

ASPAN ACADEMIC JOURNAL

PEER-REVIEWED RESEARCH BY SECONDARY
AND UNDERGRADUATE STUDENTS

PART 1, ISSUE 1

SEPTEMBER 2026

ASPANACADEMICJOURNAL.COM

EDITORIAL STAFF

EDITOR-IN-CHIEF

Dauren Omarbekov

EDITORS

Helix Nguyen

Nisha Verma

Alishba Syed

Hiya Bhagat

Andrea Estevão

Yewon Kim

Rishi Saxena

Aspan Academic Journal charges no submission, review or publication fees.

aajjournal@gmail.com

TABLE OF CONTENTS

Page 4: Dark Stars: A Cosmic Mystery with a Little Touch of Dark Dwarfs by William Heise
Page 8: To What Extent Do the Economic Benefits of Climate Change Mitigation Outweigh the Costs of Mitigation? by Kiara Shah
Page 27: Digital Diagnosis: Health Misinformation and Behavioral Changes Among Kazakhstani Youth by Aiym Shunshalina
Page 38: To What Extent Has Econophysics Been Successful as an Interdisciplinary Framework for Explaining Economic Systems and Market Phenomena? by Darsh Mishra
Page 56: Evaluating the Efficiency of AI Algorithms in the Early Detection of Pancreatic Ductal Adenocarcinoma via CT scans by Rudra Patel
Page 60: Myanmar Crisis: Rohingya Residents Fleeing for Refuge by Nisha Verma
Page 65: CRISPR Cas-9 as a Potential Cure for Wilson's Disease by Satoshi Toya
Page 112: Abstract Defiance: Fernando Zóbel and the Rise of Spanish Abstract Art in Francoist Spain by Natalia C. Siy
Page 132: BIASES IN MEDICAL DECISION MAKING by Ece Marangoz
Page 147: A Tale of Ghosts, Vengeance, and Greed (Except For When It Is Not): The History of Yotsuya Kaidan and its Adaptations by Liv Adao

Dark stars a cosmic mystery with a little touch of **Dark dwarfs**

By: William Heise

This article explores dark stars fueled by dark matter! There will be theories that align with current astrophysics with established facts in this article.

(Key Words) Dark Star, Dark Matter, Black hole, Hydrogen, Helium

What is a Dark Dwarf?

A dark dwarf is a theoretical object theorized by Jeremy Sakstein, Djuna Croon, Juri Smirnov, and Jack Streeter in late 2024 but formally published in 2025. The main idea of the article is that dark dwarfs formed just like a normal star but just less hydrogen and helium than a star like our sun. The main idea is that they form, like most brown dwarfs, dark dwarfs would be a rare group which means almost all brown dwarfs are normal fusion stars and most dark dwarfs are brown dwarfs. How they turn into dark dwarfs is because when there are in the center of the galaxy where a lot of dark matter particles would be, then the dark matter particles get absorbed by the star.

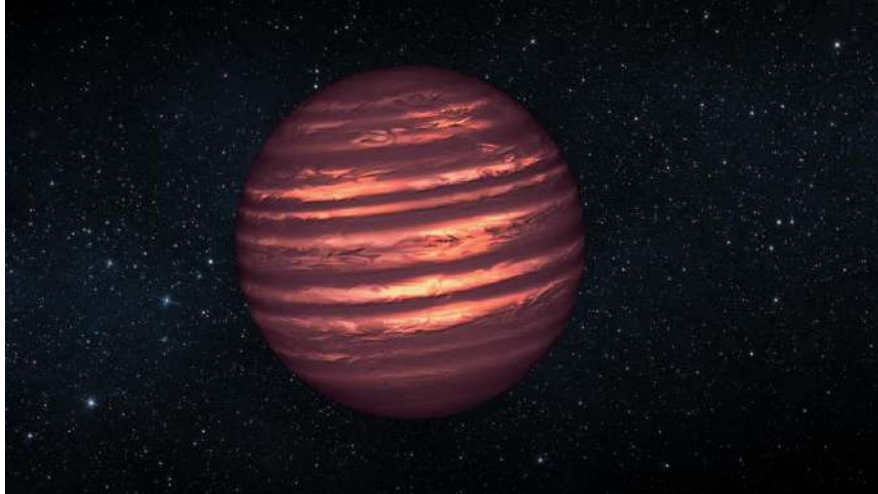
Since they do not interact with light, they go straight to the center because of the gravity of the star and start producing energy. This is proven by an astrobites article on dark stars; “The energy carried out of the inner stellar core by the dark matter particles”(Fabio Iocco, Marco Taoso, Florent Leclercq, and Georges Meynet; authors of the

article.) In the quote it says, "Energy from the core is carried by dark matter."

This mechanism only happens with a star that has less mass than our sun.

What do The Dark Matter Particles do in a Dark Dwarf?

When a brown dwarf or another small star captures dark matter, it collides with atoms and the atoms gain kinetic energy which means they get hotter. That makes the dark matter lose kinetic energy. According to the researchers Alain, Bouquet, and Pierre Salati, this happens because of the weak nuclear force which causes elastic scattering. When these dark matter particles lose kinetic energy they become concentrated and when concentrated they can collide more often because since they are in a dense state they become hotter which makes them collide. Dark matter can power stars under 0.075 solar masses because these stars are small enough to concentrate dark matter. Most of the time they are brown dwarfs that are very dim stars. It can easily power them by releasing pure energy, even though it's really good at making energy, nuclear fusion is way better at making energy than dark matter annihilation by WIMPS which are theoretical particles which stand for (Weakly Interacting Massive Particles). The reason nuclear fusion is better than dark matter for powering stars is because in more massive stars when it has enough gravity to fuse hydrogen, it dominates since bigger stars than dark dwarfs have lots more hydrogen and helium. Even though dark matter particles release more energy when they collide.



Brown dwarfs are stars that dark matter particles would flourish in. (image credit NASA/JPL-Caltech)

How to Find Dark Dwarfs

2.5 million kelvin is where lithium-7 starts to become apart of a star's nuclear fusion process. Bigger stars are hotter and go past the threshold of 2.5 million Kelvin. Since smaller stars like brown dwarfs are cooler than most other stars, it preserves lithium-7. Dark dwarfs have a lower temperature than 2.5 million kelvin which dark matter would power the star or nuclear fusion would happen which means this star is burning its energy abnormally. Telescopes like The James Webb Space Telescope, (or JWST) can find it in the light of these stars since it is in the star the light interacts with that gas. If we find lithium-7 in a large quantity in a small star it would provide evidence that dark dwarfs exist. We would likely find them in the center of galaxies. But we have never observed any dark dwarfs, they are still a theory.

Dark matter stars: The big gas clouds

Now the real first theorized Dark Matter Stars were made by Katherine Freese, Douglas Spolyar, and Paolo Gondolo in 2007. How these dark matter stars form is crazy, what happens is a big gas cloud is made mostly of hydrogen and helium. A dense “cloud” of dark matter is gravitationally attracted to the gas cloud of hydrogen and helium, and mixes with the gas cloud. Now when a star passes through this dense region of dark matter. The star captures dark matter particles because there are dark matter particles in this gas cloud and it becomes a dark matter star that is really bright. Another possibility, the gas cloud of hydrogen and helium collapses with the dark matter and forms a dark matter star. This would have happened about 200 million years after the big bang.

Sources:

(Iocco, Fabio, Taoso, Marco, Leclercq, Florent, and Meynet, George) Dark matter inside a star. Astrobites, February 12th. 2012.

(This was a summary of the work done by Freese, Katherine Spolyar, Douglas, Gondolo, Paolo. Dark matter Stars. Physical Review Letters, February 7th. 2008.)

(Bouquet, Alain, Salati, Pierre) Dark Matter Suppression on Stellar Core Convection. Astrophysical Journal, November 15th. 1989.

(Sakstein, Jeremy, Croon, Djuna, Smirnov, Juri and Streeter Jack) The Journal Of Cosmology and Astroparticle Physics. July 7th. 2025

To what extent do the economic benefits of climate change mitigation outweigh the costs of mitigation?

Author: Kiara Shah

Abstract

Climate change has emerged as one of the most significant economic challenges of the twenty-first century, generating substantial costs through its effects on agriculture, infrastructure, labour productivity, supply chains, and public finances. This paper evaluates the economic impacts of climate change mitigation by comparing the costs of mitigation with the economic consequences of inaction, while examining strategies to reduce mitigation costs and the distributional imbalances of climate policy. The study adopts a mixed-methods approach, combining qualitative analysis of economic theory and policy literature with quantitative evidence from secondary data, including macroeconomic projections, institutional reports, and peer-reviewed research.

The findings indicate that the long-term economic costs of failing to mitigate climate change substantially exceed the costs of implementing mitigation measures. Climate-related damages are shown to compound across interconnected sectors, reducing economic output, increasing fiscal pressures, and widening inequalities between developed and developing economies. The analysis further demonstrates that technological innovation, carbon pricing, policy coordination, renewable energy deployment, and energy efficiency improvements can significantly reduce mitigation costs while generating long-term economic and social benefits. However, barriers including high upfront investment requirements, policy uncertainty, institutional weaknesses, and unequal access to finance continue to slow the transition to low-carbon economies.

The paper concludes that climate change mitigation should be regarded as a corrective economic investment rather than a financial burden. Early, coordinated, and equitably financed mitigation policies are likely to deliver substantially greater long-term economic benefits than delayed action, while also reducing the disproportionate impacts of climate change on vulnerable regions.

Introduction

Climate change refers to long-term shifts in temperatures and weather patterns. Such shifts can be natural, due to changes in the sun's activity or large volcanic eruptions. But since the 1800s, human activities have been the main driver of climate change, primarily due to the burning of fossil fuels like coal, oil and gas (United Nations).

From an economic perspective, climate change represents a case of market failure arising from negative externalities. Producers and consumers of emissions-intensive goods and services bear only their private costs, while many of the damages associated with greenhouse gas emissions are imposed on society as a whole. Because these social costs are not reflected in market prices, emissions-intensive goods and services are produced and consumed in quantities greater than the socially optimal level. This inefficient allocation of resources provides the economic justification for climate change mitigation policies, which seek to internalize these external costs and align private decision-making with broader social welfare.

This paper will evaluate the economic impacts of climate change mitigation by comparing the costs of mitigation with the costs of inaction, examining strategies to reduce mitigation expenses and discussing the global distribution of impacts.

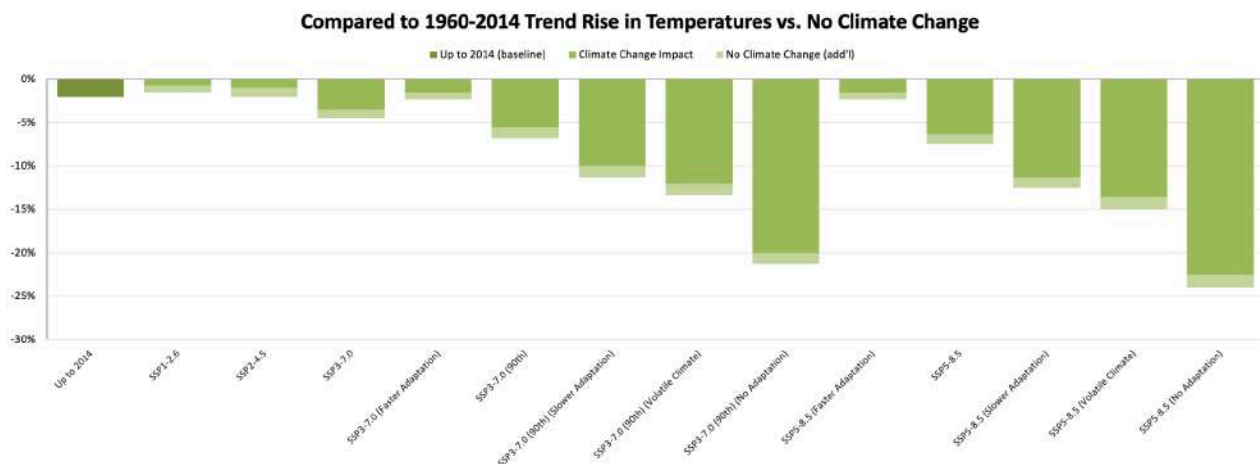


Figure 1. Change in GDP in scenarios with different degrees of climate change

Source: Eos, American Geophysical Union, adapted by the author.

Climate-related losses represent an immediate economic threat rather than a remote abstraction, with recent estimates projecting annual global costs across agriculture, infrastructure, labor productivity, and public health (Hart). This is a cumulative burden - from declining crop yields and heat-related illnesses to disrupted supply chains, climate-induced migration, and infrastructure repair amid floods, droughts, storms, and sea-level rise. As these pressures mount, they not only erode aggregate output but amplify regional inequalities - Sub-Saharan Africa could lose around 12% of GDP by 2050 and Europe and North America both losing 1-3% (IPCC, "Chapter 9").

Long-term climate projections reinforce the scale of this challenge.

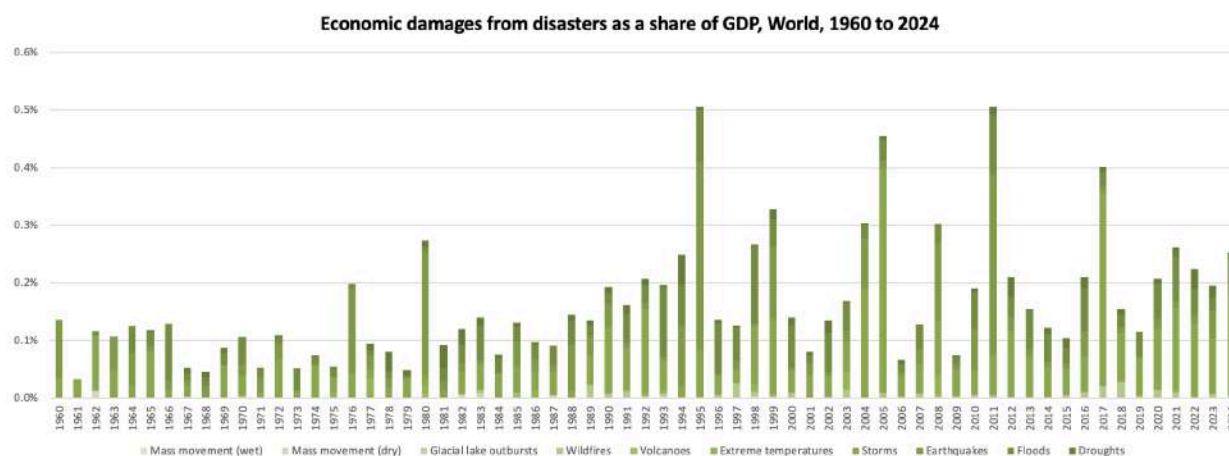


Figure 2. Economic damages from disasters as a share of GDP, World, 1960 to 2024.

Source: Our World In Data, adapted by the author.

Figure 2 shows a clear upward shift in recent decades, with higher peaks becoming more frequent over time.

In 2022, climate-related disasters generated an estimated \$313 billion in global losses (Aon). The following years have offered little reprieve. In lower-income and climate-vulnerable regions, the impacts are chronic rather than episodic: in Bangladesh, recurrent flooding is estimated to cause around \$3 billion in economic losses each year (World Bank Group). High-income economies are not insulated from these pressures - Hurricane Milton in 2024 resulted in approximately \$75 billion in damage in the United States, exposing the financial consequences of climate-intensified extremes even in affluent countries (Gallagher Re). Together, these examples illustrate how climate change produces sustained economic harm regardless of economic development level.

Methodology

This study adopts a mixed-methods research design, combining qualitative and quantitative analysis, using secondary data. The qualitative component involves analysing economic literature, policy reports, and theoretical frameworks to understand the mechanisms through which climate change affects economic outcomes and how mitigation policies influence these effects. The quantitative analysis relies on numerical projections from existing economic models and datasets, including estimates of GDP loss, mitigation costs, and sectoral impacts.

The research relies exclusively on secondary data obtained from peer-reviewed academic literature, economic modelling studies, and institutional policy reports. Key sources include publications from the IPCC, International Monetary Fund, International Energy Agency, International Labour Organization, and World Bank, alongside peer-reviewed research such as Somanathan et al. These sources provide macroeconomic projections, sector-specific impact assessments, estimates of mitigation costs, and evidence on labour productivity and climate vulnerability.

Sources were selected based on credibility, methodological transparency, and relevance to climate-economics research. Preference was given to peer-reviewed studies and publications from international economic institutions, as these typically employ established economic modelling techniques and large datasets.

This essay follows a layered structure, starting with costs of inaction, comparing them with investment and transition costs of mitigation, and finally considering whether policy design can reduce mitigation costs and their distribution across income groups.

Several economic concepts guide the analysis, including market failure due to negative externalities, public goods problems, and intergenerational cost–benefit analysis. Climate change is analysed as a global externality in which the social cost of emissions exceeds private costs, leading to inefficient market outcomes. The paper therefore evaluates mitigation policies as mechanisms for correcting this market failure.

This study relies on secondary data and long-term economic projections, which involve uncertainty. Climate-economics models depend on assumptions about future technological development, policy implementation, and climate sensitivity, which may change over time. As a result, estimates of future economic damages and mitigation costs may vary across studies.

Another limitation is that macroeconomic indicators such as GDP may not fully capture non-market impacts, including biodiversity loss or social disruption caused by climate-induced migration. Additionally, some data sources focus primarily on global averages, which may mask regional variations in climate vulnerability.

Costs of Climate Change and Mitigation Strategies

Climate change generates substantial economic costs through disruptions to agriculture, infrastructure, labor productivity, supply chains, and public finances. These effects result from increased frequency and intensity of extreme weather events, altered precipitation patterns, and rising temperatures, leading to direct damages, reduced output, and long-term fiscal burdens. Cumulative global losses from climate-related disasters exceeded \$4.5 trillion (inflation-adjusted) between 1995 and 2024 across over 9,700 events (“Climate Risk Index 2026”).

Extreme weather events such as droughts, floods, and heatwaves reduce crop yields, impair livestock productivity, and degrade soil quality, resulting in higher food prices, increased import reliance, and food insecurity. These impacts extend beyond immediate harvest losses to long-term land degradation, like salinity intrusion and erosion, that diminishes arable land and discourages investment in agricultural inputs. For instance, Bangladesh incurs approximately \$3 billion in annual losses from flooding and salinity, with rice yields in delta regions like Khulna declining by up to two-thirds (World Bank Group); similarly, Sahel droughts cost \$15-20 billion yearly through crop failures in Mali and Niger (“Mali: Strengthening Financial Resilience”).

This agricultural vulnerability disproportionately burdens lower-income economies, where primary sectors comprise 20-40% of GDP and employ over 60% of the workforce, compared to less than 5% in high-income nations (World Bank). The resulting output contractions exacerbate poverty traps, limit fiscal capacity for diversification, and amplify food insecurity, underscoring the sector's role as a critical transmission channel for climate-induced economic inequality.

Storms, floods, sea-level rise, and wildfires damage transportation networks, energy infrastructure, ports, and urban assets, incurring high reconstruction costs and extended economic interruptions. Secondary effects include reduced property values, business closures, and displacement, which further magnify these impacts.

Hurricane Milton in 2024 exemplifies the economic consequences of climate-related disasters, causing an estimated \$75 billion in total economic losses in The United States, including crop damage and widespread power outages disrupting commerce (Gallagher Re).

These infrastructure vulnerabilities impose asymmetric burdens on developing economies, where transport and energy networks often represent a high portion of GDP and exhibit lower redundancy compared to high-income countries' diversified systems. The resulting repair backlogs curtail growth dividends, exacerbate debt vulnerabilities, and hinder trade competitiveness, positioning infrastructure as a primary vector for climate-driven economic divergence between low- and high-capacity regions.

Higher temperatures and humidity reduce physical work capacity in heat-vulnerable sectors, leading to fewer effective labor hours, increased absenteeism, and elevated healthcare costs from heat-related illnesses. These losses disproportionately affect informal and outdoor workers, with ripple effects on industrial output and economic growth. In India, heat stress is projected to reduce working hours by 5.8% by 2030 (International Labour Organization 58), while annual manufacturing output falls by roughly 2% for each 1°C increase in temperature (Somanathan et al. 1815).

Weather extremes disrupt logistics infrastructure, including ports, rivers, and rail lines, increasing transport costs, causing shortages, and inflating prices across global trade networks. Prolonged recovery periods hinder exports, industrial production, and economic stabilization, particularly in export-dependent economies. Pakistan's 2022 floods illustrate this, generating \$30 billion in damages that reduced agricultural GDP by 0.9% and overall GDP by 2.2% through crop destruction in Sindh and Balochistan, alongside trade interruptions requiring \$16 billion in reconstruction; such events typically contract GDP by 1-2% while driving 4-6% food inflation (World Bank).

Supply chains amplify these shocks due to their high interdependence and reliance on just-in-time (JIT) inventory systems, where firms minimize buffer stocks to optimize capital efficiency. Climate disruptions create cascading failures: a single port closure delays components for manufacturers continents away, while inland waterway droughts (e.g., Rhine or Mississippi) sever multi-modal links, forcing costly air freight or production halts. In JIT-dominated sectors like automotive and electronics, holding 2-4 weeks' inventory, such interruptions can idle assembly lines for weeks, multiplying localized weather events into billions in global output losses and exposing the fragility of lean globalization models to climate volatility.

The sectoral analysis shows that climate change's economic costs do not accumulate in isolation but compound through interlinkages between sectors, with each channel amplifying the others over time. Agricultural yield losses drive food price inflation, which strains household budgets and slows consumption-led growth; this occurs alongside infrastructure damage that disrupts supply chains and prolongs business downtime, feeding back into labour productivity losses that reduce the tax base governments rely on to fund disaster response. This final link is particularly significant because fiscal capacity determines whether a country can invest in adaptation and resilience or become locked into repeated, increasingly costly recovery cycles.

In the short term, infrastructure damage and labour productivity losses tend to dominate, as immediate physical destruction and lost working hours are the most visible and quantifiable costs, seen in approximately \$75 billion in Hurricane Milton losses across the United States (Gallagher Re) and India's projected 5.8% working-hour losses by 2030 (International Labour Organization 58). Over the long term, however, agricultural and fiscal impacts arguably become

more significant, since degraded land and weakened public finances constrain a country's capacity to adapt to future shocks, contributing to the persistent economic losses evident in Bangladesh's recurring \$3 billion annual flood losses and Pakistan's 2.2% GDP contraction after the 2022 floods. This distinction has important policy implications: while short-term damages can often be addressed through emergency relief and reconstruction, the long-term interaction between declining fiscal space and reduced adaptive capacity requires sustained mitigation and resilience investment rather than repeated crisis response.

Climate change generates compounding economic costs because its impacts reinforce one another. Agricultural losses reduce food supply and raise prices, infrastructure damage disrupts production and trade, while declining labour productivity lowers output and household incomes. These interlinked shocks weaken long-run productive capacity, as repeated climate disasters divert capital from productive investment towards reconstruction, reduce private investment through heightened uncertainty, and slow capital accumulation.

Agriculture illustrates this dynamic most clearly. Rising temperatures, changing precipitation patterns and more frequent droughts are projected to reduce crop yields by 10-25% in many tropical regions by mid-century, increasing food price inflation and import dependence (“Chapter 5: Food, Fibre”). Because agriculture accounts for a significantly larger share of employment and GDP in developing economies, these losses reduce household incomes, weaken domestic demand and shrink government revenues simultaneously. Lower fiscal capacity limits investment in diversification, education and infrastructure, reinforcing poverty traps and making future climate shocks increasingly difficult to absorb.

Infrastructure damage further amplifies these losses. Climate-related floods, storms and sea-level rise threaten transport networks, ports, power grids and housing, while the economic cost extends far beyond reconstruction itself. Damaged infrastructure interrupts production, delays exports and fragments supply chains, reducing business activity for prolonged periods. In an increasingly interconnected global economy, disruptions in one region transmit through just-in-time production networks, raising logistics costs and causing shortages elsewhere. These spillover effects reduce trade efficiency and lower overall economic productivity, particularly in export-oriented developing economies with limited infrastructural redundancy.

Climate change also reduces labour productivity by directly constraining the quantity and quality of work that can be performed. The ILO estimates that heat stress alone could generate the equivalent of 80 million full-time jobs lost globally by 2030, primarily affecting agriculture, construction and other outdoor industries (International Labour Organization 26). Higher temperatures also increase illness, absenteeism and healthcare expenditure, further lowering effective labour supply. Since developing economies employ a larger proportion of workers in informal and outdoor sectors, productivity losses translate into disproportionately larger reductions in output and household income.

These sectoral impacts ultimately converge into a fiscal challenge. Climate shocks simultaneously increase public expenditure through disaster relief, reconstruction and healthcare while reducing tax revenues as economic activity contracts. Governments therefore finance widening fiscal deficits through additional borrowing, increasing sovereign debt burdens and, in many cases, weakening credit ratings and raising future borrowing costs. As debt servicing absorbs a growing share of public budgets, investment in education, infrastructure and productive capital is crowded out, further constraining long-term economic growth. In this sense, climate mitigation should be viewed not simply as an environmental objective but as a preventative economic investment that preserves productive capacity, reduces future fiscal liabilities and avoids the compounding costs of delayed action.

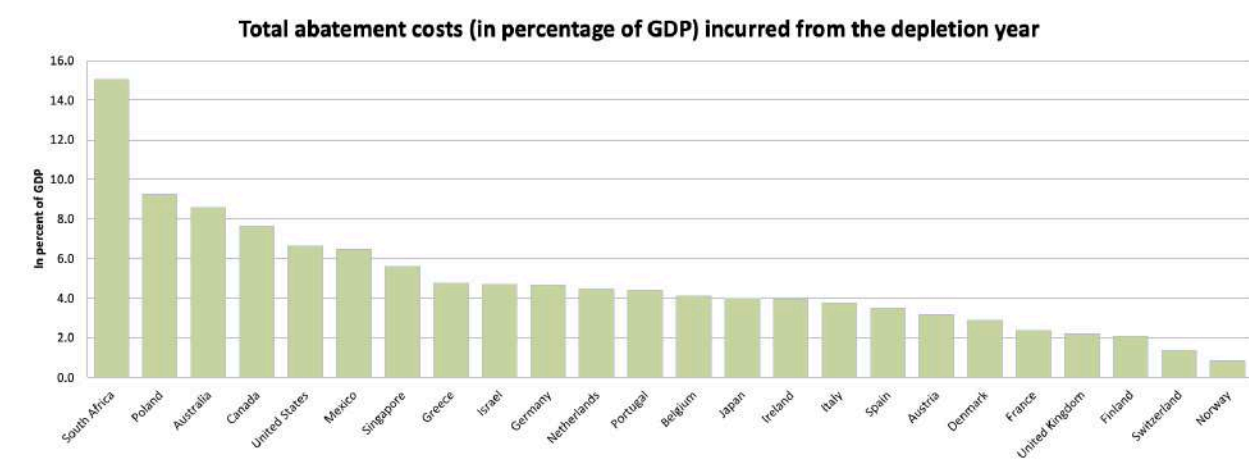


Figure 3. Total abatement costs as a percentage of GDP by country.

Source: International Monetary Fund (IMF), World Economic Outlook, adapted by the author.

To address these economic challenges, a range of mitigation strategies has been identified that can significantly reduce the overall cost of decarbonisation. These include energy efficiency improvements (reducing abatement by 20-40%), demand reductions, low-cost electrification via renewables/carbon, dietary shifts cutting land-use emissions, and capital reallocation to low-carbon sectors with net positive returns (“Chapter 5: Demand, Services”).

Technological innovation is one of the most important forces shaping mitigation costs. Over the past two decades, the price of renewable energy technologies - particularly solar and wind - has declined dramatically. Much of this decline reflects familiar economic processes such as learning-by-doing, economies of scale, and cumulative investment. As deployment expands, technologies tend to become cheaper and more efficient. This dynamic means that early investment can accelerate cost reductions rather than simply adding to them. Integrated assessment models frequently find that policies encouraging innovation reduce long-term

mitigation costs by enabling a more gradual transition and avoiding abrupt adjustments later in the century (IPCC, Climate Change 2023).

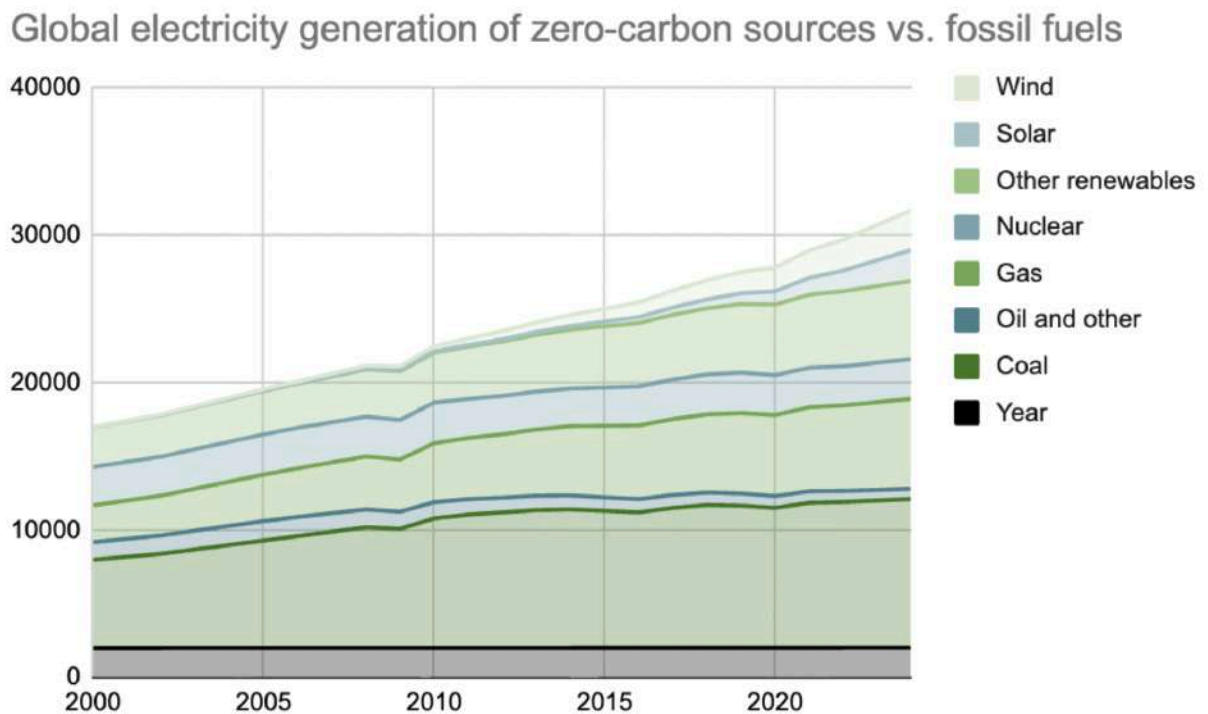


Figure 4. Global Electricity Generation of Zero-carbon Sources vs. Fossil Fuels

Source: World Resources Institute, adapted by the author.

Market-based policy instruments also play an important role. Carbon pricing, whether implemented through taxes or emissions trading systems, attempts to incorporate the social cost of emissions into market decisions. Once emissions carry a price, firms and households have an incentive to identify the least expensive ways of reducing them. Compared with rigid regulatory approaches, such market mechanisms typically allow reductions to occur where they are cheapest, lowering the total cost of achieving a given emissions target (Nordhaus 1518–23). In some cases, governments also recycle carbon pricing revenues - by reducing other taxes or providing transfers - which can further moderate the economic impact.

Carbon Pricing Around The World, 2026

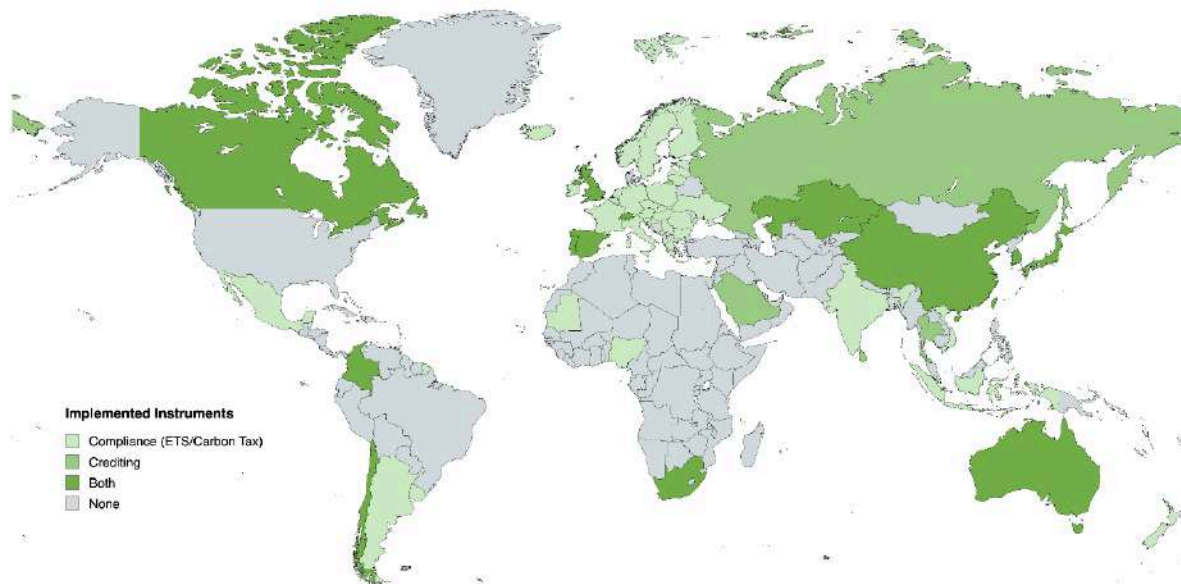


Figure 5. Carbon Pricing Instruments Around The World

Source: World Bank Group, adapted by the author.

Institutional design and policy coordination are also critical determinants of mitigation costs because they influence investment incentives and the cost of capital. When climate policies are fragmented, inconsistent, or subject to frequent change, they increase regulatory uncertainty, raising the perceived risk of low-carbon investments. Investors consequently demand higher risk premiums, increasing the cost of capital for firms and making clean energy and decarbonisation projects less financially viable. As borrowing costs rise, firms are more likely to delay or reduce private investment in new technologies, slowing the pace of the low-carbon transition. Conversely, credible long-term policy signals - such as legally binding emissions targets, stable carbon pricing mechanisms, and consistent clean energy standards - reduce uncertainty, lower financing costs, and incentivise greater private capital allocation towards low-carbon investments.

This evidence suggests that the economic cost of mitigation depends heavily on policy choices. When supported by innovation, effective markets, and credible policies, mitigation can be achieved at much lower cost. Climate change mitigation encounters significant barriers across economic, political, institutional, technological, and social domains, which collectively hinder the transition to low-emission systems.

The principal financial and market barrier to climate mitigation is not that low-carbon technologies are economically inefficient, but that they require substantial upfront capital despite generating long-term benefits. Renewable energy generation, electricity grids, battery storage,

electric vehicle infrastructure and industrial decarbonisation projects all demand large initial investments, while returns accrue gradually over decades. This financing challenge is particularly acute in developing economies, where higher sovereign risk and borrowing costs increase the cost of capital, making otherwise viable projects financially unattractive. At the same time, fossil fuel subsidies - estimated by the IMF at over \$7 trillion globally in 2022 when explicit and implicit subsidies are included (IMF) - artificially lower the price of carbon-intensive energy, distorting market signals and reducing the competitiveness of cleaner alternatives. Together, high financing costs and distorted price incentives discourage private investment and slow the pace of decarbonisation.

Political and institutional barriers further impede mitigation by increasing policy uncertainty and reducing investor confidence. Climate policies often impose immediate economic costs while their benefits materialise only over the long term, creating a time-inconsistency problem in which governments facing short electoral cycles are reluctant to implement ambitious measures. Lobbying by incumbent fossil fuel industries reinforces this tendency by delaying regulatory reforms and protecting existing assets. Frequent policy reversals, inconsistent carbon pricing and fragmented institutional responsibilities raise uncertainty surrounding future returns on low-carbon investments, increasing the risk premium demanded by investors. As financing costs rise, even economically efficient mitigation projects become more difficult to implement.

Social and distributional barriers also constrain mitigation efforts because the costs and benefits of climate policies are unevenly distributed. Carbon pricing, energy taxes and the removal of fossil fuel subsidies can increase energy and transport costs, disproportionately affecting lower-income households, while workers and regions dependent on fossil fuel industries face significant employment risks during the transition. Behavioral economics further explains resistance through present bias, whereby individuals place greater weight on immediate costs than future environmental and economic benefits, reducing public support for ambitious climate policies. Consequently, successful mitigation often depends on complementary measures such as targeted income support, worker retraining programmes and just transition policies that distribute adjustment costs more equitably while maintaining political support.

Finally, technological and infrastructure constraints limit the speed at which emissions can be reduced. Although renewable electricity has become increasingly cost-competitive, its large-scale deployment depends on expanded transmission networks, grid flexibility and energy storage to address intermittency. Similarly, emerging technologies such as carbon capture and storage (CCS), direct air capture (DAC), bioenergy with carbon capture and storage (BECCS), and advanced nuclear power offer pathways to decarbonise hard-to-abate sectors but remain constrained by high capital costs, technological uncertainty and limited commercial deployment. These challenges are expected to diminish as innovation, economies of scale and technology transfer reduce costs over time, but they remain significant barriers to rapid global mitigation in the near term.

Option	Economic Benefit	Primary Limitation	Best Use-Case
Battery systems (lithium-ion, flow) and smart grids	Stabilise renewable electricity supply, reduce curtailment losses, improves productivity through reliable 24/7 renewable integration.	Battery storage duration remains limited, while dependence on critical minerals (lithium, cobalt, nickel) creates supply chain and geopolitical risks.	Electricity systems with high shares of wind and solar where grid flexibility and storage are needed.
Carbon Capture, Utilization and Storage (CCUS)	Captures large industrial emissions, preserving capital in trade-exposed industries (e.g. cement and steel), and creates new revenue streams from CO ₂ utilisation.	Only economically viable for certain industries and depends on reliable CO ₂ transport and long-term geological storage infrastructure.	Carbon-heavy Industrial sectors where emissions cannot easily or naturally be eliminated.
Reforestation	Removes significant amounts of carbon at a relatively low cost, provides flood protection, enhances biodiversity, and increases agricultural yields.	Carbon benefits may be reversed, reducing the reliability of carbon credits. A large area of land is required to have a significant impact.	Natural carbon removal and ecosystem restoration.
Upgrading buildings, appliances and industry	Reduces energy demand, generates fuel savings and reduces grid expansion requirements.	Retrofitting existing infrastructure is logistically complex and adoption is slowed by split incentives (e.g., landlords pay while tenants benefit).	Improving energy efficiency in residential, commercial and industrial sectors.

EV fleets, charging networks and Hydrogen	Cuts oil imports, improves air quality, and prevents premature deaths annually.	Hydrogen production remains energy-intensive, while EV adoption depends on widespread charging infrastructure and critical mineral availability.	Decarbonising road transport.
---	---	--	-------------------------------

Geographic inequalities in climate change mitigation investments reflect persistent disparities between Global North and Global South regions, as conceptualized by the Brandt Line. This latitudinal divide, proposed in the 1980 Brandt Report, separates relatively affluent Northern economies (above approximately 30°N latitude) from developing Southern ones, a framework that remains pertinent to analyzing uneven mitigation access and climate risk exposure.

The Brandt Line

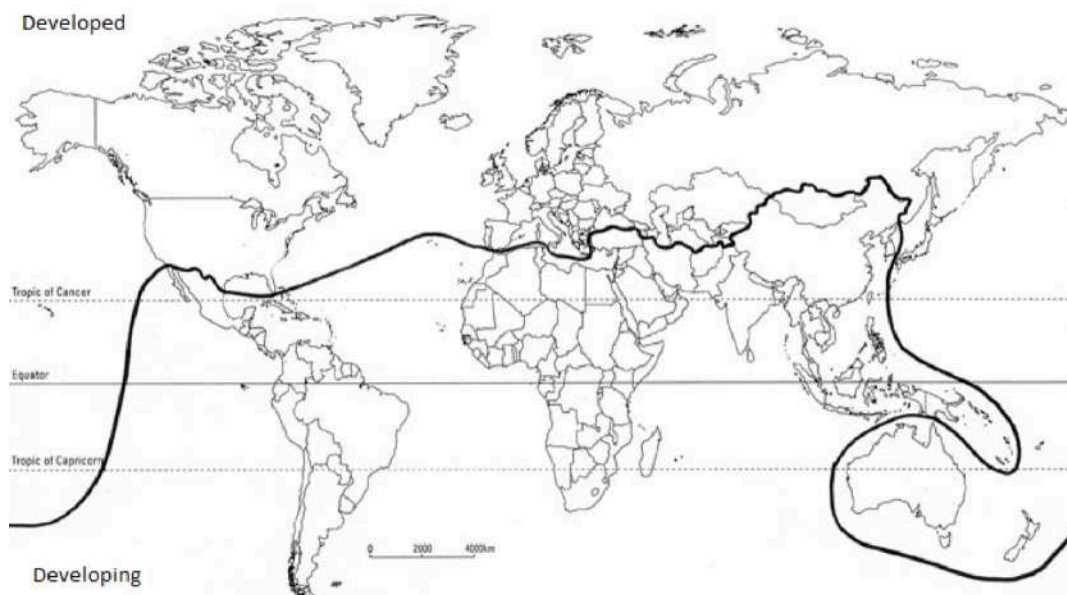


Figure 6. The Brandt Line.

Source: British International Studies Association 2020, theorised by Willy Brandt, 1980

Economies North of the Brandt Line may benefit from temperate climates, robust fiscal capacity, and established infrastructure, facilitating access to 75-80% of global clean energy investment

recorded in 2024 (totaling \$1.8 trillion). These regions experience projected GDP losses of 1-3% by 2050 under unmitigated scenarios, enabling prioritization of advanced technologies such as carbon capture pilots and battery storage (International Energy Agency).

Equitable redistribution, allocating a percentage of mitigation finance as concessional flows to high-risk Southern zones, could mitigate these dynamics and avert global losses, ensuring mitigation efforts enhance rather than exacerbate structural divides.

Conclusion & Evaluation

This paper concludes that climate change imposes significant and compounding economic costs that extend far beyond the immediate damage caused by extreme weather events. Rather than affecting individual sectors in isolation, climate change creates interconnected disruptions across agriculture, infrastructure, labour productivity, supply chains and public finances, with losses in one sector reinforcing those in others. As a result, climate change acts as a persistent drag on long-term economic growth and fiscal stability, supporting the argument that greenhouse gas emissions represent a negative externality whose social costs are not reflected in market prices.

The analysis also demonstrates that these impacts are distributed unevenly. While climate change affects all economies, developing countries experience disproportionately greater physical risks and possess fewer financial and technological resources to respond.

The evidence presented throughout this paper suggests that the long-term economic benefits of climate change mitigation outweigh its costs. Although mitigation requires substantial upfront investment, these costs are largely transitional and are incurred to reduce future economic damage. In contrast, the costs of inaction are recurring, cumulative and, in many cases, irreversible, as continued climate change progressively weakens productive capacity, increases fiscal pressures and reduces long-term economic growth. Investing in mitigation therefore represents a preventative economic investment rather than a permanent economic burden.

However, this conclusion depends on several important conditions. The magnitude of the net economic benefits is influenced by policy design, institutional quality and access to finance. Stable carbon pricing, credible long-term regulation, targeted public investment and just transition policies can significantly reduce mitigation costs while encouraging private investment. Conversely, policy uncertainty, weak institutions and limited access to affordable finance-particularly in developing economies-can increase transition costs and reduce the overall economic gains from mitigation.

Works Cited

- Aon. "2023 Weather, Climate and Catastrophe Insight." 2 Feb. 2023,
<https://www.aon.com/getmedia/f34ec133-3175-406c-9e0b-25cea768c5cf/20230125-weather-climate-catastrophe-insight.pdf>. Accessed 8 Sept. 2026.
- "Chapter 5: Demand, Services and Social Aspects of Mitigation." *Www.Ipcc.Ch*,
<https://www.ipcc.ch/report/ar6/wg3/chapter/chapter-5/>. Accessed 8 Sept. 2026.
- "Chapter 5: Food, Fibre and Other Ecosystem Products." *Www.Ipcc.Ch*,
<https://www.ipcc.ch/report/ar6/wg2/chapter/chapter-5/>. Accessed 8 Sept. 2026.
- Clay, Edward J. "The Brandt Report and International Food Problems." *Food Policy*, vol. 5, no. 4, 1 Nov. 1980, pp. 310–313,
<https://www.sciencedirect.com/science/article/pii/0306919280900603>,
10.1016/0306-9192(80)90060-3. Accessed 8 Sept. 2026.
- "Climate Risk Index 2026 - Who Suffers Most From Extreme Weather Events?"
International-Climate-Initiative.Com, 2026,
<https://www.international-climate-initiative.com/en/iki-media/publication/climate-risk-index-2026-who-suffers-most-form-extreme-weather-events-new6926ba2f44276010681742/>. Accessed 8 Sept. 2026.
- Gallagher Re. "Natural Catastrophe and Climate Report 2024." 2025,
<https://www.ajg.com/gallagherre/news-and-insights/gallagherre-natural-catastrophe-and-climate-report-2024/>. Accessed 8 Sept. 2026.
- Hart, Robert. "Climate Change Will Cost Global Economy \$38 Trillion Every Year Within 25 Years, Scientists Warn." *Forbes*, 17 Apr. 2024,

<https://www.forbes.com/sites/roberthart/2024/04/17/climate-change-will-cost-global-economy-38-trillion-every-year-within-25-years-scientists-warn/>. Accessed 8 Sept. 2026.

IMF. “IMF Fossil Fuel Subsidies Data: 2023 Update.” *IMF*, 2023,
<https://www.imf.org/en/Publications/WP/Issues/2023/08/22/IMF-Fossil-Fuel-Subsidies-Data-2023-Update-537281>. Accessed 8 Sept. 2026.

International Energy Agency. “World Energy Investment 2025.” IEA, 5 June 2025,
<https://www.iea.org/reports/world-energy-investment-2025>. Accessed 8 Sept. 2026.

International Labour Organization. Working on a Warmer Planet: The Impact of Heat Stress on Labour Productivity and Decent Work. 2019,
https://www.ilo.org/sites/default/files/wcmsp5/groups/public/@dgreports/@dcomm/@publ/documents/publication/wcms_711919.pdf. Accessed 9 Sept. 2026.

IPCC. “Chapter 9: Africa.” *Www.Ipcc.Ch*, 2022,
<https://www.ipcc.ch/report/ar6/wg2/chapter/chapter-9/>. Accessed 8 Sept. 2026.

---. *Climate Change 2023: Synthesis Report a Report of the Intergovernmental Panel on Climate Change*. 2023.

Lees, Nicholas. “The Brandt Line After Forty Years: The More North–South Relations Change, the More They Stay the Same? | BISA.” *Www.Bisa.Ac.Uk*, British International Studies Association, 23 Nov. 2020,
<https://www.bisa.ac.uk/articles/brandt-line-after-forty-years-more-north-south-relations-change-more-they-stay-same>. Accessed 8 Sept. 2026.

“Mali: Strengthening Financial Resilience to Recurrent Droughts.” *World Bank*, 26 July 2023, <https://www.worldbank.org/en/country/mali/publication/economic-update-mali-2023-building-financial-resilience-in-response-to-recurrent-droughts>. Accessed 8 Sept. 2026.

