

**Deanship of Graduate Studies
Al-Quds University**



**Pharmacogenomic and Clinical Factors Associated with
the Side Effects of Fluoropyrimidines in Palestinian
Cancer Patients**

Mohammad Khalaf Ali Dweib

Ph.D. Dissertation in Public Health

Jerusalem- Palestine

1447 / 2025

**Pharmacogenomic and Clinical Factors Associated with
the Side Effects of Fluoropyrimidines in Palestinian
Cancer Patients**

Prepared by:

Mohammad Khalaf Ali Dweib

BSc. Pharmacy – Al-Quds University, Palestine

MSc. Clinical Pharmacy – University of Jordan, Jordan

Supervisor:

Dr. Hussein Hallak

**A Dissertation Submitted in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy in
Public Health / School of Public Health**

Al-Quds University

1447 / 2025

Al-Quds University

Deanship of Graduate Studies

PhD in Public Health / School of Public Health



Dissertation Approval

Pharmacogenomic and Clinical Factors Associated with the Side Effects of Fluoropyrimidines in Palestinian Cancer Patients

Prepared by: Mohammad Khalaf Ali Dweib

Registration Number: 22112259

Supervisor: Dr. Hussein Hallak

Ph.D. Dissertation submitted and accepted, Date: 10/1/2026

The names and signatures of the examining committee members are as follows:

Head of the committee: Dr. Hussein Hallak

Signature: 

Internal examiner: Prof. Maher Khmour

Signature: 

External examiner: Prof. Rowa Ramahi

Signature: 

External examiner: Dr Adallah Rabba

Signature: 

Jerusalem- Palestine

1447/2026

Dedication

To my dear father, whose strength in illness continues to inspire me and whose love guides me each day...

To my beloved mother, for her prayers, continuous love, and the resilience she has instilled in me...

To my dearest wife, Lina, for her support, faith, and firm partnership through every challenge and success...

To my children; Omar, Ameer, Reem, and Ali; my greatest blessings, my joy, and the source of my inspiration...

To my brother Nasser, and his family, for the unbreakable bond, support, and love that enrich my life...

To my dear friends, who believed in me and encouraged me when I needed it most...

And to all who face life's challenges with courage and hope, you are the reason behind the meaning of this work.

“Non sibi sed omnibus”; Not for oneself, but for all. May the findings of this research be of great benefit for all patients.

With deepest love, this work is dedicated to you all.

Mohammad Khalaf Dweib

Declaration

I Certify that this dissertation submitted for the degree of Doctor of Philosophy in Public Health, is the result of my own research, except where otherwise acknowledged, and that this Dissertation (or any part of the same material) has not been submitted for a higher degree to any other university or institution.

Signature:

A handwritten signature in black ink, appearing to be 'Md. Khalaf Ali Dweib', written in a cursive style.

Mohammad Khalaf Ali Dweib

Date: 10/1/2026

Acknowledgments

Before every word and beyond every thought, I thank Allah, whose guidance, strength, and blessings enabled me to persevere and accomplish this work.

I am sincerely indebted to my supervisor, Dr. Hussein Hallak, for his exceptional mentorship, continuous encouragement, and invaluable insights. His expertise and dedication were fundamental in shaping the direction and quality of this research.

I would also like to extend my sincere appreciation to the distinguished teaching board members: Dr. Nuha El-Sharif, Dr. Asma Imam, Dr. Motasem Hamdan, and Dr. Bassam Abu Hamad for their constructive feedback, valuable guidance, and academic support, all of which contributed significantly to the advancement of this study.

My gratitude is further extended to my colleagues at Al-Quds University and Hebron University, whose support, collaboration, and intellectual discussions enriched my academic journey.

Finally, I owe profound thanks to my family. To my father, whose courage in illness continues to inspire me; to my mother, for her unwavering prayers, love, and strength; to my wife, Lina, for her patience, sacrifice, and steadfast support; to my children, Omar, Ameer, Reem, and Ali, for being my constant source of joy and inspiration; and to my brother Nasser and his family, for their enduring encouragement and unconditional support. Their presence has been indispensable to the completion of this work.

Mohammad Khalaf Dweib

Abstract

Introduction: Fluoropyrimidines (FPs), a cornerstone of modern chemotherapy, remain among the most prescribed and cost-effective anticancer drugs used around the world. Between 10% and 40% of patients have severe and probably fatal toxicity in the first cycles of FP treatment. Deficiency in dihydropyrimidine dehydrogenase (DPD), caused primarily by pathogenic mutations in the DPYD gene, leads to impaired clearance of FPs and results in excessive accumulation of their toxic metabolites. Testing for DPYD mutations before the beginning of treatment has become an internationally recommended strategy. Other factors such as age, gender and using other drugs were found to affect the prevalence of FP toxicity. Despite the well-proven benefit of pharmacogenomic testing, many countries are still underutilizing this testing due to many factors such as insufficient resources. Palestine represents the challenges faced by Low- and Middle-Income Countries (LMICs) in adopting pharmacogenomics in general.

Aim: This study, through its comprehensive design, aimed to evaluate the importance of pharmacogenomic testing in improving the clinical outcomes of cancer patients in Palestine by exploring the knowledge of oncology specialists and cancer patients regarding pharmacogenomic testing and determining the relationship between DPYD mutations and other clinical factors and the occurrence of side effects of FP anticancer drugs.

Methods: Study I was a cross-sectional study which utilized a survey distributed to oncologists, oncology residents, and clinical pharmacists across various hospitals in Palestine between February and May 2024. The questionnaire was adopted from a previous study conducted in Saudi Arabia and was slightly modified to suit the Palestinian context.

Study II was also a cross-sectional study which utilized a survey distributed to cancer patients that were treated with chemotherapy at three outpatient oncology clinics in the West Bank, Palestine. The questionnaire was developed based on an extensive literature review of similar studies.

In study III, DNA was extracted from blood samples of cancer patients that were using fluoropyrimidines using the salting-out method after using previously prepared standard buffers. Allele-specific Polymerase Chain Reaction (PCR) was performed in 25 μ L reactions with appropriate master mix, primers, DNA template, and nuclease-free water. The DPYD activity score (AS) was calculated by assigning values to each allele (normal = 1, decreased function = 0.5, no function = 0) and summing both alleles. Clinical data and toxicity information were acquired through a standardized analysis of the patients' electronic health records (EHRs) by trained study team who were blinded to the group in which the patient was allocated. Severe adverse events comprised toxicities with a grade no less than 3 based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results: Study I – Healthcare Providers

The questionnaire was completed by a total of 106 healthcare providers (HCPs), consisting of 57.5% specialist physicians, 27.4% clinical pharmacists, and 15.1% resident physicians. More than 70% of participants stated that they had never undergone formal training in pharmacogenomics during their career. Around 80% of participants indicated knowledge of the mutation linked to DPD deficiency and its consequences for FP toxicity. Fewer than 50% of participants indicated that they consistently or occasionally screen for DPD deficiency prior to prescribing FPs. Only 5.7% and 6.6% of participants, respectively, reported the existence of standardized DPD testing and the Palestinian Ministry of Health's promotion of DPD testing before prescribing FPs. About 60% of individuals experienced significant toxicity associated with FPs, a rate considerably higher than the global average of 10–30%. A statistically significant difference was found between HCPs working in private hospitals and those working in governmental institutions in terms of their perception of the influence of DPD testing in clinical practice ($p < 0.05$). No significant differences were seen in awareness of the most important DPYD mutations between groups of different years of experience, designation, nor hospital type ($p > 0.05$).

Study II – Patients

The study included 368 participants with an almost equal gender distribution (52.4% female, 47.6% male). Only 19.8% of participants had heard of pharmacogenomic testing, and less than 5% had undergone any pharmacogenomic test. One-third reported no understanding of the nature of this test. About 40% of participants believed that pharmacogenomic testing can help doctors choose the best treatment, while 44% trusted its accuracy. Less than half (42%) of participants indicated that they would undergo testing if it was recommended by their physician. More than half of the participants (53%) were willing to pay for the test but 5.4% indicated that patients themselves should be responsible for paying for the test, with a mean WTP of around 230 NIS and a perceived reasonable cost of about 1307 NIS. Most of participants (74%) were willing to provide a blood sample for the test.

Study III – Genetic and Clinical Data

The study included 134 participants. A high number (85.1%) of participants were found to be normal metabolizers (AS: 2), while 13.4% were intermediate metabolizers (AS: 1–1.5), and 1.5% were poor metabolizers (AS: 0–0.5). The incidence of grade ≥ 3 side effects in the sample was 17.2%. Hand-foot syndrome and severe fatigue were the most common side effects. All patients who were poor metabolizers experienced side effects, compared to one third (33.3%) of the intermediate metabolizers and 13.2% of the normal metabolizers ($p < 0.05$). Among mutation carriers treated without dose adjustment, 63.6% experienced side effects, while only 11.1% of mutation carriers with adjusted doses experienced side effects ($p < 0.05$). Treatment was interrupted in 6.7% of the participants and completely discontinued in 7.5% of them. Hospitalization due to side effects and complications was reported in 9.7% of the cases. A statistically significant difference ($p < 0.05$) was noted between patients who had a side effect and those who did not have a side effect among these clinical outcomes.

Conclusion: These findings support the main hypothesis that DPYD mutations are connected to FP side effects and that genotype-based dosing can improve treatment safety.

Palestinian patients demonstrated limited awareness, but moderate acceptance of the pharmacogenomic testing once given some information. Healthcare practitioners are generally well-informed about this important genetic component, nevertheless it is worrisome that fewer than 50% screen for DPD deficiency prior to prescribing. Routine DPYD testing and genotype-guided dosing could improve patient safety, reduce treatment interruption and hospitalization, and support precision oncology in Palestine.

Keywords: Cancer, Pharmacogenomics, Palestine, Fluoropyrimidines, DPYD, Oncology, Chemotherapy, Polymorphism, Toxicity, Side effects.

Table of Contents

Declaration	i
Acknowledgments.....	ii
Abstract	iii
Chapter One.....	1
Introduction	1
1.1 Background.....	1
1.2 Problem Statement.....	8
1.3 Significance of the study	10
1.4 Research Goal.....	11
1.5 Context	12
1.6 Dissertation Structure	13
Chapter Two	15
Literature review	15
2.1 Prevalence of DPYD mutations.....	15
2.2 Economic impact of DPYD testing	16
2.3 Clinical factors associated with FP adverse effects.....	17
2.4 Patient perspectives	17
2.5 Willingness to pay for the tests.....	18
2.6 Specialists' perspectives	18
2.7 Link to Sustainable Development Goals (SDGs).....	19
Chapter Three.....	20
Conceptual Framework	20
3.1 Integrated Framework for Pharmacogenomic Testing and Chemotherapy Safety 20	
3.2 Framework Components	20
3.3 Application of the Framework in the Dissertation	21
3.4 Anticipated Outcomes and Relevance to Health System Improvement.....	22
Chapter Four	23
Methodology.....	23
4.1 Study I: Oncology Specialists' Perceptions and Insights into Dihydropyrimidine Dehydrogenase Testing in Palestine.	23
4.2 Study II: Cancer Patients' Perspectives and Practices Regarding Pharmacogenomic Testing and Its Cost.....	26

4.3	Study III: Pharmacogenomic and clinical factors associated with the side effects of FPs	28
4.4	Ethical measures	32
4.5	Minimization of Bias	32
Chapter Five.....		34
Results.....		34
5.1	Results of study I	34
5.2	Results of study II.....	41
5.3	Results of study III	52
Chapter Six.....		61
Discussion		61
6.1	Discussion.....	61
6.2	Conclusions	75
6.3	Limitations.....	76
6.4	Recommendations	76
References.....		79
Appendices		99

List of Tables

Table 5.1: Sociodemographic characteristics of the participants	35
Table 5.2: Awareness and practices of the participants toward DPD testing.....	36
Table 5.3: Knowledge of and observation of DPD testing in practice, determined by hospital- and demographic-related factors	40
Table 5.4: Sociodemographic and clinical information of the participants.....	41
Table 5.5: Participants' understanding of pharmacogenomics and their attitudes towards their importance and accuracy	44
Table 5.6: Attitudes and preferences of participants regarding pharmacogenomic testing	45
Table 5.7: Practices and willingness to pay.....	47
Table 5.8: Maximum out-of-pocket amount and reasonable price.....	48
Table 5.9: Relationship between understanding pharmacogenomics and education, employment and income.....	49
Table 5.10: relationship between income and willingness to pay	51
Table 5.11: Relationship between age and understanding of pharmacogenomic testing....	51
Table 5.12: Relationship between thinking that pharmacogenomic tests are accurate and willingness to provide blood sample and willingness to pay	52
Table 5.13: Sociodemographic data of the participants	52
Table 5.14: Distribution of cancer types and metastases.....	54
Table 5.15: distribution of comorbidities	54
Table 5.16: Distribution of the participants based on their DPD metabolizing status	55
Table 5.17: Frequency of side effects in the participants	56
Table 5.18: Consequences of side effects.....	57
Table 5.19: Dose adjustment by side effects	58
Table 5.20: Association between side effects and adverse treatment outcomes	58
Table 5.21: Baseline characteristics by side effect occurrence	59
Table 5.22: DPD status by side effect occurrence	60
Table 5.23: Distribution of side effects by age group	60

List of Figures

Figure 3.1: Conceptual framework of the study.22

Figure 5.1: Participants who have heard of pharmacogenomic test43

Figure 5.2: Participants who performed a pharmacogenomic test44

Figure 5.3: Main concerns about pharmacogenomic testing47

List of Abbreviations

Abbreviation	Full Form
5-FU	5-Fluorouracil
AE(s)	Adverse Event(s)
AS	Activity Score
BMI	Body Mass Index
CI	Confidence Interval
CPIC	Clinical Pharmacogenetics Implementation Consortium
DPD	Dihydropyrimidine Dehydrogenase
DPWG	Dutch Pharmacogenetics Working Group
DPYD	Gene encoding Dihydropyrimidine Dehydrogenase
DNA	Deoxyribonucleic Acid
dUTP	2'-deoxyuridine-5'-triphosphate
EHR	Electronic Health Record
EMA	European Medicines Agency
EML	Essential Medicines List (WHO)
FdUMP	5-Fluoro-2'-deoxyuridine-5'-O-monophosphate
FdUTP	5-Fluoro-2'-deoxyuridine-5'-triphosphate
FP(s)	Fluoropyrimidine(s)
GRO	Growth-related Oncogene
HCP(s)	Healthcare Professional(s)
HFS	Hand-Foot Syndrome (Palmar-plantar erythrodysesthesia)
KNMP	Royal Dutch Pharmacists Association (Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie)
LMIC(s)	Low- and Middle-Income Country/Countries
LV	Leucovorin (Folinic Acid)
MENA	Middle East and North Africa
MI	Myocardial Infarction
NIS	New Israeli Shekel
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PFS	Progression-Free Survival
PGx	Pharmacogenomics
QOL	Quality of Life
SEFH	Spanish Society of Hospital Pharmacy (Sociedad Española de Farmacia Hospitalaria)
TE	Tris-EDTA Buffer
Top1	Topoisomerase 1
TS	Thymidylate Synthase
UNRWA	United Nations Relief and Works Agency

Abbreviation	Full Form
WHO	World Health Organization
WTP	Willingness to Pay

List of Appendices

Appendix 1: Ethical approvals	99
Appendix 3: Healthcare providers' consent form- English	105
Appendix 4: Healthcare providers' consent form- Arabic	107
Appendix 5: Healthcare providers' data collection form	109
Appendix 6: Patient consent form- pharmacogenomics study- English.....	114
Appendix 7: Patient consent form- pharmacogenomics study- Arabic.....	114
Appendix 8: Patient assessment tool- pharmacogenomics study	117
Appendix 9: Patient KAP consent form and questionnaire- English	122
Appendix 10: Patient KAP consent form and questionnaire- Arabic.....	130
Appendix 11: Published article	136

Chapter One

Introduction

1.1 Background

Fluoropyrimidines (FPs), a cornerstone of modern chemotherapy, remain among the most prescribed and cost-effective anticancer drugs used around the world (Hoffmann et al., 2025).

Members of the FP pharmacological chemotherapeutic drug class, such as capecitabine and 5-fluorouracil (5-FU), are important anticancer drugs. Among the several types of cancer treated with them are metastatic colorectal cancer, metastatic breast cancer, and colon cancer (Zehra et al., 2024).

Since 1977 and 2015, respectively, 5-FU and capecitabine have been included on the Essential Medicines List (EML) of the World Health Organization (WHO) (World Health Organization, 2015). In an analysis of official medications lists for 135 countries with an average earnings rate of lower than 25,000 US dollars, 5-FU was identified as one of the most accessible chemotherapeutic drugs, being listed by 81% of the countries (Robertson et al., 2016).

Functioning through its antimetabolic activity to stop cancer development, capecitabine is a precursor that is transformed through enzymatic processes to 5-FU, the effective form of the drug (De Mattia et al., 2024; A. M. Lee et al., 2014).

Despite the development of various strategies for treatment over the past decades, such as immunotherapy and radiotherapy, FPs continue to be among the main therapeutic medications used to treat a very high number of cancers, extensively enhancing patient survival and disease control (Lu et al., 2023).

Literature has shown that a significant percentage (between 10% and 40%) of patients have severe and probably fatal toxicity in the first cycles of FP treatment (Froehlich et al., 2015; Lee et al., 2014). Sometimes, the presence of toxicity causes disruption or termination of possibly effective anticancer treatment, and in particularly extreme situations, this may call for an emergency department visit or hospital admission (Amstutz et al., 2009; Deenen et al., 2016b).

1.1.1 Mechanism of action of FPs

FPs are classified as antimetabolite anti-cancer drugs, and their activity stems from intracellular transformation into active products that affect thymidine production and impact DNA- and RNA-dependent pathways. The main molecular target of FP antineoplastic action is thymidylate synthase (TS), which is essential for endogenous thymidylate (thymidine 5'-O-monophosphate) production. TS is a recognized site for tumor treatment, and virulent cancer tissues are fairly of higher dependence on endogenous thymidylate production than normal tissues, which employ the substitutional reutilization routes. The significance of interfering with TS for FP anti-tumor action is highlighted by its consistent medical utilization combined with folinic acid (Leucovorin; LV), an active folate catalyst that associates with TS in a tertiary structure with 5-Fluoro-2'-deoxyuridine-5'-O-monophosphate (FdUMP), which is the 5-FU product that permanently suppresses TS enzymatic action. Inactivating TS reduces the amount of thymidylate in cells, causing more mistakes when 2'-deoxyuridine-5'-triphosphate (dUTP) is added to DNA. Inside tissues managed using FPs, 5-fluoro-2'-deoxyuridine-5'-triphosphate (FdUTP) is similarly inappropriately embedded within DNA, which leads to topoisomerase 1 (Top1)-triggered DNA destruction (Gmeiner & Okechukwu, 2023).

FPs, including 5-fluorouracil and its oral prodrugs such as capecitabine and tegafur, undergo extensive and predominantly hepatic metabolism following administration. Prodrug formulations are first converted through sequential enzymatic steps to generate 5-fluorouracil, which then enters both anabolic and catabolic metabolic pathways. The anabolic pathway leads to the formation of active nucleotide metabolites, including fluorodeoxyuridine monophosphate and fluorouridine triphosphate, which interfere with thymidylate synthesis and nucleic acid function. In parallel, FPs are subject to rapid enzymatic degradation through pyrimidine catabolic pathways, resulting in inactive metabolites that are subsequently eliminated via renal and respiratory routes. The balance between these metabolic pathways determines systemic exposure to active metabolites and contributes to interindividual variability in pharmacokinetics. Overall, the extensive first-pass metabolism and short plasma half-life of fluoropyrimidines underscore the importance of metabolic processes in shaping their clinical activity (Ho et al., 2025).

1.1.2 FP-related toxicities

Despite being very effective, FP therapy can lead to a variety of side effects, including cardiotoxicity (Deac et al., 2020a), gastrointestinal side effects (Sonbol et al., 2025), myelosuppression (Afolabi et al., 2023) and (HFS) (Wongkraisri et al., 2025).

Therapy with FPs is connected to a very wide range of cardiovascular side effects, most commonly angina and electrocardiographic (ECG) changes. They range from emboli to coronary artery contraction, leading to different levels of myocardial ischemia presenting as angina pectoris, myocardial infarction (MI), or even sudden death. Coronary angiography has identified that the main sign of coronary disease is chest pain, characterized by conventional or atypical angina pectoris (More et al., 2021).

Devastating cardiovascular complications like acute coronary syndrome (MI), cerebral ischemia, and dysrhythmia were reported in several pharmacovigilance reports and retrospective observational studies. Recent research with control non-cancerous arms revealed that subjects with gastrointestinal tumors and no previous ischemic heart disease managed with FPs had relatively more risk of myocardial infarction (0.9%) (Shanmuganathan et al., 2021).

The exact pathophysiologic mechanism of cardiotoxicity caused by FPs has not been completely described. Numerous potential processes such as coronary vasospasm, endothelial injury, and collection of toxic by-products were advocated. The lack of arterial obstructions in the majority of subjects is not compatible with vascular thrombosis being the main cause of this toxicity. Physiologically, preclinical studies verified that 5-FU leads to vasoconstriction through protein kinase C routes (Jurczyk et al., 2021; Wong et al., 2025).

FP therapy can frequently cause adverse gastrointestinal symptoms. More than half of the patients with advanced breast tumors treated with these drugs usually experience digestive disturbances such as diarrhea (53%) and nausea (57%). Other common adverse events include oral mucositis (24%), emesis (37%), abdominal cramps (20%), difficult defecation (15%), and indigestion (8%). The capecitabine monodrug regimen was linked to ileus in 0.3% of patients. Less than 1% of patients receiving treatment develop gastric ulcers, ascites, and gastroenteritis (Northstar, 2024).

Twenty-one recorded cases of capecitabine-induced enterocolitis are described in a case report and literature review released in 2022. Among these cases, around 19% ensued when the drug was used as induction, primary, or secondary treatment (Klimko et al., 2021).

Among the adverse effects caused by chemotherapeutic drugs such as FPs is myelosuppression. Myelosuppression is an adverse effect caused by chemotherapy that results in a lowered capability of the bone marrow to produce blood cells, causing pancytopenia (Kobuchi et al., 2024). The main reason for myelosuppression is that when chemotherapy attacks tumor cells, it additionally inhibits the bone marrow cells, which are highly proliferative and poorly differentiated, leading to the suppression of all undeveloped cells with proliferative abilities. Main indicators of myelosuppression incorporate neutropenia, anemia, and thrombocytopenia, leading to adverse reactions such as fever, rash, and arthralgia. More seriously, the lower number of neutrophils and platelets may substantially increase the risk of life-threatening events caused by infection and bleeding. Additionally, when severe myelosuppression is diagnosed, it compels a reduction in chemotherapy dosage or a suspension of therapy, affecting the clinical benefits of the

treatment. Consequently, proper, early diagnosis of chemotherapy-induced myelosuppression is of supreme importance (Du et al., 2025).

HFS, which is known as Palmar-plantar erythrodysesthesia, is a dose-limiting side effect of FPs, which is characterized by painful erythema, edema, desquamation, and paresthesias over hands and feet. The incidence of HFS is highly variable, and more than half of patients receiving capecitabine suffer from it. Despite the fact that HFS is not life-threatening, it is connected with deterioration of the quality of life (QOL) and requires dose reduction of capecitabine (Ferreira et al., 2019). Studies indicate that the highest incidence of HFS is spotted in the second cycle of capecitabine, while approximately 90% of HFS will be observed by the fourth cycle of capecitabine.

The pathophysiology of HFS is incompletely recognized, but immediate toxic response is proposed as the most probable mechanism. Medication metabolite buildup in cutaneous tissue, arising from elevated amounts of the thymidine phosphorylase and higher levels of DPD enzymes in skin cells, is associated with HFS incidence. Moreover, the higher count of eccrine glandular tissues at the soles and palms can hold significant relevance because capecitabine can be eliminated by this mechanism. The nature of the dense skin layers of the palms and soles constitutes a major factor as being a storage site, which might lead to an oxidant-mediated tissue injury and generate harmful free radicals. Chemokines playing a role in this process comprise interleukins (IL), such as types 1a, 1b, 6, and 8, in addition to growth-related oncogene (GRO) and adhesion molecules such as fractalkine (CX3CL1) (Elyasi et al., 2022).

1.1.3 DPYD polymorphism

Across the genetic elements believed to have a major role in the development of FP toxicity and intolerance, the DPYD gene has received significant attention in scientific research (De Mattia et al., 2024). This gene is responsible for encoding the main enzyme that plays a very critical part in the degradation process of FPs, leading to the production of metabolites with no biological activity (Ho, Smith, Aquilante, Cicali, El Rouby, Hertz, Imanirad, Patel, Scott, Swain, Tuteja, & Hicks, 2025). Individuals with DPD deficiency possess a markedly heightened susceptibility to serious FP adverse effects. The earliest reported incidence of a subject seen with 5-FU serious adverse effects related to DPD malfunction occurred in 1985 (Tuchman et al., 1985). Consequently, the classification of persons based on their DPYD type shows potential in affecting the incidence of adverse effects (Gentile et al., 2016). Grade > 2 toxicity is shown by a significant proportion of patients with a DPYD type linked to a DPD functional deficiency (Coenen et al., 2019). For example, 73% of the DPYD*2A carriers have been found to have grade ≥ 3 toxicity (Deenen et al., 2016a). In addition to DPYD*2A, studies have shown a similarly higher risk of severe side effects for the other two variants included. Carriers of DPYD13 (c.1679T>G) have been found to experience grade ≥ 3 toxicity in approximately 50–100% of cases, with some studies indicating markedly greater risks for hematological and gastrointestinal side effects compared to individuals without this mutation (Meulendijks et al., 2015). For c.2846A>T, severe side

effects were observed in around 60–100% of carriers, with odds ratios up to 8.2 for overall side effects and 6 for diarrhea (Otero-Torres et al., 2025).

Therefore, assuming that it can avoid 20 to 30% of serious or fatal FP adverse effects and revealing an economically efficient strategy, the initial DPYD testing has a vital effect on the mitigation of treatment-induced adverse effects (Conti et al., 2020).

Many human organs express the DPYD, with hepatic and peripheral blood mononuclear cells (PBMCs) exhibiting the highest levels. DPYD, positioned on chromosome 1p21.3, is a sizable pharmacogenetically relevant gene that is roughly more than 900 kb in size. It has 23 rather minor exons (69 to 961 bp) that are separated by big non-exonic segments. A protein with over 1000 amino acid molecules is encoded by the roughly 3 kb coding sequence. Significant polymorphism is present in DPYD; the Genome Aggregation Database (gnomAD v2.1.1) contains 569 missense types and 204 synonymous types, among which 40 are expected to cause enzymatic function loss (Karczewski et al., 2020).

Clinically evident DPD deficiency is an uncommon recessively inherited disorder that has a broad array of symptoms, varying from an absence of any observable symptoms or indicators to the manifestation of severe neurological complications (Malekkou et al., 2024). In those who are affected, the activity of DPD is either absent or significantly diminished, leading to the buildup of thymine and uracil in the blood, cerebrospinal fluid, and urine. Neuroclinical features commonly present during the early stages of childhood, encompassing manifestations such as seizures, microcephaly, and impaired cognitive and motor development (de Moraes et al., 2024). The manifestation of DPD deficiency is commonly attributed to the biallelic inactivation of DPYD, where those who possess heterozygous genotypes are likely to remain without symptoms (Sharma et al., 2021). Nevertheless, those who exhibit DPD activity below 70% are deemed to be susceptible to the occurrence of severe drug toxicity when undergoing FP treatment (Hernández-Guío et al., 2024). Capecitabine toxicity is characterized by the presence of several clinical manifestations, including but not limited to debilitating diarrhea, extensive mucosal inflammation, low neutrophil count, hand-foot syndrome, and neurologic toxicities (Innocenti et al., 2020).

1.1.4 Dosing recommendations based on DPYD polymorphism

According to the FDA-official prescription guideline for capecitabine, there is currently no established safe dosage for patients with deficient DPD function. Additionally, at hand is inadequate information to support a recommended dosage for patients with incomplete DPD function, as determined by any particular biochemical assay (CAPECITABINE-Capecitabine Package Insert, 2020).

The dose guidelines for FPs (specifically capecitabine and 5-fluorouracil) were issued by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and also by the Dutch Pharmacogenetics Working Group (DPWG), taking into account the DPYD genotype. Both consensus recommendations include reducing the dosage for those with intermediate metabolizer status, characterized by reduced enzyme activity. Additionally, it is advised to avoid fluorouracil and instead choose an alternative therapeutic agent in cases of poor

metabolizers who exhibit nonexistent enzyme activity (Amstutz et al., 2018; Lunenburg et al., 2020; Royal Dutch Pharmacists Association (KNMP), 2020).

The recommendation guideline published by the CPIC in 2013 provided detailed dosing guidance for FP depending on three DPYD types linked with diminished enzymatic action. These variants include DPYD c.2846A>T (rs67376798), c.1905+1G>A (*2A, rs39818290), and c.1679T>G (*13, rs55886062). Individuals who possess a heterozygous variant are advised to undergo a 50% reduction in dosage, while those who are biallelic or compound heterozygous type carriers are advised to completely discontinue the use of FPs.

The allelic sum (AS) of each patient is calculated by adding up the scores assigned to each allele, which range from 0 to 1 dependent on their functional characterization. The allele frequencies of DPYD c.1905+1G>A or c.1679T>G are 0, indicating their absence in the clinically relevant population. On the other hand, the allele frequencies of DPYD c.2846A>T or c.1129-5923C>G are 0.5, indicating their presence in half of the clinically relevant population (Miarons et al., 2023).

For individuals with intermediate metabolizing capacity, it is advised to reduce the dosage by 25% to 50% when the AS is 1.5. Similarly, a 50% dose reduction is indicated for those with an AS of 1, while individuals with an AS ranging from 0 to 0.5 should avoid taking the medication altogether (Henricks et al., 2018).

In 2018, research findings prompted revisions to the CPIC guidelines, resulting in a recommendation of a 50% reduction in dosage for patients with an AS score of both 1 and 1.5. Additionally, after applying a well-tolerated reduction in the initial dose of the drug, the CPIC guidelines suggest a careful increase in dose in addition to concurrent therapeutic drug monitoring if it is possible. It is worth mentioning that the CPIC guidelines serve as a basis of comparison for individuals who have genetic information readily available, and they do not address the requirement of proactively discovering the DPYD genotype (CPIC, 2018).

Dose modification based on DPYD genotyping results does not seem to exert a devastating effect on the efficacy of FP-derived regimens (Henricks et al., 2019). Particularly in pooled cohorts of DPYD variant carriers, recent retrospective analyses have revealed that DPYD genotype-based dose individualization does not seem to impair the efficacy of FP-based chemotherapy, evaluated as endpoints like progression-free survival (PFS) and overall survival (OS) (Glewis et al., 2022). These outcomes fit previous data on the DPYD *2A mutation. Though protocol guidelines allow for escalation when tolerated, a possibly shorter PFS in carriers of the c.1236G>A (HapB3) allele remains a concern, especially given a significant proportion of these individuals (about 75.8%) received a fixed reduced dosage without subsequent titration. Similarly, the effect of the c.2846A>T mutation on treatment outcomes is still uncertain, mostly due to small sample sizes and variations in controlling strategies among studies. Even after a normal reduction of dose by 25%, both c.1236G>A and c.2846A>T patients continue to show particularly higher rates of severe FP-induced adverse effects than wild-type carriers. This data emphasizes the variability in DPD enzyme activity and suggests that fixed dose reductions would not provide adequate protection for

all mutation carriers. Thus, thorough clinical monitoring with tailored dosage changes depending on real-time toxicity profiles is advised more and more to maximize the balance between therapy safety and efficacy in DPYD variant carriers (Knikman et al., 2023).

1.1.5 Clinical factors

Although earlier studies clearly show the important contribution of DPYD polymorphism in determining FP toxicity, it is important to recognize that the complex nature of this phenomenon requires more extensive research. In fact, it has been estimated that a percentage between 30 and 50% of patients treated with FPs present with severe adverse reactions, despite not having a DPD deficiency linked to DPYD polymorphisms. Apart from genetic factors, several other factors have been under close examination in various studies to fully grasp the complex interaction engaged in drug toxicity under FP-based chemotherapy. Especially, factors like patient age, the existence of metastases, comorbidities, utilizing other drugs, and the count of therapy cycles have been investigated and shown relationships with therapy-associated adverse effects (Li et al., 2021a).

These results highlight the need to realize that factors other than genetic predisposition might affect individual reactions to chemotherapy and stress the need for a comprehensive approach to patient care. Integrating these multiple factors into our knowledge of FP toxicity will help us to create more complex and customized plans to minimize side effects and maximize therapy results for cancer patients (Chamorey et al., 2020; Wang et al., 2023).

Patient age is among the most often cited clinical predictors of FP toxicity. Because of age-related physiological changes, including lower renal and hepatic function, which can raise systemic drug exposure and increase the risk of adverse effects, older persons often show slower drug clearance (Garcia et al., 2018). Furthermore, common among elderly patients are polypharmacy and other comorbidities, both of which might complicate treatment and increase toxicity by pharmacodynamic interactions or organ susceptibility (Oliveira et al., 2024). Older people are generally underrepresented in clinical studies despite these hazards, which results in an evidence gap for the safe and efficient use of FPs in this population. Treating older cancer patients calls for tailored risk-benefit evaluations (Sedrak et al., 2021).

Apart from age, other clinical factors, including performance status, nutritional state, and existence of metastatic disease, have been linked to toxicity connected with treatment. Low albumin levels and poor performance status, for instance, could be reflections of a weak physiological reserve that increases patients' toxin load. Patients with hepatic or renal disease may also collect active medication metabolites, which raises their risk of gastrointestinal or hematologic problems (Challoob & Mohammed, 2024).

Moreover, dose-limiting toxicities have been associated with the total number of chemotherapy cycles and combination with other cytotoxic drugs (e.g., oxaliplatin or irinotecan) (Khali et al., 2022). Since FP is commonly used in conjunction with both biological and conventional antineoplastic therapies, such as cetuximab and bevacizumab, it can be difficult to determine the relationship between FP and specific adverse events. These

drugs, along with irinotecan and oxaliplatin, can cause myelosuppression and diarrhea similar to FP (Conti et al., 2020).

Numerous factors have been found to be linked to an increased probability of FP-associated cardiotoxicity. These factors include a history of cardiac problems, hypertension, and smoking (Li et al., 2021b).

Tailoring treatment plans, deciding starting dosages, and organizing proactive supportive care programs to minimize side effects depend on an awareness of these clinical aspects.

1.1.6 Healthcare providers' knowledge, attitudes, and practices

Even though healthcare providers are central to the adoption of pharmacogenomic testing, worldwide evidence shows a significant gap in their readiness. Studies in Europe and Asia indicate that although healthcare providers recognize the clinical value of testing, they often do not have adequate training, proper protocols, nor institutional support that are all needed for routine implementation (Ferwerda et al., 2024; Jarrar et al., 2021; Naaem et al., 2024a). This discrepancy between healthcare providers' awareness and their practice emphasizes a critical barrier to implementation (Keeling et al., 2021).

These gaps are particularly important in contexts where oncology services are extremely constrained by limited resources. Without healthcare providers' confidence in their results and clear guidance when and where to apply them, the translation of pharmacogenomic advances into safer and more individualized chemotherapy regimens remains inadequate (Shrestha et al., 2025; Sukasem et al., 2021). Evaluating healthcare providers' knowledge, attitudes, and practical barriers is consequently essential to building capacity for individualized cancer care (Moore et al., 2023).

1.1.7 Patients' knowledge, attitudes, and willingness

Patient perspectives are also very critical in shaping the feasibility of pharmacogenomic testing. Research in Europe and North America has shown that awareness about these tests remains very low, but patients' interest rises substantially once they receive simple explanations of the nature of the test and the expected benefits. This indicates that communication and education are key determinants of patient's acceptance (Veilleux & Bouffard, 2019; Zubiaur et al., 2022).

Financial and ethical considerations can also influence patients' decisions. Studies consistently reported that cost, privacy, and clarity of benefit are the most important factors that affect patients' willingness to undergo pharmacogenomic testing (Allen et al., 2022). In settings with limited resources or high out-of-pocket health expenditure, these barriers are augmented. Understanding patient attitudes and willingness to pay is therefore a necessity for proper implementation of DPYD testing (Abushanab et al., 2025a).

1.2 Problem statement

The body of existing data shows that the frequency of people having nonfunctional mutant DPYD alleles causing partial DPD deficiency shows variation among various groups

(Miarons et al., 2023). Among those with Caucasian ancestry, the frequency of these alleles ranges from 3 to 5%; a subset of 0.2% shows total DPD deficiency (Boisdron-Celle et al., 2017). Numerous studies have highlighted the clear differences in allele frequencies between Asian groups and those of African and European populations, thus stressing the need for doing studies catered to particular groups (Almashagbah et al., 2022; de With et al., 2023; Gil-Rodriguez et al., 2025; Hariprakash et al., 2018; Kim et al., 2022; Sedrak et al., 2021; Zhou & Lauschke, 2018).

Several studies have shown that individuals from the eastern and southern parts of Africa, as well as the eastern parts of Asia, do not exhibit European DPYD variations. Furthermore, non-European populations may be greatly impacted by differences that are not found in European populations, and vice versa. As a result, the testing carried out by European countries and the NHS in the UK cannot detect inherited variations in most non-European cohorts, which are going to be labelled as normal and administered standard dosages of FP medications, posing a risk of adverse effects and/or even death. In ethnically diverse communities, this could exacerbate racial and health disparities. Furthermore, because there is not enough evidence to support its use, DPYD genetic testing will not be adopted in countries with a population that is predominantly non-European (Chan et al., 2024).

Many studies conducted out in nearby countries, including Jordan and Saudi Arabia, have revealed the frequency of DPYD gene variations and their relationships with drug toxicity and disease outcomes (Alkharfy et al., 2013; Almashagbah et al., 2022; Sukkarieh et al., 2023; Yousef et al., 2018). However, it's important to understand that these studies assessed the likelihood of adverse reactions by focusing just on DPD polymorphism and neglected other clinical elements.

In addition, there have been investigations into the cost-efficiency related to DPYD genotyping before administering FP-based treatment in some countries. These studies have shown the potential advantages of this approach in preventing the occurrence of severe and sometimes lethal toxicities (Brooks et al., 2022; Deenen et al., 2016b)

Therefore, it is imperative to close this knowledge gap by means of more studies on the frequency of DPYD gene variations and their impact on the results of FP-based chemotherapy in the context of the Palestinian healthcare system. The goal of this study is to not only improve our knowledge of the genetic components of treatment toxicity but also offer direction for clinical decision-making and maybe increase the safety and efficacy of chemotherapy treatments for Palestinian patients.

In addition to DPYD genotyping, other important clinical variables, including socioeconomic factors, cancer types and stages, drug type, and number of chemotherapy cycles, will also be extensively studied. We have an opportunity to make important contributions to the general knowledge of DPYD insufficiency and the development of customized treatment approaches inside Palestine by appreciating and investigating this wide range of elements in an area of research that has not been well investigated.

Estimating the genetic prevalence of DPYD mutations is crucial, but, on the other hand, it is similarly crucial to assess the level of knowledge and attitudes of healthcare professionals towards the application of pharmacogenomic testing in actual clinical practice. Inadequate awareness or wrong beliefs among oncology specialists regarding DPYD testing, interpretation of results and subsequent dose adjustment instructions, can prevent the translation of test findings into safer chemotherapy protocols. This challenge is further compounded by systemic barriers within the fragmented healthcare system, including limited access to advanced diagnostic infrastructure, absence of standardized testing pathways, variability in institutional policies, and lack of integration of pharmacogenomic results into routine clinical decision-making.

Furthermore, patient knowledge, attitudes, and willingness to perform pharmacogenomic testing in addition to economic constraints, are important factors in the successful implementation of the testing process. Inadequate knowledge regarding the objectives, benefits, and implications of the tests may negatively affect patient acceptance, leading to lower likelihood for side effect prevention. Among many factors, personal and cultural beliefs, trust in the health system, and previous experience with testing can all affect acceptance rates.

1.3 Significance of the study

Although DPD genotyping is important and other factors have been linked to FP toxicity in other populations, our knowledge of its relevance in the framework of Palestinian cancer patients is inadequate. Not yet has any research thoroughly investigated the frequency of DPD genetic variants and their association with FP-related toxicities in this particular population. A global meta-analysis estimated that 3-5% of European people and up to 8% of the population have at least one DPYD mutation while complete DPYD deficiency was estimated to have a small prevalence of less than 0.2%. These numbers set a primitive benchmark for comparing the frequency in the Palestinian population (Adejumo et al., 2023).

