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# Allocation and distribution of anticancer drugs in the supply chain and crisis management under drug shortage conditions: A narrative review

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## Abstract

Cancer remains a leading cause of morbidity and mortality worldwide, and sustained access to anticancer medicines is indispensable for achieving curative and life prolonging outcomes. Yet global shortages of oncology drugs, especially off patent sterile injectables, have grown in frequency and duration, exposing structural fragilities across manufacturing, economics, regulation, and logistics. This narrative review synthesizes evidence on how scarce anticancer medicines are allocated and distributed during shortages, how systems manage crises, and where artificial intelligence (AI) and quantitative modeling can strengthen resilience. We summarize convergent drivers (quality related production halts, concentrated supplier bases, low margin tendering, demand shocks, regulatory bottlenecks, cold chain constraints, and external disruptions) and their uneven impacts across high income versus low- and middle-income settings. We then integrate multilevel strategies: nationally, early warning systems, critical medicine lists, diversified sourcing, and transparent stockpile release; within health systems, multidisciplinary governance, real time dashboards, conservation practices (dose rounding, vial sharing), internal redistribution, and consistent communication; and at the bedside, ethically grounded triage that prioritizes curative intent, higher expected benefit, and lack of alternatives. We map the emerging AI toolkit, including shortage forecasting, inventory optimization, supplier risk scoring, and digital twins to test allocation policies ex ante, and align it with four modeling families central to decision making under scarcity (mixed integer and stochastic optimization, discrete event and agent-based simulation, reliability and resilience modeling, and decision analytic and ethical frameworks). We conclude with a Prevention, Preparedness, Response, Recovery roadmap that links macro level incentives (resilience-oriented procurement and quality and continuity rewards), meso level data infrastructure and playbooks, and micro level shared decision making. Priorities include harmonized metrics for shortage severity and resilience, prospective evaluations of allocation policies, and cross-country collaboration to ensure that digital and analytic advances enhance equity while reducing the clinical harm of oncology drug shortages.

**Keywords:** Anticancer drugs, Supply chain, Crisis management.

## Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, and its global burden is still rising despite major advances in prevention, early detection, and treatment.[1] Recent estimates suggest that nearly 20 million new cancer cases occurred in 2022, with close to 10 million deaths, and projections indicate a substantial increase in both incidence and mortality by 2050 as populations age and grow.[1,2] These numbers translate into millions of patients whose survival and quality of life depend on sustained access to effective anticancer therapies, including conventional cytotoxic chemotherapy, targeted agents, and immunotherapies.[3,4] For many solid tumors and hematologic malignancies, there is no clinically equivalent substitute for specific drugs or combinations, so even short interruptions in supply can compromise the intent of treatment and long-term outcomes.[5,6]

Over the past decade, shortages of essential anticancer medicines have emerged as a recurrent and increasingly

visible threat to high-quality oncology care.[7] Reports from high-income countries such as the United States and members of the European Union, as well as from middle-income settings, document repeated episodes of limited availability of key oncology injectables.[8, 9] These shortages are not confined to niche or low-use agents; they frequently involve cornerstone drugs in first-line curative regimens. A recent example is the global shortage of the platinum-based chemotherapies carboplatin and cisplatin in 2023–2024, which led cancer centers to delay therapy, switch to less optimal alternatives, and deviate from evidence-based guidelines.[10, 11] Professional societies have warned that such crises can affect hundreds of thousands of patients and may erode hard-won gains in cancer survival.[12]

The consequences of oncology drug shortages are multifaceted and extend well beyond logistics. Clinically, shortages may force dose reductions, treatment delays, or the use of regimens with inferior efficacy or greater toxicity, potentially reducing cure rates and worsening symptom control.[9,13] At the health-system level, they generate substantial workload for pharmacists and clinicians, who must continuously search for alternative products, redesign treatment plans, and communicate complex changes to patients.[14,15] Shortages can also exacerbate inequities, as well-resourced institutions may secure limited supplies while smaller or resource-constrained centers face prolonged stockouts. For patients and families, the experience of having "no drug available" at a critical juncture in treatment can undermine trust in the health system and increase psychological distress at an already vulnerable time.[8,16,17]

These recurrent crises highlight the particular vulnerability of anticancer drug supply chains. Oncology medicines, especially off-patent, sterile injectable generics, sit at the intersection of complex manufacturing requirements and fragile market incentives.[18,19] Production is often concentrated in a small number of facilities and companies, many of which operate with narrow profit margins due to low prices and aggressive purchasing practices. Manufacturing of sterile injectables demands high fixed investment, stringent quality assurance, and sometimes cold-chain infrastructure; when combined with low reimbursement and limited rewards for quality, these conditions discourage redundancy and long-term investment [20]. Any disruption, such as a quality failure, contamination event, regulatory action, or shutdown of a single plant, can therefore ripple rapidly through the global market. In parallel, the geographic concentration of active pharmaceutical ingredient (API) and finished product manufacturing, often in a few countries, makes anticancer drug supply chains sensitive to geopolitical tensions, export bans, natural disasters, and transportation bottlenecks [20].

Existing literature has described many of the proximate causes and downstream effects of cancer drug shortages, and numerous professional organizations have proposed high-level policy responses [21, 22]. Studies have catalogued how low prices, concentrated production, and quality problems increase the risk of shortage, and they have documented the clinical consequences of stockouts for specific tumor types and regimens.[6,18] However, far fewer publications take a holistic view of how anticancer drugs are allocated and distributed along the entire supply chain once a shortage occurs. Similarly, the crisis-management strategies that are actually used in practice, ranging from national-level allocation rules and emergency procurement to hospital-level triage algorithms and vial-sharing protocols, are often described in isolation, without integration into a broader conceptual framework for resilience.[10, 23]

At the same time, rapid advances in data science and operations research are opening new possibilities for anticipating and mitigating shortages. Artificial intelligence (AI) and machine-learning approaches have been explored for demand forecasting, anomaly detection in manufacturing, and early warning of supply disruptions, while mathematical optimization and simulation models have been applied to design more robust pharmaceutical supply chains and to allocate scarce resources under constraints.[24,25] Yet, applications that are explicitly tailored to oncology drug supply, and that bridge technical modeling with the ethical and clinical realities of rationing life-saving therapies, remain limited and fragmented.[26]

Against this backdrop, a more integrated picture of

anticancer drug shortages is clearly needed. Rather than looking at causes, clinical impact, management strategies, or analytic tools in isolation, this narrative review brings them together along the whole supply chain. Our aim is to describe how the anticancer drug supply chain functions in practice, how it breaks down when shortages occur, and how decisions about allocation and crisis response are currently made. In doing so, we focus on four simple but connected questions: 1) What are the main drivers of anticancer drug shortages along the supply chain? 2) How are allocation and crisis-management strategies actually implemented at national, institutional, and patient levels? 3) How can artificial intelligence help with forecasting, allocation, and distribution of anticancer drugs? and 4) Which modeling approaches have been used to optimize supply and allocation under shortage conditions? Answering these questions is intended to offer a practical framework that can inform both future research and real-world efforts to build more resilient anticancer drug supply chains.

## 2. Anticancer drug supply chain and key definitions

### *2.1. Structure of the Anticancer Drug Supply Chain*

The supply chain for anticancer medicines is a multi-stage, globally connected network that transforms chemical inputs into finished products and ultimately into treatment at the bedside.[20] Although it shares many features with other pharmaceutical supply chains, several characteristics– notably the dominance of sterile injectable formulations, narrow therapeutic margins, and the limited number of qualified manufacturers– make it particularly fragile in the face of disruption.[18, 27]

At the upstream end of the chain are suppliers of raw materials and manufacturers of active APIs. These companies source basic chemical precursors and carry out complex synthesis, purification, and quality-control processes to produce the APIs that will become the "active" components of anticancer drugs. For many widely used cytotoxic agents, APIs are produced by only a handful of firms worldwide. Any regulatory action, quality failure, or interruption in the flow of raw materials at this stage can therefore propagate downstream and translate into global shortages months later.[14,18,28] Lead times are long: from an interruption in API production to a visible shortage at hospital level, several months may elapse, during which there is often limited transparency about the severity or expected duration of the problem.[14,28]

The next node consists of finished-product manufacturers, who formulate APIs into injectable or oral dosage forms, carry out sterile filling, perform batch testing, and package the medicines. For generic oncology injectables, this step requires highly specialized facilities that comply with strict good manufacturing practice standards. Sterile production lines are capital-intensive and technically demanding, which tends to limit the number of manufacturers that remain in the market, especially when prices are low.[18,29] Because switching production lines or adding new capacity is slow and expensive, the system has little slack: if one or two major producers exit the market or suspend operations, the remaining firms may not be able to absorb the excess demand quickly enough, and shortages emerge.[18, 27, 29]

After production, medicines typically move to secondary packaging and national or regional warehouses, which may be operated by the manufacturers themselves or by contracted logistics providers. Here, products are labeled for specific markets, aggregated into larger shipping units, and staged for distribution. Cold-chain requirements, for example, for certain biologics and targeted therapies that must be kept within narrow temperature ranges, add further complexity. Breakdowns in cold-chain integrity, transportation delays, or customs bottlenecks can all lead to spoilage and unplanned loss of stock.[30]

From there, products flow to wholesalers and national distributors. In many countries, a small number of large wholesalers dominate the distribution of hospital-use medicines. They aggregate demand from hundreds of hospitals and clinics, manage inventories, and allocate limited stock when supply is constrained. The incentives and contracts at this level matter greatly: tendering processes that prioritize the lowest price can push margins down to the point where only one or two suppliers remain viable, increasing the risk that any problem will quickly turn into a nationwide shortage.[14,31] Wholesalers also act as an information hub, transmitting signals about demand and availability between manufacturers and healthcare

providers, but these signals are often imperfect, delayed, or proprietary.[31]

Closer to the patient are hospital and oncology pharmacies, which form the operational heart of anticancer drug use. Pharmacists forecast local demand based on scheduled chemotherapy regimens, maintain safety stocks, prepare individualized doses (often under strict sterile compounding conditions), and coordinate closely with oncologists and nurses.[9, 32] They are also the first to experience the impact of shortages in practice: failing deliveries, partial order fulfillment, or notification that a key product is "on allocation" trigger a cascade of local responses, from checking alternative suppliers to adjusting treatment schedules. In some systems, specialized cancer centers act as regional hubs that redistribute stock to smaller hospitals, informally buffering the impact of shortages but also creating complex interdependencies.[9, 31]

Finally, outpatient oncology clinics, day-care infusion centers, community pharmacies, and patients themselves constitute the downstream end of the chain. Depending on the health system and the specific drug, treatment may be delivered exclusively in hospitals or partly through outpatient and community settings. For oral anticancer therapies dispensed in the community, retail pharmacies and mail-order services become additional nodes, each with their own inventory practices and exposure to shortage risk.[20,28] At the very end of the chain, patients experience the consequence of any upstream disruption as a delayed cycle, a modified regimen, or – in the worst case – a cancellation of planned therapy.[9, 31]

Across all of these nodes, several cross-cutting features shape vulnerability to shortages. First, lead times are long: production planning, quality testing, and international transport mean that increasing supply in response to a sudden spike in demand is rarely possible in the short term. Second, the number of qualified manufacturers is often small, especially for low-priced, off-patent injectables, so the system depends heavily on the continuous functioning of a few plants. Third, the need for sterility and, in many cases, cold-chain logistics limits flexibility; stock cannot easily be reconditioned once compromised. Finally, many actors operate with lean, just-in-time inventories for cost reasons, which reduces the buffer capacity of the system as a whole.[23] These structural characteristics provide the backdrop for understanding how and why shortages occur and why they can be so difficult to manage once they arise.

To analyze shortages systematically, it is also essential to clarify key terms that are often used inconsistently in both the literature and policy discourse.

