the HGNC gene ID used as the code. If no HGNC code issued for this gene yet, NCBI gene IDs SHALL be used. **Binding:** HUGO Gene Nomenclature Committee Gene Names (HGNC)
component: gene-mutations	0..1	BackboneElement	Gene Mutations ID
code	1..1	CodeableConcept	36908-2
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	CodeableConcept	Actual component result **Binding:** HUGO Genome Variation Society (HGVS) Nomenclature
component: gene-region-description	0..1	BackboneElement	Region Description

code	1..1	CodeableConcept	81293-3
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	0..1	String	Actual component result
component: region-coverage	0..1	BackboneElement	Region Coverage
code	1..1	CodeableConcept	region-coverage
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	0..1	String	Actual component result
component: genomic-ref-seq	0..1	BackboneElement	Genomic Reference Sequence
code	1..1	CodeableConcept	48013-7
coding	1..*	Coding	Code defined by a terminology system
system	1..1	uri	Identity of the terminology system
code	1..1	code	Symbol in syntax defined by the system
value[x]	1..1	String	Versioned genomic reference sequence identifier **Binding:** Multiple bindings acceptable (NCBI or LRG)

Table 40:Family Member History for Genetics Analysis Profile

Name	Card.	Type	Description
FamilyMemberHistory	0..*	FamilyMember History	Information about patient's relatives, relevant for patient
parent	0..*	(Complex)	Mother(s) & Father(s) – genetic & other **URL:** http://xxx
sibling	0..*	(Complex)	natural brother(s) & natural sister(s) – genetic & other **URL:** http://xxx
observations	0..*	Reference (Observation)	Genetic markers, ethnicity, etc. **URL:** http://xxx
relationship	1..1	CodeableConcept	Relationship to the subject
sex	0..1	CodeableConcept	Male | female | other | unknown
born[x]	0..1	Period, date, string	(approximate) date of birth
age[x]	0..1	Age, Range, string	(approximate) age
deceased[x]	0..1	boolean, Age, Range, date, string	Dead? How old/when?
condition	0..*	BackboneElement	Condition that the related person had
code	1..1	CodeableConcept	Condition, allergy, or intolerance suffered by relation
outcome	0..1	CodeableConcept	deceased | permanent disability | etc.
onset[x]	0..1	Age, Range, Period, string	When condition first manifested
note	0..*	Annotation	Extra information about condition

Table 41: secondary Finding Extension

Name	Card.	Type	Description
Extension	0..1	Extension	Secondary findings are genetic test results that provide information about variants in a gene unrelated to the primary purpose for the testing, most often discovered when Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS) is performed. This extension should be used to denote when a genetic finding is being shared as a secondary finding, and ideally refer to a corresponding guideline or policy statement.
url	1..1	uri	http://xxx
value[x]	1..1	CodeableConcept	Value of extension **Binding:** GeneticObservation SecondaryFindings: Codes to denote a guideline or policy statement when a genetic test result is being shared as a secondary finding.

Table 42: Followup Recommendation (Profile) (Recommended Follow Up)

Name	Card.	Type	Description
Task	0..*	Task	A task to be performed
status	1..1	code	draft | requested | received | accepted
intent	1..1	code	unknown | proposal | plan | order | original-order | reflex-order | filler order | instance-order | option
code	0..1	CodeableConcept	Task Type

CHAPTER 5

DISCUSSION

In this dissertation, we scrutinised the genetic testing information exchange in Türkiye under three facets. Initially, we provided a broad review of the adaptedness of Turkish EHR interoperability measures for the genetic testing process, i.e., system architecture, technical principles, and the available terminologies. Later, we combined the initial findings with the workflow peculiar to the genetic testing centre – reimbursement coverage and constraints about genetic test ordering. Afterwards, we queried genetic testing experts' views, opinions, and expectations on genetic testing information exchange utilising qualitative research methods. Finally, we exhibit a conceptual model of genetic information exchange for Türkiye.

Initially, we evaluated Türkiye's healthcare policies concerning the integration of genetic/genomic patient data into the National Electronic Health Records system. The assessment is based on three focal areas managed by the Turkish government:

1. **System Architecture, Technical Principles, and Terminology:** In this part, we analysed the Turkish EHR's existing system architecture, technical guidelines, and available terminologies.

2. **Governmental Regulations and Genetic/Genomic Data Representation:** Here, we examined Turkish governmental rules and regulations to determine if there are provisions for the structured representation of genetic/genomic test data within health records.

3. **Law on Protection of Personal Data (LPPD):** Finally, we weighed the implications of the enacted Law on Protection of Personal Data (LPPD) concerning genetic/genomic patient information.

The research findings indicate that the NHIS-T (National Health Information System-Türkiye) currently lacks the readiness to effectively represent and exchange structured genetic/genomic test results in a compatible manner. This deficiency stems from factors such as the continued utilisation of HL7 v3 [11], [14] [41]and the absence of Clinical Genomics implementation, both of which pose significant challenges.

One limitation arises from the absence of translated international ontology-based terminologies in Turkish, leading to the use of Health Implementation Communiqué (HIC). For instance, due to the lack of globally recognised and Turkish-translated ontology-based terminologies, Türkiye's Ministry of Health integrated oral and dental health data using HCRS and HIC [147]. Conversely, Norway's adoption of SNOMED

International for ontology-based terminologies demonstrates the significance of standardised data representation [49].Several countries and alliances worldwide have initiated precision medicine programs, often utilising HL7 FHIR for medical data exchange [22], [39], [125]. Finland's Kanta PHR, Austria's ELGA, and efforts in the UK and the US showcase the adoption of ontology-based terminologies for enhanced interoperability and data representation [12], [20], [44], [123], [148].

This dissertation underscores that existing regulations do not enforce a standardised representation of genetic tests, an essential prerequisite for seamless information exchange. Regulations mandate paper-based notifications in conjunction with non-standardized electronic records [12]. Despite the electronic submission of genetic testing results for reimbursement, the lack of a globally accepted, structured format hampers successful payment processing.

Privacy concerns related to genetic data warrant careful consideration from clinicians, legal authorities, and citizens in Türkiye. Experts recommend addressing issues such as sharing genetic information with patients, handling incidental findings, and safeguarding confidentiality [54]. Genetic data privacy differs from health data and should be treated distinctly in regulations. While global ethical standards, such as those outlined by the World Medical Association [149], [150], provide guidance, shortcomings in Türkiye include undefined genetic/genomic testing data sets, inadequate genetics-related definitions, incomplete LOINC translations [12], and more.

These deficiencies have far-reaching implications, ultimately restricting the capabilities of the genome-enabled national Electronic Health Record (EHR) system in Türkiye. Similar observations from the CSER and eMERGE working groups [36] reveal that genetic test reports are shared through paper-based methods, emails, or PDF documents. Notably, no established, structured format exists for requesting or reporting genetic tests. Genetic test results are presented like pathology reports, including analytical outcomes, findings, and directives. The absence of mandatory adoption of genetic testing standards and ontology-based terminologies compels different centres to resort to diverse coding standards based on their specific needs and educational backgrounds. This, in turn, leads to interoperability challenges.

Furthermore, the use of disease codes for phenotype description, local procedural codes for reimbursement purposes, and the absence of translated genetics-related LOINC codes for laboratories contribute to coding errors, thereby obstructing the secondary utilisation of genetic data. None of these systems adequately defines gene names or genetic sequence variations. This situation contradicts the healthcare sector's digitisation initiatives since 2003 [4], revealing a lack of aligned regulations, prompting government officials to seek paper-based reports. Implementing standards for communicating of genetic/genomic data, such as HL7 FHIR [98] or the domain analysis model for HL7 v3 Clinical Genomics [41], would benefit Türkiye and the broader global community. Regrettably, as of now, none of these standards have been adopted in Türkiye. As a specific instance, although new enabling technologies for interoperable representation of HLA (Human Leukocyte Antigen) reports have been defined [151], Türkiye has yet to structure them according to regulatory requirements [109].

The absence of nationwide allele frequency information hinders prompt decision-making based on targeted genetic testing panels, necessitating additional time and resources. This uncertainty affects the diagnosis of numerous cases. Also, essential definitions for returning results and sharing secondary findings of actionable genetic variants with patients lack legislative clarity. Consequently, experts resort to adopting global best practices, eagerly awaiting relevant regulations or codes from the MoH.

In the second section of this dissertation, we laid down three primary outcomes. Initially, we delineated the coverage of genetic/genomic testing reimbursement in Türkiye. As a second sequelae, we unveiled the expectations of genetic testing experts from policymakers using qualitative research methodology. We put forward that while recent updates on Health Implementation Communiqué (HIC) for genetic/genomic tests show some alignment with expert expectations, they remain somewhat unsatisfactory. Finally, we outlined the operational process, i.e., a workflow of genetic testing centres.

The qualitative research highlights eight themes emerging from semi-structured interviews with key experts and projects these findings with the global context. The results are anticipated to guide policymakers in developing a national-level Electronic Health Record (EHR) capable of exchanging genetic/genomic data.

For the reimbursement of genetic tests, to compare other countries and Türkiye, we decided to focus discussions on “exceptional benefits” instead of benefit catalogues. For instance, in Türkiye, unlike the US Medicare system, the MoH reimburses Whole Exome Sequencing (WES) in cases of undiagnosed diseases with explicit clinical benefits. The coverage details for US Medicare and UK NHS can be found in [48], [49].

As stated in this dissertation, HIC is updated in an ad hoc manner [12]. MoH Türkiye recognises the inadequacy of local transaction codes for genetic/genomic tests to track public health issues and generate statistical reports. Judging the recent HIC updates on genetic testing transactions with the qualitative research outcomes from the experts, the revisions seem to fall short of complementing the expectations. While radiology codes were correlated with Logical Observation Identifiers Names and Codes (LOINC) for diagnostic imaging tracking, this approach has not been extended to genetic/genomic tests.

Dwelling into the qualitative research results of this dissertation, we infer that challenges in genetic testing are not unique to Turkish healthcare but a global issue lacking a universally accepted solution. As a supporting example, Healthcare Common Procedure Coding System (HCPCS) codes are used for billing Medicare & Medicaid patients in the US. These codes primarily correspond to services, procedures, and equipment not covered by Current Procedural Terminology (CPT), which is inadequate for genetic tests. In this dissertation, we highlighted examples where gender and age-specific codes in the ICD-10 pose challenges for reimbursement and population-based statistical studies.

The limitations of this section of the dissertation are related to the ad hoc nature of the HIC and qualitative research methodology we utilised:

- For reimbursement coverage, presenting a list associating targeted gene tests with specific transaction procedures proves challenging due to the increasing number of genetic diagnosis tests and fluctuating currency rates.

- Despite a small participant group, our research sought to mitigate interviewee sampling bias through a diverse selection of corporate entities and adherence to governmental rules. The eight observed themes extend beyond participant perspectives, remaining valid for all healthcare services.

Finally, we conceptualised a model for genetic information exchange capable of EHR in this dissertation. Leaning on the literature and best practices, we used HL7 FHIR for our model. HL7 FHIR is both a fast and easily implementable medical data communication system. We requested sample genetic testing reports from the experts during the interviews and collected four examples from three different genetic testing centres. One of them has provided two reports which are representing WES. One centre provided a targeted genetic testing report, and the other shared a report that used a gene panel for genetic testing. The reports enabled us to provide a conceptual model for different types of genetic testing. As a first step, we extracted all data fields of those four different genetic test reports and generated a standard genetic testing report model that represents all four reports. Later, we compared the model with the literature, identified missing data elements, and generated a template model for genetic test reports in Türkiye. As the experts stated during the interviews, we also observe that the MoH does not mandate any genetic test report format. Centres use a style according to their previous training and traditions.

There are three live versions of FHIR:

- Balloted,

- Standard Trial Use (STU) and,

- Current Development Build (about 30minutes behind version control, may be incoherent and change rapidly).

The most recent iteration of FHIR is the Continuous Integration Build (CI-B), representing the latest controlled version. Throughout our process of modelling genetic information exchange, we utilised the latest available version, which is FHIR R5, CI-B. The specific date relevant to our study was July 15, 2023. We can list the benefits of CI-B as follows:

- Over time, FHIR undergoes continuous development. Developers enhance FHIR content by introducing new artifacts such as profiles and extensions. Furthermore, implementers worldwide contribute their feedback and the artifacts they create to HL7 FHIR developers. Once the value of these contributions is widely recognised, they are integrated into the new FHIR CI-B specifications. By adopting CI-B in our dissertation, we eliminate the need to create new artefacts, reducing redundancy and staying current with the latest developments.

- Through our observations, we have gained insight into developers' perspectives, establishing our confidence that the proposed model aligns with the global standardisation trends.

- While generating our template report, we identified specific fields that necessitate FHIR extensions. Upon reviewing the CI-B, we discovered that these aspects are relevant to our project and pose a universal challenge. In response to this challenge, developers have created artifacts within the CI-B to address and resolve these issues on a broader scale.

FHIR uses SNOMED-CT, HGNC, and LOINC as terminology standards. The most outstanding issue we encounter is that the SNOMED-CT and HGNC have not been officially endorsed and adopted as standards within Türkiye. As of March 2022, a noteworthy development occurred where the MoH incorporated HGNC into the HCRS. However, despite this inclusion, there is a notable absence of official statements, designated use cases, or implementation guidelines pertaining to utilising these codes. From our perspective, the addition was primarily aimed at monitoring tests and mitigating test redundancy, potentially leading to more efficient reimbursement practices. Besides, the Turkish translation of LOINC is insufficient to implement genetic testing information exchange [12].

Considering the progression of software development, before enacting the conceptual framework for the exchange of genetic testing data in Türkiye, the MoH and associated entities should assemble a collaborative team. This team's objective would be to create the foundational specifications known as "FHIR Türkiye Core". This term signifies a novel concept within the Turkish Health Information System. Ultimately, the outcome would be establishing a distinct and exclusive FHIR framework tailored for the Republic of Türkiye.

Creating a tailored version of FHIR specifications, such as "FHIR Türkiye Core", ensures that the healthcare information exchange standards align with the specific needs, regulations, and workflows of Türkiye's healthcare system. This custom core can encapsulate the necessary profiles, extensions, and data elements most relevant to the Turkish context. This approach would have several advantages:

1. **Alignment with Local Requirements:** FHIR Türkiye Core would account for Türkiye's unique healthcare practices, regulations, and terminologies. This ensures that the information exchanged is contextually accurate and relevant.

2. **Efficient Implementation:** Defining specific profiles and extensions that cater to the Turkish healthcare ecosystem makes the implementation process smoother and more efficient.

3. **Interoperability:** FHIR Türkiye Core would enable better interoperability among different healthcare systems within Türkiye, promoting seamless data exchange and collaboration.

4. **Consistency and Standardisation:** Creating a unique FHIR Core for Türkiye guarantees consistency in data representation and interpretation, fostering standardised practices nationwide.

5. **Future Proofing:** As Türkiye's healthcare landscape evolves, FHIR Türkiye Core can be adapted and extended to accommodate new requirements and technological advancements.

To emphasise the significance of FHIR Türkiye Core, we can illustrate this point using the "age" data element. While mapping our conceptual model with FHIR, we noticed that specific reports require the inclusion of the term "age." Upon reviewing the relevant literature, we found that focus group studies involving genetic testing experts emphasise the significance of incorporating "age" information within genetic testing reports. As a result, we integrated the concept of "age" into our standardised report template. However, it is worth noting that the basic FHIR Patient profile does not encompass the "age" data component.

Within the "Pharmacogenomics Report Implementation Guide" (Murugan et al., 2021), the eMerge team developed an extension named "age" designed for integration with the FHIR Patient profile. They presented this extension to the FHIR developer team, which subsequently included it in the Genomics Implementation Guide as a formal component (artifact).

One of the great benefits of using the recent fifth FHIR (R5) revision is incorporating additional textual content within the Genomic Implementation Guide. This paves the way for the implementers to focus on every detail within the report. These particulars were left unspecified or managed as extensions in the previous revisions. A growth in the number of extensions entails obtaining team approval initially, followed by universal implementation. This approach consequently boosts the team's oversight over interoperability.

Another critical issue is the creation of Türkiye-specific ValueSets. FHIR includes some ValueSets of its own. Translating these into Turkish might be appropriate. However, in many cases, the most suitable solution is to adapt these ValueSets using the values from the SKRS. If necessary, by expanding the SKRS fields and principal codes, we can achieve expansion in FHIR and Türkiye-specific ValueSets.

CHAPTER 6

CONCLUSION

This dissertation is composed of three separate studies. In the initial part of the review study, we outlined Türkiye's stance concerning the representation of genetic/genomic test data in Electronic Health Records (EHRs) and the exchange of interoperable information, compared to global perspectives. Due to the absence of relevant English data or internationally peer-reviewed papers, Türkiye is often excluded from worldwide studies on health systems, genetic test exchange standards, and relevant governmental regulations. In some cases, Türkiye is disregarded in international reviews or mentioned with limited details in these initiatives. Therefore, this dissertation bridges this gap and offers a valuable overview of Türkiye's status quo [12].

First requirement for incorporating genomic data into EHRs is the utilisation of ontology-based terminologies. However, the international terminologies translated into Turkish for genetic/genomic testing data within NHIS-T are inadequate. None of the terminologies mandated by regulations in Türkiye are ontology-based, and there is no requirement for standardised terminology in genetic testing regulations. The Turkish EHR data fields rely on HIC codes, and paper-based storage remains prevalent due to vague aspects of the regulations. Notably, no governmental initiative promotes using HGNC for gene names and HGVS for DNA sequence variants. Furthermore, the need to translate genetic data-related fields in LOINC presents an obstacle to the meaningful representation of genetic test outcomes in Turkish EHRs. In summary, the absence of standardised structured terminology hampers genetic data's digitalisation and secondary use[12].

Since the LPPD separately addresses genetic and health data, experts have reservations about the potential future discontinuation of genetic testing reimbursement for individuals registered with SSI in the future [12]. Additionally, recent revisions to relevant SSI articles grant Turkish government authorities the right to process individuals' health data without explicit consent. Beyond this, due to the unique nature of genetic data, there are no regulations, codes, or bylaws concerning matters like the "right to know/right not to know," "return of results," and how to convey information about "incidental findings" and "variants of unknown significance" to patients. Ethical concerns have prompted experts to follow globally accepted guidelines. Regarding jurisdiction, while Türkiye is part of UNESCO and WHO, the compatibility of Turkish legislation with WMA declarations raises doubts. In the age of artificial intelligence, the effective implementation of precision medicine is at risk of being misused unless carefully crafted regulations regarding explicit consent are in place. Additionally, concerns raised by experts regarding the reimbursement of genetics-oriented diseases

are well-founded, as the existing regulations currently lack provisions that ensure the ongoing protection of reimbursement arrangements.

From a health and science policy perspective, we strongly advocate for a thorough review of the technical aspects of health data management, terminologies, and regulations related to genetic/genomic testing in Türkiye. These measures should facilitate the secondary use of genetic/genomic data for precision medicine and other applications while adhering to FAIR (findable, accessible, interoperable, reusable) standards within Türkiye's EHR system [12].

Implementing these suggestions to address the deficiencies in Türkiye's NHIS is anticipated to yield positive national, organisational, and individual outcomes. Primarily, the genome-enabled EHR will assist clinicians in achieving a shared understanding of the interpretation of genetic tests and genomic data in their diagnoses, enhancing the perceived value of genetic data. Establishing universally accepted privacy rules and fostering trust among citizens could provide valuable nationwide genomic data for secondary use, particularly in precision medicine. Globally, genomic implementation is still in its early stages, with limited evidence for clinical utility, ethical and legal challenges, and insufficient alignment of reimbursement methods to drive transformative healthcare changes. The government-funded genomic medicine practice is crucial for generating evidence and sharing data to facilitate secondary data use. Creating a national reference database and IT infrastructure for integrating and exchanging genomic data, metadata, and health records will enrich the outcomes of genetics studies. Governments should formulate policies for legal and ethical frameworks, workforce development, clinical decision-support tools, public engagement, and education. While under-resourced countries may lack full genomic medicine implementation, they face rare diseases due to high consanguinity rates. Conversely, national initiatives and accomplishments are vital in presenting a unified voice to governments and inspiring the global community to shape future policy development and service planning [17]. By successfully implementing a structured representation of genetic data, we can leverage the meaningful use of genetic data beyond clinical diagnoses, enabling retrospective and future planning at both national and global levels [12].