Nordhaus, William D. “Revisiting the Social Cost of Carbon.” *Proceedings of the National Academy of Sciences*, vol. 114, no. 7, 2017, pp. 1518–1523, <https://doi.org/10.1073/pnas.1609244114>.

Somanathan, E., et al. “The Impact of Temperature on Productivity and Labor Supply: Evidence From Indian Manufacturing.” *Journal of Political Economy*, vol. 129, no. 6, 30 Apr. 2021, pp. 1797–1827, 10.1086/713733.

United Nations. “What Is Climate Change?” United Nations Climate Action, <https://www.un.org/en/climatechange/what-is-climate-change>. Accessed 9 Sept. 2026.

World Bank. “Increasing Productivity and Reducing Vulnerable Employment.” *The Atlas of Sustainable Development Goals 2020*, <https://datatopics.worldbank.org/sdgoalatlas/archive/2020/goal-8-decent-work-and-economic-growth/>. Accessed 8 Sept. 2026.

World Bank. “Pakistan: Flood Damages and Economic Losses Over USD 30 Billion and Reconstruction Needs Over USD 16 Billion - New Assessment.” *World Bank*, 28 Oct. 2022, <https://www.worldbank.org/en/news/press-release/2022/10/28/pakistan-flood-damages-and-economic-losses-over-usd-30-billion-and-reconstruction-needs-over-usd-16-billion-new-assessment>. Accessed 8 Sept. 2026.

World Bank Group. “Bangladesh - Country Climate and Development Report.” *World Bank*, 2022,
<https://documents.worldbank.org/en/publication/documents-reports/documentdetail/099510110202254063>. Accessed 8 Sept. 2026.

Digital Diagnosis: Health Misinformation and Behavioral Changes Among Kazakhstani Youth by Aiyim Shunshalina

Abstract

This study investigates the growing impact of health misinformation on Kazakhstani adolescents, a demographic particularly vulnerable due to their age and frequent exposure to the digital world. Utilising a mixed-methods research design, the study explores the prevalence, behavioral consequences, and potential solutions to this issue. Quantitative data were collected through a structured survey of 64 high school students. Qualitative insights were gathered via semi-structured interviews with a school psychologist and an 11th-grade student. The findings revealed that exposure to false health content is prevalent, with approximately 31.3% of respondents encountering health misinformation regularly. Furthermore, the behavioral impact is significant: 79.7% of surveyed adolescents reported altering personal health habits at least once based entirely on online content. Despite this influence, only a small fraction (15.6%) consistently verifies health information before sharing it, with the majority relying on suspicion rather than proactive fact-checking. The qualitative data underscored that underdeveloped critical thinking and limited parental guidance exacerbate this vulnerability.

Introduction

In recent years, public health experts have grown particularly concerned about the impact of misinformation (false or misleading information that is unwittingly shared) on the health behaviours of vulnerable populations, especially adolescents. The World Health Organisation Regional Office for Europe (2024), for instance, has identified this as a critical global issue and has called for widespread action to reduce the harm caused by this “infodemic”. According to Innocenti (2021), even teenagers without direct access to the Internet can be affected by misinformation because false ideas spread easily from online platforms into real-world conversations, reaching them through discussions with friends, family, and teachers.

According to recent research, the problem of misinformation in healthcare has significantly worsened in Kazakhstan. Studies confirm that Kazakhstan experiences challenges with public trust and low vaccine confidence among the general population (Eagan et al., 2025). This regional misinformation creates a challenging public health environment for youth. Therefore, understanding how false claims impact this specific demographic in the local context is essential for public health efforts.

Despite increasing access to digital platforms, there is a limited amount of research on how misinformation specifically affects the health behaviours and attitudes of Kazakhstani youth. This issue is significant, as the consequences of misinformation can impede effective healthcare, increase vaccine hesitancy, and aggravate the management of chronic disease among individuals of the current generation.

This study aims to investigate the prevalence and specific health consequences of health misinformation among Kazakhstan's young population. The study is guided by the central research question:

- How does health misinformation impact Kazakhstani adolescents?

Subquestions:

- To what extent is health misinformation prevalent among adolescents?
- What are the behavioral consequences of encountering health misinformation?
- What measures can be taken to address this problem?

This study includes an interview with the psychologist, who works closely with students at NIS, with the aim of collecting reliable professional data. Furthermore, the survey regarding students' perception of health misinformation was conducted, as well as an interview with a student to understand the personal experiences and perspectives of the target demographic. Finally, the results of the survey and interviews were analysed to answer the research questions.

Given the social and economic context of Kazakhstan, where access to accurate healthcare information may be uneven, the impact of misinformation can be harmful. Therefore, understanding the risks and consequences of health misinformation is crucial to evaluate risks and be aware of convenient measures that have the potential to address the problem.

The introduction has demonstrated the global urgency of health misinformation and established the clear need for localised research. Since Kazakhstan already struggles with low public trust (Eagan et al., 2025), finding local data on adolescents in the country is highly important. As the study also presents the most effective approaches to counter the problem, research is significant for both academic purposes and developing targeted public health literacy initiatives. The following chapter will detail the methodology, clarifying the planned survey and interviews necessary to clearly supply empirical data and answer the research questions.

Literature review

This review evaluates the psychological and behavioural consequences of health misinformation on adolescents, focusing specifically on the social and political contexts of Kazakhstan. By analysing scientific articles, this chapter identifies the specialities of false information spread and evaluates current interventions. Ultimately, this review aims to investigate how misinformation shapes adolescent health choices and find effective solutions to address the problem.

The impact of false information on young people's health behaviours has been a major issue for public health specialists in recent years. Across the written articles, a consistent relationship between health misinformation and adolescent psychological and behavioural outcomes was found. According to Schmid et al. (2023), the psychological antecedents of behaviours, such as knowledge and attitudes, can be impaired after exposure to health misinformation. A similar perspective is shared by UNICEF (2021), where authors emphasise the presence of negative consequences in both physical and mental health. Furthermore, Purba et al. (2023) argue that social media plays a crucial role in the development of health risk behaviours, such as the use of alcohol, drugs, and tobacco. From a national perspective, social networks act as a major

communication tool between mass media and the general public. Hence, some health risk behaviours can be evaluated as a direct result of the spread of health misinformation.

In contrast, Ma et al. (2026) suggest that the impact of false information on behaviour may be mitigated in the case of supportive digital environments and media skills. Therefore, social media cannot be considered only as a factor that worsens the spread of misinformation.

As it was mentioned in both articles, it is highly difficult to detect the symptoms of exposure to health misinformation. Considering that the population investigated in this research are adolescents, the real scale of the problem seems to be not fully explored. That is the research gap noticeable in most of the articles on this topic.

An evaluation of the researching society is also a significant factor that determines the rate of health misinformation. Eagan et al. (2025) report that Kazakhstan shows significant levels of vaccine hesitancy compared to other regions, with concerns primarily focused on the safety and perceived necessity of vaccines. This study suggests evidence that older generations in Kazakhstan were already exposed to false information in the healthcare sphere. According to the same source, considering political lenses, this problem often appears where there is a lack of trust in state institutions and health authorities. Hence, a social norm of criticism arises where an adolescent observes parents doubting official health advice. UNICEF (2021) highlights that misinformation moves fluidly between online and offline contexts, advocating the possibility that political distrust felt by adults can be passed down to young people through daily conversations. This leads to a "cycle of doubt" in Kazakhstan, where social media algorithms and political history combine to make health safety rumours seem more "authentic" than data supported by the government.

While much of the literature focuses on the negative consequences of digital health content, an alternative perspective suggests that social media can democratise health information. In regions with uneven access to clinics, digital platforms can serve as a crucial community support system for those who do not have consistent access to trustworthy medical institutions (Barry, 2024). In a local context, some people may argue that the hesitancy observed in Kazakhstan is a rational response to historical instances of poor medical transparency rather than just a product of exposure to false information.

Despite the progress in this field, a large knowledge gap remains in the analysis of the problem in the Central Asian landscape. There is a critical need for long-term studies that follow Kazakhstani adolescents over several years and show how their health beliefs change from childhood into early adulthood under the influence of digital misinformation.

One of the subquestions focused on measures that can undermine the negative effect of health misinformation on teens. Roozenbeek et al. (2023) emphasise that teaching people to recognise manipulation techniques before exposure is more effective than corrections. This introduces the idea of teaching children digital literacy as one of the most effective ways to address the problem. Young individuals are most influenced by corrections from peers or social networks, underscoring the need for peer-to-peer help and proactive information from social media

businesses to prevent mis/disinformation from spreading (UNICEF, 2021). Both measures include initiatives from educators, parents, technology companies, and children themselves.

An alternative suggestion concentrates on countering information through the digital world. In order to help parents manage the kind and quantity of content their children access, most digital content producers have incorporated parental controls into their browsers, games, and applications (UNICEF, 2021). In discussion of other digital approaches, Ecker et al. (2022) state that effective social media corrections come from algorithmic sources, expert groups (e.g., government health agencies), or multiple users. Therefore, it can be concluded that the discrepancy between different methods is present even in measures with similar regulatory goals.

While most of the articles are devoted to adults and children, only a few of them focus on addressing the problem among adolescents. Consequently, a gap remains in evaluating the efficiency of the mentioned methods, particularly for youths.

In summary, health misinformation significantly impairs adolescent behavioural intentions by exploiting emotional vulnerabilities and low institutional trust. While digital literacy and prebunking (a preventative measure that aims to prepare audiences to recognise and resist information risks) offer promising solutions, their effectiveness within the specific socio-political context of Kazakhstan remains unstudied. Future research should prioritise longitudinal data to understand how regional scepticism influences long-term health beliefs among Kazakhstani youth.

Methodology

The methodology section outlines the primary research methods, aiming to answer the research questions of the study. This section results in an analysis of participants' opinions regarding the issue of health misinformation's impact on Kazakhstani adolescents. Moreover, the analysis of survey responses and interview findings made by the end of this section contribute to the investigation of this problem, as well as determining the true scale of its prevalence, helping to resolve secondary research's knowledge gaps and identifying the most effective methods addressing the problem.

This study used a mixed-methods primary research design based on the analysis of participants' responses to survey questions and semi-structured interviews. The research questions investigated on the topic of health misinformation demanded both numeric data and qualitative perspectives, along with their objective evaluation; therefore, a mixed approach was selected to ensure the study's accuracy and relevance. A quantitative, cross-sectional research design was chosen to study the role of social media in public health communication and behavioural change in adolescents, as it enabled effective analysis of the relationship between studied concepts (Alaqil et al., 2024). The qualitative component, consisting of two semi-structured interviews, was included to complement the statistical data with professional and personal perspectives on the issue.

The survey was conducted across one Nazarbayev Intellectual School and one public secondary school, targeting adolescents studying between 8th and 11th grades. To ensure

representation from both public and high-performing schools, as well as different age groups and genders, a stratified convenience sampling method was used (Eagan et al., 2025). Within each stratum, convenience sampling was utilised due to the absence of a national student registry, making data collection feasible while maintaining group representation. Across these strata, a final sample size of 64 adolescents was determined using Slovin's formula. In addition to the survey, two interviews were conducted: one with a school psychologist who works closely with students at NIS to collect reliable professional data, and one with an 11th-grade student to understand the personal experiences and perspectives of the target demographic. Formal permission was obtained from school administrations prior to data collection, which included approval of parental notification procedures in accordance with institutional policy.

Data was collected using a structured survey developed specifically for this study, alongside two semi-structured interviews. The survey contained four main sections:

- Demographics (age, school type, class level, gender)
- Exposure to Health Content (source usage, frequency, credibility)
- Personal Experiences (interaction with health misinformation)
- Behaviour Change (self-reported changes in health behaviour)

The survey was prepared in Kazakh and Russian languages, and its questions were revised and piloted on a sample of 10 students to reduce ambiguity and inaccuracy. The interviews were conducted separately with a school psychologist and a student peer, using pre-prepared question guides tailored to each participant's role and knowledge. Both interviews were recorded with participants' consent and later transcribed for thematic analysis, where they underwent systematical review and coding to identify recurring themes regarding health misinformation perceptions.

Before answering the survey or participating in the interviews, participants were supplied with a document informing them of the study's purpose, risks and benefits, and provided written student assent, confirming their rights regarding data protection. The questions did not include any personal information, such as name and individual identification number, guaranteeing the anonymity and confidentiality of the study. All collected data was saved in password-protected files and was deleted after use for academic purposes.

Ultimately, this section describes the methodology used to study the prevalence and impact of health misinformation on teenagers in Kazakhstan. Mixed primary research is used to gather both numeric data from a larger proportion of the population and qualitative insights from two interviews, and the combination of a structured survey and semi-structured interviews enables a comprehensive evaluation of collected results. Ethical considerations play a crucial role in all parts of the methodology, ensuring respect and safety in research. The next chapter will focus on the results of the selected methodological approach.

Findings and Discussion

This section focuses on the results of primary research methods, particularly mixed research approaches in the form of two interviews and a survey. The data are analysed based on their

significance for the study and main patterns are discussed to explain their cause, impact, and importance. The findings and discussion section summarises the data to answer the research questions and compare the outcomes with information from the literature review. Both qualitative and quantitative methods were used to collect data and view the problem from different perspectives, focusing both on the targeted audience's responses and an expert's opinion.

The survey participants included 64 high school students from grades 8 through 11. Of these, 47 were enrolled at Nazarbayev Intellectual School (NIS), while the remaining 17 attended a public school. In terms of grade distribution, the largest groups were grade 11 and grade 10 students, accounting for 42% and 28% of the sample, respectively. Students from grades 9 and 8 made up 19% and 11% of respondents, respectively, ensuring representation across multiple year groups.

The survey aimed to collect statistics on the topics of the impact of health misinformation on Kazakhstani adolescents, mainly about its prevalence and the habits of teenagers in addressing the risks. The questions were in Kazakh and Russian since the study included an audience that speaks mainly these languages.

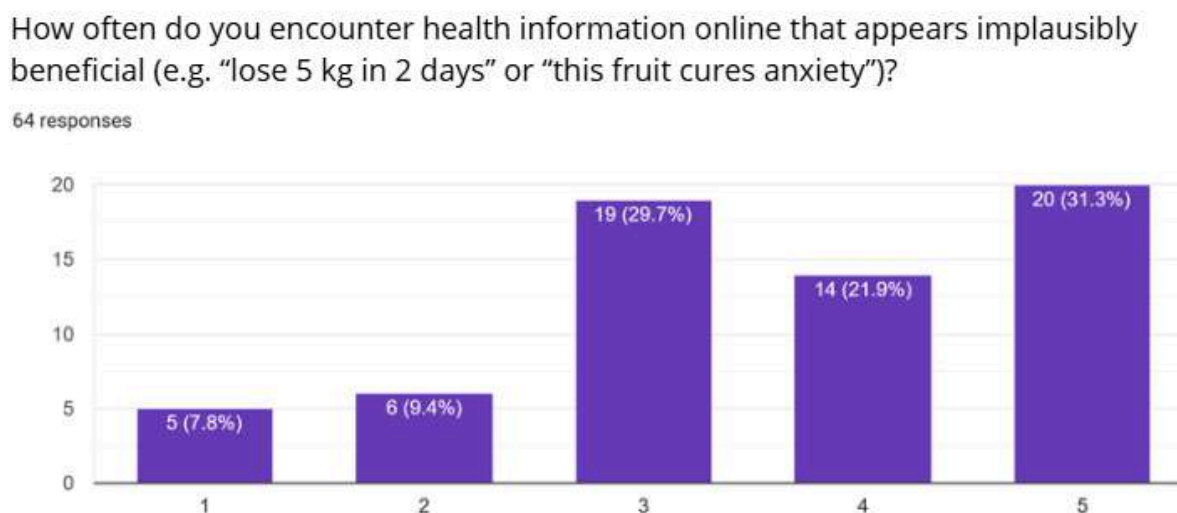


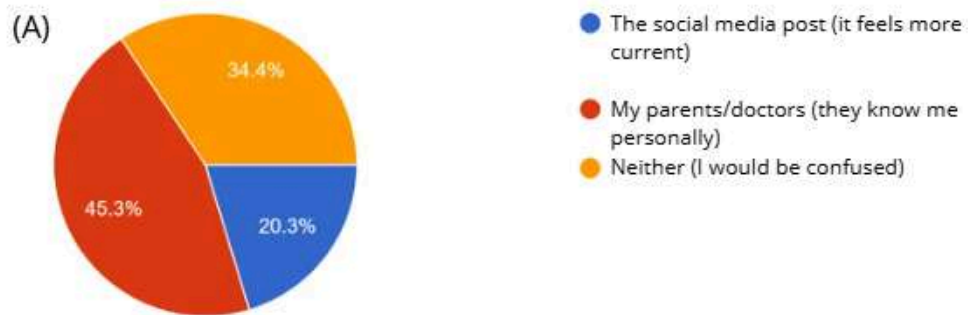
Figure 1. Frequency of Unconvincing Health Information Encountered Online

One of the questions asked participants to rate, on a scale from 1 (never) to 5 (always), how frequently they encountered health information online that appeared implausibly beneficial — for example, claims such as “lose 5 kg in 2 days” or “this fruit cures anxiety.” The distribution of responses is presented in Figure 1.

According to this, about 31.3% of respondents regularly encounter unconvincing health information, while only 7.8% of them have never faced such kind of media content. The results suggest that the studied demographic group is more likely to be exposed to doubtful health information than not, showing that the research is investigating a relevant topic.

If you saw a health post that contradicted (disagreed with) what your parents or school doctors told you, who would you be more likely to believe more?

64 responses



Have you ever changed your daily habits (e.g., diet, supplements, or sleep) based only on a video or post you saw on social media?

64 responses

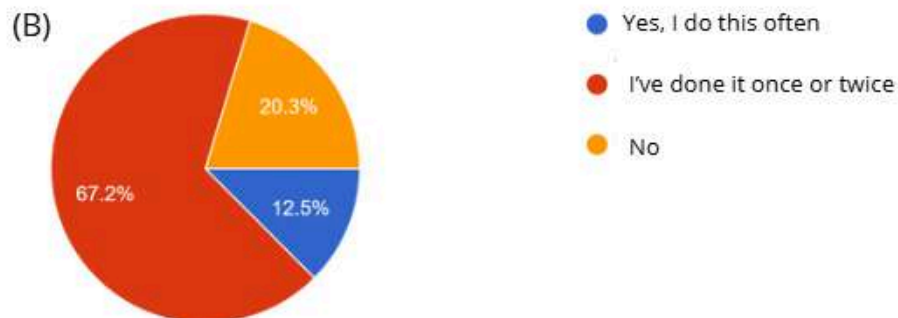


Figure 2. Adolescent Responses to Online Health Information and Behavioral Outcomes. (A) Distribution of trust choices when online health posts contradict advice from parents or medical professionals. (B) Frequency of self-reported daily habit modifications based on social media content.

Another question examined who participants would trust more if information encountered online contradicted advice from a doctor or parent. Respondents chose from three options: a social media post (described as “more current”), parents or doctors, or neither source (indicating confusion). The results are shown in Figure 2A.

Based on the pie chart, 34.4% of respondents chose not to trust anyone, while 20.3% of students preferred social media. This distribution demonstrates a pattern similar to observations in existing literature related to public trust in medical institutions in Kazakhstan (Eagan et al.,

2025). However, the small sample size of this study makes it difficult to propose a strong claim about broader regional trends.

The results presented in Figure 2B illustrate the question that asked whether participants had ever changed a personal habit - such as their diet, supplement use, or sleep schedule - solely based on social media content. Responses were grouped into three categories: “Yes, I do that often,” “I’ve done it once or twice,” and “No.”

The majority of participants, approximately 67.2%, once or twice experienced a change in their habits based on information from social networks. Only 12.5% of participants did it regularly, while 20.3% had never done it. This shows that most adolescents do not make impulsive health decisions on a regular basis. However, the fact that over three quarters (79.7%) of respondents changed their regular activities at least once suggests that social media still has an apparent influence on adolescent behaviour, even if it is not always consistent.

When you share a health-related post with friends or family, how often do you verify its scientific accuracy with an official medical source first?

64 responses



Figure 3. Verification Practices for Health-Related Posts

The fourth question explored how frequently participants verify the accuracy of health-related posts before sharing them. Four response options were offered: always verifying before sharing, verifying only if content seems suspicious, sharing first and verifying later, and not verifying at all out of trust in the author. The distribution of responses is illustrated in Figure 3.

It can be clearly seen that almost 60% of respondents verify data before sharing only if the information sounds suspicious. 14.1% of respondents do not usually check information, whereas 15.6% always do. The least popular answer, with around an 11% index, is verification after sharing. The results suggest that most adolescents care about the reliability of the information they share. Nevertheless, the fact that the majority only check information when it already seems doubtful means that convincingly presented misinformation may still be shared by accident, which remains a concern.

One interview was conducted with a school psychologist, and another with an 11th-grade student. Together, they provided both a professional and a personal perspective on health

misinformation among adolescents, which were analysed using thematic analysis to identify recurring patterns and insights.

The psychologist highlighted that the family environment plays a key role in how teenagers respond to misinformation. According to them, adolescents from stable families, where parents teach critical thinking, are less likely to be negatively affected. They also noted that teenagers are a vulnerable group since their critical thinking has not yet fully developed, making them easy to influence. Regarding the global context, she pointed out that all youth share the same internet, and hence, exposure to misinformation is not unique to Kazakhstan. Most importantly, the expert emphasised that fact-checking is the most essential skill a young person can develop by comparing information to food: if you swallow it without chewing, the consequences will be negative.

In general, the student's interview supported these findings. They shared a personal experience of following a harmful diet they found on social media, which caused dizziness and headaches. Additionally, the student participant suggested that older generations in Kazakhstan may be more vulnerable to health misinformation because they grew up in a time when information was generally more trustworthy. Both interviewees agreed that school-based education on identifying false information online would be a valuable step toward reducing its impact.

While specifically discussing the growing number of self-diagnoses, the psychologist explained that it is a common and natural behaviour: when teenagers feel uncertain, they look for explanations to feel more in control. Qualitative thematic analysis of the expert interview revealed that adolescent self-diagnosis serves primarily as a psychological mechanism to reduce ambiguity. When encountering unexplained symptoms, adolescents utilise social media labels not out of passive trustfulness, but to establish identity and certainty. As the expert noted, "a state of uncertainty is a state that many people cannot stand". This aligns with student participant's self-reported reliance on algorithmic sources when health guidance feels ambiguous.

Overall, the findings suggest that health misinformation is a common and relevant issue for Kazakhstani adolescents. While many students show some awareness of the problem, most do not consistently verify information before trusting or sharing it. The interviews revealed that undeveloped critical thinking and limited parental guidance leave teenagers particularly vulnerable. At the same time, both the survey and interview data indicate that adolescents are not entirely passive - many do question information to some degree; nonetheless, this may not be enough on its own. The results point to a need for structured media literacy education in schools that will help teenagers develop stronger fact-checking habits and make safer health decisions.

Conclusion

This research studied the central question: How does health misinformation impact Kazakhstani adolescents? In the digital age, the risks of young people's exposure to false health-related information have increased significantly, and controlling this problem in Kazakhstan is crucial for adolescents' security.

The findings from the literature review, survey, and interviews revealed observable similarities between theoretical and practical data. A key discovery was the nuanced trust dynamic among people in Kazakhstan: while Eagan et al. (2025) indicated low public trust in the country, the responses from the survey among participants in the two sampled schools indirectly supported this idea by reporting that less than half, specifically 45.3%, of the students prioritize parents and doctors over online sources when faced with conflicting health information, highlighting uncertainty about whom to trust rather than a clear preference for online sources. Furthermore, the exposure to potentially misleading or doubtful health information was found to be relevant within the studied sample as nearly one-third of the participants (31.3%) responded that they see doubtful health information on a regular basis. This aligns with Innocenti (2021), which suggested the relationship between digital mis/disinformation and children to be common in many societies. As a result, the scale of the problem was clearly identified, and more specific knowledge was gained to help address the issue in the most effective way.

The implications of these findings propose a need for action. To address the concern, schools should supplement theoretical warnings and implement practical fact-checking workshops. Both the psychologist and the student interviewee recommended active promotion of fact-checking and education of young people about this issue from a young age as primary solutions. Future research should expand this study to a national level to identify if the patterns differ in other areas of Kazakhstan, particularly those where access to professional healthcare may be more limited than in the cities.

References

- Alaqil, R. A., Alaqeel, R. A., Alhawiti, R. D., Alhawiti, A. E., Aljizani, W. F. A., Alatawi, D. M. A., & Alhawiti, H. D. (2024). The role of social media in public health communication and behavior change in adolescents. *Journal of Posthumanism*, 4(3), 920–928.
<https://doi.org/10.63332/joph.v4i3.314>
- Barry, E. (2024, May 5). It led to self-diagnosis becoming an epidemic. *The New York Times*, 9.
<https://link.gale.com/apps/doc/A792645944/SUIC?u=astanapm&sid=bookmarkSUIC&xid=239d84eb>
- Eagan, R. L., Claessens, T., Hendrickx, G., Larson, H. J., & Karafillakis, E. (2025). The state of vaccine confidence among the general public in Eastern Europe and Central Asia: A cross-sectional study in 12 countries. *Vaccine*, 67, 127849.
<https://doi.org/10.1016/j.vaccine.2025.127849>
- Ecker, U. K. H., Lewandowsky, S., Cook, J., Schmid, P., Fazio, L. K., Brashier, N., Kendeou, P., Vraga, E. K., & Amazeen, M. A. (2022). The psychological drivers of misinformation belief and its resistance to correction. *Nature Reviews Psychology*, 1, 13–29.
<https://doi.org/10.1038/s44159-021-00006-y>

- Ma, I., Sultan, M., Kozyreva, A., Lewandowsky, S., & Hertwig, R. (2026). Understanding the impact of misinformation on adolescents. *Nature Human Behaviour*, 10, 18–28. <https://doi.org/10.1038/s41562-025-02338-8>
- Purba, A. K., Thomson, R. M., Henery, P. M., Pearce, A., Henderson, M., & Katikireddi, S. V. (2023). Social media use and health risk behaviours in young people: Systematic review and meta-analysis. *BMJ*, 383. <http://dx.doi.org/10.1136/bmj-2022-073552>
- Roozenbeek, J., Culloty, E., & Suiter, J. (2023). Countering misinformation: Evidence, knowledge gaps, and implications of current interventions. *European Psychologist*, 28(3), 173–188. <https://doi.org/10.1027/1016-9040/a000498>
- Schmid, P., Altay, S., & Scherer, L. D. (2023). The psychological impacts and message features of health misinformation: A systematic review of randomized controlled trials. *European Psychologist*, 28(3), 162–172. <https://doi.org/10.1027/1016-9040/a000494>
- UNICEF Office of Global Insight and Policy. (2021). *Digital misinformation/disinformation and children*. UNICEF.
- World Health Organization Regional Office for Europe. (2024). *Health behaviour in school-aged children (HBSC) study: International report from the 2021/2022 survey (Vol. 1: Context of health)*. <https://www.who.int/europe/publications/i/item/9789289060756>

To what extent has econophysics been successful as an interdisciplinary framework for explaining economic systems and market phenomena? A review of econophysics literature on income distribution, market dynamics, and the methodological limitations of the field

By Darsh Mishra — Conducted in May, June and July 2026

A student at Heritage International Experiential School, Delhi NCR, India

Abstract

This literature review aims to summarise the ability of econophysics to serve as a viable explanation to phenomena across economic and financial contexts. In doing so this review analyses research papers across three broad themes: how income is distributed, how markets move and crash, and the criticisms the field has raised against itself. Across these multiple domains the review aims to argue that econophysics holds substantial accuracy when it comes to reproducing empirical patterns to a greater degree of effectiveness than conventional economic models. Additionally the review provides explanations and overviews of some of the field's most reputable papers while detailing the contributions they make to the field and its development.

I. Introduction

Economic systems are frequently characterised by patterns and regularities that resemble those observed in the natural sciences, despite being driven by human behaviour. Such an uncanny link between the field of economics and physics emerges from their inherent uncertainty. For example, the task of predicting the position of each individual gas molecule in a room at any point in time seems almost impossible, yet the movement of a collective of these particles can be mapped and observed to follow a predictable mathematical pattern. The field of economics presents a similar phenomenon, where no model is able to predict the changes in the spending and saving behaviours of each individual, but once again, when such individual behaviour is aggregated to represent the economy as a whole, predictable and recurring patterns emerge that are remarkably consistent across countries, time periods, and economic systems. It was such an observation that gave rise to the field of econophysics, a field that aimed to apply the tools of statistical physics to economic and financial data with the aim of explaining complex economic systems and market behaviour.

Despite drawing upon theories from physics and applying them to economics, the interdisciplinary field of econophysics is fundamentally rooted in the presence of mathematical patterns shared across both disciplines. Consequently mathematics, in particular statistics, serves as the critical link through which physical theories can be adapted to explain economic systems and market behaviour. Upon further analysis of such overlaps in the two fields by professionals, the interdisciplinary study of econophysics emerged in the late 1990s. Professionals within this field, also known as econophysicists, aimed to apply mathematical tools from statistical mechanics directly to economic data across a range of phenomena. Despite this, the field has not been able to establish itself as a distinct discipline, owing to various arguments stemming from the fact that the same factors driving economic

decisions can almost obviously not be compared to the laws governing particle systems within physics. However, the many models developed by econophysicists demonstrably represent economic data to a greater degree of accuracy than conventional economic or financial models are able to across multiple domains. Therefore, to address this gap, the following literature review aims to analyse the question: to what extent can the tools of econophysics explain economic phenomena across income distribution, market dynamics, and the methodological limitations of the field itself. In order to examine this question the following review aims to analyse three major areas of this interdisciplinary field. The first is income distribution, with the aim of assessing the extent to which the Boltzmann–Gibbs framework can accurately model the apportionment of income across an economy. The second tests the physics approach against market dynamics, with a focus on examining whether statistical mechanics can model how financial markets move and why they crash. Lastly, the third and final section evaluates the methodological limitations of this field of study, drawing on critical perspectives from within the field itself. Across these three domains, this review argues that econophysics offers a powerful descriptive framework for economic phenomena, but that the gap between describing a pattern and explaining its causes is what remains the field’s primary unresolved tension.

II. Terminology

Before turning to the literature, a brief clarification of nine recurring terms is necessary to facilitate understanding.

- The Lorenz curve plots the percentage of total income earned by various portions of the population when the population is ordered by the size of their income (Gastwirth), where perfect equality would be represented by a straight diagonal line while a concave curve suggests inequality.
- The Gini coefficient, derived from the Lorenz curve, is a measure of income or wealth inequality and condenses the Lorenz curve of an economy into a single number between 0 and 1, where 0 represents perfect equality and 1 represents complete inequality.
- The central limit theorem is a result in probability theory that establishes the normal distribution as the distribution towards which the mean of almost any large set of independent, randomly generated variables rapidly converges, which is why the normal distribution arises so commonly whenever data is aggregated (“Central Limit Theorem”).
- The efficient market hypothesis holds that financial markets efficiently process and reflect all available information, so that a security’s price already incorporates everything publicly known about it and no investor can consistently gain an edge by trading on that information (“What Is the Efficient-Market Hypothesis?”).
- The Pareto exponent is the value that governs a power-law distribution. When data following a power law is plotted on logarithmic axes it traces a straight line, and the Pareto exponent is the size of that line’s slope, where a smaller exponent corresponds to a heavier tail and a greater concentration of income or wealth at the very top.

- Universality, with respect to physics, refers to when fundamentally distinct systems hold the ability to display the same large-scale statistical behaviour. In doing so a single mathematical form recurs across such systems.
- A zero-sum situation is one in which the total quantity of something is fixed, so that any gain made by one participant is exactly matched by an equivalent loss to another, leaving the overall amount unchanged.
- The Fokker–Planck equation is a partial differential equation that describes how a probability distribution evolves and spreads over time under a diffusion process, eventually settling into a stationary form once its drift and diffusion terms come into balance.
- Volatility clustering refers to the empirical tendency for large price changes to be followed by further large changes, and small changes by small ones, so that the magnitude of returns remains correlated over time even when the direction of those returns does not.

III. Income Distribution

The Boltzmann–Gibbs Model and the Lower 95%

The early foundations that involved applying models from the study of physics to income distribution came from the works of the physicists Adrian Drăgulescu and Victor Yakovenko in the years 2000 and 2001. Within the co-authored papers between the two, titled “Evidence for the exponential distribution of income in the USA” and “Exponential and power-law probability distributions of wealth and income in the United Kingdom and the United States”, they proposed that the Boltzmann–Gibbs distribution — a probability model detailing the energy distribution among gas molecules within a closed system — is capable of describing how income is distributed across a population (Drăgulescu and Yakovenko, “Evidence”; Drăgulescu and Yakovenko, “Exponential and Power-Law”). Another such model that was assessed was the Pareto power law — a distribution first documented by the Italian economist Vilfredo Pareto in the late nineteenth century, who observed that the upper tail of the income distribution follows a power law, wherein the number of individuals earning above a given level of income falls off as a fixed power of that income, thereby concentrating a disproportionate share of total income among the highest earners (Pareto). To test these hypotheses, the researchers constructed a mathematical model within which agents would randomly exchange money with each other, mirroring the manner in which gas molecules exchange energy. All agents in the model were made to start with equal amounts of money in order to mimic how no single molecule is assigned more energy than the other in a closed system. The result of this was an exponential model that emerged as a result of exchanges taking place between the individual agents (Drăgulescu and Yakovenko, “Evidence”).

The researchers then drew upon data including that from multiple US censuses, IRS databases, as well as various other independent sources, in order to create probability distributions as well as Lorenz curves for the same. These distributions indicated that the bottom 95 percent of the American population (representing those that earned an amount below 100,000 dollars at the time) and their respective incomes followed an exponential

curve consistent with the Boltzmann–Gibbs distribution rather than the Pareto power law that had long dominated the literature on income distribution (Drăgulescu and Yakovenko, “Exponential and Power-Law”). These two findings are based upon similar yet distinct data sets; the 95 percent exponential result draws upon 1998 IRS state-level income data, whereas the analysis of the Gini coefficient is derived from 1979 to 1997 IRS data.¹ Despite this, together these two sets of data sketch a consistent picture of the US income structure across the late 1900s.

The primary mathematical model used to describe this lower subset of the population was the following:

$$P_I(r) = (1/R) \exp(-r/R)$$

where P denotes the probability density at income r , r denotes income, and R denotes the average income (Drăgulescu and Yakovenko, “Evidence”).

The researchers, using this model, found a closely aligned Gini coefficient (defined in the terminology section) of 0.5 as compared to the IRS figure of 0.46 for single-earner households (Drăgulescu and Yakovenko, “Evidence”). This further lent significant empirical weight to the researchers’ hypothesis that the Boltzmann–Gibbs distribution could meaningfully describe income across a subpart of the population, thus suggesting that the pattern was not merely a mathematical abstraction. Despite the gap of 0.04 between the model’s Gini coefficient and the IRS figure being remarkably close for a model rendered using the behaviour of gas molecules, such proximity still falls short of complete accuracy. In an attempt to probe further into such discrepancies and their theoretical implications, the researchers Yakovenko and Rosser, in their paper titled “Colloquium: Statistical mechanics of money, wealth, and income”, set out to explore whether these physical models only provided effective fits or could hold theoretical explanations for why such distributions arise in income data (Yakovenko and Rosser). Additionally, having devised a model for one subset of the population, they engaged in further investigation of the remaining top 5 percent (those earning above \$100,000) that acted as outliers to the previously utilised Boltzmann–Gibbs distribution. The exponential curve framework of the Boltzmann–Gibbs distribution led to a steep gradient of such an extent that the extremes on the x axis, representing high-income earners, were predicted to be close to zero, whereas the real data showed a significantly higher number of people at these extreme income levels, suggesting that the exponential model was consistently underpredicting this subgroup of earners. Here, the failure of the Boltzmann–Gibbs model to account for the top 5 percent of earners suggested another mathematical pattern arising within these outliers. Upon further investigation, they observed that the previously proposed Pareto power law was applicable to this subset of the population. As the income data for this subset was plotted onto a logarithmic scale, the data points formed an approximately straight line rather than a curve, a clear indication of the presence of the Pareto power-law distribution.

From Fitting to Explaining: Additive and Multiplicative Income

Coming back to the questions of the theoretical implications of these distributions posed by Yakovenko and Rosser in “Colloquium: Statistical mechanics of money, wealth and income”, the researchers focused on enhancing their model to better mirror the behaviour of economic

agents in real-world scenarios. In order to do so they treated individual income as a diffusion process: a quantity that moves up and down with time and is governed by a stochastic process. They then found that this time evolution of the income distribution function can be governed using the Fokker–Planck equation, which is a partial differential equation describing a standard manner in which a probability distribution spreads and settles under a diffusion process. Furthermore, this diffusion process is directly influenced by its two coefficients, which in this case are the fixed average size of income changes and the variance of this income size per unit time. The equation is then used to model a probability distribution that continually changes until an equilibrium state is reached. This state, reached once the two coefficients mentioned earlier equate, signifies that the probability of income moving into each earner group matches that of the income leaving that group, thus creating a stationary state. Within this state of equilibrium individual people can still move up and down income groups, yet the overall profile of the model remains the same. However, the type of stationary shape obtained focuses on another question that the researchers probed further into, the question of how an individual’s income relates to their current earnings. If an individual’s income were to change by amounts independent of their current income, as with a fixed dollar rise, the process is termed additive and its stationary solution is depicted by the exponential Boltzmann–Gibbs distribution. Whereas when income changes by amounts proportional to one’s current income, the process is termed multiplicative and its stationary solution is depicted by the Pareto power law (Yakovenko and Rosser).

The result obtained from such theoretical implications signals that the income of the lower class derives largely from fixed income rises, the sources of which can be wages and salaries, and is thus well depicted by an additive process yielding the exponential distribution. On the other hand, upper-class income comes predominantly from investments, capital gains, and other such wealth-based income streams, which tend to accrue as percentages of existing wealth and therefore scale in value with it; this is depicted by the multiplicative process, which yields the Pareto tail. This finding further adds weight to the claim that wealth is inherently self-reinforcing, or, as more commonly proclaimed, “the rich get richer and the poor get poorer,” since accumulated wealth holds the ability to generate proportional returns, allowing those with larger asset holdings to expand their wealth at an increasingly rapid rate over time (Bouchaud and Mézard). Yakovenko and Rosser also note that, despite the two processes, multiplicative and additive, describing two distinct groups of earners, there also arise situations wherein these processes can converge on a single earner. Such a situation can occur when a percentage cost-of-living adjustment (multiplicative) accompanies a fixed merit-based raise (additive). Conclusively, these regimes depict an inherent feature of the two distinct earner groups being analysed (Yakovenko and Rosser).

Testing the Two-Regime Structure Over Time

Next, the researchers aimed to test the hypothesis asserting the existence of such a two-regime structure by analysing more modern data from the IRS through the years 1983 to 2001, where they scaled each year’s income by that year’s average (or “income temperature”) in order to account for inflation and observed the pattern that followed. The data was consistent with the hypothesis, since the lower-class portion of each year collapsed into a

single exponential curve (defined by the Boltzmann–Gibbs distribution) in its stationary form. The upper tail, on the other hand, when modelled, behaved as the antithesis of the lower tail, since it did not collapse into a constant state of equilibrium but instead changed its shape over time as a result of variances in the Pareto exponent: falling from about 1.8 in 1983 to 1.4 in 2000, thus producing a heavier tail. Concurrently the share of total income held by the upper class increased from 4% to 20%. After the market downturn of 2001 this partially reversed, with the Pareto exponent rising and the income share falling as the tail contracted. This occurred as the multiplicative process is tethered to financial markets that should swell during booms and shrink during busts, which is exactly what the upper tail does. Since upper-class wealth is predominantly tied to the performance of financial assets, fluctuations in market performance through downturns and upturns are directly reflected in the shape of the distribution through expansions in the Pareto tail during periods of growth and contractions during downturns (Yakovenko and Rosser).

Description versus Explanation

Such an analysis allows us to return to our initial question of whether these physical models merely describe income data or explain it. The answer is that these models allow for an explanation of the fits they create, since through the additive and multiplicative processes a framework is created that allows for the economic mechanisms underlying these models to be dissected and understood to a greater degree. This provides an understanding of how the differences in the income streams of the upper and lower class cause volatility in the upper class's wealth, whereas the earnings of the lower class remain comparatively stable due to their reliance on fixed wages and salaries, signalling greater insulation from economic downturns as a result.

Finally, this difference ties to the ability of the upper class to risk larger proportions of their existing wealth in order to earn returns; as these returns scale with the amount of capital exposed, the resulting income changes are inherently proportional. The lower class, by contrast, earns through wages and salaries, which accrue in fixed increments and require no comparable exposure of existing income, since an individual's existing salary is not put at risk to obtain the next raise. This reflects a divide between the two classes, one that exists in the capacity to convert wealth into more wealth by assuming risk, set against income that grows in secure and fixed steps.

IV. Market Dynamics

From Income to the Market Itself

Earlier, we established that physics can provide credible frameworks for explaining how individuals' incomes evolve over time. This naturally motivates a deeper examination of one of the key mechanisms through which income and wealth are generated for a large portion of the population, the stock market. While the previous section considered financial markets as drivers of income, this section adopts a different perspective and instead focuses on the statistical properties and dynamics of the markets themselves. Additionally, this section explores whether or not physics can describe and explain the market's own statistical behaviour. Upon further analysis of this question, econophysicists returned a rather

challenging answer, an answer that questioned the world of finance’s reliance on the normal or Gaussian distribution.

The Gaussian Inheritance in Traditional Finance

Traditional finance had long been dominated by the Gaussian distribution, largely due to its integration in the many foundational theories of the field. Whether through Modern Portfolio Theory (MPT) (Markowitz) or the Black–Scholes option pricing model (Black and Scholes), the assumption of normally distributed returns has become deeply embedded within mainstream financial thought. This orthodox view originates in the work of Louis Bachelier in the early twentieth century, whose framework portrayed market fluctuations as random processes governed by the laws of probability (Bachelier).

The Gaussian model portrays markets in a largely symmetrical and thus predictable manner across various scales, yet much like in the previous section, this model too systematically underestimates the probability of extreme outliers, or tails — a shortfall that the empirical work examined below brings sharply into view. The following is a depiction of the normal distribution, with probability density on the y axis and the number of standard deviations from the mean on the x axis. The central point of the graph corresponds always to the mean on the x axis. The given percentages represent the probabilities of events that lie between one standard deviation above and below the mean, 68.27%; two standard deviations above and below the mean, 95.45%; and three standard deviations above and below the mean, 99.73% (“Bell Curve”).

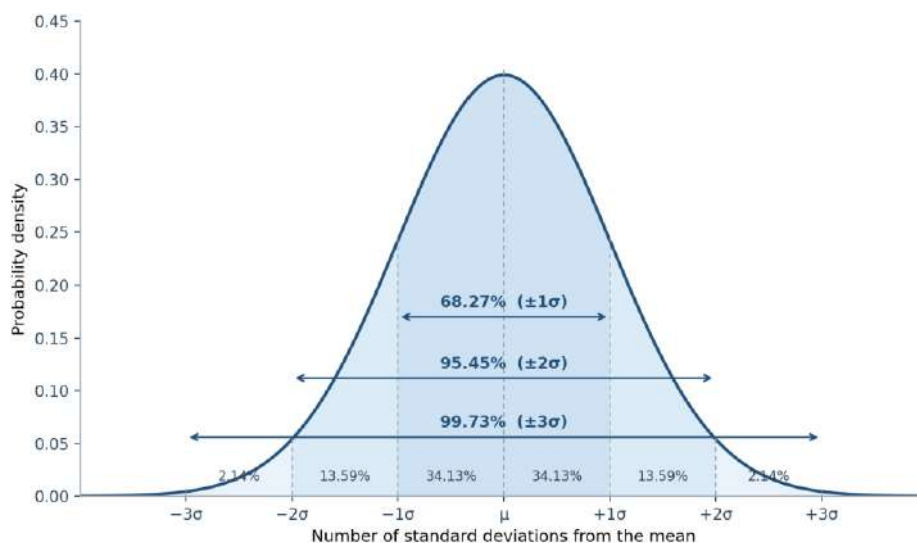


Fig 1: The normal (Gaussian) distribution, showing the proportion of events falling within one, two, and three standard deviations of the mean. Figure created by the author.

The Inverse Cubic Law: Fat Tails in the Data

The work of Gopikrishnan, Plerou, Amaral, Meyer and Stanley in their 1999 paper “Scaling of the distribution of fluctuations of financial market indices” explores an opposing theory, one that finds this traditional theory to fail when back-tested against real market data (Gopikrishnan et al.).

The issue raised by these researchers is that this model accounted for the extreme moves of the market rather sparingly and not often enough by a relatively large margin. The Gaussian model is mathematically convenient, but its convenience comes from an assumption made before real market data was examined, not from one the data supports. Gopikrishnan and the associated researchers put that assumption to a more demanding test than had been previously possible and did so by drawing on three distinct databases at various time scales: nearly 1.2 million one-minute observations of the S&P 500 across thirteen years from 1984–1996; 8,686 daily records across 35 years from 1962–1996; and 852 monthly records across 71 years from 1926–1996. Across these multiple scales they computed the probability distribution of returns and found that for moves above a few standard deviations the distribution falls off not exponentially, as a Gaussian model would suggest, but rather as a power law with an exponent of approximately $\alpha = 3$ in both the positive as well as negative tails. This behaviour is what is meant by the inverse cubic law: the tail of the distribution of returns decays as a power law whose exponent sits close to three, so that the probability of a move of a given size falls off in proportion to the inverse cube of that size. The exponent here describes the shape of the distribution rather than any dependence on distance, and its recurrence thereby overturns the Gaussian inheritance that had long dominated traditional financial modelling. Furthermore, this data was also placed outside the range of the stable distribution, another model that was proposed as a substitute for the Gaussian distribution, thus suggesting that neither the fundamental Gaussian distribution nor its closest substitute held the ability to reliably map market data (Gopikrishnan et al.).

Such deviations from real-world data present a considerable risk for the many models that incorporate or base themselves upon the Gaussian framework. Since the tails of the distribution — the very region underestimated by the model — directly impact risk, the outputs of these models can be unrepresentative of true market movements. Such tails, or large market movements, although infrequent, account for the largest market disruptions, signifying that even small underestimations of tail risk can lead to substantial errors in forecasting and risk management. Bouchaud, in his 2002 overview, on the basis of these findings suggests that the field of “finance is becoming an empirical (rather than axiomatic) science” (Bouchaud 238), thus drawing importance to the role of quantitative traders during a time period that was dominated by mindset-led rather than algorithmic investment strategies.

This result draws such significance due to its relation to econophysics in two parts: one being the presence of the inverse cubic law when the data is mapped out, and the second being the manner in which the result was devised in the first place. This result came about as a result of approaching the complex system of the market through the lens of physics, which looks at the shape the data takes and what it does rather than beginning from an axiom drawn from one’s predictions of what it might do. The Gaussian model was chosen out of ease and tractability and thus prejudged the result rather than acting as an effective model that predicted it.