### *2.2. Key Definitions*

The phrase "drug shortage" is sometimes used loosely to describe any difficulty in obtaining a medicine, but regulatory definitions are more specific.[33,34] In this review, we use the term "drug shortage" to refer to a situation in which the available supply of a medicinal product is insufficient to meet the current or projected demand at the user level, such that normal patterns of care cannot be maintained.[33,34] This definition emphasizes the mismatch between supply and demand and focuses on the point at which patient care is affected, rather than on upstream events alone.[33,35]

Related but distinct is the term "stockout", which denotes the complete absence of a given product at a particular site for a defined period of time.[33,36] A hospital may experience a stockout of a chemotherapy agent even when national authorities do not classify the issue as a formal drug shortage, for instance because other suppliers remain on the market or because the problem is considered temporary. Conversely, there can be a recognized national shortage even while some institutions still have stock on hand.[33,35,36] Recognizing this difference is important because stockouts are what clinicians and patients actually experience, whereas "shortage" is often measured at a broader, policy level.[35]

A third term, "backorder", refers to a situation in which a manufacturer or wholesaler is unable to fill new orders immediately and instead commits to delivering the product at a later date.[34] Backorders can be seen as an early warning sign: they indicate that supply is already tight and that future stockouts are likely if demand remains unchanged and no additional sources become available. However, because backorder information is not always transparent, frontline providers may only discover it when their usual orders are suddenly cut or

delayed.[28,31,37]

When supply is constrained, attention turns to "allocation" and "rationing".[22, 38] Allocation describes the operational rules and mechanisms by which limited quantities of a drug are distributed across regions, institutions, or patients. At the macro level, allocation may involve national health authorities determining how much of a scarce drug each hospital or region receives. At the meso and micro levels, it may involve hospital committees deciding how to divide a limited number of vials among different clinical services or even individual patients.[10,22,38] Rationing, in contrast, refers more explicitly to the ethical and clinical process of prioritizing some patients or indications over others when there is not enough supply to treat everyone as planned.[22] In oncology, rationing decisions may weigh curative versus palliative intent, expected magnitude of benefit, patient age or comorbidities, and other ethically sensitive criteria.[22]

Beyond these operational concepts, we also draw on terms from the field of operations research and systems engineering. "Supply chain resilience" can be understood as the ability of the supply chain to prepare for, absorb, adapt to, and recover from disruptions while maintaining an acceptable level of function.[20] Resilience encompasses preventive strategies (such as diversifying suppliers), absorptive capacity (such as stockpiles), adaptive responses (such as flexible contracts or dynamic rerouting), and recovery processes (such as root-cause analysis and structural reform).[20] It is related to, but not identical with, "robustness", which usually denotes the capacity of a system to withstand shocks without major performance degradation, often by virtue of redundancy or over-dimensioning. In highly cost-constrained pharmaceutical markets, robustness is frequently sacrificed to achieve short-term efficiency, which in turn undermines resilience.[10, 18, 28]

Finally, when discussing which products deserve special attention, we use the notion of "criticality".[39] A medicine is highly critical if the consequences of its unavailability for patient outcomes are severe and if there are few or no clinically equivalent alternatives.[39] Many anticancer drugs, particularly those used in curative regimens or for pediatric malignancies, fall into this category.[9,16,39] For such products, even a short, localized shortage can behave like a crisis rather than a routine supply issue, because there is little room for substitution or delay.[9, 16, 39]

It is also useful to distinguish between "routine" shortages and "crisis" shortages.[20] Routine shortages tend to be localized, short-lived, and manageable through standard tools such as temporary substitution, small adjustments in scheduling, or borrowing from neighboring institutions.[9,22,37] Crisis shortages, by contrast, are widespread, prolonged, and often linked to major systemic shocks such as pandemics, geopolitical tensions, export bans, or the sudden loss of a dominant manufacturer.[10,20] In crisis situations, conventional workarounds are insufficient, and more formal allocation and rationing mechanisms are required, often accompanied by policy interventions and international coordination.[20]

Together, these definitions provide a shared language for the rest of the review. By clearly distinguishing between shortages, stockouts, backorders, allocation, rationing, resilience, robustness, and criticality, and by recognizing the difference between routine and crisis situations, we can more precisely analyze how anticancer drug supply chains function under stress and what kinds of interventions are needed to protect patients when things go wrong.[10,20,28,33,39].

## 3. Drivers and Patterns of Anticancer Drug Shortages

Shortages of anticancer medicines rarely arise from a single failure. Instead, they emerge from the interaction of multiple vulnerabilities across the supply chain, from raw materials and manufacturing, to market structure, regulation, logistics, and demand, which together create a "perfect storm" for oncology drugs, especially sterile injectables and off-patent agents.[10, 18, 23, 40] As summarized in Table 1, these drivers span manufacturing, economic, demand-related, regulatory, and logistical domains.

### *3.1. Typology of drivers*

#### *3.1.1. Manufacturing and quality problems*

A large proportion of reported drug shortages can be traced back to manufacturing issues such as quality defects, contamination events, equipment failures, and the voluntary or enforced shutdown of production lines.[18,23]

Sterile injectables are particularly exposed because they require technically complex aseptic processes and rigorous environmental controls; when a single plant fails inspection, the entire facility may halt production while corrective actions are taken, abruptly removing a major share of global capacity.[18] In oncology, several episodes of contamination and GMP non-compliance at facilities producing generics such as methotrexate, cisplatin, or doxorubicin have led to prolonged shortages in multiple regions.[10, 40, 43]

Manufacturing vulnerabilities are magnified by the small number of active suppliers. Analyses of shortage databases in the USA and Europe consistently show that medicines supplied by only one or two manufacturers are far more likely to be in shortage than those with a broader supplier base.[18,23] When one producer encounters a quality problem, other manufacturers often lack the spare capacity or economic incentive to ramp up quickly, so a temporary disruption evolves into a prolonged shortage.[18,23]

### *3.1.2. Economic and market pressures*

Economic forces play a central role. Once oncology drugs lose patent protection, they often enter highly competitive tender markets where purchasers prioritize the lowest unit price.[10,18] While this can reduce spending in the short term, it also compresses profit margins to the point that manufacturers may exit unprofitable lines, defer capital investment, or reduce redundancy in their operations.[18,44] Woodcock and Wosinska famously described this as a "race to the bottom" for generic sterile injectables, in which the market fails to reward quality or resilience and instead selects for minimal cost.[18]

For oncology medicines, this dynamic has been documented in both high-income and middle-income settings, where deep discounts and single-winner tenders for essential chemotherapy agents have been associated with recurrent shortages.[9,10,44] In some cases, consolidation among manufacturers or wholesalers leads to quasi-monopolies: a single company becomes responsible for most of the global supply of a critical drug, creating extreme vulnerability if that firm encounters financial, technical, or regulatory difficulty.[10, 18, 40]

**Table 1.** Key drivers of anticancer drug shortages across the supply chain

| Driver Category | Specific Factors | Affected Supply-Chain Node | Example Oncology Drugs | Reported Clinical/Policy Impacts |
|---|---|---|---|---|
| **Manufacturing & quality** | GMP failures, contamination, equipment breakdown | API and finished-product manufacturing | Methotrexate, cisplatin, doxorubicin [10, 18, 40] | Plant shutdowns; multi-country, prolonged shortages |
| **Economic & market** | Low tender prices, single-winner contracts, low margins | Manufacturers, wholesalers | Generic platinum agents, vincristine [10,18,40] | Exit of suppliers; reduced redundancy; higher shortage risk |
| **Demand-related** | New guidelines, indication expansions, off-label use | All nodes; forecasting and inventory planning | Cyclophosphamide, rituximab [23, 40, 41] | Sudden demand spikes; cascading shortages of substitutes |
| **Regulatory & policy** | Slow approval of new sites, import barriers, export bans | Regulators, national procurement | Multiple oncology injectables [23, 42] | Delayed mitigation; shortages shifted between countries |
| **Logistics & external shocks** | Pandemic-related delays, port congestion, geopolitical risk | Global transport, API sourcing | Various chemotherapies, targeted agents [23, 43] | Extended lead times, regional disruptions |
| **HIC vs LMIC structural gaps** | Weak cold chain, financing limits, import dependence | National systems in LMICs | Vincristine, vinblastine, tamoxifen [43, 44] | Longer duration and higher severity of shortages |

#### *3.1.3. Demand-related factors*

Not all shortages are driven by supply constraints; sudden or sustained increases in demand can outstrip production capacity. Demand surges may be triggered by new clinical guidelines, broader indications, or shifts in treatment paradigms– for example, when evidence supports moving a drug from later-line to first-line therapy.[23,41] Seasonal patterns, off-label use, or stockpiling behavior by institutions anticipating future scarcity can also destabilize the balance between supply and demand.[23, 37, 41]

In oncology, real-world data show that after shortages are announced, utilization patterns often become volatile: clinicians may temporarily increase orders as a hedge, or switch to substitute regimens that then themselves become at risk of shortage.[41] Recent population-level analyses have demonstrated that shortages can drive abrupt declines in initiation rates for the affected drugs and complex shifts in the use of therapeutic alternatives.[41]

#### *3.1.4. Regulatory and policy factors*

Regulation and policy can both mitigate and exacerbate shortages. On one hand, stringent quality oversight is essential to protect patients; on the other, slow or inflexible regulatory processes can delay the approval of new suppliers or alternative presentations, prolonging or deepening shortages once they occur.[10, 23]

Examples include lengthy procedures for adding new manufacturing sites, delays in mutual recognition of inspections across jurisdictions, and barriers to importing foreign-licensed products in emergencies.[42] In addition, price regulation and reimbursement rules, if not carefully designed, may unintentionally reinforce the low-price, low-margin environment that discourages investment in capacity for essential generics.[18, 44, 45]

Policy choices at national or regional level –such as export bans, stockpiling requirements, or preferential purchasing schemes– can also shift scarcity from one country to another rather than solving the underlying capacity problem.[42, 45] This has been highlighted in recent European and international assessments, which point to uneven legal frameworks, fragmented information systems, and insufficient tools for coordinated response to cross-border shortages.[42]

#### *3.1.5. Logistics and external shocks*

Finally, logistical disruptions and external shocks (e.g. pandemics, natural disasters, geopolitical tensions, trade restrictions) have emerged as major amplifiers of shortage risk. The COVID-19 pandemic stressed global freight capacity, disrupted air and sea transport, and led to lockdown-related production slowdowns, all of which contributed to rising numbers and longer durations of shortages.[23,43]

Because manufacturing of active pharmaceutical ingredients and finished oncology products is highly concentrated in a few countries, export restrictions, tariffs, or regional conflicts can rapidly curtail supply to entire world regions. Analyses from Colombia and other middle-income countries show that shortages surged during the pandemic, with manufacturing problems and few suppliers cited as dominant causes.[43] Similar patterns are described in OECD countries, where fragile supply chains and dependence on distant suppliers have been identified as systemic vulnerabilities.[42]

### *3.2. Differences between high-income and low-/middle-income settings*

Although the proximate drivers are broadly similar worldwide, their relative importance and impact differ sharply between high-income countries (HICs) and low- and middle-income countries (LMICs). In HICs, sophisticated procurement systems, stronger regulatory capacity, and higher purchasing power often allow health systems to mitigate or buffer shortages through alternative sourcing, imports, or substitution.[23, 40] Even so, surveys of oncology pharmacists in the United States and Europe report frequent shortages leading to delays, regimen changes, increased workload, and higher costs.[9, 40]

In LMICs, structural gaps magnify vulnerability at every tier of the supply chain. Many countries rely heavily on imports for both APIs and finished oncology products, while domestic manufacturing and fill–finish capacity is limited; weaknesses in cold-chain and last-mile distribution further increase the risk that available supplies do not reach oncology centers reliably.[43,44,46] Budget constraints and fragmented procurement can force institutions to select ultra-low-cost suppliers or purchase on a spot basis, increasing exposure to supply shocks.[44]

Studies from Latin America, South Asia, and Africa have documented shortages of core oncology drugs such as vincristine, vinblastine, cyclophosphamide, idarubicin, and tamoxifen, often lasting months to years and occurring against a backdrop of baseline under-availability of essential cancer medicines.[43, 44]

Global reviews of access to oncology drugs emphasize that in many LMICs, unavailability and unaffordability coexist: even when no formal shortage is reported, hospitals may simply not stock a drug due to cost, while during shortages, scarcer supplies preferentially flow to higher-income markets able to pay more [44].

Regulatory and information infrastructures can also be thinner: shortage reporting systems are often absent or non-transparent, pharmacovigilance and quality surveillance may be limited, and weak traceability increases the risk of substandard or falsified medicines entering the market during scarcity.[43,44,46] Oncology services may also have fewer feasible substitutes (e.g., limited access to newer agents, radiotherapy capacity constraints, or supportive-care gaps), meaning that the same shortage episode can translate into deeper clinical harm and longer disruption than in HICs.[47]

Addressing these structural constraints requires both supply-side and system-side actions. Policy options described in the global oncology access and supply-chain literature include: i) pooled procurement and framework agreements with multiple qualified suppliers to reduce single-source dependence; ii) minimum buffer stocks for a short list of high-criticality chemotherapy agents, paired with rotation and expiry management; iii) streamlined regulatory pathways for emergency importation and reliance on WHO-prequalified / strict-authority approvals to accelerate access to quality-assured alternatives; and iv) investments in basic data infrastructure for forecasting and inventory visibility (e.g., standardized consumption reporting from oncology pharmacies), which can support earlier mitigation and more equitable redistribution.[20,44,47]

### *3.3. Clinical and health-system consequences*

Across settings, anticancer drug shortages have consistent and profound clinical consequences. Surveys of oncology pharmacists and clinicians repeatedly report high rates of delayed chemotherapy administration, forced changes in regimen, dose reductions, or omission of planned cycles because the preferred drug is unavailable.[9,37,40] In some studies, more than 90% of institutions reported at least one such impact during a defined period.[9, 40]

These adaptations are not benign. Shortages may push clinicians to use regimens with less robust evidence, inferior efficacy, or greater toxicity, or to substitute oral for intravenous formulations with different pharmacokinetic profiles.[10,37,40] Although robust causal data are challenging to generate, observational analyses suggest that shortages can lead to decreased treatment initiation, lower adherence, and measurable changes in population-level utilization of affected drugs, with potential implications for survival and disease control [41, 43].