In the second part of this dissertation, we presented an overview of the present state of reimbursement for genetic/genomic testing. We uncovered the expectations and motivations of genetic testing experts in Türkiye. Despite being inadequate, the efforts to establish new genetic/genomic testing processes validate the experts' anticipations. Developing targeted processes is crucial for effective data management and addressing financial aspects. Identifying the practical barriers and challenges in managing genomic test data in Türkiye holds significance on a national and international scale, offering guidance to policymakers in their strategic plans. In this dissertation, we identified ambiguous aspects within regulations governing genetic/genomic exchange and identified eight main themes from the semi-structured interviews.

Globally accepted standards facilitate information exchange within hospital and laboratory information management networks. Structural and terminological standards play a pivotal role in achieving semantic interoperability. Stakeholders in genetic data still require analogous standards and unified information exchange platforms to

facilitate the organised representation and management of genetic/genomic test outcomes. Digitalisation and standardisation in storing genetic/genomic data are imperative for advancing precision medicine and personalised disease management. Establishing Personal Health Records (PHRs) capable of supporting precision medicine is essential for genetic test results to be uniformly integrated within EHRs.

The reservations and recommendations provided by the experts in this study, aligning with their clinical workflows, should be considered by policymakers. Enhanced collaboration between policymakers and medical experts will foster the creation of health policies necessary for the structured integration of genetic test outcomes into national health information systems, such as NHIS-T.

Main contribution of this dissertation is the conceptual model for genetic testing information exchange in Türkiye using FHIR. The two initial steps of our study highlight the dissatisfaction with the NHIS-T about effectively incorporating interoperable genetic test results. Essentially, the MoH mandates using HL7 v2 or v3 to exchange information. However, the existing literature points out the inadequacy of these standards when facilitating the exchange of genomic information.

In our model, we have greatly profited from recent developments in FHIR Genomic Implementation Guide artifacts. By its definition, an artifact pertains to an object, item, or element fashioned or modified by humans, often for a particular purpose. Within the realm of HL7 FHIR, artifacts represent precise data structures, documents, or resources prescribed and employed in the HL7 FHIR standards framework to facilitate the exchange of healthcare-related data among diverse systems and entities. Particularly within implementation guides, developers generate profiles specific to certain domains, encompassing abstract profiles, resource profiles, data type profiles, extensions, value sets, code systems, and more. In HL7 FHIR, these are categorised as artifacts within a list, streamlining their use for implementers' data payloads. They serve as our navigational aids. This is the arena where the application thrives.

The contributions that we propose in this dissertation are:

- **Adoption and translation of SNOMED-CT as a Terminology Standard in Türkiye**

Although the FHIR is not supposed to be an official health information exchange standard in Türkiye, we also observed that SNOMED-CT is not translated into Turkish. The benefits of SNONMED-CT as an ontological representation system are well explained in this dissertation. Without a doubt, this issue would generate a big gap during implementation. Our model exhibits a pressing need to expand and enhance the translation to cater to the specific requirements of genetic test reporting. For instance, while we can furnish body site specifics through HCRS, these would only consist of localised codes and might lack significant context when sharing information internationally. In contrast, the ontological framework of SNOMED-CT incorporates comprehensive body site descriptions and is recognised as a worldwide standard.

- **Establishing FHIR Türkiye Core**

In this dissertation, we stressed the need to develop the FHIR Türkiye Core. A core FHIR implementation for a country means a set of profiles and extensions for the FHIR standard specifically designed to meet the needs of healthcare providers and other stakeholders within that country's healthcare system. A FHIR Country Core defines a standard set of resources and data elements essential for supporting interoperability and data exchange among different healthcare systems and organisations within that country. The core resources and elements cover a wide range of clinical, administrative, and financial data, ensuring that vital patient information can be shared and interpreted consistently across various health IT systems. The development of FHIR Core profiles and extensions involves collaboration between HL7 and various stakeholders in the healthcare community, including healthcare providers, IT professionals, policymakers, payers, vendors, government agencies, and other organisations. This collaborative approach aims to create a standard set of FHIR resources and structures that align with the specific requirements and workflows of the country's healthcare ecosystem, ultimately facilitating smoother data sharing, care coordination, and improved patient outcomes.

In the FHIR Türkiye Core scenario context, we suggest taking advantage of the existing active Turkish Data Model (Veri Modeli, VEM).

- **ValueSets Specific to Turkish Healthcare System**

Another point we propose is the development of the ValueSets specific to Turkish health information exchange. In Türkiye's HCRS, most of the ValueSets are already present, but they are not enough and comprehensive for the requirements of FHIR. The authorities can quickly fill in the gaps for requirements.

- **Notifications to FHIR Developer Team**

    - A straightforward alert that could be communicated with FHIR developers pertains to the absence of the "Family Member History for Genetics Analysis Profile" within the artifacts list. While the FHIR Genomics Implementation Guide acknowledges the presence of this profile under the General Genomic Reporting section, it has regrettably not been included in the artifacts list. In our template report creation process, linking family history data as supplementary information is imperative. Therefore, we are contemplating a gentle reminder to FHIR developers, urging them to incorporate the "Family Member History for Genetics Analysis Profile" within the artifacts list.

    - We aim to display the allelic read-depth information and illustrate the outcome in tabular format within the "Quality Control Table of the Analysis." However, we have not identified any prior efforts related to this in the FHIR context. Our strategy involves proposing to the FHIR developer team the creation of a new data type profiling for the allelic read depth segment. This profiling would use markdown to present the results tabularly, similar to the format used in our sample reports.

- **Notifications to Policy Makers**

    - In FHIR Türkiye Core, we suggest not dismissing the "Foreign Patient Type" data element. The ValueSet for this data element is already defined under HCRS and is considerably comprehensive but needs further clarification. Based on the information gathered from our individual discussions and interview results, this matter holds significance due to genetic disorders that are not exclusive to the Turkish population. Consequently, a distinction should be made in addressing these conditions.

    - Even though we initially omitted it from our design, based on the findings from the literature and insights gathered from expert interviews, we strongly recommend adding the "Sex at Birth" data element to the Patient resource in Türkiye. According to one of our interviewees, they encountered a legal challenge concerning determining sex at birth for a patient. They resolved this issue by providing the image of a test they had conducted.

The potential areas for future investigation are as follows:

- Our current dissertation does not encompass the sharing of complete test outcomes. This is primarily due to the substantial size of the test results, which would overwhelm NHIS-T's capacity to manage such voluminous genetic data in its repository. Further research is necessary to devise a solution to address this issue.

- FHIR includes a distinct module concerning privacy and security. It will become imperative in forthcoming research to align the LPPD with this module and amalgamate the outcomes within NHIS-T.

- Upon executing this theoretical model, the amassed genetic information can be de-identified and should be accessible to researchers and medical students. This yields several advantages, including enabling medical students to become familiar with using EHRs and genetic data, comprehending the significance of precision medicine and PGx, gaining hands-on exposure to processing genetic data, and extracting clinically relevant genetic insights.

- A resultant development of this study would be the creation of an EHR-integrated pedigree. This innovation reduces the time spent on manual pedigree drawings and transitions paper-based pedigrees into digital formats. Furthermore, medical trainees could better understand pedigree-related matters during their education.

- To ensure the storage and convenient retrieval of comprehensive genetic data for precision medicine, an HIS capable of information exchange should be considered for future implementation.

- Another prospective study could concentrate on integrating genotype and phenotype data into EHRs.

- Collaboration between policymakers and genetic testing experts is necessary to standardise the representation of genetic test results. This collaboration would streamline the implementation of the conceptual model while binding terminologies.

- Policymakers should establish minimum data requirements for reporting genetic tests.

We are confident this dissertation will serve as a valuable reference for implementing FHIR within the Turkish National Health Information System. We have identified practical deficiencies in the new medical information exchange tool and Türkiye's existing tools. Furthermore, the proposed conceptual model will significantly assist implementers in achieving a meaningful exchange of genetic testing data.

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APPENDICES

APPENDIX A

VIEW OF VEM_TETKİK

VEM_TETKIK

Oluşturma Tarihi : 09.05.2016

Kapsamı : Bu veri modeli görüntüsü hastaya sağlık tesisinde çalışılan laboratuvar tetkik tanım bilgilerini kapsar.

Hash Bilgisi : 04E25078D3219491C96619EEA7E85F3E

Veri Elemanları

Veri Modeli Elemanı Alan Adı	Veri Tipi	Açıklama	İlişkisel Alan ve Ek Açıklama
TETKIK_KODU	A()	Sağlık tesisinde yapılan tetkikler için Sağlık Bilgi Yönetim Sistemi tarafından üretilen tekil kod bilgisidir.	
REFERANS_TABLO_ADI	A()	Görüntünün tekil kod bilgisinin alındığı SBYS veri tabanındaki tablo adının bilgisidir.	
TETKIK_ADI	A()	Kişinin hastalığı veya durumu ile ilgili tanı ve tedaviye karar verme amacıyla yapılan veya yapılması istenen tetkikin adı bilgisidir.	
LOINC_KODU	A()	LOINC, Sağlık tesisinde laboratuvar veya radyolojik tetkik sonuçlarının sınıflandırılması için geliştirilmiş bir sınıflandırma sistemidir. LOINC kodu ile her bir tetkik tekil olarak tanımlanabilmektedir.	
HIZMET_KODU	A()	Sağlık tesisinde hastaya uygulanan işlemler için Sağlık Bilgi Yönetim Sistemi tarafından üretilen tekil kod bilgisidir.	VEM_HIZMET görüntüsündeki HIZMET_KODU bilgisidir.
RAPOR_SONUC_SIRASI	A()	Hastaya verilen tetkik sonuç raporunda tetkik veya parametrenin bulunduğu sıra bilgisidir.	
IPTAL_DURUMU	Tam Sayı	Sağlık tesisinde yapılan bir işlemin iptal edilip edilmediği bilgisidir.	İptal edilmişse "1", edilmemişse "0" yazılmalıdır.
HESAPLAMALI_TETKIK_BILGISI	Tam Sayı	Laboratuvarda yapılan tetkikler için özel bir hesaplama yöntemi kullanılıp kullanılmadığını ifade eder.	Hesaplamalı tetkik ise "1", değilse "0" yazılmalıdır.
HESAPLAMALI_TETKIK_FORMULU	A()	Laboratuvarda yapılan tetkikler için özel bir hesaplama yöntemi kullanılması durumunda kullanılan hesaplama yöntemi (formül) bilgisidir.	
KAYIT_ZAMANI	Tarih Saat	Sağlık tesisinde üretilen verinin Sağlık Bilgi Yönetim Sistemine ilk defa kayıt edildiği zaman bilgisidir.	Tetkik bilgisinin ilk kayıt edildiği zaman bilgisidir.
EKLEYEN_KULLANICI_KODU	A()	Sağlık Bilgi Yönetim Sistemi üzerinde kayıt edilen bilgilere ilişkin kayıt işlemini gerçekleştiren kullanıcı için Sağlık Bilgi Yönetim Sistemi tarafından üretilen tekil kod bilgisidir.	VEM_KULLANICI görüntüsündeki KULLANICI_KODU bilgisidir.
GUNCELLEME_ZAMANI	Tarih Saat	Sağlık Bilgi Yönetim Sistemi üzerinde kayıtlı bilgilere ilişkin güncelleme işleminin yapıldığı zaman bilgisidir.	
GUNCELLEYEN_KULLANICI_KODU	A()	Sağlık Bilgi Yönetim Sistemi üzerinde kayıtlı bilgilere ilişkin güncelleme işlemini gerçekleştiren kullanıcı için Sağlık Bilgi Yönetim Sistemi tarafından üretilen tekil kod bilgisidir.	VEM_KULLANICI görüntüsündeki KULLANICI_KODU bilgisidir.

APPENDIX B

DOCUMENTS RELATED TO INTERVIEW

Araştırmaya Gönüllü Katılım Formu

Bu araştırma, ODTÜ Tıp Bilişimi Bölümü doktora öğrencisi Ayhan Serkan ŞIK ve tez danışmanı ODTÜ Tıp Bilişimi Bölümü Öğretim Üyesi Doç. Dr. Yeşim Aydın SON tarafından yürütülen bir çalışmadır. Bu form sizi araştırma koşulları hakkında bilgilendirmek için hazırlanmıştır.

Çalışmanın Amacı Nedir? Araştırmanın amacı, Türkiye'deki Elektronik Sağlık Kayıtlarında (diğer ismiyle SağlıkNET'te) bulunmayan genetik test istem ve sonuç kayıtlarının ESK'ya entegrasyonu için gereken Minimum Sağlık Veri Setlerinin belirlenmesi ve bunun örnek bir uluslararası standartta uygulamasının gösterilmesidir. Araştırmaya katılmayı kabul ederseniz, size ileteceğim sorulara yanıt vermenizi rica edeceğim.

Bize Nasıl Yardımcı Olmanızı İsteyeceğiz? Size ileteceğim sorular aracılığı ile alanınızdaki ihtiyaçları belirlemeye çalışacağım. Ayrıca sizin tecrübeleriniz ile genetik testler için bir Minimum Sağlık Veri Seti tanımlayabilecek ve bunun sayesinde genetik testleri Elektronik Sağlık Kayıtlarına (SağlıkNET'e) entegre etmek üzere bir model oluşturabileceğim.

Sizden Topladığımız Bilgileri Nasıl Kullanacağız? Araştırmaya katılımınız tamamen gönüllülük temelinde olmalıdır. Ankette, sizden kimlik veya kurum belirleyici hiçbir bilgi istenmemektedir. Cevaplarınız tamamıyla gizli tutulacak, sadece araştırmacılar tarafından değerlendirilecektir. Katılımcılardan elde edilecek bilgiler toplu halde değerlendirilecek ve bilimsel yayımlarda kullanılacaktır. Sağladığınız veriler gönüllü katılım formlarında toplanan kimlik bilgileri ile eşleştirilmeyecektir.

Katılımınızla ilgili bilmeniz gerekenler: Katılımınız ile sizlere risk oluşturabilecek herhangi bir veri gizlemesi ya da ifşası yapılmayacaktır. Katılım sırasında sorulardan ya da herhangi başka bir nedenden ötürü kendinizi rahatsız hissederseniz cevaplama ve ses kaydı alınması işini yarıda bırakıp çıkmakta serbestsiniz. Böyle bir durumda çalışmayı uygulayan kişiye, çalışmadan çıkmak

istediğinizi söylemek yeterli olacaktır. Çalışma sonunda, bu araştırmayla ilgili sorularınız cevaplanacaktır.

Araştırmayla ilgili daha fazla bilgi almak isterseniz: Bu çalışmaya katıldığınız için şimdiden teşekkür ederiz. Araştırma hakkında daha fazla bilgi almak için ODTÜ Tıp Bilişimi Bölümü öğretim üyelerinden, tez danışmanım Doç. Dr. Yeşim Aydın Son (E-posta: yesim@metu.edu.tr) ile iletişim kurabilirsiniz.

Yukarıdaki bilgileri okudum ve bu çalışmaya tamamen gönüllü olarak katılıyorum.

(Formu doldurup imzaladıktan sonra uygulayıcıya geri veriniz).

İsim Soyad	Tarih	İmza
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TÜRKİYE'DE GENETİK TESTLERİN ELEKTRONİK SAĞLIK KAYITLARINA ENTEGRASYONU

Ayhan Serkan ŞIK

<u>Tez Başlığı</u>: Türkiye'deki Genetik Bilgi Değişimi Kodlama Standartları İçin Kavramsal Bir Tasarım

Türkiye'deki Elektronik Sağlık Kayıtlarında (ESK) **– diğer bir isimle, SağlıkNET'te –** genetik test kayıtları, uluslararası standartlara uygun şekilde tutulmamaktadır. Temelde bunun sebebi kayıtların hastalık bazlı tutulmasıdır. Zaten ESK'da halihazırda kullanılan uluslararası standartta da (ICD-10 kodlama sistemi, International Code of Diseases) genetik test kodları bulunmamaktadır.

Bunun yanı sıra, devlet tarafından geri ödemesi yapılan (SUT – Sağlık Uygulama Tebliği uyarınca ve içindeki kodlanmış uygulamalara para ödeniyor sadece) sadece 71 adet genetik test bulunmaktadır ve bunların geri ödeme kayıtlarında kodları – idiosyncratic – "nev-i şahsına münhasırdır". Uluslararası geçerliliği olan bir kodlama sistemi değildir.

Artan genetik test çeşitleri ve sonuçları, bu testlerin uluslararası standartlara uygun, yapısal (structured) bir şekilde saklanmasını zorunlu hale getirmiştir. Test sonuçları ne kadar aynı dili konuşacak şekilde tutulursa o kadar anlaşılabilir ve bu sonuçlardan o kadar derin sonuçlar çıkarılabilir olur. Hastalık dağılımları, olası genetik hastalık takipleri, kişiye özel ilaç vb. konularda daha etkin yol alınabilir.

Pek çok ülkede olduğu gibi, Türkiye'de de ESK yapılandırılırken USVS (Ulusal Sağlık Veri Sözlüğü) oluşturulmuştur. Hastalıkları belirlemekte kullanılan minimum veri elemanları belirlenerek, bunların uluslararası veri standartlarına uygulanmasıyla ESK ortaya çıkmıştır. USVS'nin amacı, karşılıklı olarak tüm paydaşların (istemci/ler, sunucu/lar vs) aynı anlamdaki veriyi, aynı amaç için kullanılabilmesidir. Veri toplamada kullanılan veri gruplarına "Minimum Sağlık Veri Seti - MSVS" denmektedir. Minimum Sağlık Veri Setleri Sağlık Bakanlığı tarafından sağlık politikaları belirlenirken kullanılmaktadır.

Yukarıdaki paragrafta bahsettiğim MSVS'ler, genetik testler için bulunmamaktadır. Bu eksiklik de, hem sağlık sistemindeki genetik kayıtçılıkta, hem de genetik test sonuçlarına göre Sağlık Bakanlığı'nın sağlık politikalarını belirlemesinde büyük eksiklikler oluşturmaktadır.

Bu tez kapsamında amacım, Türkiye'de yapılan genetik testlerin SağlıkNET/ESK'ya yapısal bir şekilde entegre edilebilmesi için gereken Minimum Sağlık Veri Setlerini (MSVS) belirlemek ve örnek bir uluslararası standart ile bunun kavramsal bir modelini oluşturmaktır.

Orta Doğu Teknik Üniversitesi

İnsan Araştırmaları Etik Kurulu (İAEK)'ya Teslim Edilip Onaylanmış

Ayhan Serkan ŞIK Tarafından Hazırlanan Mülakat Soruları

SORULAR:

1. Kurumunuzda genetik test kayıtlarını nasıl tutuyorsunuz?

    a. Kağıt bazlı mı? Elektronik ortamda mı? Nasıl yedekliyorsunuz?
    b. Verileriniz yapısal mı (structured data)? Verilerinizi sadece metin bazlı yorum şeklinde mi saklıyor ve sunuyorsunuz?
    c. Verileri saklarken ya da sunarken uyguladığınız veri standartlarınız var mı? Varsa uluslararası standartlardan birini mi kullanıyorsunuz (standardın ismi?) yoksa kendi belirlediğiniz bir kodlama standardınız mı var? (Örneğin SUT: Sağlık Uygulama Tebliği). Bir diğer tercih olarak her iki yöntemi de uyguluyor musunuz?

2. Genetik test yapılan hastalarda hangi verileri (ham, analiz sonucu, hasta raporu) ne kadar süre ile saklıyorsunuz, bu konuda sıkıntılarınız, endişeleriniz var mı? Varsa nelerdir ?

3. Pedigree/soy ağacı ve bunun önemi hakkında düşünceniz nedir?

    a. Aile hikayesi sayesinde yaptırdığınız testler ve yakaladığınız vakalar var mı?
    b. Genetik test isteminizde ve sonuç değerlendirmenizde pedigree önemli mi?
    c. Pedigree kayıtlarını nasıl tutuyorsunuz? Dijital araçlardan faydalanıyor musunuz? (Cevabınız evet ise kullandığınız yazılımın ismi?)

4. Pedigree ve genetik test kayıtlarını mahremiyet açısından değerlendirir misiniz? Çekinceleriniz var mı? Varsa nelerdir? Sizce mahremiyet nasıl korunabilir? Pedigree bilgileri paylaşılmadan önce kişi nasıl bilgilendirilmelidir? Bu bilgilerin

    a. Yerel olarak saklanması ve
    b. SağlıkNET'de saklanması

    arasında bir fark görüyor musunuz? Çekinceleriniz ya da farklı yerlerde saklanması konusundaki görüşleriniz nelerdir?