Testing Universality Across Time and Markets

Furthermore, the investigation yielded that the inverse cubic law was not a one-off appearance within a particular market and time frame but instead appears across multiple markets that have been investigated in the same manner, bringing the hypothesis more

credibility. In order to further scrutinise the inverse cubic law hypothesis, Gopikrishnan and his collaborators examined it across different contexts. The first was temporal: they distributed the returns at progressively increasing time intervals, from minutes to hours and then days. Through this they found that the shape of the distribution remained essentially the same up until the four-day mark. Only beyond four days does the distribution begin to slowly drift towards a Gaussian shape, aligning with the central limit theorem (Gopikrishnan et al.).

The second context was geographic, which aimed to test whether the inverse cubic law arises amongst various different markets and indices. In order to test for this, the researchers conducted the same analysis on day-to-day data from the NIKKEI index of Tokyo across fourteen years and the Hang Seng index of Hong Kong across eighteen years. This analysis yielded Pareto exponents of $\alpha = 3.05$ for the NIKKEI and $\alpha = 3.03$ for the Hang Seng, which, due to their proximity to the S&P 500's value of $\alpha = 3$, were considered statistically similar. This distribution being present across multiple indices, which are governed by different regulations and have varying participants along with many other differentiating factors, further added credibility to the hypothesis (Gopikrishnan et al.).

Volatility Clustering and the Efficient Market Hypothesis

Additionally, the researchers discovered another layer of structure beneath the tail that complicated the picture of markets as being random. They probed into whether or not one return can yield information about the next using something known as an autocorrelation function, which serves as a statistical measure of how strongly a move at any one given moment is statistically tied to the move a given time interval later. They plotted this correlation and found that it decays exponentially, with a characteristic decay time of about four minutes; by roughly twenty minutes the correlation falls to the “noise level”, after which the function cannot predict the direction of the next move from the previous one. The researchers state that this is in line with the efficient market hypothesis, which has long served as the orthodox justification for the random-walk view of prices. Building upon this distinction, the researchers state that if the direction of the returns is disregarded and only the size of the respective returns is taken into consideration, then a correlation exists as a slow power law that persists for months rather than minutes. This signifies that similar changes in volatility cluster together. For example, a large change in the absolute value of an index is likely to be followed by an equally large change for periods spanning multiple months. The distinction here is that while correlations exist in both the size and direction of value changes, the former is significantly stronger, with directional autocorrelation remaining comparatively weak (Gopikrishnan et al.). Additionally, the volatility result obtained from this analysis suggests a flaw in the efficient market hypothesis, since this model clearly depicts that markets are not random walks and display some degree of predictability.

In conclusion, this display of universality, despite the evident differences in the multiple indices, serves as a direct connection to the field of physics. Since finance lacks any equivalent theory to describe the occurrence of such a model, its recurrence lends further support to the application of physical models to economic and financial systems.

Crashes as Critical Points: The Log-Periodic Model

Despite Gopikrishnan and his collaborators engaging in depth with this model and its implications, they were unable to find suitable descriptions of the causes for such models to arise. The concepts of universality and scaling explored in this paper provided only a deepening of description but not explanation. Thus, the distinction between accurately describing a phenomenon and explaining its origin becomes increasingly important.

In order to build our understanding of the aforementioned tail events that are described as occurrences that create or destroy wealth, we turn to a 2001 paper by Sornette and Johansen titled “Significance of log-periodic precursors to financial crashes”. The paper treats a stock market crash as the financial counterpart of a critical point in physics, which is described as the moment a system tips over from one phase to another (Sornette and Johansen). Additionally, this paper is distinct from the many other papers included in this review due to its explanatory rather than descriptive nature.

The paper’s proposed mechanism builds upon the behaviour of traders during speculative time periods or bubbles, which it describes as increasingly peer-driven, where traders imitate one another rather than making independent investment decisions. As a result of such positive feedback, price increases are observed which invite further buying within the market. As this effect augments and such a “bubble” matures, the crash hazard rate, or the probability that the market collapses in the next instant, rises along with it. Wary investors who are aware of the increasing risk their position carries look for incentives to remain within the markets during such times; these incentives materialise in the form of price rises over even shorter periods of time, thus producing a climb in price that is not merely exponential but accelerating towards a theoretical “critical time” when plotted against the log of the time remaining until the critical time. The critical time does not necessarily signal an impending crash but rather the end of a bubble’s stability; the crash, on the other hand, is a probabilistic event that can occur at any given time near a critical point (Sornette and Johansen).

The researchers modelled the bubble as a power law and observed that the rate of price rises too increases as the model approaches the critical point; in other words, the derivative of the graph too increases at an exponential rate near the critical point. When further analysing this climb, the authors found another signature near the top of such a graph, one that was heavily emphasised throughout the paper. As the critical point approaches, the graph does not retain its smooth rise but instead forms uneven oscillations, wherein each successive crest and trough is shorter than the previous one by a fixed ratio, causing the peaks to bunch closer together as the crash nears. This end-stage oscillatory behaviour, imitating harmonic motion from physics, is what is termed “log-periodicity” and explored as a pre-emptive indicator of crashes within the paper. The paper places an emphasis on this pattern due to its constant recurrence across multiple crashes. When researchers analysed crashes across markets, asset classes, as well as time periods, they found that this pattern arose in every single one, and the two main parameters governing this signature also settled into a narrow range of values: the steepness of the power-law climb during its approach to the critical point and the rate at which the log-periodic oscillations accelerate (Sornette and Johansen).

The Model’s Predictive Record

The researchers believed that the model's practical use arises from its ability to estimate the critical time before a collapse when fit to real market data. In order to explore this claim of the model's predictive abilities, they fit the framework to two decades of pre-crash data from the Hang Seng index and compared the accuracy of the crash predictions offered by the model to the real timelines of the collapse. As a result, the model issued nine alarms, out of which five preceded actual crashes or large corrections, against four false alarms and one clear miss. The researchers agree that the model's predictive ability seems dull, and in doing so compare it to a coin toss; however, they also argue this comparison misjudges where the difficulty actually lies. The hard part, they argue, lies in identifying which two-month period out of the hundred and twenty that make up the two decades examined carries the highest risk of a crash. In order to back this claim, the researchers find that five correct alarms from the model is far more unlikely to be a product of chance than the raw tally suggests. Computing this probability through a combinatorial model, the researchers found that the odds of arriving at five correct predictions by chance within the analysed time period alone stand at roughly four in a million. Thus they conclude that the results of the model are "highly suggestive of a real significance" and strengthen the paper's claim that log-periodicity can serve its purpose as a pre-emptive signature to a crash (Sornette and Johansen 13).

Reflexivity and the Limits of the Physical Analogy

The model, however, runs into trouble once again, as its predictions hold up far less cleanly to criticism. Feigenbaum, another such economist, responds to the model by showing that if the final year of data before a crash is removed, the log-periodic signal loses its statistical significance and predicts a crash months before the real one (Feigenbaum). On the other hand, the response produced by Sornette and Johansen states that the removal of such critical data, especially that closest to what they describe as the critical point, defeats the purpose of the model itself. Despite this, this exchange exposes how much the result depends upon a very selective piece of the overall data provided to it in order to make its prediction. Feigenbaum's criticism suggests that rather than the model forcing a fit onto market data in order to make its prediction, a genuine mechanism would detect a cause in advance rather than specifically on the steep build-up to the crash.

Additionally, the researchers themselves concede a deeper theoretical flaw in the log-periodic model. Unlike the inanimate systems studied in physics, whose behaviour is wholly unaffected by any prediction made about them, the financial markets that the log-periodic model targets are populated by agents capable of reacting to the very forecasts issued about them. The researchers observe that once a crash prediction is issued by the model, a change takes place in the very system it aims to predict, since the agents within it can act upon that prediction. They set out three outcomes: one wherein no individual or "agent" heeds the warning and the crash arrives as forecasted, a win for the model but serving no real practical purpose; one wherein most individuals believe the warning and exit their positions, but in doing so bring about panic and thus accelerate the timeline of the crash; and the last wherein enough individuals act and exit their positions, allowing the bubble to deflate by itself while the crash is averted, though in this case the model would disprove itself due to the crash never arriving. In every case the forecast either fails to help or undermines the very theory that

produced it. Sornette and Johansen thus describe such markets as systems possessing “learning and reflective abilities, in contrast with the usual inanimate and unchanging physical laws of nature” (Sornette and Johansen 14). Additionally, in recent times this mechanism has only sharpened due to the rise of algorithmic and agent-based trading models. These models, unless severely differentiated, work upon similar sets of training data and thus build majorly undifferentiated strategies. As the uptake and integration of these models into the market increases, the correlated behaviour shared across a large number of them only produces herding faster and more often, thus accelerating the very crash timeline that the model aims to predict. In order to account for such a recent uptake of AI-based trading, these models must allow for the faster, more correlated herding that algorithmic trading introduces.

V. Methodological Limitations of Econophysics

The following section aims to focus on the critiques of econophysics in light of its creation as an abstract coalition between the two seemingly distinct fields of economics and physics. The criticisms that follow do not come from stern proponents of orthodox economics or physics but instead stem from researchers within the orbit of econophysics itself. The most pointed indictment, Gallegati, Keen, Lux and Ormerod’s 2006 paper titled “Worrying trends in econophysics”, is written by authors who open by acknowledging the field’s role in developing finance and economics through an abstract perspective, affirming the field’s “important empirical contributions” (Gallegati et al. 1) and that its open-minded approach to data “should be welcomed unequivocally by economists” (Gallegati et al. 2). A short time after the publishing of this paper, one of the authors, Thomas Lux, produced a long and balanced survey of the field’s achievements and shortcomings, essentially depicting that one of the field’s central critics also serves as one of its most constructive surveyors. What follows through this paper, then, is not an attack on econophysics itself but an argument among its practitioners about how the field should hold itself to account.

Neglect of Existing Economic Literature

Gallegati and his associates raise four major concerns they observe within the field, three of which are methodological in nature. The first is a lack of the effective integration of work that is already a part of economics; they argue that much of the econophysics literature turns a blind eye to findings with similar results that already exist in orthodox economics literature. The authors liken this to imagining “a new paper on quantum physics with no reference to received literature” (Gallegati et al. 2), an important shortcoming when considering that the exponential and power-law distributions detailed above only retrace a problem already considered and set aside by economists decades earlier.

Statistical Rigour and the Lognormal–Power-Law Problem

Another concern stems from the authors observing a resistance towards more rigorous statistical tests against the data econophysicists aim to analyse. The writers believe that econophysics relies too heavily on observational methods of fitting models to data without analysing the effectiveness of these fits through thorough statistical tests for the same. They believe that fitting a straight line to log-log axes and classifying it as a power law is an elementary manner of analysis that is not concrete enough to justify the claims that are built

upon such fits. The basis behind this claim stems from a finding that suggests output data from a lognormal distribution can easily be mistaken for a power law (Newman). To gain an understanding of this, a critical signature of the power law comes into play. This signature is that the power law must always trace a straight line on logarithmic axes, with the slope giving an exponent that defines this curve. This exponent is referred to as the Pareto exponent. A lognormal distribution, on the other hand, does not trace a straight line but instead forms a gentle downward curve. Despite this, from a mathematical standpoint almost any curve is indistinguishable from a straight line when viewed over a short enough stretch. As a result, when the lognormal distribution is sufficiently spread out, that “short enough stretch” can run across several orders of magnitude. This offers a direct critique of the income and wealth distributions explored earlier in Section III of this paper. Furthermore, in stating that income data is often obscured by the creation of a range of values for the same, the researchers believe that these ranges are too inexact to permit the clean characterisations the field has claimed from them. Section III of this paper explored a two-regime structure, the Boltzmann–Gibbs model that depicts the lower 95 percent of earners and the Pareto power-law tail above it for the remaining 5 percent, both of which are dissected and critiqued by Gallegati and his colleagues. Economic literature on this topic is itself split between the lognormal and exponential reading, with some of the most careful work tending toward a lognormal, and the distribution shifting over time in both regimes (Gallegati et al.). Thus this draws greater questions to the Pareto structure previously analysed in Section III.

The Conservation-of-Money Assumption

The fourth and arguably most important of Gallegati and colleagues’ concerns draws out a major structural flaw in the kinetic exchange models that build upon the Boltzmann–Gibbs analogy, a model that is utilised prominently, once again, in the income and wealth distributions. These models fall short when they assume that the monetary value of money circulating in an economy through the multiple “agents” remains constant. This serves as the primary theoretical link to distributions wherein energy is conserved, such as the Boltzmann–Gibbs model. This flaw, in considering that monetary transactions amount to a zero-sum situation, is one that directly contrasts with fundamental economics. Gallegati rightly asserts that capitalist economies are not zero-sum but instead generative in their ability to create value and income through production, which yields a net physical surplus, or, in the authors’ words, occurs when “the quantity of goods produced exceeds the inputs consumed in their production” (Gallegati et al. 5). In simpler terms, a fixed pool of money being transferred between agents cannot mimic the value creation that occurs in reality. The authors concede that despite such a model being considerably useful in scenarios such as “primitive hunter-gatherer societies, for example, or modern on-line poker tournaments” (Gallegati et al. 5), wherein no net value is added through production processes, it cannot be used to model modern-day industrial economies.

A Defence: Conservation as a Deliberate Simplification

Despite this, the authors of many of the criticised papers within the above-mentioned survey by Gallegati and colleagues would respond by asserting that the conservation problem was not overlooked but was rather an accepted flaw. The first and foremost connection of

economic data to physics derived solely from the conservation assumption, without which the many models developed within econophysics would not have come to be. Thus, the assumption above represents a deliberate compromise, one the researchers accept in order to construct an initial framework capable of explaining the broader phenomenon. This base structure can then be refined as and when the solutions to its limitations are discovered, enabling the model to improve while preserving its core methodology. Quite fittingly, this manner of developing a model mirrors that often utilised in physics, which routinely starts with a closed system and then generalises to an open one.

The Author's Own Proposal: Linking Value Injection to GDP Growth

Building on this defence, I would add a proposal of my own. As the central bank slowly injects money into the economy, at a rate relative to the economy's growth or decline, in the short run the economy sits in a semi-stable state, which the conservation assumption serves effectively. An effective method to improve the above-defined conservation structure would, in my view, be the incorporation of a value-addition or value-destruction mechanism capable of injecting or removing money (value) from the economy in a manner that tracks a country's GDP growth rate.

McCauley's Response to the Critique

Within the same journal as Gallegati and his coauthors' above-mentioned 2006 paper came a rather prompt response from the physicist and economist Joseph L. McCauley in a paper titled "Response to 'Worrying Trends in Econophysics'". However, the rebuttal does not necessarily defend all aspects of the first critique; McCauley concedes that many professionals within the field tend to have an unjustified appetite for discovering universal scaling exponents where none should generally be expected. Additionally, he concedes that conserved-money models are the wrong foundations to build economics models upon for the modern economy, since money is created and destroyed through various factors which, as explained above, the model did not account for. Furthermore, he states that fat tails, individually, occur too often throughout many economic data sets to hold significance as an explanation for the underlying factors of the models. He states that these fat tails are easy to generate when certain constraints are disregarded, and thus sets of data that do display power-law tails generate no evidence that the model is capable of identifying a unique mechanism behind them. These power-law distributions also offer little to no explanation about whether or not a model is right or flawed. He adds that many of the methods of econophysics are suitable for systems in or near a state of equilibrium, whereas real financial markets display no equilibrium at all. This is supported by the lack of empirical evidence of a statistical equilibrium ever arising in a real market (McCauley).

McCauley's main argument is narrower and stems from the fact that orthodox economics should not be utilised to justify the shortcomings of econophysics, as many of the field's foundational elements (such as utility, general equilibrium, and supply and demand curves) themselves do not rely upon an empirical basis as justification. McCauley offers a contrasting perspective on the matter of Gallegati's critiques and states that the reliance of economics upon theoretical frameworks distances the field from the true nature of economic reality and its nuances, while serving as a superficial and institutional field. Thus econophysics' data-

driven analysis and derivation of the respective theories, despite being weak in their execution, serves as a methodological improvement over the traditional field of economics (McCauley).

The Shared Verdict: Description Without Explanation

Both opposing views make compelling arguments for their respective sides, with Gallegati depicting that econophysics' implications do not align with the respective data, whereas McCauley aims to disrupt traditional economics theories themselves by classifying them as unrepresentative of the real world. Yet within the many rebuttals between the two papers, a major agreement between the two authors that may be overlooked is drawn to light and serves as the field's primary drawback. As McCauley states that fat tails are "too easy to explain" and that no real market sits at equilibrium, he concedes that econophysics is unable to viably create and provide an in-depth theoretical explanation of its many phenomena (McCauley 10). This is an area where economics itself is able to prevail, in its capacity to provide behavioural and theoretical explanations.

Lux's Survey: Achievements and Agent-Based Modelling

Thomas Lux, a coauthor of the first paper analysed within this section, had written a comprehensive survey in 2008 on the field of econophysics that occupies the constructive middle of this debate. An instrumental chapter of his work points out the contributions of the field of econophysics in various distinct ways. He credits econophysics as having two genuine achievements, the first of which is an empirical one and involves the identification of various previously unknown facts about financial markets which general economics lacked the ability to form independently. These include the cubic tail scaling of returns, volatility clustering, the recurrence of similar scaling forms across different assets, and more. The second achievement credits researchers within the field as having built interaction-based agent models that are able to mimic human behaviour and thus allow for implications to be drawn from the same (Lux).

In contrast to these achievements, Lux also draws attention to the field's inability to adequately address certain pivotal points, these points being those he and his colleagues already described in his aforementioned paper. Yet one of the most central contributions of Lux's survey describes where the field's practical value truly lies. This refers to its ability to borrow and effectively utilise the framework of agent-based modelling from physics and apply it using relevant economic data. Since the economy consists of a plethora of individuals, all influencing one another, the model is effective in capturing a wide range of "agent" behaviour that would otherwise, as a macroeconomic shortcut, be aggregated and considered as one large average "agent" instead. Lux develops this idea from the economist James B. Ramsey, who states that "macro activity is essentially the result of the interactions between agents and as such is not usefully represented by a single 'optimizer' that by definition eliminates all trade between agents and thereby ignores the interactions between them" (Ramsey qtd. in Lux 49). This suggests that a single individual behaving in a manner that maximises their own benefit does not necessitate that an entire economy must act in the same manner. This occurs as a result of people in a collective behaving in a manner that no individual within this collective intended. Thus it is due to the same mathematical 'shortcut'

or simplification through which macroeconomics is made manageable that the very fundamental interactions that form the economy are aggregated away.

The Unexplained Tail and the ‘Parallel Society’ Problem

Lastly, Lux draws attention back to one of the major issues identified by McCauley, this being the lack of explanatory power held by the power-law distribution. He suggests that in order to build our understanding of the model utilised throughout many of the field’s foundational studies, it is necessary that we “bridge the gap between the extremely simple wealth exchange processes proposed in the econophysics literature and the much more involved emergent new literature on wealth formation in economics” (Lux 43), since neither, on its own, has yet explained the Pareto tail.

Lux concludes his argument by establishing that, in his view, much of econophysics still remains “a kind of parallel society” (Lux 48), or a self-contained world of unique research papers and journals that still seem foreign to most economists. He finds that attempts to coordinate the two disciplines and build a unified field of study would not necessarily be successful on their current trajectory. Overblown claims of econophysics’ superiority (he points to McCauley by name) and a sometimes amateurish handling of economic concepts have made the field easy to dismiss. Furthermore, the log-log fits the field so heavily relies upon are seen as crude when compared to the detailed and long-established econometrics. As a path forward, for the field to fruitfully progress, he suggests taking the many effective findings of scaling regularities that resulted from this field — patterns in income, wealth, firm sizes and returns that have turned out to be far more stable than many of the headline relationships mainstream economics built its models on, the supposed link between money supply and demand being his go-to example — and pairing them with the statistical rigour the field has so far avoided. In doing so, econophysics’ data-first approach would serve as a complement to economics rather than a parallel conversation alongside it (Lux).

VI. Conclusion

The above review set out with the initial goal of assessing the degree of success econophysics achieves in explaining economic systems as well as market behaviour. The same verdict is reached across every domain analysed above: that though the subject’s data-driven approach does achieve results with greater precision than conventional models, the results are unable to provide the concrete explanation required to account for why such phenomena arise in the first place.

Each domain analysed above repeats the same story, which leads to a more philosophical question, one that asks whether or not a predictive model requires an explanatory basis if it can prove to make accurate predictions at a significant frequency. This question sits underneath the whole of this review, and it must be answered before the research question can be.

If explanation is defined solely by a model’s ability to describe and predict observed behaviour, then econophysics has already established itself as a successful framework. If explanation instead requires an understanding of the mechanisms that generate these regularities, then the field remains fundamentally incomplete. Throughout this review the

statistical patterns themselves were rarely in dispute; it was the absence of a stable foundation capable of accounting for them that repeatedly emerged as the discipline's central limitation.

The answer to the research question is therefore not direct but a divided one: econophysics succeeds almost completely as a description of economic data and falls short as an explanation of it, while remaining, throughout, an extremely useful framework for analysing that data. Perhaps its most valuable suggestion is that it is not only economic data that behaves this way, but that complex systems more broadly may be governed by universal mathematical principles. Whether those principles, on their own, amount to an explanation is a question not just for econophysics but for science as a whole.

Note

1. Drăgulescu and Yakovenko, "Exponential and Power-Law Probability Distributions," for the 1998 state-level data; Drăgulescu and Yakovenko, "Evidence for the Exponential Distribution of Income in the USA," for the earlier IRS series.

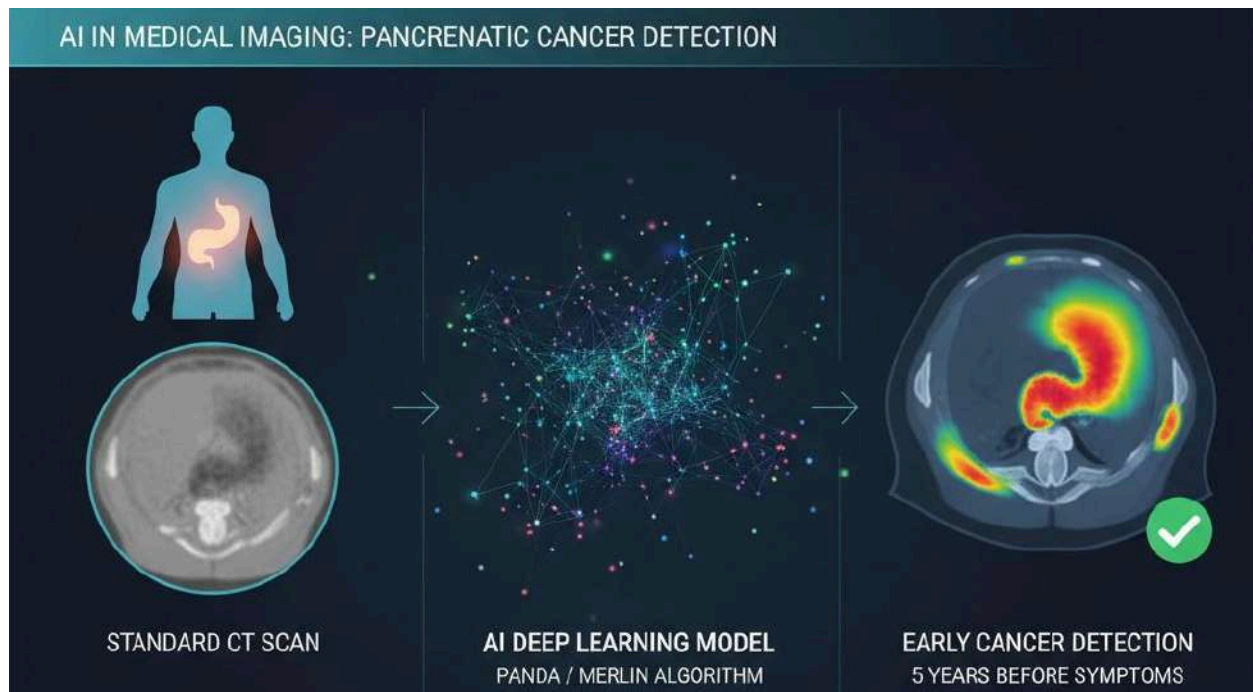
Works Cited

- Bachelier, Louis. "Théorie de la spéculation." *Annales scientifiques de l'École Normale Supérieure*, 3rd ser., vol. 17, 1900, pp. 21–86. Numdam, http://www.numdam.org/item/ASENS_1900_3_17__21_0/.
- "Bell Curve – Overview, Characteristics, Uses." *Corporate Finance Institute*, <https://corporatefinanceinstitute.com/resources/data-science/bell-curve/>.
- Black, Fischer, and Myron Scholes. "The Pricing of Options and Corporate Liabilities." *The Journal of Political Economy*, vol. 81, no. 3, 1973, pp. 637–54. The University of Chicago Press, <https://www.journals.uchicago.edu/doi/10.1086/260062>.
- Bouchaud, Jean-Philippe. "An Introduction to Statistical Finance." *Physica A: Statistical Mechanics and Its Applications*, vol. 313, nos. 1–2, 2002, pp. 238–51. ScienceDirect, <https://www.sciencedirect.com/science/article/pii/S0378437102010397>.
- Bouchaud, Jean-Philippe, and Marc Mézard. "Wealth Condensation in a Simple Model of Economy." *Physica A: Statistical Mechanics and Its Applications*, vol. 282, nos. 3–4, July 2000, pp. 536–45. arXiv, <https://arxiv.org/abs/cond-mat/0002374>.
- "Central Limit Theorem." *Encyclopædia Britannica*, <https://www.britannica.com/science/central-limit-theorem>.
- Drăgulescu, Adrian, and Victor M. Yakovenko. "Evidence for the Exponential Distribution of Income in the USA." *The European Physical Journal B*, vol. 20, no. 4, Apr. 2001, pp. 585–89. arXiv, <https://arxiv.org/abs/cond-mat/0008305>.
- Drăgulescu, Adrian, and Victor M. Yakovenko. "Exponential and Power-Law Probability Distributions of Wealth and Income in the United Kingdom and the United States." *Physica A: Statistical Mechanics and Its Applications*, vol. 299, nos. 1–2, Oct. 2001, pp. 213–21. arXiv, <https://arxiv.org/abs/cond-mat/0103544>.

- Feigenbaum, James A. “A Statistical Analysis of Log-Periodic Precursors to Financial Crashes.” *Quantitative Finance*, vol. 1, no. 3, 2001, pp. 346–60. arXiv, <https://arxiv.org/abs/cond-mat/0101031>.
- Gallegati, Mauro, et al. “Worrying Trends in Econophysics.” *Physica A: Statistical Mechanics and Its Applications*, vol. 370, no. 1, 2006, pp. 1–6. ScienceDirect, <https://www.sciencedirect.com/science/article/pii/S0378437106004225>.
- Gastwirth, Joseph L. “A General Definition of the Lorenz Curve.” *Econometrica*, vol. 39, no. 6, 1971, pp. 1037–39. JSTOR, <https://www.jstor.org/stable/1909675>.
- Gopikrishnan, Parameswaran, et al. “Scaling of the Distribution of Fluctuations of Financial Market Indices.” *Physical Review E*, vol. 60, no. 5, 1999, pp. 5305–16. arXiv, <https://arxiv.org/abs/cond-mat/9905305>.
- Lux, Thomas. “Applications of Statistical Physics in Finance and Economics.” *Kiel Working Paper*, no. 1425, Kiel Institute for the World Economy, June 2008. EconStor, <https://www.econstor.eu/handle/10419/4302>.
- Markowitz, Harry. “Portfolio Selection.” *The Journal of Finance*, vol. 7, no. 1, 1952, pp. 77–91. JSTOR, <https://www.jstor.org/stable/2975974>.
- McCauley, Joseph L. “Response to ‘Worrying Trends in Econophysics.’” *arXiv*, June 2006, <https://arxiv.org/abs/physics/0606002>. Preprint.
- Newman, M. E. J. “Power Laws, Pareto Distributions and Zipf’s Law.” *Contemporary Physics*, vol. 46, no. 5, Sept. 2005, pp. 323–51. arXiv, <https://arxiv.org/abs/cond-mat/0412004>.
- Pareto, Vilfredo. *Cours d’économie politique*. 2 vols., F. Rouge, 1896–1897.
- Sornette, Didier, and Anders Johansen. “Significance of Log-Periodic Precursors to Financial Crashes.” *arXiv*, June 2001, <https://arxiv.org/abs/cond-mat/0106520>. Preprint.
- “What Is the Efficient-Market Hypothesis? Overview and Criticisms.” *Britannica Money*, Encyclopædia Britannica, <https://www.britannica.com/money/what-is-the-efficient-market-hypothesis>.
- Yakovenko, Victor M., and J. Barkley Rosser. “Colloquium: Statistical Mechanics of Money, Wealth, and Income.” *Reviews of Modern Physics*, vol. 81, no. 4, Dec. 2009, pp. 1703–25. arXiv, <https://arxiv.org/abs/0905.1518>.

Evaluating the Efficiency of AI Algorithms in the Early Detection of Pancreatic Ductal Adenocarcinoma via CT scans

By: Rudra Patel - March 10th, 2026



Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a huge clinical challenge due to its late-stage visibility and very low five-year survival rate of about 12%¹. This report investigates the development of AI-driven screening models for finding a solution to earlier interventions and findings. The 2026 PANORAMA international study and the Stanford-led Merlin Model focused on deep learning performance in non-contrast and contrast enhanced CT scans. Findings from the research show that AI models had a mean Area Under the Receiver Operating Characteristic (AUROC) of 0.92 which exceeded the radiologist mean of 0.88². Even more, foundation models like Merlin can accurately predict future disease risk in scans that appear healthy with 75% accuracy up to 5 years in advance³. Integrating AI as a reader in standard radiology workplaces can help the detection of occult tumors, even shifting the detection and diagnosis times by several years.

Keywords: Pancreatic ductal adenocarcinoma (PDAC), Area Under the Receiver Operating Characteristic (AUROC), AI-driven screening models

Introduction

The biological nature of pancreatic cancer is shown by rapid metastasis and unclear early symptoms, leading to diagnosis when the primary tumor is inoperable ⁴. Computed Tomography (CT) is the primary source for detection that is non-invasive, but human readings are limited by “blind spots” where small tumors blend in with the surrounding pancreatic tissue ¹.

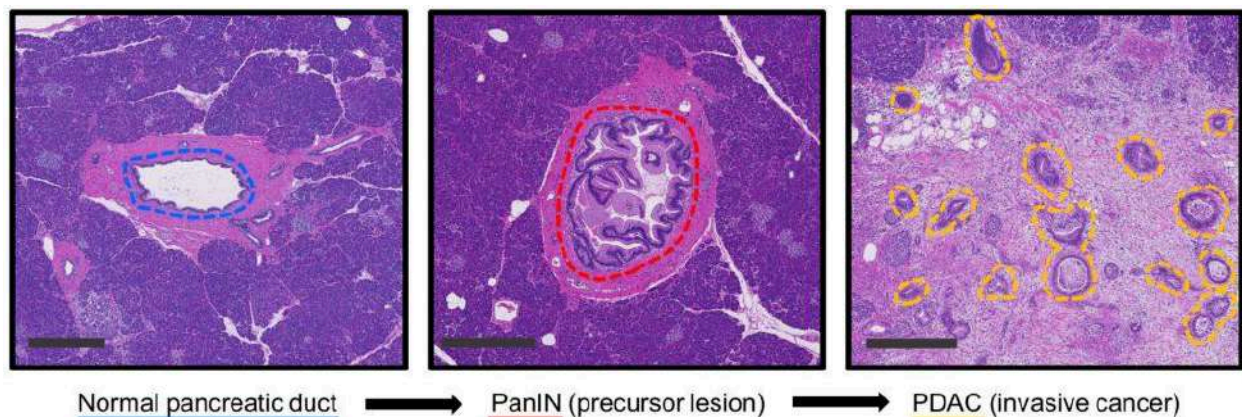


Figure 1 | Pancreatic histology including a histologically normal duct (left), a pancreatic cancer precursor lesion (PanIN, center), and pancreatic cancer (PDAC, right). From [Kiemen et al. \(2023\)](#).

The critical gap in care is not being able to detect tumors smaller than 2 cm, which have a higher chance to successfully resect it using surgery. Recent improvements in AI solve this by seeing “radiomic biomarkers” which are subtle textural patterns that are seen on scans taken for unrelated issues like abdominal pain or kidney stones⁵. These patterns are invisible to the human eye.

This report shows the shift towards opportunistic screening, and by using AI to audit every abdominal CT scan, healthcare systems can add a safety net screening for early-stage malignancies⁶.

Methods

A systematic review was conducted using PubMed and the Lancet Oncology. Key terms were “AI PDAC detection”, “convolutional neural networks” and “foundation models”. The search was focused on studies published between 2024 and March 2026.

This report focuses on the PANORAMA study (an international multi-center project) and the PANDA (Pancreatic Cancer Detection with AI) framework. These represent significant developments because they use non-contrast imaging, which was previously considered useless for cancer diagnosis¹.

The research is grounded in the use of Foundation Models. Unlike other AIs that require “labels” for every image, models like Merlin are trained on over 15,000 abdominal CTs and nearly one million diagnosis codes to understand normal vs abnormal anatomy all on its own³.

Results

Data from the 2026 PANORAMA study which included 3,440 patients across 12 countries, showed that the top three combined AI algorithms outperformed 68 experienced radiologists².

Deep learning models use Convolutional Neural Networks to analyze raw DICOM data. They process images in layers and identify abnormalities that humans cannot see. These visions help catch early ductal changes⁵.

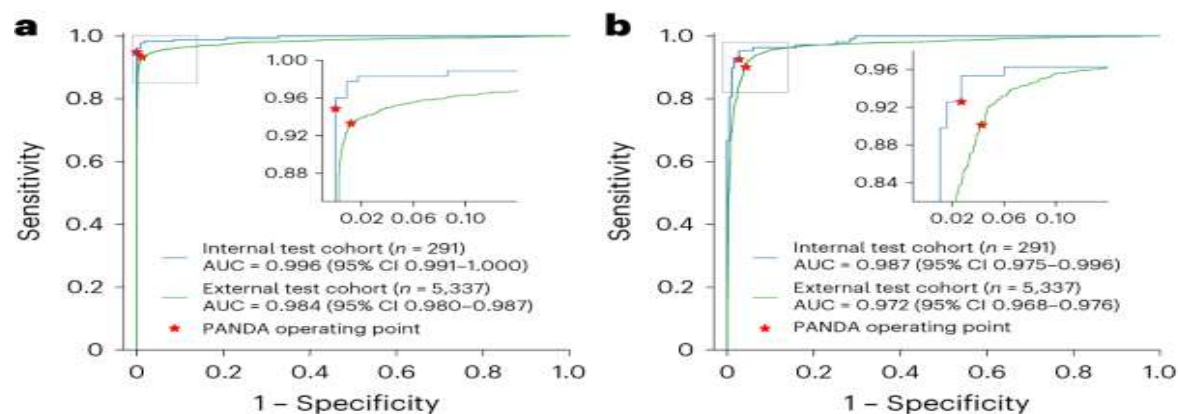


Figure 2 | Receiver operating characteristic curves of lesion detection (a) and PDAC identification (b) for the internal and external test cohorts.

<https://www.nature.com/articles/s41591-023-02640-w>

In the PANDA validation, AI generated “heatmaps” that flagged irregularities in non-contrast scans with a sensitivity of 92.9% and a specificity of 99.9%¹. This effectively allows a low-cost, non-invasive scan to match the effectiveness of high-cost contrast imaging.

Discussion

The primary objective of this report was to evaluate new improvements in medical AI. The findings show that AI systems now reliably exceed human accuracy in both detection (current cancer) and prognosis (future risk)^{2,3}.

These results show a turning point in oncology. The ability of models like Merlin to identify biomarkers up to 5 years before symptoms show means that screening is not an event anymore, but a whole background process³.

Even though high sensitivity, the nature of AI where its reasoning is not always clear is still a barrier to full clinical adoption⁶. Furthermore, false positives (averaging 2 per 1,000 scans) still require human supervision to prevent unnecessary biopsies⁵.

By 2026, AI has moved from a research experiment to a “digital co-pilot”, making sure that no warning sign of cancer, no matter how subtle, goes unnoticed.

References

1. N. Alves, et al. Combining multimodal medical imaging and artificial intelligence for the early diagnosis of pancreatic cancer. *Frontiers in Medicine*. Vol. 12, 2025, <https://doi.org/10.3389/fmed.2025.1631671>.
2. D. Rutkowski, et al. AI can detect pancreatic cancer better than radiologists. *Karolinska Institutet News*. Dec. 2025, <https://news.ki.se/ai-can-detect-pancreatic-cancer-better-than-radiologists>.
3. National Institutes of Health (NIH). AI Tool Could Help Doctors Detect Disease Earlier from CT Scans. *NIH News Release*. March 2026.
4. J. B. Smith, et al. Cancer statistics 2025: Trends in pancreatic oncology. *CA: A Cancer Journal for Clinicians*. Vol. 75, pg. 10-45, 2025.
5. 2 Minute Medicine. AI scans detect pancreatic cancer years before clinical diagnosis. *Medical News Review*. July 2025.
6. G. Dean, et al. Real-world monitoring of artificial intelligence in radiology: challenges and best practices. *Korean Journal of Radiology*. Vol. 26, pg. 1010-1021, 2025.

Myanmar Crisis: Rohingya Residents Fleeing for Refuge to be Met with None...

As of 2017, 700,000 Rohingya people crossed the border into Bangladesh (Doctors Without Borders, [2024](#)), and in 2025, this number rose to 1.2 million (Norwegian Refugee Council, [2025](#)). Additionally, 75% are women and children (UNHCR, [2026](#)). This crisis has been persistent for eight years now, marking it as a major issue globally. However, this minority has been facing struggles that go beyond eight years. To understand why Rohingya residents are fleeing in the first place, we first need to understand Myanmar's history.

On January 4th 1948, Myanmar (formally Burma) became independent from British rule. When it started to drift away from a democratic system in 1962, that is when Myanmar became dictatorial. In 1962, a military coup was hosted by General Ne Win which lasted for 28 years. (Maizland, [2022](#)). The 1974 Constitution differs from the 2008 one (current constitution) as the 1974 version focused on a social economic system, causing the economic system to deteriorate and resulting in overall corruption by 1988. (Maizland, [2022](#)). In March-September of 1988, the infamous 8888 Uprising occurred in which many in Burma protested against military rule but were suppressed when the Burmese army gained full power. (Volf, [2013](#)). In 1989, Aung San Suu Kyi, the daughter of the leader who brought the country to independence and a major leader for the democratic movement, was put under house arrest. Myanmar reached a state of political stability from 2011-2015 until 2021. In February of 2021, the military coup gained control again when Aung San Suu Kyi won. She was again arrested in 2021 as the military coup gained control again.

In 2021, the military coup imposed multiple human right violations. The people report harsh working and living conditions, and people are stripped away from freedom as the majority of the trade unions have been disbanded. (International Trade Union Confederation, [2025](#)). Decades of persecution follow minorities such as the refugees of Rohingya.

Minorities such as the Rohingyas have been experiencing displacement since 1978. Myanmar is classified as a predominantly Buddhist nation, thus conflict conspires between these two groups as the Muslim minority groups are denied Burmese citizenship (Mishra, [2025](#)). As of July 2025, 150,000 people have arrived in Bangladesh, with this being the largest movement (United Nations News, [2025](#)). In these refugee camps, many are reported to experience abuse and lack of basic necessities. To ensure these people are receiving proper care, Bangladesh refugee camps such as Cox's Bazar are able to provide health, economic stability, education, etc. through NGOs such as the International Rescue Committee. (International Rescue Committee, [2025](#)). However, Bangladesh is experiencing an overcrowding of these refugees

The Myanmar people have been experiencing for decades displacement and conflict, with around 1/3 of their population experiencing famine and food insecurity. (reliefweb, [2025](#)). Despite its plentiful natural resources, farmers lack the tools and basic necessities to get food and export it as supply chains are blocked off and heavily guarded by military groups. Myanmar's food prices also increase annually, thus making food less accessible to locals. Especially since the Rohingya people are bound to these climate change challenges, many are

displaced or have to find somewhere else to go and Myanmar refuses to allow them back (Islam, 2025). Many in Bangladesh are not happy with this, with the term “Rohingya” often used as a slur by locals – even Cox Bazar and Bhasan Char emphasize these negative connotations as Rohingyas are considered as unwelcomed and foreign (Pasha, 2025), with articles bashing Rohingyas for coming and becoming an “invasive species” as if they’re an animal (Prothom Alo, 2025). Because Bangladesh has never passed a legislation to acknowledge refugee rights, Rohingya refugees continue to live in harsh conditions, including overcrowding, lack of access to food, lack of education, etc (Norwegian Refugee Council, 2025). Statistics show that 58% feel unsafe in the refugee camps, with most of these accounts from women (Medecins Sans Frontiers, 2025). In Bangladesh, many have the hope that their children can become educated and lead a better life than they did in Myanmar – Medecins Sans Frontiers patient.



Baloch, Babar. “UNHCR: Bangladesh Has Welcomed 150,000 Rohingya Refugees in Last 18 Months.” *UNHCR US*, 11 July 2025, www.unhcr.org/us/news/briefing-notes/unhcr-bangladesh-has-welcomed-150-000-rohingya-refugees-last-18-months.

Image of Rohingya Refugees in Bangladesh at Cox’s Bazar. Includes 1 million cramped into 24 kilometers.

Due to low global funding, the Rohingya population will be at risk of collapsing as more and more people arrive. Last month, food aid had stopped, with education for 230,000 (with 630,000 arriving) being discontinued, crushing parents’ hopes of ensuring their kids are educated (Baloch, 2025).

Although multiple neighbors such as Bangladesh, Thailand, and European nations and organizations have contributed to improving quality of life for displaced Myanmaris and refugees, the people of Myanmar are not being provided the essential care they deserve when arriving in Bangladesh. Because Myanmar runs off of an illicit economy, many of the people rely on it to survive, and when it's addressed, criticism is met. This system needs to be improvised to assess the needs of the Rohingyas as clear discrimination is being met between Buddhists and Muslims. 75% of 1.2 million refugees are women, thus experiencing the most injustice in these refugee camps and in Myanmar.

If Bangladesh doesn't enact legislation to protect refugee rights, then the future holds more Rohingyas refugees and more injustice than ever, disrupting their diplomatic relations and forever changing the lives of millions more to come.

Works Cited

Baloch, Babar. "UNHCR: Bangladesh Has Welcomed 150,000 Rohingya Refugees in Last 18 Months." *UNHCR US*, 11 July 2025, www.unhcr.org/us/news/briefing-notes/unhcr-bangladesh-has-welcomed-150-000-rohingya-refugees-last-18-months.

Bangladesh. Doctors Without Borders - USA. (2025, September 29). <https://www.doctorswithoutborders.org/what-we-do/where-we-work/bangladesh>

"Eight Things You Should Know about the Rohingya Crisis in Bangladesh." *NRC*, NRC, 16 Sept. 2025, www.nrc.no/feature/2025/eight-things-you-should-know-about-the-rohingya-crisis-in-bangladesh.

"নদীতে যেভাবে ছড়িয়ে পড়ছে ক্ষতিকর সাকার বা রোহেঙ্গা মাছ." *Prothomalo*, www.prothomalo.com/video/bangladesh/j3h7aayp04. Accessed 23 Jan. 2026.

"International Trade Union Confederation - Building Workers' Power." *International Trade Union Confederation*, 2025, www.ituc-csi.org/.

Islam, Mohammad Tarikul. "The Humanitarian Crisis of the Rohingya Refugees in Bangladesh: Issues with Their Living and the Host Government's Repatriation Initiatives." *Harvard Humanitarian Initiative*, 30 Sept. 2025, hhi.harvard.edu/news/2025/09/humanitarian-crisis-rohingya-refugees-bangladesh-issues-their-living-and-host.

Maziland, L. (2022, January 31). *Myanmar's troubled history: Coups, military rule, and ethnic conflict*. Council on Foreign Relations. <https://www.cfr.org/backgrounder/myanmar-history-coup-military-rule-ethnic-conflict-rohingya>

Mishra, V. (30AD). *Rohingya plight in Myanmar, a "test for humanity"* | *UN news*. United Nations. <https://news.un.org/en/story/2025/09/1166004>

“Rohingya Refugee Crisis: Supporting the Stateless Minority Fleeing Myanmar | USA for UNHCR.” *The UN Refugee Agency*, 2026, www.unrefugees.org/emergencies/rohingya-refugee-crisis/.

“Rohingya Refugees Express Feeling Unsafe, Lacking Control over Their Future | MSF.” *Medecin Sans Frontier*, 29 Sept. 2025, www.msf.org/rohingya-refugees-express-feeling-unsafe-lacking-control-over-their-future.

Sarkar, N. “From Refugee to Slur: ‘Rohingya’ as Signifier of Otherness in Everyday Bangladesh - South Asia@lse.” *South Asia@LSE* -, 30 June 2025, blogs.lse.ac.uk/southasia/2025/06/30/from-refugee-to-slur-rohingya-as-signifier-of-otherness-in-everyday-bangladesh/.

“The IRC.” *How to Help Myanmar*, 17 Dec. 2024, www.rescue.org/article/crisis-myanmar-what-know-and-how-help.

United Nations. (2025, July 11). *150,000 Rohingya flee to Bangladesh amid renewed Myanmar violence* | *UN news*. United Nations. <https://news.un.org/en/story/2025/07/1165369>

Volf, I. (2018, November 2). *Physicians for human rights - remembering the 8888 protests in burma*. PHR. <https://phr.org/our-work/resources/remembering-the-8888-protests-in-burma/>

WFP warns one million in Myanmar to be cut off from food aid amid funding shortfall - *Myanmar*. ReliefWeb. (2025, March 14). <https://reliefweb.int/report/myanmar/wfp-warns-one-million-myanmar-be-cut-food-aid-amid-funding-shortfall>

CRISPR Cas-9 as a Potential Cure for Wilson's Disease By Satoshi Toya

Abstract

Wilson's Disease is an inherited copper metabolism disorder that is characterized by the pathological accumulation of copper throughout the body. It is caused by a mutation in the ATP7B gene – a gene that encodes a transmembrane copper-transporting protein – which inhibits the body's ability to transport copper properly. This results in the accumulation of copper in organs such as the brain and liver, which cause ophthalmological, hepatic, neurological, and psychiatric symptoms. The primary methods of treatment are chelators and zinc salts, which lower copper levels through different mechanisms; these treatments can become expensive because they need to be used continuously throughout the patient's lifetime.

However, CRISPR – an immune system used by various bacteria and archaea to eliminate invading viruses and plasmids – can be utilized as an effective gene editor, with many possible applications, including the treatment of chronic genetic diseases. The most prominent version of CRISPR used for this purpose is the CRISPR-Cas9 system. This paper aims to achieve multiple goals: to explain Wilson's Disease, mechanisms, and symptoms; to overview CRISPR and how CRISPR-Cas9 can modify DNA in genes; and to propose how CRISPR could be used to potentially permanently cure chronic genetic diseases, such as Wilson's Disease.

Introduction

Wilson's Disease is an inherited disorder of copper metabolism that causes abnormal copper accumulation in many organs, particularly the liver and brain, resulting in a wide range of symptoms^{5, 121}. This copper overload can result in a myriad of negative consequences, including oxidative stress and protein toxicity, most notably in the mitochondria.

On a molecular level, Wilson's Disease arises due to oxidative stress, copper-mediated toxicity occurs when excess dissolved copper catalyzes the formation of hydroxyl radicals in the presence of peroxides via Fenton reactions¹⁴⁸.