For health-care organizations, shortages create a substantial operational burden: pharmacy and clinical staff spend hundreds to thousands of hours annually tracking supplies, renegotiating with vendors, rewriting protocols, and informing patients about changes.[9,40] Shortages also drive up costs through the need to purchase more expensive alternatives, use of smaller vial sizes or imported products, and overtime labor dedicated to crisis management.[10, 23, 40]

Importantly, shortages can exacerbate inequities. Large, well-resourced cancer centers may be better positioned to secure scarce drugs – for example, by paying higher prices, leveraging group purchasing power, or compounding from bulk – leaving smaller or rural hospitals facing more frequent or longer stockouts.[10, 37, 44] Within countries and across borders, patients with fewer financial or social resources are more likely to experience treatment delays, cancellations, or substitutions. This inequitable pattern is particularly stark in LMICs, where shortages often overlay pre-existing gaps in access to even the most basic cancer treatments.[43, 44]

Understanding these drivers and patterns [Figure 1], including manufacturing and quality problems, economic and market forces, demand shocks, regulatory and policy constraints, and external disruptions, is essential for designing effective crisis-management strategies and long-term reforms, which are discussed in subsequent sections of the review.

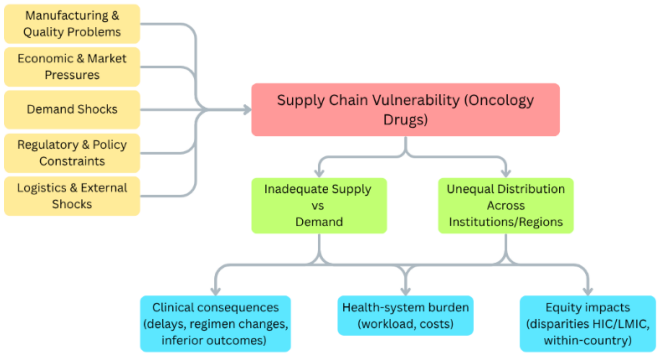


**Figure 1.** Key drivers and consequences of anticancer drug shortages across the supply chain.

## 4. Allocation and distribution strategies during shortages

When shortages of anticancer medicines occur, the question is no longer only why the supply chain failed, but how limited stock should be allocated fairly and effectively. In practice, allocation and distribution decisions are made at multiple levels, national or regional, health-system and hospital, and finally at the individual patient level, and involve a mix of logistical, clinical, and ethical considerations.[10,12,22] These strategies are summarized in Table 2 and range from centralized national stockpile allocation to bedside rationing and therapeutic substitution.

### *4.1. National and regional coordination mechanisms*

At the national and regional level, governments and regulators increasingly rely on centralized coordination structures to manage critical drug shortages. These may include national medicines-shortage task forces, formal notification systems, and central allocation of stock from strategic reserves.[10] For example, the ASHP guidelines and several European and UK documents describe structured processes that begin with early notification of a supply issue, followed by rapid risk assessment and, when needed, centralized redistribution or controlled allocation of remaining supplies.[32, 55]

Centralized approaches can take different forms. Some countries maintain national stockpiles or buffer inventories of essential medicines, including key oncology drugs, with predefined triggers for release and allocation formulas based on historical use, population needs, or burden of disease. Others use pooled procurement and framework contracts to secure supply for entire regions, which may give purchasers greater leverage to negotiate contingency clauses and multiple sourcing.[10] Policy analyses emphasize that stockpiles without transparent allocation rules risk reinforcing existing disparities if better-resourced institutions are still able to access additional supplies through separate channels.[48]

Another pillar at this level is the development of shortage reporting and early warning systems. National or regional databases, often maintained by regulators or professional societies, collate information on impending or current shortages and, in some cases, publish recommended alternatives and conservation strategies.[10] ASCO and other organizations now host clinical guidance pages that link real-time shortage data with suggested substitution regimens for specific tumor types, as seen during the recent carboplatin and cisplatin shortages.[12] These systems aim to move from reactive crisis management toward anticipatory planning, allowing hospitals to adjust inventories and treatment plans before stockouts occur.[12,56]

Finally, some jurisdictions have issued national ethical frameworks for allocating specific oncology drugs under crisis conditions. During the platinum shortage, for example, US states such as Minnesota published recommendations for prioritizing use of carboplatin and cisplatin based on intent of treatment, availability of alternatives, and potential impact on survival, to supplement local decision-making.[38]

### *4.2. Hospital and health-system strategies*

Within health systems, the frontline work of allocation and distribution is typically carried out by multidisciplinary drug shortage committees or equivalent structures. These groups often include pharmacists, oncologists, nurses, ethicists, and administrators, and are tasked with assessing the severity of the shortage, estimating projected demand, defining internal allocation rules, and communicating decisions to clinical teams.[22]

Guidance from ASCO, ASHP, and national organizations recommends a structured, stepwise process: confirm the shortage with reliable sources; characterize its expected duration and scope; inventory on-hand stock and outstanding orders; identify all indications and regimens that use the affected drug; explore therapeutic alternatives;

and then implement mitigation strategies such as conservation, substitution, and prioritization.[12,22] A simplified version of this process for a single hospital is illustrated in Figure 2, as a decision-making flowchart from shortage confirmation to final allocation and documentation.[12]

Key inventory management strategies at this level include: tightening control over ordering to prevent hoarding; redistributing stock within a health system; consolidating preparation in centralized pharmacies; and adjusting par levels for critical agents.[57] In addition, hospitals may adopt conservation practices such as vial sharing (preparing multiple patient doses from a single vial under sterile conditions), dose rounding to the nearest vial size within safe margins, and, in some cases, dose banding to standardize commonly used doses.[49-51] Evidence from oncology and critical care settings suggests that these strategies can substantially reduce waste and extend available stock without compromising clinical outcomes when used appropriately.[49-51]

Hospitals also play a central role in communication: clinicians and patients need timely, clear information about which drugs are affected, what changes are being made to regimens, and how long disruptions are expected to last.[12, 53] Poor communication can undermine trust and lead to inconsistent ad-hoc decisions across departments, whereas transparent institutional policies can promote fairness and reduce moral distress among clinicians.[22, 53]

**Table 2.** Allocation and rationing strategies for anticancer drugs during shortages

| Level | Strategy | Main advantages | Drawbacks / risks | Example context / guideline |
|---|---|---|---|---|
| National / regional | Centralized allocation of national stockpile based on burden of disease and historical use | Transparent, coordinated distribution; avoids competitive hoarding | Requires robust data and governance; may be slow to adapt | National stockpile policies, Brookings policy proposals [20] |
| | Pooled procurement and framework contracts with multiple suppliers | Increases bargaining power; encourages redundancy | Complex to implement; may disadvantage small suppliers | Regional or multi-country tenders [10, 48] |
| | Shortage reporting and early warning systems | Enables anticipatory planning by hospitals | Quality depends on timely, accurate reporting | ASCO clinical guidance pages; national shortage portals[12] |
| Hospital / health-system | Multidisciplinary drug shortage committee with formal decision process | Consistent, documented decisions; improves communication | Requires time and institutional support | ASCO and ASHP guidance for health systems[22] |
| | Conservation strategies: vial sharing, dose rounding, centralized preparation | Reduces waste; extends stock; potential cost savings | Requires strict sterility and safety controls; legal/regulatory concerns | Vial-sharing studies; NASEM recommendations[49-51] |
| | Internal redistribution and prioritization between sites in a system | Balances inequities within a network | May not address regional/national scarcity | Integrated cancer networks and hospital groups [52] |
| Patient level | Ethical triage frameworks (curative vs palliative, magnitude of benefit, lack of alternatives) | Promotes fairness and transparency; aligns with bioethical principles | Difficult conversations; potential moral distress | Unguru pediatric framework; ASCO ethical guidance[22, 38, 48] |
| | Restricting use to high-priority indications or stages | Preserves drugs for those most likely to benefit | Lower-priority patients lose access or receive inferior alternatives | State guidance for carboplatin/cisplatin allocation[38, 40] |
| | Shared decision-making and explicit informed consent about substitutions | Respects autonomy; may improve trust | Time-consuming; may be constrained by urgency | Ethical commentaries and patient-care guidance[53, 54] |

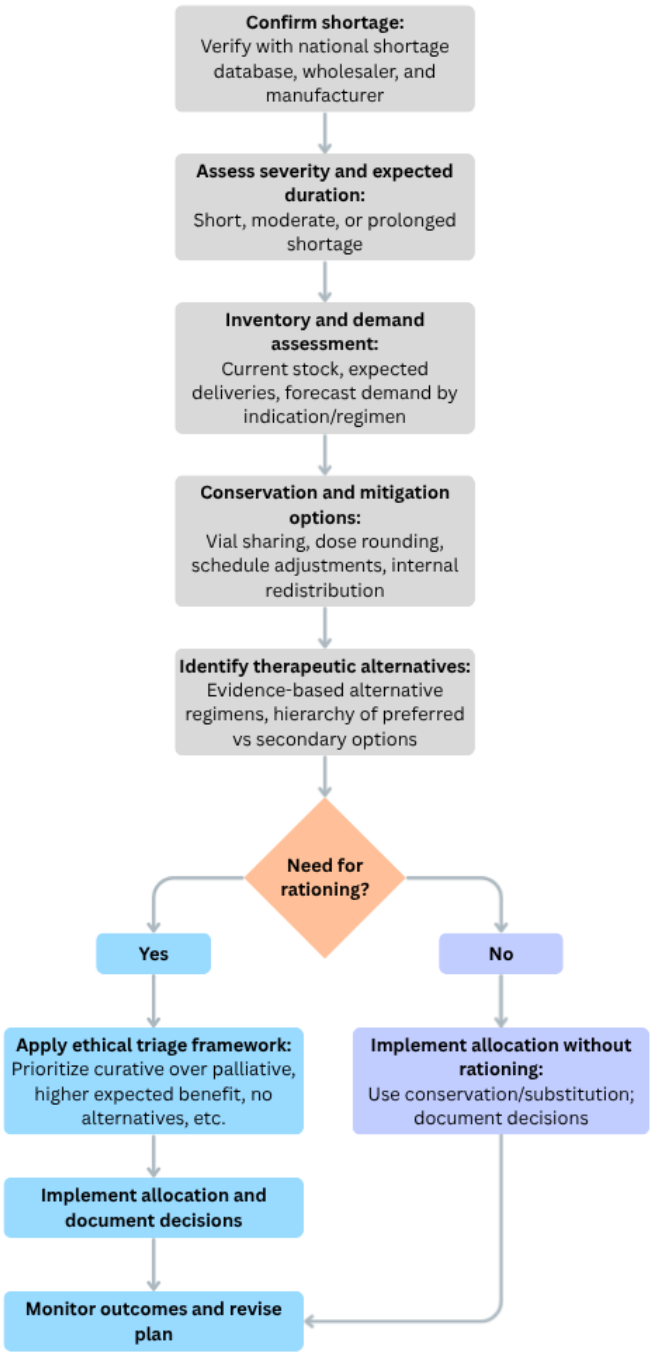


**Figure 2.** Stepwise process for hospital management and allocation of anticancer drugs in shortage situations.

### *4.3. Patient-level prioritization and ethical frameworks*

When conservation and redistribution are insufficient, hospitals must decide which patients receive scarce drugs and which do not. This is the most ethically charged aspect of oncology drug shortages. Empirical and normative work has proposed a range of criteria for patient-level prioritization, including: intent of treatment (curative vs palliative), magnitude of expected benefit, lack of effective alternatives, urgency, and vulnerability (e.g. pediatric patients, those with aggressive disease).[22, 40, 48, 56]

Unguru and colleagues, in a landmark JNCI paper on pediatric oncology, proposed a two-step allocation framework: first, mitigate the shortage by reducing waste and optimizing use (e.g. vial sharing, protocol adjustments); then, if scarcity persists, apply explicit ethical criteria to prioritize among eligible patients.[48] ASCO's recent ethical guidance for oncology drug shortages similarly recommends prioritizing curative over palliative indications, higher over lower expected benefit, and those without reasonable alternatives over those with comparably effective substitutes, while avoiding discriminatory criteria such as socioeconomic status or "first-come, first-served".[22]

Other authors have emphasized the importance of process values in rationing decisions: transparency, consistency, inclusiveness, and accountability.[38] Ethical commentaries on cancer drug shortages argue that allocation frameworks should be developed in advance, with input from patients and the public, and that decisions should be documented and open to review rather than made informally at the bedside.[38, 54]