5. Genetik testlerin Elektronik Sağlık Kayıtlarına entegrasyonu hakkında ne düşünüyorsunuz? Görüşünüz olumlu ise, nasıl bir yol haritası izlenmeli? Olumsuz ise öngördüğünüz sakıncalar nelerdir?

6. Elektronik Sağlık Kayıtları ve genetik test entegrasyonunda öncelikle hangi verileri ayrıştırıp Elektronik Sağlık Kayıtlarında bulundurmamız gerekiyor? Bu minimum veri elemanlarını belirtebilir misiniz?

7. Genetik testlerin Elektronik Sağlık Kayıtlarına entegrasyonu sürecinde hangi uluslararası standart kullanılmalı? Ulusal Sağlık Veri Sözlüğündeki gibi, genetik testler için Minimum Veri Seti nasıl oluşturulabilir ve neler göz önünde bulundurulmalıdır?

8. Her genetik test Elektronik Sağlık Kayıtlarında olmalı mıdır? Hangi genetik testler Elektronik Sağlık Kayıtlarında olmalıdır? Bu testleri belirlerken neleri göz önünde bulundurmamız gerekir?

    a. Geçerlilik
    b. Kullanılabilirlik
    c. İstenen amaç
    d. Tuttuğunuz kayıtlarda "onaylı-onaysız test" farkı

    konuları göz önünde bulundurulmalı mıdır?

9. Bu test sonuçları ne şekilde kayıtlarda yer almalı?

    a. Tüm sonuç olarak mı? Neden?
    b. Sadece test sonucunda sizlerin yaptığınız yorumlarınız mı? Neden?
    c. Hangi minimum veriler olmalı?
    d. Genetik test sonuçlarını belirleyici minimum veri seti var mı?
    e. Etik, genetik ve teknolojik yaklaşım nasıl olmalı?

10. Elektronik Sağlık Kayıtlarındaki normal klinik veri ile genetik veri sınıflandırması ve yönetimi; test riskleri açısı gözetilerek mi oluşturulmalı? Yani kişisel, sosyal, profesyonel, finansal ve sigortacılık açısından nasıl bir korunma yapısı olmalı?

11. Kişiselleştirilmiş tıpta yeri ve faydası olacağı hakkındaki görüşleriniz nelerdir?

Middle East Technical University

About to be Submitted to the Human Research Ethics Committee (İAEK) and Approved

Interview Questions Prepared by Ayhan Serkan ŞIK

QUESTIONS:

1. How do you keep genetic test records at your institution?

a. Is it paper-based or digital? How do you back it up?
b. Is your data structured? Do you store and present your data only in the form of text-based comments?
c. Do you apply any data standards when storing or presenting data? If yes, are you using one of the international standards (name of the standard?), or do you have a coding standard that you set yourself? (For example, MED: Medical Enforcement Declaration). As another choice, do you apply both methods?

2. Which type of data (raw, analysis result, patient report) and for how long do you keep the genetic test of patients? Do you have complaints or concerns in this regard? If yes, what are they?

3. What is your opinion about the pedigree?

a. Are there any tests you order and/or cases you diagnose thanks to the pedigree?
b. Is pedigree important in your genetic test request and result evaluation?
c. How do you keep Pedigree records? Do you take advantage of digital tools? (If your answer is yes, the name of the software you use?)

4. Can you command on pedigree and genetic test records for privacy? Do you have any reservations? If yes, what are they? How do you think privacy can be protected? How should the person be informed before pedigree information is shared? Do you think there is a difference between whether to store pedigree and genetic test data

a. Locally or
b. National Health Information System-Türkiye (NHIS-T)

What are your reservations or your opinions about storing in different locations?

5. What do you think about the integration of genetic tests into Electronic Health Records? If your opinion is positive, what kind of road map should be followed? If it is negative, what are the drawbacks that you foresee?

6. During the integration of genetic test with Electronic Health Records, what type of data should we store in the Electronic Health Records? Can you specify these minimum data elements?

7. Which international standard should be used in the process of integrating genetic tests into Electronic Health Records? How can the Minimum Data Set for genetic testing be created and what should be considered, as in the National Health Data Dictionary?

8. Should every genetic test be in the Electronic Health Records? What genetic tests should be in the Electronic Health Records? Should we always consider the facts listed while determining these tests?

    a. Validity
    b. Usability
    c. Desired purpose
    d. "Approved-unapproved test" difference in the records you keep

9. How should these test results be included in the records?

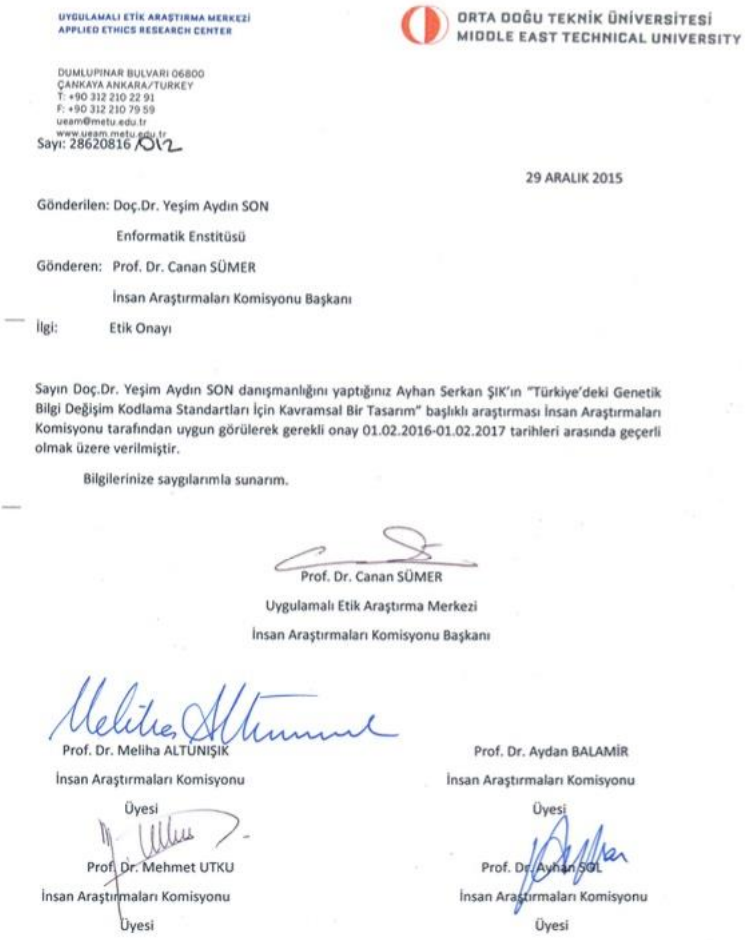
    a. Whole genetic test result? Why?
    b. Only your comments about the test result? Why?
    c. What minimum data should there be?
    d. Is there a minimum data set to determine the genetic test results?
    e. How should an ethical, genetic, and technological approach be?

10. Classification and management of normal clinical data and genetic data in Electronic Health Records; Should it be created by considering the test risks? What kind of protection structure should it have in terms of personal, social, professional, financial and insurance?

11. What are your opinions on genetic testing in terms of precision and personalized medicine?

APPENDIX C

Approval Form of METU "Human Subjects Ethics Committee



UYGULAMALI ETİK ARAŞTIRMA MERKEZİ
APPLIED ETHICS RESEARCH CENTER

ORTA DOĞU TEKNİK ÜNİVERSİTESİ
MIDDLE EAST TECHNICAL UNIVERSITY

DUMLUPINAR BULVARI 06800
ÇANKAYA ANKARA/TURKEY
T: +90 312 210 22 91
F: +90 312 210 79 59
ueam@metu.edu.tr
www.ueam.metu.edu.tr

Sayı: 28620816 /012

29 ARALIK 2015

Gönderilen: Doç.Dr. Yeşim Aydın SON
Enformatik Enstitüsü

Gönderen: Prof. Dr. Canan SÜMER
İnsan Araştırmaları Komisyonu Başkanı

İlgi: Etik Onayı

Sayın Doç.Dr. Yeşim Aydın SON danışmanlığını yaptığınız Ayhan Serkan ŞIK'ın "Türkiye'deki Genetik Bilgi Değişim Kodlama Standartları İçin Kavramsal Bir Tasarım" başlıklı araştırması İnsan Araştırmaları Komisyonu tarafından uygun görülerek gerekli onay 01.02.2016-01.02.2017 tarihleri arasında geçerli olmak üzere verilmiştir.

Bilgilerinize saygılarımla sunarım.

Prof. Dr. Canan SÜMER
Uygulamalı Etik Araştırma Merkezi
İnsan Araştırmaları Komisyonu Başkanı

Prof. Dr. Meliha ALTUNIŞIK
İnsan Araştırmaları Komisyonu
Üyesi

Prof. Dr. Aydan BALAMİR
İnsan Araştırmaları Komisyonu
Üyesi

Prof. Dr. Mehmet UTKU
İnsan Araştırmaları Komisyonu
Üyesi

Prof. Dr. Ayhan SOL
İnsan Araştırmaları Komisyonu
Üyesi

APPENDIX D

Annex B:

A. HIC Transaction Code, name, constraints, and scores of genetic testing transactions under reimbursement coverage in Türkiye (Annulled)

ANNULED			
Transaction Code	**9.A. MOLECULAR MICROBIOLOGY**	**In this group of transactions, all steps needed to achieve the result are included in the price. It is invoiced with the printed result document. Unless otherwise stated, the procedures under this heading are covered if requested by tertiary healthcare providers or specialists in gastroenterology, infectious diseases, paediatric health and diseases, internal diseases, and chest diseases.**	**Score**
908115	Covid-19 (SARS-CoV-2) Reverse Transcriptase PCR	During the pandemic, it is reimbursed by all branches upon request.	183,65
908116	Covid-19 (SARS-CoV-2) Isolation	It is not billed together with transaction 906300. It is billed together with transaction 908115.	23,07
908120	Candida PCR		173,03
908130	Chlamydia PCR		138,34

908140	CMV PCR		207,52
908150	HBV-DNA, quantitative		207,52
908160	HCV genotyping		203,28
908170	HCV-RNA, quantitative		207,52
908171	HDV-RNA, quantitative		208,13
908180	Helicobacter PCR		173,03
908190	Hepatitis G PCR		173,03
908200	Herpes PCR (Each)		173,03
908210	HIV PCR		173,03
908220	HIV RNA, quantitative		207,52
908230	Human papilloma virus (HPV)		121,20
908240	Cell cycle and DNA panel		121,20
908250	In situ hybridization and in situ PCR assays, per test		52,03
908280	Legionella PCR		138,34
908290	Mycobacteria (PCR)		173,03
908300	Mycobacteria typing (PCR)		173,03
908310	Leukocyte subgroup purification prior to molecular analysis, each group		121,20
908320	Mycoplasma PCR		173,03
908330	Parvovirus PCR		173,03
908340	Detecting CMV in CSF using PCR-microwell hybridization method		121,20
908350	Detecting EBV in CSF using PCR-microwell hybridization method		121,20
908360	Detecting HSV-1 in CSF using PCR-microwell hybridization method		121,20

908370	Detecting HSV-2 in CSF using PCR-microwell hybridization method		121,20
908380	Detecting HSV-6 in CSF using PCR-microwell hybridization method		121,20
908390	Detecting VZV in CSF using PCR-microwell hybridization method		121,20
908400	Transformation with Con A		10,41
908410	Transformation with PHA		10,41
908420	Transformation with PPD		8,77
908430	Transformation with tetanus toxin		5,31
	9.B. CYTOGENETIC EXAMINATIONS	**All stages are included. See HIC Article: 2.4.4.G-1.**	
908441	Chromosome analysis from amniotic fluid		489,71
908451	Chromosome analysis from abortion material/ Gonad biopsy/other tissues		387,69
908461	Chromosome analysis from fetal blood		367,28
908471	Chromosome analysis from bone marrow (including direct/24,48,72 and 96-hour culture studies)		367,28
908481	Chromosome analysis from chorionic villus sample (including direct/at least two cultures, banding and at least 20 metaphase analysis)		530,52
908491	Chromosomal analysis for chromosomal breakage syndromes and mutagenicity studies	It is not billed together with 908501.	326,48
908501	Chromosome analysis from peripheral blood	It is not billed together with 908491.	244,86

	9.C. MOLECULAR EXAMINATIONS	**All stages and all probes are included. Codes under this heading are not billed with each other, except for preimplantation genetic tests, prenatal genetic tests, haematological malignancies, examinations performed on recipient and donor candidates to be transplanted in health care providers with organ and tissue transplantation centres. Except for the obligations related to medical indications, DNA tests performed voluntarily by the person is not covered by the Institution. See HIC Article: 2.4.4.G-2.**	
908711	Blot analysis (southern, northern, western)	Billed only for one.	255,06
908712	DNA sequence analysis 1 reaction	Billed only for one.	142,83
908713	DNA sequence analysis 1-5 reactions	Billed only for one.	367,28
908714	DNA sequence analysis 1-10 reactions	Billed only for one.	652,95
908715	DNA sequence analysis 1-15 reactions	Billed only for one.	1.020,24
908716	DNA sequence analysis 1-20 reactions	Billed only for one.	1.428,33
908717	DNA sequence analysis 21 or more reactions	Billed only for one.	2.244,51
908718	FISH (up to 2 regions)	Billed only for one.	346,88
908719	FISH (up to 4 regions)	Billed only for one.	408,09
908720	FISH (up to 6 regions)	Billed only for one.	612,14
908721	FISH (up to 12 regions)	Billed only for one.	1.020,24
908722	FISH (up to 16 regions)	Billed only for one.	1.428,33
908723	FISH (up to 24 regions)	Billed only for one.	1.632,38
908724	MLPA	Billed only for one.	244,86
908725	PCR	Billed only for one.	81,62
908726	PCR Multiplex	Billed only for one.	204,05
908727	Real-time PCR 1 reaction	Billed only for one.	183,64

908728	Real-time PCR 1-5 reactions	Billed only for one.	285,67
908729	Real-time PCR 1-10 reactions	Billed only for one.	367,28
908730	Real-time PCR 11 and above reaction	Billed only for one.	448,90
908731	Reverse Transcriptase-PCR	Billed only for one.	265,26
908732	Reverse Transcriptase PCR Multiplex	Billed only for one.	448,90
908733	RFLP 1 enzyme	Billed only for one.	91,82
908734	RFLP 2 and above	Billed only for one.	163,24
908735	Reverse Dot Blot (1-5 mutations)	Billed only for one.	163,24
908736	Reverse Dot Blot (for 1-12 mutations)	Billed only for one.	204,05
908737	Reverse Dot Blot (for 13 or more mutations)	Billed only for one.	244,86
908738	STR analysis (for 1-5 STR range)	Billed only for one.	285,67
908739	STR analysis (for 1-8 STR range)	Billed only for one.	367,28
908740	STR analysis (for 1-16 STR range)	Billed only for one.	612,14
908741	STR analysis (for STR range 17 and above)	Billed only for one.	714,17
908742	Microarray	Billed only for one. It includes genome-wide SNP and CNV analysis at a resolution of at least 180 K and above.	847,00
908743	Molecular Karyotyping	Billed only for one. Includes genome-wide CNV analysis with at least 60K resolution.	514,25
908744	Thrombophilia panel	This test is billed for mutations in thrombophilia genes (Factor II-V-XIII, MTHFR, PAI). In case of mutation, other molecular tests are not billed for the patient.	285,67
908745	FMF/MEFV gene target region/mutation analysis	This assay is billed for FMF/MEFV gene mutations. In case of mutation, other molecular tests are not billed for the patient.	367,28

908746**(Annex: RG-11/08/2021-31565/10-c art. Effective: 11/08/2021)**	Preimplantation Genetic Diagnostic Examinations for the birth of a stem cell donor sibling	See HIC Article: 2.4.4.I-2. Each trial is billed once. HLA tissue compatibility tests are included. It is billed if performed in the Genetic Diseases Assessment Centre authorized by the Ministry of Health.	9.831,47
908747**(Annex: RG-11/08/2021-31565/10-c art. Effective: 11/08/2021)**	Preimplantation Genetic Diagnostic Tests aimed at giving birth to a healthy child	See HIC Article: 2.4.4.I-3. Each trial is billed once. It is billed if performed in the Genetic Diseases Assessment Centre authorized by the Ministry of Health.	9.274,87

B. Recent HIC Transaction Code, name, constraints, and scores of genetic testing transactions under reimbursement coverage in Türkiye. For relevant HIC item numbers at transaction group constraint definitions, please refer to Appendix E.

CURRENT			
Transaction Code	**9.A. MOLECULAR MICROBIOLOGY**	**In this group of transactions, all steps needed to achieve the result are included in the price. It is invoiced with the printed result document. Unless otherwise stated, the procedures under this heading are covered if requested by tertiary healthcare providers or specialists in gastroenterology, infectious diseases, paediatric health and diseases, internal diseases, and chest diseases.**	**Score**
908115	Covid-19 (SARS-CoV-2) Reverse Transcriptase PCR	During the pandemic, it is reimbursed by all branches upon request.	257,11
908116	Covid-19 (SARS-CoV-2) Isolation	It is not billed together with transaction 906300. It is billed together with transaction 908115.	32,29
908120	Candida PCR		242,24
908130	Chlamydia PCR		193,67
908140	CMV PCR		290,52
908150	HBV-DNA, quantitative		290,52
908160	HCV genotyping		284,59
908170	HCV-RNA, quantitative		290,52
908171	HDV-RNA, quantitative		291,38

908180	Helicobacter PCR		242,24
908190	Hepatitis G PCR		242,24
908200	Herpes PCR (Each)		242,24
908210	HIV PCR		242,24
908220	HIV RNA, quantitative		290,52
908230	Human papilloma virus (HPV)		169,68
908240	Cell cycle and DNA panel		169,68
908250	In situ hybridization and in situ PCR assays, per test		72,84
908280	Legionella PCR		193,67
908290	Mycobacteria (PCR)		242,24
908300	Mycobacteria typing (PCR)		242,24
908310	Leukocyte subgroup purification prior to molecular analysis, each group		169,68
908320	Mycoplasma PCR		242,24
908330	Parvovirus PCR		242,24
908340	Detecting CMV in CSF using PCR-microwell hybridization method		169,68
908350	Detecting EBV in CSF using PCR-microwell hybridization method		169,68

908360	Detecting HSV-1 in CSF using PCR-microwell hybridization method		169,68
908370	Detecting HSV-2 in CSF using PCR-microwell hybridization method		169,68
908380	Detecting HSV-6 in CSF using PCR-microwell hybridization method		169,68
908390	Detecting VZV in CSF using PCR-microwell hybridization method		169,68
908400	Transformation with Con A		14,57
908410	Transformation with PHA		14,57
908420	Transformation with PPD		12,27
908430	Transformation with tetanus toxin		7,43
	9.B. CYTOGENETIC EXAMINATIONS	**All stages are included. See HIC 2.4.4.G-1.**	
G100000	Chromosome Analysis, Amniotic fluid	Billed once per six months.	587,65
G100010	Chromosome Analysis, Abortion material/Gonad biopsy/Other tissue	Billed once per six months.	465,22
G100020	Chromosome Analysis, Fetal blood	Billed once per six months.	440,74
G100030	Chromosome Analysis, Bone marrow	Billed once per three months. Direct/24,48,72, and 96-hour culture studies are included.	440,74
G100040	Chromosome Analysis, Chorionic villus	Billed once per six months. Includes direct/at least two cultures, banding and at least 20 metaphase analysis.	636,62
G100050	Chromosome Analysis, Chromosomal Fracture Syndromes and Mutagenicity Studies	Billed once per six months. It is not billed together with the G100060.	391,77
G100060	Chromosome Analysis, Peripheral blood	Billed once per six months. It is not billed together with the G100050.	293,82