Recent studies of 500 solid-tumor patients treated with FPs have shown that 17% of these patients suffered $\geq$ grade 3 toxicity within 60 days of administration, resulting in an excess of 5.5 days of inpatient hospitalization and premature discontinuation of treatment in 7.8% of these cases (White et al., 2024). Consequently, by prospectively capturing similar endpoints in Palestine and cross-tabulating them with DPYD testing, this study will provide the local incidence and cost information required to tailor the available international guidelines for FP dosing in Palestine. Moreover, this study acknowledges the necessity of investigating multiple factors that could affect the course of treatment for Palestinian cancer patients. Apart from DPD genotyping, the study will take into account the particular cancer type and stage, drug type, income, and access to healthcare facilities, as well as other potentially important clinical variables. By including this wide spectrum of factors in our study, we hope to present an overall understanding of the complex interaction among genes, socioeconomic level, and clinical variables, thus leading to more customized and successful treatment plans for Palestinian cancer patients.

Successful translation of pharmacogenomic guidelines requires the acceptance of appropriate stakeholders. Subsequently, patients were asked to fill out the pre-validated questionnaire that measures their knowledge and estimates their willingness to pay. Evidence from similar LMICs indicates that patients were willing to pay around US \$50 for pharmacogenomic testing and that health literacy was positively correlated with the uptake of the test. In parallel, Palestinian oncology specialists and payers were surveyed using proper instruments similar to those that were used, for example, in Saudi Arabia, where less than 20% of specialists order pharmacogenomic testing despite their previously known clinical value (Sukkarieh et al., 2023). Identifying those behavioral and systemic barriers can inform an economic analysis and a clear roadmap for the local policymakers to ensure that research findings translate into sustainable policy and practice.

This work has great relevance for the field of oncology in Palestine since it attempts to close this important knowledge gap. By investigating the genetic polymorphisms of DPD in Palestinian cancer patients and considering a wider spectrum of factors, including gender, age, other medications, metastasis, and providers and patients' perspectives, we aim to achieve the following objectives:

- 1- Enhance Treatment Safety: A thorough knowledge of DPD genotyping in Palestinian patients together with an analysis of related variables such as gender, age, disease stage, type of tumor, medication source, and other given medications will help oncologists to identify individuals at great risk of severe capecitabine-induced toxicities. This information will help create tailored treatment plans that minimize side effects and maybe save lives.
- 2- Optimize Healthcare Resources: By avoiding unnecessary hospitalizations and treatments for toxicity management, customizing therapy according to DPD genotyping coupled with consideration of other parameters like metastases helps more effectively utilize healthcare resources.
- 3- Contribute to Precision Medicine: This study fits into the global trend toward precision medicine, in which treatment decisions are directed not just by an individual's genetic makeup but also by several elements, including gender, age, and metastatic status. More focused and powerful therapies follow this all-encompassing approach.

Ultimately, the importance of this study resides in its ability to clarify the often disregarded but crucial element of DPD genotyping while simultaneously investigating additional variables related to toxicity, thus offering a more complete knowledge of the complex interaction in cancer treatment outcomes. This will help improve the management of cancer in Palestine.

1.4 Research Goal

The main goal of this study is to closely look at how important DPD genotyping and other clinical factors like gender, age, other medications, and cancer spread are in relation to side effects from FPs in cancer patients from the Palestinian population. It also aims at assessing

the level of awareness of both the oncology specialists and cancer patients about pharmacogenomic testing related to the side effects of anticancer drugs.

1.4.1 Study Objectives:

1.4.1.1 Study number I:

- 1- Assess the awareness of HCPs (oncology specialists, residents, and clinical pharmacy practitioners) in Palestine with pharmacogenetic screening in general and DPYD screening tests in particular before administering FP to cancer patients.
- 2- Evaluate if demographic variables such as age, hospital unit, length of practical experience, and present position affect awareness.
- 3- Assess the current prevalence, utilization, and barriers to implementing DPYD testing and pharmacogenomics in Palestine.

1.4.1.2 Study number II:

- 1- Examine cancer patients' perceptions, attitudes, and practices about pharmacogenomic testing in addition to their willingness to pay for these tests in the setting of cancer therapy.
- 2- Examine sociodemographic, clinical, and financial elements associated with patients' perceptions, attitudes, and willingness to pay for and undergo pharmacogenomic testing.
- 3- Examine possible psychological, ethical, or privacy concerns affect cancer patients' acceptance or rejection of pharmacogenomic testing.
- 4- Provide recommendations for the method through which policy makers and medical professionals can raise patients' involvement, education, and equitable access to pharmacogenomic testing in cancer treatment.

1.4.1.3 Study number III:

- 1- Determine the prevalence of DPD genetic variations.
- 2- Examine the correlation between DPD genotypes and FPs-related toxicities.
- 3- Evaluate the impact of other factors on toxicity profiles.
- 4- Develop personalized treatment recommendations.
- 5- Contribute to precision medicine in oncology.
- 6- Evaluate the level of knowledge and perceptions of oncology professionals in Palestine regarding pharmacogenomic testing for DPD before administering FP.

1.5 Context

Palestine, with a population of slightly more than five million, has one of the most fragmented healthcare systems in the world.

Several entities, including the Ministry of Health, UNRWA, NGOs, and the private sector, provide healthcare in Palestine. These entities lack good communication, leading to poor coordination in service provision and instability in the care provided.

Despite being resilient towards the extreme obstacle it faces, the healthcare system has great challenges of separation due to the occupied status leading to difficult transportation,

separation between the West Bank, Gaza Strip, and East Jerusalem, lack of medical supplies, old infrastructure, and poor funding.

Financially, the healthcare system relies on governmental funding, donations, and high out-of-pocket expenditure by the citizens, causing high pressure on the households in addition to inequity in service.

Globally, according to the WHO's worldwide status report on non-communicative illnesses in 2021, 43 million deaths (75% of non-pandemic-related deaths) were related to Non-Communicable Disease (NCDs), including cardiovascular disorders (19 million) and cancer (10 million). Around three-quarters of these deaths happened in resource-limited countries (World Health Organization, 2021).

Locally, the WHO estimates that NCDs cause almost 75% of all deaths in the West Bank; from these, ischemic heart disease (IHD) makes up the highest percentage (25.4%), followed by cancer (16.5%) and diabetes mellitus (16.3%) (World Health Organization, 2016).

With a death rate of 47.8 per 100,000 people, cancer ranks second among all the causes of death in Palestine in 2023, according to the Palestinian Ministry of Health report (Palestinian Ministry of Health, 2024).

In 2023, the overall count of newly discovered cancer patients in Palestine was 3590, exhibiting an incidence rate of 122.1 for 100,000 residents. Drawing a comparison between new cases discovered in 2023 with cases diagnosed in 2022 (3408 cases), it is evident that there is a 5.3% rise in the number of new cases in 2023 (Palestinian Ministry of Health, 2024).

The numbers presented above indicate an increasing burden of cancer within a fragmented and under-resourced health system. Due to the rising incidence of cancer, especially in settings with limited resources, the need for more evidence-based and context-specific intervention also increases. Particularly, to ensure the safety and efficacy of chemotherapy regimens, such as those containing FPs, it is essential to develop a deeper understanding of all the genetic and clinical factors that influence the treatment outcomes. Within this fragile healthcare landscape, integrating interventions like DPYD can contribute to a more sustainable and equitable provision of care in addition to enhancing patient safety.

1.6 Dissertation Structure

This dissertation is divided into six chapters, each serving a main purpose to escort the reader through the research process and results:

- **Chapter 1: Introduction**

This chapter defines the foundation and context of the study, displays the problem statement, and specifies context for the research. It also explicitly describes the aim and objectives that lead the study.

- **Chapter 2: Literature Review**

This chapter demonstrates a critical review of existing literature on pharmacogenomics, including international, regional, and local studies. Gaps in the literature are identified, and the study directions are built to fill these gaps in a logical manner.

- **Chapter 3: Conceptual Framework**

The conceptual framework is detailed in this chapter. It is a collective work that consists of the main factors that affect the integration of pharmacogenomic testing into the treatment protocols of cancer patients.

- **Chapter 4: Methods**

The study design and methodology, including the study setting, population, sampling techniques, sample size, and data collection instruments are presented in this chapter.

- **Chapter 5: Results**

This chapter presents the results of the three studies. It provides a detailed analysis of the data collected through each part of the research.

- **Chapter 6: Discussion, Conclusions, Limitations and Recommendations**

This chapter discusses the results of each part in the context of the research aim and the available literature. It also considers the association with health policy and evidence-based practice guidelines, emphasizes study limitations, and specifies recommendations for future research projects and health system improvements.

Chapter Two

Literature review

2.1 Prevalence of DPYD mutations

Generally, the percentage of individuals who possess nonfunctional mutant DPYD alleles (resulting in partial DPD deficiency) and are susceptible to severe drug reactions is estimated to range from 5% to 8%. However, it is important to note that this frequency may differ across various groups (Gil-Rodriguez et al., 2025; Kim et al., 2022).

Among individuals of Caucasian descent, an estimated 3 to 5% have incomplete DPD deficiency, while roughly 0.2% display total DPD deficit. According to contemporary research findings, it has been indicated that approximately 8% of individuals of Caucasian descent possess at least one of the four most widely recognized alleles associated with altered functionality (Henricks et al., 2018).

Asian populations exhibit different allelic distribution in comparison to residents of Africa and Europe. The prevalence of c.85T>C (*9A, rs1801265) normal functionality type was found to be marginally inferior in Chinese, Korean, and Japanese inhabitants in comparison to African inhabitants. However, the frequencies of the c.2657G>A (*9B, rs1801267) normally functional type, as well as the c.295_298delTCAT (*7, rs72549309), c.703C>T (*8, rs1801266), and c.2983G>T (*10, rs1801268) nonfunctional types, remained comparable between those ethnic populations. In research involving individuals of other Asian populations, the presence of the c.1905+1G>A (*2A/*2B, rs3918290) and c.1679T>G (*13, rs55886062) alleles with nonfunctional activity was undetected. This finding highlights the infrequency of these alleles (Shin et al., 2013). A comprehensive examination of various genotyping studies conducted on populations in South Asia revealed a high

prevalence of the standard activity rs2297595 (c.496A>G) type in this region (Hariprakash et al., 2018).

In Jordan variants of DPYD gene were evident and were also significantly correlated with 5-FU toxicity. Four variants were identified, of which three were documented earlier: c.85T>C c.1740+40A>G, and c.1740+39C>T and another unique type g.97515583_97515584insA. The DPYD variant allele frequencies were 68.7% for c.85T>C, 58.7% for c.1740+40A>G, 13.1% for c.1740+39C>T, and 6.3% for the novel g.97515583_97515584insA variant (Almashagbah et al., 2022).

Another study in Jordan on 103 colorectal patients found that a certain DPYD polymorphism (DPYD 496A>G) was associated with disease free survival (DFS) (Yousef et al., 2018).

Regional studies show that pharmacogenomic information is not adequately presented in drug labelling. An analysis of drug 75 drugs approved by the Jordanian FDA found that pharmacogenomic information was complete in only 25% of oncology drugs. This is significantly lower than what is present in the US and most European countries (Jarrar et al., 2025). This highlights a gap that might lead to inadequate understanding of important pharmacogenomic information by the clinicians and lower rates of test application.

A Saudi study found that an estimated percentage of 1.3% of the population possess a combination of one functional allele and either single null allele or single allele with diminished functionality, which is indicative of an intermediate metabolizer phenotype. The study also identified the presence of the DPYD uncommon pathogenic variant (c.257C>T) within the Saudi population. This mutation has been associated with the potential for significant toxicity in individuals who are heterozygous for the mutation, as well as the possibility of lethality in cancer patients who are homozygous for the mutation and undergoing treatment with FPs (Goljan et al., 2022).

In Tunis, twelve different genetic variations were identified within the exonic location of the DPYD gene, and the DPYD alleles associated with DPD deficiency, namely DPYD2A, DPYD3 (1897 del C), and DPYD4 (G1601A), were not found in the individuals under examination. Additionally, a previously undocumented intronic polymorphism known as IVS 6–29 g>t was identified, with an allele frequency of 4.7% within the inhabitants of Tunis. This discovery represents the first description of this particular genetic variation in this population (Ben Fredj et al., 2007).

2.2 Economic impact of DPYD testing

An economic evaluation of DPYD testing before FPs for colon tumors found that amid subjects administered FPs for advanced colon cancer, detection for DPD mutations with DPYD profiling is an economically efficient technique for avoiding uncommon but serious and occasionally fatal adverse effects of FPs. In comparison to no testing for DPD malfunction, DPYD testing elevated individual costs by US \$78 and enhanced survival by 0.0038 quality-adjusted life years (QALYs), resulting in an ICER of around US \$20,000/QALY (Brooks et al., 2022).

A similar study measured the standard of care against the alternative of DPYD genotyping before administering FPs in Qatar. In their limited duration projection, DPYD testing demonstrated superiority compared to standard of care, yielding an average expenditure reduction of QAR 85,000. This economic saving shows the comprehensive cost advantages linked to the execution of DPYD testing. In their extended-duration scenario, relative to the existing standard of care, DPYD testing will yield an ICER of QAR 21,000 per QALY acquired (Abushanab et al., 2025b).

A systematic review of 29 studies comparing standard therapy with pharmacogenomic-guided therapy found that patients treated without DPYD genotyping had a higher likelihood of having more side effects, hospitalization and treatment discontinuation. In addition, publicly funded DPYD guided dosing was expected to lower the overall treatment cost of more than USD 700 thousand over the next five years (Ontario Health (Quality), 2021).

2.3 Clinical factors associated with FP adverse effects

Several other factors were identified to affect the incidence of FP adverse effects. The number of chemotherapy cycles was identified to be a factor that is positively correlated with toxicity (De Forni et al., 1992; Meydan et al., 2005; Peng et al., 2018).

Age was also identified by many studies to affect the toxicity of FPs. Age more than 60 was associated with a higher odd of FP-induced toxicity (Jensen & Sørensen, 2006; Meyer et al., 2012).

Dosing route could also affect the toxicity rate. Univariable logistic regression showed that 5-FU-based treatments were notably linked with serious toxicity in comparison to oral capecitabine-based treatments (OR, 1.69); this association was insignificant in the multivariable investigation. Patients using oral capecitabine would have more freedom to change doses during treatment depending on tolerability as 5-FU is typically administered as an IV injection with subsequent IV infusion over several days according to the therapeutic plan. The lower first cycle relative dose intensity in individuals given capecitabine in comparison to 5-FU supports this. Furthermore, unlike FP monotherapy, combined therapies were clearly linked to serious adverse events (OR, 1.69). Combined chemotherapy protocols could show intersecting adverse events with FPs, thereby adding to the high toxicity rate (Nguyen et al., 2024).

2.4 Patient perspectives

The clinical and economic consequences of DPYD testing have been extensively studied but on the other hand, patient perspectives remain a fairly underexplored area predominantly in underdeveloped settings.

Studies that were conducted in high-income countries have shown that many patients do not have an adequate understanding of pharmacogenomic principles, which may affect their acceptance of pharmacogenomic testing in clinical care (Doyle et al., 2023; G. Lee et al., 2022).

A scoping review that was published in 2024 indicated that more than 80% of the patients are willing to undergo pharmacogenomic testing, yet less than half of the patients could state what this test measures, indicating a deficit in knowledge (Lim et al., 2023a).

A study in the USA on 1060 cancer patients indicated that 82% of these patients were willing to pay less than 100 dollars for the test, and that cost was a more important barrier than waiting time or the type of sample needed (Gawronski et al., 2024).

Evidence from low-middle-income countries presents additional barriers. A scoping review of 28 low-middle-income countries reported low pharmacogenomic knowledge among healthcare professionals in addition to financial, cultural, and privacy concerns that hinder recommendation by providers and acceptance by patients (Walters et al., 2024).

Results from 30 semi-structured questionnaires with patients with cancer indicated that resources and the clinical environment were the main barriers while enthusiasm to enhance patient care was the main facilitator for DPYD testing (White et al., 2025).

Another concern raised by an ethical analysis from the WHO Eastern Mediterranean Region added the fear of genetic discrimination and uncertainty regarding data privacy, which may discourage the patients from undergoing these tests (Mubarak & Ashraf, 2024).

2.5 Willingness to pay for the tests

The willingness to pay for pharmacogenomic testing is also variable and is affected by factors such as perceived health benefit, income level, confidence in healthcare systems, and previous experience with anticancer treatment (Barrett et al., 2024; Bielinski et al., 2017a; Lemke et al., 2023).

In Palestine, the healthcare system is fragmented, and out-of-pocket expenditure is comparatively high. Consequently, evaluating willingness to pay is predominantly important to assess the possibility of incorporating DPYD testing into routine oncology practice.

2.6 Specialists' perspectives

A clear pattern is visible almost globally: high levels of knowledge about DPYD testing and its role in minimizing FP side effects, but low levels of incorporation into practice. A systematic review published in 2024 summarizing the results of 34 studies performed to assess the level of knowledge and the application of pharmacogenomic testing found that the mean level of knowledge was 60%, but the median rate of ordering of these tests was around 15%. The main reasons for such a low level were the cost, uncertain reimbursement, and the absence of global guidelines (Lim et al., 2023b).

In the Middle East, a similar image is seen. In Saudi Arabia, more than half of oncology specialists have knowledge of DPYD testing but less than 10% of them have ever ordered it for any patient (Sukkarieh et al., 2023).

In Pakistan, a qualitative study indicated that physicians endorse the principle of precision medicine; however, they visualize DPYD testing as a service only for affluent patients due to scarcity of funding and training (Naaem et al., 2024b).

A wide survey performed in Europe after the implementation of the EMA recommendations in 2020 has shown that 87% of the responding countries increased the level of pharmacogenomic testing, and reimbursement rates increased from zero to 85% in some of these countries. Obstacles such as partial reimbursement were reported in less than 15% of these locations (de With et al., 2023).

Conversely, a survey conducted in the USA revealed that only 20% of oncology specialists have ever ordered a DPYD test, and fewer than 5% of these specialists use it for more than 10% of their patients who are treated with FPs. The main stated obstacles were lack of guidelines and low perceived prevalence (Koo, Pasternak, Henry, & Sahai, 2022).

2.7 Link to Sustainable Development Goals (SDGs)

Increased focus and awareness of the SDGs in a community, together with stated specific targets, may enhance implementation effectiveness and the programs and evaluations that ensue (Yeh et al., 2022). Superior health is closely intertwined to several of the SDGs, including climate, environment, and education, and progress on related SDGs will result in co-benefits for health. Better health would also aid progress on other SDGs such as better jobs, economic enhancement, and low-income and inequities reduction (Sipido & Nagyova, 2020). NCDs are part of the (SDGs) with the following target: “*by 2030 reduce by one third [relative to 2015 levels] premature mortality from NCDs through prevention and treatment and promote mental health and well-being*” (SDG target 3.4). The indicator used to measure progression towards SDG 3.4 is called NCD4 which estimates the overall probability of death from four NCDs (cancers, cardiovascular diseases, chronic respiratory diseases, and diabetes) between precisely 30 years and precisely 70 years of age in the lack of other reasons of death (NCD Countdown 2030 collaborators, 2020). Diabetes caused four per cent of the total of premature global deaths, in addition to its contribution to premature mortality from cardiovascular diseases, cancer, renal diseases and some infectious diseases (Wou et al., 2019).

Chapter Three

Conceptual Framework

3.1 Integrated Framework for Pharmacogenomic Testing and Chemotherapy Safety

The customized conceptual framework utilized in this dissertation employs a mixture of elements from clinical science, behavioral health models, and individualized medicine to interconnect findings in a health systems perspective.

This framework corresponds to the complex nature of fluoropyrimidine-related side effects and the limited use of *DPYD* genotyping in the Palestinian cancer care system.

It combines the whole group of individual, clinical, and systematic factors that affect the adoption of pharmacogenomic testing and spot the broader policy-related and behavioral context in which the whole situation is located.

This tailored framework incorporates three intersecting provinces: decision-making at the level of the providers, patients' attitudes and behaviors, and clinical and pharmacogenomic prediction of risk.

This structure not only provides a holistic picture but also allows the researcher to explore how decisions at different levels (patients, providers, health system) communally affect chemotherapy safety and the adoption of pharmacogenomic testing.

3.2 Framework Components

The first dimension explores healthcare providers' knowledge and system readiness:

It particularly focuses on the role of oncology specialists in determining if DPYD testing is requested and adequately utilized. This is consistent with implementation frameworks which give very high importance to the influence of individual caregiver's attitudes, institutional protocols and laws, and support by the organization in adopting new clinical procedures. In this dimension, these factors are assessed through an exploration of oncology specialists' and oncology pharmacists' knowledge, attitudes, and perceived barriers.

The second dimension focuses on pharmacogenomic and clinical risk factors that contribute to FP side effects. This includes the presence of DPYD mutations, demographic variables, other comorbidities, and the nature of the chemotherapy regimen. This component follows the precision medicine template, which points out shaping treatment based on genetic and clinical properties. Pharmacogenomic testing status (a patient was tested pre-treatment or not) is considered as a moderating factor in the relationship between pharmacogenomic risk and the observed toxicity.

The third dimension discusses patient knowledge, attitudes, and willingness to pay. This part explores the degree to which patients perceive themselves to be at risk, understand the aim and the value of testing, and have the financial ability and motivation to undertake it. This area is explored in this dissertation using a survey studying knowledge, practices, and willingness to pay among cancer patients.

Overall, these three dimensions provide a general framework to guide the research. The model elevates fluoropyrimidine toxicity from being simply as a biological event to being an outcome formed by a complex interaction of clinical decisions, health system structure, patient behaviors, and pharmacogenomic risk.

3.3 Application of the Framework in the Dissertation

The framework was used as the main principle guiding the analysis of the three core studies that compose this dissertation. First, the healthcare providers component consists of a survey of oncology specialists, assessing their knowledge of pharmacogenomics and their willingness to implement DPYD testing. Second, the clinical and pharmacogenomic component builds the observational study that investigates the association between DPYD mutations and side effects in patients receiving FPs. Third, the patient component is assessed using a cross-sectional study testing patients' knowledge, attitudes, and willingness to pay for the tests.

Each of the components was connected to quantifiable variables and tested by using appropriate tools, such as validated questionnaires and clinical data collection forms. The framework allowed the research to build connections between knowledge and behavior (in both providers and patients), facilitators and barriers at the level of the system, and finally, the safety and individualization of cancer treatment in Palestine.

3.4 Anticipated Outcomes and Relevance to Health System Improvement

This dissertation is consistent with the goals of the health system in improving patient safety, enhancing evidence-based medicine, and promoting equitable access to essential advancements. The conceptual framework aims at outcomes such as:

- Higher usage of DPYD testing through tailored provider education and policy advocacy
- Lower incidence of severe FP side effects through early identification of susceptible patients
- Improved patient engagement and autonomy in treatment decisions
- Improved integration of pharmacogenomic testing into local cancer care pathways

Additionally, it is important to mention that this framework covers broader determinants of health such as affordability and trust in the health system that may influence the decision to adopt new advances in health technology. This helps the framework to be applicable to broader settings that extend beyond the mere utilization of DPYD testing in low-resource settings.

The tailored conceptual framework is presented in Figure 3.

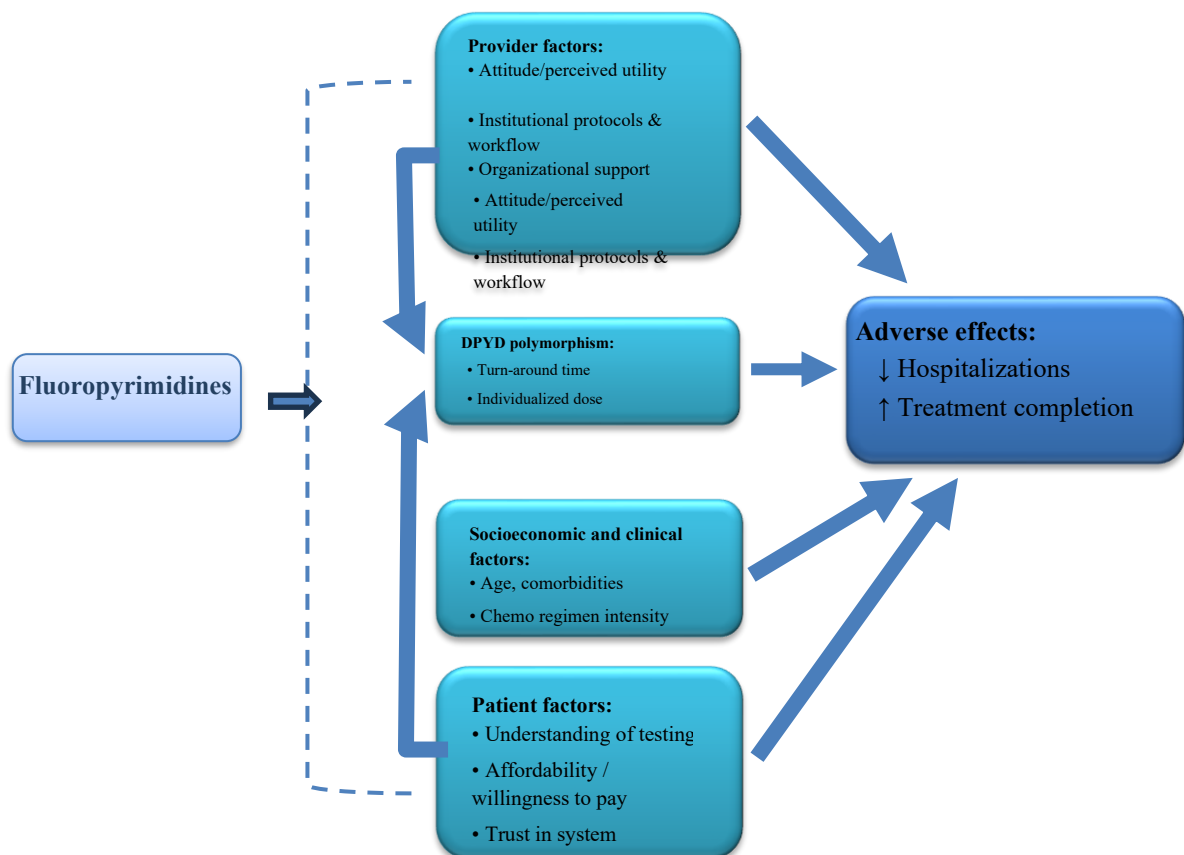


Figure 3.1: Conceptual framework of the study.

Chapter Four

Methodology

4.1 Study I: Oncology Specialists' Perceptions and Insights into Dihydropyrimidine Dehydrogenase Testing in Palestine.

4.1.1 Study Design, Setting, and Subjects

This cross-sectional study utilized a survey distributed to oncologists, oncology residents, and clinical pharmacists across various hospitals in Palestine between February and May 2024.

4.1.2 Population

Oncology specialists (physicians and pharmacists) working with cancer patients in the selected hospitals (Beit Jala, Dura, Ahli, and Augusta Victoria hospitals) including medical doctors and clinical pharmacists.

4.1.3 Inclusion Criteria

Oncology specialists, oncology residents, and clinical pharmacists in the four cancer facilities in Palestine. The number of professionals who met the criteria in the hospitals was 171.

4.1.4 Exclusion Criteria

Community pharmacists and non-cancer physicians. Retail pharmacists were excluded because no anticancer medications are dispensed through them.

4.1.5 Sample size

Prior studies have shown that the level of knowledge among HCPs on pharmacogenomics testing varied between 31% and 62% (Ahmed et al., 2020; Algahtani, 2020; Nie et al., 2022;

Obara et al., 2015). For our study conducted in Palestine, we assumed that the proportion of healthcare providers aware of DPD testing is approximately 50% ($p = 0.50$), which provides the most conservative (largest) sample size estimate. The initial sample size for estimating a single proportion was calculated using the standard formula:

$$n_0 = \frac{Z^2 \times p(1 - p)}{d^2}$$

where $Z = 1.96$ for a 95% confidence level and $d = 0.05$ for a 5% margin of error. Because the target population was finite (approximately 150 registered oncology practitioners), a finite population correction was applied:

$$n = \frac{n_0}{1 + \frac{(n_0 - 1)}{N}}$$

where $N = 150$. Based on these parameters, the required sample size was approximately 108 participants and was pragmatically set at a target of ~100 HCPs considering feasibility and anticipated non-response. Incomplete responses were excluded from the analysis.

4.1.6 Participant recruitment

The questionnaire was distributed electronically to all available healthcare professionals who work in four hospitals (two governmental, two non-governmental) that have an oncology unit.

Data collection was performed using a structured, self-administered online questionnaire that was developed on Google Forms. The survey link was distributed through official institutional communication methods, including institutional email lists and secure WhatsApp groups used for clinical coordination within the oncology departments in the above-mentioned hospitals.

Participants were initially informed about the purpose of the study, the voluntary nature of participation, and the anonymity of responses on the introductory page of the questionnaire. To prevent duplicate responses, each participant was requested to complete the questionnaire only once. Data collection was conducted over the predefined period, and reminder messages were sent to enhance response rates.

4.1.7 Study tool

The questionnaire was adopted from a previous study conducted in Saudi Arabia (Sukkariieh et al., 2023), and was slightly modified to suit the Palestinian context. These modifications included, for example, the type of healthcare provider in which the respondents worked in (Ministry of Health, private sector, UNRWA, etc.). The survey consisted of 26 items covering participant demographics and the awareness of participants regarding DPYD screening. Various types of questions were included (multiple choice questions, Likert scale, etc.). The content validity of the tool items was ensured through review by experts (three oncologists and three pharmacists) who assessed the suitability of the content, making required adjustments to confirm thorough and accurate assessment of attitudes.

The questionnaire was pilot tested among four healthcare professionals (two oncologists and two clinical pharmacists) to assess its clarity, content validity, and internal consistency. Feedback from the pilot participants indicated that the questionnaire items were clear, relevant, and appropriately structured, and no major modifications were required. Internal consistency reliability of the questionnaire was assessed using Cronbach's alpha, which demonstrated acceptable reliability across the main domains of the survey (>0.70). Responses from pilot participants were excluded from the final analysis.

4.1.8 Data analysis

Descriptive statistics were used to summarize the study variables. Categorical variables were presented as frequencies and percentages. Continuous variables were assessed for normality using visual inspection of histograms and the Shapiro–Wilk test. Normally distributed continuous variables were summarized using means and standard deviations (SD), whereas non-normally distributed variables were summarized using medians and interquartile ranges (IQR).

Inferential analysis was used to examine associations between demographic characteristics and awareness levels of pharmacogenomic testing. The chi-square test was used to compare between categorical variables when expected cell counts were adequate, while Fisher's exact test was applied when expected frequencies were smaller. A two-sided p-value of <0.05 was considered statistically significant in this analysis.

4.2 Study II: Cancer Patients' Perspectives and Practices Regarding Pharmacogenomic Testing and Its Cost

4.2.1 Study Design

This cross-sectional study utilized a survey distributed to cancer patients that were currently treated with chemotherapy at three outpatient oncology clinics (Beit Jala and Dura hospitals and Dr Hani Hour oncology clinic) in the West Bank, Palestine between January and May 2024.

4.2.2 Population

All cancer patients who were receiving or will receive chemotherapy at the time of recruitment meeting all the inclusion criteria and none of the exclusion criteria.

4.2.3 Inclusion Criteria:

- Patient with a confirmed diagnosis of cancer of any type
- Prescribed or will be prescribed chemotherapy
- Adults (≥ 18 years)
- Able to understand and provide informed consent

4.2.4 Exclusion Criteria:

- Cognitive impairment or severe psychological distress
- Age less than 18 years

4.2.5 Sample size calculation

The required sample size was estimated with the single-proportion formula for cross-sectional studies, $n = Z^2 p(1-p)/d^2$.

A conservative expected proportion of adequate knowledge (pp) of 0.50 was chosen to maximize the precision; the confidence level was set at 95 % ($Z=1.96$), and the allowable margin of error (dd) at 5 %. Substituting these values yielded $n=384$.

Because the total number of eligible oncology patients expected to attend the participating clinics during the data-collection period was approximately 1 200, a finite-population correction was applied: $n_{adj} = n/[1+(n-1)/N]=305$.

To correct for an anticipated 15 % non-response rate, the sample size was inflated to give final target sample of 350 patients.

4.2.6 Sampling Method:

Patients were chosen through convenience sampling from oncology outpatient clinics in the three hospitals (Beit Jala, Dura and Al-Ahli).

4.2.7 Data Collection Tool

A structured questionnaire that was developed based on an extensive literature review of similar studies (Asiedu et al., 2020; Cuffe et al., 2012, 2014; Gawronski et al., 2023, 2024;

Haga et al., 2016; Soueid et al., 2024). The questionnaire was initially constructed in English language. After that, it was translated into Arabic with the help of an authorized translator specializing in the medical field.

Both Arabic and English versions were reviewed by five experts who suggested minor modifications to some of the questions. The changes were discussed, and minor changes were made before final approval of the questionnaire.

A pilot study was conducted to evaluate the validity and reliability of the patient questionnaire. The pilot assessed the clarity, relevance, and comprehensibility of questionnaire items, as well as the internal consistency of the survey domains. Internal consistency reliability was examined using Cronbach's alpha, which exceeded 0.7 for each group of related questions, indicating acceptable reliability. Based on feedback from the pilot study, no major modifications were required. Data obtained from pilot participants was excluded from the final analysis.

Sections of the questionnaire:

- Section A: Sociodemographic Information
- Section B: Clinical History
- Section C: Knowledge
- Section D: Attitudes and Perceptions
- Section E: Practices and Experiences
- Section F: Willingness to Pay (WTP)
- Section G: Decision-Making Preferences

4.3 Study III: Pharmacogenomic and clinical factors associated with the side effects of FPs

4.3.1 Population

Cancer patients eligible for receiving therapy containing FPs, meeting all the inclusion criteria and none of the exclusion criteria.

4.3.2 Inclusion criteria

Patients were recruited if they were: adult patients (18 years or more), having a confirmed diagnosis of cancer by an oncology specialist and eligible for receiving chemotherapeutic cycles of treatments including FPs at time of enrollment.

4.3.3 Exclusion criteria

- Cognitive impairment or severe psychological distress
- Age less than 18 years

4.3.4 Sample size

Sample size estimation was conducted using the single-proportion formula

$$n = \frac{Z_{1-\alpha/2}^2 p(1-p)}{d^2},$$

where $Z_{1-\alpha/2}$ is the standard normal deviate corresponding to the desired confidence level, $\alpha = 0.05$ (two-sided, $Z = 1.96$), p represents the anticipated prevalence of the primary pharmacogenomic outcome based on published literature, and d denotes the acceptable margin of error. Assuming conventional statistical parameters ($\alpha = 0.05$) and a target power of $1 - \beta \geq 0.80$ for exploratory analyses, the minimum estimated sample size was approximately 90 participants. To compensate for potential missing clinical data and unsuccessful genotyping, the sample size was increased to 100 patients. Given feasibility constraints, a convenience sampling strategy was employed, and the final sample size was considered sufficient to support the study objectives while maintaining acceptable statistical precision.

4.3.5 Patient Recruitment

During their hospital visit, patients that meet the inclusion criteria were notified orally regarding the research by the researcher and given a briefing handout. The participants were requested to sign the consent form if they accepted to be enrolled in the study (attached in the appendix).

4.3.6 Intervention

Patients included in the study underwent genetic testing. Based on the result, recommendations on dose modification were conveyed to the managing physician. They were followed up for the occurrence of the study outcomes.

4.3.7 DPYD genotype testing

A total of 134 whole blood samples were collected from Beit Jala and Dura Hospitals. DNA was extracted from blood samples using the salting-out method after using previously prepared standard buffers (TKM-1, TKM-2, Triton X, SDS, NaCl, and TE). DNA quality was checked by gel electrophoresis. Specific primers were designed using NCBI Primer-BLAST to detect clinically relevant wild-type and mutant alleles (Shamaei Zadeh et al., 2025). Allele-specific PCR was performed in 25 µL reactions with appropriate master mix, primers, DNA template, and nuclease-free water (Varma et al., 2020). PCR cycling conditions included denaturation, annealing, and extension steps optimized separately for wild-type and mutant primers (Salmani et al., 2022). The DPYD activity score (AS) is calculated by assigning values to each allele (normal = 1, decreased function = 0.5, no function = 0) and summing both alleles. Scores of 2 indicate normal metabolizers, 1–1.5 intermediate metabolizers, and ≤ 0.5 poor metabolizers, with corresponding recommendations for dose reduction or avoidance of fluoropyrimidines.

4.3.7.1 DPYD Primers and Targeted Mutations

- **c.1905+1G>A (DPYD*2A)**
 - Target region: Intron 14 splice site
 - Forward primer (5'–3'): **AGGTGTTTCTGGGACAGTTT**
 - Reverse primer (5'–3'): **CCAGCATCTGAATGTGGAAG**
 - Expected amplicon size: ~250 bp
 - Expected genotypes detected: G/G (wild-type), G/A (heterozygous), A/A (homozygous)
- **c.1679T>G (DPYD*13)**
 - Target region: Exon 13
 - Forward primer (5'–3'): **TGGGCTTTACTGTGTGCTTT**
 - Reverse primer (5'–3'): **CAGGAATGGTCTGGAGTTGT**
 - Expected amplicon size: ~220 bp
 - Expected genotypes detected: T/T (wild-type), T/G (heterozygous), G/G (homozygous)
- **c.2846A>T**
 - Target region: Exon 22
 - Forward primer (5'–3'): **TCAGGATGTTCTGCTTCTC**
 - Reverse primer (5'–3'): **GGAGAAGCAGGATGAGGAAG**
 - Expected amplicon size: ~280 bp
 - Expected genotypes detected: A/A (wild-type), A/T (heterozygous), T/T (homozygous)
- **c.1236G>A (HapB3)**
 - Target region: Exon 11
 - Forward primer (5'–3'): **CCAGCTTCTTCTGTCCTCTC**
 - Reverse primer (5'–3'): **AGCACTTGGGAATGAGGAAG**
 - Expected amplicon size: ~200 bp

- Expected genotypes detected: G/G (wild-type), G/A (heterozygous), A/A (homozygous)

4.3.8 Data collection

Management information, such as regimen, dosage, and the use of radiation utilization, were gathered from the hospital electronic system. Clinical data and toxicity information were acquired through a standardized analysis of the patients' electronic health records (EHRs) by trained study team who were blinded to the group in which the patient was allocated.

Toxicity data was documented from doctor reports, admission files, hospital discharge notes, and emergency care documents. Severe adverse events (AEs) comprised toxicities with a grade no less than 3 based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The classification uses the following definitions:

- Grade 1: Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention required.
- Grade 2: Moderate: minimal, local, or noninvasive intervention indicated; limiting instrumental activities of daily living.
- Grade 3: Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening: life-threatening consequences; urgent intervention required.
- Grade 5: Death: death related to the adverse event.

Just AEs which are verified to be possibly or certainly connected to FPs were listed in the conclusion (according to CTCAE version 5.0). Depending on these assumptions, the classifications required the AE to happen within one month of FP treatment, be clinically reasonable, and not be associated with a different element of the treatment. The impact of holding and restoring the FPs was also considered if these issues ensued.

According to previous studies, the main toxicity classes considered are gastrointestinal (chiefly: loose stools, oropharyngeal mucositis, and nausea or vomiting), myelosuppression (chiefly neutropenia/febrile neutropenia, thrombocytopenia, and unexplained anemia), cardiac (instant cardiac toxicity while administering FP), and Palmar-Plantar Erythrodysesthesia (Hand-Foot Syndrome). Other AEs, where FPs are probable participants, were categorized as Other. The AEs recorded by the preliminary researchers and the credit of interconnection were revised by an oncology specialist. Disagreements in the logs were revised by the original coders and the evaluating medical oncology specialist. Participants were monitored throughout the whole management duration and until adverse effects subside.

4.3.9 Outcomes

The primary outcome was FP-related AEs (according to CTCAE version 5.0). Additional outcomes comprised FP-related AEs categorized by adverse effect type, the percentage of patients terminating FPs due to their adverse effects, and incidents of drug-related deaths.

4.3.10 Recommendations to oncologist

In patients whose results showed that they have the pre-determined types of DPYD polymorphism, results of the DPYD testing and dosage guidance were conveyed to the referring physicians. The recommendations entailed the following: for individuals without the carrier status, administer the standard of care dosage; for those identified as simple heterozygous carriers, initiate treatment with a 50% initial dosage reduction, with the possibility of dose escalation in subsequent cycles depending on participant tolerance; avoid the use of FPs in cases of homozygous carriers (Amstutz et al., 2018).