In practice, institutions often combine clinical triage criteria (e.g. prioritizing adjuvant treatment with curative intent) with practical considerations such as treatment stage (those already on therapy vs new starts), availability of clinical trials, and the feasibility of safely substituting alternative regimens.[12,22,38] Some state and provincial health departments have issued drug-specific guidance, for example, for carboplatin and cisplatin, to support local clinicians in making difficult patient-level decisions during severe shortages.[38, 40]

### *4.4. Therapeutic substitution and regimen modification*

A core component of allocation and distribution strategies in oncology is therapeutic substitution – choosing alternative agents or regimens when the preferred drug is unavailable. ASCO's clinical guidance on oncology drug shortages outlines disease-site–specific alternatives for many commonly used antineoplastic drugs, developed by expert panels during the platinum shortage.[12,40,56] These alternatives often involve substituting drugs within the same class, switching to regimens of similar efficacy, or altering sequencing, while

attempting to preserve curative potential whenever possible.[10, 12, 40]

Substitution is not without risk. Alternatives may have weaker evidence, different toxicity profiles, or less favorable administration schedules, and may increase costs or logistical complexity.[10,51,53] Guidance documents strongly encourage clinicians to weigh risk–benefit trade-offs carefully, document the rationale for changes, and discuss options transparently with patients.[12,22,53,54] Observational data from shortage episodes indicate that regimen modifications can affect treatment intensity and may have downstream consequences for outcomes, although quantifying these effects is challenging.[10, 51]

In some cases, institutions may adopt hierarchies of substitution, defining "preferred" alternatives with similar efficacy and "secondary" options to be used only when preferred choices are unavailable.[40,51] Conservation strategies such as dose rounding and vial sharing can be combined with substitution to stretch supply: for example, conserving platinum agents for patients with no good alternatives while substituting in settings where other regimens provide comparable benefit.[40,49-51] By embedding these substitution and allocation policies within explicit ethical and clinical frameworks, health systems aim to navigate shortages in a way that is as safe, fair, and coherent as possible.

### *4.5. Examples of national and institutional strategies in practice*

While principles such as early warning, transparent allocation, and conservation are widely endorsed, several jurisdictions have operationalized these into concrete programs that can serve as practical examples. In the United States, FDA's Drug Shortages Program combines mandatory manufacturer notification, a public shortage database, and active mitigation actions. Depending on the public-health risk and the underlying cause, FDA may expedite review of manufacturing changes, prioritize inspections, exercise temporary regulatory flexibility, or facilitate temporary importation from FDA-registered foreign sources to increase availability.[58]

Canada provides an example of a national, publicly searchable shortage-reporting infrastructure. Since 2017, manufacturers are required to report actual and anticipated shortages and discontinuations, which are published via the Drug Shortages in Canada website and supported by federal guidance to enable earlier system response.[59]

In the European Union, EMA (European Medicines Agency) coordinates cross-border shortage preparedness and crisis response through the Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG) and related networks. EMA's European Shortages Monitoring Platform (ESMP) enables structured reporting and monitoring of supply, demand, and availability under routine conditions and during MSSG-led preparedness or crises.[60]

Oncology-specific allocation policies have also been issued at sub-national level. During the 2023 platinum shortage, for example, the Minnesota Department of Health published ethical allocation recommendations for carboplatin and cisplatin based on intent of therapy, magnitude of benefit, and availability of alternatives, providing a template that institutions could adapt locally. At the institutional level, repeatedly cited "high-yield" strategies include establishing a multidisciplinary drug-shortage committee, standardizing conservation practices (dose rounding, vial sharing, dose banding), centralizing preparation, and coordinating redistribution across sites within integrated cancer networks.[61] Evidence from vial-sharing and dose-rounding studies indicates that these approaches can reduce waste and extend limited supplies when implemented under strict sterility and safety controls.[62]

### *4.6. AI-enabled allocation and distribution: practical examples*

AI and advanced analytics can make the strategies above more operational and anticipatory by linking real-time data to specific triggers for conservation, redistribution, or substitution.

First, machine-learning–based early-warning tools can generate shortage-risk scores for high-criticality oncology injectables using routinely collected purchasing, inventory, lead-time, and supplier signals. Published models have demonstrated the feasibility of predicting upcoming shortages weeks in advance, creating a window for pre-emptive mitigation.[63]

Second, hospitals are increasingly building dashboards that integrate purchasing, on-hand inventory, and utilization data to produce near–real-time "days-of-supply" estimates for key chemotherapy agents; these can be coupled to predictive analytics to support earlier internal redistribution and regimen planning.[64]

Third, optimization and reinforcement-learning approaches can support allocation and distribution decisions under scarcity, for example, recommending how to split limited vials across services, when to trigger inter-facility transfers, or how to set dynamic reorder points to reduce the probability of stockouts while minimizing waste.[65]

Fourth, digital-twin concepts can be used as "what-if" sandboxes: a virtual representation of an oncology drug distribution network can simulate disruption scenarios (e.g., loss of a major supplier) and test how alternative triage rules or stockpile release policies affect stockouts and treatment delays before real-world deployment.[66]

Finally, AI-supported decision tools can be embedded into clinical workflows. During high-profile oncology shortages such as carboplatin/cisplatin, institutions can translate national guidance into rule-based order verification and prioritization, while simultaneously monitoring usage and outcomes through dashboards, provided that decisions remain transparent, ethically grounded, and subject to human oversight.[67]

## 5. Crisis management and supply chain resilience framework

Crisis management for anticancer drug shortages is not only about reacting to acute stockouts; it is about building a supply chain that can prevent, absorb, adapt to, and recover from disruptions. In the resilience literature, this lifecycle is often described with the PPRR model, Prevention, Preparedness, Response, Recovery, which has recently been applied to pharmaceutical and medical product supply chains in several countries.[20, 68, 69]

For anticancer medicines, whose high criticality and limited substitutes amplify the impact of failures, a structured PPRR approach provides a useful backbone for organizing policy and operational strategies.[20, 70]

Beyond traditional resilience measures, advances in AI, optimization, and digital technologies offer new tools for proactive risk management, real-time situational awareness, and adaptive allocation of scarce oncology drugs.[71-73]

Building on these strands, this section first outlines how the PPRR model can be tailored to anticancer drug shortages and then proposes an AI-enabled resilient anticancer drug supply chain framework, summarized conceptually in Figure 3.


**Figure 3.** AI-enabled crisis-management framework for anticancer drug supply chains.

### *5.1. Applying the PPRR structure to anticancer drug shortages*

#### *5.1.1. Prevention*

Prevention focuses on reducing the likelihood and severity of disruptions before they occur. At the pharmaceutical level, this involves supplier diversification, maintaining multiple qualified sources for active pharmaceutical ingredients and finished oncology injectables rather than relying on a single low-cost manufacturer.[20, 74]

Economic modeling and empirical analyses suggest that diversification – especially across countries and regions – can significantly increase resilience, even when it slightly increases unit costs.[74, 75]

For high-criticality anticancer medicines, strategic

redundancy in production capacity (e.g. dual sourcing of key APIs, second-fill sites) is a core preventive measure.[14, 20, 70]

Prevention also includes strengthening quality management systems to reduce the risk of contamination events or GMP failures that force plants to shut down. Lessons from recent contamination crises highlight the need for robust oversight of suppliers, more stringent testing of excipients and solvents, and better traceability of inputs in the global pharmaceutical supply network.[14,69,70]

In the economic domain, prevention may require incentives for resilience-oriented manufacturing, such as value-based reimbursement or contracts that reward reliable supply and quality rather than lowest price alone, especially for off-patent oncology injectables.[14,76]

#### *5.1.2. Preparedness*

Preparedness aims to ensure that, when disruptions occur, systems are ready to respond in a structured way. A first step is risk and vulnerability assessment, including mapping the anticancer drug portfolio against dimensions such as clinical criticality, number and location of suppliers, and complexity of manufacturing and logistics.[20, 68, 69]

Several recent frameworks use multi-criteria scoring and analytic hierarchy processes to evaluate resilience of medicine supply chains at national or institutional level, often incorporating the PPRR logic explicitly.[68, 69, 77]

Preparedness also encompasses strategic stockpiling and buffer inventories for selected high-criticality oncology drugs. National and institutional guidelines increasingly recommend differentiated stock targets: higher for curative regimens and essential pediatric agents, lower for palliative or easily substitutable drugs.[20, 70, 78]

At the same time, stockpiles must be accompanied by clear rotation policies and expiry management to avoid waste.

Another element is contingency planning and scenario exercises. Health systems can develop playbooks for plausible shocks – such as loss of a major platinum supplier, geopolitical export bans, or prolonged freight disruptions – and test response options through tabletop simulations or digital twins.[20]

Preparedness also entails strengthening governance structures (e.g. national task forces, hospital shortage committees) and training clinicians and pharmacists in ethical frameworks for allocation, so that triage principles are agreed before a crisis.[20, 70]

#### *5.1.3. Response*

Response covers the immediate and short-term actions taken once a shortage is detected. A central requirement is real-time situational awareness: accurate data on available stock, expected deliveries, and demand across regions and institutions.[20]

NASEM and HHS reports emphasize the need for interoperable shortage reporting systems and improved transparency around manufacturing disruptions and inventory levels.[14, 20]

Typical response measures include emergency procurement (e.g. importing equivalent products from other jurisdictions), dynamic reallocation of stock between hospitals, and implementation of conservation and substitution protocols as described in the previous section. For anticancer drugs, this may mean reserving scarce agents for indications where no alternatives exist, while switching to substitute regimens in settings where evidence supports equivalence.[20,70,73]

Communication is also a core response function: regulators, professional societies, and institutions must provide timely guidance to clinicians and patients on expected duration, recommended alternatives, and ethical principles guiding allocation.[20]

#### *5.1.4. Recovery*

Finally, recovery involves learning from each crisis and making structural changes to reduce future risk. Post-incident root-cause analyses can identify whether the primary drivers were quality failures, economic disincentives, regulatory delays, or external shocks, and which parts of the supply chain lacked redundancy or visibility.[14,20,78]

At a policy level, recovery might lead to revising tendering practices, adjusting reimbursement to reward resilient supply, or establishing new regulatory pathways for rapid approval of alternative suppliers.[76,78]

In oncology specifically, recovery should also include evaluating clinical and equity impacts of the shortage (e.g. delayed chemotherapy cycles, altered regimens, disparities

between centers) and using these findings to refine criticality lists, stockpile policies, and triage frameworks.[70,73].

Thus, PPRR is not a linear sequence but a learning cycle that gradually strengthens the resilience of anticancer drug supply chains.

### *5.2. An AI-enabled resilient anticancer drug supply chain framework*

While the PPRR model provides a conceptual backbone, AI, optimization, and digital technologies can act as powerful enablers at each stage. Recent reviews show rapidly growing interest in AI for pharmaceutical supply chain management, particularly for demand forecasting, inventory optimization, and anomaly detection.[71,72,79]

Building on this, we propose an AI-enabled resilient anticancer drug supply chain framework with five interacting components: 1) risk and vulnerability assessment, 2) proactive supply chain design, 3) real-time sensing and prediction, 4) adaptive allocation and distribution, and 5) governance, ethics, and learning [Figure 3].

Risk and vulnerability assessment can be enhanced by data-driven tools that integrate information on manufacturing locations, supplier dependency, quality histories, transportation routes, and clinical criticality of drugs [68, 69].

Machine-learning–based clustering and network analysis of supply chain graphs can help identify single points of failure and high-impact nodes for anticancer medicines, guiding where to invest in redundancy or monitoring.[68,73]

Proactive supply chain design uses optimization models to balance cost, service level, and resilience. Multi-objective models applied to pharmaceutical supply chains show how adding backup suppliers, regional warehouses, or flexible manufacturing capacity can significantly reduce disruption risk at modest additional cost.[69, 76]

For high-criticality oncology drugs, such models can be tailored to explicitly minimize the probability of global stockouts subject to budget constraints, or to maximize expected patient coverage under different disruption scenarios.

Real-time sensing and prediction is perhaps where AI has the most immediate potential. Studies of AI-enabled vendor-managed inventory (VMI) systems in hospitals show that integrating real-time consumption data with predictive algorithms can reduce stockouts and waste while improving inventory turns.[73]

Recent reviews report AI-based forecasting models that substantially outperform traditional time-series approaches in predicting medicine demand and flagging potential shortages.[71, 72]

In the context of anticancer drugs, such tools could combine epidemiologic trends, guideline changes, and historical utilization to identify emerging mismatches between supply and demand early enough for mitigation.

Adaptive allocation and distribution can leverage both optimization and digital twin technologies. Digital twins, virtual replicas of the physical supply chain that mirror inventory, flows, and constraints in near real time, allow stakeholders to simulate disruption scenarios and test alternative allocation policies before implementing them.[80]

For example, a digital twin of an oncology drug distribution network could be used to evaluate how different triage rules or stockpile release strategies affect hospital-level stockouts and patient-level delays under various disruption profiles. Optimization algorithms can then support decisions on how to route limited doses, when to trigger emergency imports, and how to coordinate redistribution between centers.