	9.B.1. MOLECULAR CYTOGENETIC ASSESSMENTS	**All stages and all probes are included. Codes under this heading are not billed with each other, except for preimplantation genetic tests, prenatal genetic tests, haematological malignancies, examinations performed on recipient and donor candidates to be transplanted in health care providers with organ and tissue transplantation centres. Except for the obligations due to medical indications, the examinations performed on the person's request are not covered by the Institution. See HIC 2.4.4.G-1.**	
G100080	FISH, 1-2 genetic loci	Billed once per ten days. The genetic locus studied should be specified.	346,88
G100090	FISH, 3-4 genetic loci	Billed once per ten days. The genetic locus studied should be specified.	408,09
G100100	FISH, t(4;14) (p16;q32) (FGFR3/IGH)	Billed once per ten days.	346,88
G100110	FISH, t(8;21) (q22;q22) (RUNX1/RUNX1T1) (AML/ETO)	Billed once per ten days.	346,88
G100120	FISH, t(9;22) (q34;q11.2) (BCR/ABL) (Standard)	Billed once per ten days.	346,88
G100130	FISH, t(11;14) (q13;q32) (CCND1/IGH)	Billed once per ten days.	346,88
G100140	FISH, t(12;21) (p13;q22) (ETV6/RUNX1) (TEL/AML1)	Billed once per ten days.	346,88
G100150	FISH, t(15;17) (q22;q21) (PML/RARA)	Billed once per ten days.	346,88
G100160	FISH, 5q deletion (5q31; 5q33) (5q-)	Billed once per ten days.	346,88
G100170	FISH, 7q11.23 deletion (Williams Syndrome)	Billed once per ten days.	346,88
G100180	FISH, deletion 7q31	Billed once per ten days.	346,88
G100190	FISH, 7q- (7q22; 7q36)/SE7 TC	Billed once per ten days.	346,88
G100200	FISH, 11q22.3 deletion (ATM)	Billed once per ten days.	346,88
G100210	FISH, 13q14.2 deletion (RB1)	Billed once per ten days.	346,88
G100220	FISH, 17p13.1 deletion (p53)	Billed once per ten days.	346,88
G100230	FISH, 20q deletion (20q-)	Billed once per ten days.	346,88
G100240	FISH, CBFB t(16;16), inv(16) Break	Billed once per ten days.	346,88
G100250	FISH, IGH (14q32.33) Break	Billed once per ten days.	346,88

G100260	FISH, MLL (11q23.3) Break (KMT2A Break)	Billed once per ten days.	346,88
G100270	FISH, DiGeorge (N25) Syndrome	Billed once per ten days.	346,88
G100280	FISH, FGFR2-FGRFR3 Gene Fusions	Billed once per ten days.	346,88
G100290	FISH, SHOX (del Xpter-p22.32)	Billed once per ten days.	346,88
G100300	FISH, Trisomy/Monosomy 8 (CEP 8) (SE 8) (Centromere 8)	Billed once per ten days.	346,88
G100310	FISH, Trisomy/Monosomy 12 (CEP 12) (SE 12) (Centromere 12)	Billed once per ten days.	346,88
	9.C. MOLECULAR GENETIC EXAMINATIONS	**All stages are included. Codes under this heading are not billed with each other, except for preimplantation genetic tests, prenatal genetic tests, haematological malignancies, examinations performed on recipient and donor candidates to be transplanted in health care providers with organ and tissue transplantation centres. Except for the obligations due to medical indications, the examinations performed on the person's request are not covered by the Institution. See HIC 2.4.4.G-2.**	
G100330	Blot Analysis (southern, northern, western)	Billed once per ten days.	255,05
G100340	Real-Time PCR, 1 reaction	Billed once per ten days. The name of the gene studied should be indicated.	183,64
G100350	Real-Time PCR, 2-5 reactions	Billed once per ten days. The name of the gene studied should be indicated.	285,66
G100360	Real-Time PCR, 6-10 reactions	Billed once per ten days. The name of the gene studied should be indicated.	367,28
G100370	Conventional (Sanger) DNA Sequencing, 1 reaction	Billed once per ten days. The name of the gene studied should be indicated. This is not billed together with G100380, G100390, G100400, G100410, G100420, G100430, G101830, G101840, G101850, G101860 and G101870.	142,82

G100380	Conventional (Sanger) DNA Sequencing, 2-5 reactions	Billed once per ten days. The name of the gene studied should be indicated. This is not billed together with G100370, G100390, G100400, G100410, G100420, G100430, G101830, G101840, G101850, G101860 and G101870.	367,28
G100390	Next Generation DNA Sequencing, 1 Gene	Billed once per ten days. The diagnosis and the name of the gene studied should be stated. Each gene is billed once per lifetime. This is not billed with G100370, G100380, G101830, G101840, G101850, G101860 and G101870.	842,25
G100400	Next Generation DNA Sequencing Panel, 2-4 Genes	Billed once per ten days. The diagnosis and the name of the gene studied should be stated. Each gene is billed once per lifetime. This is not billed together with G100370, G100380, G101830, G101840, G101850, G101860, or G101870.	1.259,19
G100410	Next Generation DNA Sequencing Panel, 5-15 Genes	Billed once per ten days. The diagnosis and the name of the gene studied should be stated. Each gene is billed once per lifetime. This is not billed together with G100370, G100380, G101830, G101840, G101850, G101860, or G101870.	1.785,60
G100420	Next Generation DNA Sequencing Panel, 16-40 Genes	Billed once per ten days. The diagnosis and the name of the gene studied should be stated. Each gene is billed once per lifetime. This is not billed with G100370, G100380, G101830, G101840, G101850, G101860, or G101870.	2.497,50
G100430	Next Generation DNA Sequencing Panel, 41 Genes and above	Billed once per ten days. The diagnosis and the name of the gene studied should be stated. Each gene is billed once per lifetime. This is not billed together with G100370, G100380, G101830, G101840, G101850, G101860, or G101870.	3.500,00
G100440	MLPA	Billed once per ten days. The diagnosis and the name of the gene studied should be stated. Each gene is billed once per lifetime.	612,14
G100450	MLPA, BRCA1-2	Billed once per lifetime.	612,14
G100460	MLPA, CFTR	Billed once per lifetime.	612,14
G100470	MLPA, CMT (for PMP22 gene)	Billed once per lifetime.	612,14

G100480	MLPA, CYP21A2 (MLPA - CAH)	Billed once per lifetime.	612,14
G100490	MLPA, DMD	Billed once per lifetime. This test is billed for DMD/BMD. In case of mutation is observed, other molecular tests related to the same disease are not billed for the patient.	612,14
G100500	MLPA, SMA	Billed once per lifetime.	612,14
G100510	5-Alpha Reductase Deficiency (SRD5A2 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100520	21-Hydroxylase Deficiency (CYP21A2 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100530	ABL1 Gene T315I Mutation Analysis	Billed once per ten days.	183,64
G100540	ABL1 Gene Sequence Analysis	Billed once per ten days.	842,25
G100550	Adenosine Deaminase Deficiency (ADA Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100560	Severe Combined Immunodeficiency Panel (16-40 Genes)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. The diagnosis and the name of the genes studied should be stated.	2.497,50
G100570	Familial Adenomatosis Polyposis Coli (APC Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100580	Familial Breast/Ovarian Cancer (BRCA1 and BRCA2 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	1.259,19
G100590	Achondroplasia Disease (FGFR3- G380R Variant Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. This examination is billed for achondroplasia disease. In case of mutation, other molecular tests related to the same disease are not billed for the patient.	142,82
G100600	Alpha Thalassemia (Deletion Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. This examination is billed for alpha thalassemia disease. In case of mutation, other molecular tests related to the same disease are not billed for the patient.	244,85

G100610	Alpha Thalassemia (HBA Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100620	Alpha-1 Antitrypsin Deficiency (SERPINA1 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100630	Alport Syndrome (COL4A3, COL4AA, COL4A5 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	1.259,19
G100640	Ankylosing Spondylitis (HLA-B27)	Billed once per lifetime.	183,64
G100650	Apert Syndrome (FGFR2 Targeted Gene Mutation Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. This examination is billed for Apert Syndrome. In case of mutation, other molecular tests related to the same disease are not billed for the patient.	183,64
G100660	Arrhythmia Panel (41 Genes and above)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. Genes covered by the panel should be noted in the report.	3.500,00
G100670	Ataxia Telangiectasia (ATM Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100680	Bardet-Biedl Syndrome Panel (16-40 genes)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. Genes covered by the panel should be noted in the report.	2.497,50
G100690	Behçet's Disease (HLA-B5)	Billed once per lifetime.	183,64
G100700	Beta Thalassemia (HBB Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100710	Biotinidase Deficiency (BTD Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100720	C-KIT (exons 9, 11, 13, 17) Mutation Analysis	Billed once per ten days.	734,56
G100730	CADASIL Disease (NOTCH3 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100740	CALR (Calreticulin) Gene Mutation Analysis	Billed once per ten days.	367,28

G100750	Charcot-Marie-Tooth Disease Panel	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. Genes covered by the panel should be noted in the report.	3.500,00
G100760	Cornelia de Lange Syndrome Panel (2-4 genes)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. Genes covered by the panel should be noted in the report.	1.259,19
G100770	Celiac Disease (HLA-DQ2, HLA-DQ8)	Billed once per lifetime.	367,28
G100780	Diabetes Insipidus (AVP Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100790	Dihydropyrimidine Dehydrogenase Deficiency (DPYD Gene Mutation Analysis)	Billed once per ten days.	367,28
G100800	Dravet Syndrome (SCN1A Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100810	Duchenne/Becker Muscular Dystrophy (DMD Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100820	Epidermolysis Bullosa Panel (16-40 Genes)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. Genes covered by the panel should be noted in the report.	2.497,50
G100830	Fabry Disease (GLA Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100840	Phenylketonuria (PAH Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100850	FGFR2 Associated Craniosynostosis (FGFR2 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100860	FGFR3 Associated Skeletal Dysplasia (FGFR3)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. This examination is billed for achondroplasia disease. In case of mutation, other molecular tests related to the same disease are not billed for the patient.	842,25
G100870	FLT3 d835/ITD (TKD/ITD) Mutation Analysis	Billed once per ten days.	183,64

G100880	FLT3 d835/ITD (TKD/ITD) Mutation Load Analysis	Billed once per ten days. The mutation load must be specified in the result report.	367,28
G100890	FMF Disease (MEFV gene) Targeted Region/Mutation Analysis	It is billed once in a lifetime. This examination is billed for FMF disease. In case of mutation, other molecular tests related to the same disease are not billed for the patient.	367,28
G100900	FMF Disease (MEFV gene Sequence Analysis)	Billed once per lifetime.	842,25
G100910	Fragile X (FMR1 Gene CGG Triple Repeat Analysis)	Billed once per lifetime.	714,16
G100920	Friedreich's Ataxia (FXN Gene GAA Triple Repeat Analysis)	Billed once per lifetime.	714,16
G100930	Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100940	GLUT1 Deficiency (SLC2A1 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100950	Hemochromatosis (HFE Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100960	Hemophilia A (F8 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100970	Hemolytic Uremic Syndrome (CFH Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100980	Hereditary Spastic Paraplegia 4 (SPG4 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G100990	Hereditary Spastic Paraplegia Panel (41 Genes and above)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. Genes covered by the panel should be noted in the report.	3.500,00
G101000	Huntington's Disease (HTT gene CAG Triple Repeat Analysis)	Billed once per lifetime.	285,66
G101010	Somatic Mutation Panel from Extracellular Free DNA, 1-4 Genes	Billed once per six months. A medical board report with at least one medical geneticist and medical oncologist is required. The report should include genomic changes related to susceptibility and resistance to current treatments. The name of the gene studied should be indicated.	1.050,72

G101020	Somatic Mutation Panel from Extracellular Free DNA, 5-15 Genes	Billed once per six months. A medical board report with at least one medical geneticist and medical oncologist is required. The report should include genomic changes related to susceptibility and resistance to current treatments. The name of the gene studied should be indicated.	1.785,60
G101030	Somatic Mutation Panel from Extracellular Free DNA, 16-40 Genes	Billed once per six months. A medical board report with at least one medical geneticist and medical oncologist is required. The report should include genomic changes related to susceptibility and resistance to current treatments. The name of the studied genes should be indicated.	2.497,50
G101040	Somatic Mutation Panel from Extracellular Free DNA, 41 Genes and above	Billed once per six months. A medical board report with at least one medical geneticist and medical oncologist is required. The report should include genomic changes related to susceptibility and resistance to current treatments. The name of the studied gene should be indicated.	3.500,00
G101050	Mutation Analysis of IDH1 and IDH2 Genes	Billed once per six months.	448,89
G101060	Immunoglobulin Heavy Chain Mutation and Hypermutation Analysis (IGHV Gene)	Billed once per ten days. Billed for patients diagnosed with Chronic Lymphocytic Leukemia (CLL).	1.050,72
G101070	JAK2 Gene Exon 12 Mutation Analysis	Billed once per ten days.	367,28
G101080	JAK2 Gene V617F Mutation Analysis	Billed once per ten days.	367,28
G101090	Chimerism (Donor before bone marrow transplant)	Billed once per ten days.	612,14
G101100	Chimerism (patient before bone marrow transplant)	Billed once per ten days.	612,14
G101110	Chimerism (patient after bone marrow transplant)	Billed once per ten days.	612,14
G101120	Cystic Fibrosis (CFTR Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101130	Congenital Amegakaryocytic Thrombocytopenia (MPL Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101140	Li Fraumen Syndrome (TP53 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25

G101150	Lynch Syndrome Panel (5-15 genes)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. Genes covered by the panel should be noted in the report.	1.785,60
G101160	Marfan Syndrome (FBN1 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101170	Maternal Contamination	Billed once per ten days.	612,14
G101180	MEN Type 1 (MEN1Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101190	Metachromatic Leukodystrophy (ARSA Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101200	Microsatellite Instability Test	Billed once per six months.	842,25
G101210	Minimal Residual Disease Analysis	Billed once per ten days. It is billed if performed in centres authorized by the Ministry of Health and with the Next Generation DNA Sequencing method. A medical board report including at least one medical geneticist and paediatric haematologist is required.	4.489,02
G101220	Molecular inv 16 (p13;q22) CBFB-MYH11 Fusion Transcript Analysis	Billed once per ten days.	734,57
G101230	Molecular Karyotyping (up to 500K resolution)	Billed once per lifetime. Includes genome-wide SNP and CNV analysis at resolutions up to 500K.	1.011,00
G101240	Molecular Karyotyping (500K and above resolution)	Billed once per lifetime. It includes genome-wide SNP and CNV analysis at a resolution of at least 500 K and above.	1.215,00
G101250	Molecular Translocation Analysis, t(1:19) TCF3 (E2A)-PBX1	Billed once per ten days.	734,57
G101260	Molecular Translocation Analysis, t(4:11) AFF1 (AF4)-KMT2A (MLL;KMT2A)	Billed once per ten days.	734,57
G101270	Molecular Translocation Analysis, t(8;21)(q22;q22) AML1 (RUNX1)-ETO (RUNX1T1)	Billed once per ten days.	734,57
G101280	Molecular Translocation Analysis, t(9;22) (q34;q11.2) BCR-ABL Mbcr p190	Billed once per ten days.	734,57

G101290	Molecular Translocation Analysis, t(9;22) (q34;q11.2) BCR-ABL Mbcr p210	Billed once per ten days.	734,57
G101300	Molecular Translocation Analysis, t(9;22) (q34;q11.2) BCR-ABL Mbcr p230	Billed once per ten days.	734,57
G101310	Molecular Translocation Analysis, t(11;14) (q13;q32)	Billed once per ten days.	204,04
G101320	Molecular Translocation Analysis, t(12;21) (p12;q22) TEL-AML1	Billed once per ten days.	734,57
G101330	Molecular Translocation Analysis, t(14;18) (q32;q21)	Billed once per ten days.	285,66
G101340	Molecular Translocation Analysis, t(15;17) (q22;q21) PML-RARA bcr1/2/3	Billed once per ten days.	734,57
G101350	Mucopolysaccharidosis Plus Syndrome (VPS33A Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101360	Mucopolysaccharidosis Type 1 (IDUA Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101370	Mucopolysaccharidosis Type 2 (IDS Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101380	Mucopolysaccharidosis Type 3 (SGSH, NAGLU, HGSNAT, GNS Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	1.259,19
G101390	Mucopolysaccharidosis Type 4 (GALNS, GLB1 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	1.259,19
G101400	Mucopolysaccharidosis Type 6 (ARSB Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101410	Mucopolysaccharidosis Type 7 (GUSB Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101420	Mucopolysaccharidosis Type 9 (Hyaluronidase Deficiency, HYAL1 Gene Sequence analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101430	Mucopolysaccharidosis, Unclassified (Whole Panel)	Billed once per lifetime. Sequence analysis of all IDUA, IDS, GALNS, SGSH, NAGLU, HGSNAT, GNS, GLB1, HYAL1, ARSB, GUSB, VPS33A genes should be performed. The outcome report must specify all exons and disease-associated intronic regions.	1.785,60

G101440	Muscular Dystrophy Panel (41 Genes and above)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. Genes covered by the panel should be noted in the report.	3.500,00
G101450	Myotonia Congenita (CLCN1 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101460	Myotonic Dystrophy (DMPK Gene CTG Triple Repeat Analysis)	Billed once per lifetime.	285,66
G101470	Noonan Syndrome (PTPN11 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. For Noonan Syndrome, this examination is billed. In case of mutation, other molecular tests related to the same disease are not billed for the patient.	842,25
G101480	Noonan Syndrome Panel/RASopathy Panel (16-40 genes)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. Genes covered by the panel should be noted in the report.	2.497,50
G101490	Neurofibromatosis Type 1 (NF1 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101500	Neurofibromatosis Type 2 (NF2 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101510	Detection of Type A, B, D Mutation in NPM1 Gene Transcripts	Billed once per ten days.	285,66
G101520	Oculocutaneous Albinism Type 1A and Type 1B (TYR Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101530	Osteogenesis Imperfecta (COL1A1, COL1A2 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	1.259,19
G101540	Osteogenesis Imperfecta Panel (16-40 Genes)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. Genes covered by the panel should be noted in the report.	2.497,50
G101550	Autosomal Recessive Severe Congenital Neutropenia (HAX1 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101560	PDGFB-COL1A1 Fusion Analysis	Billed once per six months.	408,09
G101570	PDGFRA-FIP1L1 Fusion Analysis	Billed once per six months.	408,09

G101580	PDGFRA-PDGFRB Genes Fusion Analysis	Billed once per six months.	408,09
G101590	Peutz-Jeghers Syndrome (STK11) Gene Sequence Analysis	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101600	Preimplantation Genetic Diagnostic Examinations for the birth of a stem cell donor sibling	See HIC Article 2.4.4.I-2. Billed once for each trial. HLA tissue compatibility tests are included. It is paid conditional upon being performed in the Genetic Diseases Assessment Centre authorized by the Ministry of Health.	9.831,47
G101610	Preimplantation Genetic Diagnostic Tests aimed at giving birth to a healthy child	See HIC Article 2.4.4.I-3. Billed once for each trial. It is paid in case it is performed in the Genetic Diseases Assessment Centre authorized by the Ministry of Health.	9.274,87
G101620	PTEN Gene Sequence Analysis	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101630	Aneuploidy Analysis by QF PCR	Billed once per ten days. It is paid only for prenatal genetic tests.	612,14
G101640	RET Gene Sequence Analysis	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101650	Retinitis Pigmentosa Panel (41 Genes and above)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. Genes covered by the panel should be noted in the report.	3.500,00
G101660	RETT Syndrome (MECP2 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101670	Spinocerebellar Ataxia Panel (41 Genes and above)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. Genes covered by the panel should be noted in the report.	3.500,00
G101680	Spinocerebellar Ataxia Type 1-8 (Between ATXN1 and ATXN8, Triple Repetition Analysis	Billed once per lifetime.	714,16
G101690	Stargardt Disease (ABCA4, ELOVL4, PROM1 Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	1.259,19
G101700	Tay-Sachs Disease (HEXA Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25