4.3.11 Data Analysis

The data collected at baseline and at the follow up were cleaned, coded and entered into SPSS software for statistical analysis. For categorical factors, data were examined by Pearson chi-square analysis. Normality of data was investigated prior to analysis for the continuous variables using the Kolmogorov-Smirnov and Shapiro-Wilk statistical tests. The normally distributed variables underwent the t-test for independent samples, and their mean values have been shown.

P value of under 0.05 was considered statistically significant. Furthermore, used to find and evaluate the significance of variables in the gathered data at both baseline and follow-up interviews was logistic regression analysis.

Variables were analyzed as follows:

- 1- Sex was categorized as male or female.
- 2- Disease severity was classified as local or advanced.
- 3- The presence of other chemotherapy treatment before FP was documented as either yes or no.
- 4- The form of FP-based therapy was categorized as Capecitabine alone, 5-FU alone, or both.
- 5- The occurrence of FP-based toxicity of more than grade 3 or 4 was assessed through CTCAE V5.0 or toxicity leading to FP-based treatment stop, and it was recorded as yes or no.
- 6- The association of any surgery with FP treatment was documented as yes or no.
- 7- The involvement of radiotherapy with FP treatment was noted as yes or no.
- 8- Any type of recurrence (local, loco-regional, or metastatic) recorded was categorized as yes or no.
- 9- Age at FP-based therapy was measured in years.
- 10- The number of treatment lines, including FP treatment, was counted (N).
- 11- The sum of FP cycles was counted (N).

4.4 Ethical measures

Ethical approval to perform all three parts of the project was acquired from the administration of the School of Public Health and Ethical Committee in Al-Quds University (REF #13/24). Consequently, ethical approval was obtained from the Palestinian Ministry of Health.

Confidentiality of participants was preserved throughout the research so that only sample properties were used to distinguish the participants' data. Names were not used. The gathered data was utilized solely for study-related use.

4.5 Minimization of Bias

To improve the strength and the validity of findings and reduce systematic errors of all kinds, several strategies were utilized across all the components of the study:

4.5.1 Selection Bias

- Oncology specialists: All specialists working in oncology units in the targeted hospitals were invited to participate in the study to ensure a broad sampling frame. Inclusion and exclusion criteria were uniformly applied to all the participants.
- Patients: Recruitment of the patients was performed consecutively at the outpatient oncology clinics in the mentioned hospitals, capturing all eligible patients during their clinic visits rather than pre-selecting participants. This approach reduced the risk of over-representation of certain subgroups.
- Population correction and adjustments for non-response were applied during sample size estimation to prevent under- or over-recruitment of participants.

4.5.2 Information and Measurement Bias

- Data collection instruments: Questionnaires were adapted from validated international studies, reviewed by oncology and pharmacology experts, and then pilot-tested for clarity and cultural appropriateness. This process minimized misinterpretation and enhanced construct validity of the data.
- Translation: Forward-backward translation of the patient survey (English-Arabic-English) was performed by licensed professional medical translators to avoid loss of meaning during translation.
- Clinical data: Extraction from EHRs was standardized through structured templates and appropriate coding guidelines. Toxicity grading strictly followed the CTCAE v5.0 criteria to limit subjective interpretation.
- Laboratory analysis: DPYD genetic testing was conducted using standardized international assays. The laboratory team was trained, and procedures were immediately documented to minimize variability.

4.5.3 Observer and Interviewer Bias

- Data collectors: Researchers who were involved in data collection were trained to administer the survey neutrally to avoid suggestive language or body cues.

- Blinding: Clinical outcome assessors were blinded to the results of the participants' genetic tests to prevent differential classification of adverse events.
- Cross-checking: Toxicity reports were independently reviewed by an oncology specialist, with discrepancies resolved through consensus between the two parties.

4.5.4 Recall and Response Bias

- For specialists, the survey was designed to capture the current practices and perceptions, with Likert scales to minimize the recall burden.
- For patients, questions were phrased in simple, non-technical language to encourage accurate reporting of experiences.
- The use of anonymous self-administered questionnaires for specialists reduced social desirability bias and encouraged frank responses.

4.5.5 Data Handling and Analysis

- Data was double-checked before analysis.
- Missing data was carefully handled and cases with major gaps were excluded. Partial responses were retained with transparent reporting.
- Appropriate statistical tests were carefully chosen to match data distribution and type and to avoid misinterpretation.

Chapter Five

Results

This section delineates the results from the three interconnected studies that constitute this research. The findings of each study are presented individually to illustrate their specific objectives, techniques, and data sources.

5.1 Results of study I

The questionnaire was completed by a total of 106 HCPs, consisting of 57.5% specialist physicians, 27.4% clinical pharmacists, and 15.1% resident physicians. This distribution is similar to the composition of the study population. The majority of respondents, over 60%, received their most recent degree from a Palestinian institution, while around 40% graduated from foreign institutions. The location of the last degree may influence respondents' practices due to variations in pharmacogenomics training and exposure to DPYD testing. Foreign institutions may emphasize pharmacogenetic applications more than Palestinian institutions, leading to differences in implementation. More than 70% of the participants were 45 years old or younger.

Regarding professional experience, a majority of the participants possessed more than 8 years of expertise in working with cancer patients as seen in Table 1. Fifty percent of the participants were associated with private hospitals, while the remaining 50% were employed at governmental institutions.

Demographic data for the participants is presented in Table 5.1.

Table 5.1: Sociodemographic characteristics of the participants

Characteristics		Number	Percentage
Designation	Clinical Pharmacist	29	27.4%
	Physician	61	57.5%
	Resident	16	15.1%
Last degree location	Inside Palestine	63	59.4%
	Outside Palestine	43	40.6%
Age group	23-35 years	41	38.7%
	36-45 years	37	34.9%
	46-59 years	22	20.8%
	More than 60 years	6	5.7%
Years of experience	2-4	25	23.6%
	5-7	22	20.8%
	8-10	14	13.2%
	11 or more	45	42.5%
Hospital type	Private	54	50.9%
	Governmental	52	49.1%

A striking finding was that more than 70% of participants stated that they had never undergone formal training in pharmacogenomics during their career. However, a substantial majority of 75.5% stated that they usually prescribe FPs. Furthermore, around 80% of participants indicated knowledge of the mutation linked to DPD deficiency and its consequences for FP toxicity. Yet, fewer than 50% of participants indicated that they consistently or occasionally screen for DPD deficiency prior to prescription FPs. This discrepancy between awareness of DPYD mutations and the limited use of screening has significant implications for patient outcomes. Failure to screen for DPD deficiency may lead to severe, potentially life-threatening toxicities in patients prescribed FPs, as individuals with DPYD mutations are unable to metabolize these drugs effectively. Implementing routine screening could enhance treatment efficacy by identifying at-risk patients, enabling dose adjustments or alternative therapies, and reducing the risk of adverse events.

In addition, only 47% of participants reported that their institution had specific protocols for prescribing FPs. Notably, 60% of individuals experienced significant toxicity associated with FPs, a rate considerably higher than the global average of 10–30%. The higher toxicity rate observed in this study compared with global estimates is likely multifactorial. Possible contributing factors include a higher prevalence of reduced *DPYD* metabolizing capacity, lack of standardized prescribing and genotype-guided dose-adjustment protocols, use of full-dose regimens in high-risk patients, and patient-related factors such as older age and comorbidities. Differences in toxicity detection, grading, and reporting practices may have further contributed to this discrepancy. Furthermore, only 33% of participants had observed the influence of DPD testing in clinical practice, highlighting gaps in implementation. These challenges may be driven by the lack of infrastructure for pharmacogenomic testing, limited awareness of standardized protocols, and financial constraints that hinder the widespread adoption of DPD testing. Addressing these barriers could improve the safe and effective use of fluoropyrimidines in clinical practice. With regards to the standardization and promotion of DPD testing, a mere 5.7% and 6.6% of participants, respectively, reported the existence of standardized DPD testing and the Palestinian Ministry of Health's promotion of DPD testing before prescribing FPs. Only 1.9% of the participants concurred that an adequate amount of research is being conducted in Palestine with regards to DPD insufficiency.

The main sources used to obtain information on specific molecular testing were published practice guidelines (42%) and cancer-genomics specific guidelines (22%).

The most common types of cancer for which FPs were prescribed were colorectal cancer (19%) and breast cancer (17%).

Details of the awareness and practices of the participants are shown in Table 5.2.

Table 5.2 A: Awareness and practices of the participants toward DPD testing.

Question		Count	Percentage
Do you participate in tumor genomic board, tumor molecular board in your current institution?	No	67	63.2%
	Yes	39	36.8%
What do you mostly follow as a reference when ordering a specific molecular test?	Cancer-genomics specific guidelines	24	22.64%
	Institutional guidelines	17	16.04%
	Personal experience	20	18.87%
	Published practice guidelines	45	42.45%

Table 5.2 B: Awareness and practices of the participants toward DPD testing.

Have you received any formal training or education in pharmacogenomics?	No	77	72.6%
	Yes	29	27.4%
If yes, where did you receive your education or training in pharmacogenomics?	Continuous medical education	21	19.81%
	Experience through practice	18	16.98%
	Fellowship program	13	12.26%
	Hospital seminars	16	15.09%
	Online courses	16	15.09%
	Research	7	6.60%
	University education	15	14.15%
Do you usually prescribe FP (5-fluorouracil (5-FU) and Capecitabine) for patients with cancer?	No	26	24.5%
	Yes	80	75.5%
If yes; which type of cancer would you prescribe it for?	Colorectal cancer	21	19.81%
	Breast cancer.	19	17.92%
	Colorectal cancer	14	13.21%
	Gastric cancer	13	12.26%
	Pancreatic cancer	7	6.60%
	Head and neck cancer	8	7.55%
	Biliary tree malignancy	9	8.49%
	I am not prescriber	11	10.38%
	Nasopharyngeal carcinoma	4	3.77%
Are you aware of a mutation that causes DPD deficiency?	No	21	19.8%
	Yes	85	80.2%

Table 5.2 C: Awareness and practices of the participants toward DPD testing.

If yes; are you aware of its complications; e.g. toxicity of FP (5-fluorouracil (5-FU) and Capecitabine)?	No	22	20.8%
	Yes	84	79.2%
How often do you screen for DPD deficiency prior to prescribing FP?	Always	2	1.9%
	Never	56	52.8%
	Sometimes	48	45.3%
Are there guidelines for prescribing FP in your hospital?	No	27	25.5%
	Not sure	29	27.4%
	Yes	50	47.2%
Is there enough research being done in Palestine on screening for DPD prior to prescribing FP?	No	62	58.5%
	Not sure	42	39.6%
	Yes	2	1.9%
Have you seen patients with severe toxicity related to use of FP?	No	41	38.7%
	Yes	65	61.3%
Have you seen the impact of DPD testing in your clinical practice?	No	71	67.0%
	Yes	35	33.0%
Is there any standardization of DPD Deficiency practice done by MOH?	No	51	48.1%
	Not sure	49	46.2%
	Yes	6	5.7%
Does the MOH promote the practice of DPD deficiency test prior to FP group of medications?	No	51	48.1%
	Not sure	48	45.3%
	Yes	7	6.6%

FP: fluoropyrimidines, DPD: dihydropyrimidine dehydrogenase, MOH: Ministry of Health, 5-FU: 5-fluorouracil

A high percentage of participants displayed knowledge regarding the mutation accountable for DPD deficiency. Specifically, 72% of clinical pharmacists, 80% of physicians, and 93% of resident physicians expressed familiarity with this genetic variation ($p>0.05$)

The awareness of the mutation linked to DPD deficiency differed among respondents with different degrees of professional experience. Specifically, 84% of those with 2-4 years of experience, 90% with 5-7 years, 64% with 8-10 years, and 77% with 11 or more years indicated familiarity with this genetic variant ($p>0.05$).

An inequality in knowledge regarding the mutation accountable for DPD was noted between HCPs employed in private hospitals and those in governmental hospitals, with 87% of individuals in private hospital settings and 73% in governmental hospitals expressing familiarity with this genetic variant. This difference was not statistically significant ($p>0.05$).

Some participants reported the existence of guidelines in their individual institutions for prescribing FPs. Specifically, 37% of clinical pharmacists, 50% of physicians, and 50% of residents confirmed the presence of these guidelines ($p>0.05$).

The presence of guidelines for prescribing FPs in hospitals varied based on years of professional experience. Among individuals with 2-4 years of experience, 52% indicated the existence of guidelines. This percentage was 45% for those with 5-7 years, 57% for those with 8-10 years, and 42% for those with 11 or more years ($p>0.05$).

There was a noticeable difference in the reported prevalence of guidelines for prescribing FPs between HCPs in private hospitals and those in governmental hospitals. In private hospital settings, 57% of individuals acknowledged the presence of these guidelines, while in governmental hospitals, only 36% did so ($p>0.05$).

A small proportion of participants stated that they had witnessed the effects of DPD testing in their clinical work. Specifically, 17% of clinical pharmacists, 39% of physicians, and 37% of residents reported having this experience ($p>0.05$).

Regarding professional experience, the extent to which the effects of DPD testing were observed in clinical practice differed among individuals. Specifically, 28% of those with 2-4 years of experience, 40% with 5-7 years, 28% with 8-10 years, and 33% with 11 or more years reported witnessing such influence ($p>0.05$).

A statistically significant difference was found between HCPs working in private hospitals and those working in governmental institutions in terms of their perception of the influence of DPD testing in clinical practice, with a p-value of 0.001. More precisely, 48% of persons in private hospital settings and 17% in governmental institutions reported experiencing this effect (Table 3). Additionally, the data from Table 5.3 reveal that awareness of the DPD mutation was highest among residents (93.8%) and private hospital practitioners (87.0%). However, the presence of hospital-specific guidelines was reported more frequently in private hospitals (57.4%) than in governmental settings (36.5%), further reflecting institutional differences in support for FP-related testing. These findings highlight the need

for standardized policies across all hospital types to improve the adoption of DPD testing in clinical practice.

The institution where HCPs obtained their most recent degree did not have a significant impact on their knowledge of DPD mutations, awareness of institutional guidelines for DPD testing, or experience with its effects in clinical practice, as indicated by a p-value greater than 0.05. Details of the awareness and observation of DPD testing in practice, with regard to hospital-related and demographic variables are shown in Table 5.3.

Table 5.3: Knowledge of and observation of DPD testing in practice, determined by hospital- and demographic-related factors

Variable	Number	Are you aware of a mutation that causes DPD deficiency	Are there guidelines for prescribing Fluoropyrimidine in your hospital?	Have you seen the impact of DPD testing in your clinical practice?
Designation				
Clinical Pharmacist	29	21 (72.4%)	11 (37.9%)	5 (17.2%)
Physician	61	49 (80.3%)	31 (50.8%)	24 (39.3%)
Resident	16	15 (93.8%)	8 (50.0%)	6 (37.5%)
P value		>0.05	>0.05	>0.05
Years of experience				
2–4 years	25	21 (84.0%)	13 (52.0%)	7 (28.0%)
5–7 years	22	20 (90.9%)	10 (45.5%)	9 (40.9%)
8–10 years	14	9 (64.3%)	8 (57.1%)	4 (28.6%)
≥11 years	45	35 (77.8%)	19 (42.2%)	15 (33.3%)
P value		>0.05	>0.05	>0.05
Hospital type				
Private	54	47 (87.0%)	31 (57.4%)	26 (48.1%)
Governmental	52	38 (73.1%)	19 (36.5%)	9 (17.3%)
P value		>0.05	>0.05	0.001

Chi square test. DPD: dihydropyrimidine dehydrogenase.

5.2 Results of study II

5.2.1 Sociodemographic and Clinical Characteristics of the Participants

The study included 368 participants with an almost equal gender distribution (52.4% female, 47.6% male). The mean age of the participants was 42 years (SD=14). The most commonly reported marital status was married (38%), followed by single (33%). Secondary education was the most common educational level (32%), and around 21% reported that they were unemployed. Monthly income was mostly in the lower ranges, with 45% earning 1000–3000 NIS a month.

Breast cancer (31%) and colon cancer (31%) were the most common types of cancer affecting the participants. Stage IV was the most commonly reported stage, while 23% could not identify their cancer stage. Table 2 contains clinical details of the participants.

Sociodemographic and clinical information are shown in table 5.4.

Table 5.4 A: Sociodemographic and clinical information of the participants

Variable	Category	Number	Percent
Gender	Female	193	52.4%
	Male	175	47.6%
Marital Status	Single	124	33.7%
	Married	141	38.3%
	Divorced	38	10.3%
	Widowed	55	14.9%
	Unknown	10	2.7%
Education	None	14	3.8%
	Primary	81	22.0%
	Secondary	119	32.3%
	University	99	26.9%
	Graduate	50	13.6%
	Other/Missing	5	1.4%

Table 5.4 B: Sociodemographic and clinical information of the participants

Employment	Full-time	91	24.7%
	Part-time	43	11.7%
	None	79	21.5%
	Retired	41	11.1%
	Housewife	70	19.0%
	Other	37	10.1%
	Missing	7	1.9%
Income	≤1000	107	29.1%
	1000–3000	168	45.7%
	3000–5000	63	17.1%
	>5000	24	6.5%
	Missing	6	1.6%
Family Size	1	83	22.6%
	2	88	23.9%
	3–4	89	24.2%
	≥5	100	27.2%
	Missing	8	2.2%
Cancer Type	Breast	116	31.5%
	Colon	116	31.5%
	Lung	95	25.8%
	Other	35	9.5%
	Missing	6	1.6%

Table 5.4 C: Sociodemographic and clinical information of the participants

Cancer Stage	Stage 1	72	19.6%
	Stage 2	60	16.3%
	Stage 3	83	22.6%
	Stage 4	59	39.9%
	Missing	6	1.6%

5.2.2 Knowledge

A percentage of 19.8% of the participants have heard of pharmacogenomic testing, while only 4.9% of them claimed to have performed a pharmacogenomic test (Figure 5.1 and 5.2).

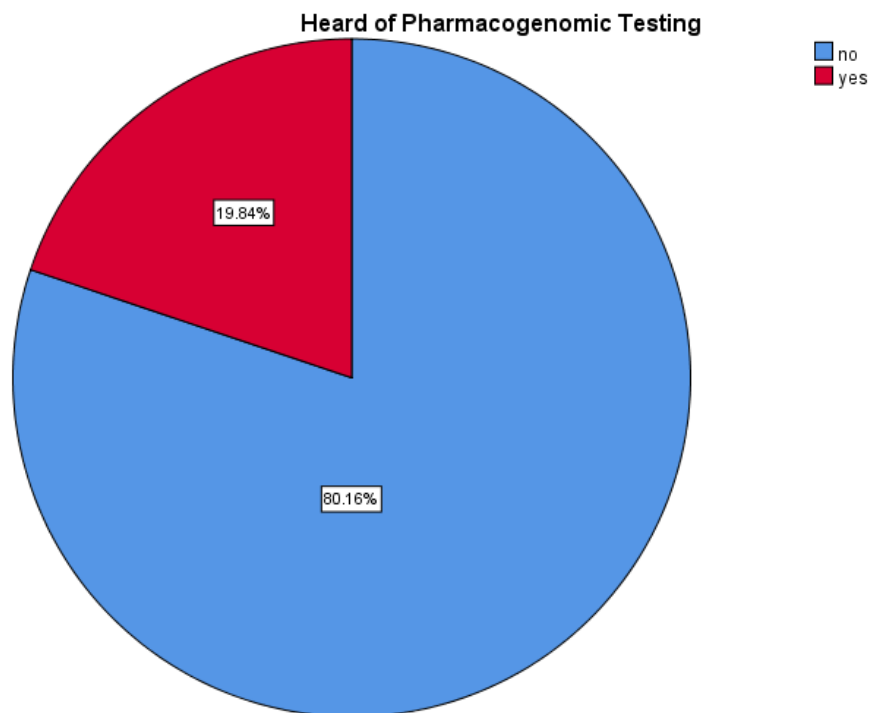


Figure 5.1: Participants who have heard of pharmacogenomic test

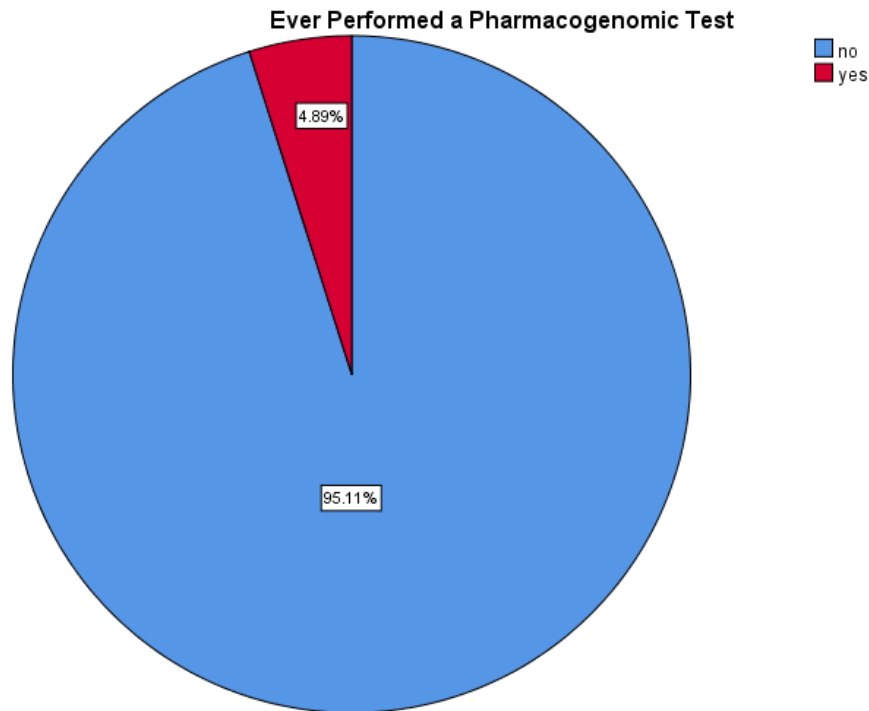


Figure 5.2: Participants who performed a pharmacogenomic test

About one third of participants (33.4%) reported no understanding of pharmacogenomic testing, with another 31% understanding “a little.” One-fifth agreed, and 17.9% strongly agreed that testing can help doctors choose the best treatment. Similar results were observed for the perceived accuracy stated by the participants. This data is shown in table 5.5.

Table 5.5 A: Participants’ understanding of pharmacogenomics and their attitudes towards their importance and accuracy

Question	Category	Number	Percentage
Understanding pharmacogenomics	Don’t understand	123	33.4%
	Understand a little	115	31.3%
	Somewhat understand	56	15.2%
	Understand well	55	14.9%
	Understand very well	19	5.2%
Pharmacogenomics Helps Doctors	Strongly Disagree	75	20.4%
	Disagree	87	23.6%
	Neutral	57	15.5%
	Agree	83	22.6%
	Strongly Agree	66	17.9%

Table 5.5 B: Participants' understanding of pharmacogenomics and their attitudes towards their importance and accuracy

Pharmacogenomics Accuracy	Strongly Disagree	77	20.9%
	Disagree	83	22.6%
	Neutral	46	12.5%
	Agree	93	25.3%
	Strongly Agree	69	18.8%

5.2.3 Attitudes and Preferences

Forty percent of participants were not concerned about insurance impact of the test, and around 40% wanted to be involved in the testing decision. A similar percentage (42%) would be more likely to test if recommended by their physician. Around two thirds of participants preferred test results to predict both treatment effectiveness and side-effects. The attitudes and preferences of participants are shown in table 5.6 while the main concerns of participants are shown in figure 5.3.

Table 5.6 A: Attitudes and preferences of participants regarding pharmacogenomic testing

Question	Response Category	Count	Percentage
Do you think pharmacogenomic testing can help avoid side effects from medications?	Strongly Disagree	71	19.3%
	Disagree	94	25.5%
	Neutral	52	14.1%
	Agree	83	22.6%
	Strongly Agree	68	18.5%
Are you worried about pharmacogenomic testing identifying another disease?	No	149	40.5%
	Yes	155	42.1%
	Not sure	64	17.4%

Table 5.6 B: Attitudes and preferences of participants regarding pharmacogenomic testing

Do you want to make sure no inherited diseases are revealed by pharmacogenomic testing?	No	157	42.7%
	Yes	147	39.9%
	Not sure	64	17.4%
Are you concerned that pharmacogenomic testing results may affect your health insurance coverage?	No	150	40.8%
	Yes	159	43.2%
	Not sure	59	16.0%
Do you want to be involved in the decision to undergo pharmacogenomic testing?	No	162	44.0%
	Yes	148	40.2%
	Not sure	58	15.8%
Would you undergo pharmacogenomic testing if your doctor recommended it?	No	151	41.0%
	Yes	158	42.9%
	Not sure	59	16.0%
Which results from pharmacogenomic testing would you prefer to receive?	Effectiveness of the medicine	27	7.3%
	Possible side effects	39	10.6%
	Both	242	65.8%
	Not sure	60	16.3%
What is the maximum time you are willing to wait for pharmacogenomic test results?	Same day	84	22.8%
	1–3 days	81	22.0%
	4–7 days	70	19.0%
	1–2 weeks	66	17.9%
	More than 2 weeks	67	18.2%

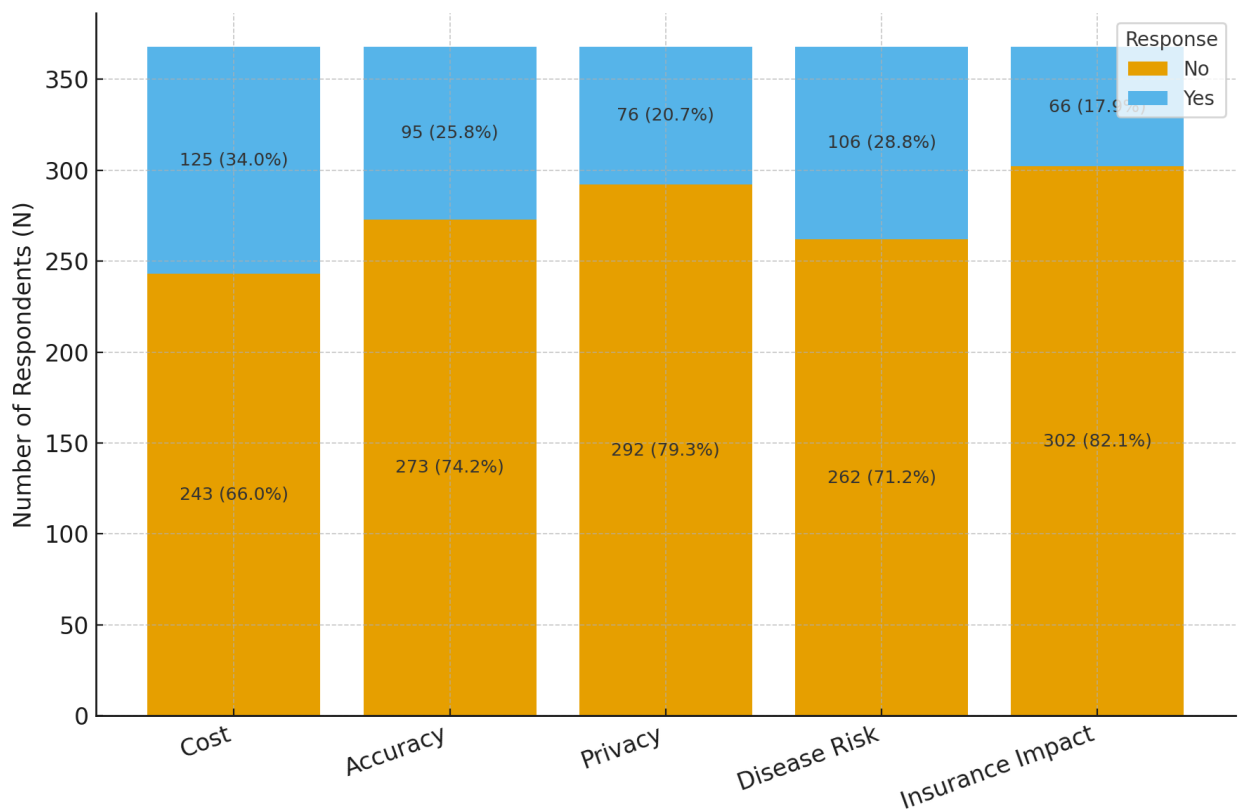


Figure 5.3: Main concerns about pharmacogenomic testing

5.2.4 Practices and Willingness to Pay

Most of the participants (74%) were willing to provide a blood sample for the test. Willingness to pay was almost evenly split between those who are willing and those who are not willing to pay for the test (53% willing to pay). The government (34%) and donors (22%) were seen as the main entities responsible for covering the cost of the test. The majority of the participants (86%) did not agree to co-pay for the test. Most of the participants stated that decision-making should be mainly shared between the participant and doctor (71%). Table 5.7 shows the details of the practices and willingness to pay.

Table 5.7 A: Practices and willingness to pay

Question	Response Category	Count (N)	%
Would you be willing to provide a blood sample for pharmacogenomic testing?	No	94	25.5%
	Yes	274	74.5%
Are you willing to pay for pharmacogenomic testing?	No	172	46.7%
	Yes	196	53.3%

Table 5.7 B: Practices and willingness to pay

Who should pay for pharmacogenomic testing?	Patient	20	5.4%
	Hospital	44	12.0%
	Government	127	34.5%
	Insurance	55	14.9%
	Donor organizations	81	22.0%
	Don't know	41	11.1%
Would you agree to co-pay for pharmacogenomic testing?	No	317	86.1%
	Yes	51	13.9%
Who should make the decision to undergo pharmacogenomic testing?	Myself	27	7.3%
	Doctor	39	10.6%
	Both patient and doctor	263	71.5%
	Someone else	39	10.6%

5.2.5 Amount Willing to Pay and Reasonable Price

The mean maximum out-of-pocket amount the participants were willing to pay was 230 NIS, while the mean reasonable price was 1307 NIS. The details are shown in table 5.8.

Table 5.8: Maximum out-of-pocket amount and reasonable price

Question	N	Minimum	Maximum	Mean	Std. Deviation
What is the maximum amount you are willing to pay out-of-pocket for pharmacogenomic testing (in NIS)?	368	0	1000	230.30	153.15
What do you consider a reasonable cost for pharmacogenomic testing (in NIS)?	368	0	3000	1307.88	779.80

NIS: New Israeli Shekels

Understanding of pharmacogenomic testing differed across demographic groups. Participants with no education were more concentrated in the “don’t understand” category (64.3%), while those with primary education were more often in “a little” (42.0%). By contrast, university and graduate participants displayed more balanced distributions, with greater shares in the “somewhat,” “well,” and “very well” categories.

Full-time workers showed more spread across all levels of understanding, with around one-third each in “don’t understand” and “a little,” but higher proportions in the “somewhat” and “well” categories compared with unemployed and part-time workers. Retired and housewives tended to cluster in lower understanding levels, though a small share reached “well” or “very well.”

Low-income groups (≤ 1000 and 1000–3000 NIS) were mainly in the “don’t understand” and “a little” categories (over 60% combined). Higher-income groups (>3000 NIS) showed a more even distribution, with modestly larger shares in the “well” and “very well” categories.

No statistically significant differences in knowledge were seen between the categories of these variables. Full details of these relationships are presented in table 5.9.

Table 5.9 A: Relationship between understanding pharmacogenomics and education, employment and income.

Demographic Variable	Category	Don't Understand	Understand a Little	Somewhat	Well	Very Well
Education	None	9 (64.3%)	3 (21.4%)	1 (7.1%)	1 (7.1%)	0 (0.0%)
	Primary	26 (32.1%)	34 (42.0%)	6 (7.4%)	9 (11.1%)	6 (7.4%)
	Secondary	39 (32.8%)	29 (24.4%)	21 (17.6%)	25 (21.0%)	5 (4.2%)
	University	31 (31.3%)	34 (34.3%)	19 (19.2%)	13 (13.1%)	2 (2.0%)
	Graduate	17 (34.0%)	13 (26.0%)	8 (16.0%)	6 (12.0%)	6 (12.0%)
	Missing	1 (20.0%)	2 (40.0%)	1 (20.0%)	1 (20.0%)	0 (0.0%)
	P value	>0.05				

Table 5.9 B: Relationship between understanding pharmacogenomics and education, employment and income.

Employment	Full-time	31 (34.1%)	28 (30.8%)	13 (14.3%)	15 (16.5%)	4 (4.4%)
	Part-time	18 (41.9%)	11 (25.6%)	6 (14.0%)	5 (11.6%)	3 (7.0%)
	None	21 (26.6%)	24 (30.4%)	16 (20.3%)	14 (17.7%)	4 (5.1%)
	Retired	13 (31.7%)	17 (41.5%)	5 (12.2%)	3 (7.3%)	3 (7.3%)
	Housewife	25 (35.7%)	21 (30.0%)	9 (12.9%)	12 (17.1%)	3 (4.3%)
	Other	12 (32.4%)	12 (32.4%)	7 (18.9%)	5 (13.5%)	1 (2.7%)
	Missing	3 (42.9%)	2 (28.6%)	0 (0.0%)	1 (14.3%)	1 (14.3%)
	P value	>0.05				
Income	≤1000 NIS	36 (33.6%)	33 (30.8%)	15 (14.0%)	21 (19.6%)	2 (1.9%)
	1000–3000 NIS	57 (33.9%)	52 (31.0%)	31 (18.5%)	17 (10.1%)	11 (6.5%)
	3000–5000 NIS	21 (33.3%)	20 (31.7%)	6 (9.5%)	12 (19.0%)	4 (6.3%)
	>5000 NIS	7 (29.2%)	8 (33.3%)	3 (12.5%)	5 (20.8%)	1 (4.2%)
	Missing	2 (33.3%)	2 (33.3%)	1 (16.7%)	0 (0.0%)	1 (16.7%)
	P value	>0.05				

NIS: New Israeli Shekels

No statistically significant association between monthly income and willingness to pay for pharmacogenomic testing ($p > 0.05$). Willingness to pay for pharmacogenomic testing was highest among participants with middle incomes (1000–5000 NIS), while both the lowest (≤ 1000 NIS) and highest (> 5000 NIS) income groups showed lower and nearly equal proportions of willingness and unwillingness. Other details of this relationship are shown in table 5.10.

Table 5.10: relationship between income and willingness to pay

Income (NIS)	Not Willing to Pay	%	Willing to Pay	%
≤1000	50	29.1%	57	29.1%
1000–3000	78	45.3%	90	45.9%
3000–5000	25	14.5%	38	19.4%
>5000	13	7.6%	11	5.6%
Missing	6	3.5%	0	0.0%

Chi square, $p > 0.05$. NIS: New Israeli Shekels

When stratified by age, no statistically significant differences were observed in participants' understanding of pharmacogenomic testing ($p > 0.05$). Across all age groups, the largest proportion of respondents reported “I don’t understand,” ranging from 28.3% in older adults to 38.5% in middle-aged adults. Younger adults showed slightly higher percentages in the “understand a little” category (33.1%), while older adults had marginally more respondents in the “well” and “very well” categories (16.7% and 6.7%, respectively). Overall, limited understanding was the predominant pattern across all age groups. These differences are shown in table 5.11.

Table 5.3: Relationship between age and understanding of pharmacogenomic testing

Age Category	Don't Understand	Understand a Little	Somewhat	Well	Very Well
Young adult (18–39)	49 (30.6%)	53 (33.1%)	27 (16.9%)	24 (15.0%)	7 (4.4%)
Middle-aged adult (40–59)	57 (38.5%)	42 (28.4%)	20 (13.5%)	21 (14.2%)	8 (5.4%)
Older adult (≥60)	17 (28.3%)	20 (33.3%)	9 (15.0%)	10 (16.7%)	4 (6.7%)

Chi square, $p > 0.05$

Participants who strongly agree or agree that pharmacogenomic testing is accurate were more likely to give a blood sample for the test and to pay for the test compared to patients who strongly disagree or disagree. Details are shown in table 5.12.

Table 5.12 A: Relationship between thinking that pharmacogenomic tests are accurate and willingness to provide blood sample and willingness to pay

Perceived Accuracy of Pharmacogenomics	Blood Sample – No	%	Blood Sample – Yes	%	Willing to Pay – No	%	Willing to Pay – Yes	%
Strongly Disagree	18	19.1 %	59	21.5%	37	21.5 %	40	20.4%
Disagree	25	26.6 %	58	21.2%	43	25.0 %	40	20.4%
Neutral	10	10.6 %	36	13.1%	19	11.0 %	27	13.8%
Agree	22	23.4 %	71	25.9%	42	24.4 %	51	26.0%
Strongly Agree	19	20.2 %	50	18.2%	31	18.0 %	38	19.4%

Chi square, $p > 0.05$

5.3 Results of study III

The study included 134 participants. The majority of the participants were female (57.5%), non-smokers (72.4%), and reported no consumption of alcohol (99.3%). Most of the participants were married (75.4%), and more than two-thirds were living in urban or village settings (70.9%). Most of the participants followed a normal diet (97.0%).

The mean age of the participants was 47 years (SD=17), while their BMI ranged from 17 to 45, with a mean of 28.1 (SD=6.6), indicating that a large proportion of them were overweight or obese. Other sociodemographic data is presented in tables 5.13A and 5.13B.

Table 5.13 A1: Sociodemographic data of the participants

Variable	Category	Count	%
Sex	Female	77	57.5%
	Male	57	42.5%
Smoking	Yes	26	19.4%
	No	97	72.4%
	Previous	11	8.2%

Table 5.13 A2: Sociodemographic data of the participants

Alcohol	Yes	1	0.7%
	No	133	99.3%
Marital Status	Divorced	4	3.0%
	Married	101	75.4%
	Single	22	16.4%
	Widowed	7	5.2%
Living Area	Camp	39	29.1%
	City	54	40.3%
	Village	41	30.6%
Diet	Normal	130	97.0%
	Vegetarian	4	3.0%

Table 5.4 B: Sociodemographic data of the participants

Variable	Minimum	Maximum	Mean	Std. Deviation
Age (years)	18	77	47.06	17.59
Weight (kg)	51	112	78.86	17.24
Height (cm)	153	181	168.15	7.97
BMI	17.0	45.7	28.12	6.60

BMI: Body mass index

Locally advanced CRC was the most common type of cancer affecting the participants. Locally advanced and metastatic cases were approximately equally present. The distribution of the cancer types and metastases is presented in table 5.14.

Table 5.14: Distribution of cancer types and metastases

Disease Status	Count	%
Gastric Cancer (GC)	25	18.7%
Locally Advanced BC	19	14.2%
Locally Advanced CRC	30	22.4%
Metastatic BC	25	18.7%
Metastatic CRC	20	14.9%
Other	15	11.2%

GC: gastric cancer, CRC: colorectal cancer, BC: breast cancer.

Other comorbidities that were present in the participants include hypertension, which was present in 28.1%; dyslipidemia, which was present in 23%; diabetes mellitus, which was present in 19.3%; and heart failure, which was present in 4.4% of the participants. Table 5.15 displays the distribution of other comorbidities.

Table 5.5: Distribution of comorbidities

Variable	Category	Count	%
DM	Yes	26	19.3%
	No	108	80.0%
HTN	Yes	38	28.1%
	No	96	71.1%
HF	Yes	6	4.4%
	No	128	94.8%
Dyslipidemia	Yes	31	23.0%
	No	103	76.3%

DM: diabetes mellitus. HTN: hypertension, HF: heart failure.

Genetic testing indicated that most of the participants (85.1%) were classified as normal DPD metabolizers (AS: 2), while 13.4% of participants were intermediate DPD metabolizers (AS: 1-1.5), and 1.5% were poor metabolizers (AS: 0-0.5). The distribution of the participants based on their DPD metabolizing status is shown in table 5.16.

Table 5.16: Distribution of the participants based on their DPD metabolizing status

DPYD variant	Common allele name	Functional effect	Genotype status	Activity score (AS)	Phenotype	Number of patients (n)	Prevalence (%)
c.1905+1 G>A	DPYD*2A	No function	Heterozygous	1.0	Intermediate metabolizer	8	6.0
c.2846A >T	—	Decreased function	Heterozygous	1.5	Intermediate metabolizer	6	4.5
c.1236G >A (HapB3)	HapB3	Decreased function	Heterozygous	1.5	Intermediate metabolizer	4	3.0
Subtotal – Intermediate metabolizers	—	—	—	—	Intermediate	18	13.4
c.1905+1 G>A + c.1679T >G	*2A / *13	No function	Compound heterozygous	0.0	Poor metabolizer	2	1.5
Subtotal – Poor metabolizers	—	—	—	—	Poor	2	1.5
No clinically relevant variant detected	Wild-type	Normal function	Wild-type	2.0	Normal metabolizer	114	85.1
Total	—	—	—	—	—	134	100

Reduced DPD function: 14.9% (95% CI: 8.9–20.9%).