Finally, governance, ethics, and learning are essential to ensure that AI-enabled systems are used responsibly. Technical outputs (e.g. risk scores, demand forecasts, recommended allocations) must be interpreted in light of ethical frameworks for rationing lifesaving therapies, with human oversight and transparent documentation of decisions.[20]

Continuous monitoring and feedback mechanisms are needed to assess whether AI-supported decisions reduce inequities or inadvertently widen them, particularly between high-resource and low-resource cancer centers.

As illustrated schematically in Figure 3, these five components surround a central goal of "Resilient Anticancer Drug Supply", with AI and modeling acting as an enabling layer that supports all PPRR phases rather than replacing existing governance structures. This

integrated perspective underscores that digital technologies are not a standalone solution, but tools that, if designed and governed well, can strengthen the prevention, preparedness, response, and recovery capacities of anticancer drug supply chains.

## 6. Role of Artificial Intelligence in managing anticancer drug supply chains

AI and machine-learning (ML) are increasingly presented as key enablers for more resilient pharmaceutical supply chains, with the most mature applications in demand forecasting, inventory optimization, logistics, and risk management.[71,72,81,82] While the majority of published work addresses medicines in general, the underlying methods are directly relevant to anticancer drugs, which are typically high-criticality, hospital-based products with complex usage patterns and severe consequences if short.[72,81] In this section, we outline how AI can support management of anticancer drug supply chains along four main dimensions: demand forecasting and shortage prediction, inventory optimization and distribution, production and supplier risk, and decision-support systems including digital twins.

### *6.1. Demand forecasting and shortage prediction*

Conventional demand forecasting in oncology pharmacies relies on historical utilization, manual extrapolation from treatment protocols, and local expert judgement. These methods struggle to capture non-linear effects such as rapid uptake of new indications, shifting clinical guidelines, or epidemic-related disruptions. Recent systematic reviews of AI in pharmaceutical supply chains report that demand forecasting is one of the most developed and frequently studied use cases, with recurrent use of ML techniques such as random forests, gradient boosting, and deep learning architectures.[71, 72, 81, 82]

For drug supply chains in general, AI-based forecasting models have been shown to outperform classical time-series methods in terms of accuracy and responsiveness, especially when multiple heterogeneous data sources are integrated (e.g. sales, epidemiology, guideline changes, promotional events).[71, 72, 83] In the cancer setting, these inputs can be enriched with tumor-specific incidence trends, stage distributions, and protocol-level dose information, enabling models to anticipate shifts such as expansion of adjuvant indications or adoption of new combination therapies.

A particularly relevant development for anticancer drug management is the use of ML to predict shortages explicitly, rather than only forecasting demand. Pall and colleagues developed a machine-learning model using pharmacy purchasing and inventory data to classify which drugs were at high risk of shortage; gradient-boosted decision trees achieved substantially better performance than logistic regression in identifying upcoming shortages several weeks in advance.[25] Similar work from hospital pharmacy settings uses supervised ML models trained on transaction histories, lead times, and supplier behavior to flag products likely to experience supply disruption, allowing pre-emptive mitigation.[84, 85]

These approaches could be adapted to the subset of parenteral oncology injectables that have historically experienced recurrent shortages. By training models specifically on anticancer drug data, combining internal consumption patterns with external signals such as regulatory alerts, manufacturing incident reports, and international shortage notifications, health systems could generate an "oncology shortage risk score" for each molecule and presentation. Such scores could then trigger earlier stockpile release, therapeutic substitution planning, or escalation to national authorities before stockouts occur.[25, 81]

### *6.2. Inventory optimization and distribution*

Beyond predicting demand, AI can support more efficient and resilient inventory management across multiple echelons of the anticancer drug supply chain. Reviews of AI in pharmaceutical supply chain management describe numerous applications of ML and optimization algorithms to determine optimal reorder points, safety stocks, and replenishment policies, often in multi-echelon networks that include central warehouses, regional depots, and hospital pharmacies.[71, 72, 82, 86]

Nuta et al., highlight how reinforcement learning and stochastic optimization models can dynamically adapt ordering policies in response to real-time demand and lead-time variability, outperforming static rules such as fixed safety-stock thresholds.[82] Kaur and colleagues

propose an AI-driven intelligent inventory-replenishment strategy that uses predictive analytics to maintain high service levels while minimizing waste and overstock, demonstrating improved performance over conventional heuristics in a simulated pharmaceutical supply chain.[86]

At the hospital level, a systematic review of automation models in hospital pharmacy shows that AI-enabled systems integrated into automated dispensing and inventory platforms can reduce stockouts and improve inventory turnover, particularly when vendor-managed inventory (VMI) models are combined with predictive demand algorithms.[84] Dedicated studies of AI-driven inventory optimization in hospital pharmacies report better alignment of safety stocks with actual variability in use, lower expiries, and fewer manual emergency orders.[73]

In anticancer drug management, these capabilities are particularly valuable because many cytotoxic and biologic agents are expensive, have limited shelf-life, and are dispensed in patient-specific doses. AI-based inventory models can learn from historical compounding and dose-rounding patterns to set differentiated safety stocks, for example, higher buffers for drugs used in curative pediatric regimens and lower for rarely used salvage therapies, while still minimizing overall capital tied up in inventory. When extended to the distribution level, ML-driven routing and allocation algorithms can help decide which cancer centers receive limited quantities first, taking into account demand forecasts, current stock, travel times, and patient catchment areas.[72, 82, 87]

### *6.3. Production, quality, and supplier risk*

A major driver of anticancer drug shortages is manufacturing disruption and quality failure, particularly in sterile injectable plants. AI has been widely explored in pharmaceutical manufacturing for process monitoring, predictive maintenance, and quality control, and these tools can indirectly reduce shortage risk.[88]

Suri's review on AI in pharmaceutical manufacturing describes how advanced analytics, including neural networks and anomaly-detection algorithms, can detect subtle drifts in process parameters, predict equipment failure, and optimize process conditions in real time, thereby decreasing batch failures and unplanned downtime.[88] In parallel, digital quality-control systems using computer vision and ML can improve defect detection in vial filling, labeling, and packaging, increasing consistency and reducing the risk of costly recalls.

From a supply-chain perspective, several AI/ML reviews emphasize the role of supplier-risk scoring and network analytics in identifying single points of failure, such as critical oncology APIs sourced from a single geography or manufacturer.[72,81,89] By combining data on supplier performance, capacity, geopolitical risk, and quality histories, AI-driven risk models can help purchasers and regulators prioritize where to build redundant capacity or require contingency plans. These capabilities are highly relevant to anticancer drugs, where loss of a single high-volume plant can precipitate global shortages.[18, 90, 91]

### *6.4. Decision-support systems and digital twins*

Finally, AI can be embedded into higher-level decision-support systems, including digital twins of pharmaceutical supply chains. Digital twins are virtual replicas of the physical supply chain that mirror assets, inventories, flows, and constraints in near real time, enabling stakeholders to simulate disruption scenarios and test alternative responses before acting.[87, 89, 92]

Santos et al. developed an internal supply chain digital twin for a pharmaceutical company, showing that it could provide accurate estimates of capacity needs and support scenario analysis for demand surges and production changes.[87] Roman and colleagues, in a state-of-the-art review of digital twins in supply chains, highlight their utility in improving visibility, agility, and resilience, particularly by allowing decision-makers to experiment with different allocation, routing, and stockpiling policies in a safe virtual environment.[89] Recent work specific to wholesale pharmaceuticals argues that digital twins, when combined with AI/ML, can optimize operations from manufacturing to last-mile delivery and support proactive rescheduling in response to shocks.[92]

For anticancer drugs, a digital twin could represent the multi-tier network from API manufacturing through fill-finish to regional warehouses and oncology pharmacies, incorporating constraints such as cold-chain capacity, vial sizes, and protocol-based demand. AI algorithms layered on top of the digital twin could automatically evaluate, for

example, how different triage rules (prioritizing curative vs palliative indications), stockpile release thresholds, or emergency import policies affect rates of hospital-level stockouts and treatment delays under various disruption scenarios.[93]

Moreover, AI-enabled shortage-prediction models, when integrated into such a twin, could trigger early warning dashboards that suggest when to shift production, reroute shipments, or adjust allocation before shortages become clinically apparent.[25, 85] Conceptually, these systems align with calls from both AI and pharmaceutical ethics literature for "augmented decision-making", where algorithmic recommendations support, but do not replace, human judgement informed by ethical frameworks and clinical expertise.[81, 94]

## 7. Modeling approaches for allocation and distribution under shortage

Quantitative modeling provides a way to move from ad-hoc crisis responses toward explicit, analyzable policies for allocating and distributing scarce medicines. For anticancer drugs, modeling can complement clinical and ethical guidance by making trade-offs transparent: which patients receive limited vials, how stock is re-distributed across centers, and how supply-chain redesign affects the probability of future stockouts. Most existing models are developed for pharmaceutical products in general, yet the underlying methods -optimization, simulation, reliability and resilience modeling, and ethical/health-economic decision models- are directly applicable to oncology drug shortages and, in some cases, have already been instantiated for chemotherapy agents.[48, 95-101]

Below, we summarize these four main families of models and highlight their relevance to anticancer drug allocation during shortages. Conceptually, they can be viewed as complementary tools that address different questions along the shortage lifecycle, as schematically grouped in a classification figure (e.g. Figure X: "Classification of modeling approaches for allocation and supply-chain decisions under anticancer drug shortage").

### *7.1. Optimization models*

Optimization models, particularly mixed-integer linear programming (MILP) and two-stage stochastic programming, are widely used to design pharmaceutical supply chains and to plan production, inventory, and distribution under disruption risk. Mousazadeh et al., developed a bi-objective MILP with a robust possibilistic formulation for pharmaceutical supply chain network design, explicitly accounting for uncertain demand and disruption risk.[95] Goswami et al., proposed an integrated framework for modeling pharmaceutical supply chains that incorporates both disruptions (e.g. facility shutdowns) and mitigation strategies such as backup capacity or alternative routes, illustrating how optimization can quantify trade-offs between cost and resilience.[96]

Two-stage stochastic programming is particularly suited for allocation under uncertainty, where first-stage decisions (e.g. plant locations, base production levels, strategic inventory) must be made before demand and disruption scenarios are known, and second-stage recourse actions (e.g. emergency shipments, reallocations) adapt to realized conditions. Kungwalsong et al., formulated such a model for a four-echelon global supply chain network under facility disruption, demonstrating that explicitly modeling disruption scenarios leads to different -and more resilient- network designs than deterministic approaches.[97]

At the operational level, Nikzad et al., designed a two-stage stochastic medical drug inventory routing problem, motivated by evidence that inappropriate distribution and inventory policies contribute to drug shortages.[98] Their model determines optimal delivery routes and replenishment quantities to clinics under uncertain demand, with the objective of minimizing expected shortage and distribution cost. Similar MILP formulations have been proposed for integrated inventory planning across multiple echelons, where shortage penalties or minimum service levels are included in the objective function.[102]

In the context of anticancer drugs, these optimization models can be adapted to:[95-98, 102]

- prioritize which cancer centers receive limited vials of a chemotherapy agent,
- determine stockpiling levels and locations for high-criticality drugs, and

- evaluate the impact of adding redundant manufacturing sites or backup suppliers on expected shortages for generic oncology injectables.