G101710	Thyroid Hormone Resistance (THRB Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101720	Thrombophilia Panel	Billed once per lifetime. The examination includes analysis for at least Factor II-V-XIII, MTHFR, PAI mutations.	285,66
G101730	Thrombopoietin Receptor MPL W515L/K Gene Analysis	Billed once per ten days.	285,66
G101740	Tuberous sclerosis (TSC1-TSC2 Genes Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	1.259,19
G101750	Sequencing the Whole Mitochondria Genome	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	3.250,00
G101760	Long QT Syndrome Panel (16-40 genes)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions. Genes covered by the panel should be noted in the report.	2.497,50
G101770	Von Hippel Lindau (VHL Wide Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101780	Warfarin (Coumadin) Resistance (VKORC1, CYP4F2, GGCX, CYP2C9)	Billed once per lifetime.	285,66
G101790	Wilson's disease (ATP7B Gene Sequence Analysis)	Billed once per lifetime. The outcome report must specify all exons and disease-associated intronic regions.	842,25
G101800	WT1 Expression Analysis	Billed once per ten days.	448,90
G101810	Y Chromosome Microdeletion Test	Billed once per lifetime.	714,16
	9.C.1. ONCOLOGICAL MOLECULAR TESTS	**All stages are included. It is billed only in oncological diagnoses if it is studied from solid tissue samples. Except for the obligations due to medical indications, the examinations performed on the person's request are not covered by the Institution. Exon(s) studied in the report, and intronic regions should be specified. See HIC 2.4.4.G-2.**	

G101830	Next Generation DNA Sequencing, somatic mutation analysis, 1 Gene	Billed once per ten days. The diagnosis and the name of the gene studied should be stated. Not billed together with G100370, G100380, G100390, G100400, G100410, G100420, G100430.	842,25
G101840	Next Generation DNA Sequencing Panel, somatic mutation analysis, 2-4 Genes	Billed once per ten days. The diagnosis and the name of the gene studied should be stated. Not billed together with G100370, G100380, G100390, G100400, G100410, G100420, G100430.	1.259,19
G101850	Next Generation DNA Sequencing Panel, somatic mutation analysis, 5-15 Genes	Billed once per ten days. The diagnosis and the name of the gene studied should be stated. Not billed together with G100370, G100380, G100390, G100400, G100410, G100420, G100430.	1.785,60
G101860	Next Generation DNA Sequencing Panel, somatic mutation analysis, 16-40 Genes	Billed once per ten days. The diagnosis and the name of the gene studied should be stated. Not billed together with G100370, G100380, G100390, G100400, G100410, G100420, G100430.	2.497,50
G101870	Next Generation DNA Sequencing Panel, somatic mutation analysis, 41 Genes and above	Billed once per ten days. The diagnosis and the name of the gene studied should be stated. Not billed together with G100370, G100380, G100390, G100400, G100410, G100420, G100430.	3.500,00
G101880	Analysis of ALK Gene Fusions	Billed once per six months.	408,09
G101890	BRAF Gene (V600K-V600E) Mutation Analysis	Billed once per ten days.	183,64
G101900	EGFR Gene (T790M, G719A and G719X) Mutation Analysis	Billed once per six months.	448,89
G101910	EGFR Gene Sequence Analysis	Billed once per six months.	842,25
G101920	ERBB2 Gene Amplification Analysis	Billed once per six months.	652,95
G101930	FGFR2-FGRFR3 Gene Fusions with Next-Generation DNA Sequencing	Billed once per six months. It includes all current therapy-related genomic changes by RNA or DNA extraction.	842,25
G101940	FGFR3 Gene G370C, R248C, S249C, Y373C Regions Mutation Analysis	Billed once per six months.	285,66
G101950	KRAS Mutation Analysis	Billed once per ten days.	448,89

G101960	Detection of New and Known Fusions of NTRK1, NTRK2 and NTRK3 Genes Related to Treatment	Billed once per six months. Billed if done with Next Generation DNA Sequencing.	1.259,19
G101970	PIK3CA Gene Mutation Analysis	Billed once per six months.	652,95
G101980	Analysis of ROS1 Gene Fusions	Billed once per six months.	408,09

C. HIC Transaction Codes of Frequently Studied Tests

FREQUENTLY STUDIED TESTS AND HIC TRANSACTION CODES		
Transaction Code	**TEST NAME**	**NOTE**
908712	ABL1	
908729 908732	BCR ABL	Reimbursed if both tests are conducted.
908729 908732	TRANSLOCATIONS	Reimbursed if both tests are conducted.
908714	Beta Thalassemia	
908717	BRCA1	
908717	BRCA2	
908730	CALR	
908729	MPL	
908730	JAK 2 MUTATION (REAL-TIME)	
908713	JAK 2 EXON 12	

908713	JAK 2 EXON 14	
908717	CTFR	
908741	FMR 1	
908741	CHIMERISM	
908745	FMF	
908744	PANEL WITH THROMBOPHIA	
908744	FII	
908744	PV	
908744	MTHFR	
908744	PAI	
908741	Y CHROMOSOME	
908713	DNA SEQUENCE ANALYSIS 1-5 REACTIONS	
908714	DNA SEQUENCE ANALYSIS 1-10 REACTIONS	
908715	DNA SEQUENCE ANALYSIS 1-15 REACTIONS	
908716	DNA SEQUENCE ANALYSIS 1-20 REACTIONS	
908717	DNA SEQUENCE ANALYSIS 21 RX AND ABOVE (INCLUDING PANEL TESTS)	
908724	MLPA	
908726	PCR MULTIPLEX	
908742	MICROARRAY	
908743	MOLECULAR CARYOTYPING	
908740	STR ANALYSIS (FOR STR RANGE 1-16)	
908741	STR ANALYSIS (FOR STR RANGE 17 AND OVER)	
908727	REAL-TIME 1 PAIR	
908728	REAL-TIME 1-5 PAIRS	

908729	REAL-TIME PCR 1-10 REACTION	
908730	REAL-TIME PCR 11 AND ABOVE REACTION	

D. HIC Transaction Code of Sample Panel Tests

SAMPLE PANEL TESTS		
HIC CODE	**PANEL NAME**	**GENES IN THE PANEL CONTENT**
908717	BRCA1 Mutation	BRCA1
908717	BRCA2 Mutation	BRCA2
908717	Familial Cancer Syndromes Mutation Panel 1	NBN, BARD1, CDH1, ATM
908717	Familial Cancer Syndromes Mutation Panel 2	PTEN, STK11, RAD51C, PALB2, BIRP1, MSH6, RAD51, CHEK2, TP53
908717	Hotspot Cancer Mutation Panel 1	ABL1, AKT1, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAS, GNAQ, HNF1A, HRAS, IDH1
908717	Hotspot Cancer Mutation Panel 2	JAK2, JAK3, IDH2, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, SRC, STK11, TP53, VHL
908717	MODY Mutation Panel 1	GCK, HNF1A
908717	MODY Mutation Panel 2	HNF1B, HNF4A
908717	Neurofibromatosis Mutation Panel 1	NF1
908717	Neurofibromatosis Mutation Panel 2	NF2
908717	Dystrophin Gene Mutation Panel	DMD

908717	Cystic Fibrosis Mutation Panel	CTFR
908717	TSC1 Mutation Panel	TSC1
908717	TSC2 Mutation Panel	TSC2
908717	Osteogenesis Imperfecta Mutation Panel 1	COL1A1, COL1A2
908717	Osteogenesis Imperfecta Mutation Panel 2	P3H1, PPIB, CRTAP, IFITM5
908717	Noonan Syndrome Mutation Panel 1	A2ML1, BRAF, CBL, HRAS, KRAS
908717	Noonan Syndrome Mutation Panel 2	MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, SOS1, SPRED1
908717	Glycogen Storage Disease Mutation Panel 1	PHKG2, PHKA2, GYS2, G6PC, SLC37A4, AGL, GBE1, PYGM, GYS1, GAA, PRKAG2
908717	Glycogen Storage Disease Mutation Panel 2	PYGL, GYG1, PGM1, PHKA1, PHKB, PGAM2, PFKM, ENO3, ALDOA, LAMP2
908717	Lysosomal Storage Diseases Mutation Panel 1	GALC, NAGA, MANBA, SMPD1, GLB1, GBA2, GBA, HEXB
908717	Lysosomal Storage Diseases Mutation Panel 2	HEXA, GNPTAB, GUSB, ARSA, ARSB, FUCA1, MAN2B1
908717	Rentinitis Pigmentosa Mutation Panel 1	ABCA4, ARL6, BBS1, BBS2, BBS4, BBS5, BBS7, BBS9, BEST1, C2ORF71, C8ORF37, CERKL, CNGA1, CNGB1, Panel NRL, OAT, PDE6A, PDE6B, PDE6C, PDE6G, PDE6H, PRCD, PROM1, RBP3, RBP4, RDH12, RGR, RHO
908717	Rentinitis Pigmentosa Mutation Panel 2	CRB1, CRX, DHDDS, EYS, FAM161A, FLVCR1, GNTPG, IDH3B, IMPG2, FSCN2, LRAT, MAK, MERTK, NR2E3, RLBP1, RP1, RP2, RP9, RPE65, RPGR, SAG, SEMA4A, SPATA7, TTC8, TULP1, USH2A, ZNF423, ZNF469, ZNF513, ZNF644

908717	Hypertrophic Cardiomyopathy Mutation Panel 1	ACTA2, ACTC1, ACTN2, CALR3, CAV1, CAV3, PRKAG2, SLC2A11, SLC52A2, SLC6A2
908717	Hypertrophic Cardiomyopathy Mutation Panel 2	SLC12A3, SLC19A2, SLC25A4, SLC22A5, SLC25A20, SLC2A10, TNNC1, TNNI3, TNNT2
908717	Congenital Ichthyosis Mutation Panel 1	LIPN, LIPH, ALOXE3, PNPLA1
908717	Congenital Ichthyosis Mutation Panel 2	TGM1, ABCA12, CYP4F22, NIPAL4, ALOX12B, TGM5
908717	Hereditary Hearing Loss Mutation Panel 1	COL11A1, COL11A2, COL2A1, COL4A3, COL4A4, COL4A5, COL9A1, COL9A2, DFNA5, MYO15A, MYO1A, MYO3A, MYO6, MYO7A
908717	Hereditary Hearing Loss Mutation Panel 2	DFNB31, DFNB59, GJB2, GJB3, GJB6, KCNQ1, KCNQ4, MYH14, MYH9, SERPINB6, SLC17A8, SLC26A4, SLC26A5, SLC4A11
908717	Glycolization Disorder Mutation Panel 1	ALG1, ALG2, ALG3, ALG6, ALG8, ALG9, ALG12, ALG13, B4GALT1, COG1
908717	Glycolization Disorder Mutation Panel 2	COG4, COG5, COG6, COG7, COG8, DOLK, DPAGT1, DPM1, DMP3, MGAT2, MOGS, MPDU1, MPI, PMM2, RFT1, SLC35A1, SLC35C1
908717	Fanconi Anaemia Mutation Panel 1	FANCA, BRCA2, BRIP1, SLX4, PALB2
908717	Fanconi Anaemia Mutation Panel 2	RAD51C, FANCM, FANCE, FANCL, FANCI, FANCC, FANCB, FANCG, FANCD2, FANCF
908717	Periodic Fever Syndromes Mutation Panel 1	MEFV, TFRS1A, NLRP3, MVK
908717	Periodic Fever Syndromes Mutation Panel 2	NOD2, IL1RN, IL10RA, IL10RB, IL10, PSTPIP1, LPIN2, PLCG2

908717	Epidermolysis Bullosa Mutation Panel 1	COL1A2, COL5A1, COL5A2, COL7A1, COL17A1, COL18A1, KRT1, KRT2, KRT4
908717	Epidermolysis Bullosa Mutation Panel 2	KRT5, KRT9, KRT10, KRT13, KRT16, KRT17, KRT74, KRT81, KRT83, KRT85, KRT86, LAMA3, LAMB3, LAMC2, ITGA3, ITGB4, ITGA6, PLEC
908717	Congenital Neutropenia Mutation Panel 1	ELANE, DNM2, USB1, GFI1
908717	Congenital Neutropenia Mutation Panel 2	WAS, HAX1, ELA2, CSF3R
908717	Bardet Biedl Mutation Panel 1	CCDC28B, BBS1, BBS2, BBS10
908717	Bardet Biedl Mutation Panel 2	ARL6, MKKS, BBS9, MKS1
908717	Limb Girdle Muscular Dystrophy Mutation Panel 1	CAPN3, SGCB, SGCA, FKRP, POMGNT1
908717	Limb Girdle Muscular Dystrophy Mutation Panel 2	DYSF, POMT1, FKTN
908717	Spinocerebellar Ataxia Mutation Panel 1	ATXN7, ATXN1, ATXN10, CACNA1A, ATXN3, PPP2R2B
908717	Spinocerebellar Ataxia Mutation Panel 2	ATXN2, TBP, STUB1, ELOVL4, SETX, KCND3, SPTBN2
908717	SMA Mutation Panel 1	SMN1
908717	SMA Mutation Panel 2	SMN2
908717	Alport Syndrome Mutation Panel 1	COL4A5
908717	Alport Syndrome Mutation Panel 2	COL4A4, COL4A3
908717	Kalmann Syndrome Mutation Panel 1	KAL1, KAL2, XLR, RROKR2
908717	Kalmann Syndrome Mutation Panel 2	PROK2, STS, GNRH1
908717	Obesity Mutation Panel 1	NROB2, POMC, SDC3, GHRL, PPARG
908717	Obesity Mutation Panel 2	UCP1, CARTPT, ADRB2, SIM1, ENPP1, ADRB3, UCP3, AGRP, MC4R

908717	Cortical Dysplasia Mutation Panel 1	LIS1, ARX, DCX, ARFGEF2, FLNA, MEKK4, TUBA1A, TUBA8, TUBB2B, TUBB3, RND2, NEUROG2, GPR56, TITF1, PIK3R2, PIK3CA
908717	Cortical Dysplasia Mutation Panel 2	AKT3, TSC1, TSC2, MTOR, CCND1, CDKN1A, CDKN1B, PTEN, DYNC1H1, VLDLR, COL4A1, SRD5A3, ATP6VOA2, DEPDC5, C12orf57, KIF2A, KIF5C, TUBG1, NDE1, EZH2, TNTC3, FKTN, POMGNT1, POMGNT2, RLN, FKRP
908717	Mitochondrial DNS Mutation Panel	
908717	Optional Modified Mutation Panel 1	
908717	Optional Modified Mutation Panel 2	
908717	Optional Modified Mutation Panel 3	
908717	Optional Modified Mutation Panel 4	
908717	Whole Exome Sequencing Mutation Panel 1	
908717	Whole Exome Sequencing Mutation Panel 2	
908717	Whole Exome Sequencing Mutation Panel 3	
908717	Whole Exome Sequencing Mutation Panel 4	
908717	Whole Exome Sequencing Mutation Panel 5	
908717	Whole Exome Sequencing Mutation Panel 6	
908717	Clinical Exome Sequencing Mutation Panel 1	
908717	Clinical Exome Sequencing Mutation Panel 2	
908717	Clinical Exome Sequencing Mutation Panel 3	
908717	Clinical Exome Sequencing Mutation Panel 4	

APPENDIX E

Genetic Testing Reimbursement Constraints in Türkiye and a Comprehensive Decision Flowchart

Note: The definitions are provided in accordance with the article numbers of the HIC [129]

Classification of Health Care Providers in Türkiye

Pursuant to Law No. 5510, health service providers are tiered by the Ministry of Health as follows.

1.4.1 - Health institutions

1.4.1.A - Primary Level State Health Care Institution

(1) Primary level health care institutions affiliated to the Ministry of Health, institutional physicians within public administrations, 112 emergency health service units, medico-social units of universities, primary health units of the Turkish Armed Forces, polyclinics belonging to municipalities.

1.4.1.B - Primary Level Private Health Institution

(1) Occupational physician, home care service providers, private polyclinics, oral and dental clinics.

1.4.1.C - Private pharmacies

(1) Private pharmacies under regulation.

1.4.2 - Health Organizations

1.4.2.A - Secondary Level State Health Care Organization

(1) State hospitals and branch hospitals that do not have training and research hospitals, district polyclinics affiliated to these hospitals, integrated district state hospitals, oral and dental health centers affiliated to the Ministry of Health, hospitals belonging to municipalities, and medical centers and branch centers belonging to public institutions, Hospice Presidency (Darülaceze) Medical Center.

1.4.2.B - Secondary Level Private Health Care Organization

(1) Hospitals licensed in accordance with the "Private Hospitals Regulation", medical centers opened within the scope of the " Regulation on Private Health care Institutions where Outpatient Diagnosis and Treatment".

1.4.2.C - Tertiary Level State Health Care Organization

(1) Training and research hospitals affiliated to the Ministry of Health, specific branch training and research hospitals, district polyclinics affiliated to these hospitals, university hospitals and health practice and research centers and institutes affiliated to these hospitals, dental faculties of universities.

1.4.3 - Health institutions/organizations that cannot be tiered in terms of health service delivery

1) Dialysis centers and other specialized treatment centers licensed by the Ministry of Health,
2) Turkish Public Health Institution Central Laboratories (Refik Saydam Hygiene Laboratories),
3) Diagnosis, examination and imaging centers and laboratories.

1.4.4 - Other health service providers that cannot be tiered in terms of health service delivery

1) Opticians,
2) Medical device and material suppliers,
3) Hot springs,
4) Private legal entities offering and/or producing indigenous medicinal products and their unincorporated branches.

- **Reimbursement Details for Genetic/Genomic Tests in Türkiye According to HIC Articles:**

2.4.4.G - Genetic tests

2.4.4.G-1 - Cytogenetic examinations

(1) In the Annex-2/B of the HIC, transaction codes included under title "9.B. "Cytogenetic Tests" title (except for the transaction codes under the sub-title "9.B.1. Molecular Cytogenetic Tests");

a) Billed by contracted/protocol tertiary health care providers. In case any test cannot be performed for any reason by contracted/protocol tertiary health care providers, they can outsource and bill by service procurement method from another licensed Genetic Diseases Assessment Centre (GDAC).

b) Billed if it is done in secondary level health care providers with GDAC which is licensed by the Ministry of Health. However, it can be outsourced and billed by service procurement from another licensed GDAC in case the test requests are preimplantation genetic tests, prenatal genetic tests, haematological malignancies, and the tests for the recipient and donor candidates to be transplanted in health care providers with organ and tissue transplantation centres.

(2) In the Annex-2/B of the HIC, transaction codes included under sub-title "9.B.1. Molecular Cytogenetic Tests";

a) Billed by contracted/protocol tertiary health care providers. In case any test cannot be performed for any reason by contracted/protocol tertiary health care providers, they can outsource and bill by service procurement method from another licensed GDAC.

b) Billed if it is done by secondary level health care providers who have GDAC which is licensed by the Ministry of Health.

(3) A report containing the detailed technical explanation of the transactions and the signed photocopy of the original device analysis result printouts including images will be attached to the invoice. In addition, signed original device printouts will be kept at the health service provider to be submitted to the Institution when requested. On the request form, the physician should state about the indication for the test, the necessity for diagnosis and whether she or he has changed the treatment protocol. A sample copy of this form should be attached to the invoice.

2.4.4.G-2 - Molecular examinations

(1) In the Annex-2/B of the HIC, transaction codes included under title “9.C. “Molecular Genetic Tests” title (except for the transaction codes under the sub-title “9.C.1. Oncological Molecular Tests”);

a) Billed by contracted/protocol tertiary health care providers. In case any test cannot be performed for any reason by contracted/protocol tertiary health care providers, they can outsource and bill by service procurement method from another licensed GDAC.

b) Billed if it is done in secondary level health care providers with GDAC which is licensed by the Ministry of Health. However, it can be outsourced and billed by service procurement from another licensed GDAC in case the test requests are preimplantation genetic tests, prenatal genetic tests, haematological malignancies, and the tests for the recipient and donor candidates to be transplanted in health care providers with organ and tissue transplantation centres.

(2) In the Annex-2/B of the HIC, transaction codes included under sub-title "9.C.1. Oncological Molecular Examinations”.

a) Billed by contracted/protocol tertiary health care providers. In case any test cannot be performed for any reason by contracted/protocol tertiary health care providers, they can outsource and bill by service procurement method from another licensed GDAC.