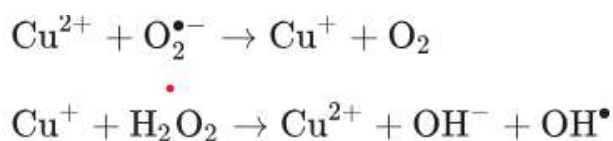


Fig 1: Fenton reaction

Hydroxyl Radicals are strong oxidants that can impede protein functionality by reacting with amino acids such as tyrosine and cysteine². This substance not only directly interacts with DNA and RNA and causes oxidative DNA damage⁵⁸, but it can also interact with fatty acids, which in turn can create lipid peroxides and aldehydes that can react with DNA or amino acids to form adducts^{48, 57, 82}. The adducts themselves are also detrimental to the patient's health as DNA adducts, for example, cause the DNA part to be damaged, which leads to its abnormal replication in the body and could cause mutations that potentially lead to conditions such as cancer¹²⁸.

Copper can directly target specific proteins in the body, most notably membrane proteins, by binding to thiol residues, resulting in the cross-linkage of these proteins¹⁷⁸. A possible result of this phenomenon is the mitochondrial membrane permeability transition (MPT), which is caused by copper directly interacting with thiol groups in important mitochondrial proteins such as the adenine nucleotide translocase^{42, 159}. Additionally, MPT can be present in organs such as the liver and brain, although the severity of MPT caused by copper varies from organ to organ¹².

Wilson's Disease Pathophysiology

Wilson's Disease is mainly caused by mutations affecting the ATP7B gene, which contains 20 introns and 21 exons, and is located on the long arm of chromosome 13 (Specifically region 13q14.3) with a genomic length of 80 kb^{119, 185}.

The protein is first synthesised in the endoplasmic reticulum, and then it is relocated to the Trans-Golgi-Network (TGN) within hepatocytes. The ATP7B gene itself is most highly expressed in the liver, but it is also found in other organs such as the kidneys, brain, and lungs¹⁸⁰.

The Genetics of Wilson's Disease

The ATP7B protein itself consists of 1465 amino acids (165 KDa) which are organized into many different parts of the protein: the phosphatase domain (A-Domain), which is identifiable by the amino acid motif TGEA alongside TGDN and GDGVND; the phosphorylation domain (P-domain), identified by the amino acid motif DKTGT; the M domain, which consists of 8 transmembrane ion channels; the nucleotide binding domain (N-Domain), identified by the amino acid motif SEHPL; and the N-Terminal metal binding domain (MBD), which contains 6 copper binding sites with the amino acid motif GMXCXXC and plays a central role in accepting copper from the copper chaperone ATOX1^{20, 33, 87, 138}.

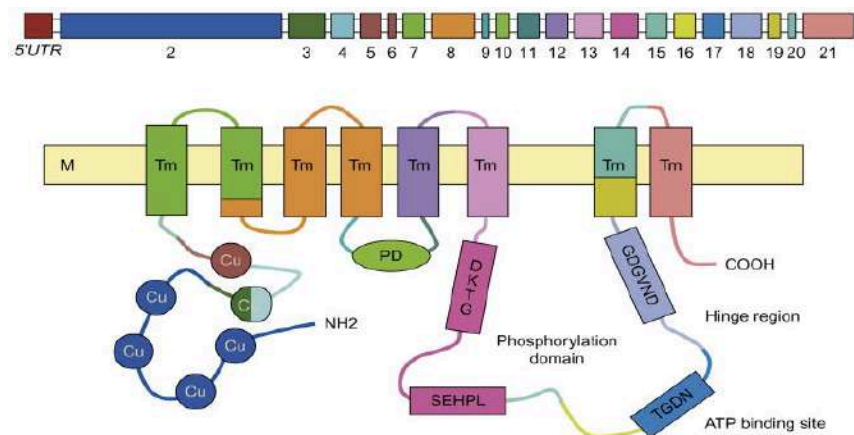


Fig 2: The general structure of the ATP7B protein
(The genetics of Wilson disease - PMC)

ATP7B is responsible for encoding a copper cation-transporting P-type ATPase that facilitates the transportation of copper between cells. These proteins are upregulated in liver

hepatocytes, and the proteins are mainly found in the Golgi Apparatus^{36, 157}. This membrane-bound transporting protein facilitates the transport of copper from the cytoplasm to the Trans-Golgi Network, where copper binds to the protein apoceruloplasmin, forming ceruloplasmin, a copper transport protein. Ceruloplasmin then enters the bloodstream to distribute copper to the rest of the organs for their necessary function^{36, 91, 98, 139}.

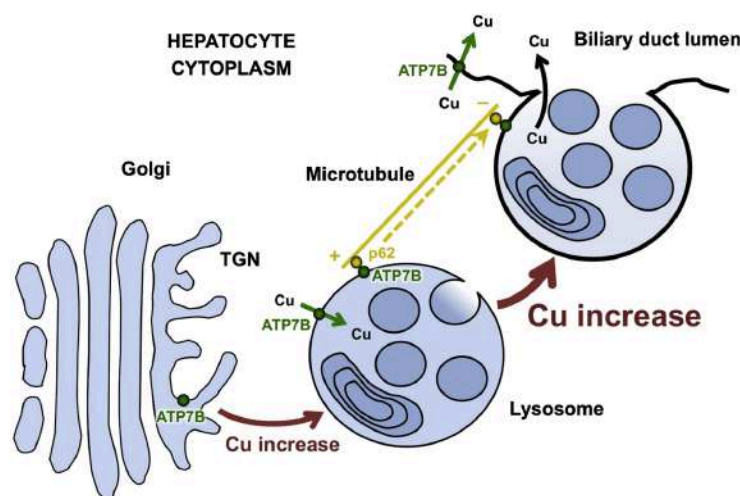


Fig 3: The general arrangement of ATP7B within the hepatocytes and its role in transporting copper

Focusing on the protein mechanism in greater detail, the active transport of copper across cell membranes begins with ATP7B binding copper at the MBD domain and transporting it across cellular membranes, driven by the hydrolysis of adenosine triphosphate (ATP). Then, the free copper binds intracellularly to GG motifs in the MBDs, followed by transport to the Cys-Pro-Cys (CPC) sequence motifs in MBD 6. Finally, the dephosphorylation of acyl-phosphate at the A-domain discharges copper across the cellular membrane¹⁸⁰.

Copper is necessary for bodily function in many ways, notably acting as a cofactor for many critical cuproenzymes essential for human metabolism¹⁵⁶.

An example of this is in Cytochrome-c oxidase, located in the inner mitochondrial membrane, which has two copper sites in the form of CuA and CuB³⁷. Cytochrome-c oxidase acts as the terminal oxidase of the mitochondrial respiratory chain in most aerobic organisms, transporting electrons from donors to a final acceptor to create ATP, simultaneously reducing molecular oxygen (O₂) into water (H₂O)³⁷.

Another example is human SOD1, a zinc-copper metalloenzyme in all cells that regulates the body's antioxidant response^{41, 107}. Functionally, SOD1 catalyzes the disproportionation of superoxide anions (O₂⁻) into molecular oxygen and hydrogen peroxide, which are further eliminated by catalase, glutathione peroxidases, and peroxiredoxins⁴¹. This biochemical process is important because without this type of regulation, the superoxide can react to produce more dangerous Hydroxyl radicals (•OH) that can cause further cellular damage^{100, 107}. Additionally,

copper is necessary for SOD1 to catalyze the disproportionation, as reduction of superoxide occurs at the copper-zinc metal center^{4, 26, 171}.

Another example of a necessary copper-containing protein is ceruloplasmin, which serves as both a copper transport protein and a ferroxidase with the ability to oxidize Fe(II) to Fe(III). Oxidation of the iron substrate allows iron to bind more strongly to transferrin, which is responsible for iron transport and distribution in the body^{38, 118, 156}. Ceruloplasmin also removes excess copper in hepatocytes through vesicles, where ceruloplasmin is excreted through the apical membrane to create bile^{98, 139}.

However, when the ATP7B gene is mutated, it causes a mutation in the copper-transporting P-type ATPase that leaves the enzyme unable to function properly¹⁰⁸. As a result, this condition leads to both the impaired incorporation of copper into ceruloplasmin³³ and the excretion of copper into bile. Copper accumulates in the liver over time, in some cases increasing copper concentrations from 5 - 20 times normal copper levels in the body²⁷. When the liver reaches its copper-carrying capacity, excess copper is released into the bloodstream and travels back to other organs, resulting in an array of problems¹⁶¹.

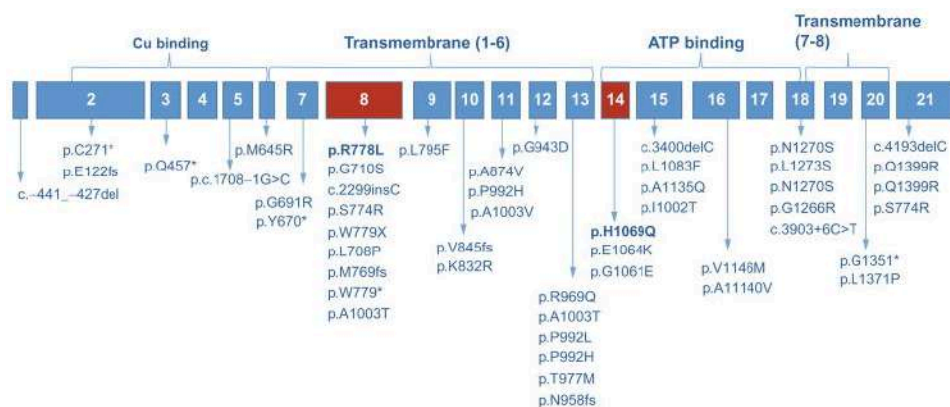


Fig 4: A schematic of the *ATP7B* gene with common mutation sites
([The genetics of Wilson disease - PMC](#))

One of the most common mutations that leads to the disease is the missense mutation H1069Q in exon 14. It's common in Central, Eastern, and Northern Europe, where approximately 50–80% of Wilson's Disease patients carry at least one H1069Q allele inherited from their parents³⁶. In this mutation, the histidine of the conserved SEHPL motif in the N-terminal domain of the *ATP7B* protein is replaced with glutamic acid, which results in N-domain protein misfolding, abnormal phosphorylation in the P-domain, and decreased ATP binding affinity¹³². This mutation can also lead to decreased thermostability and the abnormal localization of the protein to the Trans-Golgi-Network, further disrupting transport processes¹²⁹.

Symptoms

There are multiple symptoms related to Wilson's Disease.

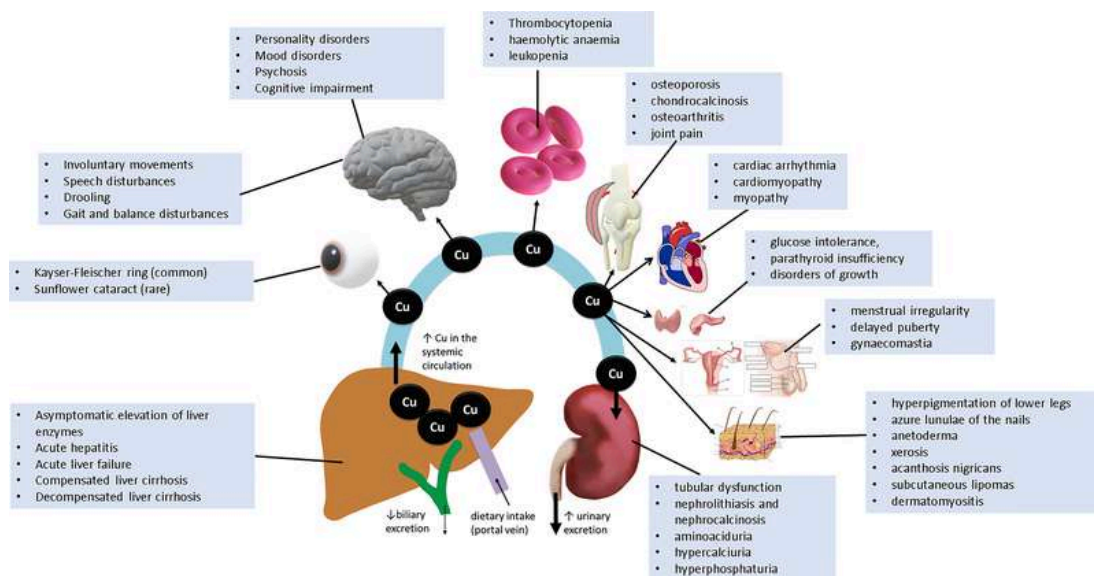


Fig 5: A listing of the organs generally affected by the excess copper caused by wilsons disease. (Nature Reviews Disease Primers article: Wilson disease - PMC)

Hepatic Symptoms

Early symptoms of Wilson's Disease usually manifest in the liver, due to excess copper buildup in hepatocytes^{5, 168}. The severity of excess copper's effect on the liver can vary due to the lack of an exact genotype-phenotype correlation to Wilson's Disease. This can result in relatively small manifestations, such as a self-limiting Hepatitis-like inflammation, and in more severe cases, cirrhosis, or the scarring of the liver, and even acute liver failure¹⁶⁸. Furthermore, cirrhosis leads to jaundice, which can serve as a visual symptom in patients with liver damage. Without treatment, chronic liver disease worsens alongside the appearance of conditions such as portal hypertension, hepatosplenomegaly, ascites, low serum albumin concentration and coagulopathy²⁷.

The severity of these hepatic diseases that can cause cirrhosis is usually reflected by the Model for End-Stage Liver Disease(MELD)⁶⁹ alongside Child-Pugh scores¹²⁷. And normally, these are determined by using abdominal ultrasound (US), CT, and MRI at diagnosis. The most common findings through these methods are events such as fatty infiltration, contour irregularity, and atrophy of the right lobe of the liver²⁷. For patients with chronic liver disease, especially those with cirrhosis, screening examinations for signs of portal hypertension and hepatobiliary malignancies¹²⁰ should be performed regularly¹⁰ and repeated depending on clinical status.

Neurological Symptoms

Neurological symptoms are the second most frequent behind hepatic symptoms and, on average, will onset around the age range of 20-30 (though outliers do exist)^{32, 121}. The most predominant manifestations are tremor, dystonia, and Parkinsonism—all of which are normally associated with dysarthria, gait and posture disturbances, drooling, and dysphagia^{93, 96, 168}. One of the most characteristic neurological symptoms is tremors (shaking or trembling movements),

which is a symptom described by about 55% of patients at diagnosis. Tremors can be either resting, postural, or kinetic, and movement is either unilateral or bilateral and occurs primarily in the arms. Over time, tremors can spread to the legs, head, and throughout the entire body²⁷.

Dystonia, or involuntary muscle contracting, is reported as one of the first Wilson's Disease symptoms in 11–65% of patients²⁷. It can involve a single body part, one segment, multiple segments like a face and a leg, or even be generalized throughout the entire body. The most characteristic representation of dystonia is an abnormal facial expression, or risus sardonicus, which consists of a fixed smile due to dystonia of the risorius muscle.

Ophthalmological Symptoms

Ophthalmological symptoms, predominantly Kayser-Fleischer Rings and sunflower cataracts^{28, 169}, both of which are caused by pathological copper accumulation in the eyes.

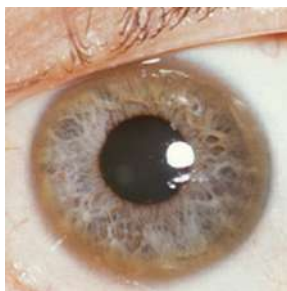


Fig 6: Kayser-Fleischer Ring viewed on the outside)
([Kayser-Fleischer rings | Radiology Reference Article | Radiopaedia.org](#))

Kayser-Fleischer Rings (KFRs) are ring-shaped copper deposits within the eyes that develop when copper is deposited throughout the cornea; a sulfur-copper complex—found only in the Descemet's membrane—then produces visible ring-shaped copper deposits in that area¹²¹. Specifically, the deposit is formed in the anterior chamber angle within the internal corneal layer of the Descemet's membrane, at the Schwalbe's line^{15, 74}.

Normally, Kayser-Fleischer rings are present in almost all people with Wilson's Disease who have developed neurological or psychiatric symptoms. However, there are exceptions, with some patients not having KFRs despite experiencing neurological symptoms¹³⁴.

And generally, the presence of these copper deposits can alter the corneal subbasal nerve plexus (SBNP)—a monolayer of fine, amyelinated nerve fibers in the cornea. One clinical study demonstrated that Wilson's Disease patients can experience corneal neuropathy as a result of this monolayer accumulation. This was determined by an evaluation of Wilson's Disease patients' eyes using corneal confocal microscopy: factors like the number of nerve fibers, nerve fiber length density, number of nerve branchings, and number of beadings were all significantly lower when compared to those unaffected by Wilson's Disease. Additionally, in Wilson's Disease patients, the fiber tortuosity was higher compared to unaffected people, indicating that there was

a lot of nerve regeneration, an indication that nerve fibers in the eyes had died off as a result of neuropathy^{68, 149}.

Kayser-Flescher Rings become visible in the superior aspect of the cornea, followed by the inferior aspect, with subsequent filling in of the medial and lateral aspects. As a result, one would have to expose the entire cornea by lifting the eyelid to properly look for KFRs¹⁵⁰.

Furthermore, KFRs are detected and diagnosed using methods such as slit lamp examination(SLE), which makes KFRs appear as a golden-brown, golden-green, green-yellow, golden-yellow, bronze or reddish-brown coloring ring in the limbic area of the cornea³⁴.

Sunflower cataracts are characterized by copper deposition in the lens capsule, distinct from the lens cortex or nucleus, forming a central disk with radiating petal-like spokes that give it its name¹²⁵. Additionally, Sunflower cataracts seem to be the result of the accumulation of various compounds in the third posterior of the lens' anterior capsule, which includes copper, sulfur, and binding-copper proteins¹⁸¹.

Sunflower cataracts typically do not impair vision and are usually detected through slit lamp examination, as they are not visible to the naked eye or an ophthalmoscope⁹⁶.

Psychiatric Symptoms

Psychiatric Symptoms appear frequently in Wilson's Disease patients³². A 2014 study suggested that psychiatric symptoms can occur before, in tandem with, or after the diagnosis and treatment of Wilson's Disease¹⁷⁷. It can appear in younger patients as declining school performance, impulsiveness, and inappropriate behavior^{142, 152}; It can often appear in older patients as paranoia, schizophrenia, or depression-but it can also commonly appear as behavioral changes³².

The most common psychiatric symptom of Wilson's Disease is mood disturbances, with about 20–60% of Wilson's Disease patients developing depression, with a high rate of suicidal attempts ranging between 4–16% of WD patients^{146, 151, 152, 177}. Adding on to this, behaviors such as emotional lability, irritability and aggression, shallow cheerfulness, euphoria, social disinhibition, hypersexuality, lack of criticism, and deficits in planning and anticipating social consequences can be due to the lesions of the frontal lobe or its pathways¹⁹.

Additionally, Behavioural and personality disorders are also a common psychiatric aspect of Wilson's Disease, with the most common manifestations being irritability, aggression, and antisocial behaviour¹²². Other psychiatric conditions, such as catatonia, anorexia nervosa, bulimia, obsessive-compulsive disorder, and attention-deficit hyperactivity disorder, have also been reported in Wilson's Disease patients^{53, 83}.

Additional Symptoms

There are still more different manifestations of Wilson's Disease. However, the effect of Wilson's Disease on other parts of the human body has been less investigated compared to organs such as the liver and brain²⁷.

One manifestation is the negative effects that the excess copper from Wilson's Disease can cause to the skeletal system, which includes osteomalacia(softening of bones) and osteoporosis(weakening of bones), with increased incidence of spontaneous fractures being observed¹⁶⁵. Additionally, the copper can negatively affect the joints, particularly larger ones, with its accumulation in the synovial membrane and cartilage being suggested as the major cause of osteoarthritis(erosion of cartilage) and accelerated degenerative changes with deformities¹⁰⁹.

Another type of manifestation is cardiovascular symptoms, with myocardial copper accumulation being able to cause cardiomyopathy(decrease of heart muscle function) and arrhythmias(irregular heartbeat)²⁷. Additionally, pathological cardiac examination done on Wilson's Disease patients has shown symptoms such as interstitial and replacement fibrosis, intramyocardial small vessel sclerosis, and focal inflammatory cell infiltration¹⁶.

Some manifestations can affect the red blood cells in Wilson's Disease patients with the excess copper in the bloodstream being able to cause symptoms such as Coombs-negative haemolytic anaemia; this alongside other symptoms may be caused through the reaction of copper with membrane lipids, or copper inhibiting sulfhydryl groups of glucose-6-phosphate dehydrogenase and glutathione reductase which all can reduce cellular antioxidant capacity which leads to oxidative damage of the haemoglobin and cell membrane in red blood cells^{40, 160}.

Last but not least, there are also renal manifestations that are caused by the renal tubular epithelium filtering the non-ceruloplasmin-bound copper in the blood that can cause excess copper buildup in the renal parenchyma, leading to renal tubular dysfunction¹⁷⁶.

Wilson's Disease Incidence / Prevalence

Initially, it was believed that the universal prevalence of Wilson's Disease ,except for a select few small isolated populations, was 1:30,000, based on a study done by Scheinberg and Sternlieb in 1984¹³⁶.

More recent data from the U.S, Europe, and Asia suggest a prevalence range of about 1:30,000-1:50,000, clarifying the 1984 study results¹³⁶. Prevalence is relatively greater in Pakistan and India, due to factors like genetic consanguinity.

Wilson's Disease Treatment Available

Once a patient has been definitively diagnosed with Wilson's Disease, treatment is provided for a patient's entire lifetime^{35, 131}.

Chelating Agents

One type of treatment for Wilson's Disease is pharmaceutical treatment that can induce cupriuresis, or the urinary excretion of copper. This is done primarily with copper chelating agents, such as D-penicillamine and Trientine, or using zinc salts that decrease the absorption of copper in the digestive tract.

D-Penicillamine functions as a chelator that binds divalent metal ions like copper with its sulfhydryl functional group (–SH) to form a water-soluble complex that is excreted out of the body through urine⁴⁷.

Trientine is another copper chelating agent and can act as an alternative to D-penicillamine, particularly for those who are unable to handle D-penicillamine. Trientine binds to copper in a 1:1 ratio to form a strong, stable complex that is excreted in the urine.

D-penicillamine and trientine result in similar patient responses; However, trientine was more likely to exacerbate the neurological effects of Wilson's Disease compared to D-penicillamine⁴⁷. Conversely, D-penicillamine treatment is more likely to be discontinued due to side effects when compared with trientine¹⁶⁶.

When considering overall performance, trientine and D-penicillamine are not inferior to one another, as evidenced by a recent randomized open-label non-inferiority trial¹⁴¹.

However, these types of treatments can be expensive. An example of this is the price for the 2 drugs around 2015, where trientine(Syprine) was \$200 per 250-mg capsule and D-penicillamine(Cuprimine) costing \$55-\$60 per 250-mg capsule¹⁸². Around 2022, the annual cost for treatment was about \$78,000 for trientine, and from \$50,000 to \$200,000 for penicillamin³.

Zinc Supplements

There are also Zinc supplements, which can have multiple versions such as zinc acetate, zinc gluconate, and zinc sulfate. However, there is no statistically significant difference between these variants in terms of the improvement of liver function¹⁸. Zinc preparations work by inducing the synthesis/creation of metallothioneins while promoting the binding of copper to these metallothioneins in the enterocyte of the small and large intestines. The copper-containing enterocyte is then disposed of through it shedding naturally into the gut lumen, then it accompanies the rest of the waste out of the body. This overall process hinders the body's absorption of copper, and prevents the further exacerbation of Wilson's Disease from increasing⁴⁷. Its effects are generally slow as a de-copperating agent, with its effects happening over time rather than manifesting as a sudden, noticeable event. As a result, it's not suitable for treating more florid symptoms such as cirrhosis¹⁴⁰. Wilson's Disease still shows progression in the first few months of treatment¹⁴. When compared to the other types of treatment for Wilson's Disease, this is the cheapest one out of all of them, with the annual cost from 2022, with \$100 worth for nutriment types, and from \$550 to \$3650 for pharmaceutical-grade Zinc³.

Liver Transplant

As a more complex and surgical option, liver transplantation also counts as a treatment for Wilson's Disease^{1, 30, 167}. This approach is based on the concept that Wilson's Disease results from gene defects, such as those in ATP7B, which impair the liver's ability to manage excess copper. Consequently, a liver transplant can be viewed as a phenotypical correction of the gene, thereby restoring copper homeostasis. Normally, liver transplantation in Wilson's Disease

patients is suggested in cases with acute liver failure or decompensated liver cirrhosis with a lack of pharmacological treatment effect. The need for a liver transplant in cases of acute liver failure should be based on a specific WD clinical scale, such as the revised King's prognostic Wilson Index³⁰. On another note, the idea of whether uncontrolled neurological disease constitutes a need for liver transplantation as the “last chance” treatment option is highly controversial^{1, 30, 167}. The problems with this treatment, however, are that it can give rise to a myriad of long-term medical complications in the patient as a result of the transplant. This can include various conditions: cardiovascular complications that account for 20% of the deaths of the patients surviving at least 3 years from a liver transplant¹²⁶; Kidney disease where up to 80% of patients 5 years after a liver transplant will develop chronic kidney disease⁵⁰; Hyperuricemia which has been reported in 14–47% of post Liver transplant patients¹¹⁶, and may be related to deteriorating renal function due to acid uric having a high renal excretion^{95, 113}; Bone complications where 65% of Liver transplant recipients were affected by Atraumatic bone fractures because of cholestatic disease⁹; and many other possible side effects.

Additionally, liver transplants themselves can cost a lot of money, with the operation itself costing about \$600,000, not including the mandatory preoperative evaluations, which can cost from \$168,000 to \$308,000, and the postoperative medications that cost from \$671,000 to \$949,000 in the 10 years that follow the procedure⁵⁵.

When considering overall treatment, the average healthcare cost for a Wilson's Disease patient, based on a 2021 study on the cost burden for Wilson's Disease patients, was about \$3,887 per month after a Wilson's Disease diagnosis¹³⁵. And when looking at a larger scale, the total cost for Wilson's Disease hospitalizations was \$20.90, \$27.23, \$24.20, and \$27.25 million US dollars for the years 2016, 2017, 2018, and 2019, respectively⁸⁶.

CRISPR History

CRISPR (or clustered regularly-interspaced short palindromic repeats) describes a family of DNA sequences found in bacteria and archaea that facilitate an adaptive immunity against mobile and exogenous genetic elements such as viruses. Since their characterization by Emmanuelle Charpentier and Jennifer Doudna, CRISPR systems are now utilized as a precise gene-editing tool that has revolutionized the field of molecular biology^{6, 23}.

CRISPRs were first detected in the *E. coli* bacteria's genome in 1987, where they were characterised as unusual insertion elements consisting of a series of 29 nucleotide repeats separated by 32 nucleotide “spacer” sequences, all of which had appeared whenever bacteria came into contact with invading phage DNA⁶⁰. At the time, scientists were unable to determine the function of these sequences due to the lack of sufficient DNA sequence data, especially for mobile genetic elements⁶¹. In 1993, CRISPRs were first observed in the archaea *Haloferax mediterranei*¹¹¹, and they were subsequently detected in an increasing number of bacterial and archaeal genomes as gene sequencing became cheaper and more widely available in the life sciences. All of these example sequences were conserved, which helped to further the understanding of their function and importance.

Research related to CRISPR came to a head in the early 2000s when two parallel breakthroughs greatly accelerated genetic research efforts.

One breakthrough was an increased understanding of the function of CRISPR as an immune defense after the discovery of the sequence similarities between the spacer regions of CRISPRs and the sequences of bacteriophages, archaeal viruses, and plasmids were reported on by three different research groups^{11, 112, 124}.

The other major discovery was that several genes previously thought to encode DNA repair proteins for hyperthermophilic archaea were actually strictly associated with CRISPR and were designated as Cas (CRISPR-associated) genes as a result^{62, 102}. Comparative genomic analysis had suggested that CRISPR and the Cas proteins both work together to constitute an immune system to protect prokaryotic cells against invading viruses and plasmids (DNA-based threats), comparable to the eukaryotic RNA interference (RNAi) system¹⁰³.

A 2007 experiment proved this hypothesis using the lactic acid bacteria *Streptococcus thermophilus*, where the molecular mechanism of the adaptive immune response to a phage infection was explained⁶.

Additionally, it was demonstrated that CRISPR sequences are transcribed into RNA that is then cleaved and loaded into CRISPR–Cas proteins, resulting in an RNA–protein complex sufficient for RNA-guided double-stranded DNA endonuclease activity^{44, 66}.

CRISPR Mechanism

Specifically, CRISPR consists of two major parts. First, a CRISPR system must contain a genome with an entire CRISPR locus that consists of an array of short direct repeats interspersed with spacer sequences where the spacers and repeats are both uniform in length, but the repeats are identical in sequence content, and the spacers are highly variable in sequence content⁷³. Second, it also consists of Cas enzyme-producing genes organized in operon(s) to allow transcription by the cell^{7, 158, 170}.

Regarding the CRISPR locus in different species of bacteria and archaea, the repeats are about 32 base pairs (bp) long on average, and the spacers are generally of a similar size in the range of 20-72bp^{49, 52, 110}. Related species may have similar repeat sequences, but there is great diversity in the sequences of both spacers and repeats in bacteria and archaea⁸⁴.

In the original immune defense system, the CRISPR–Cas mechanism of action consists of 3 primary stages: adaptation, expression, and interference. In the adaptation step, a complex of Cas proteins encounters a protospacer-adjacent motif (PAM) and causes 2 double-strand breaks in the PAM's invading DNA molecule. The resulting fragment of foreign DNA (termed protospacer, is the target) is then integrated into the CRISPR locus between 2 repeats of the CRISPR array and becomes a spacer around the proximal end of the CRISPR array³¹.

In the expression stage, the Cas gene's expression, which produces Cas proteins, and the transcription of the repeat-spacer element from the protospacer, which produces a precursor CRISPR RNA (pre-crRNA), in which proteins and accessory factors process the pre-crRNA into short mature crRNA, all occurs³¹.

Finally, in the interference step, the crRNA and Cas proteins work together to recognize and mediate the cleavage of the foreign DNA to protect the host cells from the infection^{6, 103}.

Classification of CRISPR/Cas9 Systems

CRISPR/Cas systems are divided into 2 main classes, 6 main types, and 33 subtypes. Class 1 contains multiprotein effector complexes, while class 2 is defined by a single, multidomain, multifunctional effector protein⁶⁷.

All types are distinguished by the different structures of the effector modules, which contain unique signature Cas proteins. Additionally, each type is also classified into numerous subtypes that are characterized by the subtle differences in CRISPR locus organization and encode subtype-specific Cas proteins^{56, 81, 145}.

Overall, the primary features that define the type and subtype of the CRISPR/Cas systems are the Cas genes and the proteins they encode, which functionally and genetically differ across the different variants, as shown in the various steps of CRISPR-mediated immunity.

For example, the type I and III systems(both in Class 1) both produce specialized Cas endonucleases, which process the pre-crRNAs, which mature into crRNA and assemble into a large multi-Cas protein complex capable of recognizing and cleaving nucleic acids complementary to the crRNA³¹.

Type II(which is Class 2) systems, by contrast, process pre-crRNAs with a different mechanism where a trans-activating crRNA (tracrRNA) complementary to the repeat sequences in pre-crRNA triggers pre-crRNA maturation in the presence of the double-stranded RNA-specific ribonuclease RNase III and the Cas9 protein^{29, 51}. Additionally, Cas9 is thought to be the sole protein responsible for the crRNA-guided silencing of foreign DNA^{6, 43, 137}.

The type II CRISPR-Cas, specifically, with the Cas9 protein, is an overall easier, cheaper, and more efficient gene editing tool compared to the pre-existing editing technology, such as ZFNs and TALENs³¹.

Mechanism for CRISPR-Cas 9

The CRISPR-Cas9 system-one of the most prominent and widely used gene editing tools-has the same three main stages of a CRISPR-Cas system: adaptation, expression, and interference.

Adaptation

For the adaptation stage, a complex of Cas proteins may encounter a PAM in the foreign/invading DNA, where the complex will induce 2 double strand breaks close to it; The resulting fragment of foreign DNA (Termed protospacer, is the target) is then integrated into the CRISPR locus between 2 repeats and becomes a spacer around the proximal end of the CRISPR array^{31, 158, 170}.

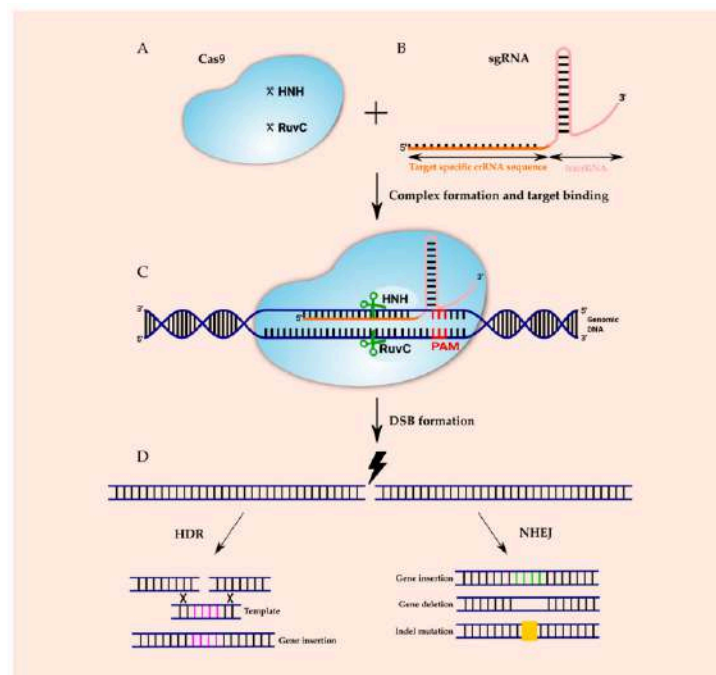
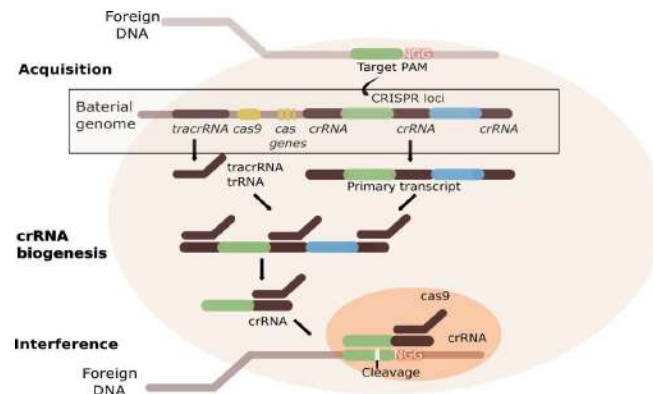


Fig 7-8: The process of CRISPR-Cas9 DNA editing

Expression

For the expression stage, two main events occur in the genome.

One event that occurs is the expression of the Cas9 gene that results in the Cas9 enzyme, a DNA endonuclease that consists of two nuclease domains—the RuvC domain, which cleaves non-complementary DNA strands, and the HNH domain, which cleaves complementary DNA strands—that are responsible for inducing a double-strand break in the target DNA sequence³¹.

The other event—which occurs within the CRISPR Locus—is the transcription of the repeat-spacer element derived from the protospacer, which yields pre-crRNA (**precursor-CRISPR RNA**). Additionally, transactivating crRNAs (*tracrRNA*) are also produced from another section in the CRISPR locus.

The tracrRNA anneals with the pre-crRNA and directs the maturation of the pre-crRNA into mature crRNA in the presence of the endoribonuclease RNase III and Cas9(also called Csn1) protein^{17, 29, 64}. The resulting crRNA is also reduced to a length of 20 nucleotides(nt) through trimming of the 5' end by other nucleases⁶⁴.

This results in a single-guide RNA (sgRNA) composed of two parts: the crRNA, whose 20 nt 5' end sequence is complementary to the protospacer in the target DNA, and the tracrRNA that's connected to the crRNA which will help bind the entire sgRNA to the Cas9 protein³¹.

Overall, the result of these 2 parallel processes is that a CRISPR–Cas9/sgRNA genome editing complex capable of searching for its target is formed, with the sgRNA binding the complex to the target DNA, and the Cas9 protein actually editing the DNA⁶³.

Interference

Ultimately, the interference stage consists of the Cas9/sgRNA searching for its target, with its search and recognition process requiring both a complementary nt base pairing between the 20-nt crRNA and a protospacer in the target DNA, as well as the presence of the Cas9's corresponding PAM sequence that's close to the target site^{44, 66}.

The PAM sequence is crucial for the complex's ability to differentiate between the CRISPR locus itself and foreign sequences, preventing autoimmunity¹⁰⁵, and even single mutations in the PAM can disable Cas9's DNA cleaving ability in vitro while allowing foreign DNA to avoid the complex^{8, 65, 66}. The PAM sequence that the most common Cas9 type SpCas9(from *Streptococcus pyogenes*) corresponds with is 5'-NGG-3', with N being any 1 of the 4 DNA nucleotides^{24, 59}.

Cas9 initiates the target DNA search for the complex by first probing for its corresponding PAM sequence before interrogating the DNA adjacent to the PAM to check for potential guide-RNA complementarity¹⁴⁷. The target recognition itself occurs through 3-dimensional collisions where Cas9 rapidly splits from the DNA that doesn't contain the appropriate PAM sequence, and the dwell time depends on the complementarity between guide RNA and adjacent DNA when the proper PAM sequence is present^{77, 101, 147}.

Once Cas9 has found the target site with the appropriate PAM sequence, it triggers local DNA denaturing, which causes the DNA strand to split in 2 at the PAM-adjacent target site; this is followed by the crRNA binding to the complementary target strand to form a RNA-DNA hybrid alongside the displaced noncomplementary DNA strand—which is all termed as the R-loop—from the PAM-proximal to PAM-distal ends^{147, 153}.

After the R-loop is formed, the Cas9 is now activated for DNA cleavage¹⁴⁷. The Cas9's two nuclease domains each cut one strand of the target three bp from the PAM sequence to produce a mainly blunt double strand break(DSB)^{44, 66}.

After this, two possible DNA repair mechanisms can occur as a result of the DSB from the Cas9 enzyme: non-homologous end joining (NHEJ) and homology-directed repair (HDR)^{54, 94}.

NHEJ consists of the repair of the DSB by joining DNA fragments through an enzymatic process in the absence of exogenous homologous DNA. This process is active in all phases of the

cell cycle. It is a predominant and efficient cellular repair mechanism that is most active in cells, but it is error-prone and may result in the random insertion/deletion (indels) of base pairs at the cleavage site, which can lead to the generation of frameshift mutation or premature stop codon^{92, 115, 133, 172}.

In contrast, HDR is a highly precise repair mechanism that requires the use of a homologous DNA template and is the most active in the late S and G2 phases of the cell cycle. In CRISPR gene editing, HDR requires a large amount of homologous donor (exogenous) DNA templates from either sister chromatids or foreign DNA, which is used in precise insertions and base substitutions at the DSB site^{13, 90, 94}.

Applications for CRISPR-Cas9

In general, the CRISPR-Cas9 system could be used for many applications.

Functional Genome Screening

One application of CRISPR-Cas9 is in genome functional screening to identify key genes involved in various biological processes across different biological models. It's being used in genome-wide, targeted loss-of-function screens as an alternative screening system to RNA interference (RNAi)³⁹. An instance of this is when a genome-scale CRISPR–Cas9 knockout (GeCKO) library was used to identify genes essential for cell viability in cancer and pluripotent stem cells and was then used to screen for genes whose loss is involved in resistance to vemurafenib (treatment for late-stage melanoma) in a melanoma model¹⁴³. Additionally, other studies have identified host genes important for the intoxication of cells by diphtheria and anthrax toxins using the GeCKO library, which was supported by functional validation¹⁷⁵.

Overall, the application of CRISPR screening in functional genomics is helping researchers to discover new gene functions and, in the future, may help explore the molecular mechanisms of a variety of cellular functions³¹.

Virus Treatment

Another application is related to its potential use as a therapy for chronic viral infections⁸⁵. Most antiviral therapies for conditions such as human immunodeficiency virus(HIV) and hepatitis B virus (HBV) aren't a clinical cure because of the inability to remove the viral genome from the infected host cell due to a latent state where viruses minimize their activity inside the host cell to avoid host immune surveillance. As a result, the latency-related life cycles of these viruses play a key role in the incurability of chronic infections, and patients with the virus will have to take antiviral drugs for the rest of their lives.

But CRISPR itself has shown great promise for the treatment of different viral infections in experiments: one instance is in a study where CRISPR–Cas9 has been shown to inhibit HBV replication and gene expression with the inhibition sustained for 3 days after the CRISPR–Cas9 administration, and the results suggest that the Cas system may provide a simple, inexpensive and short-term process for mammalian genome modification¹⁷⁴; CRISPR–Cas9 delivered by

lentivirus significantly decreasing HIV-1 replication in infected primary CD4+ T cell cultures and reducing the viral load in ex vivo CD4+ T cell culture obtained from HIV-1 infected patients suggests that CRISPR-Cas9 can act as a new type of therapy for HIV, and CRISPR-Cas9 may be used as a novel and efficient platform for the cure of AIDS itself⁷⁰; CRISPR-cas9 when used on a Burkitt's lymphoma cell line with latent Epstein-Barr virus (EBV) infection was able to get rid of EBV completely for 25% of the cells, and caused significant EBV load decrease for another 50% of the treated cells when compared to the untreated ones¹⁶².

Overall, the use of CRISPR-Cas9 as an antiviral strategy is a promising prospect, with various in vitro and in vivo studies, giving rise to potential clinical applications for humans that could result in treatment or prevention methods for pathogenic viral infections in humans.

Combating Antibiotic-Resistant Bacteria

CRISPRs can also be used to control and combat antibiotic-resistant bacteria.

One experiment where 2 CRISPR-dCas9 systems were used to repress antibiotic resistance in MRSA (Methicillin-resistant *Staphylococcus aureus*-a human pathogen which is resistant to β -lactam antibiotics such as penicillin) by targeting the *mecA* methicillin resistance gene resulted in a 77% decrease in gene expression in the CRISPR-treated samples, but it did not kill the bacteria, which makes it a viable option for treatment against antibiotic-resistant bacteria¹⁶³.

Another experiment with MRSA introduced a nonviral delivery method (Known as Cr-Nanocomplex) for CRISPR targeting *mecA* (major antibiotic resistance gene involved in MRSA,) which consisted of SpCas9 covalently modified with a cationic polymer called polyethyleneimine (bPEI), as the carrier for packaging sgRNA and boosting their delivery to bacteria. Furthermore, the cultured MRSA strains which were treated with the Cr-Nanocomplex were not able to grow in agar media, including oxacillin at the dose 6 $\mu\text{g/mL}$, while the untreated samples could grow^{71, 164}.

Overall, the use of CRISPR-Cas9 to specifically remove resistance genes in bacteria can be a powerful tool to counteract antibiotic resistance and could be a part of the solution to keep antibiotics working; CRISPR-Cas9 would also have to be used as a conventional broad-spectrum antibiotic, which can potentially target only antibiotic-resistant bacteria while leaving the rest alone³¹.

Cancer Therapy

Another application is CRISPR as a potential cancer treatment³¹. This is shown through multiple studies and experiments. One is in an experiment where epidermal growth factor receptor (EGFR) mutations in EGFR mutation-bearing tumors in vivo were targeted by CRISPR-Cas9 through adenovirus vector delivery which had disrupted the EGFR mutation (L858R) and resulted in cancer cell death and significant reduction of tumor size⁸⁰.

Another is in a study where CRISPR-Cas9 was used to generate chimeric antigen receptor T (CAR-T) cells, which can recognize specific antigens on cancer cells. These CAR-T

cells were used in therapy for patients with acute lymphoblastic leukemia which targeted CD19 and resulted in an effective treatment for the lymphoblastic leukemia while being related to a high remission rate for patients where Stem-cell transplantation was ineffective¹⁰⁶. Some problems face CRISPR cancer therapy, however. One of these problems is the lack of a safe and efficient delivery mechanism that can be applied in clinical trials, alongside the fact that tumor heterogeneity caused by tumors normally having different subclones with different DNA mutations within can make creating the treatment difficult with CRISPR^{21, 46}.

Another problem is editing efficiency, as the effectiveness of DSB repair with HDR and NHEJ can vary in different cell types and states, and the potentially low editing efficiency caused by that factor in certain cells can cause a lack of effectiveness from the treatment^{25, 173}.

Additionally, Cas9—due to being a protein of bacterial origin—can activate the body's immune system, again lowering the effectiveness of the treatment²².

But despite all the problems, CRISPR is still crucial in cancer research³¹; If its safety, specificity, and efficacy is optimized enough for clinical use, then it could be a widespread cancer treatment.

CRISPR Base Editing

Base editing is a form of genome editing that enables the direct and irreversible conversion of one basepair to another at a target genomic locus without requiring DSBs, or HDR processes with their necessary donor DNA templates^{78, 79, 117}. Compared to the standard genome editing methods to introduce point mutations, base editing can do so more efficiently⁷⁹, with far less problems such as stochastic insertions/deletions (indels) or translocations^{76, 78, 79, 117, 130, 184}.

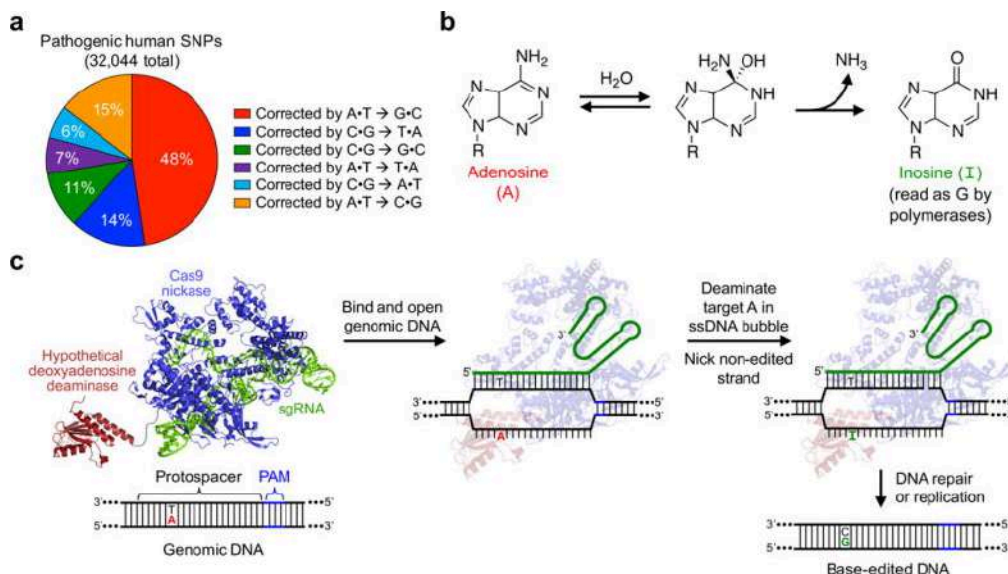


Fig 9: In b, the deamination of Adenosine to Inosine, which is read as G by polymerases. In c, the general structure of how an ABE would work with a deoxyadenosine deaminase working alongside an enzymically impaired Cas9, alongside sgRNA to find a spot in the target DNA and catalyze the deamination of Adenosine to Inosine⁴⁵

There are two main categories of Base editors(BE): cytosine base editors (CBEs) and adenine base editors (ABEs), which are all used with sgRNA for guidance³¹.