### *7.2. Simulation models*

Optimization models typically assume steady-state behavior and simplified dynamics. In contrast, simulation approaches -including discrete-event simulation (DES), agent-based models (ABM), and system dynamics- are well suited for capturing the complex, time-dependent behavior of hospital systems and supply chains during a shortage. DES is now a standard tool in health services research to model patient flows, resource queues, and service processes.[103, 104] A recent MDPI review of DES in healthcare examined over 600 studies and documented increasing use of DES to analyze capacity, waiting times, and resource utilization in hospitals.[104]

For medicines specifically, Nabayiga et al. conducted a systematic review of simulation models in medicine supply chains, showing applications across inventory management, distribution network design, and disruption analysis.[26] Several studies use DES or hybrid simulation to test how alternative logistics policies (e.g. order-up-to levels, delivery frequencies, central vs. decentralized stock) affect stockout risk and costs in pharmaceutical distribution.[26,105] Gan et al., recently proposed a simulation-driven approach for quantifying medical resource shortages in a hospital alliance, using a computational model to estimate shortage degrees at each hospital and evaluate different allocation strategies within the alliance.[105]

Applied to anticancer drugs, DES or hybrid simulation can model patient arrival patterns, protocol-driven dosing, and ward capacity, and then simulate how specific shortage management strategies -dose capping, schedule delays, inter-hospital sharing, affect waiting times and missed cycles for different tumor types. Simulation also allows exploration of rare but high-impact disruption scenarios (e.g. sudden loss of a major supplier) without risking patient harm, offering a testbed for hospital or national policies before real-world implementation.[26, 103-105]

### *7.3. Reliability and resilience modeling*

A third strand of work focuses on reliability and resilience of pharmaceutical supply networks, often combining probabilistic models with optimization. Tucker and Daskin introduced what is arguably the first explicit pharmaceutical supply chain reliability model, estimating expected shortages, time-to-shortage, and time-to-recovery under different network configurations.[27] Using data from major drug-shortage databases and a case example of a generic injectable oncology drug, they showed that adding a backup supplier or improving recovery speed can substantially reduce expected shortage frequency, albeit at some cost.[27]

Complementary work by Bastani et al., developed a resilience model for pharmaceutical and medical device supply chains during disasters, identifying behavioral and organizational determinants (e.g. governance, information infrastructure) that influence responsiveness.[106] Although qualitative, this framework can be linked with quantitative reliability models by treating resilience dimensions as parameters that affect disruption rates and recovery times. Together, such models help policymakers evaluate which resilience investments (e.g. redundancy, flexibility, information systems) yield the greatest reduction in shortage risk for critical drug classes, including anticancer agents.[27, 106]

### *7.4. Ethical and health-economic models*

Finally, several modeling studies explicitly integrate ethical principles and patient outcomes into allocation decisions for scarce cancer medicines. In pediatric oncology, Unguru et al. proposed a normative, two-step ethical framework for allocating life-saving chemotherapy and supportive care drugs during shortages, combining strategies to minimize waste with prioritization based on modified utilitarian criteria (maximizing total benefit while respecting limits on differential treatment).[48] Building on this, Russell et al. developed a decision-analytic model to guide allocation of a scarce chemotherapy drug in a pediatric cancer service, comparing first-come–first-served, age-based, and efficiency-based strategies under different shortage severities.[99] Their analysis showed that no policy is costless: each improves outcomes for some patients while worsening them for others, illustrating the value of modeling to make such trade-offs explicit.[99]

More recently, Hantel et al., constructed a stochastic modeling framework to compare alternative allocation strategies during intermittent chemotherapy shortages in adults.[100] Using simulated patient cohorts and treatment pathways, they estimated overall survival under policies that prioritize, for example, patients with curative intent, those with the fewest alternative regimens, or a first-come–first-served rule. The model demonstrated that prioritizing patients with curative intent and limited alternatives can improve population survival compared with default allocation, while still raising important questions about fairness.[100] In a companion perspective, the same group argued that simulation and decision modeling can provide "model solutions" that make ethical goals -such as maximizing benefit, promoting equity, and respecting procedural justice- operational in the context of cancer medicine shortages.[101]

These ethical and health-economic models are directly relevant for anticancer drug shortages because they bridge qualitative ethical guidance with quantitative outcomes, enabling clinicians, ethicists, and policymakers to test how different prioritization rules, substitution thresholds, or stockpile release policies might affect survival, quality-adjusted life years, and equity across patient groups.[48,99-101] When combined with the optimization, simulation, and reliability models described above, they contribute to a more complete toolbox for designing allocation and distribution strategies that are not only efficient and resilient, but also ethically defensible.

## 8. Management and Policy Implications

Translating evidence on anticancer drug shortages into action requires a multi-level strategy that aligns national and international policy (macro), health-system and hospital governance (meso), and day-to-day practice of clinicians, pharmacists, and patients (micro). Recent work on oncology drug shortages and broader medicine supply chains converges on the view that piecemeal fixes are insufficient; durable solutions require coordinated reforms across these levels, informed by data, modeling, and ethical frameworks.[10, 23, 42, 107]

### *8.1. Macro level: National and international policy*

At the macro level, oncology drug shortages expose structural weaknesses in pricing, industrial policy, and international coordination. Analyses of anticancer drug shortages in high-income countries highlight how aggressive tendering and low reimbursement for generic injectable chemotherapy erode manufacturers' margins, discourage investment, and promote market exit, particularly for cytotoxic and platinum-based agents.[10,23] Policy proposals increasingly argue for "resilience-oriented" pricing and reimbursement, in which payers reward reliable supply, quality, and redundancy (e.g. multiple qualified sites) rather than purely the lowest unit price.[10, 81, 107]

The OECD Health Policy Studies report "Securing Medical Supply Chains in a Post-Pandemic World" recommends that countries identify critical medicines (including many oncology drugs) and ensure diversified sourcing, minimum domestic or regional production capacity, and contractual incentives for buffer inventories and business continuity planning.[107] These recommendations echo findings from a recent scoping review, which concluded that many current interventions remain reactive and that proactive measures, such as industrial incentives, greater transparency, and regional collaboration, are underused.[42]

Macro-level policy should also include national or regional stockpiles for selected high-criticality anticancer medicines, with explicit criteria for inclusion, rotation policies, and release triggers. Evidence from pandemic-era disruptions suggests that stockpiles are most effective when embedded in a wider governance framework that links them to early warning systems and cross-border solidarity mechanisms, rather than being hoarded nationally.[107, 108]

Internationally, oncology drug shortages have prompted calls for better data sharing and coordinated response. Malta and colleagues argue for global platforms that integrate regulatory alerts, shortage notifications, and manufacturing incidents to support joint action by regulators, professional societies, and civil society.[10] The OECD similarly emphasizes that long-term resilience depends on collaboration between governments and industry, including transparent mapping of supply chains, shared risk assessments, and joint investments in critical

capacity [107]. For low- and middle-income countries, systematic reviews highlight the need to align global policies with local realities, where fragile financing and dependence on imports magnify the impact of global oncology shortages.[23, 46]

### *8.2. Meso level: Health-system and hospital governance*

At the meso level, health systems and hospitals are where policies become operational. Scoping and narrative reviews consistently identify institutional governance structures, such as multidisciplinary drug-shortage committees, standardized operating procedures (SOPs), and integrated information systems, as central to effective management.[23,42] These committees typically include oncology pharmacists, clinicians, ethicists, and administrators, and are responsible for risk assessment, internal allocation rules, and communication.

Hospitals are encouraged to implement formal shortage management protocols that specify steps from early detection and verification of a shortage, through inventory review, conservation measures, therapeutic substitution, and (if needed) triage decisions.[23,109] Experience from cancer centers suggests that such protocols reduce variability, increase transparency, and mitigate moral distress among staff when difficult allocation decisions must be made.[81, 109]

Data infrastructure is another meso-level priority. Cornelissen et al. note that many published interventions lack robust monitoring and evaluation, and call for dashboards that integrate purchasing, inventory, and utilization data to support proactive management.[42] Advanced centers are starting to link these dashboards with predictive analytics, allowing pharmacy teams to see projected days-of-stock for key oncology drugs and to coordinate redistribution within networks before crises escalate.[81, 82]

Health-system policies also need to address equity across institutions. Surveys show that large academic centers are often better able to secure limited oncology drugs than smaller or community practices, raising concern about uneven access within the same health system.[108] Regional cancer networks and group purchasing arrangements can be leveraged to create solidarity mechanisms, such as central coordination of scarce vials and explicit criteria for inter-facility transfers, to prevent systematic disadvantage of smaller centers.

### *8.3. Micro level: Clinician, pharmacist, and patient practices*

At the micro level, policy translates into clinical behavior, patient experience, and shared decision-making. Qualitative and editorial work in oncology emphasizes that drug shortages are not purely logistical events; they profoundly affect the therapeutic relationship and patients' trust in the health system.[108]

Faiman, writing for advanced oncology practitioners, stresses the need for transparent communication with patients about the nature of the shortage, the rationale for any treatment change, and the expected impact on prognosis, as well as documentation of discussions in the medical record.[108] Pathak and colleagues similarly argue that structured patient education can mitigate anxiety and support adherence when regimens are modified or delayed because of cancer drug shortages.[109,110] Early evidence suggests that patients prefer management strategies that are openly disclosed and discussed early in the course of treatment, even when decisions are difficult.[110]

Beyond information-giving, shortages create a natural setting for shared decision-making (SDM), where clinicians and patients jointly consider alternative regimens, weigh trade-offs between efficacy and toxicity, and align choices with patient values.[108,111] However, systematic reviews of SDM in oncology highlight persistent barriers, including time pressure, uncertainty, and limited training.[111] Embedding decision aids and communication training into shortage preparedness plans can help clinicians navigate these conversations more consistently and equitably.

Pharmacists, meanwhile, play a frontline role in implementing conservation strategies (dose rounding, vial sharing, centralized compounding) and in verifying the safety and feasibility of therapeutic substitutions. Policy documents increasingly recognize clinical oncology pharmacy as a key component of "oncology stewardship," with responsibilities that extend beyond technical dispensing to stewardship of scarce anticancer drugs.[108, 109].

### *8.4. Integrating AI and modeling into policy design*

Finally, there is growing consensus that AI and quantitative modeling should be embedded into policy-making, not just technical operations. Recent reviews of AI and machine learning in pharmaceutical supply chains show how predictive models can identify high-risk products, optimize safety stocks, and simulate disruption scenarios.[81,82,112] For oncology, national or regional shortage monitoring platforms could integrate real-time utilization and inventory data with AI-based early-warning algorithms, flagging increased risk of shortage for specific chemotherapies and triggering predefined escalation pathways.

At the macro level, outputs from stochastic and optimization models can inform industrial and procurement policy; for example, quantifying how much domestic or regional capacity for generic oncology injectables is needed to keep expected shortage frequency below a target threshold, or what level of supplier diversification balances cost and resilience.[10, 81, 107] At the meso level, simulation models of hospital networks can test alternative allocation rules and inter-facility sharing mechanisms before they are written into policy. At the micro level, digital tools and decision aids, potentially supported by AI, can help embed ethical triage criteria and SDM principles into everyday clinical practice rather than leaving decisions to informal bedside discretion.[108, 111-113]

## 9. Research Gaps and Future Directions

Despite a rapidly expanding literature on drug shortages and pharmaceutical supply chains, important knowledge gaps remain, especially for anticancer medicines. Existing reviews consistently highlight that evidence is fragmented, dominated by high-income settings, and often focused on descriptive case reports rather than robust, comparative or model-based analyses.[42,45,114] This limits our ability to design, test, and scale solutions that are both clinically effective and systemically resilient.

### *9.1. Data gaps and measurement challenges*

A first and fundamental gap is the lack of high-quality, standardized data on oncology drug shortages and supply flows, particularly in low- and middle-income countries (LMICs). Global reviews and expert commentaries describe substantial barriers to accessing cancer medicines in LMICs but also note that empirical data on the frequency, duration, and clinical impact of shortages are sparse and heterogeneous.[43, 44, 47] For example, Sabogal De La Pava and Tucker's case study from Colombia shows how even basic metrics, such as the duration of shortages and the classes of affected drugs, are difficult to compile systematically, and are rarely linked to downstream patient outcomes.[43] Similar observations arise from broader scoping and systematic reviews, which find that shortage surveillance systems are concentrated in North America and Europe, use differing definitions, and often lack detailed information on oncology-specific stockouts.[42,45,114].