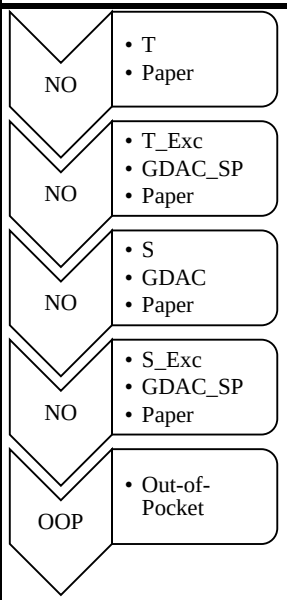
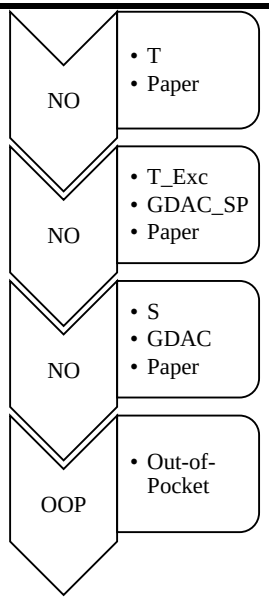
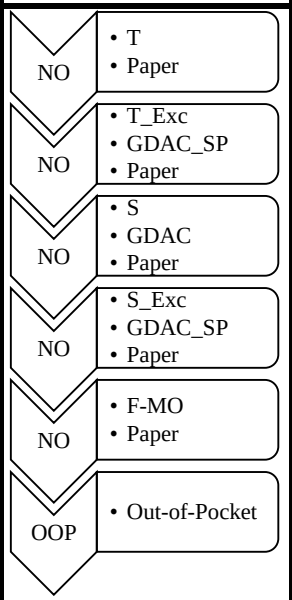
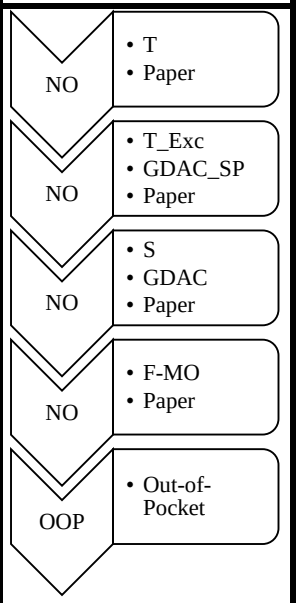
b) Billed if it is done in secondary level health care providers with GDAC which is licensed by the Ministry of Health.

(3) Except for the obligations related to forensic or medical indications, the tests requested and performed voluntarily by the individual are not covered by the

Institution (out-of-pocket). A report containing the detailed technical explanation of the transactions and the signed photocopy of the original device analysis result printouts including images will be attached to the invoice. In addition, signed original device printouts will be kept at the health service provider to be submitted to the Institution when requested. On the request form, the physician should state about the indication for the test, the necessity for diagnosis and whether she or he has changed the treatment protocol. A sample copy of this form should be attached to the invoice.

- **A flowchart for reimbursement decision and related abbreviations and detailed definitions**

Abbreviation	Condition	Status	Definition
P	Primary Level Health Care Institution	State	Primary health care institutions affiliated to the Ministry of Health, institutional physicians within public administrations, 112 emergency health service units, medico-social units of universities, primary health units of the Turkish Armed Forces, polyclinics belonging to municipalities.
		Private	Occupational physician, home care service providers, private polyclinics, oral and dental clinics.
S	Secondary Level Health Care Organisation	State	State hospitals and branch hospitals that do not have training and research hospitals, district polyclinics affiliated to these hospitals, integrated district state hospitals, oral and dental health centers affiliated to the Ministry of Health, hospitals belonging to municipalities, and medical centers and branch centers belonging to public institutions, Hospice Presidency (Darülaceze) Medical Center. **NOTE 1:** Secondary level health care centres **ARE NOT** supposed to possess Genetic Disease Assessment Centres
		Private	Hospitals licensed in accordance with the "Private Hospitals Regulation", medical centers opened within the scope of the " Regulation on Private Health care Institutions where Outpatient Diagnosis and Treatment". **NOTE 1:** Secondary level health care centres **ARE NOT** supposed to possess Genetic Disease Assessment Centres
T	Tertiary Level Official Health Care Organization		Training and research hospitals affiliated to the Ministry of Health, specific branch training and research hospitals, district polyclinics affiliated to these hospitals, university hospitals and health practice and research centers and institutes affiliated to these hospitals, dental faculties of universities. **NOTE 2:** Tertiary level health care centres **ARE** supposed to possess Genetic Disease Assessment Centres **NOTE 3:** For reimbursement, tertiary level health care centres have to establish a contract/protocol with the MoH and SSI
GDAC	Genetic Disease Assessment Centre		
GDAC_SP	Genetic Disease Assessment Centre_sp		Outsourced, service procurement of GDAC
T_Exc	Tertiary Level Official Health Care Organization which cannot perform a specific genetic test for any reason.		In case any test cannot be performed for any reason by contracted/protocol tertiary health care providers, they can outsource and bill by service procurement method from another licensed Genetic Diseases Assessment Center (GDAC).
S_Exc	Secondary Level Health Care Organisation which requested tests for specific cases of patients		Secondary level health care centres can outsource and bill by service procurement from another licensed GDAC in case the test requests are: preimplantation genetic tests, prenatal genetic tests, hematological malignancies, and the tests for the recipient and donor candidates to be transplanted in health care providers with organ and tissue transplantation centers.
Paper	Paper-based documentation attached to invoice for reimbursement		A report containing the detailed technical explanation of the transactions and the signed photocopy of the original device analysis result printouts including images will be attached to the invoice. In addition, signed original device printouts will be kept at the health service provider to be submitted to the Institution when requested. On the request form, the physician should state about the indication for the test, the necessity for diagnosis and whether she or he has changed the treatment protocol. A sample copy of this form should be attached to the invoice.
F - MO	Forensic Issues or Obligatory due Medical Indications		A genetic test request due forensic issues or medical indication obligations.

9.A	9.B	9.B.1	9.C	9.C.1
Unless otherwise stated, it is covered if requested by tertiary health care providers or specialists in gastroenterology, infectious diseases, paediatric health and diseases, internal diseases, and chest diseases.				

9.A: Molecular Microbiology Tests Transaction Group	
9.B: Cytogenetic Tests Group	9.B.1: Molecular Cytogenetic Tests Group
9.C: Molecular Genetic Tests Group	9.C.1: Oncological Molecular Tests Group
T: Tertiary Level Health Care Centres	GDAC_SP: Outsourced Genetic Disease Assessment Centre, Service Procurement
S: Secondary Level Health Care Centres	T_Exc: Exception for Tertiary Level Health Care Centres
P: Primary Level Health Care Centres	S_Exc: Exception for Secondary Level Health Care Centres
GDAC: Genetic Disease Assessment Centre	F-MO: Forensic Issues or Obligatory due Medical Indications
Paper: Paper-based Report Obligation	

APPENDIX F

This Appendix delivers the processes we utilised during the genetic test report template generation. Additionally, we lay down the concepts extracted using the sample genetic test reports. Finally, we represent the concept matches with the sample genetic test report data elements.

We collected four sample genetic test reports from three genetic testing centres. One of the reports is targeted genetic test, other is the report on the result of genetic testing panel. Two of them are Whole Exome Sequencing test reports. In the below figures, you can find the genetic testing reports' scans. They are collected from the interviewee experts and anonymised. Each report is analysed as a use case, and before the reports, the summary of the use case is added in this Appendix. After each report, we provide the concepts that we extract.

Later, we show the process about how we generated the template genetic test report, extract the concepts, match concepts with the data fields of the template report, and finally map those concepts with FHIR resources.

- **Report No: 1**

In the first report, the test was performed on targeted genes based on a service request from a clinician to analyse whether the subject has genetically oriented Mediterranean fever or not. The centre stated specimen details and the genes assayed for the specific test panel on purpose. They provided the result as non-pathogenic and added their analysis comments.

/2015

Sayın Prof. Dr.]

Talep etmiş olduğunuz genetik test sonuçları aşağıdadır.

Dosya No	:
Hastanın Adı Soyadı	:
Cinsiyeti	:
Örneği Gönderen Doktor	:
Adres/Tel/Faks	:
Örneğin Geliş Tarihi	: 08/01/2016
Örneğin Analiz Tarihi	:
Örnek Numarası	: FMF-16-166
Testin Nedeni	: FMF tanısının doğrulanması
Örnek Türü	: Periferik kan
Taranan Mutasyonlar	: E148Q, M680I/a, M680I/c, M694V, V726A
Metod	: PCR-RFLP / Agaroz Jel Elektroforezi
Sonuç	:
Yorum	: Genetik danışma verilmelidir. İleri tetkik (DNA dizi analizi) önerilir.

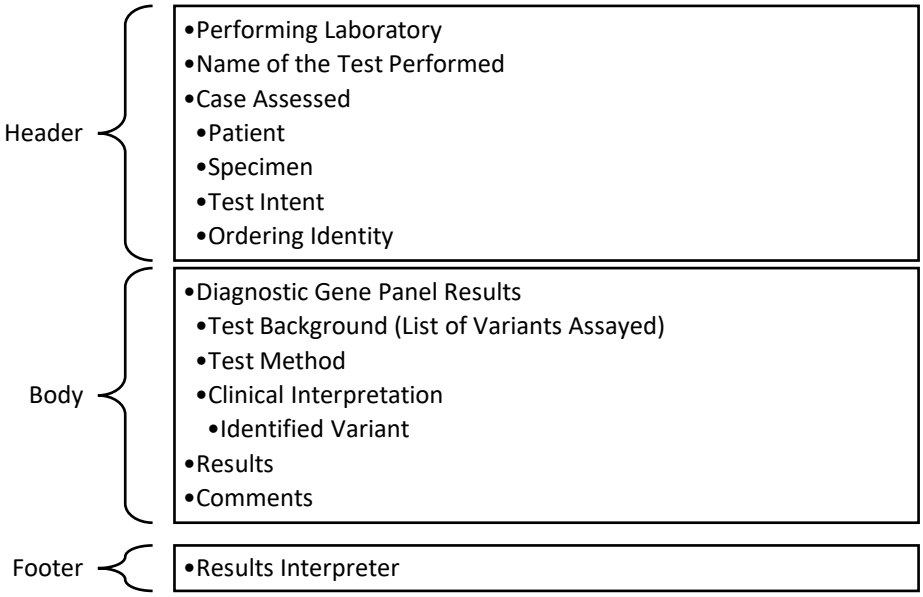
Saygılarımla,

Doç. Dr.

Address Field

Sayfa 1/1

The concepts for Report No:1 are executed as follows.



- **Report No: 2**

The second report was performed upon personal request. The laboratory assessed the genetic origin of thrombocyte disease using a gene panel covering more than 4800 genes (test performed methodology and references). They exploited the pathogenicity and added further associated diseases with this variant other than the test intent.

MOLEKÜLER GENETİK RAPORU

Hastanın Adı- Soyadı:	[redacted]
Protokol No:	
Başvuru Tarihi:	
Rapor Tarih:	
Refere Eden Hekim/ Kurum:	Kişisel başvuru
Klinik Bulgular ve Endikasyon:	Trombosit hastalığı
Materyal türü:	EDTA'lı periferik kan örneği
Örnek alımı:	Merkezimizde alınan ornek
Kullanılan yöntem:	Yeni nesil sekanslama (Next Generation Sequencing)
Çalışılan genler	Trusight One sekans paneli http://genetica-ag.ch/wp-content/uploads/2013/11/Genliste.pdf

Sonuç:

***MYH9* GENİ NM_002473.5**

c.4546G>T (p.Val1516Leu) (p.V1516L) (Heterozigot)

(Açıklamayı okuyunuz.)

Yorum:

Hastada yapılan >4800 gene ait dizileme analizinde tespit edilen değişiklik daha önce tanımlanmış ve hastalık ile ilişkisi bildirilen (HGMD:CM066926) ve insiliko değerlendirme araçlarına göre de yüksek olasılıkla hastalık nedeni olan bir değişikliktir.

Mutasyon tespit edilen gendeki değişiklikler birden fazla hastalığa (May-Heggiin anomaly, Fechtner syndrome, Macrothrombocytopenia and progressive sensorineural deafness, Sebastian syndrome..vb) neden olmaktadır (http://omim.org/entry/160775). Hastanın bulgularının bu hastalıklar açısından ne oranda uyumlu olduğunun klinik olarak değerlendirilmesi gereklidir.

Hastalık otozomal dominant olarak kalıtılmakta olup anne ve babadan çalışma yapılması önerilir. Ayrıca anne ve babada yapılacak olan değerlendirme bu değişikliğin hastalık nedeni olup olmadığının değerlendirilmesinde de faydalıdır. Aileye genetik danışmanlık verilmesi uygundur.

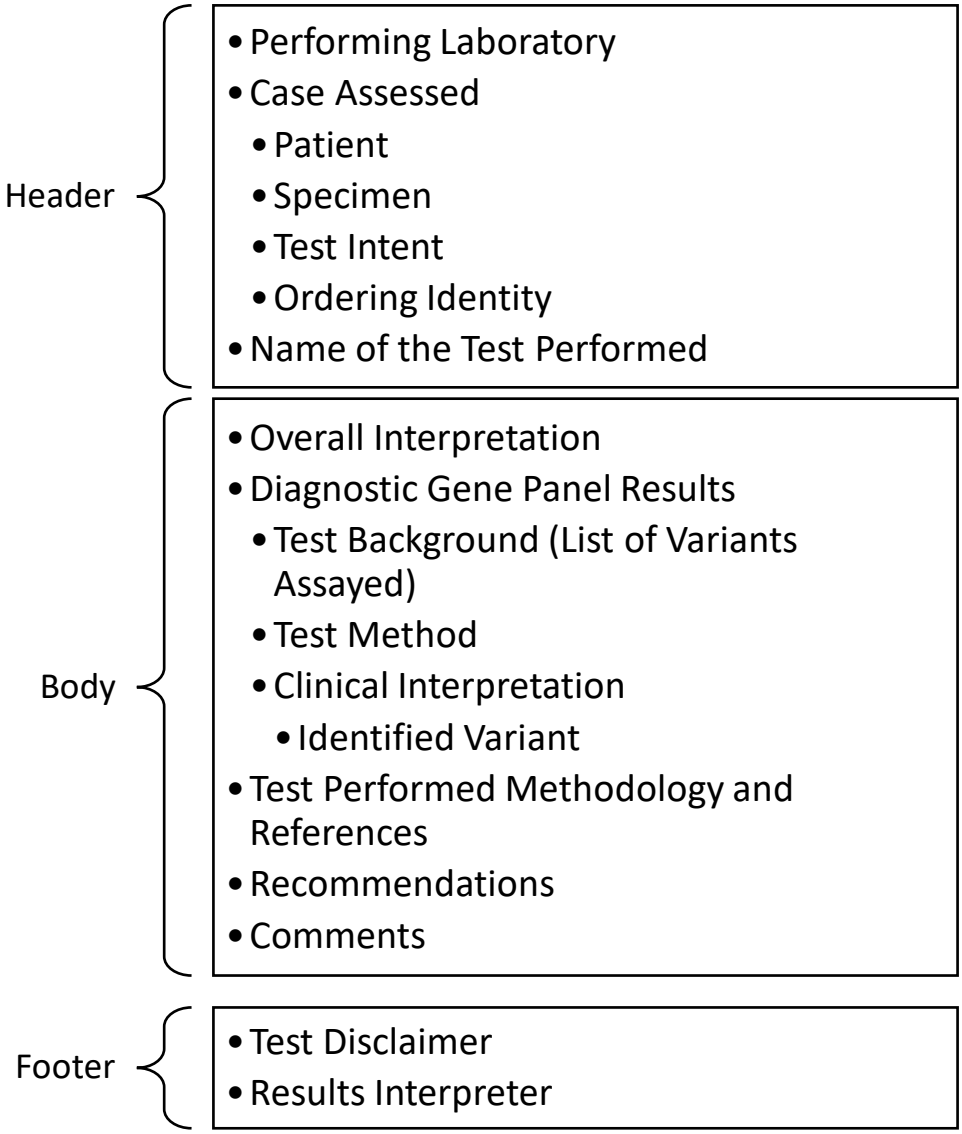
Aileye genetik danışmanlık verilmesi uygundur.

Önemli Not:

Bu test ile elde edilen veriler mevcut güncel bilimsel veriler ışığında ve merkezimize verilen klinik bilgiler doğrultusunda değerlendirilmiştir. Bu analizde tespit edilen veriler, başka klinik ihtiyaçlar doğrultusunda ileride yeniden analiz edilebilir. Böyle bir durum olması halinde merkezimiz ile temas edilmesi rica olunur.

Analizi sırasında yaklaşık % 5 oranında DNA bölgesi teknik nedenlerle değerlendirilememektedir. Bu nedenle hastalığa neden olan bazı ek bulgular olmasına rağmen tespit edilememiş olabilir.

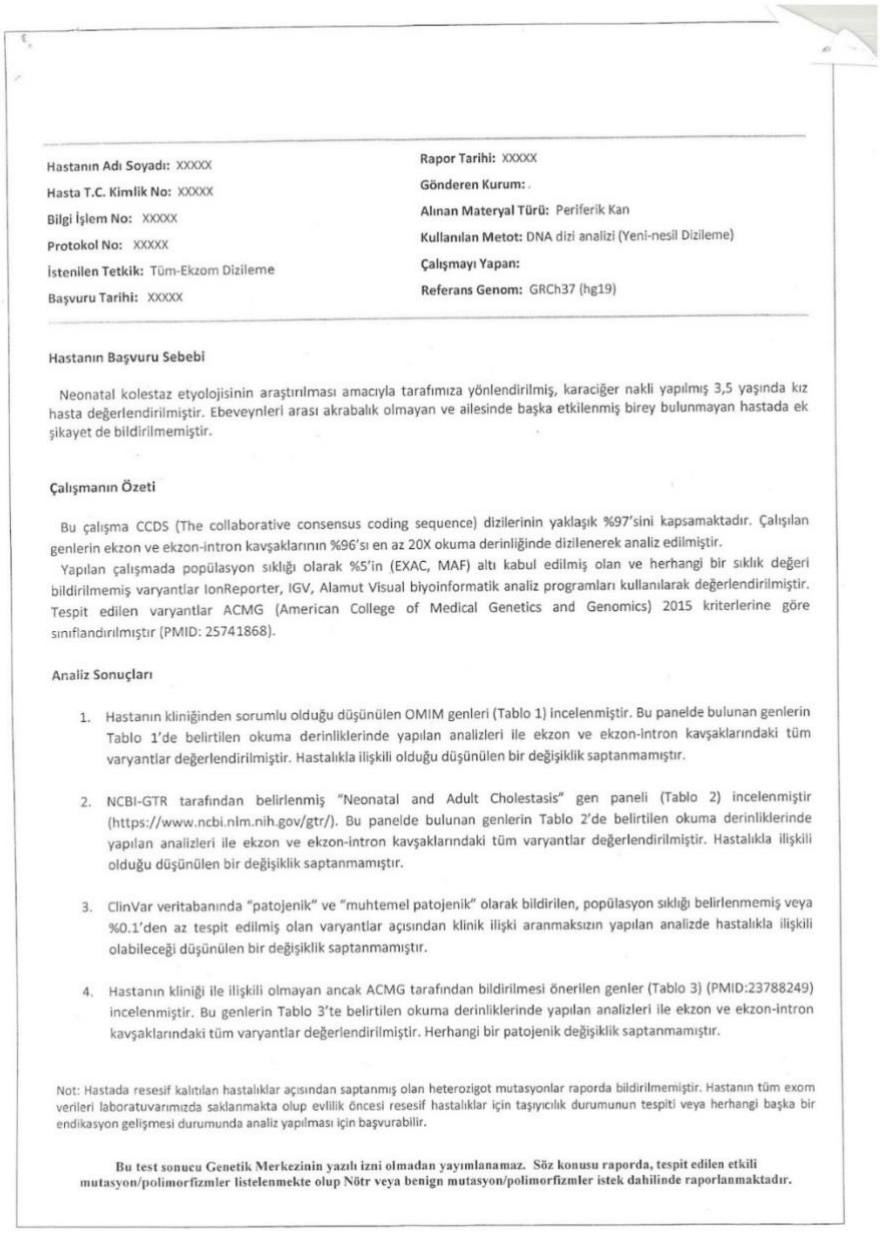
Relevant concepts are depicted as below.



- **Report No: 3**

The third report was generated upon Whole Exome Sequencing (WES) request. After evaluating the subject's condition and providing the gene coverage, the experts drilled down the analysis results, including ACMG incidental findings.

The third report is composed of two pages.