Regarding CBEs, one of the most commonly used versions are 3rd generation designs (CBE3), which consist of four main parts:

The first piece is a catalytically impaired CRISPR-Cas9 mutant that is unable to create DSBs (known as nuclease-dead Cas9 or dCas9 for short), the second is a single-strand-specific enzyme capable of converting one base to another with an example in this case being a cytidine deaminase that converts Cytosine(C) to Uracil(U) within a 5-nt window in a single-stranded DNA containing bubble created by the Cas9, 3rd is a uracil glycosylase inhibitor (UGI) that impedes uracil removal and the downstream processes that decrease the base editing efficiency and product purity⁷⁸, and the 4th is an enzymatic nickase that nicks the other non-edited DNA strand complimentary to the first strand, directing cellular DNA repair processes to replace the G-containing DNA strand^{78, 79}.

With all these components, BE3 can carry out the conversion of C•G to T•A efficiently and permanently in many different organisms, from bacteria and plants^{97, 179}, to things such as mice^{75, 130, 183} and human embryos^{88, 89}.

Base editors have expanded in capability through the development of base editors with different properties: different PAM compatibilities⁷⁶, narrower editing windows⁷⁶, enhanced DNA specificity¹³⁰, and small-molecule dependence¹⁵⁴.

Regarding ABEs, these are a relatively recent development, but they share similarities with CBEs in terms of their mechanical design, except for some major differences. One big difference is that CBEs and ABEs have a different single-strand-specific enzyme capable of converting one base to another, with ABEs having a deoxyadenosine deaminase that can catalyze the deamination of Adenine to Inosine in DNA where the Inosine is interpreted as Guanine^{45, 72}. A note about this is that there were no naturally occurring single-stranded DNA Adenine deaminases; only RNA adenosine deaminases were found, which were all unable to edit DNA⁴⁵.

But it was engineered through the directed evolution of *Escherichia coli*'s tRNA adenosine deaminase(TadA) which was chosen since it shares homology with the APOBEC enzyme (cytidine deaminase) used in the previous CBEs, and some APOBECs bind single-stranded DNA in a conformation that resembles tRNA bound to the TadA¹⁴⁴.

The experiment first consisted of introducing a C•G to T•A mutation in the CamR gene of *Escherichia coli*—a gene that codes for chloramphenicol resistance in bacteria—in the form of an H193Y substitution that would weaken the bacteria's chloramphenicol resistance⁴⁵. Then, the researchers had created unbiased libraries of *Escherichia coli*(ec)/TadA-dCas9 fusions that contained mutations only in the adenine deaminase portion of the construct to avoid altering the favorable properties of the Cas9 portion of the editor, and were then transferred into the *E. coli* harboring the CamR H193Y mutation with the idea that A•T to G•C conversion at the H193Y mutation should restore chloramphenicol resistance, linking the TadA's Adenine base editing activity to bacterial survival⁴⁵.

The surviving bacterial colonies that were able to catalyze the A•T to G•C in the CamR gene had the TadA mutations, A106V and D108N⁴⁵. These mutated TadAs were then incorporated into a mammalian codon-optimized TadA–Cas9 nickase fusion construct, where the dCas9 was replaced with the Cas9 D10A nickase used in BE3 to manipulate cellular DNA repair to favor the desired base editing outcomes⁷⁹ alongside a C-terminal nuclear localization signal (NLS)⁴⁵. The resulting TadA*–XTEN–nCas9–NLS construct—where TadA* is the new TadA variant and XTEN is a 16-amino acid linker used in BE33— was designated as ABE1.2, which was capable of carrying out very low efficiency, but observable A•T to G•C editing⁴⁵.

From here on out, efforts would be made to optimize ABEs through engineering a single-chain heterodimer, consisting of a wild-type non-catalytic TadA monomer and an evolved TadA monomer(TadA-TadA*). And further work would result in prominent versions such as ABE7.10 and ABE8e that would convert A•T to G•C base pairs efficiently with very high product purity and very low rates of indels^{45, 72}.

Additionally, ABEs compared with CBEs yield a far cleaner product with fewer mistakes and reports of significant off-target (A-to-non-G) edits to date⁷². Adding on to this, unlike CBEs with their UGI mediated inhibition of Uracil-DNA glycosylase(UDG-enzyme that removes Uracil), ABE editing in cells that lacked alkyl adenine DNA glycosylase (AAG)—the enzyme known to recognize and remove inosine in DNA which would in theory inhibit ABE ability—failed to increase the editing efficiency or product purity compared with cells containing AAG, which shows the sheer converting power of ABE compared to CBE⁷².

CRISPR's Use for Curing Chronic Disease

CRISPR-Cas9 base editing could be used to cure chronic genetic diseases, such as Wilson's Disease, that would otherwise be incurable and require treatment for the rest of the patient's lifetime. This would be done by first identifying the specific mutation in the target gene (ATP7B in this case) that results in the disease. Mutations can occur in multiple different places on a gene, such as H1069Q and R778L in patients with Wilson's Disease, making genomic screening a valuable and necessary precursor to a newly designed treatment. The mutation itself can be of types that are in different places within the gene for each person which would require the use of genomic screening, with Wilson's Disease having many different missense mutations, such as H1069Q and R778L. Once the mutation is identified, the sequence of the mutation area would be inserted into a CRISPR locus, where the proper sgRNA would be generated alongside Cas9 with an engineered base editor; this would then form the basis for a Cas9/sgrNA genome editing complex. The complex would then be injected into the patient in a specific bodily region most affected by the disease. For Wilson's Disease, a medical team would most likely target the liver for gene editing complex delivery. Finally, the patient would be monitored to ensure there are no negative effects from treatment.

The most apparent benefit is that CRISPR-Cas9 base editing would possibly be able to cure the genetic disease for good; moreover, another benefit is that with a one-time treatment, the

patient receiving it would never have to spend additional money on temporary treatments, saving thousands of dollars a year.

The idea of CRISPR curing a genetic disease has been made a reality quite recently. A real-life example of CRISPR-based editing used to treat disease is the case of an infant named “KJ” who received treatment for a rare inherited metabolic disease in 2025, detailed in a study by The New England Journal of Medicine. Specifically, KJ experienced a severe carbamoyl phosphate synthetase 1 (CPS1) deficiency. This is a rare genetic disease that causes the lack of a liver enzyme in the liver needed to convert ammonia (generated from the normal breakdown of proteins in the body to urea), which causes ammonia to build up to toxic levels in the subject and can damage organs such as the brain and liver. Patients with CPS1 deficiency, like KJ would normally be treated with a liver transplant; however, to undergo a liver transplant, patients would need to be medically stable and old enough to handle such a major procedure—neither of which was true for KJ.

Ahrens-Nicklas and Kiran Musunuru MD, PhD (Barry J. Gertz Professor for Translational Research in Penn’s Perelman School of Medicine) are co-corresponding authors on the published report and began collaborating in 2023 to study the possibility of creating customized gene editing therapies for rare metabolic disorders. They had mainly focused on urea cycle disorders. Soon after KJ’s birth, they were able to identify KJ’s specific variant of CPS1 through genetic sequencing. The team, including Nicklas and Musunuru, was able to design and manufacture a CRISPR-based editing therapy in 6 months. In late February 2025, the treatment was delivered to KJ’s liver via nanoparticles to correct KJ’s lack of functional CPS1 enzyme, and then he received follow-up doses in March and April of 2025. As of the time of reporting, KJ has experienced no serious side effects from treatment; additionally, KJ has been able to increase consumption of protein and has been weaned off of nitrogen scavenger medication. KJ has also demonstrated recovery from certain typical childhood illnesses like rhinovirus (virus that’s predominant cause of common cold) without ammonia building up in his body. Longer follow-up is needed to fully evaluate the benefits of the therapy, but so far the treatment seems promising¹¹⁴.

Although KJ will need to be monitored carefully for the rest of his life due to possible immunogenic or genetic side effects, his case demonstrates the possibility for CRISPR to be able to treat genomic diseases that would otherwise put great strain and pressure on thousands of people.

Acknowledgements

Thanks to Dr. Daniel Plymire and Theodore Press for providing assistance in the form of helpful discussions and inspiration for the paper.

Works Cited

1. Ahmad, Ahsan, et al. "Liver Transplantation for Wilson Disease." *Handbook of Clinical Neurology*, vol. 142, 2017, pp. 193–204. *PubMed*,
<https://doi.org/10.1016/B978-0-444-63625-6.00016-1>.
2. *Andrés: Impact of Reactive Species on Amino Acids—Biol...* - Google Scholar.
https://scholar.google.com/scholar_lookup?title=Impact%20of%20reactive%20species%20on%20amino%20acids-biological%20relevance%20in%20proteins%20and%20induced%20pathologies&publication_year=2022&author=C.M.C.%20Andr%C3%A9s&author=J.M.%20P%C3%A9rez%20de%20la%20Lastra&author=C.%20Andr%C3%A9s%20Juan&author=F.J.%20Plou&author=E.%20P%C3%A9rez-Lebe%C3%B1a. Accessed 27 July 2025.
3. Avan, Abolfazl, et al. "The Role of Zinc in the Treatment of Wilson's Disease." *International Journal of Molecular Sciences*, vol. 23, no. 16, Jan. 2022, p. 9316.
www.mdpi.com, <https://doi.org/10.3390/ijms23169316>.
4. Banci, Lucia, et al. "Human Superoxide Dismutase 1 (hSOD1) Maturation through Interaction with Human Copper Chaperone for SOD1 (hCCS)." *Proceedings of the National Academy of Sciences of the United States of America*, vol. 109, no. 34, Aug. 2012, pp. 13555–60. *PubMed*, <https://doi.org/10.1073/pnas.1207493109>.
5. Bandmann, Oliver, et al. "Wilson's Disease and Other Neurological Copper Disorders." *The Lancet. Neurology*, vol. 14, no. 1, Jan. 2015, pp. 103–13. *PubMed Central*,
[https://doi.org/10.1016/S1474-4422\(14\)70190-5](https://doi.org/10.1016/S1474-4422(14)70190-5).
6. Barrangou, Rodolphe, et al. "CRISPR Provides Acquired Resistance against Viruses in Prokaryotes." *Science (New York, N.Y.)*, vol. 315, no. 5819, Mar. 2007, pp. 1709–12.

- PubMed*, <https://doi.org/10.1126/science.1138140>.
7. Bhaya, Devaki, et al. “CRISPR-Cas Systems in Bacteria and Archaea: Versatile Small RNAs for Adaptive Defense and Regulation.” *Annual Review of Genetics*, vol. 45, 2011, pp. 273–97. *PubMed*, <https://doi.org/10.1146/annurev-genet-110410-132430>.
 8. Bikard, David, et al. “CRISPR Interference Can Prevent Natural Transformation and Virulence Acquisition during In Vivo Bacterial Infection.” *Cell Host & Microbe*, vol. 12, no. 2, Aug. 2012, pp. 177–86. *www.cell.com*, <https://doi.org/10.1016/j.chom.2012.06.003>.
 9. Bjøro, K., et al. “Secondary Osteoporosis in Liver Transplant Recipients: A Longitudinal Study in Patients with and without Cholestatic Liver Disease.” *Scandinavian Journal of Gastroenterology*, vol. 38, no. 3, Mar. 2003, pp. 320–27.
 10. Boga, Salih, et al. “Hepatic Features of Wilson Disease.” *Handbook of Clinical Neurology*, vol. 142, 2017, pp. 91–99. *PubMed*, <https://doi.org/10.1016/B978-0-444-63625-6.00009-4>.
 11. Bolotin, Alexander, et al. “Clustered Regularly Interspaced Short Palindrome Repeats (CRISPRs) Have Spacers of Extrachromosomal Origin.” *Microbiology (Reading, England)*, vol. 151, no. Pt 8, Aug. 2005, pp. 2551–61. *PubMed*, <https://doi.org/10.1099/mic.0.28048-0>.
 12. Borchard, Sabine, et al. “The Exceptional Sensitivity of Brain Mitochondria to Copper.” *Toxicology in Vitro*, vol. 51, Sept. 2018, pp. 11–22. *ScienceDirect*, <https://doi.org/10.1016/j.tiv.2018.04.012>.
 13. Branzei, Dana, and Marco Foiani. “Regulation of DNA Repair throughout the Cell Cycle.” *Nature Reviews. Molecular Cell Biology*, vol. 9, no. 4, Apr. 2008, pp. 297–308. *PubMed*, <https://doi.org/10.1038/nrm2351>.

14. Brewer, George J., et al. "Treatment of Wilson Disease with Ammonium Tetrathiomolybdate: IV. Comparison of Tetrathiomolybdate and Trientine in a Double-Blind Study of Treatment of the Neurologic Presentation of Wilson Disease." *Archives of Neurology*, vol. 63, no. 4, Apr. 2006, pp. 521–27. *PubMed*, <https://doi.org/10.1001/archneur.63.4.521>.
15. Broniek-Kowalik, Karina, et al. "Anterior Segment Optical Coherence Tomography (AS-OCT) as a New Method of Detecting Copper Deposits Forming the Kayser-Fleischer Ring in Patients with Wilson Disease." *Acta Ophthalmologica*, vol. 97, no. 5, Aug. 2019, pp. e757–60. *PubMed*, <https://doi.org/10.1111/aos.14009>.
16. Buksińska-Lisik, Małgorzata, et al. "Cardiac Assessment in Wilson's Disease Patients Based on Electrocardiography and Echocardiography Examination." *Archives of Medical Science : AMS*, vol. 15, no. 4, July 2019, pp. 857–64. *PubMed Central*, <https://doi.org/10.5114/aoms.2017.69728>.
17. C, Liao, and Beisel Cl. "The tracrRNA in CRISPR Biology and Technologies." *Annual Review of Genetics*, vol. 55, Nov. 2021. *pubmed.ncbi.nlm.nih.gov*, <https://doi.org/10.1146/annurev-genet-071719-022559>.
18. Camarata, Michelle A., et al. "Zinc Maintenance Therapy for Wilson Disease: A Comparison Between Zinc Acetate and Alternative Zinc Preparations." *Hepatology Communications*, vol. 3, no. 8, July 2019, pp. 1151–58. *PubMed Central*, <https://doi.org/10.1002/hep4.1384>.
19. Carta, Mauro Giovanni, et al. "Bipolar Disorders and Wilson's Disease." *BMC Psychiatry*, vol. 12, May 2012, p. 52. *PubMed*, <https://doi.org/10.1186/1471-244X-12-52>.
20. Cater, Michael A., et al. "Intracellular Trafficking of the Human Wilson Protein: The

- Role of the Six N-Terminal Metal-Binding Sites.” *The Biochemical Journal*, vol. 380, no. Pt 3, June 2004, pp. 805–13. *PubMed*, <https://doi.org/10.1042/BJ20031804>.
21. Chen, Minjiang, et al. “CRISPR-Cas9 for Cancer Therapy: Opportunities and Challenges.” *Cancer Letters*, vol. 447, Apr. 2019, pp. 48–55. *PubMed*, <https://doi.org/10.1016/j.canlet.2019.01.017>.
 22. Cheng, Xing, et al. “CRISPR/Cas9 for Cancer Treatment: Technology, Clinical Applications and Challenges.” *Briefings in Functional Genomics*, vol. 19, no. 3, May 2020, pp. 209–14. *PubMed*, <https://doi.org/10.1093/bfpg/ela001>.
 23. Cong, Le, et al. “Multiplex Genome Engineering Using CRISPR/Cas Systems.” *Science (New York, N.Y.)*, vol. 339, no. 6121, Feb. 2013, pp. 819–23. *PubMed*, <https://doi.org/10.1126/science.1231143>.
 24. Cong, Le, and Feng Zhang. “Genome Engineering Using CRISPR-Cas9 System.” *Methods in Molecular Biology (Clifton, N.J.)*, vol. 1239, 2015, pp. 197–217. *PubMed*, https://doi.org/10.1007/978-1-4939-1862-1_10.
 25. Cox, David Benjamin Turitz, et al. “Therapeutic Genome Editing: Prospects and Challenges.” *Nature Medicine*, vol. 21, no. 2, Feb. 2015, pp. 121–31. *PubMed Central*, <https://doi.org/10.1038/nm.3793>.
 26. Culotta, Valeria Cizewski, et al. “Activation of Superoxide Dismutases: Putting the Metal to the Pedal.” *Biochimica Et Biophysica Acta*, vol. 1763, no. 7, July 2006, pp. 747–58. *PubMed*, <https://doi.org/10.1016/j.bbamcr.2006.05.003>.
 27. Czlonkowska, Anna, et al. “Nature Reviews Disease Primers Article: Wilson Disease.” *Nature Reviews. Disease Primers*, vol. 4, no. 1, Sept. 2018, p. 21. *PubMed Central*, <https://doi.org/10.1038/s41572-018-0018-3>.

28. Członkowska, Anna, and Tomasz Litwin. "Wilson Disease - Currently Used Anticopper Therapy." *Handbook of Clinical Neurology*, vol. 142, 2017, pp. 181–91. *PubMed*, <https://doi.org/10.1016/B978-0-444-63625-6.00015-X>.
29. Deltcheva, Elitza, et al. "CRISPR RNA Maturation by Trans-Encoded Small RNA and Host Factor RNase III." *Nature*, vol. 471, no. 7340, Mar. 2011, pp. 602–07. *PubMed*, <https://doi.org/10.1038/nature09886>.
30. Dhawan, Anil, et al. "Wilson's Disease in Children: 37-Year Experience and Revised King's Score for Liver Transplantation." *Liver Transplantation: Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*, vol. 11, no. 4, Apr. 2005, pp. 441–48. *PubMed*, <https://doi.org/10.1002/lt.20352>.
31. E, Janik, et al. "Various Aspects of a Gene Editing System-CRISPR-Cas9." *International Journal of Molecular Sciences*, vol. 21, no. 24, Dec. 2020. *pubmed.ncbi.nlm.nih.gov*, <https://doi.org/10.3390/ijms21249604>.
32. European Association for Study of Liver. "EASL Clinical Practice Guidelines: Wilson's Disease." *Journal of Hepatology*, vol. 56, no. 3, Mar. 2012, pp. 671–85. *PubMed*, <https://doi.org/10.1016/j.jhep.2011.11.007>.
33. Fatemi, Negah, and Bibudhendra Sarkar. "Molecular Mechanism of Copper Transport in Wilson Disease." *Environmental Health Perspectives*, 110 Suppl 5, no. Suppl 5, Oct. 2002, pp. 695–98. *PubMed*, <https://doi.org/10.1289/ehp.02110s5695>.
34. Fenu, M., et al. "Kayser-Fleischer Ring in Wilson's Disease: A Cohort Study." *European Journal of Internal Medicine*, vol. 23, no. 6, Sept. 2012, pp. e150-156. *PubMed*, <https://doi.org/10.1016/j.ejim.2012.04.005>.

35. Ferenci, Peter, et al. "Diagnosis and Phenotypic Classification of Wilson Disease." *Liver International: Official Journal of the International Association for the Study of the Liver*, vol. 23, no. 3, June 2003, pp. 139–42. *PubMed*, <https://doi.org/10.1034/j.1600-0676.2003.00824.x>.
36. Ferenci. "Regional Distribution of Mutations of the ATP7B Gene in Patients with Wilson Disease: Impact on Genetic Testing." *Human Genetics*, vol. 120, no. 2, Sept. 2006, pp. 151–59. *PubMed*, <https://doi.org/10.1007/s00439-006-0202-5>.
37. Ferguson-Miller, Shelagh, and Gerald T. Babcock. "Heme/Copper Terminal Oxidases." *Chemical Reviews*, vol. 96, no. 7, Nov. 1996, pp. 2889–908. *PubMed*, <https://doi.org/10.1021/cr950051s>.
38. Festa, Richard A., and Dennis J. Thiele. "Copper: An Essential Metal in Biology." *Current Biology*, vol. 21, no. 21, Nov. 2011, pp. R877–83. *www.cell.com*, <https://doi.org/10.1016/j.cub.2011.09.040>.
39. Ford, Kyle, et al. "Functional Genomics via CRISPR-Cas." *Journal of Molecular Biology*, vol. 431, no. 1, Jan. 2019, pp. 48–65. *PubMed Central*, <https://doi.org/10.1016/j.jmb.2018.06.034>.
40. Forman, S. J., et al. "Hemolytic Anemia in Wilson Disease: Clinical Findings and Biochemical Mechanisms." *American Journal of Hematology*, vol. 9, no. 3, 1980, pp. 269–75. *PubMed*, <https://doi.org/10.1002/ajh.2830090305>.
41. Fridovich, Irwin. "Superoxide Radical and Superoxide Dismutases." *Oxygen and Living Processes*, edited by Daniel L. Gilbert, Springer, 1981, pp. 250–72. *Springer Link*, https://doi.org/10.1007/978-1-4612-5890-2_13.
42. García, Noemí, et al. "Copper Induces Permeability Transition through Its Interaction

- with the Adenine Nucleotide Translocase.” *Cell Biology International*, vol. 31, no. 9, Sept. 2007, pp. 893–99. *ScienceDirect*, <https://doi.org/10.1016/j.cellbi.2007.02.003>.
43. Garneau, Josiane E., et al. “The CRISPR/Cas Bacterial Immune System Cleaves Bacteriophage and Plasmid DNA.” *Nature*, vol. 468, no. 7320, Nov. 2010, pp. 67–71. *PubMed*, <https://doi.org/10.1038/nature09523>.
 44. Gasiunas, Giedrius, et al. “Cas9–crRNA Ribonucleoprotein Complex Mediates Specific DNA Cleavage for Adaptive Immunity in Bacteria.” *Proceedings of the National Academy of Sciences*, vol. 109, no. 39, Sept. 2012, pp. E2579–86. *pnas.org (Atypon)*, <https://doi.org/10.1073/pnas.1208507109>.
 45. Gaudelli, Nicole M., et al. “Programmable Base Editing of A•T to G•C in Genomic DNA without DNA Cleavage.” *Nature*, vol. 551, no. 7681, Nov. 2017, pp. 464–71. *PubMed Central*, <https://doi.org/10.1038/nature24644>.
 46. Gerlinger, Marco, et al. “Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing.” *The New England Journal of Medicine*, vol. 366, no. 10, Mar. 2012, pp. 883–92. *PubMed Central*, <https://doi.org/10.1056/NEJMoa1113205>.
 47. Ghosh, Upasana, et al. “Challenges and Dilemmas in Pediatric Hepatic Wilson’s Disease.” *World Journal of Hepatology*, vol. 15, no. 10, Oct. 2023, pp. 1109–26. *PubMed*, <https://doi.org/10.4254/wjh.v15.i10.1109>.
 48. Girotti, Albert W. “Mechanisms of Lipid Peroxidation.” *Journal of Free Radicals in Biology & Medicine*, vol. 1, no. 2, Jan. 1985, pp. 87–95. *ScienceDirect*, [https://doi.org/10.1016/0748-5514\(85\)90011-X](https://doi.org/10.1016/0748-5514(85)90011-X).
 49. Godde, James S., and Amanda Bickerton. “The Repetitive DNA Elements Called CRISPRs and Their Associated Genes: Evidence of Horizontal Transfer among

- Prokaryotes.” *Journal of Molecular Evolution*, vol. 62, no. 6, June 2006, pp. 718–29. *PubMed*, <https://doi.org/10.1007/s00239-005-0223-z>.
50. Gonwa, T. A., et al. “End-Stage Renal Disease (ESRD) after Orthotopic Liver Transplantation (OLT) Using Calcineurin-Based Immunotherapy: Risk of Development and Treatment.” *Transplantation*, vol. 72, no. 12, Dec. 2001, pp. 1934–39. *PubMed*, <https://doi.org/10.1097/00007890-200112270-00012>.
 51. Gottesman, Susan. “Microbiology: Dicing Defence in Bacteria.” *Nature*, vol. 471, no. 7340, Mar. 2011, pp. 588–89. *PubMed*, <https://doi.org/10.1038/471588a>.
 52. Grissa, Ibtissem, et al. “The CRISPRdb Database and Tools to Display CRISPRs and to Generate Dictionaries of Spacers and Repeats.” *BMC Bioinformatics*, vol. 8, May 2007, p. 172. *PubMed Central*, <https://doi.org/10.1186/1471-2105-8-172>.
 53. Gwirtsman, H. E., et al. “Case Report of Anorexia Nervosa Associated with Wilson’s Disease.” *The International Journal of Eating Disorders*, vol. 13, no. 2, Mar. 1993, pp. 241–44. *PubMed*, [https://doi.org/10.1002/1098-108x\(199303\)13:2%253C241::aid-eat2260130213%253E3.0.co;2-y](https://doi.org/10.1002/1098-108x(199303)13:2%253C241::aid-eat2260130213%253E3.0.co;2-y).
 54. Haapaniemi, Emma, et al. “CRISPR-Cas9 Genome Editing Induces a P53-Mediated DNA Damage Response.” *Nature Medicine*, vol. 24, no. 7, July 2018, pp. 927–30. *PubMed*, <https://doi.org/10.1038/s41591-018-0049-z>.
 55. Habka, Dany, et al. “Future Economics of Liver Transplantation: A 20-Year Cost Modeling Forecast and the Prospect of Bioengineering Autologous Liver Grafts.” *PloS One*, vol. 10, no. 7, 2015, p. e0131764. *PubMed*, <https://doi.org/10.1371/journal.pone.0131764>.

56. Haft, Daniel H, et al. "A Guild of 45 CRISPR-Associated (Cas) Protein Families and Multiple CRISPR/Cas Subtypes Exist in Prokaryotic Genomes." *PLoS Computational Biology*, vol. 1, no. 6, Nov. 2005, p. e60. *PubMed Central*, <https://doi.org/10.1371/journal.pcbi.0010060>.
57. Halliwell, Barry, and John M. C. Gutteridge. "[1] Role of Free Radicals and Catalytic Metal Ions in Human Disease: An Overview." *Methods in Enzymology*, vol. 186, Academic Press, 1990, pp. 1–85. *Oxygen Radicals in Biological Systems Part B: Oxygen Radicals and Antioxidants. ScienceDirect*, [https://doi.org/10.1016/0076-6879\(90\)86093-B](https://doi.org/10.1016/0076-6879(90)86093-B).
58. Halliwell: *Hydroxyl Radical Is a Significant Player...* - *Google Scholar*. https://scholar.google.com/scholar_lookup?title=Hydroxyl%20radical%20is%20a%20significant%20player%20in%20oxidative%20DNA%20damage%20in%20vivo&publication_year=2021&author=B.%20Halliwell&author=A.%20Adhikary&author=M.%20Dingfelder&author=M.%20Dizdaroglu. Accessed 27 July 2025.
59. Hirano, Seiichi, et al. "Structural Basis for the Altered PAM Specificities of Engineered CRISPR-Cas9." *Molecular Cell*, vol. 61, no. 6, Mar. 2016, pp. 886–94. *PubMed*, <https://doi.org/10.1016/j.molcel.2016.02.018>.
60. Ishino, Y, et al. "Nucleotide Sequence of the Iap Gene, Responsible for Alkaline Phosphatase Isozyme Conversion in Escherichia Coli, and Identification of the Gene Product." *Journal of Bacteriology*, vol. 169, no. 12, Dec. 1987, pp. 5429–33. *journals.asm.org (Atypon)*, <https://doi.org/10.1128/jb.169.12.5429-5433.1987>.
61. Ishino, Yoshizumi, et al. "History of CRISPR-Cas from Encounter with a Mysterious Repeated Sequence to Genome Editing Technology." *Journal of Bacteriology*, vol. 200,

- no. 7, Mar. 2018, p. 10.1128/jb.00580-17. *journals.asm.org (Atypon)*,
<https://doi.org/10.1128/jb.00580-17>.
62. Jansen, Ruud, et al. “Identification of Genes That Are Associated with DNA Repeats in Prokaryotes.” *Molecular Microbiology*, vol. 43, no. 6, Mar. 2002, pp. 1565–75. *PubMed*,
<https://doi.org/10.1046/j.1365-2958.2002.02839.x>.
63. Jiang, Fuguo, et al. “A Cas9–Guide RNA Complex Preorganized for Target DNA Recognition.” *Science*, vol. 348, no. 6242, June 2015, pp. 1477–81. *science.org (Atypon)*,
<https://doi.org/10.1126/science.aab1452>.
64. Jiang, Fuguo, and Jennifer A. Doudna. “CRISPR–Cas9 Structures and Mechanisms.” *Annual Review of Biophysics*, vol. 46, no. Volume 46, 2017, May 2017, pp. 505–29.
www.annualreviews.org, <https://doi.org/10.1146/annurev-biophys-062215-010822>.
65. Jiang, Wenyan, et al. “RNA-Guided Editing of Bacterial Genomes Using CRISPR–Cas Systems.” *Nature Biotechnology*, vol. 31, no. 3, Mar. 2013, pp. 233–39. *www.nature.com*,
<https://doi.org/10.1038/nbt.2508>.
66. Jinek, Martin, Krzysztof Chylinski, et al. “A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity.” *Science*, vol. 337, no. 6096, Aug. 2012, pp. 816–21. *science.org (Atypon)*, <https://doi.org/10.1126/science.1225829>.
67. Jinek, Martin, Alexandra East, et al. “RNA-Programmed Genome Editing in Human Cells.” *eLife*, vol. 2, Jan. 2013, p. e00471. *PubMed Central*,
<https://doi.org/10.7554/eLife.00471>.
68. Kallinikos, Panagiotis, et al. “Corneal Nerve Tortuosity in Diabetic Patients with Neuropathy.” *Investigative Ophthalmology & Visual Science*, vol. 45, no. 2, Feb. 2004, pp. 418–22. *PubMed*, <https://doi.org/10.1167/iovs.03-0637>.

69. Kamath, Patrick S., et al. "The Model for End-Stage Liver Disease (MELD)." *Hepatology (Baltimore, Md.)*, vol. 45, no. 3, Mar. 2007, pp. 797–805. *PubMed*, <https://doi.org/10.1002/hep.21563>.
70. Kaminski, Rafal, et al. "Elimination of HIV-1 Genomes from Human T-Lymphoid Cells by CRISPR/Cas9 Gene Editing." *Scientific Reports*, vol. 6, Mar. 2016, p. 22555. *PubMed Central*, <https://doi.org/10.1038/srep22555>.
71. Kang, Yoo Kyung, et al. "Nonviral Genome Editing Based on a Polymer-Derivatized CRISPR Nanocomplex for Targeting Bacterial Pathogens and Antibiotic Resistance." *Bioconjugate Chemistry*, vol. 28, no. 4, Apr. 2017, pp. 957–67. *PubMed*, <https://doi.org/10.1021/acs.bioconjchem.6b00676>.
72. Kantor, Ariel, et al. "CRISPR-Cas9 DNA Base-Editing and Prime-Editing." *International Journal of Molecular Sciences*, vol. 21, no. 17, Aug. 2020, p. 6240. *PubMed Central*, <https://doi.org/10.3390/ijms21176240>.
73. Karginov, Fedor V., and Gregory J. Hannon. "The CRISPR System: Small RNA-Guided Defense in Bacteria and Archaea." *Molecular Cell*, vol. 37, no. 1, Jan. 2010, p. 7. *PubMed Central*, <https://doi.org/10.1016/j.molcel.2009.12.033>.
74. Kelly, Claire, and Marinos Pericleous. "Wilson Disease: More than Meets the Eye." *Postgraduate Medical Journal*, vol. 94, no. 1112, June 2018, pp. 335–47. *PubMed*, <https://doi.org/10.1136/postgradmedj-2017-135381>.
75. Kim, Kyoungmi, et al. "Highly Efficient RNA-Guided Base Editing in Mouse Embryos." *Nature Biotechnology*, vol. 35, no. 5, May 2017, pp. 435–37. *PubMed*, <https://doi.org/10.1038/nbt.3816>.
76. Kim, Y. Bill, et al. "Increasing the Genome-Targeting Scope and Precision of Base

- Editing with Engineered Cas9-Cytidine Deaminase Fusions.” *Nature Biotechnology*, vol. 35, no. 4, Apr. 2017, pp. 371–76. *PubMed Central*, <https://doi.org/10.1038/nbt.3803>.
77. Knight, Spencer C., et al. “Dynamics of CRISPR-Cas9 Genome Interrogation in Living Cells.” *Science*, vol. 350, no. 6262, Nov. 2015, pp. 823–26. *science.org (Atypon)*, <https://doi.org/10.1126/science.aac6572>.
78. Komor, Alexis C., Kevin T. Zhao, et al. “Improved Base Excision Repair Inhibition and Bacteriophage Mu Gam Protein Yields C:G-to-T:A Base Editors with Higher Efficiency and Product Purity.” *Science Advances*, vol. 3, no. 8, Aug. 2017, p. eaao4774. *PubMed Central*, <https://doi.org/10.1126/sciadv.aao4774>.
79. Komor, Alexis C., Yongjoo B. Kim, et al. “Programmable Editing of a Target Base in Genomic DNA without Double-Stranded DNA Cleavage.” *Nature*, vol. 533, no. 7603, Apr. 2016, pp. 420–24. *PubMed Central*, <https://doi.org/10.1038/nature17946>.
80. Koo, Taeyoung, et al. “Selective Disruption of an Oncogenic Mutant Allele by CRISPR/Cas9 Induces Efficient Tumor Regression.” *Nucleic Acids Research*, vol. 45, no. 13, July 2017, pp. 7897–908. *PubMed Central*, <https://doi.org/10.1093/nar/gkx490>.
81. Koonin, Eugene V., et al. “Diversity, Classification and Evolution of CRISPR-Cas Systems.” *Current Opinion in Microbiology*, vol. 37, June 2017, pp. 67–78. *PubMed Central*, <https://doi.org/10.1016/j.mib.2017.05.008>.
82. Krumova, Katerina, and Gonzalo Cosa. *Overview of Reactive Oxygen Species*. *books.rsc.org*, <https://books.rsc.org/books/edited-volume/1491/chapter/996688/Overview-of-Reactive-Oxygen-Species>. Accessed 27 July 2025.
83. Kumawat, B. L., et al. “Wilson’s Disease Presenting as Isolated Obsessive-Compulsive

- Disorder.” *Indian Journal of Medical Sciences*, vol. 61, no. 11, Nov. 2007, pp. 607–10.
84. Kunin, Victor, et al. “Evolutionary Conservation of Sequence and Secondary Structures in CRISPR Repeats.” *Genome Biology*, vol. 8, no. 4, 2007, p. R61. *PubMed*, <https://doi.org/10.1186/gb-2007-8-4-r61>.
 85. Lee, Choongho. “CRISPR/Cas9-Based Antiviral Strategy: Current Status and the Potential Challenge.” *Molecules*, vol. 24, no. 7, Apr. 2019, p. 1349. *PubMed Central*, <https://doi.org/10.3390/molecules24071349>.
 86. Lee, David Uihwan, et al. “The Cost Implications of Wilson Disease among Hospitalized Patients: Analysis of US Hospitals.” *European Journal of Gastroenterology & Hepatology*, vol. 36, no. 7, July 2024, pp. 929–40. *PubMed Central*, <https://doi.org/10.1097/MEG.0000000000002777>.
 87. Lenartowicz, Małgorzata, and Wojciech Krzeptowski. “[Structure and function of ATP7A and ATP7B proteins--Cu-transporting ATPases].” *Postepy Biochemii*, vol. 56, no. 3, 2010, pp. 317–27.
 88. Li, Guanglei, et al. “Highly Efficient and Precise Base Editing in Discarded Human Triprenuclear Embryos.” *Protein & Cell*, vol. 8, no. 10, Oct. 2017, pp. 776–79. *PubMed Central*, <https://doi.org/10.1007/s13238-017-0458-7>.
 89. Liang, Puping, et al. “Correction of β -Thalassemia Mutant by Base Editor in Human Embryos.” *Protein & Cell*, vol. 8, no. 11, Nov. 2017, pp. 811–22. *PubMed Central*, <https://doi.org/10.1007/s13238-017-0475-6>.
 90. Lin, Steven, et al. “Enhanced Homology-Directed Human Genome Engineering by Controlled Timing of CRISPR/Cas9 Delivery.” *eLife*, vol. 3, p. e04766. *PubMed Central*, <https://doi.org/10.7554/eLife.04766>.

91. Linder, MC, et al. "Copper Transport." *The American Journal of Clinical Nutrition*, vol. 67, no. 5, May 1998, pp. 965S-971S. *ScienceDirect*, <https://doi.org/10.1093/ajcn/67.5.965S>.
92. Lino, Christopher A., et al. "Delivering CRISPR: A Review of the Challenges and Approaches." *Drug Delivery*, vol. 25, no. 1, May 2018, pp. 1234–57. *PubMed Central*, <https://doi.org/10.1080/10717544.2018.1474964>.
93. Litwin, Tomasz, et al. "Psychiatric Disturbances as a First Clinical Symptom of Wilson's Disease - Case Report." *Psychiatria Polska*, vol. 50, no. 2, 2016, pp. 337–44. *PubMed*, <https://doi.org/10.12740/PP/45218>.
94. Liu, Mingjie, et al. "Methodologies for Improving HDR Efficiency." *Frontiers in Genetics*, vol. 9, Jan. 2019, p. 691. *PubMed Central*, <https://doi.org/10.3389/fgene.2018.00691>.
95. Longenecker, Joseph C., et al. "Hyperuricemia after Orthotopic Liver Transplantation: Divergent Associations with Progression of Renal Disease, Incident End-Stage Renal Disease, and Mortality." *BMC Nephrology*, vol. 18, no. 1, Mar. 2017, p. 103. *PubMed*, <https://doi.org/10.1186/s12882-017-0518-5>.
96. Lorincz, Matthew T. "Neurologic Wilson's Disease." *Annals of the New York Academy of Sciences*, vol. 1184, Jan. 2010, pp. 173–87. *PubMed*, <https://doi.org/10.1111/j.1749-6632.2009.05109.x>.
97. Lu, Yuming, and Jian-Kang Zhu. "Precise Editing of a Target Base in the Rice Genome Using a Modified CRISPR/Cas9 System." *Molecular Plant*, vol. 10, no. 3, Mar. 2017, pp. 523–25. *PubMed*, <https://doi.org/10.1016/j.molp.2016.11.013>.
98. Lutsenko, Svetlana, et al. "Function and Regulation of Human Copper-Transporting

- ATPases.” *Physiological Reviews*, vol. 87, no. 3, July 2007, pp. 1011–46.
journals.physiology.org (Atypon), <https://doi.org/10.1152/physrev.00004.2006>.
99. M, Asmamaw, and Zawdie B. “Mechanism and Applications of CRISPR/Cas-9-Mediated Genome Editing.” *Biologics : Targets & Therapy*, vol. 15, Aug. 2021.
pubmed.ncbi.nlm.nih.gov, <https://doi.org/10.2147/BTT.S326422>.
 100. M Fetherolf, Morgan, et al. “Oxygen-Dependent Activation of Cu,Zn-Superoxide Dismutase-1.” *Metallomics: Integrated Biometal Science*, vol. 9, no. 8, Aug. 2017, pp. 1047–59. *PubMed*, <https://doi.org/10.1039/c6mt00298f>.
 101. Ma, Hanhui, et al. “CRISPR-Cas9 Nuclear Dynamics and Target Recognition in Living Cells.” *Journal of Cell Biology*, vol. 214, no. 5, Aug. 2016, pp. 529–37.
Silverchair, <https://doi.org/10.1083/jcb.201604115>.
 102. Makarova, Kira S., L. Aravind, et al. “A DNA Repair System Specific for Thermophilic Archaea and Bacteria Predicted by Genomic Context Analysis.” *Nucleic Acids Research*, vol. 30, no. 2, Jan. 2002, pp. 482–96. *PubMed*,
<https://doi.org/10.1093/nar/30.2.482>.
 103. Makarova, Kira S., Nick V. Grishin, et al. “A Putative RNA-Interference-Based Immune System in Prokaryotes: Computational Analysis of the Predicted Enzymatic Machinery, Functional Analogies with Eukaryotic RNAi, and Hypothetical Mechanisms of Action.” *Biology Direct*, vol. 1, Mar. 2006, p. 7. *PubMed*,
<https://doi.org/10.1186/1745-6150-1-7>.
 104. Makarova, Kira S, et al. “Unification of Cas Protein Families and a Simple Scenario for the Origin and Evolution of CRISPR-Cas Systems.” *Biology Direct*, vol. 6, July 2011, p. 38. *PubMed Central*, <https://doi.org/10.1186/1745-6150-6-38>.

105. Marraffini, Luciano A., and Erik J. Sontheimer. "Self versus Non-Self Discrimination during CRISPR RNA-Directed Immunity." *Nature*, vol. 463, no. 7280, Jan. 2010, pp. 568–71. *www.nature.com*, <https://doi.org/10.1038/nature08703>.
106. Maude, Shannon L., et al. "Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia." *The New England Journal of Medicine*, vol. 371, no. 16, Oct. 2014, pp. 1507–17. *PubMed Central*, <https://doi.org/10.1056/NEJMoa1407222>.
107. McCord, J. M., and I. Fridovich. "Superoxide Dismutase. An Enzymic Function for Erythrocuprein (Hemocuprein)." *The Journal of Biological Chemistry*, vol. 244, no. 22, Nov. 1969, pp. 6049–55.
108. Medici, Valentina, and Janine M. LaSalle. "Genetics and Epigenetic Factors of Wilson Disease." *Annals of Translational Medicine*, vol. 7, no. Suppl 2, Apr. 2019, p. S58. *PubMed Central*, <https://doi.org/10.21037/atm.2019.01.67>.
109. Menerey, K. A., et al. "The Arthropathy of Wilson's Disease: Clinical and Pathologic Features." *The Journal of Rheumatology*, vol. 15, no. 2, Feb. 1988, pp. 331–37.
110. Mojica, F. J., C. Díez-Villaseñor, et al. "Biological Significance of a Family of Regularly Spaced Repeats in the Genomes of Archaea, Bacteria and Mitochondria." *Molecular Microbiology*, vol. 36, no. 1, Apr. 2000, pp. 244–46. *PubMed*, <https://doi.org/10.1046/j.1365-2958.2000.01838.x>.
111. Mojica, F. J., G. Juez, et al. "Transcription at Different Salinities of Haloferax Mediterranei Sequences Adjacent to Partially Modified PstI Sites." *Molecular Microbiology*, vol. 9, no. 3, Aug. 1993, pp. 613–21. *PubMed*, <https://doi.org/10.1111/j.1365-2958.1993.tb01721.x>.
112. Mojica, Francisco J. M., et al. "Intervening Sequences of Regularly Spaced

- Prokaryotic Repeats Derive from Foreign Genetic Elements.” *Journal of Molecular Evolution*, vol. 60, no. 2, Feb. 2005, pp. 174–82. *PubMed*, <https://doi.org/10.1007/s00239-004-0046-3>.
113. Moreno, J. M., et al. “Chronic Renal Dysfunction after Liver Transplantation in Adult Patients: Prevalence, Risk Factors, and Impact on Mortality.” *Transplantation Proceedings*, vol. 35, no. 5, Aug. 2003, pp. 1907–08. *PubMed*, [https://doi.org/10.1016/s0041-1345\(03\)00642-0](https://doi.org/10.1016/s0041-1345(03)00642-0).
 114. Musunuru, Kiran, et al. “Patient-Specific In Vivo Gene Editing to Treat a Rare Genetic Disease.” *New England Journal of Medicine*, vol. 392, no. 22, June 2025, pp. 2235–43. *Taylor and Francis+NEJM*, <https://doi.org/10.1056/NEJMoa2504747>.
 115. Musunuru. “The Hope and Hype of CRISPR-Cas9 Genome Editing: A Review.” *JAMA Cardiology*, vol. 2, no. 8, Aug. 2017, pp. 914–19. *PubMed*, <https://doi.org/10.1001/jamacardio.2017.1713>.
 116. Neal, D. A., et al. “Hyperuricemia, Gout, and Renal Function after Liver Transplantation.” *Transplantation*, vol. 72, no. 10, Nov. 2001, pp. 1689–91. *PubMed*, <https://doi.org/10.1097/00007890-200111270-00021>.
 117. Nishida, Keiji, et al. “Targeted Nucleotide Editing Using Hybrid Prokaryotic and Vertebrate Adaptive Immune Systems.” *Science (New York, N.Y.)*, vol. 353, no. 6305, Sept. 2016, p. aaf8729. *PubMed*, <https://doi.org/10.1126/science.aaf8729>.
 118. Ogun, Aminat S., and Adebayo Adeyinka. “Biochemistry, Transferrin.” *StatPearls*, StatPearls Publishing, 2025. *PubMed*, <http://www.ncbi.nlm.nih.gov/books/NBK532928/>.
 119. Petrukhin, K., et al. “Mapping, Cloning and Genetic Characterization of the Region Containing the Wilson Disease Gene.” *Nature Genetics*, vol. 5, no. 4, Dec. 1993, pp.