In total, 20 of 134 participants (14.9%) demonstrated reduced DPD metabolizing capacity (intermediate or poor metabolizers). The estimated prevalence was associated with a 95% confidence interval of 8.9%–20.9%, reflecting the level of uncertainty related to the sample size.

Side effects occurred in 17.2% of the participants. The most frequently reported side effect was hand-and-foot syndrome, which occurred in 6.7% of participants, followed by fatigue or weakness (6%). Other side effects are presented in table 5.17.

Table 5.17 A: Frequency of side effects in the participants

Side Effect	Grade	Count	%
Diarrhea	Grade 3	1	0.7%
	No	133	99.3%
Oral mucositis	Grade 3	3	2.2%
	Grade 4	3	2.2%
	No	128	95.5%
Nausea/vomiting	Grade 3	2	1.5%
	No	132	98.5%
Neutropenia	Grade 4	3	2.2%
	No	131	97.8%
Thrombocytopenia	Grade 3	2	1.5%
	Grade 4	1	0.7%
	No	131	97.8%
Chest pain	Grade 3	4	3.0%
	Grade 4	1	0.7%
	No	129	96.3%
Dyspnea	Grade 3	2	1.5%
	Grade 4	2	1.5%
	No	130	97.0%
Cardiogenic shock	Grade 4	1	0.7%
	No	133	99.3%
Arrhythmia	Grade 3	1	0.7%
	No	133	99.3%

Table 5.17 B: Frequency of side effects in the participants

Hand-and-Foot Syndrome	1	9	6.7%
	No	125	93.3%
Dermatitis	Grade 3	2	1.5%
	Grade 4	1	0.7%
	No	131	97.8%
Fatigue/weakness	Grade 3	4	3.0%
	Grade 4	4	3.0%
	No	126	94.0%
Fever	Grade 3	4	3.0%
	Grade 4	1	0.7%
	No	129	96.3%
Edema	Grade 4	1	0.7%
	No	133	99.3%

Treatment was interrupted due to side effects in 6.7% of the participants and completely discontinued in 7.5% of them. Hospitalization due to side effects and complications was reported in 9.7% of the cases. The consequences of side effects are presented in table 5.18.

Table 5.18: Consequences of side effects

Variable	Category	Count	N %
Treatment Interrupted	No	125	93.3%
	Yes	9	6.7%
Treatment Discontinued	No	124	92.5%
	Yes	10	7.5%
Hospitalization	No	121	90.3%
	Yes	13	9.7%

Among the 11 patients with DPYD mutations who received a full dose of FP without adjustment, seven (63.6%) experienced side effects, while four (36.4%) did not experience any related side effects. On the other hand, among the nine patients with DPYD mutations whose doses were adjusted based on their DPYD status according to guideline recommendations, only one (11.1%) experienced side effects, while eight (88.9%) did not experience any related side effects. The association between dose adjustment and side effects was statistically significant ($p < 0.05$). This data is shown in table 5.19.

Table 5.19: Dose adjustment by side effects

Dose adjustment	Side effect			
	No		Yes	
	Count	Row N %	Count	Row N %
No	4	36.4%	7	63.6%
Yes	8	88.9%	1	11.1%

Fisher's exact test

Treatment was interrupted in nine patients, discontinued in eight patients, and 13 patients were hospitalized among the 23 patients who experienced side effects. In contrast, in the 111 patients who did not suffer any side effects, treatment was discontinued in two, while it was not interrupted in any of them, and none of them were hospitalized. All these differences were statistically significant (Fisher's exact test, $p < 0.001$). These values are presented in table 5.20.

Table 5.20: Association between side effects and adverse treatment outcomes

Outcome	Side Effect: Yes (n=23)	Side Effect: No (n=111)	Chi-square p-value
Treatment Interrupted	9 (39.1%)	0 (0.0%)	<0.001
Treatment Discontinued	8 (34.8%)	2 (1.8%)	<0.001
Hospitalization	13 (56.5%)	0 (0.0%)	<0.001

Fisher's exact test

In the participants who experienced side effects ($n = 23$), most were females (65.2%), non-smokers (78.3%), married (73.9%), and living in cities (52.2%), while almost all reported no alcohol use (100%) and followed a normal diet (95.7%). Diabetes mellitus (21.7%), hypertension (30.4%), and dyslipidemia (34.8%) were more frequent among those with side effects compared to those without side effects. Heart failure was uncommon in both groups

(4.3% vs. 4.5%). None of these differences (except marital status) was statistically significant. These differences are summarized in table 5.21.

Table 5.21: Baseline characteristics by side effect occurrence

Variable	Category	Side Effect: Yes (n=23)	Side Effect: No (n=111)
Sex	Female	15 (65.2%)	62 (55.9%)
	Male	8 (34.8%)	49 (44.1%)
Smoking	No	18 (78.3%)	79 (71.2%)
	Passive	2 (8.7%)	9 (8.1%)
	Yes	3 (13.0%)	23 (20.7%)
Alcohol	No	23 (100.0%)	110 (99.1%)
	Yes	0 (0.0%)	1 (0.9%)
Marital Status	Divorced	1 (4.3%)	3 (2.7%)
	Married	17 (73.9%)	84 (75.7%)
	Single	1 (4.3%)	21 (18.9%)
	Widowed	4 (17.4%)	3 (2.7%)
Living Area	Camp	5 (21.7%)	34 (30.6%)
	City	12 (52.2%)	42 (37.8%)
	Village	6 (26.1%)	35 (31.5%)
Diet	Normal	22 (95.7%)	108 (97.3%)
	Vegetarian	1 (4.3%)	3 (2.7%)
DM	No	18 (78.3%)	90 (81.1%)
	Yes	5 (21.7%)	21 (18.9%)
HTN	No	16 (69.6%)	80 (72.1%)
	Yes	7 (30.4%)	31 (27.9%)
HF	No	22 (95.7%)	106 (95.5%)
	Yes	1 (4.3%)	5 (4.5%)
Dyslipidemia	No	15 (65.2%)	88 (79.3%)
	Yes	8 (34.8%)	23 (20.7%)

DM: diabetes mellitus. HTN: hypertension, HF: heart failure. Fisher's exact test

Both of the patients who are poor metabolizers experienced side effects, compared to one third (33.3%) of the intermediate metabolizers and 13.2% of the normal metabolizers ($p < 0.05$). These numbers are shown in table 5.22.

Table 5.22: DPD status by side effect occurrence

DPD Status	Side Effect: No (n=111)	Side Effect: Yes (n=23)
Normal	99 (86.8%)	15 (13.2%)
Intermediate	12 (66.7%)	6 (33.3%)
Poor	0 (0.0%)	2 (100.0%)

Fisher's exact test

The data does not show any significant association between age and side effects ($p > 0.05$). The proportion of patients with side effects was similar between the age groups. Younger adults and middle-aged adults showed a similar percentage of side effects (35%) while older adults had a percentage of 38%. The data is shown in table 5.23.

Table 5.23: Distribution of side effects by age group

Age category	Side effect			
	No		Yes	
	Count	N %	Count	N %
39 or less	38	35.2%	7	35.0%
40-59	42	38.9%	7	35.0%
60 or more	28	25.9%	6	30.0%

Pearson's Chi-square.

Testing indicated that the majority of continuous variables were normally distributed, permitting the use of parametric statistical analyses

Chapter Six

Discussion

This study includes discussion of all parts of the dissertation, conclusion, limitations and recommendations.

6.1 Discussion

Cancer is still considered one of the leading causes of morbidity and mortality worldwide, and chemotherapy still plays a central role in cancer treatment across all health settings (Obeagu & Obeagu, 2024). Among available chemotherapeutic agents, FPs are still widely used as first-line or adjuvant therapies for numerous types of cancer such as colorectal, breast, gastric, and other solid tumors (D'Amato et al., 2025; Krishnan, 2025). Their extensive application results from their superior efficacy, relative affordability compared to novel targeted therapies, and being recommended by international oncology guidelines (Deac et al., 2020b). However, the therapeutic benefits of FPs are hindered by their toxicity profile as between 10% and 40% of patients receiving them develop severe adverse effects and around 0.5–1% experience fatal toxicities (Etienne-Grimaldi et al., 2023; Glewis et al., 2022). These toxicities include gastrointestinal complications such as mucositis and diarrhea, hematologic toxicities such as myelosuppression, dermatologic reactions such as hand-foot syndrome, and cardiotoxic effects, all of which can disrupt or even prevent continuation of cancer treatment (Wigle et al., 2023).

The variability in patients' tolerance to FPs has been related, in a large part, to differences in their metabolism mediated by the enzyme DPD, which is responsible for the metabolism of 80–90% of administered FPs into their inactive metabolites (Zhou & Lauschke, 2022). Deficiency in DPD, caused primarily by pathogenic mutations in the DPYD gene, leads to impaired clearance of FPs and results in excessive accumulation of their toxic metabolites.

The relationship between DPYD mutations and increased FP toxicity is now well-established among various ethnicities (Deenen et al., 2016b; Henricks et al., 2018). Consequently, testing for DPYD mutations before the beginning of treatment has become an internationally recommended strategy that aids to predict the risk of toxicity and enable genotype-based adjustment of doses, thereby improving patient safety.

International medical practice guidelines, including those from the CPIC, EMA, and ESMO, now advocate for DPYD testing before the administration of FPs (Kleinjan et al., 2019; Peeters et al., 2025). In Europe, for example, the widespread employment of these guidelines' recommendations has led to significant reductions in FP side effects leading to reductions in hospitalization rates, improvements in QoL, and substantial healthcare cost reductions (Hedtke et al., 2025; Roncato et al., 2024). However, the global adoption of DPYD testing remains highly variable. In high-income countries such as France and the Netherlands, DPYD testing is becoming a routine. On the other hand, in many lower-income countries, such as those in the MENA region, implementation of DPYD testing remains relatively insufficient due to barriers including cost, worse infrastructure, limited awareness of providers and patients, and lack of structured national guidelines (Almashagbah et al., 2022; Sukkarieh et al., 2023).

Palestine represents the challenges faced by LMICs in adopting pharmacogenomics in general. The burden of cancer is increasing, caused by demographic changes, epidemiological transition, and lifestyle factors (Abu-El-Noor et al., 2023). Despite that, oncology services are still constrained by limited resources, fragmented governance systems, and the high dependence on external funding and referrals. In such a context, the integration of pharmacogenomics into regular healthcare could be considered as a luxury, due to the presence of competing priorities such as securing chemotherapy supply chains or ensuring access to basic medical imaging (Mitwalli et al., 2023). Simultaneously, the high toxicity burden of FPs in cancer patients usually leading to hospitalization and treatment delays signifies a clinical and financial problem that may potentially be improved through proper implementation of DPYD testing (Maqdasawi et al., 2025).

Against this context, this dissertation aimed to explore DPYD testing in Palestine from three interrelated perspectives:

- **Healthcare providers** (oncologists, residents, and clinical pharmacists): their knowledge, attitudes, and practices are key to whether testing is considered, recommended, and implemented.
- **Cancer patients**: their knowledge, practices, and WTP impact the acceptance and feasibility of integrating pharmacogenomics into the national clinical practice guidelines.
- **Genetic and clinical evidence**: by means of laboratory-based genotyping of actual patient samples and toxicity outcome assessment. This provides empirical confirmation of the prevalence of risk mutations and their association with FP toxicity in Palestinian cancer patients.

Although each of the three perspectives provides unique insights, together, they form a triangulated evidence base, that offers both depth and breadth. The provider component reveals systemic and professional barriers to implementation while the patient component highlights acceptance, trust, and financial constraints facing the patients. The genetic component provides objective evidence of clinical need associated with the actual patient outcomes.

The novelty of this dissertation lies in being the first comprehensive exploration of DPYD testing in Palestine and also in its integration of these three perspectives. While previous studies in the Middle East have separately examined provider knowledge (Sukkarieh et al., 2023), patient knowledge and attitudes (Soueid et al., 2024), or the prevalence of mutations (Almashagbah et al., 2022), none have triangulated all the three components together.

This design allows for richer integration: for example, understanding that patients' WTP depends on physicians' endorsement, which in turn depends on adequate providers' training, which has to be justified by evidence of clinical benefit in the local patient population (Dhanda et al., 2020; Hassan et al., 2024; Rozza et al., 2025).

Consequently, the dissertation both contributes local evidence to global pharmacogenomic literature and also illustrates how LMICs can approach precision medicine realistically. The findings reveal both readiness and barriers, awareness without adequate practice among providers, willingness with financial constraints among patients, and significant but preventable toxicity among genetic carriers. Together, these three aspects highlight the feasibility of pharmacogenomic testing in Palestine while also underscoring the systemic amendments required for its proper integration.

The following sections discuss each of the components in details, comparing their findings with global literature, interpreting their implications into practice, and synthesizing them into policy, practice, and research recommendations for Palestine and other LMICs.

6.1.1 Study I

The result emphasizes a notable deficiency in training regarding pharmacogenomics and implementation of pharmacogenomic testing among HCPs. Although most participants indicate that they have not received formal training in pharmacogenomics, no differences were observed between roles, such as residents, clinical pharmacists, and physicians. Despite this lack of training across all groups, a significant percentage still administer FPs, underscoring the need for comprehensive educational initiatives to improve safety and efficacy in clinical practice. This difference indicates that numerous HCPs may lack comprehensive knowledge regarding the complex nature of pharmacogenomics and its implications for drug therapy. This gap highlights the urgent need for targeted educational initiatives and training programs to bridge the knowledge deficit among HCPs. Incorporating pharmacogenomics into medical and pharmacy curricula, as well as offering continuing education opportunities, could enhance practitioners' understanding and improve the safe and effective use of FPs. This is particularly critical given the potential for severe adverse drug reactions in patients with DPYD gene variants.

It is encouraging to notice that almost 80% of HCPs have a high level of awareness about the mutation linked to DPD deficiency and its impact on fluoropyrimidine toxicity. This suggests that healthcare practitioners are generally well-informed about this important genetic component. Nevertheless, it is worrisome that fewer than 50% of the participants stated that they screen for DPD deficiency prior to prescribing FPs. This gap between awareness and practice may be attributed to financial and logistical barriers, such as the high cost of DPD testing, limited availability of testing facilities, and a lack of institutional protocols, which hinder the integration of pharmacogenetic testing into routine clinical practice. The lack of implementation in this domain may result in a higher likelihood of severe toxicity in patients with DPD deficiency who receive FPs.

The indication that less than half of the participants reported their institution having explicit standards for administering FPs implies a deficiency in uniformity within this domain. This lack of standardized protocols can lead to inconsistent practices, increasing the risk of adverse drug reactions and compromising patient safety. Without clear guidelines, HCPs may fail to screen for DPD deficiency, resulting in suboptimal dosing or inappropriate treatment that could reduce treatment efficacy and expose patients to potentially severe toxicity. The absence of clear recommendations may lead to variations in prescribing practices and potentially result in inferior outcomes for patients. For example, some practitioners may omit screening for DPD deficiency altogether, leading to standard dosing that could cause severe toxicity in patients with the mutation, while others might delay treatment adjustments due to uncertainty or lack of access to testing. Such inconsistencies can compromise both patient safety and the overall efficacy of FP-based therapies.

The significant incidence of serious toxicity associated with FPs (more than half) is alarming and emphasizes the necessity for enhanced management measures. This rate appears to be higher than the global average, where severe toxicity typically ranges between 10-30% in patients receiving FPs. Such a stark contrast highlights potential gaps in screening practices, dosing adjustments, or patient monitoring in the local context, underscoring the urgent need for standardized protocols and broader implementation of DPD deficiency testing. One method to reduce this risk is through DPYD testing, which can identify patients who have a higher chance of experiencing toxicity as a result of DPD deficiency. Nevertheless, the very low percentage of observations regarding the influence of DPD testing in clinical practice (merely 33%) implies that this testing may not be extensively adopted or acknowledged as being beneficial among HCPs. To improve adoption, strategies such as integrating DPD testing into national treatment guidelines, subsidizing the cost of testing to reduce financial barriers, and conducting educational campaigns to raise awareness about its clinical value could be implemented. Additionally, policies mandating the inclusion of pharmacogenomics in medical and pharmacy curricula and incentivizing healthcare institutions to adopt routine screening protocols may further promote the use of DPD testing.

The low rates of standardization of DPD testing and promotion by the Ministry of Health underscore the necessity for heightened awareness and implementation of this crucial component of personalized medical care. Implementing standardized protocols and actively

promoting DPYD testing has the potential to enhance uniformity in healthcare institutions and ultimately enhance patient outcomes.

This indicates a lower-than-anticipated adoption of a screening test that is already regarded as a standard procedure in numerous other countries like France and the Netherlands (Lunenbourg et al., 2020; Wörmann et al., 2020). Consequently, our findings emphasize the significance of promoting DPD screening prior to the administration of fluoropyrimidines.

The results uncover a significant pattern in the knowledge of the mutation associated with DPD insufficiency across HCPs. Resident physicians demonstrated the greatest level of familiarity, with clinical pharmacists and physicians following closely behind. Curiously, there was a variation in awareness depending on professional experience, with individuals in the intermediate range (5-7 years) demonstrating the highest level of familiarity. The variance seen could be ascribed to the evolution of training methods or the influence of emerging research at this particular phase of their professional lives. Moreover, the discrepancy in understanding between private and governmental hospital settings implies possible variations in instructional tools or focus on pharmacogenomics in these settings.

The data reveals a notable difference in the existence of guidelines for prescribing FPs among various categories of HCPs and hospital environments. Guideline availability varied across clinical pharmacists, physicians, and residents, with physicians and residents being more likely to have guidelines compared to clinical pharmacists. The difference can be attributed to the inherent characteristics of their positions and duties within the healthcare system, since physicians and residents typically exhibit greater direct engagement in making prescription decisions in comparison to clinical pharmacists. Additionally, differences in funding, institutional priorities, and resource allocation between hospital environments may further contribute to this variation. Private hospitals, for example, may have more resources to develop and implement comprehensive guidelines, whereas governmental institutions may face budget constraints and competing healthcare priorities.

Curiously, the correlation between the presence of guidelines and years of professional experience was not consistently observed, contrary to what one might anticipate. This implies that factors beyond experience, like institutional agendas, resources, or the importance given to standardizing prescribing practices, might influence the creation or execution of these guidelines.

The noticeable difference in the availability of guidelines between private and governmental hospital settings highlights the impact of institutional factors on the existence of prescribing guidelines. Private hospitals are more likely to have established guidelines compared to public hospitals due to their greater resources and emphasis on quality improvement programs.

Consequently, these findings emphasize the importance of having clear and easily available guidelines for prescribing fluoropyrimidines in all healthcare environments, regardless of the practitioner's level of expertise or type of facility. These suggestions can assist in guaranteeing secure and efficient prescription practices, eventually enhancing patient results.

The analysis indicates a difference in how various groups of HCPs perceive the effects of DPD testing in clinical practice. Clinical pharmacists, physicians, and residents had varying degrees of expertise in observing the impact of DPD testing. Among them, physicians had the highest percentage of respondents who reported having such experience. The variation in results can be linked to differences in roles and duties, since physicians are more inclined to have direct participation in patient care decisions where DPD testing has an effect on treatment options. To address this variation, targeted training programs on pharmacogenomic applications and the clinical importance of DPD testing should be developed for all healthcare roles. Additionally, implementing policies that promote interdisciplinary collaboration could help ensure that all practitioners are equally informed and involved in decisions related to DPD testing.

Interestingly, the correlation between the observation of the impact of DPD testing and years of work experience was not consistently positive. This implies that variables other than experience, such as exposure to training or access to resources, can affect the probability of detecting the effects of DPD testing in clinical practice. To address this issue, targeted training programs focused on pharmacogenomics and the clinical applications of DPD testing should be implemented across all experience levels. Additionally, ensuring equitable access to testing facilities and resources within healthcare institutions can help bridge this gap and improve the integration of DPD testing into routine practice.

The observed statistically significant difference between HCPs in private and public institutions in terms of their observation of the impact of DPD testing underscores the role of institutional determinants. Private hospitals may possess stronger resources and prioritize individualized medicine, resulting in a greater probability of witnessing the effects of DPD testing in comparison to government hospitals.

The results of this study closely correspond to the findings of studies carried out in nearby nations. A study carried out in Saudi Arabia also found a lack of proper genetic testing before administering FPs, as well as a lack of awareness about established recommendations for genetic testing (Sukkarieh et al., 2023).

Research conducted in the United States revealed that although the majority of oncologists recognize the heightened risk of toxicity in patients with DPD deficiency and are open to adjusting the dose of FP appropriately, only a small percentage of them believe in the effectiveness of DPYD testing. Less than one-fifth of oncologists have ever requested the test, and only very small numbers have ordered it for at least 10% of their patients receiving FP treatment. The limited occurrence of DPD insufficiency and the absence of guideline recommendations are significant obstacles to broader acceptance and implementation (Koo, Pasternak, Henry, Sahai, et al., 2022).

The comparison to similar studies in Saudi Arabia and the U.S. provides valuable context for understanding global challenges in implementing DPD testing. Cultural and economic factors may contribute to these similarities and differences. For instance, in Saudi Arabia, a lack of widespread genetic literacy and reliance on traditional practices may hinder

awareness and adoption of genetic testing. In the U.S., despite higher access to advanced technologies, skepticism about the cost-effectiveness of testing and varying guideline recommendations may explain the limited use of DPYD testing. These findings underscore the need for tailored strategies, such as improving awareness, aligning guidelines, and addressing cultural and economic barriers, to enhance the adoption of DPD testing in diverse healthcare systems.

The cost of DPD testing includes not only the direct expenses of genetic analysis but also the infrastructural investments required for laboratory capacity, equipment, and trained personnel. In Palestine, the lack of established pharmacogenomics programs and limited access to specialized genetic testing facilities further complicate implementation. Additionally, regulatory barriers, such as the absence of national guidelines or policies mandating pre-treatment DPD screening, contribute to inconsistent adoption across healthcare institutions. Overcoming these challenges will require coordinated efforts to integrate pharmacogenomics into clinical practice, improve healthcare infrastructure, and establish clear regulatory frameworks to support the safe and cost-effective use of FP-based therapies.

A study evaluating the application of DPD deficiency testing in Europe, both before and after the recommendations made by the European Medicines Agency (EMA), revealed a rise in the utilization of both genotyping and phenotyping techniques following the guidelines. The implementation of municipal norms has also seen an increase. In 2021, the reimbursement coverage for both tests experienced an improvement, with just a limited number of nations not providing coverage. Although significant obstacles persisted, a smaller number of experts mentioned concerns around reimbursement and recognition after the suggestions were made. In general, quarter of respondents indicated that they encountered no obstacles in implementing the new testing procedure after the recommendations were made (de With et al., 2023). These European practices could serve as a model for Palestine by demonstrating the value of clear national guidelines, improved reimbursement policies, and increased advocacy for testing. Adapting these strategies in Palestine would require collaboration between healthcare policymakers, institutions, and the Ministry of Health to establish unified protocols and allocate resources to make DPD testing more accessible and feasible.

The development of second-generation FPs alternatives like CF10, which exhibit lower systemic toxicity and greater anti-tumor activity, aligns with the goals of reducing the burden of adverse events associated with current treatment regimens. These advancements may also reduce reliance on DPD testing, especially in resource-limited settings where implementation barriers persist. However, integration of such therapies into clinical practice would still require robust training, guideline updates, and resource allocation to ensure equitable access and effective use Click or tap here to enter text. Click or tap here to enter text.

Emerging research into innovative FP formulations offers promising solutions to mitigate toxicity while enhancing efficacy. For instance, Okechukwu et al. (2024) demonstrated that CF10, a second-generation FP(Okechukwu et al., 2024b).

To address the identified gaps, it is imperative to implement actionable measures aimed at enhancing the safe and effective use of FPs. National training programs on pharmacogenomics should be established to equip HCPs with the knowledge necessary to integrate genetic testing, such as DPD deficiency screening, into routine practice. Additionally, integrating DPD testing protocols into existing healthcare systems and making them a mandatory component of treatment guidelines could standardize practices and reduce toxicity risks. These initiatives, coupled with efforts to subsidize the cost of testing and improve accessibility, would significantly enhance patient safety and optimize treatment outcomes.

Policy changes proposed to the Ministry of Health could include mandating DPD testing as a standard pre-treatment requirement for FPs, subsidizing testing costs to improve accessibility, and establishing nationwide protocols to ensure uniform implementation across healthcare institutions. Additionally, incorporating pharmacogenomics into medical education and professional training programs could foster a culture of personalized medicine. These measures would enhance early detection of DPD deficiency, minimize severe toxicity risks, and improve overall treatment outcomes.

Despite promising awareness levels, the lack of widespread implementation and uniformity in practices highlights the pressing need for actionable measures. Addressing these challenges through targeted training, policy reforms, and resource allocation could significantly enhance patient safety and treatment outcomes. Building on these insights, the conclusion will outline practical recommendations and propose avenues for future research to bridge these gaps effectively.

To ensure patient safety and align with international best practices, the Palestinian Ministry of Health should take concrete steps to promote the integration of DPD testing into clinical practice. Establishing national guidelines mandating DPYD genotyping or DPD enzyme activity testing for patients receiving fluoropyrimidines is essential, with a focus on high-risk groups such as those with a history of severe toxicity, renal or hepatic impairment, or a family history of DPD deficiency. Oncology protocols should incorporate mandatory pre-treatment DPD testing for colorectal, gastric, and breast cancer patients receiving 5-FU or capecitabine. Additionally, investments should be made to expand laboratory infrastructure, ensuring that molecular and biochemical diagnostic facilities are equipped to conduct DPYD testing, alongside training programs for healthcare professionals to properly interpret and utilize results. To increase awareness and adherence, educational campaigns and continuing medical education (CME) programs should be implemented, highlighting the role of DPD testing in preventing severe adverse drug reactions. Given financial constraints, the Palestinian Ministry of Health should explore subsidies, public-private partnerships, and integration into health insurance schemes to make testing more accessible and affordable. Finally, a national registry should be established to track testing uptake, FP toxicity cases,

and clinical outcomes, enabling continuous policy refinement and improved accessibility over time. Implementing these measures will enhance patient safety, optimize FP therapy, and reduce the incidence of severe drug-related toxicity in Palestine.

6.1.2 Study II

This study is the first to examine how Palestinian cancer patients view pharmacogenomic testing. The findings show strong acceptance but low awareness. These patterns align with global data and reveal major gaps in local systems.

6.1.2.1 Knowledge of Pharmacogenomic Testing

Overall awareness and uptake of pharmacogenomic testing were low, and many participants demonstrated limited understanding of its purpose and application. In contrast, only a small subset of respondents reported being sufficiently familiar with pharmacogenomic testing, highlighting a clear knowledge gap. These findings are similar to global data: in Saudi Arabia, patient awareness was only about 17% (Sukkarieh et al., 2023) while in the U.S., awareness was around 28% (Haga et al., 2016).

The low levels of knowledge in Palestine therefore are similar to international experience but are more intense because of the lack of structured patient education programs and limited integration of genetic testing into clinical practice (Soueid et al., 2024). Notably, participants with higher education and higher income showed better understanding. Health literacy, including functional and genetic literacy, likely plays a critical role in shaping patients' comprehension and engagement with pharmacogenomic testing. This highlights how social disparities may worsen inequities in access to genomic advances (Zhang et al., 2022). Addressing these gaps will require technical adoption in addition to tailored educational interventions to empower patients across different socioeconomic backgrounds.

6.1.2.2 Attitudes Toward Testing

Despite their poor knowledge, patient attitudes were generally positive. Less than half of the participants believed that pharmacogenomic testing can help doctors choose the best treatment, while almost the same percentage trusted its accuracy. Similar attitudes were reported in Canada and the USA; around half of patients expressed favorable views once the test was explained (Asiedu et al., 2020).

Remarkably, around half of the participants indicated that they would undergo testing if it was recommended by their physician. This reflects the great influence of healthcare professionals, as also shown in European studies where physician endorsement was the strongest predictor of uptake (Edris et al., 2022; Truong et al., 2020). For Palestine, this suggests that training oncologists and pharmacists to counsel patients can substantially increase test acceptance within patients. Concerns about insurance discrimination were relatively high compared to the U.S., where up to 30% worry about this (A. A. Lemke et al., 2018), reflecting the stronger role the insurance locally plays. This high level of concern could facilitate implementation, because ethical barriers may be as pressing as financial ones (Y. M. Lee et al., 2018).

6.1.2.3 Preferences and Practices

Two-thirds of the participants preferred their pharmacogenomic results to predict both the treatment effectiveness and the risk of side effects, being similar to international findings which indicate that patients appreciate information about both efficacy and safety (Magavern et al., 2025; Olson et al., 2017). Most of the participants were willing to provide a blood sample, which is also similar to willingness rates between 65–80% in Europe and Asia (Haga et al., 2016).

Decision-making choices showed that most of the participants were in favor of sharing the decision-making with their doctor rather than leaving the decision to the doctor alone. This reflects a growing demand for autonomy in a system that has traditionally been doctor-driven. For practice, this indicates that introducing pharmacogenomic testing in Palestine should be accompanied by structured decision-making sharing frameworks to ensure that patients remain active partners in their care.

6.1.2.4 Willingness to Pay and Cost Perceptions

The amount of money the participants were willing to pay for the test, and the perceived “reasonable” cost are below the usual cost of pharmacogenomic testing in high-income countries (300–600 USD). US patients reported WTP of 100–400 USD (Bielinski et al., 2017b) while in Europe, patients typically expect full coverage by public health systems (Peruzzi et al., 2025).

Waiting time for the result was almost distributed evenly between all the periods, so more than half of the participants were willing to wait for less than one week. As test results usually need a period of about two weeks for accurate results, this can be considered among the most significant barriers to implementation of the testing process.

In Palestine, a high percentage expected that the government and donors should cover the cost, while only a very small percentage felt patients should pay for the test. This underscores the reality that financial barriers not attitudinal barriers are the greatest challenge to implementation of the testing process (Abbas et al., 2025; Gibson et al., 2017). From a policy perspective, introducing pharmacogenomic testing will require external funding or integration into government health programs, otherwise uptake will remain lower than expected. In the Palestinian context, continuous political instability further restricts health system financing, laboratory capacity, and sustainability of care, creating more structural barriers that distinguish Palestine from many other LMICs and may further delay proper adoption of pharmacogenomic services.

6.1.2.5 Sociodemographic differences

Higher education and higher income were associated with better knowledge, while age and employment showed less pronounced effects. These results are consistent with worldwide data, where socioeconomic status is the key predictor of pharmacogenomic knowledge (Asiedu et al., 2020; Chapdelaine et al., 2021). Interestingly, the willingness to pay was not strongly linked to income, indicating that financial limitations are prevalent and not limited to lower-income groups (Bignucolo et al., 2023; Zhang et al., 2022).

Additionally, participants who believed that pharmacogenomic testing was accurate were more likely to agree to give blood samples and to pay for the test. This confirms international findings that trust in medical procedure's validity is a critical driver of uptake and highlights the importance of clear communication between physicians, healthcare institutions and patients (Marzo et al., 2022; Truong et al., 2020).

Across all dimensions, Palestinian patients demonstrated limited awareness, but moderate acceptance of the pharmacogenomic testing once given some information. This is similar to international experience and highlights education, physician engagement, and financial support as the three drivers for successful implementation of the whole procedure. If these barriers are addressed, pharmacogenomic testing could be integrated into clinical chemotherapeutic practice in Palestine and potentially improve treatment safety and outcomes.

6.1.3 Study III

This study aimed to determine the effect of DPYD genetic variants on FP toxicity in the Palestinian cancer patients. We found that a minority of patients carried DPYD variants related to reduced DPD enzyme activity. The incidence of grade ≥ 3 side effects in the sample was comparable to previous studies in other populations. Hand-foot syndrome and severe fatigue were the most common side effects. DPYD genotype was strongly associated with side effect risk. These findings support the main hypothesis that DPYD mutations are connected to FP side effects and that genotype-based dosing can improve treatment safety.

6.1.3.1 DPYD Metabolizer Status

The observed distribution of DPD metabolizer phenotypes in this study highlights the clinical relevance of DPYD genotyping in this population. Approximately 15% of patients were abnormal DPD metabolizers (intermediate or poor), a proportion on the higher end of that reported in other populations. For instance, 8% of patients were found to carry DPYD mutant alleles in a large prospective European study (Henricks et al., 2018). The higher rates in this study may reflect genetic differences or the inclusion of the DPYD c.1236G>A mutation, which shows variable frequency across ethnic groups.

In Jordan, a pharmacogenetic study identified several DPYD mutations linked to FP toxicity in colorectal cancer patients. This shows that DPD polymorphisms are present and clinically important in Middle Eastern populations (Almashagbah et al., 2022). This data suggests that a fraction of patients in our region carry DPYD mutations that may predispose them to FP toxicity. Consequently, early identification of these patients is critical. Our study adds regional data to the global literature and reinforces the importance of integrating DPYD genotyping into cancer treatment.

The finding that around 15% of the sample had reduced DPD metabolic capacity underscores a clear opportunity for personalized medicine to improve safety in the Palestinian cancer therapy.

Worldwide, DPYD variants associated with decreased function show marked differences across populations. In European populations, the combined carrier frequency of clinically important variants is estimated at 5 to 7 percent (Nguyen et al., 2024). Within Europe, these frequencies also vary remarkably; they are around 2% overall, but shown to be reaching 3.3% in Germany, 2.6% in the Netherlands, and approximately 2.4% in Finland while other variants remain closer to 1% or below (Amstutz et al., 2018; Zhou & Lauschke, 2022).

Outside Europe, prevalence is generally lower, around 0.2% in East Asia and Africa, about 0.8% in Latin populations, and about 0.7% in Ashkenazim (Zhou & Lauschke, 2022). In East Asians, these variants are nearly absent (<0.1%), while in South Asians prevalence is somewhat higher at 0.3–1.5%, and in Middle Eastern groups it is about 0.3% (Chan et al., 2024). In populations of African origin, an additional decreased-function variant occurs at about 2 percent on average, with a range of 1 to 4 percent. Variants common in Europeans are rare in these groups (Chan et al., 2024).

To our knowledge, this is the first study to assess the prevalence of the clinically important DPYD mutations in Palestine and their impact on the toxicity of FPs. This study will help fill this clinical gap in pharmacogenomics and help create a more patient-specific choice of therapy and individualization of treatment.

6.1.3.2 FP-Related Toxicity and DPYD Genotype Associations

Consistent with the known toxicity profile of FU, about one in six patients (17.2%) experienced severe FP-related side effects in this study. This rate is similar to previous studies, which indicate that around 10–40% of patients on FPs develop serious toxicity (Henricks et al., 2018). Our slightly lower observed rate may reflect the benefit of genotype-based dose adjustments or differences in treatment regimens.

The variety of side effects we observed led by hand-foot syndrome and severe fatigue followed by gastrointestinal mucositis, myelosuppression, and cardiotoxicity is similar to the toxicity patterns documented in other studies (De With et al., 2023; de With et al., 2023). For example, studies in metastatic colorectal cancer have reported that diarrhea, mucositis, bone marrow suppression, and hand-foot syndrome are among the most frequent grade ≥ 3 side effects of FPs (Alzahrani et al., 2023). The results confirm that classic FP side effects are prevalent in this setting. This reinforces that FP toxicity is a universal clinical challenge.

Specifically, the current data demonstrates a clear association between DPYD mutations and toxicity risk. In other words, patients carrying a DPYD mutation were 2–3 times more likely to suffer a severe side effect than those with the normal enzyme. This trend is similar to extensive evidence from other populations which indicates that DPYD mutation carriers have a significantly elevated risk of severe FP side effects. Mechanistically, DPD deficiency leads to decreased degradation of FPs and accumulation of toxic metabolites, which may exacerbate cardiotoxicity in addition to gastrointestinal and hematologic toxicity through enhanced systemic exposure and endothelial injury (Deenen et al., 2016b; Glewis et al., 2022; Otero-Torres et al., 2025; Traynor, 2024; White et al., 2025).

These results strongly support these observations in the context of a Middle Eastern, providing realistic evidence that DPYD genotypes meaningfully influence toxicity risk. Notably, both of the patients in this study who were poor metabolizers (DPYD activity score ≤ 0.5) experienced severe side effects, showing the clear risk of treating individuals with DPD mutations with full-dose FPs.

These findings are also in line with global evidence showing that patients who have decreased-function DPYD variants are significantly more prone to experience severe FP-related side effects. Large analyses have demonstrated that mutation carriers face evidently higher risks of hospitalization and treatment-related mortality compared to non-carriers (de Moraes et al., 2024).

Research shows that DPYD deficiency accounts for 40 to 60 percent of the most severe FP-related side effects in chemotherapy practice (Chan et al., 2024). This highlights the importance of considering patient genetic makeup as a key factor in chemotherapy safety across populations (Hishinuma et al., 2022).

Worldwide, the estimated prevalence of grade ≥ 3 side effects in patients treated with FPs is between 10–30% while up to 1% of them may experience treatment-related death. These rates are much higher than in patients without DPYD mutations. Pre-treatment DPYD testing should be regarded as a practical strategy to reduce toxicity and improve treatment outcomes (De Mattia et al., 2024).

In summary, the strong connection between DPYD mutations and side effects observed in the study's participants highlights the predictive value of DPYD genotyping for identifying individuals at higher risk of adverse outcomes on FP therapy.

6.1.3.3 Other clinical factors

In addition to genetic factors, several clinical factors also were shown to affect toxicity risk in this study. Patients with older age did not tend to have a higher rate of severe side effects compared with younger patients indicating that age alone is not a predictive factor for toxicity in this population. This observation, however, differs from older studies showing that age-related changes in drug metabolism and having other comorbidities increase the risk of treatment toxicity (Boisdron-Celle et al., 2017).

Female patients were seen to have relatively higher susceptibility to toxicity than male patients. Similar results have been described in previous literature and are thought to be caused by pharmacokinetic differences, hormonal factors, and smaller average body surface area in women compared to men (Özdemir et al., 2022).

Having other comorbidities was shown to affect the likelihood of side effects. Patients with hypertension, diabetes and dyslipidemia had a higher percentage of side effects compared to those without. Although these differences were not statistically significant, they appear to contribute to increasing the vulnerability of the patients to chemotherapy-induced side effects. This is similar to previous studies where comorbidities were not shown to be

consistent independent predictors of chemotherapy induced side effects (Boisdron-Celle et al., 2017).

Sociodemographic factors such as smoking, dietary habits and living area did not show any statistically significant relationship with the prevalence of side effects. Interestingly, marital status was the only baseline factor that was shown to be significantly associated with the occurrence of side effects. Although the biological explanation for this is unclear, previous studies have shown that psychosocial support can improve adherence and tolerability of chemotherapy among married patients (Kroenke et al., 2018).

6.1.3.4 Impact of Genotype-Guided Dose Adjustment on Outcomes

A major finding of the study is that pre-treatment DPYD genotyping with adjusted-dose therapy was associated with markedly improved safety outcomes. It shows the protective effect of genotype-based dosing. Other studies report similar results. Henricks et al. found that pre-treatment dose reductions of 25 to 50 percent for DPYD variant carriers normalized 5-FU exposure and lowered the risk of grade 3 or higher toxicity. The toxicity rate in carriers then matched the rate seen in non-carriers (Henricks et al., 2018). These findings align with international guidelines. CPIC and EMA recommend pre-treatment DPYD testing and genotype-based dose adjustments as standard clinical practice (Amstutz et al., 2018; Lunenburg et al., 2020).

In that analysis, DPYD*2A heterozygous carriers who received a 50 percent dose reduction had about 31 percent incidence of severe toxicity, compared to 72 percent at full dose (Ho, Smith, Aquilante, Cicali, El Rouby, Hertz, Imanirad, Patel, Scott, Swain, Tuteja, Hicks, et al., 2025). A 2022 meta-analysis of 17 studies also found that pharmacogenetics-based FP dosing lowered the relative risk of severe side effects by about 68 percent compared to standard dosing (Glewis et al., 2022).

In this study, severe side effects were strongly linked to adverse outcomes. More than half of patients with grade 3 or higher toxicity required hospitalization or emergency care. About 34.8 percent had to discontinue treatment. By contrast, none of the patients without severe toxicity were hospitalized and treatment discontinuation in that group was less than 2%. This important contradiction which is also reported in prior literature (Tentoni et al., 2024) indicates how toxicity affects cancer therapy. Therefore, reducing toxicity through individualized dosing can lead to more continuous treatment and potentially better overall outcomes. Data in this study indicates that DPYD genotyping led to relatively lower rates of treatment interruption and discontinuation in the study sample, as the doses were precisely adjusted in patients at risk. By reducing the probability of side effects and avoiding unnecessary treatment interruption and discontinuation, better outcomes are attained, leading to improved survival.