Hastanın Adı Soyadı: XXXXX
Hasta T.C. Kimlik No: XXXXX
Bilgi İşlem No: XXXXX
Protokol No: XXXXX
İstenilen Tetkik: Tüm-Ekzom Dizileme
Başvuru Tarihi: XXXXX

Rapor Tarihi: XXXXX
Gönderen Kurum:
Alınan Materyal Türü: Periferik Kan
Kullanılan Metot: DNA dizi analizi (Yeni-nesil Dizileme)
Çalışmayı Yapan:
Referans Genom: GRCh37 (hg19)

Hastanın Başvuru Sebebi

Neonatal kolestaz etyolojisinin araştırılması amacıyla tarafımıza yönlendirilmiş, karaciğer nakli yapılmış 3,5 yaşında kız hasta değerlendirilmiştir. Ebeveynleri arası akrabalık olmayan ve ailesinde başka etkilenmiş birey bulunmayan hastada ek şikayet de bildirilmemiştir.

Çalışmanın Özeti

Bu çalışma CCDS (The collaborative consensus coding sequence) dizilerinin yaklaşık %97'sini kapsamaktadır. Çalışılan genlerin ekzon ve ekzon-intron kavşaklarının %96'sı en az 20X okuma derinliğinde dizilenerek analiz edilmiştir.
Yapılan çalışmada popülasyon sıklığı olarak %5'in (EXAC, MAF) altı kabul edilmiş olan ve herhangi bir sıklık değeri bildirilmemiş varyantlar IonReporter, IGV, Alamut Visual biyoinformatik analiz programları kullanılarak değerlendirilmiştir. Tespit edilen varyantlar ACMG (American College of Medical Genetics and Genomics) 2015 kriterlerine göre sınıflandırılmıştır (PMID: 25741868).

Analiz Sonuçları

1. Hastanın kliniğinden sorumlu olduğu düşünülen OMIM genleri (Tablo 1) incelenmiştir. Bu panelde bulunan genlerin Tablo 1'de belirtilen okuma derinliklerinde yapılan analizleri ile ekzon ve ekzon-intron kavşaklarındaki tüm varyantlar değerlendirilmiştir. Hastalıkla ilişkili olduğu düşünülen bir değişiklik saptanmamıştır.

2. NCBI-GTR tarafından belirlenmiş "Neonatal and Adult Cholestasis" gen paneli (Tablo 2) incelenmiştir (https://www.ncbi.nlm.nih.gov/gtr/). Bu panelde bulunan genlerin Tablo 2'de belirtilen okuma derinliklerinde yapılan analizleri ile ekzon ve ekzon-intron kavşaklarındaki tüm varyantlar değerlendirilmiştir. Hastalıkla ilişkili olduğu düşünülen bir değişiklik saptanmamıştır.

3. ClinVar veritabanında "patojenik" ve "muhtemel patojenik" olarak bildirilen, popülasyon sıklığı belirlenmemiş veya %0.1'den az tespit edilmiş olan varyantlar açısından klinik ilişki aranmaksızın yapılan analizde hastalıkla ilişkili olabileceği düşünülen bir değişiklik saptanmamıştır.

4. Hastanın kliniği ile ilişkili olmayan ancak ACMG tarafından bildirilmesi önerilen genler (Tablo 3) (PMID:23788249) incelenmiştir. Bu genlerin Tablo 3'te belirtilen okuma derinliklerinde yapılan analizleri ile ekzon ve ekzon-intron kavşaklarındaki tüm varyantlar değerlendirilmiştir. Herhangi bir patojenik değişiklik saptanmamıştır.

Not: Hastada resesif kalıtılan hastalıklar açısından saptanmış olan heterozigot mutasyonlar raporda bildirilmemiştir. Hastanın tüm exom verileri laboratuvarımızda saklanmakta olup evlilik öncesi resesif hastalıklar için taşıyıcılık durumunun tespiti veya herhangi başka bir endikasyon gelişmesi durumunda analiz yapılması için başvurabilir.

Bu test sonucu Genetik Merkezinin yazılı izni olmadan yayımlanamaz. Söz konusu raporda, tespit edilen etkili mutasyon/polimorfizmler listelenmekte olup Nötr veya benign mutasyon/polimorfizmler istek dahilinde raporlanmaktadır.

Tablo 1: OMIM Kolestaz İlişkili Genler

Gen Adı	% 20x Coverage*	Gen Adı	% 20x Coverage	Gen Adı	% 20x Coverage	Gen Adı	% 20x Coverage	Gen Adı	% 20x Coverage
ABCB11	%94	*ATP8B1*	%88	*DCDC2*	%92	*NOTCH2*	%98	*TJP2*	%97
ABCB4	%84	*CLDN1*	%80	*JAG1*	%97	*NR1H4*	%92		

Tablo 2: NCBI-GTR Neonatal and Adult Cholestasis Panel Genleri

Gen Adı	%20x Coverage*	Gen Adı	% 20x Coverage	Gen Adı	% 20x Coverage	Gen Adı	% 20x Coverage	Gen Adı	% 20x Coverage	Gen Adı	% 20x Coverage
ABCB11	%94	*CFTR*	%90	*INVS*	%90	*NPHP4*	%97	*PEX2*	%83	*SLC27A5*	%95
ABCB4	%84	*CLDN1*	%80	*JAG1*	%97	*NR1H4*	%92	*PEX26*	%100	*SMPD1*	%93
ABCC2	%98	*CYP27A1*	%100	*LIPA*	%82	*PEX1*	%82	*PEX3*	%79	*TJP2*	%97
ABCG5	%100	*CYP7A1*	%86	*MKS1*	%100	*PEX10*	%90	*PEX5*	%100	*TMEM216*	%100
ABCG8	%94	*CYP7B1*	%100	*MPV17*	%100	*PEX11B*	%100	*PEX6*	%96	*TRMU*	%92
AKR1D1	%100	*DGUOK*	%100	*NOTCH2*	%98	*PEX12*	%100	*PEX7*	%77	*UGT1A1*	%100
ATP8B1	%88	*DHCR7*	%91	*NPC1*	%100	*PEX13*	%100	*PKHD1*	%97	*VPS33B*	%96
BAAT	%100	*FAH*	%100	*NPC2*	%100	*PEX14*	%100	*POLG*	%100		
C14orf133	%100	*HNF1B*	%100	*NPHP1*	%88	*PEX16*	%87	*SERPINA1*	%100		
CC2D2A	%94	*HSD3B7*	%91	*NPHP3*	%82	*PEX19*	%100	*SLC25A13*	%87		

Tablo 3: ACMG Tarafından Patojenik Mutasyon Bulunduğu Durumda Bildirimesi Önerilen Genleri

Gen Adı	% 20x Coverage*	Gen Adı	% 20x Coverage	Gen Adı	% 20x Coverage	Gen Adı	% 20x Coverage	Gen Adı	% 20x Coverage	Gen Adı	% 20x Coverage
ACTA2	%100	*DSP*	%96	*MSH6*	%96	*PKP2*	%100	*SDHB*	%100	*TP53*	%100
ACTC1	%100	*FBN1*	%98	*MUTYH*	%94	*PMS2*	%84	*SDHC*	%100	*TPM1*	%88
APC	%95	*GLA*	%91	*MYBPC3*	%95	*PRKAG2*	%89	*SDHD*	%100	*TSC1*	%100
APOB	%95	*KCNH2*	%87	*MYH11*	%95	*PTEN*	%86	*SMAD3*	%85	*TSC2*	%97
BRCA1	%86	*KCNQ1*	%85	*MYH7*	%98	*RB1*	%85	*STK11*	%93	*VHL*	%100
BRCA2	%84	*LDLR*	%100	*MYL2*	%100	*RET*	%100	*TGFBR1*	%100	*WT1*	%93
CACNA1S	%100	*LMNA*	%100	*MYL3*	%100	*RYR1*	%97	*TGFBR2*	%100		
COL3A1	%91	*MEN1*	%93	*MYLK*	%96	*RYR2*	%93	*TMEM43*	%86		
DSC2	%96	*MLH1*	%90	*NF2*	%94	*SCN5A*	%98	*TNNI3*	%100		
DSG2	%90	*MSH2*	%93	*PCSK9*	%100	*SDHAF2*	%100	*TNNT2*	%100		

*Genin ekzon ve ekzon-intron kavşaklarının en az 20x okuma derinliğinde yüzde kaçının kapsandığı bilgisi

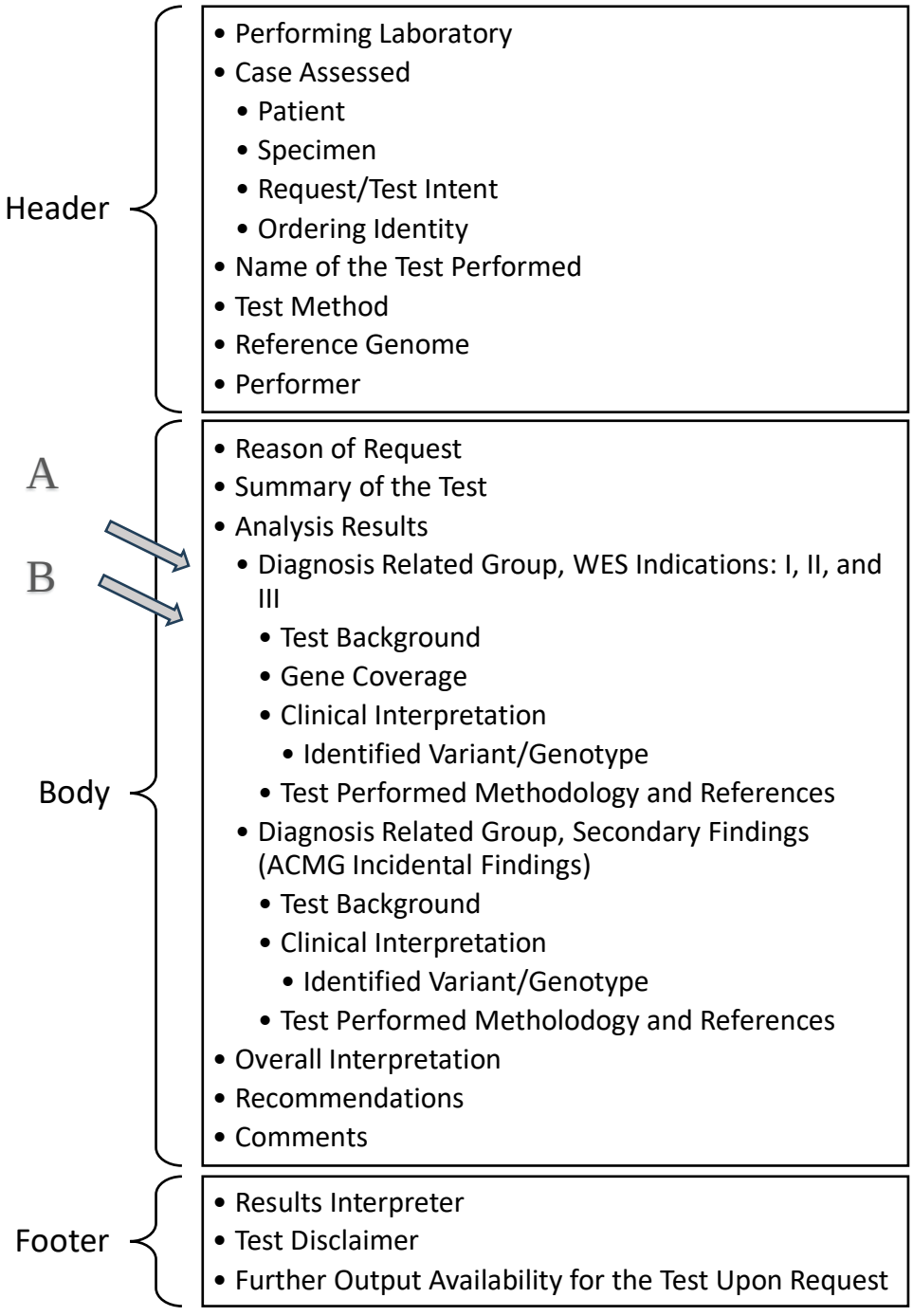
Tıbbi Genetik Uzmanı

Tıbbi Genetik Uzmanı

Bu çalışma Ion Torrent S5 sisteminde (Thermo Fisher Scientific) yapılmıştır ve testin doğruluk oranı çalışılan DNA bölgesinin özelliğine göre değişiklik gösterebilir. Yapılan çalışma ile büyük delesyon ve duplikasyonlar, intronik bölge ve UTR (Untranslated Region) mutasyonları, uniparental dizomi ile meydana gelen hastalıklar, tekrar dizisi hastalıkları, metilasyon bozukluğu, dengeli kromozomal değişiklikler (translokasyon, inversiyon), mitokondriyal genoma bağlı hastalıklar saptanamaz.

Bu test sonucu Genetik Merkezinin yazılı izni olmadan yayımlanamaz. Söz konusu raporda, tespit edilen etkili mutasyon/polimorfizmler listelenmekte olup Nötr veya benign mutasyon/polimorfizmler istek dahilinde raporlanmaktadır.

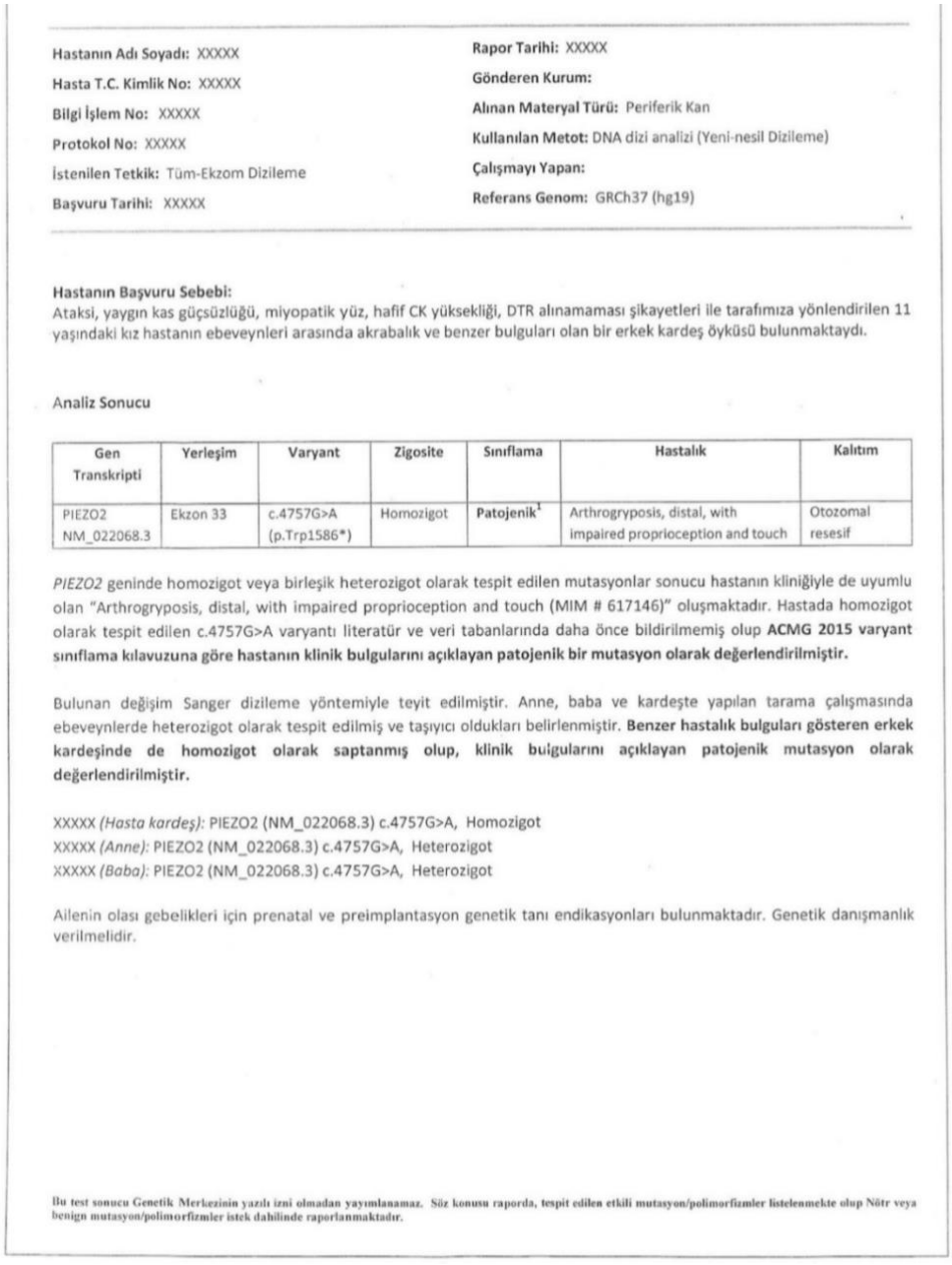
Relevant concepts for the third report are as follows:



- **Report No: 4**

In our last report, a WES request was executed and reported. Identified variants, their pathogenicity, and a variant registered under the ACMG incidental finding list are exhibited in the report. This report also includes the family history of the subject together with relevant family members' variant details. The Quality Control Table of the Analysis is added at the very end.

The fourth report is composed of three pages.



Hastanın Adı Soyadı: XXXXX
Hasta T.C. Kimlik No: XXXXX
Bilgi İşlem No: XXXXX
Protokol No: XXXXX
İstenilen Tetkik: Tüm-Ekzom Dizileme
Başvuru Tarihi: XXXXX

Rapor Tarihi: XXXXX
Gönderen Kurum:
Alınan Materyal Türü: Periferik Kan
Kullanılan Metot: DNA dizi analizi (Yeni-nesil Dizileme)
Çalışmayı Yapan:
Referans Genom: GRCh37 (hg19)

Hastanın Başvuru Sebebi:
Ataksi, yaygın kas güçsüzlüğü, miyopatik yüz, hafif CK yüksekliği, DTR alınamaması şikayetleri ile tarafımıza yönlendirilen 11 yaşındaki kız hastanın ebeveynleri arasında akrabalık ve benzer bulguları olan bir erkek kardeş öyküsü bulunmaktaydı.

Analiz Sonucu

Gen Transkripti	Yerleşim	Varyant	Zigosite	Sınıflama	Hastalık	Kalıtım
PIEZO2 NM_022068.3	Ekzon 33	c.4757G>A (p.Trp1586*)	Homozigot	**Patojenik**[1]	Arthrogryposis, distal, with impaired proprioception and touch	Otozomal resesif

PIEZO2 geninde homozigot veya birleşik heterozigot olarak tespit edilen mutasyonlar sonucu hastanın kliniğiyle de uyumlu olan "Arthrogryposis, distal, with impaired proprioception and touch (MIM # 617146)" oluşmaktadır. Hastada homozigot olarak tespit edilen c.4757G>A varyantı literatür ve veri tabanlarında daha önce bildirilmemiş olup **ACMG 2015 varyant sınıflama kılavuzuna göre hastanın klinik bulgularını açıklayan patojenik bir mutasyon olarak değerlendirilmiştir.**

Bulunan değişim Sanger dizileme yöntemiyle teyit edilmiştir. Anne, baba ve kardeşte yapılan tarama çalışmasında ebeveynlerde heterozigot olarak tespit edilmiş ve taşıyıcı oldukları belirlenmiştir. **Benzer hastalık bulguları gösteren erkek kardeşinde de homozigot olarak saptanmış olup, klinik bulgularını açıklayan patojenik mutasyon olarak değerlendirilmiştir.**

XXXXX *(Hasta kardeş):* PIEZO2 (NM_022068.3) c.4757G>A, Homozigot
XXXXX *(Anne):* PIEZO2 (NM_022068.3) c.4757G>A, Heterozigot
XXXXX *(Baba):* PIEZO2 (NM_022068.3) c.4757G>A, Heterozigot

Ailenin olası gebelikleri için prenatal ve preimplantasyon genetik tanı endikasyonları bulunmaktadır. Genetik danışmanlık verilmelidir.

Bu test sonucu Genetik Merkezinin yazılı izni olmadan yayımlanamaz. Söz konusu raporda, tespit edilen etkili mutasyon/polimorfizmler listelenmekte olup Nötr veya benign mutasyon/polimorfizmler istek dahilinde raporlanmaktadır.