- 338–43. *PubMed*, <https://doi.org/10.1038/ng1293-338>.
120. Pfeifferberger, Jan, et al. “Hepatobiliary Malignancies in Wilson Disease.” *Liver International: Official Journal of the International Association for the Study of the Liver*, vol. 35, no. 5, May 2015, pp. 1615–22. *PubMed*, <https://doi.org/10.1111/liv.12727>.
121. Pfeiffer, Ronald F. “Wilson’s Disease.” *Seminars in Neurology*, vol. 27, no. 2, Apr. 2007, pp. 123–32. *PubMed*, <https://doi.org/10.1055/s-2007-971173>.
122. Portala, K., et al. “Psychopathology in Treated Wilson’s Disease Determined by Means of CPRS Expert and Self-Ratings.” *Acta Psychiatrica Scandinavica*, vol. 101, no. 2, Feb. 2000, pp. 104–09. *PubMed*, <https://doi.org/10.1034/j.1600-0447.2000.90085.x>.
123. Posadas, Yanahi, et al. “Copper Binding and Protein Aggregation: A Journey from the Brain to the Human Lens.” *RSC Chemical Biology*, vol. 4, no. 12, pp. 974–85. *PubMed Central*, <https://doi.org/10.1039/d3cb00145h>.
124. Pourcel, C., et al. “CRISPR Elements in *Yersinia Pestis* Acquire New Repeats by Preferential Uptake of Bacteriophage DNA, and Provide Additional Tools for Evolutionary Studies.” *Microbiology (Reading, England)*, vol. 151, no. Pt 3, Mar. 2005, pp. 653–63. *PubMed*, <https://doi.org/10.1099/mic.0.27437-0>.
125. Prasad, Durga, and Arpita Bhriguvanshi. “Ocular Manifestations of Liver Disease in Children: Clinical Aspects and Implications.” *Annals of Hepatology*, vol. 19, no. 6, 2020, pp. 608–13. *PubMed*, <https://doi.org/10.1016/j.aohep.2019.11.009>.
126. Pruthi, J., et al. “Analysis of Causes of Death in Liver Transplant Recipients Who Survived More than 3 Years.” *Liver Transplantation: Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*, vol. 7, no. 9, Sept. 2001, pp. 811–15. *PubMed*,

- <https://doi.org/10.1053/jlts.2001.27084>.
127. Pugh, R N. “Pugh’s Grading in the Classification of Liver Decompensation.” *Gut*, vol. 33, no. 11, Nov. 1992, p. 1583. *PubMed Central*, <https://doi.org/10.1136/gut.33.11.1583>.
128. Rajalakshmi, T. R., et al. “DNA Adducts-Chemical Addons.” *Journal of Pharmacy & Bioallied Sciences*, vol. 7, no. Suppl 1, Apr. 2015, pp. S197-199. *PubMed*, <https://doi.org/10.4103/0975-7406.155901>.
129. Ralle, Martina, et al. “Wilson Disease at a Single Cell Level: Intracellular Copper Trafficking Activates Compartment-Specific Responses in Hepatocytes.” *The Journal of Biological Chemistry*, vol. 285, no. 40, Oct. 2010, pp. 30875–83. *PubMed*, <https://doi.org/10.1074/jbc.M110.114447>.
130. Rees, Holly A., et al. “Improving the DNA Specificity and Applicability of Base Editing through Protein Engineering and Protein Delivery.” *Nature Communications*, vol. 8, June 2017, p. 15790. *pmc.ncbi.nlm.nih.gov*, <https://doi.org/10.1038/ncomms15790>.
131. Roberts, Eve A., et al. “Diagnosis and Treatment of Wilson Disease: An Update.” *Hepatology (Baltimore, Md.)*, vol. 47, no. 6, June 2008, pp. 2089–111. *PubMed*, <https://doi.org/10.1002/hep.22261>.
132. Rodriguez-Granillo, Agustina, et al. “Stability and ATP Binding of the Nucleotide-Binding Domain of the Wilson Disease Protein: Effect of the Common H1069Q Mutation.” *Journal of Molecular Biology*, vol. 383, no. 5, Nov. 2008, pp. 1097–111. *PubMed*, <https://doi.org/10.1016/j.jmb.2008.07.065>.
133. Román-Rodríguez, Francisco José, et al. “NHEJ-Mediated Repair of CRISPR-Cas9-Induced DNA Breaks Efficiently Corrects Mutations in HSPCs from

- Patients with Fanconi Anemia.” *Cell Stem Cell*, vol. 25, no. 5, Nov. 2019, pp. 607-621.e7. *PubMed*, <https://doi.org/10.1016/j.stem.2019.08.016>.
134. Ross, M. E., et al. “Late-Onset Wilson’s Disease with Neurological Involvement in the Absence of Kayser-Fleischer Rings.” *Annals of Neurology*, vol. 17, no. 4, Apr. 1985, pp. 411–13. *PubMed*, <https://doi.org/10.1002/ana.410170421>.
 135. Rustgi, Vinod K., et al. “Wilson’s Disease: An Analysis of Health Care Use and Cost Burden of Commercially Insured Adults in the United States.” *Hepatology Communications*, vol. 6, no. 2, Feb. 2022, pp. 389–98. *PubMed*, <https://doi.org/10.1002/hep4.1812>.
 136. Sandahl, Thomas Damgaard, et al. “The Prevalence of Wilson’s Disease: An Update.” *Hepatology (Baltimore, Md.)*, vol. 71, no. 2, Feb. 2020, pp. 722–32. *PubMed*, <https://doi.org/10.1002/hep.30911>.
 137. Sapranaukas, Rimantas, et al. “The Streptococcus Thermophilus CRISPR/Cas System Provides Immunity in Escherichia Coli.” *Nucleic Acids Research*, vol. 39, no. 21, Nov. 2011, pp. 9275–82. *PubMed Central*, <https://doi.org/10.1093/nar/gkr606>.
 138. Sazinsky, Matthew H., et al. “Structure of the ATP Binding Domain from the Archaeoglobus Fulgidus Cu⁺-ATPase.” *The Journal of Biological Chemistry*, vol. 281, no. 16, Apr. 2006, pp. 11161–66. *PubMed*, <https://doi.org/10.1074/jbc.M510708200>.
 139. Scheiber, Ivo Florin, et al. “Pathogenesis of Wilson Disease.” *Handbook of Clinical Neurology*, vol. 142, 2017, pp. 43–55. *PubMed*, <https://doi.org/10.1016/B978-0-444-63625-6.00005-7>.
 140. Schilsky, Michael L., Eve A. Roberts, et al. “A Multidisciplinary Approach to the Diagnosis and Management of Wilson Disease: Executive Summary of the 2022 Practice

- Guidance on Wilson Disease from the American Association for the Study of Liver Diseases.” *Hepatology (Baltimore, Md.)*, vol. 77, no. 4, Apr. 2023, pp. 1428–55. *PubMed*, <https://doi.org/10.1002/hep.32805>.
141. Schilsky, Michael L., Anna Czlonkowska, et al. “Trientine Tetrahydrochloride versus Penicillamine for Maintenance Therapy in Wilson Disease (CHELATE): A Randomised, Open-Label, Non-Inferiority, Phase 3 Trial.” *The Lancet. Gastroenterology & Hepatology*, vol. 7, no. 12, Dec. 2022, pp. 1092–102. *PubMed*, [https://doi.org/10.1016/S2468-1253\(22\)00270-9](https://doi.org/10.1016/S2468-1253(22)00270-9).
 142. Seniów, Joanna, et al. “Self-Rated Emotional Functioning of Patients With Neurological or Asymptomatic Form of Wilson’s Disease.” *The Clinical Neuropsychologist*, vol. 17, no. 3, Aug. 2003, pp. 367–73. *Taylor and Francis+NEJM*, <https://doi.org/10.1076/clin.17.3.367.18085>.
 143. Shalem, Ophir, et al. “Genome-Scale CRISPR-Cas9 Knockout Screening in Human Cells.” *Science (New York, N.Y.)*, vol. 343, no. 6166, Jan. 2014, pp. 84–87. *PubMed Central*, <https://doi.org/10.1126/science.1247005>.
 144. Shi, K., et al. “Structural Basis for Targeted DNA Cytosine Deamination and Mutagenesis by APOBEC3A and APOBEC3B.” *Nature Structural & Molecular Biology*, vol. 24, no. 2, Feb. 2017, pp. 131–39. *PubMed Central*, <https://doi.org/10.1038/nsmb.3344>.
 145. Shmakov, Sergey, et al. “Diversity and Evolution of Class 2 CRISPR–Cas Systems.” *Nature Reviews. Microbiology*, vol. 15, no. 3, Mar. 2017, pp. 169–82. *PubMed Central*, <https://doi.org/10.1038/nrmicro.2016.184>.
 146. Srinivas, K., et al. “Dominant Psychiatric Manifestations in Wilson’s Disease: A

- Diagnostic and Therapeutic Challenge!” *Journal of the Neurological Sciences*, vol. 266, nos. 1–2, Mar. 2008, pp. 104–08. *PubMed*, <https://doi.org/10.1016/j.jns.2007.09.009>.
147. Sternberg, Samuel H., et al. “DNA Interrogation by the CRISPR RNA-Guided Endonuclease Cas9.” *Nature*, vol. 507, no. 7490, Mar. 2014, pp. 62–67. *PubMed*, <https://doi.org/10.1038/nature13011>.
148. *Stohs: Oxidative Mechanisms in the Toxicity of Metal Ions - Google Scholar*. https://scholar.google.com/scholar_lookup?title=Oxidative%20mechanisms%20in%20the%20toxicity%20of%20metal%20ions&publication_year=1995&author=S.J.%20Stohs&author=D.%20Bagchi. Accessed 27 July 2025.
149. Sturniolo, Giacomo Carlo, et al. “Small Fiber Peripheral Neuropathy in Wilson Disease: An In Vivo Documentation by Corneal Confocal Microscopy.” *Investigative Ophthalmology & Visual Science*, vol. 56, no. 2, Feb. 2015, pp. 1390–95. *Silverchair*, <https://doi.org/10.1167/iovs.14-15004>.
150. Sussman, W., and I. H. Scheinberg. “Disappearance of Kayser-Fleischer Rings. Effects of Penicillamine.” *Archives of Ophthalmology (Chicago, Ill.: 1960)*, vol. 82, no. 6, Dec. 1969, pp. 738–41. *PubMed*, <https://doi.org/10.1001/archophth.1969.00990020730003>.
151. Svetel, M., et al. “Long-Term Outcome in Serbian Patients with Wilson Disease.” *European Journal of Neurology*, vol. 16, no. 7, July 2009, pp. 852–57. *PubMed*, <https://doi.org/10.1111/j.1468-1331.2009.02607.x>.
152. Svetel, Marina, et al. “Neuropsychiatric Aspects of Treated Wilson’s Disease.” *Parkinsonism & Related Disorders*, vol. 15, no. 10, Dec. 2009, pp. 772–75. *ScienceDirect*, <https://doi.org/10.1016/j.parkreldis.2009.01.010>.

153. Szczelkun, Mark D., et al. "Direct Observation of R-Loop Formation by Single RNA-Guided Cas9 and Cascade Effector Complexes." *Proceedings of the National Academy of Sciences*, vol. 111, no. 27, July 2014, pp. 9798–803. *pnas.org* (Atypon), <https://doi.org/10.1073/pnas.1402597111>.
154. Tang, Weixin, et al. "Aptazyme-Embedded Guide RNAs Enable Ligand-Responsive Genome Editing and Transcriptional Activation." *Nature Communications*, vol. 8, June 2017, p. 15939. *PubMed Central*, <https://doi.org/10.1038/ncomms15939>.
155. Tanzi, R. E., et al. "The Wilson Disease Gene Is a Copper Transporting ATPase with Homology to the Menkes Disease Gene." *Nature Genetics*, vol. 5, no. 4, Dec. 1993, pp. 344–50. *PubMed*, <https://doi.org/10.1038/ng1293-344>.
156. Tapiero, H., et al. "Trace Elements in Human Physiology and Pathology. Copper." *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*, vol. 57, no. 9, Nov. 2003, pp. 386–98. *PubMed Central*, [https://doi.org/10.1016/s0753-3322\(03\)00012-x](https://doi.org/10.1016/s0753-3322(03)00012-x).
157. Terada, K., et al. "ATP7B (WND) Protein." *The International Journal of Biochemistry & Cell Biology*, vol. 30, no. 10, Oct. 1998, pp. 1063–67. *PubMed*, [https://doi.org/10.1016/s1357-2725\(98\)00073-9](https://doi.org/10.1016/s1357-2725(98)00073-9).
158. Terns, Michael P., and Rebecca M. Terns. "CRISPR-Based Adaptive Immune Systems." *Current Opinion in Microbiology*, vol. 14, no. 3, June 2011, pp. 321–27. *PubMed Central*, <https://doi.org/10.1016/j.mib.2011.03.005>.
159. Verity, M. Anthony, and J. K. Gambell. "Studies of Copper Ion-Induced Mitochondrial Swelling in Vitro." *Biochemical Journal*, vol. 108, no. 2, June 1968, pp. 289–95. *Silverchair*, <https://doi.org/10.1042/bj1080289>.

160. Walshe, J. M. “The Acute Haemolytic Syndrome in Wilson’s Disease--a Review of 22 Patients.” *QJM: Monthly Journal of the Association of Physicians*, vol. 106, no. 11, Nov. 2013, pp. 1003–08. *PubMed*, <https://doi.org/10.1093/qjmed/hct137>.
161. Walshe, J. M., and G. Potter. “The Pattern of the Whole Body Distribution of Radioactive Copper (^{67}Cu , ^{64}Cu) in Wilson’s Disease and Various Control Groups.” *The Quarterly Journal of Medicine*, vol. 46, no. 184, Oct. 1977, pp. 445–62.
162. Wang, Jianbin, and Stephen R. Quake. “RNA-Guided Endonuclease Provides a Therapeutic Strategy to Cure Latent Herpesviridae Infection.” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 111, no. 36, Sept. 2014, pp. 13157–62. *PubMed Central*, <https://doi.org/10.1073/pnas.1410785111>.
163. Wang, Karissa, and Matthew Nicholaou. “Suppression of Antimicrobial Resistance in MRSA Using CRISPR-dCas9.” *American Society for Clinical Laboratory Science*, vol. 30, no. 4, Oct. 2017, pp. 207–13. Research and Reports. *clsjournal.ascls.org*, <https://doi.org/10.29074/ascls.30.4.207>.
164. Wang, Ming, et al. “Efficient Delivery of Genome-Editing Proteins Using Bioreducible Lipid Nanoparticles.” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 113, no. 11, Mar. 2016, pp. 2868–73. *PubMed Central*, <https://doi.org/10.1073/pnas.1520244113>.
165. Weiss, Karl Heinz, Mart Van de Moortele, et al. “Bone Demineralisation in a Large Cohort of Wilson Disease Patients.” *Journal of Inherited Metabolic Disease*, vol. 38, no. 5, Sept. 2015, pp. 949–56. *PubMed*, <https://doi.org/10.1007/s10545-015-9815-y>.
166. Weiss, Karl Heinz, Florentine Thurik, et al. “Efficacy and Safety of Oral Chelators in Treatment of Patients with Wilson Disease.” *Clinical Gastroenterology and Hepatology*:

- The Official Clinical Practice Journal of the American Gastroenterological Association*, vol. 11, no. 8, Aug. 2013, pp. 1028-1035.e1-2. *PubMed*, <https://doi.org/10.1016/j.cgh.2013.03.012>.
167. Weiss, Karl Heinz, Mark Schäfer, et al. "Outcome and Development of Symptoms after Orthotopic Liver Transplantation for Wilson Disease." *Clinical Transplantation*, vol. 27, no. 6, 2013, pp. 914–22. *PubMed*, <https://doi.org/10.1111/ctr.12259>.
 168. Weiss, Karl Heinz, and Michael Schilsky. "Wilson Disease." *GeneReviews®*, edited by Margaret P. Adam et al., University of Washington, Seattle, 1993. *PubMed*, <http://www.ncbi.nlm.nih.gov/books/NBK1512/>.
 169. Wiebers, D. O., et al. "The Ophthalmologic Manifestations of Wilson's Disease." *Mayo Clinic Proceedings*, vol. 52, no. 7, July 1977, pp. 409–16. *PubMed*, <https://pubmed.ncbi.nlm.nih.gov/875462/>.
 170. Wiedenheft, Blake, et al. "RNA-Guided Genetic Silencing Systems in Bacteria and Archaea." *Nature*, vol. 482, no. 7385, Feb. 2012, pp. 331–38. *PubMed*, <https://doi.org/10.1038/nature10886>.
 171. Wong, P. C., et al. "Copper Chaperone for Superoxide Dismutase Is Essential to Activate Mammalian Cu/Zn Superoxide Dismutase." *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 6, Mar. 2000, pp. 2886–91. *PubMed*, <https://doi.org/10.1073/pnas.040461197>.
 172. Yang, Han, et al. "Methods Favoring Homology-Directed Repair Choice in Response to CRISPR/Cas9 Induced-Double Strand Breaks." *International Journal of Molecular Sciences*, vol. 21, no. 18, Sept. 2020, p. 6461. *PubMed Central*, <https://doi.org/10.3390/ijms21186461>.

173. Yin, Hao, et al. "Therapeutic Genome Editing by Combined Viral and Non-Viral Delivery of CRISPR System Components in Vivo." *Nature Biotechnology*, vol. 34, no. 3, Mar. 2016, pp. 328–33. *PubMed Central*, <https://doi.org/10.1038/nbt.3471>.
174. Zhen, S., et al. "Harnessing the Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR)/CRISPR-Associated Cas9 System to Disrupt the Hepatitis B Virus." *Gene Therapy*, vol. 22, no. 5, May 2015, pp. 404–12. *PubMed*, <https://doi.org/10.1038/gt.2015.2>.
175. Zhou, Yuexin, et al. "High-Throughput Screening of a CRISPR/Cas9 Library for Functional Genomics in Human Cells." *Nature*, vol. 509, no. 7501, May 2014, pp. 487–91. *PubMed*, <https://doi.org/10.1038/nature13166>.
176. Zhuang, Xiao-Hui, et al. "Analysis of Renal Impairment in Children with Wilson's Disease." *World Journal of Pediatrics: WJP*, vol. 4, no. 2, May 2008, pp. 102–05. *PubMed*, <https://doi.org/10.1007/s12519-008-0019-5>.
177. Zimbrea, Paula C., and Michael L. Schilsky. "Psychiatric Aspects of Wilson Disease: A Review." *General Hospital Psychiatry*, vol. 36, no. 1, 2014, pp. 53–62. *PubMed*, <https://doi.org/10.1016/j.genhosppsych.2013.08.007>.
178. Zischka, Hans, et al. "Liver Mitochondrial Membrane Crosslinking and Destruction in a Rat Model of Wilson Disease." *The Journal of Clinical Investigation*, vol. 121, no. 4, Apr. 2011, pp. 1508–18. www.jci.org, <https://doi.org/10.1172/JCI45401>.
179. Zong, Yuan, et al. "Precise Base Editing in Rice, Wheat and Maize with a Cas9-Cytidine Deaminase Fusion." *Nature Biotechnology*, vol. 35, no. 5, May 2017, pp. 438–40. *PubMed*, <https://doi.org/10.1038/nbt.3811>.
180. CHANG, IRENE J., and SI HOUN HAHN. "The Genetics of Wilson Disease."

- Handbook of Clinical Neurology*, vol. 142, 2017, pp. 19–34. *PubMed Central*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5648646/>.
181. Chevalier, Kevin, et al. “Eye Involvement in Wilson’s Disease: A Review of the Literature.” *Journal of Clinical Medicine*, vol. 11, no. 9, Apr. 2022, p. 2528. *PubMed Central*, <https://doi.org/10.3390/jcm11092528>.
182. Schilsky, Michael L., et al. “Costly Choices for Treating Wilson’s Disease.” *Hepatology (Baltimore, Md.)*, vol. 61, no. 4, Apr. 2015, pp. 1106–08. *PubMed*, <https://doi.org/10.1002/hep.27663>.
183. Chadwick, Alexandra C., et al. “In Vivo Base Editing of PCSK9 as a Therapeutic Alternative to Genome Editing.” *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 37, no. 9, Sept. 2017, pp. 1741–47. *PubMed Central*, <https://doi.org/10.1161/ATVBAHA.117.309881>.
184. Komor, Alexis C., et al. “Editing the Genome Without Double-Stranded DNA Breaks.” *ACS Chemical Biology*, vol. 13, no. 2, Feb. 2018, pp. 383–88. *PubMed Central*, <https://doi.org/10.1021/acscchembio.7b00710>.
185. Bull, P. C., et al. “The Wilson Disease Gene Is a Putative Copper Transporting P-Type ATPase Similar to the Menkes Gene.” *Nature Genetics*, vol. 5, no. 4, Dec. 1993, pp. 327–37. *PubMed*, <https://doi.org/10.1038/ng1293-327>.

Abstract Defiance: Fernando Zóbel and the Rise of Spanish Abstract Art in Francoist Spain by Natalia C. Siy

Abstract

Spanish-Filipino painter and collector Fernando Zobel played a vital role in the propagation and preservation of abstract art in Francoist Spain and the Philippines, and the institutionalisation of the same. Zobel stood at the intersection of history and modern art by offering fresh perspectives not only through his own art but also through his advocacy, support, and endeavours in cultural preservation. This paper examines his life and legacy through a close reading of Zobel's art and its cultural context- most notably the founding of the Museo de Arte Abstracto Español in Cuenca and the Ateneo Art Gallery in Manila. Using a qualitative, interpretive approach, this study interprets how Zobel's art and legacy constituted a quiet yet potent form of aesthetic dissent against the rigid, state-sanctioned realism of Francoist Spain and its dominant influence on Spanish modern art at the time. Shaped by his transnational identity and informed by contemporary socio-political context, Zobel's abstraction offered an alternative vision of cultural preservation and artistic freedom by bridging continents, methods, and ideologies.

Fernando Zóbel and the Rebirth of Spanish Modern Art

On a limestone spur in central Spain, the small medieval city of Cuenca sits regally, high above the Huécar and Júcar rivers. Founded by the Moors in the 8th century, it has been witness to generations of history. In its current incarnation, Cuenca is a UNESCO World Heritage Site, promoting its cultural and historical significance. But beyond Cuenca's well-preserved medieval and colonial architecture, indeed, behind the walls of its famous *Casas Colgadas* or Hanging Houses, Cuenca holds another attraction to be proud of, the *Museo de Arte Abstracto Español*.

Founded by Fernando Zóbel, a Spanish-Filipino painter, scholar, and patron in 1966, this museum represents more than just a collection of paintings—it marks a turning point in the story of Spanish Modern Art. Before the Spanish Civil War brought Franco to power, modern art was gaining momentum in Spain. Surrealism, in particular, began to flourish with artists like Salvador Dalí and Joan Miró achieving international recognition. But after Franco took control, his regime used art to shape public opinion and promote its own ideologies. Franco enforced strict censorship and endorsed an “official” style of art that reflected the values of his dictatorship. Artists were expected to work in realistic styles on primarily Catholic subjects or those that glorified the military, if not glorifying the dictator himself. However, within this restrictive cannon, a new style emerged, one born in post-modern Europe and the West, which made its way to Spain through travel and exposure to contemporary art beyond Spain, and upended the preconceived notions of the enforced traditional art: abstraction. And one artist who both advocated for and practiced this new art style in Spain during the era of realism and restriction was the Manila-born Fernando Zobel. This paper delves into Fernando Zóbel's life. It

examines how his work bridged continents, ideologies, and artistic traditions through his deliberate turn to abstraction and his visionary establishment of modern art institutions. It explores how he enacted a form of aesthetic dissent that preserved cultural memory, fostered artistic freedom, and as a result, reimagined the role of modernism in shaping national identity in both Spain and the Philippines.

Fernando Zóbel, shaped both by his transnational identity and his experiences on the American East Coast; both by tradition and modernity; both by deep scholarship and a love for experimentation, had a different vision. His abstract works—delicate, thoughtful, precise—stood in quiet contrast to the dominant artistic style of Francoist Spain. While the regime demanded realism in art, Zóbel's deeply held beliefs about artistic responsibility and cultural preservation not only informed the reflective, calligraphic quality of his work but also motivated his efforts to support and institutionalize abstract art in Spain and in the Philippines. His founding of the *Museo de Arte Abstracto Español* in Cuenca and the Ateneo Art Gallery in Manila stand as key expressions of this dual commitment – to creating art and securing its future. In this way, subtly challenging the prevailing traditionalism in art through modern abstraction, thus positioning abstraction as a form of intellectual and cultural resistance— a soft “aesthetic dissent.”

This paper has employed an extensive qualitative and interpretive approach outlined in the next section, followed by an introduction to the socio-political climate of post WW2 Spain, and then an exploration into the nature of the art and culture scene under the Franco regime to contextualise the detailed study of Fernando Zobel. Then comes a deep dive into the artist's early years and his emerging style through his various influences before the subsequent, more nuanced and detailed analysis of his artistic voice and body of work. The examination then continues to further explore Zobel's role, beyond that of the artist, in the context of Francoist Spain and how the work and experiences of his youth led to his lasting impact on the art scene, not just as an artist, but as a collector and advocate dedicated to cultural preservation. This study concludes with a final reflection on his legacy in both Abstract Modernism in Spain and the Philippines and his lasting impact on the development and preservation of cultural identity.

Methodologies

This study employs a qualitative, interpretive approach combining several approaches. First, this study utilizes art historical formal analyses of key works across the breadth of Zobel's artistic career at different points in his aesthetic development (Saetas, Serie Negra, etc) to study how his evolving style differed from the tradition and what this connotated. Second, historical examination and contextualisation of the socio-political climate of Francoist Spain was employed to illustrate the constraints and restrictions artists had to face under the regime, juxtaposed with new developing movements outside. Third, a biographical analysis of Zobel's transnational background from boyhood to higher education, personal connections, family, and roots was conducted to contextualise the evolution of both his artistic pursuit and style. Fourth, a cultural critique was used for examining his role in advocacy through the establishment and support of museums and art collections as acts of cultural preservation and resistance directly

resulting from his personal experience with erasure in a post WW2 era. Finally, comparative studies linking a multitude of influences such as American Abstraction, Japanese techniques, and Philippine traditions were employed to demonstrate the hybridity and innovation in Zobel's work.

This combination of stylistic, biographical, historical, and interpretive analysis supports the position that Zobel's contributions not only impacted the art world through the influence of his own art but also through his advocacy and support of emerging modernist movements and, as a result, were deeply intertwined with acts of cultural resilience and aesthetic dissent. These methods can be justified because they enact a comprehensive and nuanced understanding of Zóbel's work and actions within their complex socio-historical context. Specifically, art historical analysis involves a detailed examination of Zobel's stylistic evolution and thematic interests. They reveal how formal choices in the visual medium can act as subtle forms of messaging and, in this case, resistance. Thus, this approach is essential to substantiate claims about aesthetic dissent embedded within his artworks. Next, a contextual historical inquiry positions Zobel's endeavours within the broader socio-political context of Francoist Spain. This provides the necessary background and contextual cues to accurately interpret his artistic development, the deeper meaning behind his work, and thus the intention and impact of the same. Understanding these cues clarifies the significance of his non-confrontational approach.

Further, biographical critique provides insight into how Zóbel's transnational identity and personal experiences informed his artistic philosophy and institutional decisions, which further support the personal, cultural, potentially political, and definitively socially conscious motivations behind and nature of his work. Next, the cultural critique through archival and institutional research establishes justification for the exploration of the impact of Zobel's patronage— such as the founding of independent museums which contributed to both the preservation and promotion of modernist art, functioning as tangible acts of cultural agency under repression. Finally, comparative analysis contextualises Zobel in the global modernist environment. This illustrates the multicultural and transnational influences on his work- that is, its hybrid-like quality— which in turn is a direct artistic opposition to the artistic tradition of Francoist Spain. Thus, its very existence is the definition of aesthetic dissent.

Collectively, these methods come together and provide a rigorous, interdisciplinary framework that substantiates the thesis that Zóbel's artistic practice and advocacy together constitute forms of aesthetic dissent amidst oppressive political conditions in Francoist Spain.

The Franco Regime and the Socio-Political Climate of Postwar Spain

To understand Zóbel and the trajectory of his artistic work in Spain, it is essential to first consider the sociopolitical climate of Francoist Spain – a context that profoundly shaped the country's cultural and artistic landscape.

General Francisco Franco was a rebel leader during the Spanish Civil War. The Nationalistas carried him to power at the end of the war in 1939, and he ruled, thereafter, as a dictator until his

death in 1975. However, the majority of the European and Spanish intelligentsia had allied with the defeated Republicans so the new regime was left with little intellectual respectability—moreover, Picasso's *Guernica* (1937) had exposed the ruthlessness of the Franco regime to the world. Many artists had died or were living in exile as a result of the civil war and those that remained lived in a vacuum (Slomski; "Art and Diplomacy"). Thus, "The Franco regime became more concerned with control of possible alternative cultures through censorship than with the creation of an original culture" (Slomski). However, liberal elements survived and continued to assert their presence despite this repression. A quiet countercultural movement began to take shape—artists turned to abstraction, symbolism, and experimental forms as a means of subtle resistance. They formed collectives and began travelling to art metropolises around the world in order to keep up with the international art community and develop their work beyond the stifling, regulated traditions supported and enforced by the regime.

Under Franco for years, Spain was isolated, poor, and plagued by internal strife (Scott). In World War II, they had allied with the Axis powers and were spared from the worst of the war's destruction. But this was also the reason Spain was not included in the Marshall Plan after the war, which would rebuild much of Western Europe and bring in economic stability. Thus, Spain continued to lag behind its European counterparts in terms of economic, political, and cultural development. But the forces that would change Spain's course were on the horizon. The war had brought devastation on many countries and populations, and widespread discontent created fertile ground for the rise of communism, which led to the onset of the Cold War between the United States and the Communist bloc. Fortuitously, "Franco was a devout anti-Communist dating back to the Civil War; this made him attractive to the United States" (Scott), which helped keep the dialogue between the two nations, and thus the two cultures open.

Isolation to Internationalism: Modern Art and Francoist Cultural Diplomacy

In the meantime, a new art movement had been growing in New York City through the 1940s and 1950s. Abstract Expressionism emerged as the dominant movement in the international art world, where it came to symbolize post-war freedom, individuality, and artistic innovation – values in stark contrast to the cultural repression of Francoist Spain. Artists such as Jackson Pollock, Willem de Kooning, and Mark Rothko were pioneers of this new movement that "served to unite the two dominant aspects of abstract expressionist art: a non-figurative commitment that reduced representational objects to basic geometric forms (abstraction) and the improvisational brushstrokes expressing emotion or conceptual states (expressionism)" (Toteva 364). It was at this time that Fernando Zóbel left Manila to pursue his studies at Harvard, and it was this very exposure to American Art during his education and early career that allowed him to engage with abstract expressionism not just through imitation, but through thoughtful adaptation. "It was upon seeing an exhibition of Mark Rothko, one of the American Abstract Expressionists, in 1955 that Zóbel realized abstraction's potential" (Paras-Perez 38).

In 1953, the US and Spain signed the Pacts of Madrid — three executive agreements that essentially brought Spain out from isolation. In the later decades of his rule, Franco began permitting some types of modern art, provided they weren't observed as critical of his regime. This became an opportunity: "Keen to brush off its image as a poor and backward dictatorship, Spain put modern art at the forefront of its efforts to present the country internationally as sophisticated and progressive" ("Art and Diplomacy"). "Seizing on cultural diplomacy as a key component of its nationalist agenda, the regime marketed Spain's abstract artists as members of an international avant-garde while at the same time emphasizing the "Spanishness" of their art." Soon after the signing of the pacts, two exhibitions of modern art assembled by the New York City MoMa were shown in Barcelona (1956) and Madrid (1958). In exchange, Spanish art was exhibited at the MoMA (New Spanish Painting and Sculpture, 1960), and at the Tate Gallery in London. Thus, the arts spearheaded Spain's efforts to break free from the long-standing isolation that had defined its postwar identity.

It was within this shifting cultural landscape that Fernando Zóbel would find his place—not just as an artist, but as an advocate for new ideas and modern aesthetics. His life, work, and conservation efforts would come to reflect the very internationalism that Spain, emerging from decades of isolation, sought to project—yet simultaneously restricted under Franco.

Making of a Modernist: Zóbel, The Early Years



Fig. 1. Fernando Zóbel in the year of his graduation from Harvard University, 1949.

Fernando Zobel was a businessman, a painter, an art collector, and a general citizen of the world. He was born in the Philippines in 1924 to one of the country's wealthiest *insulares*¹ families, engaged in many businesses and industries. Even as a child, his family took him on many travels, and he was able to see the world (Paterno). Because of his father's businesses, the family was constantly on the move, and Zóbel spent his early years in the Philippines and Spain, as well as the rest of Europe (he spent a short time at school in Switzerland), returning to the Philippines as a young adult in 1936. He completed his primary education in the Philippines and was preparing to leave for university abroad when World War II broke out. This prevented him from leaving the country and so he enrolled at the University of Santo Tomas in Manila. However, at 18, he developed a spinal condition that necessitated him staying bedridden for a year. It was during this convalescence that he picked up a sketch book and rediscovered his love for drawing and art— in his own words;

¹ Insulares

“For a whole year, I was bedridden. I had all the time in the world to think, and it was then that I started to consider the idea of becoming an artist” (Zóbel, interview).

World War II was devastating for the Philippines, especially for Manila, where intense bombings left the city in ruins and resulted in the widespread destruction of its artistic and cultural heritage. Zóbel, the young man who was already beginning to explore his interest in art, bore witness to this tragedy. So when he was finally able to leave for Harvard University in 1946, he left “behind a city reduced to ashes as a result of the Japanese resistance and the American bombardments of World War II” (Pereda). This destruction of cultural heritage, including artworks and vital primary sources, created a profound gap in the ability to reconstruct and understand Philippine history. Something that the young Zóbel not only understood, but built his beliefs about cultural preservation around— the conservation and preservation of art, culture, and heritage. Zobel would return home to the Philippines and would establish the Ateneo Art Gallery, partly as a cultural reconstruction. “For Zóbel imagined the future having seen a beloved city brought to its knees by World War II” (Veric).

Zobel thrived in Boston. He was a successful student, engaged in learning about history and literature, but continued to be an active participant in the world he was in. He was introduced to and became enamored by the works of modern artists. He immersed himself in the Boston art community, and his exploration and appreciation of the avant-garde and modern blossomed. He admired the works of Boston Expressionist painters such as Hyman Bloom and Jim and Reed Pfeufer, he even developed a close friendship with Bloom and was mentored by Reed Pfeufer, which heavily influenced his art style. In his early years at Harvard, Zóbel’s paintings reflected the Boston School’s style of romanticism and symbolic expressionism. Many of his earliest works were landscapes in figuration. Zobel held his first ever exhibit in Boston in 1951 as part of the Boston Expressionists. He was active at the Harvard Alumni Bulletin, creating weekly caricatures for them. It was while there that he published an article for the Harvard Alumni Bulletin (1948-1952) which revealed his particular fascination with the avant-garde artist, architect, and the founder of the Bauhaus movement, Walter Gropius (Pereda). He remained increasingly drawn to abstraction. But his time in the US was coming to a close. He returned to Manila in 1952 ostensibly to work for his family business. By this time, painting was already central to Zóbel’s intellectual and creative life.

Upon returning to Manila after his studies at Harvard, Zóbel immersed himself in the local art scene, befriending and supporting young, up-and-coming painters like himself. He exhibited with artists of the Philippine Art Gallery, which was the nucleus for the development and exhibition of modern art in the Philippines at that time. His paintings, while showing modernist tendencies, still portrayed the textures of daily existence in the Philippines.

Gesture, Line, and Space: The Artistic Evolution of Zóbel’s Abstract Style

Like most Filipino painters of the day, Zobel took inspiration from the scenes that were in his reality — religious processions, local customs, and street life. However, unlike most Filipino painters then, he stepped away from painting them in figurative realism, breaking away from the

traditional art the likes of Fernando Amorsolo, who was widely recognized as the most gifted artist of that era. Amorsolo, “the pastoral painter whose light, in the opinion of Quijano de Manila, evoked the “rapture of a sensualist” in love with the Philippine earth” (Veric).

Zóbel was as much an intellectual as he was an artist, he engaged in a lifelong dialogue with both the past and the future. Though his work is unmistakably modern, he consistently honored the artistic traditions from which he drew inspiration. This reverence is perhaps most evident in his long-running series *Diálogos*, in which he entered into visual conversations with great artists of the past. Each canvas in the series reads as a discussion between Zóbel and the masterpieces that had shaped his own artistic vision. “Yet, he wasn’t just interpreting that work or paying homage to the original artist. Through his own paintings, he propelled the original work of art into a future that he thought they ought to have, a future he created by pulling on an emotion he retained from these inner conversations, paring them down to their essences” (Zóbel, *AAP Bulletin*).



(Processional Float), 1953. Polymer on wood, 119 × 59.5 cm. Ateneo Art Gallery.

Perhaps it was the intellectual in Zobel that attracted him to this alternative idea of a non-objective art, which would later be called abstract. Zobel began stepping away from figuration: “His *Carroza* (1953), which won the gold prize in the modern category of the 1953 semi-annual competition of the Art Association of the Philippines, was an abstracted form of the ornately decorated float used for religious processions in the Catholic country. Even then, he was less preoccupied with capturing the essence of a subject than its form” (Chikiamco). “The art critic Ricaredo Demetillo wrote on Zóbel’s art then: “The subject matter of Zóbel’s paintings generally is of a representational nature, even when he is at his most abstract. You somehow feel that he is concerned with purging the object of its surface features to reveal the form beneath, that he eschews the retinal impression to contemplate purely thingness and compositional relationship of objects” (Demetillo). Zobel taught an “Introduction to Contemporary Painting” class at the Ateneo de Manila University in the early 1950s and included in his lecture notes the following: a “painting need have no relation with the appearance of natural objects. It can deal with either emotions (organic school: abstract expressionism) or with constructions (geometric school)” (Zóbel, “Lecture Outline” 190). Clearly, he was moving away from the figurative school, shifting the focus from realistic external forms toward the expression of inner reality of emotion and concept.

Upon the invitation of Boston mentors Jim Pfeufer and Reed Champion, Zóbel returned to the United States in 1954 as an artist in residence at the Rhode Island School of Design. Zóbel

took advantage of the time to explore the art scenes and galleries in Providence, Boston, and New York. He attended an exhibit of a then relatively unknown Mark Rothko and was completely enraptured by Rothko's use of color not merely as form, but as expressive content. "He would later remark: "Rothko's demonstration convinced me completely...I felt obliged to paint, but I had abandoned the need to represent" (Magaz Sangro 119). He began exploring his own approach within this non-figurative, non-objective form of painting. It was upon returning to Manila that Zobel took a business trip to Japan. His experience of Japan reflected in both his artistic and intellectual perceptions. This had a profound effect on how he thought of his art. In Zóbel's *Saeta* series, the influence of Eastern techniques — particularly the use of negative space and gestural brushstrokes — begins to emerge. Zóbel's *Saetas* were thematic of "movement expressed metaphorically through the use of line. The movement of leaves, blades of grass, trees, birds, people; movement observed, sensed, never imitated, but, I hope, translated" (Pérez-Madero 19).

After Zobel's exposure to the American artist Mark Rothko, he ultimately solidified his move into abstraction permanently. He began to discover his own speed and style, and welcomed the oriental influence from his time in Japan; and it was the intersection of all of these experiences which solidified the creation of Zobel's *Saeta* series in 1957. Arguably, his most well-known series of works.

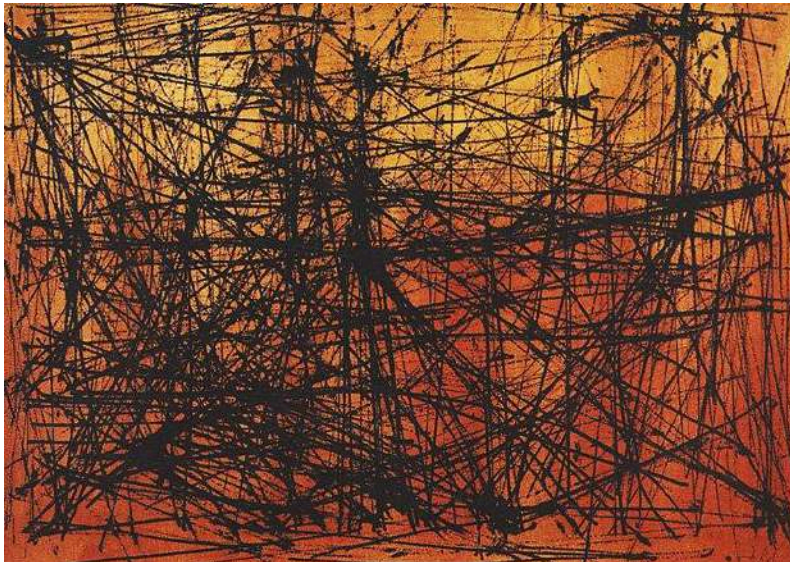


Fig. 3. Fernando Zóbel, **Saeta 22**, 1957, oil on canvas, 61 × 91 cm. Jose Joya collection.

Saetas 22 is a part of the *Saetas* series that can be selected to discuss the sum of the whole. Measuring 61 x 91 cm, the canvas has been washed in a mix of red and orange hues, with black lines densely populating the surface. With the lines so evenly dispersed, Zobel makes minimal use of negative space, unlike his later work *Icaro*. Regardless of their prevalence throughout the canvas, there is evidence that Zobel was intentional with the placement of these

lines. They converge to make focal points that form an implied grid across the canvas. It is these points that draw the gaze of the spectator initially. Despite the innate static nature of lines, they are responsible for the dynamic quality of this composition. This dynamism has been derived from the intentional congestion of the densely populated line work— creating a sense of movement that constantly draws the viewer’s gaze frantically across the composition. The lines vary in width, with some being more precise and surgical and others heavier handed. The placement of each, while adhering to some type of grid, feels frenetic and rushed.

In Saetas 22, the tension is fostered by gesture and motion as opposed to the contrast seen in *Icaro*. It’s a geometric entanglement, converging at angles and sharp edges. This is also a



Fig. 4. Akira Nakata, Taizō-in, Myōshin-ji Complex, Rinzai Zen Buddhism, Kyoto, 1404, Muromachi Period; with later additions, Shōwa Period.

major point where we see the Japanese influence on Zóbel’s art, that is, “Zóbel moves away from expressionist dramatism and bases his works on the nakedness of the line and the movement suggested through these strokes, which cross the space and intermingle in the painting. With this method, he achieves that vibrant and disturbing effect of Japanese gardens that at the same time makes us feel calm and tranquility.”²

Interestingly, this sharpness is juxtaposed against the warm, softly-blended palette of the gradient-like background. Fiery yellow and vermillion make Saetas 22 reminiscent of a cloudless sky at sunset, with the same seamless blended quality of setting light, thus making the geometry of the linework over it all the more striking through the sheer contrast. The previously mentioned tension, the brilliance of the saturated palette, all suggest a certain liveliness, a notion further implied through the choice of colour as warm palettes suggest heat, a quality that usually signifies life and therefore movement.

Thus, the influence of American abstraction is undeniable- Pollock’s overlapping dynamic lines, De Kooning’s hurried brushstrokes, and Rothko’s dual coloured warm palettes have been reimagined together in Zobel’s art.

² Japanese gardens reframe Japan’s natural landscapes, which embody both awe and terror.



Fig. 5. Jackson Pollock, **Autumn Rhythm**, 1950. Oil on canvas. The Metropolitan Museum of Art, New York.



Fig. 6. Willem de Kooning, **Gotham News**, 1955. Oil on canvas. Albright-Knox Art Gallery, Buffalo.



Fig. 7. Mark Rothko, **Orange, Red, Yellow**, 1961. Oil on canvas. Mark Rothko Foundation.

This subject, unlike Zobel's previous works, is pure abstraction, with no discernible suggestions of natural forms. This could be interpreted as referencing emotions, which are individually messy yet inherently structured in their humanity, but the general undertone of this composition is chaos— whose intense and restless feeling prevails throughout the whole work.

Following Saetas, a definitive turning point appeared in Zobel's work. Having explored his art through the lenses of his American Abstraction influences, the rest of his body of work found its own distinctive identity— one which grew and evolved with him for the rest of his career and became the hallmark of his artistic identity.

One of Zobel's most acclaimed and revered collections of works is the Serie Negra. The series can be traced back to 1959, when Zobel's artistic style took a turn after he became increasingly familiar with Spanish Abstractionism. In integrating the movements' key features, such as sharp geometric forms and contrasts, and calligraphic elements, Zobel no longer limited himself to expression via lines. Instead, he dry-brushed the canvas, mixing softer forms with harder ones, and used the negative space as a tool, and began to step away from vibrant, complex, and saturated colour palettes, elements previously freely featured in his work. Zobel himself said:

“After almost two years, I began to realize that my use of color was quite arbitrary (...). Any combination of two colors, as long as it had a certain vibration, could serve me. I think that for a work of art, what [proves] not to be necessary is superfluous, even distracting, weakening and hindering. Little by little, I eliminated color until I was left with black strokes on a white background.”



Fig. 8. Fernando Zóbel, *Ícaro*, 1962. Oil on canvas, 137.5 × 200 cm. Ayala Museum.

Icaro (1962) is one of his more widely known works from this time. Employing dry brush techniques with oil on canvas, the form in this composition is more representational than the pure abstraction of *Saetas 22*.

While the majority of the canvas is occupied by negative space, most of the form is concentrated to the lower center of the canvas with wider, less intense brushwork tapering off upward. The juxtaposition between the untouched white of the canvas and the dark black of the paint gives the form more weight and tension through visual contrast, and this, combined with – negative space surrounding the form, gives it the illusion of being suspended mid-air. The composition contains an interesting blend of both gestural and intentional strokes, featuring thin and sharp linework that converges into smudges and swashes of dry paint– reminiscent of the effect of a motion blur. Moreover, the gestural strokes create a dynamic quality that serves to further suggest movement. They swoop outwards almost like extended wings.

Furthermore, the varying opacity of some strokes and areas gives the impression of translucence. These gaps and strokes, where the black fades away and tapers off, create the illusion that parts of the form appear to be catching light while others fade to black, suggesting a shape formed of denser mass. There is no distinct light source, but the white evokes feelings of light regardless– and it occupies a space in this composition almost as a material rather than a compositional feature.

While the Spanish influence can be observed, as mentioned previously in the compositional and technical elements, *Icaro* echoes another school that Zobel observed. His time in Japan exposed him to many of the traditional ink and watercolour drawings, and certain elements of *Icaro* illustrate the Japanese style as well. The contrast and duality of black and white, the gestural strokes where pigment and brushstroke seem to lift off the surface, and the use of negative space are all reminiscent of traditional Japanese ink painting.

All of these factors— line, stroke, negative space, movement— converge and a representational form emerges: a figure with a smaller body and larger wing span, made not of a single condensed form but suggestive rather of many smaller forms coming together. While the image first appears abstract, the implied movement suggests wings and flight, and through Gestalt principles³, the spectator can observe a bird soaring across the canvas.

Though this may be a simple canvas with a singular element in its composition, the complexity of what it suggests can not be ignored. There's an undercurrent of tension in the work made through compositional elements that's offset by the thematic peace that birds represent. And this contradiction and duality can be observed across the artwork. There are motifs of light versus dark, motion versus stillness, and gestural versus intentional, figuration versus abstraction. Every element within the work is at odds with another, in what is perhaps an intentional dichotomy by the artist. Thus, *Saetas 22* and *Icaro* showcase a convergence of influences and exploration at the intersection of which Zobel begins to discover his own unique artistic sensibility. Zobel found his own unique style.

Having discovered an artistic sensibility amalgamated from his various experiences, Zobel continued to refine it until it became an unmistakable part of his artistic identity. This can be observed in most of his works since *Series Negra*. The *Orsillas* series, which came later in Zobel's career, was a series of studies from his studio in Cuenca. They were analytical breakdowns of his most familiar view and demonstrated his firm commitment to the abstract movement. Of these, *La Vista X* (1974) is a prime example of Zobel connecting observational art to his particular style of abstraction— in many ways, it echoes *Series Negra* and is an evolution of his style.

La Vista X is an observational piece which is meant to showcase the view from Zobel's studios, in keeping with the theme of the series. The large expanse of negative space that dominates most of the canvas serves to act not just as a stylistic element in this case but also as a form: Zobel is showing the spectator a view from his window, and this view has been enclosed in a rectangular shape with the colors being contained to the same and situated higher up on the canvas. These compositional cues contextualize the piece and make up for the lack of details within the piece itself: "The composition of the paintings is directly related to that of the landscape itself. He [Zobel] leaves behind the river, the reflections, and the relations of color, to enter this time in the stony and arboreal masses of the nature of Cuenca; synthesizing everything to the maximum, eliminating all the distractions that the landscape carries with it. In the works of



Fig. 9. Fernando Zóbel, **Ink Painting**, 1962. Ink on paper. The Metropolitan Museum of Art, New York.

³Gestalt principles explain why humans view visual items as wholes or unified patterns rather than as discrete components.

this stage, we can clearly see the mental process and the painter's capacity for synthesis, converting the materiality of the rocks, the trees, and the houses into a slight tremor on the canvas in which even the color disappears, only supported by the composition of the landscape reduced to its minimum expression."