Additionally, from the perspective of the health-system, genotype-based dose modification has also been proven to reduce the hospitalization costs and improve the cost-effectiveness of chemotherapy, mainly by preventing avoidable severe side effects (Deenen et al., 2016b).

However, equitable access to routine DPYD testing remains inconsistent across different countries, particularly in those with low- or middle-income, limiting the global reach of these safety benefits (Hishinuma et al., 2022). Based on the high number of at-risk patients in this population, improving access to DPYD testing in Palestine can lead to a meaningful improvement in patient safety despite the limited resources available.

In summary, implementing genotype-guided dosing improves patient safety and may also help preserve the integrity of the treatment course by decreasing the likelihood of treatment interruption or discontinuation.

6.2 Conclusions

The level of knowledge of healthcare providers regarding the importance of pharmacogenomics and its perceived role in improving patient safety was shown to be adequate. However, there was a great gap in knowledge, awareness of available guidelines, and confidence in the interpretation and application of the test results. A high number of oncology specialists expressed concern about the lack of adequate local infrastructure including a specialized pharmacogenomics laboratory and absence of structured, well-verified institutional protocols to lead dose adjustment based on genetic test findings. These gaps suggest that although the clinical community is interested, further capacity building is essential before pharmacogenomic testing can be routinely applied.

The patient survey gave a complementary point of view, as it indicated that patients are both aware of and anxious about chemotherapy-related side effects. Most of the participants expressed their willingness to undergo genetic testing if it could reduce their risk of severe side effects, hospitalizations, or treatment delays. Specifically, many of the participants indicated their willingness to pay for these services, although their financial capacity varied widely, and concerns about equitable access were clearly evident. This reinforces the aforementioned issue that while demand and acceptance exist, policy structures and health-financing mechanisms are necessary to ensure that testing does not become a privilege that is available only to wealthier patients.

Finally, the genotyping component demonstrated the presence of clinically significant DPYD variants among Palestinian cancer patients, and that their presence may lead to an increased risk of FP-induced side effects. These findings are consistent with international data and indicate that the risks observed globally are also highly relevant within the Palestinian cancer patients. Particularly, the frequency of some mutations appeared to be comparable to the rates that are reported in other populations, providing a solid foundation for clinical translation.

Altogether, these three parts of evidence meet to prove that pharmacogenomic testing is clinically recommended and also socially and financially acceptable in Palestine. Yet, adopting this evidence into practice is restricted by many factors such as limited infrastructure, financial problems, and the absence of clear policy frameworks.

Therefore, this contributes new scientific knowledge and practical insights into how precision medicine may be introduced into a healthcare system with very limited resources. Ultimately, the findings strongly support integration of pharmacogenomic testing into national cancer treatment strategies as a method of improving treatment safety, reducing avoidable morbidity, and moving Palestinian oncology closer to international standards of personalized care.

6.3 Limitations

This dissertation included three interrelated studies exploring healthcare providers' perspectives, patients' knowledge and willingness to pay, and clinical outcomes of DPYD genotyping in FP-treated patients. While the findings of the dissertation give valuable insights, few limitations should be recognized.

- 1- **Study design.** The healthcare provider and patient surveys were cross-sectional in design, which limits their causal interpretation. The pharmacogenomic part of the study was observational and therefore susceptible to confounding from clinical and treatment-related factors. Among the important limitations is that many of the patients were using combination regimens, so some of the side effects might have been caused by other medications or treatments.
- 2- **Sampling and generalizability.** Participants were chosen from the selected oncology centers in the West Bank. Although these are key local hospitals, the results may not represent practices and outcomes in all Palestinian regions or healthcare settings.
- 3- **Self-reported and clinical data.** The responses of the patients may have been influenced by recall bias or social desirability bias. In the genotyping study, adverse events were recorded from files of the hospital, which may not capture all toxicity events that actually occurred.
- 4- **Genetic coverage.** The laboratory testing included the major DPYD mutations that are known to have important clinical effects but did not concentrate on rare mutations.
- 5- **Sample size and subgroup analysis.** Some genotype subgroups, especially poor metabolizers, were small in number, which limited the precision of comparisons between subgroups.
- 6- **Outcome scope.** The pharmacogenomic analysis focused on acute grade ≥ 3 toxicities. Other long-term outcomes such as treatment efficacy, patient survival, or quality of life of the patients were beyond the scope of the study.

Taken together, these limitations show the practical challenges naturally faced in conducting pharmacogenomic and behavioral research in settings with limited resources. They should be considered when interpreting the findings and in designing future studies.

6.4 Recommendations

1. **Integration into Clinical Guidelines**
 - Pharmacogenomic testing should be incorporated into national and institutional chemotherapy protocols as a necessary step before initiating treatment

- Structured and locally adapted dose-adjustment recommendations should be communicated to oncology specialists. These recommendations should be aligned with international recommendations.

2. Capacity Building and Professional Education

- Intensive training programs should be designed to strengthen the knowledge of oncology specialists regarding pharmacogenomics and increase their practical confidence in applying test results.
- Pharmacogenomic modules should be integrated into undergraduate and postgraduate medical curricula, which will help institutionalize knowledge in the long term.
- Training workshops, continuous medical education programs, exchange opportunities and international cooperation processes should be encouraged to improve medical staff expertise.

3. Laboratory Infrastructure

- To improve local medical capacity, a specialized pharmacogenomics laboratory should be established. It should have trained personnel and accurate machinery capable of performing all kinds of pharmacogenomic tests.
- As a temporary solution while local capacity is being developed, regional collaborations with neighboring countries could provide the required results.
- Standardized reporting protocols and quality assurance mechanisms that ensure clinical reliability should be developed through partnership between the government and the local institutions.

4. Patient-Centered Implementation

- All implementation strategies must keep in mind affordability and equity. Co-payment or partial insurance coverage could be explored, but, due to limited resources, donor or governmental aid will be necessary to avoid large disparities between recipients.
- Patient education campaigns should explain the purpose and benefits of pharmacogenomic testing. This can help patients perform informed decision-making and build mutual trust between patients and treatment systems.
- In addition, counseling services should be performed prior to the testing process to explain and respond to ethical concerns, data privacy issues, and practical implications of the testing process.

5. Policy, Regulation, and Financing

- A regulatory framework that governs pharmacogenomic testing, covering accreditation, payments, and various ethical considerations should be established through a partnership between the MOH, health institutions and representatives of the public sector.
- Health insurance companies and other governmental bodies should be engaged in the policy development process to include pharmacogenomic testing in essential health packages.

6. Research and Monitoring

- Large, multicenter studies should be conducted to draw a clearer picture of the frequency and spectrum of important genetic mutations in Palestine and their relationship with clinically important drugs.
- Prospective clinical trials or cohort studies should be conducted to evaluate the actual impact of pharmacogenomic testing on reducing toxicity, hospitalization, treatment costs and mortality rate.
- Cost-effectiveness analyses should be performed by health economy experts to demonstrate and strengthen the case for policy adoption.
- A national registry of chemotherapy toxicity incidents and genotyping results would allow ongoing monitoring, quality improvement, and research.
- Integration of clinical pharmacy services into pharmacogenomic workflows should be prioritized, with clinical pharmacists actively involved in interpreting test results, supporting fluoropyrimidine dose optimization, and coordinating pharmacogenomic-guided therapy within multidisciplinary oncology teams.
- Empowering clinical pharmacists as implementation leaders through targeted pharmacogenomics training and formal inclusion in institutional and national guideline development will strengthen the translation of pharmacogenomic evidence into routine clinical practice, particularly in resource-limited healthcare settings such as Palestine.

References

- Abbas, M. O., Rahma, A. T., Elbarazi, I., Ali, B. R., Patrinos, G. P., Nagy, F., Osman, A., Alneyadi, R. K., Alshamsi, A. S., Alraqabani, M., Al-Mahayri, Z., & Al-Maskari, F. (2025). Knowledge and Views of Patients With Cardiovascular Disease Toward Pharmacogenomics in The United Arab Emirates. *Clinical and Translational Science*, 18(8). <https://doi.org/10.1111/cts.70300>
- Abu-El-Noor, N., Aljeesh, Y., Aliwaini, S., Alhamss, S., Darwish, R., & Abu-El-Noor, M. (2023). Identifying Priorities and Needs to Improve Oncology Research in the Gaza Strip, Palestine. *Journal of Multidisciplinary Healthcare, Volume 16*, 2529–2541. <https://doi.org/10.2147/JMDH.S422167>
- Abushanab, D., Mohamed, S., Abdel-latif, R., Moustafa, D. A., Marridi, W., Elazzazy, S., Badji, R., Al-Muftah, W., Ismail, S. I., Bujassoum, S., Al-Thani, A., Al-Badriyeh, D., & Al Hail, M. (2025a). Dihydropyrimidine Dehydrogenase Deficiency (DPYD) Genotyping-Guided Fluoropyrimidine-Based Adjuvant Chemotherapy for Breast Cancer. A Cost-Effectiveness Analysis. *Clinical Drug Investigation*, 45(3), 151–163. <https://doi.org/10.1007/s40261-024-01413-8>
- Abushanab, D., Mohamed, S., Abdel-latif, R., Moustafa, D. A., Marridi, W., Elazzazy, S., Badji, R., Al-Muftah, W., Ismail, S. I., Bujassoum, S., Al-Thani, A., Al-Badriyeh, D., & Al Hail, M. (2025b). Dihydropyrimidine Dehydrogenase Deficiency (DPYD) Genotyping-Guided Fluoropyrimidine-Based Adjuvant Chemotherapy for Breast Cancer. A Cost-Effectiveness Analysis. *Clinical Drug Investigation*, 45(3), 151–163. <https://doi.org/10.1007/s40261-024-01413-8>
- Adejumo, P. O., Aniagwu, T. I. G., Awolude, O. A., Adedokun, B., Kochheiser, M., Sowunmi, A., Popoola, A., Ojengbede, O., Huo, D., & Olopade, O. I. (2023). Cancer Genetic Services in a Low- to Middle-Income Country: Cross-Sectional Survey Assessing Willingness to Undergo and Pay for Germline Genetic Testing. *JCO Global Oncology*, 9. <https://doi.org/10.1200/GO.21.00140>
- Afolabi, B. L., Mazhindu, T., Zedias, C., Borok, M., Ndlovu, N., & Masimirembwa, C. (2023). Pharmacogenetics and Adverse Events in the Use of Fluoropyrimidine in a Cohort of Cancer Patients on Standard of Care Treatment in Zimbabwe. *Journal of Personalized Medicine*, 13(4), 588. <https://doi.org/10.3390/jpm13040588>
- Ahmed, N. J., Alrawili, A. S., & Alkhawaja, F. Z. (2020). Knowledge and Awareness on Personalized Medicine amongst Health Care Specialists and University Students in Health Colleges in Saudi Arabia. *Journal of Pharmaceutical Research International*, 177–183. <https://doi.org/10.9734/jpri/2020/v32i1630741>
- Algahtani, M. (2020). Knowledge, perception, and application of pharmacogenomics among hospital pharmacists in Saudi Arabia. *Risk Management and Healthcare Policy*, 13, 1279–1291. <https://doi.org/10.2147/RMHP.S267492>

- Allen, J. D., Pittenger, A. L., & Bishop, J. R. (2022). A Scoping Review of Attitudes and Experiences with Pharmacogenomic Testing among Patients and the General Public: Implications for Patient Counseling. *Journal of Personalized Medicine*, 12(3), 425. <https://doi.org/10.3390/jpm12030425>
- Almashagbah, N. A., Mahasneh, A. A., & Bodoor, K. G. (2022). Pharmacogenetic Study of the Dihydropyridine Dehydrogenase Gene in Jordanian Patients with Colorectal Cancer. *Asian Pacific Journal of Cancer Prevention*, 23(9), 3061–3069. <https://doi.org/10.31557/APJCP.2022.23.9.3061>
- Alzahrani, S., Al Doghaither, H., Al-ghafari, A., & Pushparaj, P. (2023). 5-Fluorouracil and capecitabine therapies for the treatment of colorectal cancer (Review). *Oncology Reports*, 50(4), 175. <https://doi.org/10.3892/or.2023.8612>
- Amstutz, U., Farese, S., Aebi, S., & Largiadér, C. R. (2009). Dihydropyrimidine dehydrogenase gene variation and severe 5-fluorouracil toxicity: A haplotype assessment. *Pharmacogenomics*, 10(6), 931–944. <https://doi.org/10.2217/pgs.09.28>
- Amstutz, U., Henricks, L. M., Offer, S. M., Barbarino, J., Schellens, J. H. M., Swen, J. J., Klein, T. E., McLeod, H. L., Caudle, K. E., Diasio, R. B., & Schwab, M. (2018). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. *Clinical Pharmacology and Therapeutics*, 103(2), 210–216. <https://doi.org/10.1002/cpt.911>
- Asiedu, G. B., Finney Rutten, L. J., Agunwamba, A., Bielinski, S. J., St. Sauver, J. L., Olson, J. E., & Rohrer Vitek, C. R. (2020). An Assessment of Patient Perspectives on Pharmacogenomics Educational Materials. *Pharmacogenomics*, 21(5), 347–358. <https://doi.org/10.2217/pgs-2019-0175>
- Barrett, D., Sibalija, J., & Kim, R. B. (2024). Patients' Experiences of a Precision Medicine Clinic. *Journal of Patient Experience*, 11. <https://doi.org/10.1177/23743735241229384>
- Ben Fredj, R., Gross, E., Chouchen, L., B'Chir, F., Ben Ahmed, S., Neubauer, S., Kiechle, M., & Saguem, S. (2007). Mutational spectrum of dihydropyrimidine dehydrogenase gene (DPYD) in the Tunisian population. *Comptes Rendus - Biologies*, 330(10), 764–769. <https://doi.org/10.1016/j.crv.2007.08.003>
- Bielinski, S. J., St Sauver, J. L., Olson, J. E., Wieland, M. L., Vitek, C. R., Bell, E. J., McGree, M. E., Jacobson, D. J., McCormick, J. B., Takahashi, P. Y., Black, J. L., Caraballo, P. J., Sharp, R. R., Beebe, T. J., Weinshilboum, R. M., Wang, L., & Roger, V. L. (2017a). Are patients willing to incur out-of-pocket costs for pharmacogenomic testing? *The Pharmacogenomics Journal*, 17(1), 1–3. <https://doi.org/10.1038/tpj.2016.72>

- Bielinski, S. J., St Sauver, J. L., Olson, J. E., Wieland, M. L., Vitek, C. R., Bell, E. J., McGree, M. E., Jacobson, D. J., McCormick, J. B., Takahashi, P. Y., Black, J. L., Caraballo, P. J., Sharp, R. R., Beebe, T. J., Weinshilboum, R. M., Wang, L., & Roger, V. L. (2017b). Are patients willing to incur out-of-pocket costs for pharmacogenomic testing? *The Pharmacogenomics Journal*, 17(1), 1–3.
<https://doi.org/10.1038/tpj.2016.72>
- Bignucolo, A., De Mattia, E., Roncato, R., Peruzzi, E., Scarabel, L., D'Andrea, M., Sartor, F., Toffoli, G., & Cecchin, E. (2023). Ten-year experience with pharmacogenetic testing for DPYD in a national cancer center in Italy: Lessons learned on the path to implementation. *Frontiers in Pharmacology*, 14.
<https://doi.org/10.3389/fphar.2023.1199462>
- Boisdron-Celle, M., Capitain, O., Faroux, R., Borg, C., Metges, J. P., Galais, M. P., Kaassis, M., Bennouna, J., Bouhier-Leporrier, K., Francois, E., Baumgaertner, I., Guerin-Meyer, V., Cojocarasu, O., Roemer-Becuwe, C., Stampfli, C., Rosenfeld, L., Lecompte, T., Berger, V., Morel, A., & Gamelin, E. (2017). Prevention of 5-fluorouracil-induced early severe toxicity by pre-therapeutic dihydropyrimidine dehydrogenase deficiency screening: Assessment of a multiparametric approach. *Seminars in Oncology*, 44(1), 13–23.
<https://doi.org/10.1053/j.seminoncol.2017.02.008>
- Brooks, G. A., Tapp, S., Daly, A. T., Busam, J. A., & Tosteson, A. N. A. (2022). Cost-effectiveness of DPYD Genotyping Prior to Fluoropyrimidine-based Adjuvant Chemotherapy for Colon Cancer. *Clinical Colorectal Cancer*, 21(3), e189–e195.
<https://doi.org/10.1016/j.clcc.2022.05.001>
- CAPECITABINE-capecitabine package insert. (2020). www.fda.gov
- Challoob, M. A., & Mohammed, N. S. (2024). Assessing the Hepatotoxic Effects of Fluoropyrimidine Chemotherapy in Male Iraqi Colorectal Cancer Patients. *Cureus*.
<https://doi.org/10.7759/cureus.58126>
- Chamorey, E., Francois, E., Etienne, M. C., Ferrero, J. M., Peyrade, F., Barranger, E., Bozec, A., Largillier, R., Cassuto, O., Viotti, J., Schiappa, R., & Milano, G. (2020). DPD status and fluoropyrimidines-based treatment: High activity matters too. *BMC Cancer*, 20(1). <https://doi.org/10.1186/s12885-020-06907-0>
- Chan, T. H., Zhang, J. E., & Pirmohamed, M. (2024). DPYD genetic polymorphisms in non-European patients with severe fluoropyrimidine-related toxicity: a systematic review. *British Journal of Cancer*, 131(3), 498–514. <https://doi.org/10.1038/s41416-024-02754-z>
- Chapdelaine, A., Lamoureux-Lamarche, C., Poder, T. G., & Vasiliadis, H.-M. (2021). Sociodemographic Factors and Beliefs About Medicines in the Uptake of

- Pharmacogenomic Testing in Older Adults. *Pharmacogenomics*, 22(3), 125–135.
<https://doi.org/10.2217/pgs-2020-0077>
- Coenen, M. J. H., Paulussen, A. D. C., Breuer, M., Lindhout, M., Tserpelis, D. C. J., Steyls, A., Bierau, J., & van den Bosch, B. J. C. (2019). Evolution of Dihydropyrimidine Dehydrogenase Diagnostic Testing in a Single Center during an 8-Year Period of Time. *Current Therapeutic Research*, 90, 1–7.
<https://doi.org/10.1016/j.curtheres.2018.10.001>
- Conti, V., De Bellis, E., Manzo, V., Sabbatino, F., Iannello, F., Dal Piaz, F., Izzo, V., Charlier, B., Stefanelli, B., Torsiello, M., Iannaccone, T., Coglianese, A., Colucci, F., Pepe, S., & Filippelli, A. (2020). A Genotyping/Phenotyping Approach with Careful Clinical Monitoring to Manage the Fluoropyrimidines-Based Therapy: Clinical Cases and Systematic Review of the Literature. *Journal of Personalized Medicine*, 10(3), 113. <https://doi.org/10.3390/jpm10030113>
- CPIC. (2018). *CPIC® Guideline for Fluoropyrimidines and DPYD*.
- Cuffe, S., Hon, H., Qiu, X., Masroor, S., De Souza, B., McFarlane, G., Wong, C.-K. A., Tobros, K., Azad, A. K., Hasani, E., Rozanec, N., Leighl, N. B., Atehortua, N. A., Alibhai, S. M. H., Xu, W., Issa, A. M., & Liu, G. (2012). Cancer patients' and physicians' preferences for decision making regarding pharmacogenomic testing (PGT). *Journal of Clinical Oncology*, 30(34_suppl), 13–13.
https://doi.org/10.1200/jco.2012.30.34_suppl.13
- Cuffe, S., Hon, H., Qiu, X., Tobros, K., Wong, C. K. A., De Souza, B., McFarlane, G., Masroor, S., Azad, A. K., Hasani, E., Rozanec, N., Leighl, N., Alibhai, S., Xu, W., Issa, A. M., & Liu, G. (2014). Cancer patients acceptance, understanding, and willingness-to-pay for pharmacogenomic testing. *Pharmacogenetics and Genomics*, 24(7), 348–355. <https://doi.org/10.1097/FPC.0000000000000061>
- D'Amato, M., Iengo, G., Massa, N., & Carlomagno, C. (2025). Dihydropyrimidine dehydrogenase polymorphisms in patients with gastrointestinal malignancies and their impact on fluoropyrimidine tolerability: Experience from a single Italian institution. *World Journal of Gastrointestinal Oncology*, 17(1).
<https://doi.org/10.4251/wjgo.v17.i1.96822>
- De Forni, M., Malet-Martino, M. C., Jaillais, P., Shubinski, R. E., Bachaud, J. M., Lemaire, L., Canal, P., Chevreau, C., Carrie, D., Soulie, P., Roche, H., Mihura, J., Martino, R., Bernadet, P., & Bugat, R. (1992). Cardiotoxicity of High-Dose Continuous Infusion Fluorouracil: A Prospective Clinical Study. In *Journal of Clinical Oncology* (Vol. 10, Issue 11).
- De Mattia, E., Milan, N., Assaraf, Y. G., Toffoli, G., & Cecchin, E. (2024). Clinical Implementation of Rare and Novel DPYD Variants for Personalizing Fluoropyrimidine Treatment: Challenges and Opportunities. In *International Journal*

- de Moraes, F. C. A., de Almeida Barbosa, A. B., Sano, V. K. T., Kelly, F. A., & Burbano, R. M. R. (2024). Pharmacogenetics of DPYD and treatment-related mortality on fluoropyrimidine chemotherapy for cancer patients: a meta-analysis and trial sequential analysis. *BMC Cancer*, 24(1), 1210. <https://doi.org/10.1186/s12885-024-12981-5>
- de With, M., Sadlon, A., Cecchin, E., Haufröid, V., Thomas, F., Joerger, M., van Schaik, R. H. N., Mathijssen, R. H. J., Largiadèr, C. R., & ‘The Working Group on the Implementation of DPD-deficiency Testing in Europe.’ (2023). Implementation of dihydropyrimidine dehydrogenase deficiency testing in Europe. *ESMO Open*, 8(2), 101197. <https://doi.org/10.1016/j.esmoop.2023.101197>
- Deac, A. L., Burz, C. C., Bocsan, I. C., & Buzoianu, A. D. (2020a). Fluoropyrimidine-induced cardiotoxicity. *World Journal of Clinical Oncology*, 11(12), 1008–1017. <https://doi.org/10.5306/wjco.v11.i12.1008>
- Deac, A. L., Burz, C. C., Bocsan, I. C., & Buzoianu, A. D. (2020b). Fluoropyrimidine-induced cardiotoxicity. *World Journal of Clinical Oncology*, 11(12), 1008–1017. <https://doi.org/10.5306/wjco.v11.i12.1008>
- Deenen, M. J., Meulendijks, D., Cats, A., Sechterberger, M. K., Severens, J. L., Boot, H., Smits, P. H., Rosing, H., Mandigers, C. M. P. W., Soesan, M., Beijnen, J. H., & Schellens, J. H. M. (2016a). Upfront Genotyping of *DPYD* * 2A to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis. *Journal of Clinical Oncology*, 34(3), 227–234. <https://doi.org/10.1200/JCO.2015.63.1325>
- Deenen, M. J., Meulendijks, D., Cats, A., Sechterberger, M. K., Severens, J. L., Boot, H., Smits, P. H., Rosing, H., Mandigers, C. M. P. W., Soesan, M., Beijnen, J. H., & Schellens, J. H. M. (2016b). Upfront genotyping of *DPYD**2A to individualize fluoropyrimidine therapy: A safety and cost analysis. *Journal of Clinical Oncology*, 34(3), 227–234. <https://doi.org/10.1200/JCO.2015.63.1325>
- Dhanda, D. S., Veenstra, D. L., Regier, D. A., Basu, A., & Carlson, J. J. (2020). Payer Preferences and Willingness to Pay for Genomic Precision Medicine: A Discrete Choice Experiment. *Journal of Managed Care & Specialty Pharmacy*, 26(4), 529–537. <https://doi.org/10.18553/jmcp.2020.26.4.529>
- Doyle, T. A., Schmidt, K. K., Halverson, C. M. E., Olivera, J., Garcia, A., Shugg, T. A., Skaar, T. C., & Schwartz, P. H. (2023). Patient understanding of pharmacogenomic test results in clinical care. *Patient Education and Counseling*, 115, 107904. <https://doi.org/10.1016/j.pec.2023.107904>
- Du, Y., Liu, Y., Fang, R., Cai, L., Song, Y., Ma, S., Yu, H., Gao, J., Xiong, H., Zhang, H., Li, B., & Zheng, H. (2025). Risk Prediction of Myelosuppression Following First-line

- Chemotherapy in Colorectal Cancer. *Journal of Cancer*, 16(4), 1379–1396.
<https://doi.org/10.7150/jca.104412>
- Edris, A., Callier, E., & Lahousse, L. (2022). Precision medicine from a citizen perspective: a survey of public attitudes towards pharmacogenomics in Flanders. *BMC Medical Genomics*, 15(S3), 193. <https://doi.org/10.1186/s12920-022-01308-7>
- Elyasi, S., Rasta, S., Taghizadeh-Kermani, A., & Hosseini, S. (2022). Topical henna and curcumin (Alpha®) ointment efficacy for prevention of capecitabine induced hand-foot syndrome: A randomized, triple-blinded, placebo-controlled clinical. *DARU Journal of Pharmaceutical Sciences*, 30(1), 117–125. <https://doi.org/10.1007/s40199-022-00438-8>
- Etienne-Grimaldi, M.-C., Pallet, N., Boige, V., Ciccolini, J., Chouchana, L., Barin-Le Guellec, C., Zaanani, A., Narjoz, C., Taieb, J., Thomas, F., & Loriot, M.-A. (2023). Current diagnostic and clinical issues of screening for dihydropyrimidine dehydrogenase deficiency. *European Journal of Cancer*, 181, 3–17.
<https://doi.org/10.1016/j.ejca.2022.11.028>
- Ferreira, M. N., Ramseier, J. Y., & Leventhal, J. S. (2019). Dermatologic conditions in women receiving systemic cancer therapy. *International Journal of Women's Dermatology*, 5(5), 285–307. <https://doi.org/10.1016/j.ijwd.2019.10.003>
- Ferwerda, M. E., Wright, J. A., El Melik, R. M., Swen, J. J., & Houwink, E. J. (2024). Pharmacogenetic educational needs and the role of pharmacogenetics in primary care: a focus group study with multiple perspectives. *Frontiers in Pharmacology*, 15.
<https://doi.org/10.3389/fphar.2024.1404370>
- Froehlich, T. K., Amstutz, U., Aebi, S., Joerger, M., & Largiadèr, C. R. (2015). Clinical importance of risk variants in the dihydropyrimidine dehydrogenase gene for the prediction of early-onset fluoropyrimidine toxicity. *International Journal of Cancer*, 136(3), 730–739. <https://doi.org/10.1002/ijc.29025>
- Garcia, R. A. G., Saydoff, J. A., Bamat, M. K., & von Borstel, R. W. (2018). Prompt treatment with uridine triacetate improves survival and reduces toxicity due to fluorouracil and capecitabine overdose or dihydropyrimidine dehydrogenase deficiency. *Toxicology and Applied Pharmacology*, 353, 67–73.
<https://doi.org/10.1016/j.taap.2018.06.012>
- Gawronski, B. E., Cicali, E. J., McDonough, C. W., Cottler, L. B., & Duarte, J. D. (2023). Exploring perceptions, knowledge, and attitudes regarding pharmacogenetic testing in the medically underserved. *Frontiers in Genetics*, 13.
<https://doi.org/10.3389/fgene.2022.1085994>
- Gawronski, B. E., Salloum, R. G., & Duarte, J. D. (2024). Estimating preferences and willingness to pay for pharmacogenetic testing in populations who are medically

- underserved: a discrete choice experiment. *Frontiers in Pharmacology*, 15. <https://doi.org/10.3389/fphar.2024.1384667>
- Gentile, G., Botticelli, A., Lionetto, L., Mazzuca, F., Simmaco, M., Marchetti, P., & Borro, M. (2016). Genotype-phenotype correlations in 5-fluorouracil metabolism: A candidate DPYD haplotype to improve toxicity prediction. *Pharmacogenomics Journal*, 16(4), 320–325. <https://doi.org/10.1038/tpj.2015.56>
- Gibson, M. L., Hohmeier, K. C., & Smith, C. T. (2017). Pharmacogenomics Testing in a Community Pharmacy: Patient Perceptions and Willingness-to-pay. *Pharmacogenomics*, 18(3), 227–233. <https://doi.org/10.2217/pgs-2016-0161>
- Gil-Rodriguez, A., Recarey-Rama, S., Rodríguez-Viyuela, A., Cruz, R., Barros, F., Carracedo, A., & Maroñas, O. (2025). Differences in DPYD Population Frequencies Observed in Galicians Compared to Europeans and Spanish from PhotoDPYD Study. *Pharmaceuticals*, 18(4), 515. <https://doi.org/10.3390/ph18040515>
- Glewis, S., Alexander, M., Khabib, M. N. H., Brennan, A., Lazarakis, S., Martin, J., Tie, J., Lingaratnam, S., & Michael, M. (2022). A systematic review and meta-analysis of toxicity and treatment outcomes with pharmacogenetic-guided dosing compared to standard of care BSA-based fluoropyrimidine dosing. *British Journal of Cancer*, 127(1), 126–136. <https://doi.org/10.1038/s41416-022-01779-6>
- Gmeiner, W. H., & Okechukwu, C. C. (2023). Review of 5-FU resistance mechanisms in colorectal cancer: clinical significance of attenuated on-target effects. *Cancer Drug Resistance*, 6(2), 257–272. <https://doi.org/10.20517/cdr.2022.136>
- Goljan, E., Abouelhoda, M., ElKalioby, M. M., Jabaan, A., Alghithi, N., Meyer, B. F., & Monies, D. (2022). Identification of pharmacogenetic variants from large scale next generation sequencing data in the Saudi population. *PLoS ONE*, 17(1 January). <https://doi.org/10.1371/journal.pone.0263137>
- Haga, S. B., Mills, R., Moaddeb, J., Allen Lapointe, N., Cho, A., & Ginsburg, G. S. (2016). Patient Experiences with Pharmacogenetic Testing in a Primary Care Setting. *Pharmacogenomics*, 17(15), 1629–1636. <https://doi.org/10.2217/pgs-2016-0077>
- Hariprakash, J. M., Vellarikkal, S. K., Keechilat, P., Verma, A., Jayarajan, R., Dixit, V., Ravi, R., Senthivel, V., Kumar, A., Sehgal, P., Aradhana, A., Sonakar, A. K., Ambawat, S., Giri, A. K., Philip, A., Sivadas, A., Faruq, M., Bharadwaj, D., Sivasubbu, S., & Scaria, V. (2018). Pharmacogenetic landscape of DPYD variants in south Asian populations by integration of genome-scale data. *Pharmacogenomics*, 19(3), 227–241. <https://doi.org/10.2217/pgs-2017-0101>
- Hassan, S., Masri, H., Sawalha, I., & Mortensen, B. (2024). Perceived barriers and opportunities of providing quality family planning services among Palestinian midwives, physicians and nurses in the West Bank: a qualitative study. *BMC Health Services Research*, 24(1), 786. <https://doi.org/10.1186/s12913-024-11216-4>

- Hedtke, M., Ast, V., Leidheiser, J., Kessler, A., Neumaier, M., Hofheinz, R.-D., & Haselmann, V. (2025). The Path to Clinical Implementation of DPYD Pharmacogenetic Testing: Long-Term Experience from an External Quality Assessment Provider and a University Testing Center. *Oncology Research and Treatment*, 1–10. <https://doi.org/10.1159/000546912>
- Henricks, L. M., Lunenburg, C. A. T. C., de Man, F. M., Meulendijks, D., Frederix, G. W. J., Kienhuis, E., Creemers, G. J., Baars, A., Dezentjé, V. O., Imholz, A. L. T., Jeurissen, F. J. F., Portielje, J. E. A., Jansen, R. L. H., Hamberg, P., ten Tije, A. J., Droogendijk, H. J., Koopman, M., Nieboer, P., van de Poel, M. H. W., ... Schellens, J. H. M. (2018). DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *The Lancet Oncology*, 19(11), 1459–1467. [https://doi.org/10.1016/S1470-2045\(18\)30686-7](https://doi.org/10.1016/S1470-2045(18)30686-7)
- Henricks, L. M., van Merendonk, L. N., Meulendijks, D., Deenen, M. J., Beijnen, J. H., de Boer, A., Cats, A., & Schellens, J. H. M. (2019). Effectiveness and safety of reduced-dose fluoropyrimidine therapy in patients carrying the DPYD*2A variant: A matched pair analysis. *International Journal of Cancer*, 144(9), 2347–2354. <https://doi.org/10.1002/ijc.32022>
- Hernández-Guío, A., Ángel Calleja-Hernández, M., Corno-Caparrós, A., Zayas-Soriano, M., Bernabéu-Martínez, M. Á., & Gutiérrez-Nicolás, F. (2024). Clinical impact of DPYD genotyping and dose adjustment in candidates for fluoropyrimidine treatment. *Heliyon*, 10(23). <https://doi.org/10.1016/j.heliyon.2024.e40808>
- Hishinuma, E., Narita, Y., Obuchi, K., Ueda, A., Saito, S., Tadaka, S., Kinoshita, K., Maekawa, M., Mano, N., Hirasawa, N., & Hiratsuka, M. (2022). Importance of Rare DPYD Genetic Polymorphisms for 5-Fluorouracil Therapy in the Japanese Population. *Frontiers in Pharmacology*, 13. <https://doi.org/10.3389/fphar.2022.930470>
- Ho, T. T., Smith, D. M., Aquilante, C. L., Cicali, E. J., El Roubi, N., Hertz, D. L., Imanirad, I., Patel, J. N., Scott, S. A., Swain, S. M., Tuteja, S., & Hicks, J. K. (2025). A Guide for Implementing DPYD Genotyping for Systemic Fluoropyrimidines into Clinical Practice. *Clinical Pharmacology and Therapeutics*. <https://doi.org/10.1002/cpt.3567>
- Ho, T. T., Smith, D. M., Aquilante, C. L., Cicali, E. J., El Roubi, N., Hertz, D. L., Imanirad, I., Patel, J. N., Scott, S. A., Swain, S. M., Tuteja, S., Hicks, J. K., & Pharmacogenomics Global Research Network Publication Committee. (2025). A Guide for Implementing DPYD Genotyping for Systemic Fluoropyrimidines into Clinical Practice. *Clinical Pharmacology and Therapeutics*. <https://doi.org/10.1002/cpt.3567>
- Hoffmann, E., Toepell, A., Peter, A., Böke, S., De-Colle, C., Steinle, M., Niyazi, M., & Gani, C. (2025). Management of patients with reduced dihydropyrimidine

- dehydrogenase activity receiving combined 5-fluorouracil-/capecitabine-based chemoradiotherapy. *Strahlentherapie Und Onkologie*, 201(7), 679–686.
<https://doi.org/10.1007/s00066-024-02287-7>
- Innocenti, F., Mills, S. C., Sanoff, H., Ciccolini, ; Joseph, Lenz, H.-J., & Milano, G. (2020). *All You Need to Know About DPYD Genetic Testing for Patients Treated With Fluorouracil and Capecitabine: A Practitioner-Friendly Guide*.
<https://doi.org/10.1200/OP.20>
- Jarrar, Y., Hakooz, N., Ajamieh, M. A., Shawagfeh, K., Zaidan, R., & Al Shareef, O. (2025). Evaluation of pharmacogenomic information in drug labeling: a case study from Jordan. *Personalized Medicine*, 1–7.
<https://doi.org/10.1080/17410541.2025.2531734>
- Jarrar, Y., Musleh, R., Ghanim, M., AbuKhader, I., & Jarrar, Q. (2021). Assessment of the need for pharmacogenomics education among pharmacists in the West Bank of Palestine. *International Journal of Clinical Practice*, 75(9).
<https://doi.org/10.1111/ijcp.14435>
- Jensen, S. A., & Sørensen, J. B. (2006). Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. *Cancer Chemotherapy and Pharmacology*, 58(4), 487–493. <https://doi.org/10.1007/s00280-005-0178-1>
- Jurczyk, M., Król, M., Midro, A., Kurnik-Łucka, M., Poniatowski, A., & Gil, K. (2021). Cardiotoxicity of Fluoropyrimidines: Epidemiology, Mechanisms, Diagnosis, and Management. *Journal of Clinical Medicine*, 10(19), 4426.
<https://doi.org/10.3390/jcm10194426>
- Karczewski, K. J., Francioli, L. C., Tiao, G., Cummings, B. B., Alföldi, J., Wang, Q., Collins, R. L., Laricchia, K. M., Ganna, A., Birnbaum, D. P., Gauthier, L. D., Brand, H., Solomonson, M., Watts, N. A., Rhodes, D., Singer-Berk, M., England, E. M., Seaby, E. G., Kosmicki, J. A., ... MacArthur, D. G. (2020). The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature*, 581(7809), 434–443.
<https://doi.org/10.1038/s41586-020-2308-7>
- Keeling, N. J., Dunn, T. J., Bentley, J. P., Ramachandran, S., Hoffman, J. M., & Rosenthal, M. (2021). Approaches to assessing the provider experience with clinical pharmacogenomic information: a scoping review. *Genetics in Medicine*, 23(9), 1589–1603. <https://doi.org/10.1038/s41436-021-01186-x>
- Khali, K. A., Musalm, H. S., Hassan, M. A., & Mahmoud, I. A. (2022). Triplet (FOLFOXIRI) Versus Doublet (FOLFOX or FOLFIRI) Regimen as First Line Treatment in Metastatic Colorectal Carcinoma, a Prospective Phase II, Randomized Controlled Trial. *Asian Pacific Journal of Cancer Prevention*, 23(10), 3421–3429.
<https://doi.org/10.31557/APJCP.2022.23.10.3421>

- Kim, W., Cho, Y. A., Kim, D. C., & Lee, K. E. (2022). Elevated Risk of Fluoropyrimidine-Associated Toxicity in European Patients with DPYD Genetic Polymorphism: A Systematic Review and Meta-Analysis. *Journal of Personalized Medicine*, 12(2). <https://doi.org/10.3390/jpm12020225>
- Kleinjan, J. P., Brinkman, I., Bakema, R., van Zanden, J. J., & van Rooijen, J. M. (2019). Tolerance-based capecitabine dose escalation after DPYD genotype-guided dosing in heterozygote DPYD variant carriers. *Anti-Cancer Drugs*, 30(4), 410–415. <https://doi.org/10.1097/CAD.0000000000000748>
- Klimko, A., Tieranu, C. G., Olteanu, A. O., Preda, C. M., & Ionescu, E. M. (2021). Capecitabine-Induced Terminal Ileitis: Case Report and Literature Review. *Cureus*. <https://doi.org/10.7759/cureus.14621>
- Knikman, J. E., Wilting, T. A., Lopez-Yurda, M., Henricks, L. M., Lunenburg, C. A. T. C., de Man, F. M., Meulendijks, D., Nieboer, P., Droogendijk, H. J., Creemers, G. J., Mandigers, C. M. P. W., Imholz, A. L. T., Mathijssen, R. H. J., Portielje, J. E. A., Valkenburg-Van Iersel, L., Vulink, A., van der Poel, M. H. W., Baars, A., Swen, J. J., ... Cats, A. (2023). Survival of Patients With Cancer With DPYD Variant Alleles and Dose-Individualized Fluoropyrimidine Therapy—A Matched-Pair Analysis. *Journal of Clinical Oncology*, 41(35), 5411–5421. <https://doi.org/10.1200/JCO.22.02780>
- Kobuchi, S., Arimoto, M., & Ito, Y. (2024). Translational Pharmacokinetic-Toxicodynamic Model of Myelosuppression for Dose Optimization in Combination Chemotherapy of Capecitabine and Oxaliplatin from Rats to Humans. *The Journal of Pharmacology and Experimental Therapeutics*, 390(3), 318–330. <https://doi.org/10.1124/jpet.124.002260>
- Koo, K., Pasternak, A., Henry, L., & Sahai, V. (2022). Survey of us medical oncologists practices and-beliefs regarding DPYD testing before fluoropyrimidine. *CARE DELIVERY*, 18(6), 456–465.
- Koo, K., Pasternak, A., Henry, L., Sahai, V., & Hertz, D. (2022). Survey of US Medical Oncologists' Practices and Beliefs Regarding DPYD Testing Before Fluoropyrimidine Chemotherapy. *JCO Oncol Pract*, 18(6).
- Krishnan, A. (2025). Optimizing fluoropyrimidine therapy through dihydropyrimidine dehydrogenase polymorphism testing. *World Journal of Gastrointestinal Oncology*, 17(5). <https://doi.org/10.4251/wjgo.v17.i5.101320>
- Kroenke, C. H., Hershman, D. L., Gomez, S. L., Adams, S. R., Eldridge, E. H., Kwan, M. L., Ergas, I. J., Kubo, A., & Kushi, L. H. (2018). Personal and clinical social support and adherence to adjuvant endocrine therapy among hormone receptor-positive breast cancer patients in an integrated health care system. *Breast Cancer Research and Treatment*, 170(3), 623–631. <https://doi.org/10.1007/s10549-018-4774-2>