Closely related is the absence of agreed metrics for "resilience" and "severity" of drug shortages. A recent HHS/ASPE report on measuring supply chain resilience notes that there is no consensus on core indicators (e.g. time-to-recover, maximum tolerable downtime, redundancy indices) or on how to operationalize resilience for generic injectables and biologics.[115] In parallel, reliability modeling of pharmaceutical supply chains, such as Tucker and Daskin's work on generic injectable oncology drugs, depends on assumptions about disruption probabilities and recovery rates that are difficult to validate in the absence of standardized data.[27] Future research needs to develop harmonized severity scales and resilience indicators specific to oncology medicines, ideally co-designed by regulators, payers, and clinicians, and integrated into national or international shortage reporting systems.[27, 114, 115]

### *9.2. Limited integration of AI prediction with allocation and policy models*

Another prominent gap is the disconnection between predictive AI models and decision-making frameworks. Machine-learning tools have demonstrated promising performance in predicting upcoming drug shortages using pharmacy sales and inventory data.[25] Pall et al.'s model, for example, was able to anticipate shortage status one month in advance across a large set of drugs using routinely collected community-pharmacy data [25]. However, most such models stop at prediction: they do not specify how these forecasts should feed into concrete

allocation, stockpiling, or procurement decisions at national or institutional level.[45, 114]

Conversely, optimization and stochastic programming models for supply-chain design and inventory routing propose sophisticated strategies to minimize expected shortage risk or cost under disruption scenarios, but typically assume exogenous probabilities or scenario structures rather than linking them to real-time predictive analytics.[27] There are almost no published examples where AI-based shortage prediction is embedded within an optimization or simulation framework that then recommends dynamic allocation rules for scarce anticancer drugs. Bridging this gap, through integrated AI–operations research architectures that couple prediction with explicit, ethically informed decision rules, is an important frontier for research and for translational work with regulators and health systems.[25, 27, 114]

### *9.3. Patient-level outcomes, equity, and ethics in modeling*

A third set of gaps relates to the limited incorporation of patient-level outcomes and equity considerations into quantitative models of oncology drug allocation. Ethical frameworks for prioritizing scarce chemotherapy and supportive drugs, such as the one proposed by Unguru et al., for childhood cancer, articulate values like maximizing benefit, treating people equally, and giving priority to the worst-off.[48] Subsequent modeling studies, such as Russell et al.'s decision model for pediatric chemotherapy allocation and Hantel et al.'s stochastic model of intermittent chemotherapy shortages, demonstrate that different allocation rules yield meaningfully different survival outcomes.[99, 100]

Yet, these models are relatively few, often focused on specific pediatric or hematologic contexts, and rarely linked with real-world data on survival, toxicity, or quality of life.[48,99,100] Tucker's "Drug Shortage Era" scoping review notes that most empirical studies still focus on process metrics (e.g. treatment delay, regimen change) rather than patient-centered outcomes, and almost none examine distributional effects across socioeconomic or racial groups.[114] Future work should combine real-world outcome data, health-economic modeling, and ethical analysis to evaluate how alternative prioritization and substitution policies affect survival, toxicity, and equity across cancer populations. This includes designing prospective or quasi-experimental studies around natural experiments when shortages occur, rather than relying solely on hypothetical scenarios.[48, 99, 100, 114]

### *9.4. Digital twins and real-time data integration*

The rapid development of digital twin (DT) technologies in healthcare presents another underexplored opportunity. Recent scoping reviews show a proliferation of digital twin applications in precision medicine, clinical operations, and health-system management, but few, if any, implementations focused on medicine supply chains or oncology drug allocation.[93,116] Katsoulakis et al. highlight the potential of DTs to integrate real-time data streams, simulate complex systems, and test "what-if" scenarios for health services, while also emphasizing major challenges in data governance, interoperability, and validation.[116] Elkefi and Asan similarly conclude that most DT projects remain conceptual or pilot-scale, with limited evidence on their impact on decision-making and outcomes.[93]

For anticancer drug shortages, there is a clear research gap in developing and validating digital twins of multi-tier oncology supply chains that integrate manufacturing, distribution, and hospital pharmacy data, along with AI-based demand and shortage forecasts. Such twins could be used as experimental sandboxes to evaluate triage rules, stockpile triggers, and emergency import policies before real-world deployment. Research questions include how to represent ethical priorities within DT-driven decision-support systems, how to calibrate models with incomplete or noisy data, and how to ensure that DT-enabled policies do not inadvertently worsen inequities between centers or countries.[10, 93, 116]

### *9.5. Global and implementation perspectives*

Finally, there is a broad need for implementation research and cross-country comparative studies. Barrios et al. describe access to oncology drugs as a "global crisis," but note that evidence on the effectiveness of specific interventions (e.g. pooled procurement, regional stockpiles, managed entry agreements) is limited and highly context-dependent.[4] Case studies from LMICs, including Colombia, underscore that national financing,

regulatory capacity, and health-system organization strongly shape how global oncology shortages translate into local patient harm, yet these factors are only superficially explored in most models.[43, 47]

Scoping and systematic reviews repeatedly call for more robust evaluation of policies and organizational innovations, including before–after analyses, natural experiments, and mixed-methods studies that capture both quantitative outcomes and stakeholder experiences.[42,43,45] Future research should prioritize multi-country consortia that combine data, modeling, and qualitative inquiry, with particular attention to under-represented regions. Such work is essential to ensure that proposed AI tools, digital twins, and resilience metrics are not only methodologically sophisticated, but also feasible, acceptable, and beneficial across diverse oncology care contexts.[10, 42-45, 47, 93, 114, 116]

## 10. Conclusions

Anticancer drug shortages arise from the intersection of structural vulnerabilities, concentrated manufacturing, fragile economics for sterile generics, long lead times, and cold-chain constraints, and external shocks such as pandemics, geopolitical frictions, and transport disruptions. Their clinical and organizational consequences are profound: treatment delays, suboptimal substitutions, increased workload and costs, and widening inequities across and within health systems. A purely reactive posture is inadequate for products with high criticality and limited substitutes. This review proposes an integrated framework that couples a multi-level governance approach (macro policy, meso health-system operations, micro clinical practice) with the resilience cycle of Prevention–Preparedness–Response–Recovery. At the macro level, resilience-oriented procurement and industrial policy (diversified suppliers, strategic stockpiles, quality and continuity incentives) should be paired with transparent, interoperable shortage surveillance. At the meso level, hospitals need formal playbooks, multidisciplinary shortage committees, and data infrastructure for anticipatory redistribution, conservation, and ethical triage. At the micro level, consistent communication and shared decision-making are essential to sustain trust when substitutions or prioritization are unavoidable. AI and quantitative modeling can accelerate this shift from ad hoc crisis management to principled, data-driven decisions: forecasting demand and shortage risk; optimizing multi-echelon inventories and routing; supporting ethical allocation through decision-analytic models; and testing policies in digital twins before real-world deployment. Yet, these tools require trustworthy data, robust governance, and explicit safeguards for fairness. Finally, closing evidence gaps -especially in low- and middle-income settings, demands harmonized metrics for shortage severity and resilience, prospective evaluations of allocation policies, and cross-country collaboration. The framework articulated here offers a practical scaffold for policy and operations, and a roadmap for research that strengthens resilience while preserving equity and clinical benefit in oncology care.

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**Competing interests**

The authors declare that they have no competing interests.

**Abbreviations**

Active Pharmaceutical Ingredient: API; Good Manufacturing Practice: GMP; High-Income Countries: HICs; Low- and Middle-Income Countries: LMICs; National Academies of Sciences, Engineering, and Medicine: NASEM; Organisation for Economic Co-operation and Development: OECD; American Society of Clinical Oncology: ASCO; American Society of Health-System Pharmacists: ASHP; U.S. Food and Drug Administration: FDA; European Medicines Agency: EMA; Executive Steering Group on Shortages and Safety of Medicinal Products: MSSG; European Shortages Monitoring Platform: ESMP; Prevention, Preparedness, Response, Recovery: PPRR; U.S. Department of Health and Human Services: HHS; Office of the Assistant Secretary for Planning and Evaluation: ASPE; Artificial Intelligence: AI; Machine Learning: ML; Vendor-Managed Inventory: VMI; Mixed-Integer Linear Programming: MILP; Discrete-Event Simulation: DES; Agent-Based Models: ABMs; Shared Decision-Making: SDM.

### Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.


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By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

## References


1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-63. doi:10.3322/caac.21834 PMid:38572751
2. Bizuayehu HM, Ahmed KY, Kibret GD, Dadi AF, Belachew SA, Bagade T, et al. Global Disparities of Cancer and Its Projected Burden in 2050. JAMA Netw Open. 2024;7(11):e2443198. doi:10.1001/jamanetworkopen.2024.43198 PMid:39499513 PMCid:PMC11539015
3. Robertson J, Barr R, Shulman LN, Forte GB, Magrini N. Essential medicines for cancer: WHO recommendations and national priorities. Bull World Health Organ. 2016;94(10):735-42. doi:10.2471/BLT.15.163998 PMid:27843163 PMCid:PMC5043203
4. Jenei K, Aziz Z, Booth C, Cappello B, Ceppi F, de Vries EGE, et al. Cancer medicines on the WHO Model List of Essential Medicines: processes, challenges, and a way forward. Lancet Glob Health. 2022; 10(12):e1860-e6. doi:10.1016/S2214-109X(22)00376-X PMid:36183737
5. Metzger ML, Billett A, Link MP. The impact of drug shortages on children with cancer--the example of mechlorethamine. N Engl J Med. 2012;367(26):2461-3. doi:10.1056/NEJMp1212468 PMid:23268661
6. Becker DJ, Talwar S, Levy BP, Thorn M, Roitman J, Blum RH, et al. Impact of oncology drug shortages on patient therapy: unplanned treatment changes. J Oncol Pract. 2013;9(4):e122-8. doi:10.1200/JOP.2012.000799 PMid:23942928 PMCid:PMC3710178
7. Gatesman ML, Smith TJ. The Shortage of Essential Chemotherapy Drugs in the United States. N Engl J Med. 2011;365(18):1653-5. doi:10.1056/NEJMp1109772 PMid:22040130
8. Eid D, Jabbour J, Moujaes E, Kourie HR, Safieddine M, Kattan J. Impact of the economic crisis and drug shortage on Lebanese cancer patients' care. World J Clin Oncol. 2024;15(5):644-52. doi:10.5306/wjco.v15.i5.644 PMid:38835845 PMCid:PMC11145953
9. McBride A, Hudson-DiSalle S, Pilz J, Hamm M, Boring B, Buie LW, et al. National Survey on the Effect of Oncology Drug Shortages in Clinical Practice: A Hematology Oncology Pharmacy Association Survey. JCO Oncol Pract. 2022;18(8):e1289-e96. doi:10.1200/OP.21.00883 PMid:35544740
10. Malta M, Christian M, Cadwallader AB. Oncology Drug Shortages: Impacts, Policy Reforms, and Advocacy Imperatives. Cancer J. 2025;31(5). doi:10.1097/PPO.0000000000000784 PMid:41002877 PMCid:PMC12459138
11. Jenei K, Lythgoe MP, Vokinger KN. Shortages of essential cancer medicines: who is responsible and what are the possible solutions? Lancet Oncol. 2024;25(1):23-6. doi:10.1016/S1470-2045(23)00470-9 PMid:38181805
12. Santos ES, Oliver TK, Lacchetti C, Geisel R, Wilfong LS, Fader AN, et al. Drug Shortages in Oncology: ASCO Clinical Guidance for Alternative Treatments. JCO Oncol Pract. 2023;20(1):19-32. doi:10.1200/OP.23.00545 PMid:37963306
13. Goldsack JC, Reilly C, Bush C, McElligott S, Bristol MN, Motanya UN, et al. Impact of shortages of injectable oncology drugs on patient care. Am J Health Syst Pharm. 2014;71(7):571-8. doi:10.2146/ajhp130569 PMid:24644117
14. Ventola CL. The drug shortage crisis in the United States: causes, impact, and management strategies. P T. 2011;36(11):740-57.
15. Caulder CR, Mehta B, Bookstaver PB, Sims LD, Stevenson B. Impact of Drug Shortages on Health System Pharmacies in the Southeastern United States. Hosp Pharm. 2015;50(4):279-86. doi:10.1310/hpj5004-279 PMid:26448658 PMCid:PMC4589883
16. Reich L, Knopf KB. The Oncology Drug Shortages and Its Impact on Community Hospitals. Cancer J. 2025;31(5). doi:10.1097/PPO.0000000000000794 PMid:41002879
17. Cherny NI, Sullivan R, Torode J, Saar M, Eniu A. ESMO International Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in countries outside of Europe. Ann Oncol. 2017;28(11):2633-47. doi:10.1093/annonc/mdx521 PMid:28950323 PMCid:PMC5834140
18. Woodcock J, Wosinska M. Economic and technological drivers of generic sterile injectable drug shortages. Clin Pharmacol Ther. 2013; 93(2):170-6. doi:10.1038/clpt.2012.220 PMid:23337525
19. McLaughlin M, Kotis D, Thomson K, Harrison M, Fennessy G, Postelnick M, et al. Empty shelves, full of frustration: consequences of drug shortages and the need for action. Hosp Pharm. 2013; 48 (8): 617-8. doi:10.1310/hpj4808-617 PMid:24421528 PMCid:PMC3847976
20. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on Security of America's Medical Product Supply Chain. In: Shore C, Brown L, Hopp WJ, editors. Building Resilience into the Nation's Medical Product Supply Chains. Washington (DC): National Academies Press (US); 2022.
21. Socal MP, Acha J, Yang CY, Sun Y, Dada M, Dai T, et al. Key Drivers and Mitigation Strategies of Oncology Drug Shortages 2023 to 2025. Cancer J. 2025;31(5). doi:10.1097/PPO.0000000000000791 PMid:41002876 PMCid:PMC12459136
22. Hantel A, Spence R, Camacho P, Bradbury AR, Denburg AE, Jagsi R, et al. ASCO Ethical Guidance for the Practical Management of