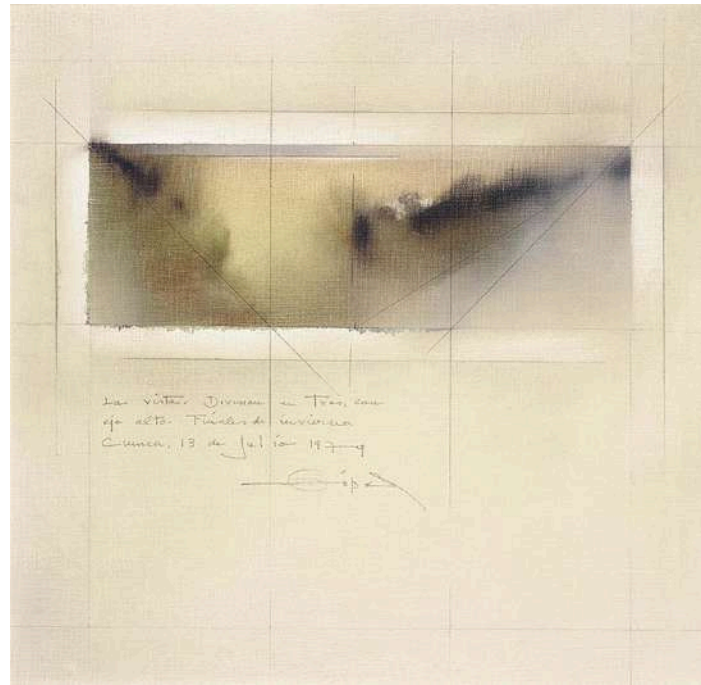


Fig. 10. Fernando Zóbel, **La Vista X**, 1974. Oil on canvas, 40 × 40 cm. Private Collection.

Moreover, the negative space can be interpreted as the wall of his studio. As a stylistic element, it makes the window the focal point of the composition, with everything else around it acting as a visual break. Much like *Icaro*, rather than detail and form, carefully considered context, layout, and brushwork give rise to a subject rather than a direct visual representation.

The canvas is largely a uniform eggshell hue, which complements the colour values in the “window.” Muted earth tones, olive green, cream, white, brown, beige, white and black have all been softly blended together within the confines of the window shape. Similar tonal variations help the different hues blend together and create the effect of a soft light dispersed over a frosted pane, where one can make out colour and shape but not form. The diffused lighting makes it feel softer and calmer, and this haziness is suggestive of a semi-forgotten nostalgic memory— creating a sense of intimacy between the artist and the viewer with composition as a medium.

This is further supported by the thin, light pencil lines and annotations made over the painted artwork. While the central form is blurred and ambiguous, the hand-drawn lines are thin and precise in nature, and intersect to form what looks to be an architectural or grid-like surface division over the view. In this, it is reminiscent of a technical drawing, where different parts of a landscape have been divided up for an observational study. Unlike his previous works, in both

Saetas and Series Negra, these lines feel more dignified and forgiving, forming a structure that helps the viewer contextualise and make sense of the subject instead of an abstraction. The handwritten inscription below it feels more personal, like a note or a reminder, and bridges the disconnect between the abstraction of the natural world with the more controlled and detailed personal connection.

This overall sense of intimacy, borne from the nature of the subject– that is, the artist’s literal perspective of a landscape, the diffused tones to suggest memory, the annotations and line work reminiscent of a diary entry that glimpse into his mind– makes the whole piece feel more personal, a result of which is a powerful sense of connection between viewer and artist that seems to transcend time, physical space, and even at time, context. The duality of soft formless composition and detailed notes and structural lines is yet another dichotomy, one of many that can be observed in Zobel’s work– this one blending the line between emotion and analysis.

Collector, Curator, and Creator: Zóbel’s Role and Contributions to Modern Art in the Philippines and Spain

Thus, Fernando Zóbel advanced his own artistic vision, evident both in his choice of subject matter and in his methods of execution. His conception of the future of art remained steadfast, regardless of the circumstances he faced. “The modern in Zobel may be construed, then, not simply as a formal style but, rather, as an aesthetic sensibility inseparable from the profound hope he felt” (Veric).

In 1959, Zóbel was invited to hold a solo exhibit at Madrid’s Galería Biosca. The exhibition is Zóbel’s first in Spain, featuring paintings from the *Saetas* series alongside his new *Serie Negra* works. He then participated in another exhibition, a collective this time, with the Spanish artists Chillida, Oteiza, Miro-Artigas, Tapies, and Palenzuela at Madrid’s Sala Darro which became a significant turning point in Zobel’s life: “At this exhibition, Zóbel identified with the Spanish painters of his generation and this became one of the reasons why he decided to leave the Philippines and the world of business to devote himself entirely to painting” (Veric).

But not before he bequeathed his private collection, consisting of post-war Philippine Modernist Art and some of the finest collections of prints and drawings of Western masters, to the Ateneo de Manila University, where Zóbel taught Contemporary Art in the 1950s. This collection would form the backbone of the Ateneo Art Gallery, which opened in 1960, the first museum dedicated to Modern Art in the Philippines. Whether by design or circumstance alone, his gift to the Ateneo de Manila University contributed significantly to the rebuilding of an artistic and cultural heritage in the Philippines. His collection was “more than a matter of taste, the choice was a philosophical vision that sought to rebuild the aesthetic artifact of the country. A reconstruction that began not with historical relics but, rather, with contemporary works that enabled robust imaginations of the future.” In some respects, the loss of much of the Philippines’ artistic heritage, which Zóbel had witnessed in WWII, would underscore the enduring nature of Zóbel’s legacy, giving the modern a lasting and singular power.

When Zóbel initially moved to Spain, the political climate under Franco made it a difficult time to be an abstractionist and a modernist, as such movements ran counter to the regime's cultural agenda. Even when the political climate had relaxed, the Francoist government's stance toward the avant-garde was one of ambivalence — there was no open opposition, but neither was there an offer of support. So Zóbel had to pave his own way. Just as he had actively collected modern Filipino art, he had also begun to do the same with Spanish art. As abstraction was not the officially sanctioned art of the Franco regime, there was no support for abstract artists in Spain for many years. Thus, even as Spain slowly came out of isolation, and her artists were celebrated as avant-garde to lend an appearance of modernity and openness to the Franco regime, they remained largely under-appreciated within their own country. Spanish artists received acclaim in other countries, but then came home and had no venue to exhibit or show their work. So when the young Zóbel discovered Spanish modernist art on a trip to Spain in the 1950s, he was troubled to find that much of their best art was being acquired by collectors abroad. Thus, he became a supporter of modern Spanish artists like Chillida, Tàpies, Luis Feito, and Antonio Saura, Gustavo Torner, and Gerardo Rueda⁴, the latter two whom he would form lifelong friendships with and would be key to the establishment of the *Museo de Arte Abstracto Español*. Artist, patron, collector— Zobel's immersion in the art world was inextricably tied to every aspect of his very being.

While living in Spain, Fernando Zóbel's private collection of Spanish modernist art grew, and as it grew, so did its significance. Soon, Zóbel became determined to share it with a domestic audience; "It was not too far-fetched for Zóbel (who had the ability, critical demand, an innate generosity, the drive and the intellectual and cultural capacity, as well as that small dose of pragmatism that must exist behind great ideas) to feel in the early sixties the moral duty to show those paintings that he had collected with so much faith and passion" (Villalba Salvador 205–236). Despite being regarded as a bold undertaking in light of Spain's political climate at the time, Zobel's initiative moved forward, and with these extended discussions with fellow artists, the idea of opening a museum gradually took shape. It was upon the suggestion of Zóbel's good friend and Cuenca native, Gustavo Torner⁵, that Zóbel came upon the property in Cuenca that would eventually house the *Museo de Arte Abstracto Español* in the historic *Casas Colgadas*, the Hanging Houses of Cuenca.

From Patron to Pioneer: Fernando Zóbel's Enduring Legacy in Abstract Modernism and Cultural Identity

On June 30, 1966, the Spanish Museum of Abstract Art formally opened: "At the center of the front row stands Zóbel himself, arms crossed and smiling modestly, surrounded by artists who had defined—and would continue to shape—the course of Spanish abstraction. From geometric experimentation to gestural informality, from kinetic art to textured matter painting, the group represents the rich diversity of the Spanish avant-garde in the 1950s and 60s. The photograph is

⁴ These painters were influential in postwar Spanish abstract painting and are credited with promoting geometric abstraction, expressionism, and informalism in Spain.

⁵ Gustavo Torner (1925–2021), Spanish painter and sculptor, noted for his role in postwar abstraction.

more than a record of an art event—it is a document of cultural resistance and creative solidarity. Amid the restrictive climate of Franco’s Spain, these individuals gathered to inaugurate a museum built not by state decree, but by artists themselves, fueled by shared ideals of artistic freedom, experimentation, and mutual respect” (Veric).

The *Museo de Arte Abstracto Español* was, in fact, more than a physical museum. For Fernando Zóbel envisioned bringing together a community of like-minded artists who ran the museum with Zóbel, thus also making it the first artist-run museum in Spain and the center of modern art in the 60’s. He established a museum of Spanish abstract art, operating independently



Fig. 11. Fernando Nuño, Fernando Zóbel and Artists at the Inauguration of the Museum of Spanish Abstract Art, Cuenca, 1966.

of the Franco regime’s cultural framework.

Beyond the museum itself, he actively invited artists to settle in Cuenca, transforming it into a thriving center for artistic creation. “I think we can almost say that the Cuenca museum was the first democratic museum in the country because it didn’t ask anyone’s permission to do anything,” (Villalba Salvador 205–236).

Zóbel held a unique position in art history; he stood at the forefront of a new cultural dawn for both Spain and the Philippines, while being the instrument that quietly challenged the boundaries of the old order. Without direct confrontation or protest, Zóbel steadfastly upheld his modernist ideals, guiding his audience to appreciate the full breadth and depth of modernism through his own art and his

collection. Stepping away from the “approved, enforced” tradition in his artworks, supporting fellow artists to explore beyond canon by providing means and opportunity, and finally, committing himself to the preservation and advocacy of emerging styles, was his three-pronged approach that quietly challenged restrictions and tradition in favour of innovation and creative evolution. His influence on both Spanish and Filipino abstract art was substantial; through his patronage and advocacy, he lent legitimacy — and even a degree of popularity — to abstract art at a time when figurative realism dominated the art scene. His confidence and bravado, perhaps rooted in the privilege into which he was born, imbued him with an air of assurance and authority.

Fernando Zóbel’s contributions to art and art history are beyond measure. His paintings breathe with a quiet transcendence, like whispers of wind across water, carrying both the weight and the tenderness of his subjects.

In an age when figurative art and realism commanded the stage, Zóbel walked a different path. It was his peculiar cultural resistance to the prevailing traditionalism that set him apart —

an insistence on searching beyond convention, on finding forms that could speak to both the mind and the heart. This was his aesthetic dissent. In Zóbel's own words: "The realist focuses on that loaf of bread, that flower, I'd like to create a climate in which the bread, the flower, were born of the viewer's imagination" (Jones).

Zóbel combined the rare qualities of the passion of a painter, the zeal of a collector, and the imagination of a visionary to dream of creating a museum. Add to this his exquisite taste, rigorous academic training, insatiable intellectual curiosity, and economic means to cultivate those qualities, and it is clear that without Zóbel, the Spanish abstract movement would have suffered enormously (Veric).

For both Spain and the Philippines, Zóbel helped shape the future of artistic culture. As Filipino author, poet, scholar, and curator Charlie Samuya Veric wrote: "He was modern because his sense of debt was located in the future, seeing it as an unrealized place of redemption" (Veric). This vision was realized not only through his paintings but also through the museums founded through his generous patronage. In doing so, he helped define the path of modern and abstract art in both the Philippines and Spain by giving the public access and platforms to further understand and appreciate these movements. By building these world-class institutions, he created enduring repositories of visual culture, securing a legacy that would serve future generations. It is true that "without Zóbel's trailblazing vision – and without the artists and works and ideas he gathered inside the Hanging Houses almost 60 years ago – Spain would have taken far longer to establish itself as the cultural engine it became after the post-Franco return to democracy" (Zóbel, interview).

Art plays a major role in shaping national identity. It is inseparable from the creation of culture. In this sense, Fernando Zóbel cultivated a culture and shaped an identity that extended beyond what was officially recognized. Yet his divergence was always a quiet one — mirrored in the serenity of his works. Zóbel's art was, in the end, a quiet defiance — an insistence that beauty need not shout, that meaning could reside in restraint, and that the truest images are those that echo in both the eye and the heart.

Works Cited

- Aguas, J. J. "The Role of Arts in Preserving/Transforming National Identity in Times of Change: Filipino Context." *The Asian Conference on Ethics, Religion & Philosophy 2018 Official Conference Proceedings*, 2018,
https://www.academia.edu/36898766/The_Role_of_Arts_in_Preserving_Transforming_National_Identity_in_Times_of_Change_Filipino_Context.
- Brennen, Bonnie S. *Qualitative Research Methods for Media Studies*. Routledge, 2021.
- Cabañas, Pilar. "Fernando Zóbel, In Search of an Identity: 1953, First Notes of a Travel to Japan." *Philippine Studies*, vol. 56, no. 2, 2008, pp. 213–37.
- Concepcion, Grace Liza Y. "Juan Luna as Nationalist Painter and Hero: Examining Configurations of Public Memory in the Philippines." *South East Asia Research*, vol. 32, no. 4, 2024, pp. 387–403.
- Cruz, May Lyn L. *Entangled Relations: Signs and Consequences of Conflated Patronage at the Metropolitan Museum of Manila from 1976–1986*. MS thesis, State University of New York at Buffalo, 2015.
- Demetillo, Ricaredo. "Fernando Zóbel: Man and Artist." Publication unknown, c. 1956. PKL Archives ART VI, 124, Kalaw-Ledesma Foundation, Inc.
- Denzin, Norman K. *Strategies of Qualitative Inquiry*. Vol. 2, Sage, 2008.
- Eduque, Michaela. *Valuing the Filipino Identity in the Local Philippine Art Scene: Nationalism and the Philippine Core Values Through Amorsolo, Zóbel and Bencab*. MS thesis, Sotheby's Institute of Art–New York, 2025.
- Fontán del Junco, Manuel. "'Massive and Exciting Impact': Show Celebrates Spain's First Abstract Art Museum." By Sam Jones, *The Guardian*, 26 Apr. 2024.
- Goizueta, Elizabeth Thompson. *Cuenca: City of Spanish Abstraction; Repression and Resistance*. Exhibition catalogue, McMullen Museum of Art, Boston College, 11 Feb.–2 June 2019.
- Joaquin, Nick. Biographical note. National Artist of the Philippines for Literature.
- Jones, Sam. "'Massive and Exciting Impact': Show Celebrates Spain's First Abstract Art Museum." *The Guardian US*, 26 Apr. 2024.
- Lopa, Trickey. "Fernando Zobel at The Prado: Painting the Future by Seeing the Past." *The Philippine Star*, 26 Nov. 2022.

- Magaz Sangro, Antonio. *Zóbel: Pintura y Dibujos*. Translated by Sofia Molina de Starnes, 1959. Reprint, Galería Cayón, 2015.
- Moxey, Keith P. F. *The Practice of Theory: Poststructuralism, Cultural Politics, and Art History*. Cornell University Press, 1994.
- Paras-Perez, Rod. *Fernando Zóbel*. Manila: Eugenio Lopez Foundation, Inc., 1990.
- Paterno, Ma. Elena. *Fernando Zobel: The Man Who Painted Ideas*. 2nd ed., 2024.
- Pereda, Felipe. “Fernando Zobel-Montojo: Brief Life of an Abstract Painter: 1924–1984.” *Harvard Magazine*, Jan.–Feb. 2023, Features.
- Praepipatmongkol, Chanon. *Postwar Abstraction and Practices of Knowledge: Fernando Zobel and Chang Saetang*. Dissertation, 2020.
- Quizon, Cherubim A. “Indigenism, Painting and Identity: Mixing Media under Philippine Dictatorship.” *Asian Studies Review*, vol. 29, no. 3, 2005, pp. 287–300.
- Thomas, Darrin, and Gabby Jed C. Galgao. “A Filipino Painter’s Perspective of Filipino Identity: What Makes Philippine Contemporary Paintings Truly Filipino.” *Printed in the Philippines*, ISSN 2599-5294, 2019, p. 60.
- van der Wall, Hidde. “Philippine Modernities and Their Contradictions: Cultural Responses, Contentions, Imaginaries.” *Perspectives in the Arts and Humanities Asia*, vol. 10, no. 2, 2020, p. 4.
- Veric, Charlie Samuya. “Fernando Zobel and the Making of the Ateneo Art Gallery: Modern Art, Postcolonial Statehood, and the Utopian Imagination in Twentieth-Century Philippines.” *Perspectives in the Arts and Humanities Asia*, vol. 7, no. 1, 2017, article 2.
- Wa-Mbaleka, Safary, and Arceli Rosario, editors. *The SAGE Handbook of Qualitative Research in the Asian Context*. Sage, 2022.
- White, Robert E., and Karyn Cooper. *Qualitative Research in the Post-Modern Era*. Springer, 2022.
- Zeta, Euodia B., et al. “Reflections of Social Issues in the Philippines Through Contemporary Painting.” *Printed in the Philippines*, ISSN 2599-5294, 2021, p. 133.
- Zóbel de Ayala, Fernando. “Lecture Outline for the Course Introduction to Contemporary Painting.” Ateneo de Manila University Graduate School, 1954–55. In Paras-Perez, *Fernando Zóbel*, Eugenio Lopez Foundation, Inc., 1990, p. 190.

- Zóbel, Fernando. *Carroza* (Processional Float). 1953. Polymer on wood, 119 × 59.5 cm. Ateneo Art Gallery Collection. “Carroza.” *Encyclopedia of Philippine Art Digital Edition*, Cultural Center of the Philippines, 18 Nov. 2020, epa.culturalcenter.gov.ph/3/82/2161/. Accessed 19 Sept. 2025.
- Zóbel, Fernando. *El Patio III (calle Vírgenes)*. 1980. Oil, pastel, and acrylic on canvas, 119.4 × 159.7 cm. Fundación Juan March Collection. “El Patio III (calle Vírgenes).” *Fundación Juan March*, www.fernandozobel.es/en/paintings.html. Accessed 19 Sept. 2025.
- Zóbel, Fernando. *Ícaro*. 1962. Oil on canvas, 137.5 × 200 cm. Ayala Museum. “Ícaro.” *Artsy*, www.artsy.net/artwork/fernando-zobel-icaro. Accessed 19 Sept. 2025.
- Zóbel, Fernando. *Ink Painting*. 1962. Ink on paper. The Metropolitan Museum of Art, New York. www.metmuseum.org/art/collection/search/53228. Accessed 19 Sept. 2025.
- Zóbel, Fernando. *La Vista X*. 1974. Oil on canvas, 40 × 40 cm. Private Collection. “La Vista X.” *Fernando Zóbel*, www.fernandozobel.es/en/paintings.html. Accessed 19 Sept. 2025.
- Zóbel, Fernando. *Saeta 22*. 1957. Oil on canvas, 61 × 91 cm. Jose Joya Collection. “Saeta 22.” *Encyclopedia of Philippine Art Digital Edition*, Cultural Center of the Philippines, 18 Nov. 2020, epa.culturalcenter.gov.ph/3/82/2287/. Accessed 19 Sept. 2025.
- Zóbel, Fernando. *Fernando Zóbel in the Museum of Spanish Abstract Art, Cuenca, 1966*. Fernando Zóbel Official Website, fernandozobel.es/en/museum.html. Accessed 19 Sept. 2025.
- Zóbel, Fernando. “Paintings.” Fernando Zóbel, <https://fernandozobel.es/en/paintings.html>. Accessed 23 Sept. 2025.
- “Fernando Zóbel in the Year of His Graduation from Harvard University, 1949.” *Fernando Zóbel: Chronology*, www.fernandozobel.es/en/chronology.html. Accessed 19 Sept. 2025.

BIASES IN MEDICAL DECISION MAKING

Ece Marangoz

Uskudar American Academy, Istanbul, Turkey

ecemarangoz2026@gmail.com

Edoardo Gallo: edoardo.gallo@gmail.com

Abstract

The healthcare sector presents high-pressure, time-sensitive decision-making environments, where clinicians are often required to make swift judgments. Among the most prevalent are confirmation bias, the tendency to seek or prioritize information that supports pre-existing beliefs, and anchoring bias, the overreliance on initial information when forming diagnoses. Both can significantly distort judgment and compromise patient care. This literature review explores how these biases contribute to distortions in clinical judgment. Drawing on behavioral research and case-based examples, the literature review argues that longstanding issues in medical error and misdiagnosis may be better addressed by incorporating bias-awareness into health policy and clinical practice. Emerging bias-aware technologies that account for human cognitive limitations offer promising avenues for improving diagnostic accuracy and reducing errors in clinical settings.

Key Words: Confirmation Bias, Anchoring Bias, Diagnosis, Emergency, Systematic.

1. Introduction and Background

Traditional economic theory assumes decision-makers act rationally and with complete information. Behavioral economics, however, challenges this by recognizing the systematic cognitive biases and irrational tendencies that often influence real-world choices. The health sector offers a rich area for behavioral economic analysis, considering the complex choices involved, the urgency of decisions, and the significant reliance on expert guidance. Healthcare decisions often take place under stress, uncertainty, and a lack of balanced information between patients and providers. Moreover, healthcare often involves 'credence goods'—services whose quality is difficult to assess even after they've been used. This makes patients particularly reliant on a physician's judgment. Behavioral economics helps us understand these dynamics by showing how heuristics, framing effects, default options, and biases like confirmation and anchoring can distort medical decision-making. The consequences of such distortions are far from theoretical. A 2023 study published in *BMJ Quality & Safety* estimates that approximately 371,000 people die and another 424,000 are permanently disabled each year in the United States due to diagnostic errors—totaling nearly 800,000 people experiencing serious harm annually (Merelli, 2023). As David Newman-Toker, the lead author and director of the Center for Diagnostic Excellence at Johns Hopkins, notes, misdiagnosis may be the most common cause of death or disability from medical malpractice, though many cases go undetected and the true number could be even higher (2023, Newman-Toker). As emphasized in *Nudge* by Thaler and Sunstein (2008), health has long been a central domain for applying behavioral interventions like default options and planning prompts to improve public health outcomes. For example, behavioral tools such as 'nudges' have successfully improved public health outcomes, from

increasing vaccination rates through default appointments to enhancing medication adherence with automated reminders. These interventions utilize insights from concepts like loss aversion, status quo bias, and time-inconsistent preferences to guide individuals toward healthier behaviors. Despite these successes, many aspects of clinical decision-making are still underexplored from a behavioral economics perspective. This literature review aims to investigate how specific cognitive biases—confirmation bias and anchoring bias—influence medical decision-making, particularly in high-stakes clinical environments. In doing so, it contributes to a growing body of work that challenges the assumption of rationality in professional judgment and highlights the need for bias-aware frameworks in medical practice. In the following sections, this article first examines confirmation bias in clinical contexts, outlining its psychological underpinnings, and illustrates its impact through research examples such as emergency medicine case studies and Alzheimer's biomarker studies. It then analyzes anchoring bias, detailing empirical evidence and real-world diagnostic delays, with an emphasis on high-risk settings such as emergency departments. For each bias, it examines proposed mitigation strategies at both the individual and system levels, including metacognitive training, diagnostic timeout, and bias-aware decision support tools. The discussion concludes by integrating these findings into a broader framework for designing healthcare environments that reduce diagnostic error while respecting the role of clinical intuition.

1.1 The Unique Environment in Healthcare

Healthcare is a unique intersection of economics, psychology, and high-stakes decision-making. While most people imagine hospitals, doctors, and patients when thinking of healthcare, the system extends far beyond its physical components. Becoming a physician is a long, demanding journey: students first take rigorous coursework and the MCAT, then enter four years of medical school, followed by 3 to 7 years of residency training under intense clinical supervision. Even after residency, physicians must continue lifelong education to stay updated in their fields. Despite this extensive preparation, physicians remain vulnerable to cognitive errors. Medical professionals operate under constant pressure, navigating life-or-death decisions often with incomplete information, time constraints, and emotional intensity. The intensive care unit presents a setting where clinicians must make rapid judgments under uncertainty, frequently without clear guidelines and with significant consequences (Evans, 2021). These conditions create an environment highly open to cognitive errors. Even before entering clinical practice, medical students begin developing decision-making habits rooted in intuitive (System 1) and analytical (System 2) thinking, yet they often receive little structured guidance in managing these processes (Sanders & McHugh, 2021). This complex environment, worsened by information asymmetry between patients and providers, renders healthcare particularly susceptible to biases in both clinical and policy decisions. Understanding how behavioral economics principles apply in this context is crucial to improving health outcomes.

1.2 The Role of Cognitive Biases in Clinical Judgment

Throughout the entire treatment process, practitioners continually gather information and make informed decisions. Every client-worker relationship involves a complex process that includes gathering personal information, having conversations, and storing all of it. This information is then used for making comparisons, identifying correlations, and forming predictions. The

process relies heavily on cognitive activities, which are highly open to potential biases. As a result, there is a significant risk of error in these cognitive tasks.

When examining cognitive biases in clinical judgment, it is important to distinguish between implicit and explicit biases, both of which contribute to health and healthcare disparities. Explicit biases are conscious attitudes and assumptions that individuals can recognize and directly report; they often underlie discriminatory acts such as racism, sexism, and homophobia. In contrast, implicit biases are unconscious attitudes and beliefs about characteristics such as race, ethnicity, age, ability, and gender. These implicit biases operate outside of conscious awareness and can only be measured indirectly, but they subtly influence judgment and behavior in clinical settings.

Diagnostic errors are mistakes that occur due to missed or delayed diagnoses. These errors have been increasing rapidly and have drawn significant attention in recent years. Studies estimate that diagnostic errors occur in up to 15% of medical cases. No physician is entirely immune to such errors, regardless of their experience or expertise. Approximately 7.4% of physicians in the United States are involved in medical malpractice claims annually, with diagnostic errors being one of the leading causes of litigation. These errors often result from system breakdowns, such as communication failures or workflow issues, as well as from faulty clinical reasoning caused by cognitive biases. In many cases, both factors are involved.

A study by Graber and colleagues, which analyzed 100 diagnostic error cases, revealed that most errors had multiple contributing causes. Both system-related issues and cognitive biases were commonly present. These findings highlight the critical need to examine the role of cognitive biases in clinical judgment, as they significantly contribute to diagnostic errors and compromise the quality of care.

2. Confirmation bias

Psychologist Raymond Nickerson defines confirmation bias as “seeking or interpreting evidence in a way that is biased toward existing beliefs, expectations, or a given hypothesis.” (Nickerson, 1998, pp. 175). More simply, it is our tendency to seek, interpret, and recall information in ways that support what we already believe or expect. As Hahn and Harris (2014) explain, this bias can manifest in a variety of ways: selectively gathering evidence, resisting contradictory data, failing to consider alternatives, and overestimating the validity of our existing views. Confirmation bias can be motivated, meaning people are consciously or unconsciously driven to confirm a preferred outcome, or unmotivated, occurring even when people reinforce beliefs they do not want to be true (Nickerson, 1998; Steel, 2018). Although often associated with motivated reasoning (Kunda, 1990), confirmation bias often operates as an automatic and unconscious cognitive shortcut. As Klayman and Myers & DeWall note, people naturally favor information that supports their prior beliefs while ignoring or dismissing contradictory evidence.

This process is closely tied to System 1 thinking, the fast, intuitive, and low-effort way of thinking identified by Kahneman. In contrast, System 2 thinking is more deliberate and analytical, capable of overriding initial impulses but requiring more time and mental resources.

In the fast-paced, high-pressure environment of clinical practice, physicians often rely on System 1 out of necessity, making them particularly susceptible to confirmation bias.

One of the most well-known demonstrations of confirmation bias comes from a classic lab experiment by Peter Wason, who studied how individuals test hypotheses. Participants are shown a sequence of three numbers—2, 4, 6—and are told that these numbers follow a rule. Their goal was to discover the actual rule by proposing additional sequences, after which they would be told whether their new sequences conformed to the rule. Most participants assumed the rule was “increasing by twos” and suggested sequences like “8, 10, 12” or “20, 22, 24” that were confirmed to be true. What they failed to do, however, was test disconfirming examples like “2, 3, 4” or “10, 11, 13” that could potentially refute their hypotheses. In reality, the original rule was simply “any sequence that increases.” Participants failed to discover the correct rule because they only sought evidence that confirmed their initial ideas and avoided generating sequences that could refute them. This experiment revealed a well-established cognitive bias: when forming beliefs or judgments, people are more likely to seek confirming evidence than to question their assumptions. Crucially, this process occurs even when individuals are explicitly told to scientifically test their hypotheses, highlighting that confirmation bias is not just a logical error but also an innate human flaw in information processing.

One area where the consequences of this bias become especially evident is in the diagnostic process. Diagnosis is typically made in two steps: first, doctors make a prediction based on the patient's initial symptoms; then they gather more information to confirm or refine that prediction. Ideally, this second step keeps doctors open to new information. However, confirmation bias often gets in the way. Instead of fairly considering all the evidence, doctors might unconsciously look for or put more weight on information that supports their first impression, while overlooking or downplaying anything that goes against it. This pattern, called premature closure, is a frequent result of confirmation bias. Once doctors settle on a diagnosis, they might stop exploring other possibilities too soon.

A particularly compelling example comes from Jesse Pines, who presents a case study of a 51-year-old patient, “Mr. W,” who suffered from severe back pain and was misdiagnosed due to a series of cognitive and systemic errors stemming from confirmation bias. In scenario 1, the emergency physician (EP) was influenced by a colleague's prior diagnosis and a nurse's framing of the patient as someone seeking medication. Under pressure and cognitive overload, the EP reconfirmed the initial impression of musculoskeletal pain without performing a full examination or laboratory work and discharged the patient based on selective interpretation of the data.

Critically, this decision overlooked clinical red flags such as fever (100.5°F) and tachycardia (HR: 105), which were early signs of a serious underlying infection. This scenario reflects broader trends: diagnostic errors are the leading cause of malpractice claims in emergency departments, and one-third of malpractice cases in emergency departments are attributed to missed or delayed diagnoses (Pines, 2006). Furthermore, a 1993 multicenter study found that approximately 2% of patients with acute myocardial infarction were incorrectly discharged from the emergency department, demonstrating that initial diagnostic impressions—if left unchecked—can have life-threatening consequences.

The importance of slowing down cognitive shortcuts becomes even clearer in Scenario 2, where the same patient is thoroughly evaluated again and diagnosed with a spinal epidural abscess, a rare but potentially fatal condition. When properly examined, Mr. W had a higher fever (102.2°F), an elevated ESR (47 mm/hr), a WBC count of $11.8 \times 10^3/\text{mm}^3$, and a recent history of intravenous drug use—all diagnostic clues that had been missed in the earlier encounter due to cognitive fixation and confirmatory thinking. The risk of missing such a diagnosis is not insignificant: spinal epidural abscesses have a mortality rate of 5–15%, and up to 45% of patients experience permanent neurological deficits if treatment is delayed. While this clinical report is not a randomized trial, it reflects the real-world consequences of cognitive bias under common emergency room conditions: fatigue, high patient volume, and fragmented communication.

Pines also cites a study of trauma patients in which judgment errors were observed in 100% of resuscitations, highlighting the extent of cognitive pitfalls when clinicians are forced to make rapid decisions. These data generally emphasize that confirmation bias is not a subtle or occasional problem but a common and important feature of diagnostic reasoning in emergency medicine. To mitigate these risks, Pines advocates for explicit training in metacognition and Bayesian reasoning, as well as structural reforms such as cognitive challenge strategies and protocol-based decision support tools that can help healthcare providers pause, reassess, and consider alternative diagnoses under pressure.

Confirmation bias doesn't just affect doctors during treatment—it also shows up in how scientific research is done, especially in the study of Alzheimer's disease (AD). For many years, most research has focused on what's called the "amyloid cascade hypothesis," which suggests that a protein called amyloid-beta ($A\beta$) causes brain damage that leads to Alzheimer's. Because this idea became so dominant, scientists have tended to focus on evidence that supports it and ignore studies that suggest other causes—a clear example of confirmation bias. As new technologies like brain scans and spinal fluid tests became available, researchers began diagnosing Alzheimer's based on these protein markers (amyloid and tau) even when patients didn't show memory loss or other symptoms. This shift has increased the risk of overdiagnosing people who have these biological signs but may never develop the disease. In this case, confirmation bias may have slowed progress by keeping science narrowly focused on one theory for too long.

A review by Souchet et al. (2023) highlights that amyloid-related tests exhibit variable sensitivity (64–100%) but generally low specificity (around 66.5%), meaning that approximately one-third of individuals without AD test positive and nearly 20% of those who develop AD test negative, complicating diagnosis and treatment. Autopsy studies reveal that many cognitively healthy older individuals harbor significant amyloid and tau pathology, calling into question their role as definitive disease indicators. Such evidence challenges the view that these biomarkers definitively indicate Alzheimer's. Longitudinal studies, including the A4 Study, show that many amyloid-positive but cognitively normal individuals do not develop dementia, suggesting these markers signal risk rather than certainty. Despite this, the prevailing focus on amyloid has created a self-reinforcing cycle, where positive test results are interpreted as proof of disease and contrary evidence is rationalized away or overlooked. As Souchet notes, this persistence "It is

hypothesized that such a persistent focus [on amyloid biomarkers] might be influenced by confirmation bias in the field.” (Souchet, 2023, p.9).

Longitudinal studies, such as the A4 Study, have found that only a minority of amyloid-positive but cognitively normal participants show cognitive decline over the years, suggesting that these markers signal risk but are not definitive of progression. This ingrained belief in the centrality of amyloid creates a self-reinforcing cycle in which positive tests are viewed as evidence of AD and opposing evidence is rationalized, exemplifying confirmation bias.

This has serious clinical implications: expensive anti-amyloid drugs like lecanemab, which can cause harmful side effects, may be overprescribed to patients who do not actually have Alzheimer's disease, leading to unnecessary risks and increased healthcare costs. Recognizing and addressing this bias is crucial to improving the accuracy and ethics of Alzheimer's diagnosis and treatment.

The consequences of unchecked confirmation bias are very extensive. Because confirmation bias continues to subtly influence clinical thinking, it leads to both under- and overdiagnosis, delays in care, and costly medical errors. Understanding how this bias manifests in real-world healthcare is an important first step toward creating systems that minimize its effects.

To effectively reduce confirmation bias in medical decision-making, a multifaceted and system-wide approach is essential. Because confirmation bias influences how clinicians seek, interpret, and recall information, solutions must target both individual cognition and the broader structures that shape clinical and scientific practice. Rather than relying solely on intuition or experience, clinicians can benefit from tools and habits that prompt reflective, evidence-based reasoning.

One proven strategy involves implementing structured pauses in the diagnostic process. These deliberate moments of reflection, known as diagnostic “timeouts,” encourage clinicians to reassess initial impressions and actively seek disconfirming evidence. Graber et al. (2014) found that such cognitive challenge strategies increased diagnostic accuracy by 17–20% in emergency simulations.

Differential diagnosis checklists serve a similar function by expanding the diagnostic framework and preventing premature closure. Their use has been shown to reduce errors by 18% in complex cases (Sibbald et al., 2013), while electronic decision support tools integrated into health records have reduced diagnostic delays by 23% in high-risk scenarios (Schiff et al., 2015). These interventions create a cognitive buffer against bias by slowing automatic reasoning and injecting deliberate scrutiny into the decision-making process.

Equally important is the development of metacognitive awareness, the ability to monitor and review one's own thought processes. Rollwage and Fleming (2021) found in a large-scale decision simulation that individuals with high metacognitive efficiency were able to adaptively use confirmation bias, achieving higher accuracy when new evidence emerged after the initial

judgment. This finding suggests that the bias itself is not always harmful, but rather becomes problematic when not supported by reflection.

Training clinicians to adjust their confidence, recognize when they might be wrong, and remain open to corrective information transforms confirmation bias from a burden into a tool that can be managed and, in some cases, evaluated.

Beyond individual cognition, team-based practices offer powerful safeguards. Collaborative case reviews, structured handoffs, and interdisciplinary rounds can disrupt biased diagnostic momentum. O'Hare et al. (2018) reported a 36% reduction in significant diagnostic discrepancies in critical care settings when such practices were implemented.

Feedback mechanisms play a similar role: regular audits and diagnostic reviews help identify recurring error patterns; studies such as Haskel (2007) show a 25% reduction in recurring diagnostic errors following structured feedback. These collaborative and iterative processes broaden the perspective of individual clinicians and create a culture that values uncertainty and second opinions, an important antidote to cognitive fixation.

Confirmation bias also operates at the research and policy levels, particularly in how diseases are defined and studied. For example, in Alzheimer's research, the long-standing dominance of the amyloid cascade hypothesis has shaped both diagnostic criteria and drug development, despite growing evidence that amyloid positivity does not reliably predict cognitive decline.

This reflects a deeper pattern: as a theoretical model gains momentum, supporting evidence is emphasized, while conflicting data are minimized or rationalized. To address this, researchers should adopt practices that reduce circular reasoning and selective interpretation. Longitudinal cohort studies can help confirm whether biomarkers truly predict meaningful outcomes over time, rather than assuming their presence equates to disease.

Souchet et al. (2023) advocate for redefining Alzheimer's disease using outcome-predictive biomarkers instead of pathology-based ones, aiming to reduce the risk of overdiagnosis and inappropriate treatment. Pre-registering hypotheses and prioritizing independent replication trials reduces the risk of confirmation bias in scientific reporting. Preregistration involves publicly documenting a study's research questions, hypotheses, methods, and planned analyses before data collection begins. This process prevents researchers from retroactively adjusting their hypotheses to fit the results (a practice known as HARKing), which can distort scientific conclusions and falsely inflate the impression of support for a theory. By committing to a specific research area in advance, researchers are held accountable for objectively testing their original ideas, rather than interpreting uncertain results to confirm their expectations. Similarly, independent replication experiments serve as a safeguard against selective reporting or unintentional biases that might arise in original studies. When other research teams (ideally with no vested interest in the outcome) replicate the study using the same methods, they test whether the original findings are robust or simply the result of chance, methodological flaws, or confirmation bias. If a result can be consistently replicated by different groups, it becomes more reliable and less likely to be influenced by the original researchers' assumptions. Preregistration and replication together create a more transparent and self-correcting scientific process, helping

to distinguish truly valid findings from those influenced by cognitive biases or selective interpretation. Additionally cost-effectiveness analyses ensure that treatments, such as anti-amyloid drugs, are evaluated not only based on their biological targets but also on their actual patient benefits.

Together, these interventions represent a comprehensive strategy for managing confirmation bias in medicine. They do not, and should not be the goal, to eliminate bias entirely. Instead, they recognize that cognitive shortcuts are part of human reasoning and that their risks can be mitigated through reflection, transparency, and carefully designed systems.

When supported by metacognitive skills and institutional mechanisms, even a deep-seated bias like confirmation bias can be transformed from a source of error into an opportunity for improved accuracy, better outcomes, and more ethical care.

3 Anchoring Bias

Anchoring bias is a cognitive heuristic in which individuals disproportionately rely on initial information, the “anchor,” when making judgments, even when subsequent evidence suggests they should have adjusted their judgments (Tversky & Kahneman, 1974). In one of their classic experiments, Tversky and Kahneman asked participants to spin a wheel of fortune set to stop at either 10 or 65. Participants were then asked whether the percentage of African countries in the United Nations was higher or lower than the number on the wheel and then asked to provide their own estimates. Strikingly, those who saw the wheel stop at 10 gave an average 25% estimate, while those who saw it stop at 65 gave an average 45% estimate. Despite knowing the number was random and irrelevant, participants' judgments were biased toward it. This simple but powerful experiment demonstrates how even arbitrary anchors can unconsciously shape decision-making.

This bias takes on even greater significance in medicine. Clinicians often form premature diagnostic impressions based on limited information (such as triage notes or initial symptoms), which can disproportionately influence subsequent testing and treatment decisions. Emotional states can exacerbate this effect; Bodenhausen et al. (2000) found that sadness reduces cognitive flexibility and increases reliance on anchors. These pressures are particularly important in high-risk, fast-paced environments such as emergency departments, where time constraints and stress can narrow the diagnostic focus and delay recognition of alternative conditions.

Ly et al. (2023) provide clear evidence of anchoring bias affecting clinical decision-making in emergency medicine through a large-scale cross-sectional analysis of 108,019 Veterans Affairs emergency department visits. The study focused on patients with congestive heart failure (CHF) presenting with shortness of breath (SOB), a common symptom in both CHF exacerbation and pulmonary embolism (PE). A key consideration was the “reason for visit” section documented by triage nurses prior to physician assessment. When CHF was explicitly mentioned in this initial documentation, it served as an anchor for subsequent clinical decisions. Anchoring bias occurs when decision-makers overrely on initial information and fail to adequately adjust their judgments with new data. Here, physicians who received triage notes emphasizing CHF tended to narrowly focus on CHF as the cause of symptoms and frequently neglected alternative

diagnoses such as PE. Consequently, when CHF was mentioned, physicians ordered significantly fewer PE diagnostic tests (8.8% vs. 13.4%; difference, -4.6 percentage points; 95% confidence interval [CI], -5.7 to -3.5) and delayed tests by an average of 15.5 minutes (90.4% vs. 74.9 minutes; 95% CI, 5.7 to 25.3). At the same time, testing for CHF exacerbation using B-type natriuretic peptide (BNP) increased by 6.9 percentage points (78.0% vs. 71.1%; 95% CI, 4.3 to 9.4). The mechanism is clear: the triage note served as an anchor that shaped physicians' initial expectations and led them to cognitively focus on CHF. This finding led to disproportionate testing for CHF, even when clinical symptoms warranted, and underassessment of PE—a hallmark of anchoring bias, which is typical of underadjustment from the initial anchor.

Although PE diagnoses were lower when CHF was noted during the emergency department visit (0.08% vs. 0.23%; difference, -0.15 percentage points; 95% CI, -0.23 to -0.08), 30-day PE diagnosis rates did not differ significantly (1.2% vs. 1.1%; difference, 0.06 percentage points; 95% CI, -0.23 to 0.36). This suggests that anchoring bias leads to delayed rather than missed PE diagnoses, potentially impacting timely patient care.

Delays in the diagnosis of pulmonary embolism (PE) due to anchoring bias are clinically significant because PE is a potentially life-threatening condition that requires prompt diagnosis and treatment. Studies show that early diagnosis and anticoagulant therapy can significantly reduce mortality rates. According to the American Heart Association, the estimated mortality rate for untreated PE is up to 30%, but with timely diagnosis and intervention, this rate decreases significantly, often to less than 10%. Delays in diagnosis increase the risk of complications such as right ventricular failure, recurrent embolism, and chronic thromboembolic pulmonary hypertension, all of which contribute to higher morbidity and healthcare costs.

A similar clinical scenario illustrating the detrimental effects of anchoring bias involves a 29-year-old man initially suspected of having a polysubstance overdose. The clinical team focused on this diagnosis due to the patient's presentation and positive drug screens, which delayed further investigations. After the patient's condition worsened, imaging revealed a large brain tumor that caused life-threatening complications. This case highlights how focusing on the initial diagnosis can overshadow potentially more serious alternative conditions, leading to delayed diagnosis and adverse outcomes. Such examples highlight the critical importance of clinicians remaining vigilant against cognitive biases to ensure timely and accurate diagnosis in high-risk medical conditions such as pulmonary embolism.

The case involves a 29-year-old man known for chronic headaches. He was brought to the emergency department (ED) under a police escort for suspected multiple substance overdose. He reported experiencing a suspected seizure and ingesting an unknown quantity of medications, including clonazepam, sumatriptan, and ibuprofen. However, he could not provide specific information about when or in what quantity the medication was ingested. During his initial examination in the ED, he experienced confusion, bradycardia, and hypertension. A urine drug screen was positive for amphetamines, benzodiazepines, and cannabinoids. Based on these findings and the context, the medical team focused on a diagnosis of drug overdose as the primary explanation for the patient's altered mental state.

Over the next several hours, the patient's condition worsened; he became increasingly drowsy and intermittently agitated, requiring soft restraints for safety. On his first day in the hospital, he was lethargic, unresponsive, and hypoxic on room air. A code blue was called, and the patient was intubated and transferred to the Intensive Care Unit (ICU). A neurological reexamination revealed fixed and dilated pupils, and an urgent CT scan of the head was performed. The imaging revealed a large, 10-cm hyperdense mass in the right frontal lobe, accompanied by severe swelling (vasogenic edema), uncal herniation, and hydrocephalus. These findings were highly suspicious for a meningioma or brain tumor.

A detailed history taken from the patient's mother revealed a distinct pattern of personality changes, bizarre behavior, memory loss, worsening headaches, and gait disturbances over the years. The mother initially assumed these symptoms were related to drug use, contributing to her diagnosis of overdose. She also confirmed that the number of pills remaining in the prescription bottles was consistent with the patient's statement and did not indicate an overdose. Consequently, the patient was referred to a tertiary hospital for neurosurgical intervention, but unfortunately, he died from complications related to the brain tumor and its associated herniation.

This tragic outcome highlights how fixating on an initial diagnosis of drug overdose can lead to a critical delay in recognizing the true underlying condition. By overlooking alternative explanations early on, the clinical team missed the opportunity for timely diagnosis and intervention, potentially altering the patient's prognosis. Thus, anchoring bias not only compromised the quality of care but also directly impacted patient survival, demonstrating the profound implications of cognitive biases in medical decision-making.

A similarly instructive scenario is described in Case 6 by Waldrop (2017), which exemplifies anchoring bias in pediatric emergency medicine. The case involved a 15-year-old female with known sickle cell disease (SCD) who presented with abdominal pain described as distinct from her typical vaso-occlusive episodes. Despite this clinically significant clue, the emergency department (ED) team made an early diagnosis of a routine pain crisis based on the patient's history of frequent ED visits and perceived drug-seeking behavior. Anchoring bias, reinforced by confirmation bias, led the team to discharge the patient after administering opioid analgesia without performing imaging or laboratory tests beyond the initial workup.

Within 24 hours, her condition worsened, and further evaluation revealed portal vein thrombosis, a life-threatening vascular complication. While Waldrop's report did not provide patient-specific mortality data, portal vein thrombosis has a reported mortality rate of 10–20% in untreated acute cases, and delayed diagnosis significantly increases the risk of bowel ischemia, liver failure, and long-term morbidity. This case quantifies the risk of anchoring bias: a 24-hour delay in diagnosis in a time-sensitive vascular emergency directly jeopardized the patient's survival. Clinically, this vignette illustrates how attachment to the past and reputation can override critical new information, narrow the diagnostic framework, and delay the recognition of emergencies. In high-pressure emergency situations where time constraints, cognitive load, and negative emotional bias combine, such attachment can have disastrous consequences. Waldrop (2017) emphasizes that mindfulness and diagnostic thinking, including explicit recognition of cognitive

dissonance and deliberate diagnostic pauses, are key strategies for neutralizing attachment, maintaining broad discrepancies, and reducing the risk of life-threatening delays.

A promising solution to address bias in medical decision-making involves the integration of bias-aware algorithmic support systems, as proposed by Ahsen et al. (2019). In their study of mammography decision-making processes, they showed that radiologists' interpretations were systematically influenced by prior clinical risk information, a clear indicator of bias-based assessment. To mitigate this, they developed an algorithmic prediction framework that explicitly accounts for human bias by modeling both the systematic variation caused by bias and the associated variability in decision-making processes.