- Lee, A. M., Shi, Q., Pavey, E., Alberts, S. R., Sargent, D. J., Sinicrope, F. A., Berenberg, J. L., Goldberg, R. M., & Diasio, R. B. (2014). DPYD variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). *Journal of the National Cancer Institute*, 106(12). <https://doi.org/10.1093/jnci/dju298>
- Lee, G., Varughese, L. A., Conway, L., Stojinski, C., Ashokkumar, S., Monono, K., Matthai, W., Kolansky, D. M., Giri, J., & Tuteja, S. (2022). Attitudes toward pharmacogenetics in patients undergoing *CYP2C19* testing following percutaneous coronary intervention. *Personalized Medicine*, 19(2), 93–101. <https://doi.org/10.2217/pme-2021-0064>
- Lee, Y. M., Manzoor, B. S., Cavallari, L. H., & Nutescu, E. A. (2018). Facilitators and Barriers to the Adoption of Pharmacogenetic Testing in an Inner-City Population. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 38(2), 205–216. <https://doi.org/10.1002/phar.2077>
- Lemke, A. A., Hulick, P. J., Wake, D. T., Wang, C., Sereika, A. W., Yu, K. D., Glaser, N. S., & Dunnenberger, H. M. (2018). Patient Perspectives Following Pharmacogenomics Results Disclosure in an Integrated Health System. *Pharmacogenomics*, 19(4), 321–331. <https://doi.org/10.2217/pgs-2017-0191>
- Lemke, L. K., Alam, B., Williams, R., Starostik, P., Cavallari, L. H., Cicali, E. J., & Wiisanen, K. (2023). Reimbursement of pharmacogenetic tests at a tertiary academic medical center in the United States. *Frontiers in Pharmacology*, 14. <https://doi.org/10.3389/fphar.2023.1179364>
- Li, C., Ngorsuraches, S., Chou, C., Chen, L., & Qian, J. (2021a). Risk Factors of Fluoropyrimidine Induced Cardiotoxicity among Cancer Patients: A Systematic Review and Meta-analysis. In *Critical Reviews in Oncology/Hematology* (Vol. 162). Elsevier Ireland Ltd. <https://doi.org/10.1016/j.critrevonc.2021.103346>
- Li, C., Ngorsuraches, S., Chou, C., Chen, L., & Qian, J. (2021b). Risk Factors of Fluoropyrimidine Induced Cardiotoxicity among Cancer Patients: A Systematic Review and Meta-analysis. *Critical Reviews in Oncology/Hematology*, 162, 103346. <https://doi.org/10.1016/j.critrevonc.2021.103346>
- Lim, C. X., Bozkurt, A., Chen, Z. Y., Hird, A., Wickens, J., Lazarakis, S., Hussainy, S. Y., & Alexander, M. (2023a). Healthcare professionals' and consumers' knowledge, attitudes, perspectives, and education needs in oncology pharmacogenomics: A systematic review. In *Clinical and Translational Science* (Vol. 16, Issue 12, pp. 2467–2482). John Wiley and Sons Inc. <https://doi.org/10.1111/cts.13672>
- Lim, C. X., Bozkurt, A., Chen, Z. Y., Hird, A., Wickens, J., Lazarakis, S., Hussainy, S. Y., & Alexander, M. (2023b). Healthcare professionals' and consumers' knowledge, attitudes, perspectives, and education needs in oncology pharmacogenomics: A

- systematic review. *Clinical and Translational Science*, 16(12), 2467–2482.
<https://doi.org/10.1111/cts.13672>
- Lu, Y., Pan, W., Deng, S., Dou, Q., Wang, X., An, Q., Wang, X., Ji, H., Hei, Y., Chen, Y., Yang, J., & Zhang, H.-M. (2023). Redefining the Incidence and Profile of Fluoropyrimidine-Associated Cardiotoxicity in Cancer Patients: A Systematic Review and Meta-Analysis. *Pharmaceuticals*, 16(4), 510. <https://doi.org/10.3390/ph16040510>
- Lunenburg, C. A. T. C., van der Wouden, C. H., Nijenhuis, M., Crommentuijn-van Rhenen, M. H., de Boer-Veger, N. J., Buunk, A. M., Houwink, E. J. F., Mulder, H., Rongen, G. A., van Schaik, R. H. N., van der Weide, J., Wilffert, B., Deneer, V. H. M., Swen, J. J., & Guchelaar, H. J. (2020). Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene–drug interaction of DPYD and fluoropyrimidines. *European Journal of Human Genetics*, 28(4), 508–517.
<https://doi.org/10.1038/s41431-019-0540-0>
- Magavern, E. F., Marengo, G., Sivathasan, C., Mezzanzanica, M., Wright, A. J., Keen, J., Sharma, V., McDermott, J. H., Duckett, C., McCormick, D., Simmonds, S., Walters, E., Weinman, J., Parry, V., Newman, W. G., & Caulfield, M. J. (2025). A United Kingdom nationally representative survey of public attitudes towards pharmacogenomics. *QJM: An International Journal of Medicine*.
<https://doi.org/10.1093/qjmed/hcaf035>
- Malekkou, A., Tomazou, M., Mavrikiou, G., Dionysiou, M., Georgiou, T., Papaevripidou, I., Alexandrou, A., Sismani, C., Drousiotou, A., Grafakou, O., & Petrou, P. P. (2024). A novel large intragenic DPYD deletion causing dihydropyrimidine dehydrogenase deficiency: a case report. *BMC Medical Genomics*, 17(1), 78.
<https://doi.org/10.1186/s12920-024-01846-2>
- Maqdasawi, A., Ghanayiem, R., Khalaf, M., Amer, R., Mosleh, S., & Shawahna, R. (2025). Recognition of cancer chemotherapy adverse effect by patients: a cross-sectional study from Palestine. *BMC Cancer*, 25(1), 1149.
<https://doi.org/10.1186/s12885-025-14563-5>
- Marzo, R. R., Ahmad, A., Islam, Md. S., Essar, M. Y., Heidler, P., King, I., Thiagarajan, A., Jermisittiparsert, K., Songwathana, K., Younus, D. A., El-Abasiri, R. A., Bicer, B. K., Pham, N. T., Respati, T., Fitriyana, S., Faller, E. M., Baldonado, A. M., Billah, M. A., Aung, Y., ... Yi, S. (2022). Perceived COVID-19 vaccine effectiveness, acceptance, and drivers of vaccination decision-making among the general adult population: A global survey of 20 countries. *PLOS Neglected Tropical Diseases*, 16(1), e0010103. <https://doi.org/10.1371/journal.pntd.0010103>
- Meulendijks, D., Henricks, L. M., Sonke, G. S., Deenen, M. J., Froehlich, T. K., Amstutz, U., Largiadèr, C. R., Jennings, B. A., Marinaki, A. M., Sanderson, J. D., Kleibl, Z., Kleiblova, P., Schwab, M., Zanger, U. M., Palles, C., Tomlinson, I., Gross, E., van Kuilenburg, A. B. P., Punt, C. J. A., ... Schellens, J. H. M. (2015). Clinical relevance

- of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: A systematic review and meta-analysis of individual patient data. *The Lancet Oncology*, 16(16), 1639–1650. [https://doi.org/10.1016/S1470-2045\(15\)00286-7](https://doi.org/10.1016/S1470-2045(15)00286-7)
- Meydan, N., Kundak, I., Yavuzsen, T., Oztop, I., Barutca, S., Yilmaz, U., & Alakavuklar, M. N. (2005). Cardiotoxicity of de Gramont's regimen: Incidence, clinical characteristics and long-term follow-up. *Japanese Journal of Clinical Oncology*, 35(5), 265–270. <https://doi.org/10.1093/jjco/hyi071>
- Meyer, C. C., Calis, K. A., Burke, L. B., Walawander, C. A., & Grasela, T. H. (2012). *Symptomatic Cardiotoxicity Associated with 5-Fluorouracil*. <https://doi.org/10.1002/j.1875-9114.1997.tb03748.x>
- Miarons, M., Manzanque Gordón, A., Riera, P., Gutiérrez Nicolás, F., Abdel-Kader Martin, L., Agustín, M. J., Alcacera López, M. A., Alonso Castañé, M. D., Álvarez Martín, T., Beloqui, J. J., Bernal Noguera, S., Burgos San José, A., Cachafeiro Pin, A. I., Castellote Belles, L., Conde-Estévez, D., Corrales Paz, M., Díez García, M., Do Pazo Oubiña, F., Fernández Fradejas, J., ... Vuelta Arce, M. (2023). Allelic Frequency of DPYDb Genetic Variants in Patients With Cancer in Spain: The PhotoDPYD Study. *The Oncologist*, 28(5), e304–e308. <https://doi.org/10.1093/oncolo/oyad077>
- Mitwalli, S., Hammoudeh, W., Giacaman, R., & Harding, R. (2023). Access to advanced cancer care services in the West Bank-occupied Palestinian territory. *Frontiers in Oncology*, 13. <https://doi.org/10.3389/fonc.2023.1120783>
- Moore, C., Lazarakis, S., Stenta, T., Alexander, M., Nguyen, R. P., Elliott, D. A., & Conyers, R. (2023). A systematic review of knowledge, attitude and practice of pharmacogenomics in pediatric oncology patients. *Pharmacology Research & Perspectives*, 11(6). <https://doi.org/10.1002/prp2.1150>
- More, L. A., Lane, S., & Asnani, A. (2021). 5-FU Cardiotoxicity: Vasospasm, Myocarditis, and Sudden Death. *Current Cardiology Reports*, 23(3), 17. <https://doi.org/10.1007/s11886-021-01441-2>
- Mubarak, S., & Ashraf, M. (2024). Ethics considerations for precision medicine research and genetic testing in low- and middle-income countries. *Eastern Mediterranean Health Journal*, 30(6), 455–460. <https://doi.org/10.26719/2024.30.6.455>
- Naaem, R., Hashmi, F. K., Yaqub, S., & Mohamed Noor, D. A. (2024a). Qualitative assessment of knowledge, attitude and practice of oncologists about precision medicine in cancer patients- study from Lahore, Pakistan. *PLOS ONE*, 19(4), e0299010. <https://doi.org/10.1371/journal.pone.0299010>
- Naaem, R., Hashmi, F. K., Yaqub, S., & Mohamed Noor, D. A. (2024b). Qualitative assessment of knowledge, attitude and practice of oncologists about precision

- medicine in cancer patients- study from Lahore, Pakistan. *PLOS ONE*, 19(4), e0299010. <https://doi.org/10.1371/journal.pone.0299010>
- NCD Countdown 2030 collaborators. (2020). NCD Countdown 2030: pathways to achieving Sustainable Development Goal target 3.4. *The Lancet*, 396(10255), 918–934. [https://doi.org/10.1016/S0140-6736\(20\)31761-X](https://doi.org/10.1016/S0140-6736(20)31761-X)
- Nguyen, D. G., Morris, S. A., Hamilton, A., Kwange, S. O., Steuerwald, N., Symanowski, J., Moore, D. C., Hanson, S., Mroz, K., Lopes, K. E., Larck, C., Musselwhite, L., Kadakia, K. C., Koya, B., Chai, S., Osei-Boateng, K., Kalapurakal, S., Swift, K., Hwang, J., & Patel, J. N. (2024). Real-World Impact of an In-House Dihydropyrimidine Dehydrogenase (*DPYD*) Genotype Test on Fluoropyrimidine Dosing, Toxicities, and Hospitalizations at a Multisite Cancer Center. *JCO Precision Oncology*, 8. <https://doi.org/10.1200/PO.23.00623>
- Nie, X., Jia, T., Hu, X., Li, S., Zhang, X., Wu, C., Zhang, Y., Chen, J., Shi, L., & Lu, C. Y. (2022). Clinical Pharmacists' Knowledge of and Attitudes toward Pharmacogenomic Testing in China. *Journal of Personalized Medicine*, 12(8). <https://doi.org/10.3390/jpm12081348>
- Northstar. (2024, December 2). *Label: CAPECITABINE tablet, film coated*.
- Obara, T., Obara, T., Obara, T., Abe, S., Satoh, M., Gutiérrez Ubéda, S. R., Yoshimachi, S., & Goto, T. (2015). Awareness regarding clinical application of pharmacogenetics among Japanese pharmacists. *Pharmacogenomics and Personalized Medicine*, 8, 35–41. <https://doi.org/10.2147/PGPM.S71813>
- Obeagu, E. I., & Obeagu, G. U. (2024). Breast cancer: A review of risk factors and diagnosis. *Medicine*, 103(3), e36905. <https://doi.org/10.1097/MD.00000000000036905>
- Okechukwu, C. C., Ma, X., Sah, N., Mani, C., Palle, K., & Gmeiner, W. H. (2024a). Enhanced Therapeutic Efficacy of the Nanoscale Fluoropyrimidine Polymer CF10 in a Rat Colorectal Cancer Liver Metastasis Model. *Cancers*, 16(7). <https://doi.org/10.3390/cancers16071360>
- Okechukwu, C. C., Ma, X., Sah, N., Mani, C., Palle, K., & Gmeiner, W. H. (2024b). Enhanced Therapeutic Efficacy of the Nanoscale Fluoropyrimidine Polymer CF10 in a Rat Colorectal Cancer Liver Metastasis Model. *Cancers*, 16(7). <https://doi.org/10.3390/cancers16071360>
- Oliveira, R. F., Oliveira, A. I., Cruz, A. S., Ribeiro, O., Afreixo, V., & Pimentel, F. (2024). Polypharmacy and drug interactions in older patients with cancer receiving chemotherapy: associated factors. *BMC Geriatrics*, 24(1). <https://doi.org/10.1186/s12877-024-05135-6>
- Olson, J. E., Rohrer Vitek, C. R., Bell, E. J., McGree, M. E., Jacobson, D. J., St. Sauver, J. L., Caraballo, P. J., Griffin, J. M., Roger, V. L., & Bielinski, S. J. (2017). Participant-

- perceived understanding and perspectives on pharmacogenomics: the Mayo Clinic RIGHT protocol (Right Drug, Right Dose, Right Time). *Genetics in Medicine*, 19(7), 819–825. <https://doi.org/10.1038/gim.2016.192>
- Ontario Health (Quality). (2021). DPYD Genotyping in Patients Who Have Planned Cancer Treatment With Fluoropyrimidines: A Health Technology Assessment. In *Ontario Health Technology Assessment Series* (Vol. 21, Issue 14). <https://hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and->
- Otero-Torres, S., Rodríguez-Mauriz, R., Fort-Casamartina, E., Clopés-Estela, A., Soler-Rotllant, F., Fontanals-Martínez, S., & Montero-Pérez, O. (2025). DPYD Genotyping, Fluoropyrimidine Dosage and Toxicity: An Umbrella Review of Systematic Reviews. *Pharmaceuticals*, 18(5), 727. <https://doi.org/10.3390/ph18050727>
- Özdemir, B. C., Gerard, C. L., & Espinosa da Silva, C. (2022). Sex and Gender Differences in Anticancer Treatment Toxicity: A Call for Revisiting Drug Dosing in Oncology. *Endocrinology*, 163(6). <https://doi.org/10.1210/endocr/bqac058>
- Palestinian Ministry of Health. (2024). *MOH annual report, 2023*.
- Peeters, S. L. J., Meulendijks, D., Kadric, Z., Ibrovic, S., Creemers, G., Milosevic, V., van de Poll, M., Simkens, L. H. J., Deiman, B. A. L. M., Gelderblom, H., Guchelaar, H., Thijs, A. M. J., & Deenen, M. J. (2025). Real-world study on fluoropyrimidine-related toxicity outcomes in cancer patients with select *DPYD* variant alleles that received *DPYD* genotype-guided dosing. *International Journal of Cancer*, 157(9), 1898–1911. <https://doi.org/10.1002/ijc.70005>
- Peng, J., Dong, C., Wang, C., Li, W., Yu, H., Zhang, M., Zhao, Q., Zhu, B., Zhang, J., Li, W., Wang, F., Wu, Q., Zhou, W., Yuan, Y., Qiu, M., & Chen, G. (2018). Cardiotoxicity of 5-fluorouracil and capecitabine in Chinese patients: a prospective study. *Cancer Communications*, 38(1). <https://doi.org/10.1186/S40880-018-0292-1>
- Peruzzi, E., Roncato, R., De Mattia, E., Bignucolo, A., Swen, J. J., Guchelaar, H., Toffoli, G., & Cecchin, E. (2025). Implementation of pre-emptive testing of a pharmacogenomic panel in clinical practice: Where do we stand? *British Journal of Clinical Pharmacology*, 91(2), 270–282. <https://doi.org/10.1111/bcp.15956>
- Robertson, J., Barr, R., Shulman, L. N., Forte, G. B., & Magrini, N. (2016). Essential medicines for cancer: WHO recommendations and national priorities. *Bulletin of the World Health Organization*, 94(10), 735–742. <https://doi.org/10.2471/BLT.15.163998>
- Roncato, R., Bignucolo, A., Peruzzi, E., Montico, M., De Mattia, E., Foltran, L., Guardascione, M., D’Andrea, M., Favaretto, A., Puglisi, F., Swen, J. J., Guchelaar, H.-J., Toffoli, G., & Cecchin, E. (2024). Clinical Benefits and Utility of Pretherapeutic *DPYD* and *UGT1A1* Testing in Gastrointestinal Cancer. *JAMA*

Network Open, 7(12), e2449441.

<https://doi.org/10.1001/jamanetworkopen.2024.49441>

Royal Dutch Pharmacists Association (KNMP). (2020). *Dutch Pharmacogenetics Working Group (DPWG). Pharmacogenetic Guidelines*.

Rozza, H. H., Elhoseny, T. A., Abbas, S. H., & Mosallam, R. A. (2025). Patients' willingness to pay for health care quality improvement under universal healthcare coverage in Egypt. *Journal of the Egyptian Public Health Association*, 100(1), 15. <https://doi.org/10.1186/s42506-025-00195-x>

Salmani, M., Ghaderi, B., Fotoohi, A., Omid-Shafa'at, R., Vahabzadeh, Z., Fotouhi, O., & Abdi, M. (2022). Introducing a simple and cost-effective RT-PCR protocol for detection of DPYD*2A polymorphism: the first study in Kurdish population. *Cancer Chemotherapy and Pharmacology*, 90(5), 389–397. <https://doi.org/10.1007/s00280-022-04472-w>

Sedrak, M. S., Freedman, R. A., Cohen, H. J., Muss, H. B., Jatoi, A., Klepin, H. D., Wildes, T. M., Le-Rademacher, J. G., Kimmick, G. G., Tew, W. P., George, K., Padam, S., Liu, J., Wong, A. R., Lynch, A., Djulbegovic, B., Mohile, S. G., & Dale, W. (2021). Older adult participation in cancer clinical trials: A systematic review of barriers and interventions. *CA: A Cancer Journal for Clinicians*, 71(1), 78–92. <https://doi.org/10.3322/caac.21638>

Shamaei Zadeh, A., Roberts, D., Williams, A., Pandey, D., & Villano, J. L. (2025). Dihydropyrimidine enzyme activity and its effect on chemotherapy toxicity: importance of genetic testing. *Cancer Chemotherapy and Pharmacology*, 95(1), 26. <https://doi.org/10.1007/s00280-024-04740-x>

Shanmuganathan, J. W. D., Kragholm, K., Tayal, B., Polcwiartek, C., Poulsen, L. Ø., El-Galaly, T. C., Fosbøl, E. L., D'Souza, M., Gislason, G., Køber, L., Schou, M., Nielsen, D., Søgaard, P., Torp-Pedersen, C. T., Mamas, M. A., & Freeman, P. (2021). Risk for Myocardial Infarction Following 5-Fluorouracil Treatment in Patients With Gastrointestinal Cancer. *JACC: CardioOncology*, 3(5), 725–733. <https://doi.org/10.1016/j.jaccao.2021.11.001>

Sharma, B. B., Rai, K., Blunt, H., Zhao, W., Tosteson, T. D., & Brooks, G. A. (2021). Pathogenic DPYD Variants and Treatment-Related Mortality in Patients Receiving Fluoropyrimidine Chemotherapy: A Systematic Review and Meta-Analysis. *Oncologist*, 26(12), 1008–1016. <https://doi.org/10.1002/onco.13967>

Shin, J. G., Cheong, H. S., Kim, J. Y., Kim, L. H., Han, C. S., Kim, J. O., Kim, H. D., Kim, Y. H., Chung, M. W., Han, S. Y., & Shin, H. D. (2013). Screening of dihydropyrimidine dehydrogenase genetic variants by direct sequencing in different ethnic groups. *Journal of Korean Medical Science*, 28(8), 1129–1133. <https://doi.org/10.3346/jkms.2013.28.8.1129>

- Shrestha, S., Watts, G., & Geiger, S. (2025). Exploring healthcare personnel's knowledge, barriers, and innovative approaches in personalised oncology medicine: a scoping review. *Critical Public Health*, 35(1).
<https://doi.org/10.1080/09581596.2025.2520410>
- Sipido, K. R., & Nagyova, I. (2020). Health research and knowledge translation for achieving the sustainable development goals: Tackling the hurdles. *European Journal of Public Health*, 30, 136–140. <https://doi.org/10.1093/eurpub/ckaa032>
- Sonbol, M. B., Bekaii-Saab, T., & Larsen, C. M. (2025). Fluoropyrimidine Therapy in Gastrointestinal Cancer. *JACC: CardioOncology*.
<https://doi.org/10.1016/j.jaccao.2025.02.006>
- Soueid, R., Michael, T. J. F., Cairns, R., Charles, K. A., & Stocker, S. L. (2024). A Scoping Review of Pharmacogenomic Educational Interventions to Improve Knowledge and Confidence. *American Journal of Pharmaceutical Education*, 88(3), 100668. <https://doi.org/10.1016/j.ajpe.2024.100668>
- Sukasem, C., Jantararoungtong, T., & Koomdee, N. (2021). Pharmacogenomics research and its clinical implementation in Thailand: Lessons learned from the resource-limited settings. *Drug Metabolism and Pharmacokinetics*, 39, 100399.
<https://doi.org/10.1016/j.dmpk.2021.100399>
- Sukkarieh, H. H., AlSagoor, T., Alnuhait, M., Bustami, R., Bryson, S., Adem, F. M. K., Abdalla, H., & Karbani, G. (2023). Awareness and attitudes of oncology specialists toward dihydropyrimidine dehydrogenase testing in Saudi Arabia. *Cancer Reports*, 6(2). <https://doi.org/10.1002/cnr2.1704>
- Tentoni, N., Combs, R., Hwang, M., Ward, S., McCracken, A., Lowe, J., & Howard, S. C. (2024). Long-Term Outcomes of 5-Fluorouracil-Related Early-Onset Toxicities: A Retrospective Cohort Study. *Cancers*, 16(23), 4050.
<https://doi.org/10.3390/cancers16234050>
- Traynor, K. (2024). DPYD testing makes fluoropyrimidine chemotherapy safer. *American Journal of Health-System Pharmacy : AJHP : Official Journal of the American Society of Health-System Pharmacists*, 81(9), e197–e198.
<https://doi.org/10.1093/ajhp/zxae058>
- Truong, T. M., Lipschultz, E., Schierer, E., Danahey, K., Ratain, M. J., & O'Donnell, P. H. (2020). Patient insights on features of an effective pharmacogenomics patient portal. *Pharmacogenetics and Genomics*, 30(9), 191–200.
<https://doi.org/10.1097/FPC.0000000000000413>
- Tuchman, M., Stoeckeler, J. S., Kiang, D. T., O'Dea, R. F., Ramnaraine, M. L., & Mirkin, B. L. (1985). Familial Pyrimidinemia and Pyrimidinuria Associated with Severe Fluorouracil Toxicity. *New England Journal of Medicine*, 313(4), 245–249.
<https://doi.org/10.1056/NEJM198507253130407>

- Varma, A., Jayanthi, M., Dubashi, B., Shewade, D. G., & Sundaram, R. (2020). Genetic influence of *DPYD*9A* polymorphism on plasma levels of 5-fluorouracil and subsequent toxicity after oral administration of capecitabine in colorectal cancer patients of South Indian origin. *Drug Metabolism and Drug Interactions*, 35(4). <https://doi.org/10.1515/dmpt-2020-0133>
- Veilleux, S., & Bouffard, M. (2019). Knowledge and understanding of pharmacogenomic testing among patients and health care professionals: A scoping review. *Patient Education and Counseling*, 102(11), 2001–2009. <https://doi.org/10.1016/j.pec.2019.06.008>
- Walters, S., Aldous, C., & Malherbe, H. (2024). Knowledge, attitudes, and practices of primary healthcare practitioners in low- and middle-income countries: a scoping review on genetics. *Journal of Community Genetics*, 15(5), 461–474. <https://doi.org/10.1007/s12687-024-00721-y>
- Wang, Y., Wang, W., Dong, H., Wang, G., Chen, W., Chen, J., & Chen, W. (2023). Risk factors for fluoropyrimidine-induced cardiotoxicity in colorectal cancer: A retrospective cohort study and establishment of a prediction nomogram for 5-FU induced cardiotoxicity. *Frontiers in Oncology*, 13. <https://doi.org/10.3389/fonc.2023.1017237>
- White, C., Kendall, G., Millington, T., Corcoran, B., Paul, C., Scott, R. J., & Ackland, S. (2024). Evaluation of early fluoropyrimidine toxicity in solid organ cancer patients: a retrospective observational study in Australia. *Internal Medicine Journal*, 54(9), 1506–1514. <https://doi.org/10.1111/imj.16463>
- White, C., Paul, C., Liet, E., Kalpage, D., Mossman, D., Ziolkowski, A., Ackland, S., & Scott, R. J. (2025). Implementing DPYD genotyping to predict chemotherapy toxicity in Australia: a feasibility study. *Internal Medicine Journal*, 55(5), 741–748. <https://doi.org/10.1111/imj.16576>
- Wigle, T. J., Medwid, S., Ross, C., Schwarz, U. I., & Kim, R. B. (2023). DPYD Exon 4 Deletion Associated with Fluoropyrimidine Toxicity and Importance of Copy Number Variation. *Current Oncology*, 30(1), 663–672. <https://doi.org/10.3390/curroncol30010051>
- Wong, C.-K., Ho, I., Choo, A., Lau, R., Ma, T.-F., Chiu, A. C. H.-O., Lam, T.-H., Lin, M., Leung, R. W.-H., Chor-Cheung Tam, F., Foo, D. C. C., & Tse, H.-F. (2025). Cardiovascular safety of 5-fluorouracil and capecitabine in colorectal cancer patients: real-world evidence. *Cardio-Oncology*, 11(1), 3. <https://doi.org/10.1186/s40959-024-00294-2>
- Wongkraisri, C., Chusuwanrak, K., Laocharoenkeat, A., Chularojanamontri, L., Nimmannit, A., & Ithimakin, S. (2025). Randomized controlled trial on the efficacy

- of topical urea-based cream in preventing capecitabine-associated hand-foot syndrome. *BMC Cancer*, 25(1), 275. <https://doi.org/10.1186/s12885-025-13684-1>
- World Health Organization. (2015). *The selection and use of essential medicines: Twentieth report of the WHO Expert Committee 2015 (including 19th WHO Model List of Essential Medicines and 5th WHO Model List of Essential Medicines for Children)*.
- World Health Organization. (2016). *Palestine health profile 2015*. World Health Organization. Regional Office for the Eastern Mediterranean. <https://apps.who.int/iris/handle/10665/250374>
- World Health Organization. (2021). *Noncommunicable diseases*. <http://apps.who.int/iris/bitstream/handle/10665/250131/9789241511247-eng.pdf;jsessionid=7E9F1BBD6B29CBC9B2CB0C83CDF412C5?sequence=1>
- Wörmann, B., Bokemeyer, C., Burmeister, T., Köhne, C. H., Schwab, M., Arnold, D., Blohmer, J. U., Borner, M., Brucker, S., Cascorbi, I., Decker, T., De Wit, M., Dietz, A., Einsele, H., Eisterer, W., Folprecht, G., Hilbe, W., Hoffmann, J., Knauf, W., ... Hofheinz, R. D. (2020). Dihydropyrimidine Dehydrogenase Testing prior to Treatment with 5-Fluorouracil, Capecitabine, and Tegafur: A Consensus Paper. *Oncology Research and Treatment*, 43(11), 628–636. <https://doi.org/10.1159/000510258>
- Wou, C., Unwin, N., Huang, Y., & Roglic, G. (2019). Implications of the growing burden of diabetes for premature cardiovascular disease mortality and the attainment of the Sustainable Development Goal target 3.4. In *Cardiovascular Diagnosis and Therapy* (Vol. 9, Issue 2, pp. 140–149). AME Publishing Company. <https://doi.org/10.21037/cdt.2018.09.04>
- Yeh, S. C., Hsieh, Y. L., Yu, H. C., & Tseng, Y. H. (2022). The Trends and Content of Research Related to the Sustainable Development Goals: A Systemic Review. In *Applied Sciences (Switzerland)* (Vol. 12, Issue 13). MDPI. <https://doi.org/10.3390/app12136820>
- Yousef, A. M., Zawiah, M., Al-Yacoub, S., Kadi, T., Tantawi, D. a., & Al-Ramadhani, H. (2018). The association of polymorphisms in folate-metabolizing genes with response to adjuvant chemotherapy of colorectal cancer. *Cancer Chemotherapy and Pharmacology*, 82(2), 237–243. <https://doi.org/10.1007/s00280-018-3608-6>
- Zehra, K., Banu, A., Can, E., & Hülya, C. (2024). Fisetin and/or capecitabine causes changes in apoptosis pathways in capecitabine-resistant colorectal cancer cell lines. *Naunyn-Schmiedeberg's Archives of Pharmacology*. <https://doi.org/10.1007/s00210-024-03145-0>
- Zhang, L., Jacobson, P. A., Johnson, A. N. K., Gregornik, D. B., Johnson, S. G., McCarty, C. A., & Bishop, J. R. (2022). Public Attitudes toward Pharmacogenomic Testing and

Establishing a Statewide Pharmacogenomics Database in the State of Minnesota. *Journal of Personalized Medicine*, 12(10), 1615.
<https://doi.org/10.3390/jpm12101615>

Zhou, Y., & Lauschke, V. M. (2022). Population pharmacogenomics: an update on ethnogeographic differences and opportunities for precision public health. *Human Genetics*, 141(6), 1113–1136. <https://doi.org/10.1007/s00439-021-02385-x>

Zubiaur, P., Prósper-Cuesta, D. N., Novalbos, J., Mejía-Abril, G., Navares-Gómez, M., Villapalos-García, G., Soria-Chacartegui, P., & Abad-Santos, F. (2022). Patients' Perceptions of Pharmacogenetic Testing and Access to Their Results: State of the Art in Spain and Systematic Review. *Journal of Personalized Medicine*, 12(2), 270.
<https://doi.org/10.3390/jpm12020270>

Appendices

Appendix 1: Ethical approvals

Al-Quds University
Jerusalem
School of Public Health



جامعة القدس
القدس
كلية الصحة العامة

التاريخ: 2024/2/17

الرقم: REF. 13/24

عزيري الطالب محمد ذويب المحترم
برنامج الدكتوراة في الصحة العامة

الموضوع: موافقة لجنة أخلاقيات البحث العلمي

قامت اللجنة الفرعية لأخلاقيات البحث التابعة لكلية الصحة العامة بمراجعة مشروع الرسالة بعنوان:

"Pharmacogenomic and clinical factors associated with the side effects of fluoropyrimidines in Palestinian cancer patients"

المقدم من (مشرف البحث/د. حسين الحلاق).

يعتبر مشروعك مستوفياً لمتطلبات أخلاقيات البحث في جامعة القدس.

نتمنى لكم كل التوفيق في تسير المشروع.

ملاحظة: في حالة الحاجة الى موافقة من اللجنة المركزية في الجامعة، تستطيع التقدم باستخدام هذه

الموافقة على الرابط: <https://research.alquds.edu/en/ethics/48-how-to-apply.html>

رئيسة اللجنة الفرعية لأخلاقيات البحث

كلية الصحة العامة

د. نهى الشريف

نسخة/ أعضاء لجنة البحث

نسخة/ الملف

Jerusalem Branch/Telefax 02-2799234
Gaza Branch/Telefax 08-2644220 -2644210
P.O. box 51000 Jerusalem

فرع القدس / تليفاكس 02-2799234
فرع غزة / تليفاكس 08-264420-2644210
ص.ب. 51000 القدس

بسم الله الرحمن الرحيم

Al-Quds University
Jerusalem
School of Public Health



جامعة القدس
القدس
كلية الصحة العامة

التاريخ: 2024/2/26

حضرة الدكتور عبدالله قواسمة المحترم

مدير وحدة التعليم الصحي والبحث العلمي/ وزارة الصحة الفلسطينية

الموضوع: تسهيل مهمة الطالب محمد انوب

تحية طيبة وبعد،،

يقوم الطالب محمد خلف علي انوب (برنامج دكتوراه الصحة العامة/ كلية الصحة العامة/ جامعة القدس)، بإعداد بحث أطروحة الدكتوراه بإشراف الدكتور حسين الحلاق وبمعنوان:

“Pharmacogenomic and clinical factors associated with the side effects of fluoropyrimidines in Palestinian cancer patients”.

الهدف الرئيسي من هذا البحث هو إجراء فحص شامل لأهمية التمييط الجيني لجين دي بي دي فيما يتعلق بالآثار الضارة المرتبطة بالفلوروبيريميدين لمرضى السرطان من السكان الفلسطينيين. بالإضافة إلى تطوير تقييم شامل من خلال النظر في المتغيرات المساهمة الأخرى، مثل الجنس والعمر واستخدام الدواء المتزامن والحالة الانتشارية للمرض، مع الهدف النهائي المتمثل في صياغة توصيات الجرعة المستتيرة بهذه الاعتبارات التي تشمل جميع العوامل وسيسشارك في جمع البيانات كل من راية فطاظمة، ولين البو.

تشمل الدراسة جزئين رئيسيين الأول: المعرفة والاتجاهات والممارسات لدى أخصائيين الأورام تجاه اختبار DPD وهي تستهدف جميع أطباء الأورام والصيادلة السريريين. والثاني: العوامل الفارماكوجينومية والسريرية المرتبطة بالآثار الجانبية للفلوروبيريميدينات وتشمل مرضى السرطان المؤهلين لتلقي علاج يحتوي على FU 5 أو capecitabine ، يستوفون جميع المعايير الشاملة ولا يستوفون أي من المعايير الاستبعادية. وهم البالغين والذين (عمرهم أكثر من ١٨ عامًا)، المصابين بمرض السرطان ومشخصين بواسطة أخصائي الأورام والمؤهلين لتلقي جرعات علاجية من التركيب التي تحتوي على FU 5 أو capecitabine في وقت الاختيار وذلك في مستشفى بيت جالا الحكومي، ومستشفى دورا الحكومي. وهو بحاجة الى جمع البيانات للعلاج، بما في ذلك التركيب، والجرعة، واستخدام الإشعاع، من سجلات الصيدلية. وسيتم الحصول على المتغيرات السريرية وبيانات السمية من خلال استعراض موحد لسجلات الصحة الإلكترونية (EHRs) للمرضى من قبل العاملين في الدراسة المدربين الذين يجهلون المجموعة التي تم تخصيص المريض لها. وسيتم توثيق

Jerusalem
P.O.Box 51000
Telefax +970-2-2799234
Email: sphealth@admin.alquds.edu

فرع القدس / تلفاكس 02-2799234
ص.ب. 51000 القدس
البريد الإلكتروني: sphealth@admin.alquds.edu

بسم الله الرحمن الرحيم

Al-Quds University
Jerusalem
School of Public Health



جامعة القدس
القدس
كلية الصحة العامة

بيانات السمية من ملاحظات العيادة، وسجلات الدخول، وملخصات الخروج، وتقارير قسم الطوارئ. وستشمل الأحداث الضارة الشديدة (AEs) السمية بدرجة أكبر من أو تساوي 3 وفق المعايير المشبعة عالمياً. سيتم أخذ عينة دم من المرضى الذين يوافقون على المشاركة في الدراسة من قبل الطبيب المشارك (د. هاني أبو الحور). وسيتم تحليلها جينياً في مختبرات كلية الطب في جامعة القدس - ابوديس. لذا نرجو من حضرتكم مساعدته وتسهيل مهمة الطالب والسماح له بتوزيع استبانة الدراسة وجمع البيانات المطلوبة وعمل الفحوصات اللازمة على عينة الدراسة ليتسنى له انهاء متطلبات بحث الاطروحة. علماً بان المعلومات ستكون سرية ولأغراض البحث العلمي فقط.

شاكرين لكم حسن تعاونكم،،،

كلية الصحة العامة
Faculty of Public Health



د. حازم اغا

عميد كلية الصحة العامة

نسخة: الملف.

Jerusalem
P.O.Box 51000
Telefax +970-2-2799234
Email: sphhealth@admin.alquds.edu

فرع القدس / تلفاكس 02-2799234
ص.ب. 51000 القدس
البريد الإلكتروني: sphhealth@admin.alquds.edu



Ref.:
Date:.....

الرقم: ٥٥٢/٢٠٢٤
التاريخ: ٢٠٢٤/١٢/٢٤

عطوفة الوكيل المساعد لشؤون المستشفيات والطوارئ المحترم،،
تعبية واحترام،،،

الموضوع: تسهيل مهمة بحث

يرجى تسهيل مهمة الطالب: محمد خلف علي انوبيب - برنامج دكتوراه الصحة العامة/ جامعة القدس، وبإشراف د. حسين الحلاق في عمل بحث بعنوان:

"Pharmacogenomic and clinical factors associated with the side effects of fluoropyrimidines in Palestinian cancer patients".

من خلال السماح للطالب بجمع معلومات عن طريق تعبئة استبانة من قبل الاطباء ومن قبل المرضى بعد اخذ موافقتهم وموافقة الطبيب المشرف على العلاج، وعدم التدخل في طبيعة العلاج السريري او الادوية المقدمة للمرضى، بل الحصول على معلومات عن طريق المشاهدة فقط، والحصول على عينة دم من المرضى بمساعدة الطاقم الصحي بعد اخذ موافقتهم. وذلك في:

- مستشفى بيت جالا - مستشفى دورا

على ان يتم الالتزام بالسياسات واخلاقيات البحث العلمي، وعدم التعرض للمعلومات التعريفية للمرضى. على ان يتم تزويد الوزارة بنسخة PDF من نتائج البحث، التعهد بعدم النشر لحين الحصول على موافقة الوزارة على نتائج البحث.

مع الاحترام،،،

د. عبد الله القواسمي
رئيس وحدة التعليم الصحي والبحث العلمي



نسخة: عميد كلية الصحة العامة المحترم/ جامعة القدس

Research Ethics Committee
Committee's Decision Letter

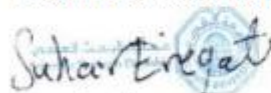
Date: July 8, 2025
Ref No: 577/REC/2025

Dears Dr. Hussein Hallak, Mr. Mohammad Dweib,

This letter serves as confirmation that the Research Ethics Committee has reviewed and approved the amendment to your previously approved study Title: "Pharmacogenomic and clinical factors associated with the side effects of fluoropyrimidines in Palestinian cancer patients" Reference number (REF: 24/13), originally approved by the research ethics subcommittee of Public health on 17/02/2024. The approved amendment on 8/7/2025, includes the addition of structured interviews with participants. All ethical obligations, including informed consent and data protection, must continue to be upheld in accordance with the original and amended protocols.

Sincerely,

Suheir Ereqat, PhD
Associate Professor of Molecular Biology



Research Ethics Committee Chair

Cc. Prof. Hanna Abdel Nour - President
Cc. Members of the committee
Cc. file



Ref.:
Date:.....

الرقم:
التاريخ:

الأخ مدير عام الإدارة العامة للمستشفيات المحترم،،،
تعبية وامتهام...