Hastada saptanan ACMG 2016 klavuzuna göre raporlanması önerilen mutasyonlar:

Gen Transkripti	Yerleşim	Varyant	Zigosite	Sınıflama	Hastalık	Kalıtım
TNNT2 NM_000364.3	Ekzon 17	c.853C>T (p.Arg285Cys)	Heterozigot	**Muhtemel patojenik**[2]	Cardiomyopathy, dilated, 1D Cardiomyopathy, familial restrictive, 3 Cardiomyopathy, hypertrophic, 2 Left ventricular noncompaction 6	Otozomal Dominant

TNNT2 geninde heterozigot olarak tespit edilen mutasyonlar sonucunda tabloda belirtilen klinik durumlar oluşmaktadır. Hastada heterozigot olarak saptanan c.853C>T varyantının patojenitesi ile ilişkili olarak çok sayıda laboratuvar bildirimde bulunmuş ve sınıflandırılması konusunda net bir karara varılamamıştır (ClinVar 2018, rs121964857).

Bulunan değişim Sanger dizileme yöntemiyle teyit edilmitir. ACMG 2015 varyant sınıflandırma klavuzuna göre muhtemel patojenik olarak değerlendirilmiştir.

Bu mutasyonun ailede etkilenme riski olan bireylerde taranması ve mutasyon saptanan kişilerde periyodik kardiyoloji kontrolü önerilir.

[1]ACMG (American College of Medical Genetics and Genomics) 2015 varyant sınıflandırma kılavuzuna göre seçimi yapılan kriterler: PVS1— Fonksiyon kaybının (Loss of function) bilinen hastalık mekanizması olduğu bir gende null varyant (nonsense, frameshift, kanonik + - 2 splice bölgesi, başlatma kodonu, tek veya çoklu ekzon delesyonu). PM2— Exome Sequencing Project, 1000 Genomes Project veya Exome Aggregation Consortium çalışmalarında kontrol bireylerde tespit edilmemiş veya çok düşük sıklıkta bildirilmiştir. PP3— Çeşitli in silico değerlendirmelerde gen/gen ürünü üzerinde zararlı etkisi tahmin edilmiştir. Mevcut kanıtlara dayanarak c.4757G>A değişimi patojenik varyant olarak değerlendirilmiştir.

[2]ACMG (American College of Medical Genetics and Genomics) 2015 varyant sınıflandırma kılavuzuna göre seçimi yapılan kriterler: PM2— Exome Sequencing Project, 1000 Genomes Project veya Exome Aggregation Consortium çalışmalarında kontrol bireylerde tespit edilmemiş veya çok düşük sıklıkta bildirilmiştir. PM5—Farklı bir missense değişimin patojenik olarak saptandığı bir aminoasitte yeni bir missense değişim. PP2— Düşük benign missense varyasyon oranı olan ve missense varyantlarının hastalığın ana mekanizması olduğu bir gende missense varyant PP3— Çeşitli in silico değerlendirmelerde gen/gen ürünü üzerinde zararlı etkisi tahmin edilmiştir. PP5 – Güvenilir bir kaynak yakın zamanda varyantı patojenik olarak rapor etmektedir. Mevcut kanıtlara dayanarak c.853C>T değişimi muhtemel patojenik varyant olarak değerlendirilmiştir.

Bu test sonucu Genetik Merkezinin yazılı izni olmadan yayımlanamaz. Söz konusu raporda, tespit edilen etkili mutasyon/polimorfizmler listelenmekte olup Nötr veya benign mutasyon/polimorfizmler istek dahilinde raporlanmaktadır.

Çalışmanın Özeti

1. Test sonucunda elde edilen verilerin analizi ve mutasyonların yorumlanması, hastaya ait tarafımıza bildirilen klinik bilgiler doğrultusunda yapılmıştır ve nihai tanıyı koymak için hastanın klinik bulgularıyla birlikte değerlendirilmelidir.

2. Çalışma yeni nesil dizileme yöntemiyle yapılmıştır (NextSeq, Illumina) ve testin doğruluk oranı çalışılan DNA bölgesinin özelliğine göre değişiklik gösterebilir. Yapılan çalışma ile poliploidi, anöploidi, halka (ring) kromozomlar, yapısal kromozom anomalileri, büyük delesyon ve duplikasyonlar, dengeli kromozomal değişiklikler (translokasyon, inversiyon), uniparental dizomi, tekrar dizisi hastalıkları, mitokondriyal genoma bağlı hastalıklar saptanamaz.

3. Bu test yalnızca ekzon ve ekzon-intron kavşaklarını kapsar ve test sonucunda bu bölgelerdeki frameshift insersiyon/delesyonlar, non-frameshift insersiyon/delesyonlar, non-sinonim varyantlar, splice bölgesi donor-akseptör varyantları raporlanır. Sinonim varyantlar, UTR ve derin intron varyantları dışlanmaktadır.

4. Analizler sırasında varyantların yorumlanması için farklı veri tabanlarının belirli versiyonları kullanılır. Bunlar: Human Genome hg19/GRCh37, RefSeq (release 61), dbSNP (v147), 1000 Genomes phase3, gnomAD, ExAC03'tür.

5. Minör allel frekansı %5'ten yüksek olan (1000 Genomes, ExAC ve gnomAD veri tabanlarında) mutasyonlar değerlendirmeye alınmamıştır.

6. Tespit edilen varyantlar ACMG (American College of Medical Genetics and Genomics) 2015 kriterlerine göre sınıflandırılmıştır (PMID: 25741868).

7. Analizler sonucunda hastanın kliniğiyle ilişkili olan patojenik, muhtemel patojenik ve klinik önemi bilinmeyen olarak sınıflandırılmış varyantlar raporlanır. Benin ve muhtemel benin varyantlar istek dahilinde raporlanır.

8. Hastanın kliniği ile ilişkili olmayan ancak ACMG tarafından bildirilmesi önerilen genler (PMID:23788249) incelenmiştir. Bu genlere ait bulunan sonuçlar *"Hastada saptanan ACMG 2016 klavuzuna göre raporlanması önerilen mutasyonlar"* isimli tabloda verilmiştir.

9. Hastada resesif kalıtılan hastalıklar açısından saptanmış olan heterozigot mutasyonlar raporda bildirilmemiştir. Hastanın tüm-ekzom verileri laboratuvarımızda saklanmakta olup, evlilik öncesinde resesif hastalıklar için taşıyıcılık durumunun tespit edilmesi veya yeni bir endikasyon gelişmesi durumunda analiz yapılması için başvurabilir.

Çalışmanın Kalite Kontrol Tablosu

Parametreler	*Değerler (Normal aralık)*
Hedef bölgenin kapsanması	97.81%
Hedef bölgenin en az 4x derinliğinde kapsanması (coverage)	97.50% (>96.7%)
Hedef bölgenin en az 20x derinliğinde kapsanması (coverage)	96.23%
Hedef bölgenin ortalama dizileme derinliği	116.76 (>100)

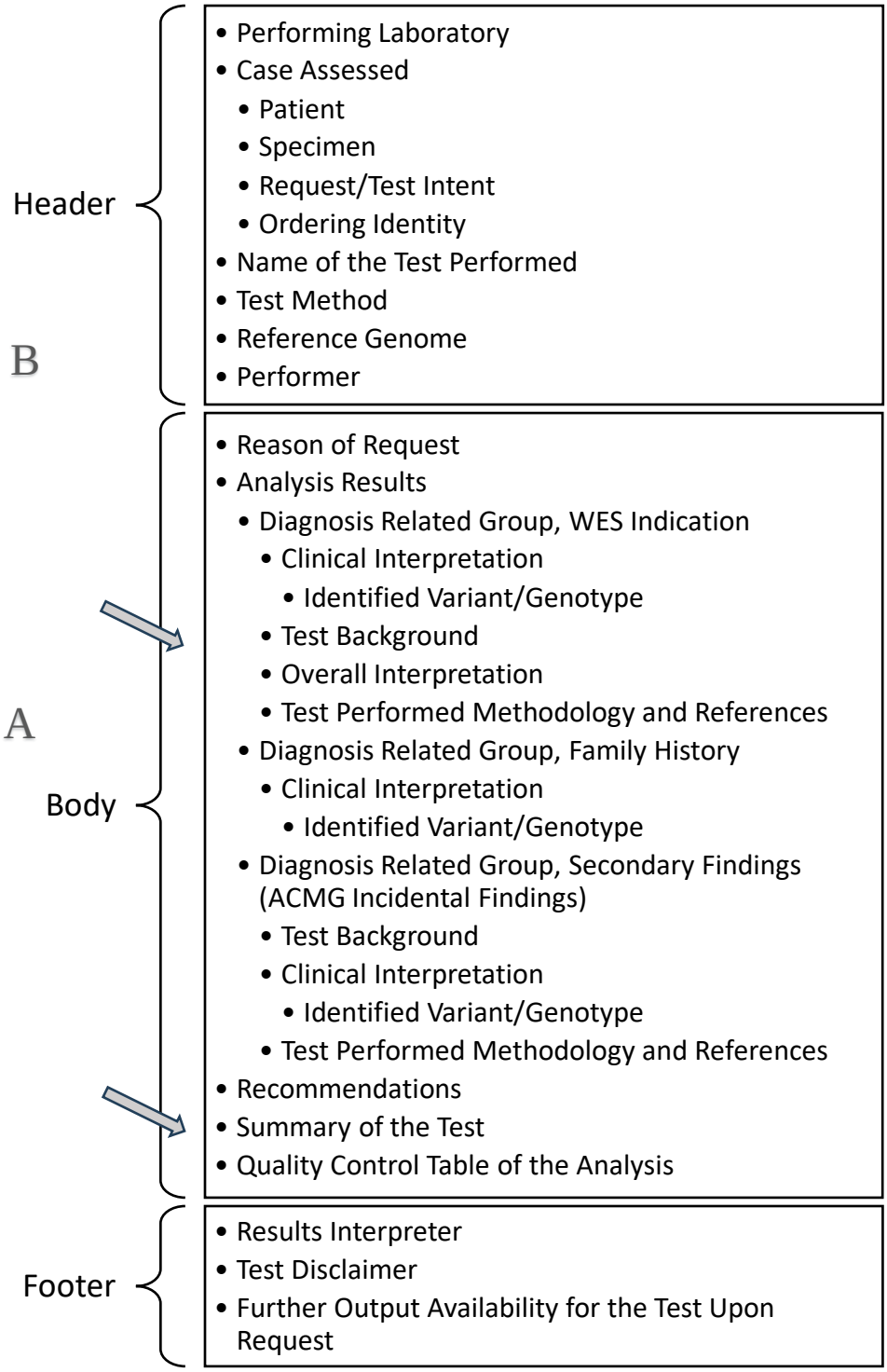
Tıbbi Genetik Uzmanı

Tıbbi Genetik Uzmanı

Bu test sonucu Genetik Merkezinin yazılı izni olmadan yayımlanamaz. Söz konusu raporda, tespit edilen etkili mutasyon/polimorfizmler listelenmekte olup Nötr veya benign mutasyon/polimorfizmler istek dahilinde raporlanmaktadır.

Relevant concepts for the fourth and the final report is depicted below.

Please note the unstructured report layout; contrarily to Report No: 3, the same centre inserted the Summary of the Test concept after the analysis part.



To begin, we initially extracted the data field names from sample genetic testing reports from three different centres, conducting this process separately for each centre.

CENTRE #1	**CENTRE #2**	**CENTRE #3**
Dosya No	Hastanın Adı Soyadı	Hastanın Adı Soyadı
Hastanın Adı Soyadı	Protokol No	Hasta T.C. Kimlik No
Cinsiyeti	Başvuru Tarihi	Bilgi İşlem No
Örneği Gönderen Doktor	Rapor Tarihi	Protokol No
Adres/Tel/Faks	Refere Eden Hekim/Kurum	**İstenilen Tetkik**
Örneğin Geliş Tarihi	Klinik Bulgular ve Endikasyon	Başvuru Tarihi
Örneğin Analiz Tarihi	Materyal Türü	Rapor Tarihi
Örnek Numarası	Örnek Alımı	Gönderen Kurum
Testin Nedeni	Kullanılan Yöntem	Alınan Materyal Türü
Örnek Türü	**Çalışılan Genler**	Kullanılan Metot
Taranan Mutasyonlar	**Sonuç**	Çalışmayı Yapan
Metod	Yorum	Referans Genom
Sonuç	Önemli Not (SORUMLULUK REDDİ)	Hastanın Başvuru Sebebi
Yorum		Çalışmanın Özeti
		Analiz Sonuçları
		Çalışmanın Kalite Kontrol Tablosu
		(SORUMLULUK REDDİ*)

In the subsequent step, we eliminated any redundancies and consolidated the remaining data into a single table. This resulted in the creation of a genetic testing diagnostic report template that encompasses information from all three distinct sample reports. This template serves as the foundational structure for our genetic test report within the conceptual model we are developing.

MERKEZ ADI		
Dosya No	Hastanın Adı Soyadı	Protokol No
Hasta T.C. Kimlik No	Cinsiyeti	Yaşı
Başvuru Tarihi	Bilgi İşlem No	Gönderen Kurum
Gönderen Doktor	Örneği Gönderen Kurum	Örneği Alan Kişi
Adres/Tel/Faks	İstenilen Tetkik	Örneğin Geliş Tarihi
Örneğin Analiz Tarihi	Örnek Numarası	Örnek Alımı (Lokasyon)
Hastanın Başvuru Sebebi	Klinik Bulgular ve Endikasyon	Örnek Türü
İstenilen Tetkik	Çalışılan Genler	Metot
Yorum	Çalışmayı Yapan	Referans Genom
Çalışmanın Özeti	Çalışmanın Kalite Kontrol Tablosu	Sorumluluk Reddi

We divided this template into three distinct sections, each separated by bold and double split borders, as shown in the table below. Specifically, the report header is positioned at the top, the report body is located in the middle, and the report footer is situated at the bottom.

MERKEZ ADI	
Hastanın Adı Soyadı	Rapor Tarihi
Hasta T.C. Kimlik No	Başvuru Tarihi
Dosya No	Gönderen Kurum
Bilgi İşlem No	Gönderen Doktor
Protokol No	Gönderen Adres/Tel/Faks
Cinsiyeti	Örnek Türü
YAŞI	Doğum Tarihi
Örneği Gönderen Kurum	İstenilen Tetkik
Örneği Alan Kişi	Örneğin Geliş Tarihi
Örnek Alımı (Lokasyon)	Örnek Numarası
Testin Metodu	Çalışılan Genler
Referans Genom	Örneğin Analiz Tarihi
Çalışmayı Yapan	

Hastanın Başvuru Sebebi
Klinik Bulgular ve Endikasyon
Çalışmanın Özeti
Yorum
Çalışmanın Kalite Kontrol Tablosu

Sorumluluk Reddi
İstek Üzerine Yapılabilecek Diğer Testler

Lastly, we presented an enumeration of the extracted concepts within the genetic testing diagnostic report use case, utilising both the data elements and the report content. Furthermore, we established mappings between these concepts and the data elements within the template for the genetic test report.

NOTE: For the sake of completeness of the Appendix, this part is the repetition of Section 4.4.2, Table 19, Table 20 and Table 21.

- **Concept numbers and enumeration:**

No	Concept Name
1	Performing Laboratory
2	Patient
3	Specimen
4	Request/Test Intent
5	Ordering Identity
6	Name of the Test Performed
7	Test Method
8	Reference Genome
9	Performer
10	Reason of Request
11	Summary of the Test
12	Analysis Results
13	Overall Interpretation
14	Test Background
15	Clinical Interpretation
16	Identified Variant/Genotype
17	Gene Coverage (List of Variants Assayed)
18	Test Performed Methodology and References
19	Family History
20	Secondary Findings (ACMG Incidental Findings)
21	Recommendations
22	Quality Control Table of the Analysis
23	Results Interpreter
24	Test Disclaimer
25	Further Output Availability for the Test Upon Request
EX-1	Age

Template report and concept enumeration mapping (**M: Main Report Itself, EX: Extension**)

MERKEZ ADI			**1**
Hastanın Adı Soyadı	**2**	Rapor Tarihi	**M**
Hasta T.C. Kimlik No	**2**	Başvuru Tarihi	**M**
Dosya No	**2**	Gönderen Kurum	**5**
Bilgi İşlem No	**2**	Gönderen Doktor	**5**
Protokol No	**2**	Gönderen Adres/Tel/Faks	**5**
Cinsiyeti	**2**	Örnek Türü	**3**
YAŞI	**EX-1**	Doğum Tarihi	**2**
Örneği Gönderen Kurum	**5**	İstenilen Tetkik	**4**
Örneği Alan Kişi	**3**	Örneğin Geliş Tarihi	**3**
Örnek Alımı (Lokasyon)	**3**	Örnek Numarası	**3**
Testin Metodu	**7**	Çalışılan Genler	**17**
Referans Genom	**8**	Örneğin Analiz Tarihi	**M**
Çalışmayı Yapan	**9**		

Hastanın Başvuru Sebebi	**10**
Klinik Bulgular ve Endikasyon	**12, 13, 14, 15, 16, 17, 18, 19, 20**
Çalışmanın Özeti	**11**
Yorum	**21**
Çalışmanın Kalite Kontrol Tablosu	**22**

Sorumluluk Reddi	**24**
İstek Üzerine Yapılabilecek Diğer Testler	**25**

Final mapping of template genetic testing report data – elements, concept name, FHIR resource name, and the Artifact name.

Concept Name	**FHIR Resource**	**Artifact Name** *(Artifact No)*
Report	DiagnosticReport	Genomics Report *(i)*
Performing Laboratory Requester Organisation	Organization	Organization *(ii)*
Patient	Patient	Patient *(iii)*
Specimen	Specimen	Specimen *(iv)*
Request/Test Intent	ServiceRequest	ServiceRequest *(v)*
Name of the Test Performed	PlanDefinition	PlanDefinition Resource *(vi)*
Test Background Test Performed Methodology and References	Extension	Related Artifact *(vii)*
Test Disclaimer Test Method Further Output Availability for the Test Upon Request	Extension	Annotation Code *(viii)*
Reference Genome	Observation	Genomics Finding Abstract Profile *(ix)* • component: reference-sequence-assembly
Performer	PractitionerRole	PractitionerRole *(x)*

Results Interpreter Ordering Identity	Practitioner	Practitioner *(xi)*
Reason of Request	Extension	Genomic Report Note (If there is a possibility of transporting the content of the note in a structured manner the usage of CodedAnnotation is forbidden and the corresponding data structures SHALL be used.) *(xii)* (Used as a component under DiagnosticReport)
	Extension	supportinginfo (Other information that may be relevant to this event) *(xiii)* (Used as a component under DiagnosticReport)
Summary of the Test	Observation	Genomics Base/Implication *(xiv)* • component: conclusion-string
Analysis Results	Observation	Observation *(xv)*
Overall Interpretation	Observation	OverallInterpretation *(xvi)*
Clinical Interpretation	Observation	Diagnostic Implication: *(xvii)* • component: clinical-significance
Identified Variant/Genotype Quality Control Table of the Analysis	Observation	Variant *(xviii)*

Gene Coverage (List of Variants Assayed)	Observation	RegionStudied *(xix)* • component: gene-studied
Family History	FamilyMemberHistory	**None** • FamilyMemberHistoryForGeneticsAnalysis Profile *(xx)*
Secondary Findings (ACMG Incidental Findings)	Observation	secondaryFinding *(xxi)*
Recommendations	Task	Follow Up Recommendation *(xxii)*

CURRICULUM VITAE

PERSONAL INFORMATION

Surname, Name: Şık, Ayhan Serkan

Nationality: Republic of Türkiye

Date and Place of Birth:

Marital Status: Single

Phone:

email:

EDUCATION

Degree	Institution	Year of Graduation
MS	METU, Department of Electrical and Electronics, Biomedical Engineering	2003
BS	METU, Department of Physics	1998
High School	Yükseliş College	1993

WORK EXPERIENCE

Year	Place	Enrollment
2020-Present	Ankara Medipol University	Instructor
2016-2018	TÜMAŞ, Sri Lanka, Colombo	Hospital Planner, Biomedical Engineer
2015-2016	Etlik City Hospital	Chief Biomedical Engineer
2009-2016	Başkent University	Instructor
2008-2009	TAEK	Research and Development Engineer
2001-2006	METU II	Research Assistatnt

FOREIGN LANGUAGES

Native Turkish, Advanced English, Basic German, Basic Italian

PUBLICATIONS

A. S. Şık, A. U. Aydınoğlu, and Y. Aydın Son, 'Assessing the readiness of Turkish health information systems for integrating genetic/genomic patient data: System architecture and available terminologies, legislative, and protection of personal data', *Health Policy (New York)*, vol. 125, no. 2, pp. 203–212, Feb. 2021, doi: 10.1016/J.HEALTHPOL.2020.12.004.

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