By refactoring radiologists' assessments and incorporating unbiased clinical and imaging data, the algorithm produced more accurate cancer risk estimates and improved expected patient outcomes measured in life years. This approach offers a broader solution to anchoring bias: combining human expertise with algorithmic calibration to ensure that initial impressions do not disproportionately determine final diagnoses. In high-risk settings like emergency medicine, similar bias-sensitive decision-support tools can encourage clinicians to reassess early anchors, expand differential diagnoses, and reduce the risk of delayed or missed diagnoses.

Anchoring bias will always be a part of human cognition, but its consequences in clinical decision-making are not inevitable. Through conscious deliberation, team-based checks, and algorithmic calibration, clinicians can prevent early anchors from becoming fatal extremes. Combating anchoring bias is not about eliminating intuition; it's about ensuring that intuition is held accountable to the evidence.

4 Conclusion

This literature review examined how two specific cognitive biases—confirmation bias and anchoring bias—impact medical decision-making in both clinical and research contexts. By analyzing emergency medicine cases, Alzheimer's research, and real-world diagnostic failures, the literature review showed how these biases shape physician judgment and contribute to missed or delayed diagnoses. It also evaluated concrete solutions, including decision support tools, diagnostic timeouts, and metacognitive training. Ultimately, the findings suggest that improving clinical outcomes depends not on eliminating intuitive thinking, but on designing systems that support reflective, evidence-based reasoning without ignoring human cognitive tendencies. A balanced approach that respects physician expertise while reducing cognitive error holds the greatest promise for safer, more accurate healthcare.

Many existing debiasing methods fail because they rely on assumptions that are incompatible with physicians' natural ways of thinking and making decisions. As Norman and Eva (2020) emphasize, physicians are often most vulnerable to diagnostic errors when they attempt to override intuitive System 1 thinking by overriding analytical System 2 processes. Successful diagnoses often rely on intuitive judgment rather than formal reasoning, making it difficult to challenge these ingrained cognitive habits. Therefore, effective debiasing approaches must adopt a broader perspective that integrates physicians' expertise and intuition rather than attempting to replace or override them. This requires developing conceptual models and technological tools

that are compatible with both the cognitive structures of the human mind and the practical demands of clinical work.

Future research should focus on creating healthcare technologies that facilitate productive interactions between clinicians and artificial expert systems, providing support at every stage of the medical decision-making process. Such tools should support the development of implicit knowledge and robust intuition, as well as analytical reasoning, and encourage the balanced use of System 1 and System 2 thinking. One promising area is the use of hybrid models, such as fuzzy cognitive maps, that combine human expertise with analytical algorithms. These techniques can increase physicians' awareness of diagnostic cognitive processes and encourage active participation and motivation in the decision-making process. Unlike current debiasing or fully automated data mining approaches, such balanced systems aim to reduce common errors such as premature closure and overconfidence by integrating cognitive knowledge with technological support.

Consequently, debiasing strategies and decision support systems must demonstrate scientific validity and personal relevance to be adopted in daily practice. Raising awareness of cognitive biases should be supported by training and tools that promote a cognitively focused diagnostic process. Clinician collaboration can enhance the effectiveness of decision support tools and foster intuitive diagnostic skills within evidence-based medicine frameworks. This balanced approach offers a path to reducing diagnostic errors and improving patient outcomes without undermining the valuable role of physician intuition.

References

Ahsen, Mehmet Eren, et al. "When Algorithmic Predictions Use Human-Generated Data: A Bias-Aware Classification Algorithm for Breast Cancer Diagnosis." *Information Systems Research*, vol. 30, no. 1, 2019, pp. 97–116. JSTOR, <https://www.jstor.org/stable/48758523>.

Arkes, Hal R. "The Consequences of the Hindsight Bias in Medical Decision Making." *Current Directions in Psychological Science*, vol. 22, no. 5, 2013, pp. 356–360. <https://www.jstor.org/stable/41333450>.

Bodenhausen, Galen V., et al. "Sadness and Susceptibility to Judgmental Bias: The Case of Anchoring." *Psychological Science*, vol. 11, no. 4, 2000, pp. 320–23. JSTOR, <http://www.jstor.org/stable/40063840>.

Croskerry, Pat. "A Universal Model of Diagnostic Reasoning." *Academic Medicine*, vol. __, no. __, pp. __. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2864081/>.

---. "From Mindless to Mindful Practice—Cognitive Bias and Clinical Decision Making." *New England Journal of Medicine*, vol. __, no. __, 2022, pp. __. <https://www.nejm.org/doi/pdf/10.1056/NEJMp2201180>.

---. "The Importance of Cognitive Errors in Diagnosis and Strategies to Minimize Them." *Academic Medicine*, vol. __, no. __, __, pp. __. <https://onlinelibrary.wiley.com/doi/epdf/10.1197/j.aem.2005.07.028>.

Croskerry, Pat, et al. "Cognitive Debiasing 2: Impediments to and Strategies for Change." *BMJ Quality & Safety*, vol. __, no. __, __, pp. __. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6110024/pdf/10.1177_1751143717746566.pdf.

FitzGerald, Chloë, and Samia Hurst. "Implicit Bias in Healthcare Professionals: A Systematic Review." *BMC Medical Ethics*, vol. 18, 2017, p. 19. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5304800/>.

Gonzalez, Chad M., et al. "Reducing Implicit Bias: Association of a Longitudinal Faculty Development Program with Perceptions of Bias." *Journal of General Internal Medicine*, vol. __, no. __, __, pp. __. <https://www.jstor.org/stable/48635302>.

Graber, Mark L. "The Need for Cognitive Science in Diagnosis and Diagnostic Error Research." *Academic Medicine*, vol. __, no. __, __, pp. __. <https://www.jstor.org/stable/23483849>.

Hall, William J., et al. "Implicit Racial/Ethnic Bias among Health Care Professionals and Its Influence on Health Care Outcomes: A Systematic Review." *American Journal of Public Health*, vol. 105, no. 12, 2015, pp. e60–e76. [https://www.ajpmonline.org/article/S0749-3797\(16\)00063-5/fulltext](https://www.ajpmonline.org/article/S0749-3797(16)00063-5/fulltext).

LeBlanc, Vicki R., et al. "The Impact of Emotional Stress on Clinical Reasoning Performance." *Medical Education*, vol. __, no. __, __, pp. __. <https://www.jstor.org/stable/26523588>.

Ly, David P., Peter G. Shekelle, and Ziad Obermeyer. "Evidence for Anchoring Bias During Physician Decision-Making." *JAMA Internal Medicine*, vol. 183, no. 8, 2023, pp. 818–823. <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2806464>.

Ly, David P., Peter G. Shekelle, and Zirui Song. "Evidence for Anchoring Bias During Physician Decision-Making." *JAMA Internal Medicine*, vol. 183, no. 8, 2023, pp. 818–823, doi:10.1001/jamainternmed.2023.2366.

Meyer, Andria N. D., et al. "Frequency of Diagnostic Errors in Outpatient Care: A Systematic Review." *BMJ Quality & Safety*, vol. __, no. __, __, pp. __. <https://www.jstor.org/stable/44318688>.

Montgomery, Kathryn. "How Doctors Think: Clinical Judgment and the Practice of Medicine." *The Journal of Medicine and Philosophy*, vol. __, no. __, __, pp. __. <https://www.jstor.org/stable/3464683>.

Norman, Geoff. "Dual Processing and Diagnostic Errors." *Advances in Health Sciences Education*, vol. __, no. __, __, pp. __. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6110024/pdf/10.1177_1751143717746566.pdf.

Redelmeier, Donald A., and Amos Tversky. "Discrepancy between Medical Decisions for Individual Patients and for Groups." *New England Journal of Medicine*, vol. __, no. __, __, pp. __. <https://www.jstor.org/stable/27146390>.

Rehana, Rita W., and Najia Huda. "A Common Heuristic in Medicine: Anchoring." *Annals of Medical and Health Sciences Research*, vol. 11, no. 5, 2021, pp. 1461–1463. <https://www.amhsr.org/articles/a-common-heuristic-in-medicine-anchoring.pdf>.

Saposnik, Gustavo, et al. "Cognitive Biases Associated with Medical Decisions: A Systematic Review." *BMC Medical Informatics and Decision Making*, vol. 16, 2016, p. 138. <https://www.mdpi.com/2624-8611/5/4/71>.

Shirley, Katherine, and Jonathan D. Derman. "Cognitive Bias in Dermatology: A Review." *Journal of the American Academy of Dermatology*, vol. __, no. __, __, pp. __. [https://www.jaad.org/article/S0190-9622\(19\)32285-6/fulltext](https://www.jaad.org/article/S0190-9622(19)32285-6/fulltext).

Spencer, Steven J., et al. "The Role of Stereotyping in Medical Decision Making." *Journal of Applied Social Psychology*, vol. __, no. __, __, pp. __. <https://www.jstor.org/stable/25763860>.

Stat News. "Misdiagnoses Cost the U.S. 800,000 Deaths and Serious Disabilities Every Year, Study Finds." *Stat News*, 21 July 2023, <https://www.statnews.com/2023/07/21/misdiagnoses-cost-the-u-s-800000-deaths-and-serious-disabilities-annually-study/>.

Waldrop, Ron D. "Medical Decision-Making Errors Due to Faulty Heuristics in the Pediatric Emergency Department and the Use of Mindfulness." *Journal of Pediatrics & Neonatal Care*, vol. 7, no. 4, 2017, pp. 299. <https://doi.org/10.15406/jpnc.2017.07.00299>.

Wegwarth, Odette, et al. "Hindsight Bias in Medical Decision Making." *Medical Decision Making*, vol. __, no. __, __, pp. __. <https://www.jstor.org/stable/25763860>.

Yap, Katie, et al. "The Role of Cognitive Biases in Clinical Judgment and Decision Making." *Journal of Evaluation in Clinical Practice*, vol. __, no. __, __, pp. __. <https://link.springer.com/article/10.1007/s10670-020-00252-1>.

Zhang, Qian, et al. "Cognitive Biases in Clinical Diagnosis: A Review." *International Journal of Molecular Sciences*, vol. 24, no. 24, 2023, p. 17544. <https://www.mdpi.com/1422-0067/24/24/17544>.

A Tale of Ghosts, Vengeance, and Greed (Except For When It Is Not): The History of *Yotsuya Kaidan* and its Adaptations By Liv Adao

Abstract

This paper discusses the evolution of the traditional Japanese *Yotsuya Kaidan* ghost story by analyzing its two main characters within Japanese cinematic adaptations in the U.S. occupied period of 1949 and culturally confused period of 1959. This analysis is then compared against the original kabuki play written in 1825, in order to understand why the adaptations made certain changes, and to what effect. This analysis intends to show the way a story's message is a reflection of the beliefs and values of the time in which it was produced, and how contemporary history and events—like occupation, censorship, cultural confusion—will inevitably bleed into the media that is created during them, and thus are important context to recognize when analyzing film. Through thorough analysis of both film and contemporary history, this paper finds that there is always more nuance beneath the surface of what a film is trying to say, and how it chooses to say it, and the best way to uncover this nuance is through deeper understanding of historical and cultural context.

I. Introduction

The tale of *Yotsuya kaidan*, or the ghost of Yotsuya, is often lovingly titled one of the most well-known ghost stories in Japan. It is a tale of a dishonourable samurai and his scorned wife bent on revenge, and has captivated audiences for centuries. *Yotsuya Kaidan* was originally a play written in 1825 by Tsuruya Nanboku IV, and has been adapted over 30 times since it first entered Japanese culture.

Of those 30, there are two of particular interest due to the time period they were produced in. *Yotsuya Kaidan* (1949), directed by Keisuke Kinoshita, was produced in the time after World War II when Japan was under occupation by the United States and facing strict media censorship in order to “modernize” and “westernize” the perceived backward and pre-modern country. *Yotsuya Kaidan* (1959), directed by Nobuo Nakagawa, was made seven years after occupation had ended, when Japan was at a crossroads within its own national identity; the years of forced occupation had left them with a modern and prosperous economy, but to the detriment of their own culture and traditions. Consequently, these adaptations are more than just the original story retold—and in many cases even contain drastic changes to characters or plot.

Leaning heavily on historical context as an explanation, this paper seeks to answer the question of why these changes were made and what effect they served on the greater themes of each respective iteration of the story. By analyzing both the 1949 and 1959 film in comparison to the original 1825 play, this paper will offer understandings of what each respective story is trying to say, and why that message is relevant and indicative of the time period it was produced in.

II. Literature Review and Methodology

This paper adopts a historical approach to film, building on the work of key scholars, including LeGacy, Brothers, and Donovan, in order to investigate why the Yotsuya Kaidan adaptations make certain narrative changes, and assert that the answer lies within the time period in which they were created.

LeGacy uses reception theory—which states the importance of an audience in ascribing meaning to a text—to argue that “Invasion of the Body Snatchers” is a reflection of Cold War anxieties in the U.S, and that is why it was so popular upon release. He highlights the role of the U.S. audience in ascribing meaning to the film through their own lived experience at the time, regardless of the creators’ intentions. Alternatively, Brothers uses a social and political institutional approach when discussing the 1954 movie “Gojira.” He describes the public sentiment of the United States in Japan at the time and the political climate of the country after World War II and the U.S.’s occupation of Japan. He asserts that these are extremely relevant in the creation of the film, even directly quoting the creator of the film describing his desire for the film to be a strong allegory for the bombing of Japan and a way for the public of Japan to feel represented in their trauma. Though the two approaches differ, both writers describe the historical context of the film, either using it to explain the mindset of the creator or of the audience to support their respective points about the allegorical nature of the two films. Similar to both Brothers and LeGacy, Donovan employs the historical context of each time period discussed to explain why and how the yōkai (traditional Japanese demon) trope evolved the way it did in Japanese cinema. Donovan ultimately argues that the evolution of yōkai in Japanese fiction can be seen as a direct reflection of the historical evolution of Japanese values and identity, and specifically touches on how J-horror films post-U.S. occupation, commonly featuring faithful yōkai interpretations, can be seen as a return to traditional Japanese culture that was not encouraged or even allowed during the censorship of the U.S. occupation. These are the main film theories that are utilized throughout this paper.

The Yotsuya kaidan myth is the focus of this paper because of its significant presence in Japan as a quintessential ghost story. Thus, it is a good reflection of Japanese culture and values through the years as they change and evolve. The two adaptations in 1949 and 1959 respectively were chosen because these time periods feature important cultural shifts and chaos within history. This heightened historical relevance further enhances the ability to assume changes within the respective plots are influenced by these significant eras.

III. Iemon’s Timeline

This section of the paper will focus on the main character of Iemon and his transformation and changes in the adaptations discussed. His personality and narrative treatment change and evolve within these adaptations, respective to their eras of creation.

1825: The Original Iemon

Yotsuya Kaidan was originally written by Tsuruya Nanboku IV in 1825 and performed as *kabuki*, a traditional form of Japanese theater. Iemon, our *rōnin*, or masterless samurai, is set to

be divorced from his wife, Oiwa, because Oiwa's father Samon has discovered that Iemon stole from Samon in order to marry Oiwa in the first place. Iemon cannot stand this injustice, and thus murders Samon. Iemon claims innocence to his wife, and promises he will enact vengeance on the killer. Instead of pretending to keep his promise, Iemon is occupied by his rich neighbor Kihee, whose granddaughter is deeply in love with Iemon and desperate to have him. Kihee schemes how to get Oiwa out of the way, and sends her an ointment that horribly disfigures her. After Oiwa uses the ointment, Iemon then threatens his servant and tells him to go and force himself upon Oiwa in order to give Iemon a valid reason to divorce Oiwa on the grounds of cheating. Iemon instead is left with Oiwa's corpse, as she discovered Iemon's plot and accidentally killed herself while in a rage. He thinks little of it and simply hides her body, claiming she ran off to have an affair. Iemon then goes to his wedding and remarries, but the next day he sees Oiwa's ghost next to him, and he stabs her, only to realize it was actually his new wife. Oiwa's angry spirit has returned to haunt Iemon for his wrongdoings, and Iemon flees in terror to the mountains trying in vain to escape Oiwa. In the end, Iemon's brother-in-law, Yomoshichi, after receiving visions and pleas from Oiwa's ghost, finds him in the mountains and kills him.

In Tsuruya Nanboku IV's play, Iemon is the model of sinful and dishonourable behaviors that are to be punished. He is a samurai, sworn to bushidō, a specific set of codes that align with traditional Japanese values based on Confucian principles like loyalty, altruism, and trustworthiness. However, he blatantly disregards these codes within the story. His loyalty to his wife and her family is quickly pushed aside when he realizes he has a better opportunity with his rich neighbor's granddaughter, and he goes to cruel lengths to achieve his own personal goals. As Balmain put it, Iemon unflinchingly "places his self-interest before the needs of the community" (54).

This is uniquely problematic under the context of Japan's *ie* system, which is the traditional Japanese social structure that denotes the flow of responsibility and duty (Balmain 36). For example, familial responsibility fell to the head of household (typically eldest son), who then was held responsible to their large community, and then to the emperor (Balmain 36). The *ie* system is based upon a strong sense of obligation to your community, but also a generosity and sympathy towards each other that discourages conflict and takes precedence over any obligation you might have (Balmain 37).

Iemon acts in direct opposition to this system by weighing his own personal goals as more important than the harmony of his family and community. His actions and hubris are "threatening to the very structures of Japanese society according to which the individual should put duty and obedience before personal desire" (Balmain 57). Consequently, Iemon's immoral actions must be punished. Donovan describes the way that in traditional Japanese storytelling, people who transgressed moral obligations were punished by *yōkai* (loosely translated to monsters), who would uphold justice and order (13). Thus, Oiwa returns as a ghost to enact her vengeance on her cruel husband Iemon. This narratively enforces the idea that violating "the moral and ethical laws of the community" (Balmain 56) will not go unpunished, and Iemon

serves as a warning created to scare people about the idea going against cultural codes and beliefs.

1949: Iemon as Japan

Keisuke Kinoshita's *Yotsuya Kaidan* (1949) sees Iemon's (Ken Uehara) immorality and responsibility displaced onto other characters, most notably well-known criminal gangster Naosuke (Osamu Takizawa), who is on the lam after escaping prison and narratively described as the "literal incarnation of evil" (1:25:15). Iemon's original crimes are either erased entirely—in the case of Iemon murdering Oiwa's (Kinuyo Tanaka) father and lying about it—or transferred to Naosuke. Additionally, Iemon becomes an unintentional participant in his own demise because of his subservience to Naosuke, falling in line with common western rhetoric of the importance of individual free will and agency (Geary). Iemon, in his complicity to Naosuke evils, ends up having to murder his own wife out of compassion, his hand being forced by the painful and disfiguring ointment that Naosuke secretly poisoned. He then is tormented by extreme hallucinations from his shame and cannot recover from his actions, scaring off his new wife and making his reputation worse than it ever was before. At the end of the film Naosuke and a blackmailed Iemon attempt to steal from Iemon's new wife's household, only to accidentally start a house fire and die. Iemon is punished within the narrative time and time again for going along with Naosuke's plans without exerting his own agency over his life. Kinoshita's film stresses the importance of actively pursuing your own goals, because the alternative is to wind up like Iemon.

In Kinoshita's film, evil Naosuke is the one actually responsible for most of Iemon's cruelty and aggression, and is even explicitly blamed by Iemon. He is the one who comes up with the evil scheme to divorce Oiwa in favor of the rich doctor's daughter, Oume (Hisako Yamane), and pushes Iemon to go through with it. At every step of the way, Kinoshita's Iemon is hesitant to go along with Naosuke's scheme, and even outright rejects Naosuke when he says Iemon should kill Oiwa to easily get rid of her. Oiwa only dies when she is horribly disfigured by an ointment Naosuke sneakily gave her, and Iemon mercily kills her because of the unbearable pain she is in. But even as Iemon kills his wife with his own two hands, he blames Naosuke for what has happened: "Naosuke, you did that to her face!" (*Yotsuya Kaidan Part One* 1:21:18). This furthers the parallel of Iemon and Japan, as Iemon's cruelty is seen as his hand being forced by Naosuke's manipulation, much like Japan rewrote their imperial aggression as simple defense (Lowenstein 91). Later, a witness to the crime confesses to the police that in fact "[Naosuke] is the one who killed Oiwa" (*Yotsuya Kaidan Part Two* 0:59:05), completely erasing the role that Iemon had in the murder and placing all the blame on Naosuke, paralleling how Japan erased its own aggressive role in World War II after the fact. The audience also eventually learns that Naosuke is even to blame for Iemon's condition as a poor *rōnin*, as Naosuke robbed Iemon's lord under his watch, causing Iemon to lose his position. So Naosuke is not only to blame for Oiwa's death and Iemon's cruelty, but also for the financial desperation Iemon lives in that pushed him to such extremes in the first place.

Kinoshita's unique interpretation of Iemon can be seen as a direct parallel of what Lowenstein describes as the "pronounced shift in Postwar Japanese cultural representation that covers over Japan's pre-Hiroshima imperial aggressions in favor of post-Hiroshima national victimhood" (86). This shift can be seen in the change of common national imagery in Japan. During the war, Japanese propaganda consisted of images of young men bravely going to fight for their country, showcasing Japan as a strong and heroic nation. After Hiroshima in 1945, however, Japanese national imagery shifted starkly to featuring things like the "A-Bomb Maiden," or a young (and innocent) woman tragically suffering from illnesses reminiscent of bombing victims (Lowenstein 86). Japan's cultural shift from belligerent champion of the East Asian peninsula to the victim of western aggression is incredibly important context in order to properly understand Iemon's character in Keisuke Kinoshita's adaptation.

Kinoshita's version of Iemon inverts the traditional 1825 villain, uniquely going to great lengths to pardon Iemon and view him sympathetically as a victim of Naosuke. Kinoshita's sympathetic Iemon suggests a direct parallel to Japan and its national identity and the victimization complex in the Postwar era. After all, it's no coincidence that as Japan was entering a new era of deflecting blame and responsibility, a century-old villain was suddenly depicted as tragic and innocent.

This divergence from the original serves to tell a different story about Iemon, one that is ultimately in line with Japan's own narrative of innocence and victimhood at the time. No longer is Iemon (Japan) a cruel and aggressive patriarch, so hungry for increased power and money that they will abandon their own moral duties to achieve their goals. Rather, Kinoshita's Iemon (and Postwar Japan) is a battered and down-on-their-luck soul living in poverty and disgrace, making them unfortunate victims of manipulation and prodding.

This fear of passivity and complicity is a new addition to the *Yotsuya Kaidan* story, and is likely due to western influence during occupation. In terms of values and ideologies that the United States wanted to embed in Japanese society, individualism was near the top. Pre-Hiroshima Japan was known for its intense patriotism and religious reverence for their emperor, and such a strong sense of duty to their nation that they would welcome death over surrender. The United States' greatest fear was, at this point in time, history repeating itself in Japan, with a dictatorship or worse: falling to communism. Their perceived solution to the issue was to jam the concept of individualism down a staunchly collectivist country's throat, and *Yotsuya Kaidan* (1949) is a great example of this. Kinoshita's lesson of the film thus differs greatly from the original story, due to the historical context of World War II and manipulative dictators, and the western idea of the importance of agency and free will.

1959: Iemon As Modernity

Nobuo Nakagawa offered his interpretation of the popular ghost story in *Yotsuya Kaidan* (1959). His film is the one most often brought up when discussing the story and its legacy, and for good reason. Nakagawa's film is a faithful adaptation and triumphant return to the traditional story of Iemon (Shigeru Amachi) and Oiwa (Katsuko Wakasugi). Iemon is back to being the

greedy and selfish rōnin he is known as, and any changes to the original story serve to *worsen* his actions. Oiwa's death here is not caused by accident or mercy killing, but by a knowing and willing Iemon poisoning his wife's tea. But although Nakagawa's character is extremely similar to Nanboku's, due to the historical and cultural context of post-occupation Japan, his actions and personality take on a new meaning as reflections of new western ideals of individualism and personal ambition.

After the occupation, the enforced modernity and development of consumerism and urbanization in Japan led to a miraculous economic growth and their GNP (gross national product) increased to second only to the United States (Balmain 53). However, as Standish points out, this drastic change to Japanese society did not come without faults. With men constantly at work fueling the new Japanese economy, women were left fending for their children with little or no help, and the individual became increasingly alienated from those around them (Standish 309). This degradation of prewar Japanese society at the hands of western and modern ideals did not go unnoticed. The writer Yukio Mishima, in 1961, published the book *Patriotism*, promoting the code of bushidō and its traditional morals, in response to what he viewed as spiritual degeneracy in Japan (Balmain 53). Mishima even went so far as to form a private militia, the *Tatenokai*, or Secret Society, in order to preserve traditional Japanese national identity, and attempted a failed uprising at a Japanese Self-Defense Forces military base, after which he committed ritual suicide or *seppuku* while crying out "Long live the emperor."

This pushback against modern ideals within Japanese society through occupation paints Iemon's character in a new light. He is no longer just breaking bushido and rejecting his filial duties, but also actively pursuing western ideals of personal greed and ambition. From the very moment Iemon is introduced, he is a man desperate to raise his social status. In Nakagawa's film, Iemon starts out as an unmarried man, pleading for Oiwa's hand in marriage to her father, Samon (Shinjirō Asano), in hopes that aligning himself with their family will give him more opportunities and greater respect. However, Samon rejects Iemon and insults his pride and honor in the same breath, which prompts Iemon to lash out in anger and kill Samon. He then lies and manipulates Oiwa to marry him, promising he will seek vengeance for this murder. Then, when a better opportunity presents itself in the form of young, wealthy Oume (Junko Ikeuchi), Iemon sees it as only natural to move on from his nagging wife to bigger and brighter things.

These actions, especially after U.S. occupation, read as uniquely targeted towards the western idea of individual ambition and ruthless pursuit of goals. This was the cultural shift occurring in Japan at the time, as their economy quickly became a competitive capitalist market that naturally emphasized the individual over the community. Salecl describes the way that consumerist economies are inherently focused on catering to an individual, and the way it promotes individuals constantly improving and bettering their own lives. Iemon is falling in line with this thinking as he attempts to improve his own individual life through marriages. He rejects traditional Japanese values and beliefs in favor of personal betterment and ambition; he kills Oiwa—here representing tradition and Iemon and Japan's literal past—in order to move forward into the modern future with Oume.

Nakagawa, however, rejects the notion of the supremacy of western and modern ideals through his narration. Iemon, after killing and manipulating those he needed to, seems to achieve his “happy ending,” with Oume and his newfound riches and social status. Ultimately, though, Oiwa’s ghost is sent to teach Iemon, and also the audience, a lesson about the consequences of abandoning your national identity, and your cultural ties and responsibilities. While Iemon’s modern ideals and values do for a time help him achieve his ambitions, Nakagawa stresses the fact that there is no way to move forward without leaving some ghosts behind that will come back to haunt you.

In his inception in 1825, Iemon was a disgraceful samurai who served as an example of the punishment that would be inflicted on those who broke traditional Japanese societal codes and norms. His inability to put the good of his community above himself leads him to pursue his goals to violent extents, and his death at Oiwa’s hands is the satisfying conclusion to his arc of selfishness and dishonour. A century later, in 1949, Japan was undergoing a shift in their own national identity from Asian heroes to post-war victims. Thus, the Iemon seen in Kinoshita’s film is a sympathetic man who is less “evil” and more gullible to being manipulated to do cruel things. Iemon’s heinous crimes in the original play are completely omitted from this version of the play, paralleling the way Japan as a country would censor their war-time losses and fatal mistakes. Iemon’s main crime in 1949 is his passivity and allowing other characters make decisions and choices for him. With the context of the U.S. occupation at the time attempting to enforce and imbue western and modern ideas on a traditional Japan, this narrative messaging is read as yet another parallel to contemporary issues. When Nakagawa adapted the myth in 1959, Japan was no longer under occupation, but still under the influence of western ideas that actively jeopardized and contrasted their traditional beliefs. Nakagawa’s film reflects this conflict between tradition and modernity in its main characters’ conflict. Iemon is the picture of western greed, attempting to get rid of his traditional wife in order to financially prosper, and he is scorned and punished within the narrative accordingly. This again showcases the way that historical and cultural context greatly impacts the films produced within them. Throughout the years, Iemon has had changes done to his character and narrative role, and these changes create a different message or meaning to the original story that falls in line with the contemporary moment.

IV. Oiwa Through The Years

Next, this paper will analyze Iemon’s wife, and narrative partner, Oiwa. While Oiwa’s character and personality stay relatively similar throughout the discussed adaptations, the *narrative* changes how it views that personality and depicts it accordingly. She is always a traditional and loyal wife, but throughout Japanese history as cultural ideals have shifted and changed, so too does the story’s representation of Oiwa.

1825: The Original Oiwa

In Tsuruya Nanboku IV's 1825 *Yotsuya Kaidan* kabuki play, Oiwa is an unhappy wife to rōnin Iemon, and is working with her father to divorce him when her father is murdered. This forces Oiwa to then stay her marriage with Iemon, as he is her only hope of seeking vengeance for her father's killer. But Iemon only continues to mistreat and neglect Oiwa, especially after she gives birth and struggles with postpartum sickness. She is sent a mysterious ointment that disfigures her, and Iemon comes home and insults her newfound hideousness. Oiwa's servant, Takuetsu, attempts to force himself on her, but is so disgusted that he takes pity on her and reveals her evil husband's plan to divorce Oiwa on the grounds of cheating and remarry their rich neighbor's granddaughter. Oiwa is so enraged by this news that she accidentally stabs herself with a nearby dagger, cursing Iemon and vowing vengeance as she dies. She returns as a spirit to haunt and terrorize Iemon on his wedding day, causing him to kill both his new wife and grandfather-in-law and flee in terror to the mountains. Oiwa then sends visions to her brother-in-law in his dreams to kill Iemon and enact her vengeance, and is finally able to rest peacefully.

In the original 1825 story, Oiwa, as a ghost, and a literal remnant of the past, represents the way dishonourable actions will come back to haunt their perpetrators. She serves the traditional purpose of yōkai in Japanese storytelling, keeping the world in a state of order that abides by national values and beliefs by punishing Iemon for his transgressive behavior (Donovan 13). She supports the main lesson of the play about the consequences of greed and unchecked ambition and the importance of respecting your duties and cultural identity. By contrast, Iemon acts in a dishonourable and cruel way and thus must be punished and shown the error of his ways by Oiwa, the representation of all the values Iemon lacks.

Oiwa shows consistent filial piety for her family throughout the play, in contrast to Iemon's selfish individualism. After her father is killed, she insists on Iemon finding the murderer and bringing justice to her father's memory. Under the *ie* system, whereby filial piety is valued above all else, Iemon is now the head of Oiwa's family, and Oiwa expects him to be loyal to his duties to her father above all else. As a woman in feudal Japan, there were limited ways that Oiwa and women like her could exert power and agency over their lives. For Oiwa, the only way to see her father's revenge brought about was for Iemon to pursue it. But, of course, Iemon demonstrates that he has no loyalty to Oiwa's family throughout the play. Oiwa remains loyal to Iemon despite his cruel words and reprimands towards her. After Iemon comes home when Oiwa has been disfigured, he insults her appearance, steals her things to pawn off, and says he has changed his mind about helping Oiwa find her father's killer. Iemon does all of these things as she is in immense pain from the medicine she has been given, but despite this, Oiwa rejects her servant Takuetsu's advances when he attempts to force himself on her: "Woman as I am, I was born a warrior's daughter and am now the wife of another" (Nanboku 68). Oiwa puts aside her personal desires and hatred for Iemon and remains loyal to her obligations as a wife and daughter of a respectable warrior. This ironically contrasts with Iemon at this same point in the play going off to marry another woman, completely disrespecting his duties to his family and thinking only of his personal desires.

Oiwa's character markedly contrasts that of Iemon. Thus, their conflict within the play represents a wider theme of loyalty to cultural ties and identity. Although Iemon achieved temporary victories through his manipulations and deceit, Oiwa achieves the final victory over Iemon as she kills him and is able to rest peacefully in the afterlife. Her triumph represents the play's messaging on the value of cultural identities and duties and the way that one will never really be able to leave this identity behind without dire consequences.

1949: There's No Ghosts in this Ghost Story

In Kaisuke Kinoshita's rendition of the popular tale, Oiwa (Kinuyo Tanaka) is a hollowed-out character that reflects the growing popularity and enforcing of western beliefs and ways of living under U.S. occupation. The 1949 film removes the supernatural elements from the original 1825 play in favor of a more rational western ideology around death. Kinoshita's Oiwa serves to also enforce the occupation ideals of the "right" woman, as she is directly contrasted with her sister as an example of how passive women are actually at fault for the violence and abuse perpetrated against them.

Kinoshita's film robs Oiwa of her ability to enact revenge by depicting her in an incredibly rational way, falling in line with the popular western belief at the time. Historian Scherer explains that "in intellectual discourse, belief in ghosts and other supernatural beings was treated as backward and belonging to the premodern past" (80). Oiwa in her ghostly form, then, could not be allowed to exist under occupation that was centered around modernizing Japan. Therefore Oiwa is no longer a moral yōkai seeking vengeance for the wrongs that were done to her, but rather cinematically coded with intentional framework (Scherer 85) as a figment of Iemon's guilt conscience.

Oiwa's drastic change within the narrative is reflective of the way U.S. occupation policed the way Japanese people, specifically women, could "correctly" express themselves. This can be seen in the way the film treats Oiwa compared to her sister Osode (also Kinuyo Tanaka). Oiwa is described as kind to a fault and too shy and retiring, which serves to place blame upon her for the abuse she suffers at the hands of her husband. She is narratively punished with death for being loyal to Iemon and refusing to divorce him, and his cruelties are seen as valid retaliations in the face of Oiwa's nagging neediness and devotion to her husband. This attempts to teach the audience that subservience and passivity are qualities to be avoided, which falls in line with the ideology that U.S. occupation officials wanted to get across. Even as Oiwa dies from her husband's own blade, she issues no cries of rage or vengeance, merely crying from the pain. Her passivity follows her all the way to the grave, and the perpetrators of her death are never properly punished or taught a lesson.

The qualities that spell disaster in Oiwa's life are then juxtaposed with Osode's character and her happy ending. Once her sister has died, Osode realizes something strange is afoot, and actively fights for an investigation into the disappearance of Oiwa. She works closely with the police and alongside her husband to see justice be brought to her and her family. She is an equal partner in her marriage and is often seen giving orders to her husband, Yomoshichi, in her

impassioned search for answers. In this way, Osode blatantly rejects traditional Japanese beliefs of subservience to the husband and placing communal good above personal goals. However, this dismissal and outright shunning of traditional Japanese culture is never seen as a negative, because this dismissal is everything that the U.S. occupation is hoping to achieve. Osode is depicted as the perfect modern woman who “acts of her own volition [and] pursues her goals rationally” (Scherer 84). Her willingness to actively pursue her goals and fight for what she believes in—regardless of how many traditional beliefs she rejects—is rewarded by her happy ending. She is able to get justice for her sister as she learns who is responsible for her death and attempts to capture them with the help of the police. Although the chaotic ending of the film instead features a burning house that kills both Naosuke and Iemon before they can receive proper punishment, Osode still ends the film walking off away from the burning house with her husband and future child. Kinoshita’s depiction of Osode upholds the ideas U.S. occupation was trying to enforce. Osode is only able to get her happy ending *because* she breaks away from traditional Japanese gender ideals and instead prescribes to western ideals of free will, ambition, and modernity.

This film serves as a brilliant example of the way that directors can twist and change a character and story based on the political ideologies and historical context of the time. Oiwa’s character in its essence does not change greatly—minus her ghostly identity. In both the 1825 play and Kinoshita’s 1949 adaptation, she is a fiercely loyal and devoted wife who cares deeply for her community and family more than her own wellbeing, poignantly representing traditional Japanese standards and culture. The difference shines, however, in how this personality is treated within the narrative. In the play, Oiwa’s traditionalism is what gives her power. She is quite literally a representation of the past that comes back to haunt and punish those that would scorn her. But Kinoshita’s film views Oiwa’s traditionalism as backward and pathetic, the ultimate reason for her downfall. Her traditional beliefs and filial subservience are narratively punished, similarly to how traditional Japanese beliefs were criticized and outright banned from films under occupation. Though the character is constant, different time periods interpreted the same character in vastly different ways due to their respective places in history. Under a harsh occupation that was designed to strip Japan of its national identity and replace it with western values, Oiwa’s traditionalism was naturally seen as a clear disadvantage where it never had been in the past. By comparison, Osode’s rejection of how a traditional Japanese woman should act in favor of new western and modern ideas is the direct reason why she can find justice and peace after her sister’s murder. These characters, especially compared to their original counterparts, reflect the U.S. occupation’s desire to convince Japanese people of the supremacy of modernity over traditionalism.

1959: Oiwa’s Return

In Nakagawa’s adaptation *Yotsuya Kaidan* (1959), Oiwa (Katsuko Wakasugi) is a joyous return to her original character in the play as a representation of tradition and upholder of justice. Her ghostly return for vengeance is brought back, and she again symbolizes the return of

tradition and pre-occupation culture where modernity would see them dismantled. However, Nakagawa's Oiwa's story is made more rich and intense than the 1825 original through the historical context of the moment.

Nakagawa's film affirms the right and supremacy of tradition six years after a brutal occupation that attempted to modernize Japan. To tell this classic Japanese ghost story so faithfully after so many traditional Japanese stories had been censored and blacklisted during the occupation sent forth its own message of the importance of respecting tradition and national history and identity.

Oiwa's return to her classic ghostly self is just one example of a broader cultural rejoicing in tradition through media. Donovan described the way that traditional *yōkai* post-occupation were depicted with astounding accuracy, and how this reflects the larger cultural shift of respecting and paying homage to national Japanese identity (9). He cites how Oiwa, specifically, in the 1959 film is visually represented extremely similar to old woodblock prints of her in the 1800s, and how in her ghostly form she retains the outfit and wounds she had as she died, like traditional Japanese ghosts (Donovan 11-12). The commitment to Oiwa's visual and narrative representation can be seen throughout the entire film, and Nakagawa's valuing of tradition and classic Japanese culture is on full display.

Even though there was a large rejoicing in traditional Japanese beliefs in many parts of the country, Japan was still incredibly modernized when it came to their economy. Their economy had grown substantially on a global scale and it was all thanks to the adoption of modern and western ideas. This led to conflicting perspectives from citizens and confused personal identities. Many enjoyed the newfound wealth in the pockets of themselves and their great nation; others, however, saw Japan as bastardizing itself and hollowing out its own culture in order to simply be richer. This national tension and conflict between modern ideas and traditional values is the main breeding ground for Nakagawa's film.

Nakagawa's faithful interpretation of the original Oiwa allows for a distinct metaphor to emerge in which Oiwa is the representation of traditional Japanese beliefs that comes in conflict with the selfishly motivated Iemon, who here represents the modern ideas that are only possible by rejecting tradition. There is no clearer example of this than with Iemon's desire to socially and financially advance himself (like 1950s Japan) by remarrying, and needing to leave his old wife (tradition) behind to achieve this goal. But just like the past, and our own cultural identities, Oiwa comes back to literally and metaphorically haunt Iemon. Michael Dylan Foster writes about how ghosts in stories are "the banished Other [that] returns, causing [those around them] to anxiously question their modern ways of interpreting the world around them" (117-118). Within this framework, Oiwa's ghostly return is detrimental to Iemon's view of how to see the world. He believed he had achieved greatness by leaving his old wife (and likewise, tradition) behind, only to realize they were never truly gone, only waiting to reappear.

Unlike Kinoshita's 1949 film, which attempts to convince the public of the validity of modern ideals like free will and ambition, Nakagawa wholeheartedly depicts tradition as the inevitable winner of the contemporary conflict, as the film ends with Oiwa floating above

Iemon's death, cradling her baby, smiling. Despite the push towards modern ideas supported by a growing economy, he clearly believed that, just like Iemon, Japan would face the consequences of completely renovating their national identity in the pursuit of more wealth.

Though Oiwa has stayed a similar character throughout the adaptations discussed, the specific way she is narratively seen and interpreted changes drastically depending on the cultural and historical context. In the original play, she represents the consequences of breaking samurai code and disrespecting your culture. Her ghostly return is an explicit example of how dishonourable actions will always come back to haunt those who make them. In Kinoshita's 1949 adaptation, due to the censorship of the U.S. occupation, Oiwa no longer returns as a ghost, and does not teach any lessons to Iemon. In fact, due to the conscious and subconscious effort by the occupation to enforce modernized ideals of agency and free will, Oiwa's passivity as a traditional wife is narratively punished and seen as a bad thing to fit the western narrative of the time. With Nakagawa's film in 1959, however, we see the brilliant return to the Oiwa of old, who comes back as a ghost to teach Iemon the lesson of pursuing modernity at the expense of tradition and national culture. This parallels Japan's actions at the time, as they modernized and followed western ideals within their economy which led to financial prosperity to the detriment of their national culture and identity that was being actively shunned. Analyzing Oiwa through these different lenses proves the importance of analyzing films further and always asking questions about why a director made a change or decision regarding characters and their behavior or personality.

V. Conclusion: Putting It All Together

The Yotsuya kaidan myth, since its introduction to Japanese culture in 1825, has changed and evolved in its many adaptations through the years. These changes can be read as explicit references and responses to the cultural and national shifts that were occurring at the time of each film's production. This paper specifically highlighted these changes through analysis of the main characters of the myth in each adaptation.

In 1825, the story serves as a reflection of contemporary cultural values. Iemon's character disregards Japanese customs about the importance of community and filial loyalty, instead pursuing his own selfish ambition and desires. This puts him at odds directly with Oiwa, who is killed to further Iemon's dishonorable pursuits, and thus he is punished within the narrative by Oiwa to teach the lesson that one's breaking of cultural codes will always have consequences deeper than one can understand. Oiwa comes back to show the way that the past can come back to haunt you, literally. Nanboku's kabuki play asserts the importance of the cultural hierarchy of loyalty and respect within Japan through both of the main characters.

In 1949, the story being told by Kinoshita is vastly different. Under U.S. occupation bent on modernizing a "backward" country, Kinoshita was unable to fully adapt the story faithfully due to strict censorship restrictions. This is seen most clearly in the lack of Oiwa's ghostly return for vengeance against Iemon, which hollows out her character. Oiwa's character is also viewed in a much more negative light compared to how Nanboku represented her. Although her actual

character stays constant, the western occupying force that was subtly affecting Japanese thoughts saw Oiwa's passivity and traditional wifely behaviors as a symptom of Japan's "backward" culture, and therefore necessitated a different approach. In order to properly introduce western ideas of a modern woman, the film spends substantial amounts of time blaming Oiwa for her own death and abuse because she was simply too passive and kind-hearted. Through this, the western ideals of the proper way a woman should act bleed into the film by demonizing Oiwa's previously proper behavior in favor of a more assertive and independent woman, as seen in her sister, Osode. The other largest change occurs in Iemon's character, and can be traced back to the cultural shift in national identity after the bombing of Hiroshima and Nagasaki, wherein Japan swapped their previous aggressive imperialist attitude for a victim complex that left them completely innocent of the crimes they committed during and directly preceding the war. Thus, Iemon's personality as a cruel and greedy villain is changed in a way that subtly parallels Japan's own cultural shift. He is now an ultimately innocent husband who is simply manipulated into doing evil deeds by the true villain Naosuke. Furthermore, Iemon's weakness lies not in his breaking of cultural codes, but of his passivity in the face of Naosuke's manipulations. This new direction with Iemon's character can further be supported by western influence with ideas about independence and individual free will. Ultimately, in the 1949 film, both Oiwa and Iemon's main flaw is their passivity, which leads to their respective unfortunate endings.

In 1959, Nakagawa's film is a joyous return to the original story and characters, falling in line with the cultural trend of the time. After occupation ended, Japanese artists were able to depict traditional Japanese tropes and *yōkai* without fear of censorship. This return to tradition in many cases also reflected a cultural pushback that many citizens felt after the forced modernization of the occupation. Although this modernizing of Japan had some positive effects, primarily the enhanced economy, many felt that these accomplishments came at the cost of the Japanese national identity. This conflict can be felt in Nakagawa's depictions of Iemon and Oiwa. Although they're very faithful to their original characters, the story they tell and themes they symbolize are unique to this time period. Iemon's greed and personal ambition now parallels the darker contemporary urge to pursue modernity at the expense of one's own culture. Oiwa, then, represents the tradition that the Japanese needed to hold onto, according to Nakagawa. Though Iemon tried to get rid of Oiwa to further his own social and financial status, she came back to haunt him, literally, and remind him of the oaths he had broken. Iemon and Oiwa's conflict reflects the wider cultural confusion of a country caught between modernity and tradition, and the film, when understood in the full context of that historical moment, can be seen as a reminder to any Japanese citizen who would try to leave tradition behind, like Iemon did. The film asserts the longevity and dominant nature of tradition and past values.

The evolution of the *Yotsuya Kaidan* myth and its adaptations traces the evolution of Japan's national identity and cultural shifts throughout the decades. The two inform and affect each other, and analyzing one allows for a deeper understanding of the other. To fully appreciate the stories that are told in certain historical moments, it is paramount to analyze the aspects of history that inevitably bleed into the media. Conversely, deeply analyzing film can open a

doorway into understanding its respective history and culture. When decisions are made in the filmmaking process, culture and history are always behind the scenes, working in some way or another, as seen in the example of the many *Yotsuya Kaidan* films.

Bibliography

- Balmain, Colette. *Introduction to Japanese Horror Film*. Edinburgh University Press, 2008. *JSTOR*. Accessed 18 June 2025.
- Brothers, Peter H. "Japan's Nuclear Nightmare: How the Bomb Became a Beast Called 'Godzilla.'" *Cinéaste*, vol. 36, no. 3, 2011, pp. 36-40. *JSTOR*. Accessed 7 June 2025.
- Donovan, F. "The Evolution of Yōkai in Japanese Horror Cinema from the 1950's to the Present." vol. 1, no. 1, 2024, pp. 9-19. *Institute of Art, Design + Technology*. Accessed 7 June 2025.
- Geary, Dan. "Butts, Blood, and Bombs: The American Occupation's Effect on Japanese Cinema." *Cinesthesia*, vol. 10, no. 2, 2020. *JSTOR*. Accessed 7 June 2025.
- Legacy, Arthur. "'The Invasion of the Body Snatchers': A Metaphor for the Fifties." *Literature/Film Quarterly*, vol. 6, no. 3, 1978, pp. 285-92. *JSTOR*. Accessed 8 June 2025.
- Lowenstein, Adam. "Japan: Unmasking Hiroshima: Demons, Human Beings, and Shindo Kaneto's Onibaba." *Shocking Representation: Historical Trauma, National Cinema, and the Modern Horror Film*, Columbia University Press, 2006, pp. 83-110. *JSTOR*. Accessed 26 June 2025.
- Scherer, Elisabeth. "Haunting Gaps: Gender, Modernity, Film and the Ghosts of Yotsuya Kaidan." *Journal of Modern Literature in Chinese 12.1*, vol. 12, no. 1, 2014, pp. 73-88. *JSTOR*. Accessed 30 June 2025.
- Standish, Paul. "Democratic Participation and the Body Politic." *Educational Theory*, vol. 55, no. 4, 2005. Wiley Online Library, <https://onlinelibrary.wiley.com/doi/10.1111/j.1600-4469.2004.00218.x-i1>. Accessed 27 July 2025.
- Thompson, Kristin, et al. *Film History: An Introduction: 2025 Release*. McGraw-Hill Education, 2025. *JSTOR*. Accessed 27 July 2025.