الموضوع: تسهيل مهمة بحث

يرجى التكرم بتسهيل مهمة الطالب: محمد خلف علي انويب - برنامج دكتوراه الصحة العامة/ جامعة القدس، وبإشراف د. حسين الحلاق في عمل بحث بعنوان:

"Pharmacogenomic and clinical factors associated with the side effects of fluoropyrimidines in Palestinian cancer patients"

من خلال السماح للطالب بجمع معلومات عن طريق تعبئة استبانة من قبل مرضى السرطان بعد اخذ موافقتهم، تتعلق بمعرفتهم بالفحوصات الجينية التي يمكن ان تقلل من احتمالية تعرضهم للاثار الجانبية لادوية العلاج الكيماوي. علما أن هذا العمل بالتعاون مع د هاني ابو الحور، وذلك في:

- مستشفى بيت جالا - مستشفى دورا

على ان يتم الالتزام باساليب واخلاقيات البحث العلمي، وعدم التعرض للمعلومات التعريفية للمرضى. على ان يتم تزويد الوزارة بنسخة PDF من نتائج البحث، التعهد بعدم النشر لحين الحصول على موافقة الوزارة على نتائج البحث.

مع الامتثال...

د. عبد الله القواسمي
رئيس وحدة التعليم الصحي والبحث العلمي



نسخة: عميد كلية الصحة العامة المحترم/ جامعة القدس

Appendix 2: Healthcare providers' consent form- English



School of Public Health – Al-Quds University

Consent Form for Participants

Study: "Knowledge, Attitudes, and Practices of Oncology Specialists Regarding Pharmacogenomic Testing for Fluoropyrimidines"

Dear Participant,

I am student Mohammad Dweib conducting this research as part of my doctoral dissertation in Public Health at Al-Quds University, School of Public Health, under the supervision of Dr. Hussein Hallak.

This study aims to assess the knowledge, attitudes, and practices of oncology specialists regarding pharmacogenomic testing for fluoropyrimidines. Participation involves completing a questionnaire. All information collected will be kept strictly confidential. Participation is voluntary, and you may withdraw at any time without any consequences.

Your participation in this study includes:

- Completing a questionnaire regarding knowledge, attitudes, and practices of oncology specialists related to pharmacogenomic testing for fluoropyrimidines.

Signing this form means that I agree to the following:

Statement	Yes	No
I have been informed about the purpose of this study by the researcher.	☐	☐
I have been informed that my personal information and all information collected during this research will remain confidential and will be used for scientific purposes only.	☐	☐

I understand that I have the right to withdraw from the study at any time.	☐	☐
I have the option not to answer any question I choose.	☐	☐

Participant's Name: _____ Signature: _____ Date: _____

Researcher's Name: _____ Signature: _____ Date: _____

If you have any questions or need additional information, please contact: 0569941337

Appendix 3: Healthcare providers' consent form- Arabic



كلية الصحة العامة- جامعة القدس

نموذج الموافقة للمشاركة

دراسة: "معرفة وتوجهات وممارسات أخصائيي الامراض السرطانية حول الفحوص الجينية المتعلقة باستخدام ادوية فلوروبيريميدين"

عزيزي المشارك في البحث:

انا الطالب محمد ذويب أقوم بإجراء بحث حيث يهدف هذا البحث إلى التعرف على معرفة وتوجهات وممارسات اخصائيي الامراض السرطانية حول الفحوص الجينية المتعلقة باستخدام ادوية فلوروبيريميدين كمتطلب لرسالة الدكتوراة في الصحة العامة في جامعة القدس كلية الصحة العامة تحت اشراف الدكتور حسين الحلاق.

تتضمن هذه الدراسة تعبئة الاستبيان. نؤكد بانه سيتم التعامل بجميع المعلومات التي سيتم جمعها خلال هذه الدراسة بسرية تامة. لذا نرجو من حضرتكم التعاون بالإجابة على أسئلة الاستبانة، علما بأن المشاركة طوعية وأن هذه المعلومات ستستخدم لغرض البحث العلمي فقط، ويمكنك اختيار الانسحاب في أي وقت دون مواجهة أي عواقب. تتضمن هذه مشاركتك في هذه الدراسة على التالي

تعبئة استبيان عن مدى معرفة وتوجهات وممارسات اخصائيي الامراض السرطانية حول الفحوص الجينية المتعلقة باستخدام ادوية فلوروبيريميدين.

التوقيع على هذا النموذج يعني أنني أوافق على ما يلي		
لا	نعم	لقد تم إبلاغي عن هدف الدراسة من قبل الباحث
لا	نعم	تم ابلاغي بأن معلوماتي الشخصية والمعلومات التي سيتم جمعها من هذه الدراسة البحثية ستبقى سرية وسوف تستخدم من أجل البحث العلمي فقط
لا	نعم	أدرك أن لدي الحق في الانسحاب من الدراسة في أي وقت
لا	نعم	لدي خيار عدم الإجابة عن أي سؤال أحده

نموذج الموافقة للمشاركة

دراسة: " معرفة وتوجهات وممارسات اخصائيي الامراض السرطانية حول الفحوص الجينية المتعلقة باستخدام ادوية فلوروبيريميدين "

اسم المشارك _____ التوقيع _____ التاريخ _____

اسم الباحث _____ التوقيع _____ التاريخ _____

إذا كان لديك أي سؤال أو كنت بحاجة إلى أي معلومات، فيرجى الاتصال بـ 0569941337

Appendix 4: Healthcare providers' data collection form



كلية الصحة العامة- جامعة القدس

Awareness and Attitudes of Healthcare Providers toward Dihydropyrimidine Dehydrogenase (DPD) Testing with Fluoropyrimidines in Palestine.

Please answer the following questions.

Demographic information

Designation

Physician.

Resident.

Clinical Pharmacist.

Degree Obtained

Inside Palestine.

Outside Palestine.

Age group

23-35 years.

36-45 years.

46-59 years.

>60 years.

Years of Experience

< 2

2-4

5-7

8-10

> 10

Hospital

Dora Governmental Hospital .

Augusta Victoria Hospital / المطلاع

An-Najah National University Hospital.

Istishari Arab Hospital .

Palestine Hospital / حرملة

Other Governmental Hospitals : _____

Other Private Hospitals : _____

Type of Hospital You Work in:

Specialized oncology Center.

Primary/secondary care.

Another tertiary center.

Do you participate in tumor genomic board, tumor molecular board in your current institution?

Yes

No

What do you mostly follow as a reference when ordering a specific molecular test?

Published practice guidelines.

Institutional guidelines.

Personal experience.

Cancer-genomics specific guidelines.

Other (please specify): _____

Have you received any formal training or education in pharmacogenomics?

Yes

No

If yes, where did you receive your education or training in Pharmacogenomics? (you can select more than one choice if applicable)

University education.

Scientific conferences.

Hospital seminars.

Continuous medical education (CME).

Online courses.

Fellowship program.

Research.

Experience through practice.

No formal training.

Other (please specify): _____

Dihydropyrimidine Dehydrogenase Deficiency (DPD):

Do you usually prescribe Fluoropyrimidine (5-fluorouracil (5-FU) and Capecitabine) for patients with Cancer?

Yes

No

If yes; which type of cancer would you prescribe it for?

Colorectal cancer.

Breast cancer.

Other types of cancer: _____

Are you aware of a mutation that causes Dihydropyrimidine Dehydrogenase Deficiency? (DPD)?

Yes

No

If yes; are you aware of its complications; e.g. PD toxicity of Fluoropyrimidine (5-fluorouracil (5-FU) and Capecitabine)?

Yes

No

How often do you screen for DPD deficiency prior to prescribing Fluoropyrimidine?

a) Always

b) Sometimes

c) Never

Are there guidelines for prescribing Fluoropyrimidine in your hospital?

Yes

No

Not sure

Is there enough research being done in Palestine on screening for DPD prior to prescribing Fluoropyrimidine?

Yes

No

Not sure

Have you seen patients with severe toxicity related to use of Fluoropyrimidine?

Yes

No

Have you seen the impact of DPD testing in your clinical practice?

a) Yes

b) No

Is there any standardization of Dihydropyrimidine Dehydrogenase (DPD) Deficiency practice done by ministry of health?

Yes

No

Not sure

Does the ministry of health promote the practice of Dihydropyrimidine Dehydrogenase (DPD) Deficiency test prior to Fluoropyrimidine (FP) group of medications?

Yes

No

Not sure

Thank you

Appendix 5: Patient consent form- pharmacogenomics study- English



Consent to Participate in a Scientific Research Study

Research Title: Pharmacogenomic and Clinical Factors Associated with Fluoropyrimidine Side Effects in Palestinian Cancer Patients

Principal Investigator: Mohammad Khalaf Dweib

Research Supervisor: Dr. Hussein Hallak

Dear participant,

This research is conducted by the School of Public Health at Al-Quds University and aims to improve the quality of life of patients.

Please note the following:

- Your participation in this study is completely voluntary. It is intended to benefit the community, scientific research in general, and cancer patients in particular.
- If you choose to participate, your name will remain confidential, and you have the right to withdraw at any time without any consequences.
- The Research Ethics Committee at Al-Quds University has approved the study. This committee is the institutional reference body for research and studies.

I, the undersigned participant, have read and understood the information above, and based on that, I agree to take part in this research.

Signature: _____ Date: _____

The questionnaire consists of 24 questions divided into four sections. Please answer all questions to ensure accuracy in handling the data.

Thank you for your valuable participation.

Research Team

For questions or communication, please contact: 0569941337

Appendix 6: Patient consent form- pharmacogenomics study- Arabic

الموافقة على المشاركة في بحث علمي

عنوان البحث: العوامل الفارماكوجينية والسريية المرتبطة بآثار الجوانب الجانبية للفلوروبريميدين في مرضى
السرطان الفلسطينيين

اسم الباحث الرئيسي: محمد خلف اذويب

اسم المشرف على البحث: د. حسين الحلاق

اخي \ اختي المتطوع (ة) هذا البحث هو أحد الأبحاث الطبية التي تقوم بها كلية الصحة العامة في جامعة القدس
ويهدف الى تحسين نوعية حياة المرضى.

ارجو ان ابين ما يلي:

ان مشاركتك في هذا البحث طوعية تماما، ومن شأنها افادة المجتمع وعملية البحث العلمي بشكل عام، وافادة
مرضى الصرع بشكل خاص.

في حال مشاركتك بالبحث، سيبقى اسمك طبي الكتمان، ويحق لك الانسحاب متى شئت من دون أي أثر يذكر عليك.
يجدر الإشارة ان لجنة البحث العلمي في جامعة القدس قد وافقت على اجراء البحث، وتعتبر هي اللجنة المؤسسية
والمرجعية للبحوث والدراسات.

انا المتطوع (ة) قرأت المعلومات المذكورة أعلاه وفهمتها، وبناءً عليه فأنتني أوافق على المشاركة في البحث.

التوقيع: _____ التاريخ: _____

تتكون الاستبانة من (24) سؤال مقسمة الى أربعة اقسام. رجاء الالتزام بالإجابة على جميع الأسئلة لضمان دقة التعامل مع البيانات الموجودة.

شكراً على مشاركتك القيمة
فريق البحث

للاتصال والتواصل يرجى استعمال الرقم التالي: 0569941337

Appendix 7: Patient assessment tool- pharmacogenomics study

Pharmacogenomic and clinical factors associated with the side effects of fluoropyrimidines in Palestinian cancer patients

Participant assessment tool

Participant number: _____ Location: _____ Date: _____

Sociodemographic factors

Sex: ☐ Male ☐ Female

Age: _____

Weight: _____

Height: _____

BMI: _____

Smoking: ☐ Yes ☐ No ☐ Previous

Alcohol intake: ☐ Yes ☐ No ☐ Previous

Clinical factors

Other comorbidities:

Disease status:

☐ Locally advanced CRC

- ☐ Metastatic CRC
- ☐ Locally advanced BC
- ☐ Metastatic BC
- ☐ GC
- ☐ Other: _____

Previously treated with chemotherapy: ☐ Yes ☐ No

Type: _____

Duration: _____

Date of cessation: _____

Treatment regimen: _____

Radiation use: ☐ Yes ☐ No

Genetic factors

DPYD gene result: _____

Score: _____

Patient DPD classification:

- ☐ DPYD Normal Metabolizer
- ☐ DPYD Intermediate Metabolizer
- ☐ DPYD Poor Metabolizer

Recommendation to physician:

- ☐ Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.
- ☐ Reduce starting dose based on activity score followed by titration of dose based on toxicity or therapeutic drug monitoring.
- ☐ Activity score 1: Reduce dose by 50%
- ☐ Activity score 1.5: Reduce dose by 25% to 50%
- ☐ Activity score 0.5: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose

with early therapeutic drug monitoring.

☐ Activity score 0: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.

Physician decision:

☐ Approve recommendation

☐ Reject recommendation

☐ Modify recommendation

Modification (if applicable): _____

Recommendation applied: ☐ Yes ☐ No

Dose: _____

Toxicities

Toxicity: ☐ Yes ☐ No

Gastrointestinal

Type	Severity	Date	Frequency
☐ Diarrhea			
☐ Oral mucositis			
☐ Nausea/vomiting			
☐ Other gastrointestinal			

Myelosuppression

Type	Severity	Date	Frequency
☐ neutropenia/febrile neutropenia			

☐ Thrombocytopenia			
☐ Unexplained anemia			
☐ Other Myelosuppression			

Cardiac

Type	Severity	Date	Frequency
☐ Chest pain			
☐ Palpitation			
☐ Dyspnea			
☐ Cardiogenic shock			
☐ Arrhythmia			
☐ Abnormal echo			
☐ Elevation of myocardial enzyme			
☐ Other			

Skin and Subcutaneous

Type	Severity	Date	Frequency
☐ Hand-and-Foot Syndrome			
☐ Dermatitis			
☐ Nail Disorder			
☐ Alopecia			
☐ Other			

General

Type	Severity	Date	Frequency
☐ Fatigue/weakness			
☐ Pyrexia			
☐ Edema			
☐ Pain			
☐ Other			

Complications

Treatment interruptions: ☐ Yes ☐ No

Treatment discontinuation due to toxicity: ☐ Yes ☐ No

Hospitalization: ☐ Yes ☐ No

Treatment-related death: ☐ Yes ☐ No

Appendix 8: Patient KAP consent form and questionnaire- English



Consent to Participate in a Scientific Research Study

Research Title: Cancer Patients' Opinions and Experiences Regarding Pharmacogenomic Testing and Its Cost

Principal Investigator: Mohammad Khalaf Dweib

Research Supervisor: Dr. Hussein Hallak

Dear participant,

This research is conducted by the School of Public Health at Al-Quds University and aims to improve the quality of life of patients.

Please note the following:

- Your participation in this study is completely voluntary. It is intended to benefit the community, scientific research in general, and cancer patients in particular.
- If you choose to participate, your name will remain confidential, and you have the right to withdraw at any time without any consequences.
- The Research Ethics Committee at Al-Quds University has approved the study. This committee is the institutional reference body for research and studies.

I, the undersigned participant, have read and understood the information above, and based on that, I agree to take part in this research.

The questionnaire consists of 31 questions divided into seven sections. Please answer all questions to ensure accuracy in handling the data.

Thank you for your valuable participation.

Research Team

For questions or communication, please contact: 0569941337



School of Public Health – Al-Quds University

Participant Consent Form

Cancer Patients' Opinions and Experiences Regarding Pharmacogenomic Testing and Its Cost

Signing this form means I agree to the following:

Statement	Yes	No
I have been informed about the purpose of this study by the researcher.	☐	☐
I have been informed that my personal information and all information collected during this study will remain confidential and will be used for scientific research purposes only.	☐	☐
I understand that I have the right to withdraw from this study at any time.	☐	☐
I have the option not to answer any question I choose.	☐	☐

Participant's Name: _____ Signature: _____ Date: _____

Researcher's Name: _____ Signature: _____ Date: _____

If you have any questions or need additional information, please contact:

Mohammad Khalaf Dweib
Email: mohammadd@hebron.edu

Thank you for your valuable participation.
Research Team

Questionnaire: Cancer Patients' Opinions and Experiences Regarding Pharmacogenomic Testing and Its Cost

Section 1: Demographic Information

How old are you? _____

What is your gender?

Male

Female

What is your marital status?

Single

Married

Divorced

Widowed

What is your highest level of education?

No education

Primary

Secondary

University

Postgraduate

What is your current employment status?

Full-time

Part-time

Unemployed

Retired

Housewife

Other

What is your monthly income?

Less than 1000 NIS

1000–3000

3000–5000

More than 5000

How many people live in your household?

One

Two

3–4

Five or more

Section 2: Clinical History

What type of cancer were you diagnosed with?

Colon

Breast

Lung

Other

What is your cancer stage?

Stage I

Stage II

Stage III

Stage IV

Not sure

What treatment(s) are you currently receiving?

Chemotherapy

Radiotherapy

Surgery

Targeted therapy

Other

Have you ever heard of genetic or pharmacogenomic testing?

Yes

No

Have you ever undergone a genetic test?

Yes

No

Section 3: Knowledge

How well do you understand pharmacogenomic testing?

Do not understand

A little

Somewhat

Well

Very well

Do you think pharmacogenomic testing can help your doctor choose the best treatment?

Strongly disagree

Disagree

Neutral

Agree

Strongly agree

Do you think pharmacogenomic testing is accurate?

Strongly disagree

Disagree

Neutral

Agree

Strongly agree

Section 4: Beliefs

Pharmacogenomic testing can help avoid medicines that cause side effects.

Strongly disagree

Disagree

Neutral

Agree

Strongly agree

Would you feel worried if the test revealed risk for another disease?

Yes

No

Not sure

Would you only want the test if it did not reveal inherited cancer risk?

Yes

No

Not sure

Would you be concerned that the results could affect your health insurance?

Yes

No

Not sure

Would you like to participate in the decision of whether or not to undergo the test?

Yes

No

Not sure

Would you be more willing to undergo the test if your doctor recommended it?

Yes

No

Not sure

What would you prefer the test results to predict?

Risk of side effects

Treatment effectiveness

Both

Not sure

What is the maximum waiting time you can accept for test results?

Same day

1–3 days

4–7 days

1–2 weeks

More than 2 weeks

What are your concerns about pharmacogenomic testing?

Cost

Accuracy

Privacy

Disease risk

Insurance impact

No concerns

Section 5: Experiences and Practices

Would you be willing to provide a blood sample for pharmacogenomic testing?

Yes

No

Section 6: Willingness to Pay

Are you willing to pay for pharmacogenomic testing if it helps guide your cancer treatment?

Yes

No

What is the maximum amount (in NIS) you would pay out-of-pocket? _____

What price do you consider reasonable for a pharmacogenomic test? _____

Who do you think should bear the cost of the test?

Patient

Hospital

Government

Insurance

Donors

Don't know

Would you agree to co-pay if part of the cost is covered by the government or donors?

Yes

No

Section 7: Decision-Making

Who do you prefer makes the decision about undergoing pharmacogenomic testing?

Myself

My doctor

Both

Someone else

Thank you for taking the time to complete this questionnaire.

With best regards,

Research Team

Appendix 9: Patient KAP consent form and questionnaire- Arabic



الموافقة على المشاركة في بحث علمي

عنوان البحث: آراء وتجارب مرضى السرطان بشأن الاختبارات الدوائية الجينية وتكلفتها

اسم الباحث الرئيسي: محمد خلف أدويب

اسم المشرف على البحث: د. حسين حلاق

أخي \ اختي المتطوع (ة) هذا البحث هو أحد الأبحاث الطبية التي تقوم بها كلية الصحة العامة في جامعة القدس ويهدف الى تحسين نوعية حياة المرضى.

أرجو ان ابين ما يلي:

ان مشاركتك في هذا البحث طوعية تماما، ومن شأنها افادة المجتمع وعملية البحث العلمي بشكل عام، وافادة مرضى السرطان بشكل خاص.

في حال مشاركتك بالبحث، سيبقى اسمك طبي الكتمان، ويحق لك الانسحاب متى شئت من دون أي أثر يذكر عليك.

يجدر الإشارة ان لجنة البحث العلمي في جامعة القدس قد وافقت على اجراء البحث، وتعتبر هي اللجنة المؤسسية والمرجعية للبحوث والدراسات.

انا المتطوع (ة) قرأت المعلومات المذكورة أعلاه وفهمتها، وبناءً عليه فأنتني أوافق على المشاركة في البحث.

تتكون الاستبانة من (31) سؤال مقسمة الى سبعة اقسام. رجاء الالتزام بالإجابة على جميع الأسئلة لضمان دقة التعامل مع البيانات الموجودة.

شكراً على مشاركتك القيمة

فريق البحث

للاتصال والتواصل يرجى استعمال الرقم التالي: 0569941337



كلية الصحة العامة- جامعة القدس

نموذج الموافقة للمشاركين

اراء وتجارب مرضى السرطان لاختبارات فحص التوافق الجيني مع الادوية وتكلفتها

التوقيع على هذا النموذج يعني أنني أوافق على ما يلي			
1	لقد تم إبلاغي عن هدف الدراسة من قبل الباحث	نعم	لا
2	تم إبلاغي بأن معلوماتي الشخصية والمعلومات التي سيتم جمعها من هذه الدراسة البحثية ستبقى سرية وسوف تستخدم من أجل البحث العلمي فقط	نعم	لا
3	أدرك أن لدي الحق في الانسحاب من الدراسة في أي وقت	نعم	لا
4	لدي خيار عدم الإجابة عن أي سؤال أحده	نعم	لا

اسم المشارك/ة----- التوقيع----- التاريخ-----

اسم الباحث----- التوقيع----- التاريخ-----

إذا كان لديك أي سؤال أو كنت بحاجة إلى أي معلومات، فيرجى الاتصال بـ

محمد خلف ذويب

mohammadd@hebron.edu

شكراً على مشاركتك القيمة

فريق البحث

آراء وتجارب مرضى السرطان لاختبارات فحص التوافق الجيني مع الادوية، وتكلفتها

القسم الأول: المعلومات الديموغرافية

كم عمرك؟ _____

ما هو جنسك؟ ☐ ذكر ☐ أنثى

ما هي حالتك الاجتماعية؟

غير متزوج متزوج مطلق أرمل

ما هو أعلى مستوى تعليمي وصلت إليه؟

بدون تعليم ابتدائي ثانوي
جامعي دراسات عليا

ما هو وضعك الوظيفي الحالي؟

موظف او عامل بدوام كامل موظف او عامل بدوام جزئي عاطل عن العمل
متقاعد ربة منزل أخرى

ما هو دخلك الشهري؟

أقل من 1000 شيكل من 1000 إلى 3000 شيكل
من 3000 إلى 5000 شيكل أكثر من 5000 شيكل

كم عدد الأشخاص الذين يعيشون في منزلك؟

شخص شخصين
3-4 أشخاص خمسة أشخاص أو أكثر

القسم الثاني: التاريخ السريري

ما نوع السرطان الذي تم تشخيصك به؟

سرطان القولون سرطان الثدي

سرطان الرئة أخرى (يرجى التحديد) _____

ما هي مرحلة السرطان لديك؟

المرحلة الأولى	المرحلة الثانية	المرحلة الثالثة
المرحلة الرابعة	لست متأكدًا	
ما العلاج الذي تتلقاه حاليًا؟ (اختر كل ما ينطبق)		
علاج كيميائي	علاج إشعاعي	جراحة
علاج موجه	أخرى	

هل سمعت سابقًا عن الفحوصات الجينية أو الفحوصات المتعلقة بالأدوية؟

نعم لا

هل أجريت فحصًا جينيًا من قبل؟

نعم لا

القسم الثالث: المعرفة

ما مدى فهمك لاختبار فحص التوافق الجيني مع الأدوية؟

لا أفهمه قليلاً إلى حد ما جيداً جيد جداً

هل تعتقد أن الفحوصات الجينية يمكن أن تساعد طبيبك في اختيار أفضل علاج لك؟

أعارض بشدة أعارض أوافق أوافق بشدة

هل تعتقد أن اختبار فحص التوافق الجيني مع الأدوية دقيق؟

أعارض بشدة أعارض أوافق أوافق بشدة

القسم الرابع: الاعتقادات

يمكن لاختبار فحص التوافق الجيني مع الأدوية أن يساعد في تجنب الأدوية التي تسبب آثارًا جانبية.

أعارض بشدة أعارض محايد

أوافق أوافق بشدة

هل ستشعر بالقلق إذا كشف اختباري عن خطر الإصابة بمرض آخر.

نعم لا لست متأكدًا

هل سترغب بإجراء الفحص فقط إذا لم يكشف خطر الإصابة بالسرطان الوراثي.

نعم لا لست متأكدًا

هل ستشعر بالقلق من أن تؤثر نتائج الفحص على تأمين الصحة الخاص بك.

نعم لا لست متأكدًا

هل سترغب في أن تشارك في قرار إجراء الاختبار من عدمه.

نعم لا لست متأكدًا

هل ستكون أكثر استعدادًا لإجراء الفحص إذا أوصى به طبيبك؟

نعم لا لست متأكدًا

ما الذي تفضل أن تتنبأ به نتائج الفحص؟

خطر الآثار الجانبية فعالية العلاج

كلاهما لست متأكدًا

ما هو الحد الأقصى لعدد الأيام الذي يمكنك انتظاره للحصول على نتائج الفحص؟

نفس اليوم من 1 إلى 3 أيام من 4 إلى 7 أيام

من أسبوع إلى أسبوعين أكثر من أسبوعين

ما هي مخاوفك من اختبار فحص التوافق الجيني مع الأدوية؟ (اختر جميع ما ينطبق)

التكلفة الدقة الخصوصية

خطر الأمراض تأثير على التأمين لا توجد مخاوف

القسم الخامس: التجارب والممارسات

هل ترغب في تقديم عينة دم لإجراء اختبار دوائي جيني؟

لا

نعم

القسم السادس: الاستعداد للدفع

هل أنت مستعد لدفع تكلفة اختبار دوائي جيني إذا ساعد في توجيه علاج السرطان الخاص بك؟

لا

نعم

ما هو الحد الأقصى للمبلغ (بالشيكل) الذي يمكنك دفعه من جيبك لإجراء الفحص؟ _____

ما هو السعر الذي تعتبره معقولاً لاختبار دوائي جيني؟ _____

من تعتقد أنه يجب أن يتحمل تكلفة هذا الفحص؟

الحكومة

المستشفى

المريض

لا أعلم

الداعمون

التأمين

هل توافق على المشاركة في دفع التكلفة إذا تم تغطية جزء منها من قبل الحكومة أو جهة داعمة أخرى؟

لا

نعم

القسم السابع: اتخاذ القرار

من تفضل أن يتخذ القرار بشأن إجراء اختبار فحص التوافق الجيني مع الادوية؟

شخص اخر، من

انا وطبيبي

طبيبي

انا

شكراً لتخصيصك وقتاً لتعبئة الاستبانة

مع تحيات فريق البحث

Appendix 10: Published article

ORIGINAL ARTICLE **OPEN ACCESS**

Oncology Specialists' Perceptions and Insights Into Dihydropyrimidine Dehydrogenase Testing in Palestine

Mohammad Dweib^{1,2}  | Hussein Hallak³ | Hani Hour⁴ | Asmahan Alzeer⁴ | Raya Fatafta² | Leen Albaw²

¹College of Public Health, Al-Quds University, Jerusalem, Palestine | ²College of Pharmacy and Medical Sciences, Hebron University, Hebron, Palestine | ³College of Pharmacy, Al-Quds University, Jerusalem, Palestine | ⁴Palestinian Ministry of Health, Ramallah, Palestine

Correspondence: Mohammad Dweib (mohammadd@hebron.edu)

Received: 30 October 2024 | **Revised:** 19 May 2025 | **Accepted:** 28 May 2025

Funding: The authors received no specific funding for this work.

Keywords: cancer | capecitabine | fluoropyrimidines | genetic testing | pharmacogenomics

ABSTRACT

Background: This study evaluated awareness, prevalence, and utilization of dihydropyrimidine dehydrogenase (DPD) testing and pharmacogenomics among oncologists, residents, and clinical pharmacists working in Palestinian hospitals.

Aim: This study aimed to assess the knowledge and opinions of HCPs specializing in oncology in Palestine regarding screening for DPYD testing prior to prescribing FP.

Methods: A cross-sectional survey was distributed to 106 HCPs across various hospitals in Palestine.

Results: A notable deficiency in training and implementation of pharmacogenomics was observed, with over 70% of participants lacking formal training in the field. Although there is high awareness of DPD deficiency and its impact, fewer than 50% of participants screen for DPD deficiency prior to prescribing fluoropyrimidines (FP). Standardization and promotion of DPD testing are low, and guidelines for prescribing FP are lacking, leading to variations in clinical practice.

Conclusion: These findings highlight the need for enhanced training, standardized protocols, and increased awareness to improve patient safety and outcomes in cancer treatment in Palestine.

1 | Introduction

Capecitabine and 5-fluorouracil are chemotherapeutic agents belonging to the FP class. These agents are commonly used for the treatment of several cancers, such as colorectal and breast cancer [1, 2].

It has been shown that a significant proportion of patients receiving these agents, ranging from 10% to 40% of people, experience severe and potentially life-threatening toxicity in the initial stages of FP treatment [3, 4]. Toxicity can lead to the disruption or cessation of treatment. In severe cases, it may require emergency department visits or hospital admissions [5–7].

Reduced activity of the DPD enzyme, which metabolizes around 80%–90% of the administered 5-FU to inactive 5,6-dihydro-5-fluorouracil and is the rate-controlling enzyme for the inactivation of 5-FU, primarily encoded by the DPD gene (DPYD), is considered among the genetic factors implicated in the development of FP intolerance, attracting considerable attention in scientific research, especially clinical research focusing on toxicity prediction [8]. DPD deficiency leads to toxicity by impairing the metabolism of 5-FU, preventing its breakdown into the inactive metabolite 5,6-dihydro-5-FU. Consequently, 5-FU accumulates in the body, causing excessive levels of its active metabolites (FdUMP, FdUDP, and FdUTP). These metabolites interfere

This is an open access article under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2025 The Author(s). *Cancer Reports* published by Wiley Periodicals LLC.

Cancer Reports, 2025; 8:e70251
<https://doi.org/10.1002/cnr2.70251>

1 of 11

with DNA replication and RNA synthesis, leading to cytotoxic effects in rapidly dividing cells. This disruption causes severe toxicities, including myelosuppression, neurotoxicity, and gastrointestinal damage, which can be life-threatening in individuals who have partial or complete DPD deficiency [9]. The categorization of individuals according to their DPYD genotype holds promise in mitigating the occurrence of unfavorable outcomes [10]. This led to the recommendation of DPYD testing prior to treatment with these medications in most parts of Europe and Canada [11].

In addition to genetic factors, other factors, such as age, comorbidities, concurrent medications, and treatment cycles, have also been studied for their role in FP-induced toxicity. Notably, variables such as patient age, the presence of metastasis, the presence of comorbidities, using other medications, and the number of treatment cycles have been explored and have revealed associations with treatment-related toxicity [12].

In many high-income countries, such as those in Europe and Canada, DPD deficiency testing is increasingly integrated into routine clinical practice before administering 5-FU-based chemotherapy, as recommended by the European Society for Medical Oncology (ESMO) guidelines. These guidelines emphasize the importance of screening patients for *DPYD* gene mutations to prevent severe toxicity, particularly in colorectal cancer treatment [13, 14].

Recent studies have further highlighted the significance of integrating pharmacogenomic testing into routine oncology practice, particularly in screening for DPYD variants. Despite the well-documented risks associated with DPYD deficiency, routine pretreatment testing remains inconsistent across different healthcare systems due to logistical, financial, and regulatory challenges [15]. The implementation of systematic DPYD screening has been shown to enhance patient safety while being cost-effective by reducing severe adverse drug reactions and hospitalizations. Large-scale pharmacogenomics analyses have further demonstrated that preemptive DPYD genotyping significantly decreases treatment-related complications and aligns with the broader shift toward personalized medicine [16].

Efforts to standardize DPYD testing across different regions have gained momentum. In Europe, pharmacogenomic guidelines for fluoropyrimidine chemotherapy have led to increased accessibility and reduced toxicity rates [17]. Similarly, the Pharmacogenomics Global Research Network has been working to promote the adoption of DPYD testing globally, aiming to ensure equitable access to pharmacogenomic interventions [18]. However, differences in testing rates persist, underscoring the need for stronger policy frameworks and clinician education to maximize the clinical benefits of DPYD screening [19].

Expanding the role of healthcare professionals (HCPs), particularly pharmacists, in implementing pharmacogenomic testing may further support the routine integration of DPYD testing in oncology settings. Pharmacists have been recognized as key stakeholders in advancing pharmacogenomic initiatives due to their expertise in medication management and patient counseling [20]. Moreover, targeted educational programs for

oncologists and pharmacists have shown promising results in increasing awareness and acceptance of DPYD testing as a standard component of fluoropyrimidine therapy [21]. A multidisciplinary approach—incorporating standardized guidelines, institutional support, and education—is crucial for successfully embedding DPYD screening into routine clinical practice.

Recent advancements in fluoropyrimidine drug development have introduced CF10, a second-generation fluoropyrimidine polymer designed to enhance efficacy while reducing systemic toxicity. Preclinical studies have shown that CF10 is well-tolerated and remains effective even in models simulating DPD inhibition, suggesting its potential as a safer alternative for patients with DPD deficiency. This emerging therapy may help mitigate the risks associated with fluoropyrimidine chemotherapy and could serve as an alternative approach in resource-limited settings where routine DPYD testing is not widely available [22, 23].

Despite the importance of DPYD genotyping and the correlation of other factors with FP toxicity in other populations [24–26], there is a significant gap in our understanding concerning its applicability and significance in the context of Palestinian cancer patients. To date, no studies have conducted a comprehensive examination of the prevalence of DPYD genetic variations or other clinical factors and their correlation with FP-related toxicities within this specific population.

This study aimed to assess the knowledge and opinions of HCPs specializing in oncology in Palestine regarding screening for DPYD testing prior to prescribing FP. The specific objectives of this study were:

- (1) to evaluate the awareness of HCPs (oncologists, residents, and clinical pharmacists) in Palestine with pharmacogenetic screening in general and DPYD screening tests in particular before administering FP to cancer patients;
- (2) to evaluate if demographic variables such as age, hospital department, duration of work experience, and current designation affect awareness;
- (3) to assess the current prevalence, utilization, and barriers to implementing DPYD testing and pharmacogenomics in Palestine.

2 | Materials and Methods

This cross-sectional study utilized a survey distributed to oncologists, oncology residents, and clinical pharmacists across various hospitals in Palestine between February and May 2024. The questionnaire was adopted from a previous study conducted in Saudi Arabia [21] and was slightly modified to suit the Palestinian context. These modifications included, for example, the type of healthcare provider in which the respondents worked (Ministry of Health, private sector, UNRWA, etc.) The survey consisted of 26 items covering participant demographics and the awareness of participants regarding DPYD screening. Various types of questions were included

(multiple choice questions, Likert scale, etc.) The content validity of the questionnaire items was ensured through review by experts (three oncologists and three pharmacists) who assessed the appropriateness of the content, making necessary modifications to ensure comprehensive and accurate assessment of attitudes.

The survey was pilot-tested by four professionals (two oncologists and two pharmacists). No major improvements were suggested, so no modifications were performed. Their responses were not included in the analysis.

The questionnaire was distributed electronically to all available health care professionals who work in four hospitals (two governmental, two nongovernmental) that have an oncology unit.

2.1 | Inclusion Criteria

All oncologists, oncology residents, and clinical pharmacists in the four cancer centers in Palestine. The number of professionals who met the criteria in the hospitals was 171.

2.2 | Exclusion Criteria

Retail pharmacists, outpatient pharmacists, and nononcology doctors. Retail pharmacists were excluded because no anticancer medications are dispensed through them.

2.3 | Sample Size

Prior studies have shown that the level of knowledge among HCPs on pharmacogenomics testing varied between 31% and 62% [27–30]. For our study conducted in Palestine, we made the assumption that the level of awareness of DPD testing is roughly 50%. To achieve the required precision level of 5% and a confidence interval of 95%, and taking into account the information provided by the Palestinian health authorities that there are around 150 registered practitioners in oncology, we needed to recruit 100 HCPs in order to meet the aim of our study. Incomplete responses were not included in the analysis.

3 | Results

The questionnaire was completed by a total of 106 HCPs, consisting of 57.5% specialist physicians, 27.4% clinical pharmacists, and 15.1% resident physicians. This distribution is similar to composition of the study population. The majority of respondents, over 60%, received their most recent degree from a Palestinian institution, while around 40% graduated from foreign institutions. The location of the last degree may influence respondents' practices due to variations in pharmacogenomics training and exposure to DPYD testing. Foreign institutions may emphasize pharmacogenetic applications more than Palestinian institutions, leading to differences in implementation.

More than 70% of the participants were 45 years old or younger.

TABLE 1 | Sociodemographic characteristics of the participants.

Characteristics		Number	Percentage
Designation	Clinical pharmacist	29	27.4
	Physician	61	57.5
	Resident	16	15.1
Last degree location	Inside Palestine	63	59.4
	Outside Palestine	43	40.6
Age group	23–35 years	41	38.7
	36–45 years	37	34.9
	46–59 years	22	20.8
	More than 60 years	6	5.7
Years of experience	2–4	25	23.6
	5–7	22	20.8
	8–10	14	13.2
	11 or more	45	42.5
Hospital type	Private	54	50.9
	Governmental	52	49.1

Regarding professional experience, a majority of the participants possessed more than 8 years of expertise in working with cancer patients as seen in Table 1. Fifty percent of the participants were associated with private hospitals, while the remaining 50% were employed at governmental institutions.

Demographic data for the participants is presented in Table 1.

A striking finding was that more than 70% of participants stated that they had never undergone formal training in pharmacogenomics during their career. However, a substantial majority of 75.5% stated that they usually prescribe FPs. Furthermore, around 80% of participants indicated knowledge of the mutation linked to DPD deficiency and its consequences for FP toxicity. Yet, fewer than 50% of participants indicated that they consistently or occasionally screen for DPD deficiency prior to prescription FPs. This discrepancy between awareness of DPYD mutations and the limited use of screening has significant implications for patient outcomes. Failure to screen for DPD deficiency may lead to severe, potentially life-threatening toxicities in patients prescribed FPs, as individuals with DPYD mutations are unable to metabolize these drugs effectively. Implementing routine screening could enhance treatment efficacy by identifying at-risk patients, enabling dose adjustments or alternative therapies, and reducing the risk of adverse events.

In addition, only 47% of participants reported that their institution had specific protocols for prescribing FPs. Notably, 60% of individuals experienced significant toxicity associated with FPs, a rate considerably higher than the global average of 10%–30%. This difference may be influenced by several factors, including

variations in dosing strategies, differences in patient monitoring, and inconsistent adherence to international treatment guidelines. Furthermore, only 33% of participants had observed the influence of DPD testing in clinical practice, highlighting gaps in implementation. These challenges may be driven by the lack of infrastructure for pharmacogenomic testing, limited awareness of standardized protocols, and financial constraints that hinder the widespread adoption of DPD testing. Addressing these barriers could improve the safe and effective use of fluoropyrimidines in clinical practice. With regards to the standardization and promotion of DPD testing, a mere 5.7% and 0.0% of participants, respectively, reported the existence of standardized DPD testing and the Palestinian Ministry of Health's promotion of DPD testing before prescribing FPs. Only 1.9% of the participants concurred that an adequate amount of research is being conducted in Palestine with regards to DPD insufficiency.

The main sources used to obtain information on specific molecular testing were published practice guidelines (37.7%) and cancer-genomics specific guidelines (13.2%).

The most common types of cancer for which FPs were prescribed were colorectal cancer (29%) and breast cancer (27%).

Details of the awareness and practices of the participants are shown in Table 2.

A high percentage of participants displayed knowledge regarding the mutation accountable for DPD deficiency. Specifically, 72% of clinical pharmacists, 80% of physicians, and 93% of resident physicians expressed familiarity with this genetic variation ($p > 0.05$).

The awareness of the mutation linked to DPD deficiency differed among respondents with different degrees of professional experience. Specifically, 84% of those with 2–4 years of experience, 90% with 5–7 years, 64% with 8–10 years, and 77% with 11 or more years indicated familiarity with this genetic variant ($p > 0.05$).

An inequality in knowledge regarding the mutation accountable for DPD was noted between HCPs employed in private hospitals and those in governmental hospitals, with 87% of individuals in private hospital settings and 73% in governmental hospitals expressing familiarity with this genetic variant ($p > 0.05$).

Some participants reported the existence of guidelines in their individual institutions for prescribing FPs. Specifically, 37% of clinical pharmacists, 50% of physicians, and 50% of residents confirmed the presence of these guidelines ($p > 0.05$).

The presence of guidelines for prescribing FPs in hospitals varied based on years of professional experience. Among individuals with 2–4 years of experience, 52% indicated the existence of guidelines. This percentage was 45% for those with 5–7 years, 57% for those with 8–10 years, and 42% for those with 11 or more years ($p > 0.05$).

There was a noticeable difference in the reported prevalence of guidelines for prescribing FPs between HCPs in private hospitals and those in governmental hospitals. In private hospital

settings, 57% of individuals acknowledged the presence of these guidelines, while in governmental hospitals, only 36% did so ($p > 0.05$).

A small proportion of participants stated that they had witnessed the effects of DPD testing in their clinical work. Specifically, 17% of clinical pharmacists, 39% of physicians, and 37% of residents reported having this experience ($p > 0.05$).

Regarding professional experience, the extent to which the effects of DPD testing were observed in clinical practice differed among individuals. Specifically, 28% of those with 2–4 years of experience, 40% with 5–7 years, 28% with 8–10 years, and 33% with 11 or more years reported witnessing such influence ($p > 0.05$).

A statistically significant difference was found between HCPs working in private hospitals and those working in governmental institutions in terms of their perception of the influence of DPD testing in clinical practice, with a $p = 0.001$. More precisely, 48% of persons in private hospital settings and 17% in governmental institutions reported experiencing this effect (Table 3). Additionally, the data from Table 3 reveal that awareness of the DPD mutation was highest among residents (93.8%) and private hospital practitioners (87.0%). However, the presence of hospital-specific guidelines was reported more frequently in private hospitals (57.4%) than in governmental settings (36.5%), further reflecting institutional differences in support for fFP-related testing. These findings highlight the need for standardized policies across all hospital types to improve the adoption of DPD testing in clinical practice.

The institution where HCPs obtained their most recent degree did not have a significant impact on their knowledge of DPD mutations, awareness of institutional guidelines for DPD testing, or experience with its effects in clinical practice, as indicated by a $p > 0.05$. Details of the awareness and observation of DPD testing in practice, with regard to hospital-related and demographic variables, are shown in Table 3.

4 | Discussion

The result emphasizes a notable deficiency in training regarding pharmacogenomics and implementation of pharmacogenomic testing among HCPs. Although most participants indicate that they have not received formal training in pharmacogenomics, no differences were observed between roles, such as residents, clinical pharmacists, and physicians. Despite this lack of training across all groups, a significant percentage still administer FPs, underscoring the need for comprehensive educational initiatives to improve safety and efficacy in clinical practice. This difference indicates that numerous HCPs may lack comprehensive knowledge regarding the complex nature of pharmacogenomics and its implications for drug therapy. This gap highlights the urgent need for targeted educational initiatives and training programs to bridge the knowledge deficit among HCPs. Incorporating pharmacogenomics into medical and pharmacy curricula, as well as offering continuing education opportunities, could enhance practitioners' understanding and improve the safe and effective use of FPs.

TABLE 2 | Practices, awareness, and attitudes of participants toward DPD testing.

		Count	Percentage
Do you participate in tumor genomic board, tumor molecular board in your current institution?	No	67	63.2
	Yes	39	36.8
What do you mostly follow as a reference when ordering a specific molecular test?	Cancer-genomics specific guidelines	24	22.64
	Institutional guidelines	17	16.04
	Personal experience	20	18.87
	Published practice guidelines	45	42.45
Have you received any formal training or education in pharmacogenomics?	No	77	72.6
	Yes	29	27.4
If yes, where did you receive your education or training in pharmacogenomics?	Continuous medical education (CME)	21	19.81
	Experience through practice	18	16.98
	Fellowship program	13	12.26
	Hospital seminars	16	15.09
	Online courses	16	15.09
	Research	7	6.60
	University education	15	14.15
Do you usually prescribe FP (5-fluorouracil [5-FU] and Capecitabine) for patients with cancer?	No	26	24.5
	Yes	80	75.5
If yes; which type of cancer would you prescribe it for?	Colorectal cancer	21	19.81
	Breast cancer	19	17.92
	Colorectal cancer	14	13.21
	Gastric cancer	13	12.26
	Pancreatic cancer	7	6.60
	Head and neck cancer	8	7.55
	Biliary tree malignancy	9	8.49
	I am not prescriber	11	10.38
	Nasopharyngeal carcinoma	4	3.77
Are you aware of a mutation that causes DPD deficiency?	No	21	19.8
	Yes	85	80.2
If yes; are you aware of its complications; e.g., PD toxicity of FP (5-fluorouracil [5-FU] and Capecitabine)?	No	22	20.8
	Yes	84	79.2
How often do you screen for DPD deficiency prior to prescribing FP?	Always	2	1.9
	Never	56	52.8
	Sometimes	48	45.3
Are there guidelines for prescribing FP in your hospital?	No	27	25.5
	Not sure	29	27.4
	Yes	50	47.2

(Continues)

TABLE 2 | (Continued)

		Count	Percentage
Is there enough research being done in Palestine on screening for DPD prior to prescribing FP?	No	62	58.5
	Not sure	42	39.6
	Yes	2	1.9
Have you seen patients with severe toxicity related to use of FP?	No	41	38.7
	Yes	65	61.3
Have you seen the impact of DPD testing in your clinical practice?	No	71	67.0
	Yes	35	33.0
Is there any standardization of DPD Deficiency practice done by MOH?	No	51	48.1
	Not sure	49	46.2
	Yes	6	5.7
Does the MOH promote the practice of DPD deficiency test prior to FP group of medications?	No	51	48.1
	Not sure	48	45.3
	Yes	7	6.6

This is particularly critical given the potential for severe adverse drug reactions in patients with DPYD gene variants.

It is encouraging to notice that almost 80% of HCPs have a high level of awareness about the mutation linked to DPD deficiency and its impact on fluoropyrimidine toxicity. This suggests that healthcare practitioners are generally well-informed about this important genetic component. Nevertheless, it is worrisome that fewer than 50% of the participants stated that they screen for DPD deficiency prior to prescribing FPs. This gap between awareness and practice may be attributed to financial and logistical barriers, such as the high cost of DPD testing, limited availability of testing facilities, and a lack of institutional protocols, which hinder the integration of pharmacogenetic testing into routine clinical practice. The lack of implementation in this domain may result in a higher likelihood of severe toxicity in patients with DPD deficiency who receive FPs.

The indication that fewer than 50% of the participants reported their institution having explicit standards for administering FPs implies a deficiency in uniformity within this domain. This lack of standardized protocols can lead to inconsistent practices, increasing the risk of adverse drug reactions and compromising patient safety. Without clear guidelines, HCPs may fail to screen for DPD deficiency, resulting in sub-optimal dosing or inappropriate treatment that could reduce treatment efficacy and expose patients to potentially severe toxicity. The absence of clear recommendations may lead to variations in prescribing practices and potentially result in inferior outcomes for patients. For example, some practitioners may omit screening for DPD deficiency altogether, leading to standard dosing that could cause severe toxicity in patients with the mutation, while others might delay treatment adjustments due to uncertainty or lack of access to testing. Such inconsistencies can compromise both patient safety and the overall efficacy of FP-based therapies.

The significant incidence of serious toxicity associated with FPs (about 60%) is alarming and emphasizes the necessity for enhanced management measures. This rate appears to be higher than the global average, where severe toxicity typically ranges between 10% and 30% in patients receiving FPs. Such a stark contrast highlights potential gaps in screening practices, dosing adjustments, or patient monitoring in the local context, underscoring the urgent need for standardized protocols and broader implementation of DPD deficiency testing. One method to reduce this risk is through DPYD testing, which can identify patients who have a higher chance of experiencing toxicity as a result of DPD deficiency. Nevertheless, the very low percentage of observations regarding the influence of DPD testing in clinical practice (merely 33%) implies that this testing may not be extensively adopted or acknowledged as being beneficial among HCPs. To improve adoption, strategies such as integrating DPD testing into national treatment guidelines, subsidizing the cost of testing to reduce financial barriers, and conducting educational campaigns to raise awareness about its clinical value could be implemented. Additionally, policies mandating the inclusion of pharmacogenomics in medical and pharmacy curricula and incentivizing healthcare institutions to adopt routine screening protocols may further promote the use of DPD testing.

The low rates of standardization of DPD testing (5.7%) and promotion by the Ministry of Health (6.6%) underscore the necessity for heightened awareness and implementation of this crucial component of personalized medical care. Implementing standardized protocols and actively promoting DPYD testing has the potential to enhance uniformity in healthcare institutions and ultimately enhance patient outcomes.

This indicates a lower-than-anticipated adoption of a screening test that is already regarded as a standard procedure in numerous other countries like France and the Netherlands [9, 31]. Consequently, our findings emphasize the significance

TABLE 3 | Knowledge of and observation of DPD testing in practice, determined by hospital- and demographic-related factors.

			Are you aware of a mutation that causes DPD deficiency	Are there guidelines for prescribing Fluoropyrimidine in your hospital?	Have you seen the impact of DPD testing in your clinical practice?
Designation	Clinical Pharmacist	29	21 (72.4%)	11 (37.9%)	5 (17.2%)
	Physician	61	49 (80.3%)	31 (50.8%)	24 (39.3%)
	Resident	16	15 (93.8%)	8 (50.0%)	6 (37.5%)
Years of experience	2–4	25	21 (84.0%)	13 (52.0%)	7 (28.0%)
	5–7	22	20 (90.9%)	10 (45.5%)	9 (40.9%)
	8–10	14	9 (64.3%)	8 (57.1%)	4 (28.6%)
	11+	45	35 (77.8%)	19 (42.2%)	15 (33.3%)
Hospital type	Private	54	47 (87.0%)	31 (57.4%)	26 (48.1%)
	Governmental	52	38 (73.1%)	19 (36.5%)	9 (17.3%)

of promoting DPD screening prior to the administration of fluoropyrimidines.

The results uncover a significant pattern in the knowledge of the mutation associated with DPD insufficiency across HCPs. Resident physicians demonstrated the greatest level of familiarity, with clinical pharmacists and physicians following closely behind. Curiously, there was a variation in awareness depending on professional experience, with individuals in the intermediate range (5–7 years) demonstrating the highest level of familiarity. The variance seen could be ascribed to the evolution of training methods or the influence of emerging research at this particular phase of their professional lives. Moreover, the discrepancy in understanding between private and governmental hospital settings implies possible variations in instructional tools or focus on pharmacogenomics in these settings.

The data reveals a notable difference in the existence of guidelines for prescribing FPs among various categories of HCPs and hospital environments. Guideline availability varied across clinical pharmacists, physicians, and residents, with physicians and residents being more likely to have guidelines compared to clinical pharmacists. The difference can be attributed to the inherent characteristics of their positions and duties within the healthcare system, since physicians and residents typically exhibit greater direct engagement in making prescription decisions in comparison to clinical pharmacists. Additionally, differences in funding, institutional priorities, and resource allocation between hospital environments may further contribute to this variation. Private hospitals, for example, may have more resources to develop and implement comprehensive guidelines, whereas governmental institutions may face budget constraints and competing healthcare priorities.

Curiously, the correlation between the presence of guidelines and years of professional experience was not consistently observed, contrary to what one might anticipate. This implies that factors beyond experience, like institutional agendas, resources, or the importance given to standardizing prescribing practices, might influence the creation or execution of these guidelines.

The noticeable difference in the availability of guidelines between private and governmental hospital settings highlights the impact of institutional factors on the existence of prescribing guidelines. Private hospitals are more likely to have established guidelines compared to public hospitals due to their greater resources and emphasis on quality improvement programs.

Consequently, these findings emphasize the importance of having clear and easily available guidelines for prescribing fluoropyrimidines in all healthcare environments, regardless of the practitioner's level of expertise or type of facility. These suggestions can assist in guaranteeing secure and efficient prescription practices, eventually enhancing patient results.

The analysis indicates a difference in how various groups of HCPs perceive the effects of DPD testing in clinical practice. Clinical pharmacists, physicians, and residents had varying degrees of expertise in observing the impact of DPD testing. Among them, physicians had the highest percentage of respondents who reported having such experience. The variation in results can be linked to differences in roles and duties, since physicians are more inclined to have direct participation in patient care decisions where DPD testing has an effect on treatment options. To address this variation, targeted training programs on pharmacogenomic applications and the clinical importance of DPD testing should be developed for all healthcare roles. Additionally, implementing policies that promote interdisciplinary collaboration could help ensure that all practitioners are equally informed and involved in decisions related to DPD testing.

Interestingly, the correlation between the observation of the impact of DPD testing and years of work experience was not consistently positive. This implies that variables other than experience, such as exposure to training or access to resources, can affect the probability of detecting the effects of DPD testing in clinical practice. To address this issue, targeted training programs focused on pharmacogenomics and the clinical applications of DPD testing should be implemented across all experience levels. Additionally, ensuring equitable access to testing facilities and

resources within healthcare institutions can help bridge this gap and improve the integration of DPD testing into routine practice.

The observed statistically significant difference between HCPs in private and public institutions in terms of their observation of the impact of DPD testing underscores the role of institutional determinants. Private hospitals may possess stronger resources and prioritize individualized medicine, resulting in a greater probability of witnessing the effects of DPD testing in comparison to government hospitals.

The results of this study closely correspond to the findings of studies carried out in nearby nations. A study carried out in Saudi Arabia also found a lack of proper genetic testing before administering FPs, as well as a lack of awareness about established recommendations for genetic testing [21].

Research conducted in the United States revealed that although the majority of oncologists recognize the heightened risk of toxicity in patients with DPD deficiency and are open to adjusting the dose of FP appropriately, only a small percentage of them believe in the effectiveness of DPYD testing. Just 20% of oncologists have ever requested the test, and only 3% have ordered it for at least 10% of their patients receiving FP treatment. The limited occurrence of DPD insufficiency and the absence of guideline recommendations are significant obstacles to broader acceptance and implementation [32].

The comparison to similar studies in Saudi Arabia and the United States provides valuable context for understanding global challenges in implementing DPD testing. Cultural and economic factors may contribute to these similarities and differences. For instance, in Saudi Arabia, a lack of widespread genetic literacy and reliance on traditional practices may hinder awareness and adoption of genetic testing. In the United States, despite higher access to advanced technologies, skepticism about the cost-effectiveness of testing and varying guideline recommendations may explain the limited use of DPYD testing. These findings underscore the need for tailored strategies, such as improving awareness, aligning guidelines, and addressing cultural and economic barriers, to enhance the adoption of DPD testing in diverse healthcare systems.

The cost of DPD testing includes not only the direct expenses of genetic analysis but also the infrastructural investments required for laboratory capacity, equipment, and trained personnel. In Palestine, the lack of established pharmacogenomics programs and limited access to specialized genetic testing facilities further complicate implementation. Additionally, regulatory barriers, such as the absence of national guidelines or policies mandating pretreatment DPD screening, contribute to inconsistent adoption across healthcare institutions. Overcoming these challenges will require coordinated efforts to integrate pharmacogenomics into clinical practice, improve healthcare infrastructure, and establish clear regulatory frameworks to support the safe and cost-effective use of FP-based therapies.

A study evaluating the application of DPD deficiency testing in Europe, both before and after the recommendations made by the European Medicines Agency (EMA), revealed a rise in the utilization of both genotyping and phenotyping techniques following

the guidelines. The implementation of municipal norms has also seen an increase. In 2021, the reimbursement coverage for both tests experienced an improvement, with just a limited number of nations not providing coverage. Although significant obstacles persisted, a smaller number of experts mentioned concerns around reimbursement and recognition after the suggestions were made. In general, 25% of respondents indicated that they encountered no obstacles in implementing the new testing procedure after the recommendations were made [33]. These European practices could serve as a model for Palestine by demonstrating the value of clear national guidelines, improved reimbursement policies, and increased advocacy for testing. Adapting these strategies in Palestine would require collaboration between healthcare policymakers, institutions, and the Ministry of Health to establish unified protocols and allocate resources to make DPD testing more accessible and feasible.

The development of second-generation FPs alternatives like CF10, which exhibit lower systemic toxicity and greater antitumor activity, aligns with the goals of reducing the burden of adverse events associated with current treatment regimens. These advancements may also reduce reliance on DPD testing, especially in resource-limited settings where implementation barriers persist. However, integration of such therapies into clinical practice would still require robust training, guideline updates, and resource allocation to ensure equitable access and effective use [22].

Emerging research into innovative FP formulations offers promising solutions to mitigate toxicity while enhancing efficacy. For instance, Okechukwu et al. (2024) demonstrated that CF10, a second-generation FP [22].

To address the identified gaps, it is imperative to implement actionable measures aimed at enhancing the safe and effective use of FPs. National training programs on pharmacogenomics should be established to equip HCPs with the knowledge necessary to integrate genetic testing, such as DPD deficiency screening, into routine practice. Additionally, integrating DPD testing protocols into existing healthcare systems and making them a mandatory component of treatment guidelines could standardize practices and reduce toxicity risks. These initiatives, coupled with efforts to subsidize the cost of testing and improve accessibility, would significantly enhance patient safety and optimize treatment outcomes.

Policy changes proposed to the Ministry of Health could include mandating DPD testing as a standard pretreatment requirement for FPs, subsidizing testing costs to improve accessibility, and establishing nationwide protocols to ensure uniform implementation across healthcare institutions. Additionally, incorporating pharmacogenomics into medical education and professional training programs could foster a culture of personalized medicine. These measures would enhance early detection of DPD deficiency, minimize severe toxicity risks, and improve overall treatment outcomes.

Despite promising awareness levels, the lack of widespread implementation and uniformity in practices highlights the pressing need for actionable measures. Addressing these challenges through targeted training, policy reforms, and resource

allocation could significantly enhance patient safety and treatment outcomes. Building on these insights, the conclusion will outline practical recommendations and propose avenues for future research to bridge these gaps effectively.

To ensure patient safety and align with international best practices, the Palestinian Ministry of Health should take concrete steps to promote the integration of DPD testing into clinical practice. Establishing national guidelines mandating DPYD genotyping or DPD enzyme activity testing for patients receiving fluoropyrimidines is essential, with a focus on high-risk groups such as those with a history of severe toxicity, renal or hepatic impairment, or a family history of DPD deficiency. Oncology protocols should incorporate mandatory pretreatment DPD testing for colorectal, gastric, and breast cancer patients receiving 5-FU or capecitabine. Additionally, investments should be made to expand laboratory infrastructure, ensuring that molecular and biochemical diagnostic facilities are equipped to conduct DPYD testing, alongside training programs for HCPs to properly interpret and utilize results. To increase awareness and adherence, educational campaigns and continuing medical education (CME) programs should be implemented, highlighting the role of DPD testing in preventing severe adverse drug reactions. Given financial constraints, the Palestinian Ministry of Health should explore subsidies, public-private partnerships, and integration into health insurance schemes to make testing more accessible and affordable. Finally, a national registry should be established to track testing uptake, FP toxicity cases, and clinical outcomes, enabling continuous policy refinement and improved accessibility over time. Implementing these measures will enhance patient safety, optimize FP therapy, and reduce the incidence of severe drug-related toxicity in Palestine.

5 | Conclusions

This study highlights critical gaps in the understanding and implementation of pharmacogenomics among HCPs in Palestine, especially oncologists and clinical pharmacists, regarding the prescription and management of FPs. While there is a significant level of knowledge about DPD deficiency and its implications, this awareness does not consistently translate into practice. The absence of comprehensive DPD deficiency screening before prescribing FPs increases the risk of toxicity, leading to severe complications such as hospitalizations or life-threatening adverse effects. Key barriers contributing to this issue include limited resources, insufficient protocols, and the absence of standardized guidelines.

To address these gaps, it is imperative that healthcare institutions, policymakers, and educational bodies take immediate steps to integrate DPD testing into routine oncology practice. This can be achieved through the development of standardized protocols, investment in accessible diagnostic resources, and the implementation of targeted educational programs to enhance HCPs' competency in pharmacogenomics. Additionally, future research should explore the cost-effectiveness of DPD testing in Palestine and assess the impact of targeted educational interventions on increasing testing rates and improving patient safety.

Additionally, policymakers and healthcare leaders must prioritize the integration of pharmacogenomic testing into clinical

practice to align with international standards and enhance patient outcomes. A concerted effort to establish clear guidelines, improve institutional infrastructure, and promote awareness is essential to advancing personalized medicine in Palestine. The time to act is now—by strengthening pharmacogenomic practices, we can significantly improve cancer treatment safety and efficacy, ensuring better care for patients.

While this study provides valuable insights into the gaps in pharmacogenomics implementation, it is limited by its sample size and geographic scope, warranting future research involving larger and more diverse populations to explore additional barriers to DPD testing. To address these challenges, collaboration with international organizations and the initiation of pilot training programs could serve as practical first steps to enhance knowledge and establish best practices. Furthermore, these findings emphasize the urgent need for national guidelines that standardize DPD testing prior to FP therapy, ensuring consistent clinical practice and reducing toxicity risks. Integrating such testing into existing healthcare protocols would not only optimize patient safety and treatment outcomes but also align Palestine's healthcare practices with international standards, advancing the implementation of personalized medicine in oncology.

While this study provides valuable insights into the gaps in pharmacogenomics implementation, it is subject to certain limitations. The sample size, though adequate, may not fully represent all oncology practitioners in Palestine, potentially limiting the generalizability of the findings. Additionally, the study's cross-sectional design restricts the ability to establish causal relationships between barriers to DPD testing and clinical outcomes. Moreover, the geographic scope of the study may not capture variations in institutional practices across different healthcare settings. Future research involving larger and more diverse populations, as well as longitudinal studies, would help further explore additional barriers and facilitators of DPD testing adoption. To address these challenges, collaboration with international organizations and the initiation of pilot training programs could serve as practical first steps to enhance knowledge and establish best practices. Furthermore, these findings emphasize the urgent need for national guidelines to standardize DPD testing prior to FP therapy, ensuring consistent clinical practice and reducing toxicity risks. Integrating such testing into existing healthcare protocols would not only optimize patient safety and treatment outcomes but also align Palestine's healthcare practices with international standards, advancing the implementation of personalized medicine in oncology.

Author Contributions

Asmahan Alzeer: formal analysis (equal), investigation (equal), writing – original draft (equal).

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics of Al-Quds University (REF 13/24, Date: 17/2/2024), for studies involving humans.

Consent

Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data is available upon request from the corresponding author.

References

1. S. N. Hoon, P. K. H. Lau, A. M. White, M. K. Bulsara, P. D. Banks, and A. D. Redfern, "Capecitabine for Hormone Receptor-Positive Versus Hormone Receptor-Negative Breast Cancer," *Cochrane Database of Systematic Reviews* 2021 (2021): 10–11.
2. J. W. G. Derksen, K. C. Smit, A. M. May, and C. J. A. Punt, "Systematic Review and Non-Inferiority Meta-Analysis of Randomised Phase II/III Trials on S-1-Based Therapy Versus 5-Fluorouracil- or Capecitabine-Based Therapy in the Treatment of Patients With Metastatic Colorectal Cancer," *European Journal of Cancer* 166 (2022): 73–86.
3. S. Glewis, M. Alexander, M. N. H. Khabbazi, et al., "A Systematic Review and Meta-Analysis of Toxicity and Treatment Outcomes With Pharmacogenetic-Guided Dosing Compared to Standard of Care BSA-Based Fluoropyrimidine Dosing," *British Journal of Cancer* 127 (2022): 126–136, <https://doi.org/10.1038/s41416-022-01779-6>.
4. Y. Cura, C. Pérez-Ramírez, A. Sánchez-Martín, et al., "Influence of Single-Nucleotide Polymorphisms on Clinical Outcomes of Capecitabine-Based Chemotherapy in Colorectal Cancer Patients: A Systematic Review," *Cancers (Basel)* 15 (2023): 5–21.
5. M. J. Deenen, D. Meulendijks, A. Cats, et al., "Upfront Genotyping of DPYD*2A to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis," *Journal of Clinical Oncology* 34 (2016): 227–234, <https://doi.org/10.1200/JCO.2015.63.1325>.
6. U. Amstutz, S. Farese, S. Acbi, and C. R. Largiadér, "Dihydropyrimidine Dehydrogenase Gene Variation and Severe 5-Fluorouracil Toxicity: A Haplotype Assessment," *Pharmacogenomics* 10 (2009): 931–944, <https://doi.org/10.2217/pgs.09.28>.
7. B. Yang, X. Xie, D. Lv, et al., "Capecitabine Induces Hand-Foot Syndrome Through Elevated Thymidine Phosphorylase-Mediated Locoregional Toxicity and GSDME-Driven Pyroptosis That Can Be Relieved by Tipiracil," *British Journal of Cancer* 128 (2023): 219–231, <https://doi.org/10.1038/s41416-022-02039-3>.
8. D. Meulendijks, L. M. Henricks, G. S. Sonke, et al., "Clinical Relevance of DPYD Variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as Predictors of Severe Fluoropyrimidine-Associated Toxicity: A Systematic Review and Meta-Analysis of Individual Patient Data," *Lancet Oncology* 16 (2015): 1639–1650, [https://doi.org/10.1016/S1470-2045\(15\)00286-7](https://doi.org/10.1016/S1470-2045(15)00286-7).
9. B. Wörmann, C. Bokemeyer, T. Burmeister, et al., "Dihydropyrimidine Dehydrogenase Testing Prior to Treatment With 5-Fluorouracil, Capecitabine, and Tegafur: A Consensus Paper," *Oncology Research and Treatment* 43 (2020): 628–636, <https://doi.org/10.1159/000510258>.
10. G. Gentile, A. Botticelli, L. Lionetto, et al., "Genotype-Phenotype Correlations in 5-Fluorouracil Metabolism: A Candidate DPYD Haplotype to Improve Toxicity Prediction," *Pharmacogenomics Journal* 16 (2016): 320–325, <https://doi.org/10.1038/tpj.2015.56>.
11. D. L. Hertz, D. M. Smith, S. A. Scott, J. N. Patel, and J. K. Hicks, "Response to the FDA Decision Regarding DPYD Testing Prior to Fluoropyrimidine Chemotherapy," *Clinical Pharmacology and Therapeutics* 114 (2023): 768–779.
12. C. Li, S. Ngorsuraches, C. Chou, L. Chen, and J. Qian, "Risk Factors of Fluoropyrimidine Induced Cardiotoxicity Among Cancer Patients: A Systematic Review and Meta-Analysis," *Critical Reviews in Oncology/Hematology* 162 (2021): 10–14.
13. G. Argilés, J. Tabernero, R. Labianca, et al., "Localised Colon Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up," *Annals of Oncology* 31 (2020): 1291–1305, <https://doi.org/10.1016/j.annonc.2020.06.022>.
14. A. Cervantes, R. Adam, S. Roselló, et al., "Metastatic Colorectal Cancer: ESMO Clinical Practice Guideline for Diagnosis, Treatment and Follow-Up," *Annals of Oncology* 34 (2023): 10–32, <https://doi.org/10.1016/j.annonc.2022.10.003>.
15. F. C. A. de Moraes, A. B. de Almeida Barbosa, V. K. T. Sano, F. A. Kelly, and R. M. R. Burbano, "Pharmacogenetics of DPYD and Treatment-Related Mortality on Fluoropyrimidine Chemotherapy for Cancer Patients: A Meta-Analysis and Trial Sequential Analysis," *BMC Cancer* 24 (2024): 1210, <https://doi.org/10.1186/s12885-024-12981-5>.
16. B. Tamraz and A. P. Venook, "DPYD Pharmacogenetics: To Opt-In or to Opt-Out," *JCO Oncology Practice* 20 (2024): 1009–1011, <https://doi.org/10.1200/OP.24.00255>.
17. R. Nogueiras-Álvarez and I. Pérez Francisco, "Pharmacogenetics in Oncology: A Useful Tool for Individualizing Drug Therapy," *British Journal of Clinical Pharmacology* 90 (2024): 2483–2508, <https://doi.org/10.1111/bcp.16181>.
18. K. Surprenant, L. Murray, K. Merritt, M. Hopkins, and J. McIntyre, "Give Patients the Choice to Test for DPD Deficiency Before Fluoropyrimidine Chemotherapy," *JCO Oncology Practice* 21 (2025): 264–265, <https://doi.org/10.1200/OP.24.00443>.
19. K. Traynor, "DPYD Testing Makes Fluoropyrimidine Chemotherapy Safer," *American Journal of Health-System Pharmacy* 81 (2024): e197–e198, <https://doi.org/10.1093/ajhp/xxae058>.
20. T. T. Ho, D. M. Smith, C. L. Aquilante, et al., "A Guide for Implementing DPYD Genotyping for Systemic Fluoropyrimidines Into Clinical Practice," *Clinical Pharmacology and Therapeutics* 117 (2025): 1194–1208, <https://doi.org/10.1002/cpt.3567>.
21. H. H. Sukkarieh, T. AlSagoor, M. Alnuhait, et al., "Awareness and Attitudes of Oncology Specialists Toward Dihydropyrimidine Dehydrogenase Testing in Saudi Arabia," *Cancer Reports* 6 (2023): 3–6, <https://doi.org/10.1002/cnr2.1704>.
22. C. C. Okechukwu, X. Ma, N. Sah, C. Mani, K. Falle, and W. H. Gmeiner, "Enhanced Therapeutic Efficacy of the Nanoscale Fluoropyrimidine Polymer CF10 in a Rat Colorectal Cancer Liver Metastasis Model," *Cancers (Basel)* 16 (2024): 1360, <https://doi.org/10.3390/cancers16071360>.
23. N. Sah, A. A. Shaik, G. Acharya, et al., "Receptor-Based Strategies for Overcoming Resistance in Cancer Therapy," *Receptor* 3 (2024): 425–443, <https://doi.org/10.3390/receptors3040021>.
24. N. A. Almashagbah, A. A. Mahasneh, and K. G. Bodoor, "Pharmacogenetic Study of the Dihydropyrimidine Dehydrogenase Gene in Jordanian Patients With Colorectal Cancer," *Asian Pacific Journal of Cancer Prevention* 23 (2022): 3061–3069, <https://doi.org/10.31557/APJCP.2022.23.9.3061>.
25. Y. Zhou and V. M. Lauschke, "Comprehensive Overview of the Pharmacogenetic Diversity in Ashkenazi Jews," *Journal of Medical Genetics* 55 (2018): 617–627, <https://doi.org/10.1136/jmedgenet-2018-105429>.
26. E. Goljan, M. Abouelhoda, M. M. ElKalioby, et al., "Identification of Pharmacogenetic Variants From Large Scale Next Generation Sequencing Data in the Saudi Population," *PLoS One* 17 (2022): e0263137, <https://doi.org/10.1371/journal.pone.0263137>.
27. N. J. Ahmed, A. S. Alrawili, and F. Z. Alkhwaja, "Knowledge and Awareness on Personalized Medicine Amongst Health Care Specialists and University Students in Health Colleges in Saudi Arabia," *Journal*

of *Pharmaceutical Research International* 32, no. 16 (2020): 177–183, <https://doi.org/10.9734/jpri/2020/v32i1630741>.

28. M. Algahtani, "Knowledge, Perception, and Application of Pharmacogenomics Among Hospital Pharmacists in Saudi Arabia," *Risk Management and Healthcare Policy* 13 (2020): 1279–1291, <https://doi.org/10.2147/RMHP.S267492>.

29. X. Nie, T. Jia, X. Hu, et al., "Clinical Pharmacists' Knowledge of and Attitudes Toward Pharmacogenomic Testing in China," *Journal of Personalized Medicine* 12 (2022): 1348, <https://doi.org/10.3390/jpm12081348>.

30. T. Obara, S. Abe, M. Satoh, S. R. Gutiérrez Ubieda, S. Yoshimachi, and T. Goto, "Awareness Regarding Clinical Application of Pharmacogenetics Among Japanese Pharmacists," *Pharmacogenomics and Personalized Medicine* 8 (2015): 35–41, <https://doi.org/10.2147/PGPM.S71813>.

31. C. A. T. C. Lunenburg, C. H. van der Wouden, M. Nijenhuis, et al., "Dutch Pharmacogenetics Working Group (DPWG) Guideline for the Gene–Drug Interaction of DPYD and Fluoropyrimidines," *European Journal of Human Genetics* 28 (2020): 508–517, <https://doi.org/10.1038/s41431-019-0540-0>.

32. K. Koo, A. Pasternak, L. Henry, V. Sahai, and D. Hertz, "Survey of US Medical Oncologists' Practices and Beliefs Regarding DPYD Testing Before Fluoropyrimidine Chemotherapy," *JCO Oncology Practice* 18 (2022): 3–6.

33. M. De With, A. Sadlon, E. Cecchin, et al., "Implementation of Dihydropyrimidine Dehydrogenase Deficiency Testing in Europe," *ESMO Open* 8, no. 2 (2023): 101197, <https://doi.org/10.1016/j.esmoop.2023.101197>.

ملخص

العوامل الجينية الدوائية والعوامل السريرية المرتبطة بالآثار الجانبية لأدوية الفلوروبيريميدينات عند مرضى السرطان الفلسطينيين

إعداد: محمد خلف علي ادويب

إشراف: د. حسين حلاق

مقدمة: تُعدّ الفلوروبيريميدينات، وهي أحد أهم النواع في العلاج الكيميائي الحديث، من بين أكثر أدوية السرطان شيوعًا وفعالية من حيث التكلفة حول العالم. يعاني ما بين 10% و 40% من المرضى من سمية شديدة، وربما مميتة، خلال الدورات الأولى من علاج الفلوروبيريميدينات. يؤدي نقص إنزيم دي بي دي، الناتج أساسًا عن طفرات مُمرضة في جين دي واي بي دي، إلى ضعف في اخراج الفلوروبيريميدينات، ويؤدي إلى تراكم مفرط لنواتجها السامة. أصبح اختبار طفرات دي واي بي دي قبل بدء العلاج استراتيجية مُوصى بها دوليًا. وقد وُجد أن عوامل أخرى، مثل العمر والجنس واستخدام أدوية أخرى، تؤثر على حدوث سمية الفلوروبيريميدينات. على الرغم من الفائدة المُثبتة لاختبارات الجينات الدوائية، لا تزال العديد من الدول لا تستخدم هذا الاختبار بشكل كافٍ بسبب عوامل عديدة، مثل نقص الموارد. تُمثل فلسطين أحد التحديات التي تواجهها الدول ذات الدخل المنخفض والمتوسط في تبني علم الجينات الدوائية بشكل عام. الهدف: هدفت هذه الدراسة، من خلال تصميمها الشامل، إلى تقييم أهمية الاختبارات الجينية الدوائية في تحسين النتائج السريرية لمرضى السرطان في فلسطين من خلال استكشاف معرفة أخصائيي الأورام ومرضى السرطان فيما يتعلق بالاختبارات الجينية الدوائية، وتحديد العلاقة بين طفرات جين دي واي بي دي والعوامل السريرية الأخرى وحدث الآثار الجانبية لأدوية الفلوروبيريميدينات المضادة للسرطان.

المنهجية: الدراسة الأولى دراسة مقطعية استخدمت استبيانًا وُزَّعَ على أطباء الأورام، والأطباء المقيمين في قسم الأورام، والصيادلة السريريين في مستشفيات مختلفة في فلسطين بين شباط وإيار 2024. استُوحى الاستبيان من دراسة سابقة أُجريت في المملكة العربية السعودية، وعُدَّ بشكل طفيف ليناسب السياق الفلسطيني.

الدراسة الثانية أيضًا دراسة مقطعية استخدمت استبيانًا وُزَّعَ على مرضى السرطان الذين عولجوا بالعلاج الكيميائي في ثلاث عيادات أورام خارجية في الضفة الغربية في فلسطين. طُوِّرَ الاستبيان بناءً على مراجعة شاملة للأدبيات لدراسات مماثلة.

في الدراسة الثالثة، استُخرج الحمض النووي (دي أن إيه) من عينات دم مرضى السرطان الذين يستخدمون الفلوروبيريدينيات بطريقة بعد استخدام محاليل عازلة قياسية مُجهزة مسبقًا. أُجري تفاعل البوليميراز المتسلسل (بي سي آر) الخاص بالأليل في تفاعلات سعة 25 ميكرولتراً باستخدام مزيج رئيسي مناسب، وبادئات، ونموذج حمض نووي، وماء خالٍ من النوكلياز. حُسبت درجة نشاط الجين بتعيين قيم لكل أليل (طبيعي = 1، انخفاض الوظيفة = 0.5، انعدام الوظيفة = 0) وجمع كلا الأليلين. تم الحصول على البيانات السريرية ومعلومات السمية من خلال تحليل موحد للسجلات الصحية الإلكترونية للمرضى من قبل فريق دراسة مُدرَّب. شملت الآثار الجانبية الشديدة حالات سمية لا تقل عن 3 درجات، وذلك وفقًا لمعايير المصطلحات الشائعة للآثار الجانبية للمعهد الوطني للسرطان، الإصدار 5.0.

النتائج:

الدراسة الأولى - مقدمو الرعاية الصحية

أكمل الاستبيان من قبل 106 من مقدمي الرعاية الصحية، منهم 57.5% أطباء متخصصون، و27.4% صيادلة سريريين، و15.1% أطباء مقيمون. أفاد أكثر من 70% من المشاركين بأنهم لم يتلقوا تدريبًا رسميًا في علم الجينيات الدوائي خلال مسيرتهم المهنية. أشار حوالي 80% من المشاركين إلى معرفتهم بالطفرة المرتبطة بنقص إنزيم دي بي دي وعواقبه على سمية أدوية الفلوروبيريدينيات. أشار أقل من 50% من المشاركين إلى أنهم يقومون بفحص نقص إنزيم دي بي دي بشكل مستمر أو من حين لآخر قبل وصف أدوية الفلوروبيريدينيات. أفاد 5.7% و6.6% فقط

من المشاركين، على التوالي، بوجود اختبار موحد لإنزيم دي بي دي، وتشجيع وزارة الصحة الفلسطينية على إجراء اختبار دي بي دي قبل وصف أدوية الفلوروبيريبيديونات. عانى حوالي 60% من الأفراد من سمية كبيرة مرتبطة بأدوية الفلوروبيريبيديونات، وهي نسبة أعلى بكثير من المتوسط العالمي الذي يتراوح بين 10% و 30%.

الدراسة الثانية: المرضى

شملت الدراسة 368 مشاركًا بتوزيع شبه متساوٍ بين الجنسين (52.4% إناث، 47.6% ذكور). ولم يسمع سوى 19.8% من المشاركين عن الاختبارات الجينية الدوائية، بينما خضع أقل من 5% منهم لأي لهذا الاختبار. وأفاد ثلث المشاركين بعدم فهمهم لطبيعة هذا الاختبار. ويعتقد حوالي 40% من المشاركين أن الاختبارات الجينية الدوائية يمكن أن تساعد الأطباء في اختيار أفضل علاج، بينما يثق 44% منهم بدقتها. وأشار أقل من نصف المشاركين (42%) إلى أنهم سيخضعون للاختبار إذا أوصى به طبيبهم. وكان أكثر من نصف المشاركين (53%) على استعداد لدفع ثمن الاختبار، بمتوسط استعداد للدفع يبلغ حوالي 230 شيكل جديد، وبتكلفة معقولة متصورة تبلغ حوالي 1307 شيكل جديد. وكان معظم المشاركين (74%) على استعداد لتقديم عينة دم للاختبار.

الدراسة الثالثة - البيانات الجينية والسريرية

شملت الدراسة 134 مشاركًا. وُجد أن نسبة كبيرة (85.1%) من المشاركين لديهم أيض طبيعي (درجة نشاط 2)، بينما كان 13.4% منهم لديهم أيض متوسط (درجة نشاط 1-1.5)، و 1.5% منهم لديهم أيض ضعيف (درجة نشاط 0-0.5). بلغت نسبة حدوث الآثار الجانبية من الدرجة اكبر او يساوي 3 في العينة 17.2%. وكانت متلازمة اليد والقدم والتعب الشديد أكثر الآثار الجانبية شيوعًا. عانى كلا المريضين ذوي الأيض الضعيف من آثار جانبية، مقارنة بثلاث (33.3%) من ذوي الأيض المتوسط و 13.2% من ذوي الأيض الطبيعي. من بين حاملي الطفرة الذين عولجوا دون تعديل الجرعة، عانى 63.6% من الآثار الجانبية، بينما عانى 11.1% فقط من حاملي الطفرة الذين عولجوا بجرعات معدلة من آثار جانبية. انقطع العلاج لدى 6.7% من المشاركين وتوقف تمامًا لدى

7.5% منهم. تم الإبلاغ عن دخول المستشفى بسبب الآثار الجانبية والمضاعفات لدى 9.7% من الحالات.

الاستنتاج:

تدعم هذه النتائج الفرضية الرئيسية القائلة بأن طفرات جين دي واي بي دي مرتبطة بالآثار الجانبية لـ الفلوروبيريميدينات، وأن تحديد الجرعات بناءً على النمط الجيني يمكن أن يُحسّن من سلامة العلاج. أظهر المرضى الفلسطينيون وعيًا محدودًا، ولكن قبولًا متوسطًا لعلم الجينات الدوائية.