Oncology Drug Shortages. J Clin Oncol. 2024;42(3):358-65. doi:10.1200/JCO.23.01941 PMid:38061010
23. Shukar S, Zahoor F, Hayat K, Saeed A, Gillani AH, Omer S, et al. Drug Shortage: Causes, Impact, and Mitigation Strategies. Front Pharmacol. 2021;12:693426. doi:10.3389/fphar.2021.693426 PMid:34305603 PMCid:PMC8299364
24. Franco C. A simulation model to evaluate pharmaceutical supply chain costs in hospitals: the case of a Colombian hospital. Daru. 2020;28(1):1-12. doi:10.1007/s40199-018-0218-0 PMid:30565158 PMCid:PMC7214596
25. Pall R, Gauthier Y, Auer S, Mowaswes W. Predicting drug shortages using pharmacy data and machine learning. Health Care Manag Sci. 2023;26(3):395-411. doi:10.1007/s10729-022-09627-y PMid:36913071 PMCid:PMC10009839
26. Nabayiga H, Meer RVD, Agha MSA. A systematic review of simulation models in medicine supply chain management: Current state and emerging trends. Decis Anal J. 2025;14:100555. doi:10.1016/j.dajour.2025.100555
27. Tucker EL, Daskin MS. Pharmaceutical supply chain reliability and effects on drug shortages. Comput Ind Eng. 2022;169:108258. doi:10.1016/j.cie.2022.108258
28. Aronson JK, Heneghan C, Ferner RE. Drug shortages. Part 2: Trends, causes and solutions. Br J Clin Pharmacol. 2023;89(10): 2957-63. doi:10.1111/bcp.15853 PMid:37455465
29. Donohue JM, Angus DC. National Shortages of Generic Sterile Injectable Drugs: Norepinephrine as a Case Study of Potential Harm. JAMA. 2017;317(14):1415-7. doi:10.1001/jama.2017.2826 PMid:28322412
30. Yu YB, Briggs KT, Taraban MB, Brinson RG, Marino JP. Grand Challenges in Pharmaceutical Research Series: Ridding the Cold Chain for Biologics. Pharm Res. 2021;38(1):3-7. doi:10.1007/s11095-021-03008-w PMid:33555493 PMCid:PMC7869771
31. Pauwels K, Simoens S, Casteels M, Huys I. Insights into European drug shortages: a survey of hospital pharmacists. PLoS One. 2015; 10 (3):e0119322. doi:10.1371/journal.pone.0119322 PMid:25775406 PMCid:PMC4361582
32. Fox ER, McLaughlin MM. ASHP guidelines on managing drug product shortages. Am J Health Syst Pharm. 2018;75(21):1742-50. doi:10.2146/ajhp180441 PMid:30061155
33. Aronson JK, Heneghan C, Ferner RE. Drug shortages. Part 1. Definitions and harms. Br J Clin Pharmacol. 2023;89(10):2950-6. doi:10.1111/bcp.15842 PMid:37455356
34. De Weerdt E, Simoens S, Casteels M, Huys I. Toward a European definition for a drug shortage: a qualitative study. Front Pharmacol. 2015;6:253. doi:10.3389/fphar.2015.00253 PMid:26578963 PMCid:PMC4626567
35. Fox ER, Sweet BV, Jensen V. Drug shortages: a complex health care crisis. Mayo Clin Proc. 2014;89(3):361-73. doi:10.1016/j.mayocp.2013.11.014 PMid:24582195
36. Aronson JK. When I use a word Drug stock-outs. BMJ. 2025; 389:r1088. doi:10.1136/bmj.r1088 PMid:40409788
37. Shukar S, Shahid MH, Zhang J, Din SM, Khan FU, Fang Y, et al. Pharmacists' approach to oncology medicine shortages: results of a cross-sectional survey in Pakistan. BMJ Open. 2023;13(9):e070634. doi:10.1136/bmjopen-2022-070634 PMid:37723107 PMCid:PMC10510916
38. Jagsi R, Spence R, Rathmell WK, Bradbury A, Peppercorn J, Grubbs S, et al. Ethical considerations for the clinical oncologist in an era of oncology drug shortages. Oncologist. 2014;19(2):186-92. doi:10.1634/theoncologist.2013-0301 PMid:24449096 PMCid:PMC3926786
39. Cherif Chefchaouni A, Moutaouakkil Y, Adouani B, Tadlaoui Y, Lamsaouri J, Bousliman Y. Impact of anti-cancer drugs shortages in oncology and hematology departments in a Moroccan hospital. J Oncol Pharm Pract. 2022;28(4):822-6. doi:10.1177/10781552211008212 PMid:33840285
40. Westin J, Sherwood S, Hagerty K, Gralow J. Crisis of Cancer Drug Shortages: Understanding the Causes and Proposing Sustainable Solutions. JCO Oncol Pract. 2025;OP-25-00381. doi:10.1200/OP-25-00381 PMid:40591897
41. Pineda-Moncusí M, Rekkas A, Martínez Pérez Á, Leis A, Lopez Gomez C, Fey E, et al. Changes in use and utilisation patterns of drugs with reported shortages between 2010 and 2024 in Europe and North America: a network cohort study. Lancet Public Health. 2025;10(10):e835-e47. doi:10.1016/S2468-2667(25)00194-X PMid:40992879
42. Cornelissen N, Zielhuis SW, van den Bemt PMLA, van den Bemt BJF. Causes and management of drug shortages: a scoping review. Res Social Adm Pharm. 2025. doi:10.1016/j.sapharm.2025.10.008 PMid:41168038
43. Sabogal De La Pava ML, Tucker EL. Drug shortages in low- and middle-income countries: Colombia as a case study. J Pharm Policy Pract. 2022;15(1):42. doi:10.1186/s40545-022-00439-7 PMid:35698240 PMCid:PMC9189796
44. Barrios C, de Lima Lopes G, Yusof MM, Rubagumya F, Rutkowski P, Sengar M. Barriers in access to oncology drugs - a global crisis. Nat Rev Clin Oncol. 2023;20(1):7-15. doi:10.1038/s41571-022-00700-7 PMid:36380066 PMCid:PMC9665041
45. Kanan M, Alraya R, Aljabri A, Alsaadi B, Althubyani M, Alamri S, et al. Tackling Drug Shortages: An In-Depth Systematic Review Protocol. Pharm Pract (Granada). 2025;23(1):1-8. doi:10.18549/PharmPract.2025.2.3127
46. Alfaouri M, Jaaron AAM, Igudia E. Pharmaceutical Supply Chain Management Challenges in Developing Countries: A Systematic Literature Review. J Afr Bus. 2025;26(4):798-841. doi:10.1080/15228916.2025.2532943
47. Fundytus A, Sengar M, Lombe D, Hopman W, Jalink M, Gyawali B, et al. Access to cancer medicines deemed essential by oncologists in 82 countries: an international, cross-sectional survey. Lancet Oncol. 2021;22(10):1367-77. doi:10.1016/S1470-2045(21)00463-0 PMid:34560006
48. Unguru Y, Fernandez CV, Bernhardt B, Berg S, Pyke-Grimm K, Woodman C, et al. An Ethical Framework for Allocating Scarce Life-Saving Chemotherapy and Supportive Care Drugs for Childhood Cancer. J Natl Cancer Inst. 2016;108(6):djv392. doi:10.1093/jnci/djv392 PMid:26825103
49. Liu H, Zou L, Song Y, Yan J. Cost analysis of implementing a vial-sharing strategy for chemotherapy drugs using intelligent dispensing robots in a tertiary Chinese hospital in Sichuan. Front Public Health. 2022;10:936686. doi:10.3389/fpubh.2022.936686 PMid:36211656 PMCid:PMC9534289
50. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Committee on Implications of Discarded Weight-Based Dosing. In: Nass SJ, Lustig TA, Amankwah FK, Shortliffe EH, editors. Medications in Single-Dose Vials: Implications of Discarded Drugs. Washington (DC): National Academies Press (US); 2021.
51. Burry LD, Barletta JF, Williamson D, Kanji S, Maves RC, Dichter J, et al. It Takes a Village Contending With Drug Shortages During Disasters. Chest. 2020;158(6):2414-24. doi:10.1016/j.chest.2020.08.015 PMid:32805237 PMCid:PMC7426714
52. Chen E, Goold S, Harrison S, Ali I, Makki I, Kent SS, et al. Drug

shortage management: A qualitative assessment of a collaborative approach. PLoS One. 2021;16(4):e0243870. doi:10.1371/journal.pone.0243870 PMid:33891609 PMCid:PMC8064571
53. Nierengarten MB. Guidance for patient care during drug shortages: Current and ongoing drug shortages that include two of the most widely used chemotherapy agents for treating common cancers are compounding the stress for patients and oncologists. Cancer. 2023;129(19):2924-5. doi:10.1002/cncr.34992 PMid:37656152
54. Melidis C, Vantsos M. [Comment] Ethical and practical considerations on cancer recommendations during COVID-19 pandemic. Mol Clin Oncol. 2020;13(3):5. doi:10.3892/mco.2020.2075 PMid:32754319 PMCid:PMC7391840
55. Ravela R, Airaksinen M, Lyles A. State of the European Union's early notification obligation for drug shortages: enforcement and compliance in eight European countries (2020-2022). J Pharm Policy Pract. 2023;16(1):135. doi:10.1186/s40545-023-00646-w PMid:37936250 PMCid:PMC10629130
56. DeBoer RJ, Fadelu TA, Shulman LN, Van Loon K. Applying Lessons Learned From Low-Resource Settings to Prioritize Cancer Care in a Pandemic. JAMA Oncol. 2020;6(9):1429-33. doi:10.1001/jamaoncol.2020.2976 PMid:32761149
57. George S, Elrashid S. Inventory Management and Pharmaceutical Supply Chain Performance of Hospital Pharmacies in Bahrain: A Structural Equation Modeling Approach. Sage Open. 2023;13(1): 21582440221149717. doi:10.1177/21582440221149717
58. U.S. Food and Drug Administration. 7 Things to Know About Drug Shortage Management [Internet]. Silver Spring (MD): FDA; 2024 [cited 2025]. Available from: https://www.fda.gov/drugs/news-events-human-drugs/7-things-know-about-drug-shortage-management
59. Government of Canada. Drug shortages in Canada: Regulations and guidance. Ottawa: Health Canada; 2025.
60. European Medicines Agency. European Shortages Monitoring Platform fully operational for monitoring of shortages in the EU. Amsterdam: EMA; 2025.
61. Michigan Department of Health. Recommendations for Ethical Allocation of Carboplatin and Cisplatin. Lansing (MI): MDH; 2023.
62. Rajangom KS, Erenay FS, He Q-M, Figueiredo R, Chan KKW, Cheung MC, et al. Cancer Drug Wastage and Mitigation Methods: A Systematic Review. Value Health. 2025;28(1):148-60. doi:10.1016/j.jval.2024.08.006 PMid:39343092
63. Song I. Predictive Analytics on Drug Shortages and Future Challenges: A Review. HIRA. 2025;5(2):85-97. doi:10.52937/hira.25.5.2.e4
64. Wai DF, Merchant RF, Donneyong MM. Optimizing Medication Distribution in Automated Dispensing Cabinets: Dashboard Implementation and Evaluation. J Pharm Pract. 2023;36(6):1404-11. doi:10.1177/08971900221118159 PMid:35953085
65. Bednarski BP, Singh AD, Jones WM. On collaborative reinforcement learning to optimize the redistribution of critical medical supplies throughout the COVID-19 pandemic. J Am Med Inform Assoc. 2021;28(4):874-8. doi:10.1093/jamia/ocaa324 PMid:33295626 PMCid:PMC7799039
66. Shah A, Khan S, Arman M. Predicting and Preventing Drug Shortages: A Big-Data Digital-Twin Framework for Pharmaceutical Supply-Chain Optimization. J Econ Finance Account Stud. 2024;6:116-26. doi:10.32996/jefas.2024.6.6.9
67. Kulkarni Kale U, Vemulapalli G. Integrating AI into the Clinical Workflows Across the Cancer Care Continuum: Opportunities and Challenges. Cancer J. 2025;31(6). doi:10.1097/PPO.0000000000000799 PMid:41252130
68. Dienes B, Qorri D, Felföldi J. Pharma supply chain resilience. A systematic review. Appl Stud Agribus Commer. 2024;18. doi:10.19041/APSTRACT/2024/1/8
69. Ravangard R, Raeyat Mohtashami A, Bouzanjani A, Siadat N, Ahmadi Marzaleh M. Assessing the Resilience of the Supply Chain of Medicines and Consumables during Disasters Based on the World Economic Forum Framework: A Case of Iran. Disaster Med Public Health Prep. 2025;19:1-9. doi:10.1017/dmp.2025.10192 PMid:40968779
70. Takawira B, Pooe D, Samuels A. Assessing Disruptions In Pharmaceutical Supply Chains: A Qualitative Study Of Resilience And Risks In The South African Context. J Supply Chain Manag. 2024;11:43-62.
71. Vadaga AK, Dokuburra UR, Nekkanti H, Gudla SS, R KK. Digital transformation in pharmaceuticals: The impact of AI on supply chain management. Intell Hosp. 2025;1(1):100008. doi:10.1016/j.inhs.2025.100008
72. Roy A, Mohapatra A, Sharwan C, Kumar A, Kumar S, Maholay A, et al. Artificial Intelligence in pharmaceutical supply chain management: A systemic review. World J Biol Pharm Health Sci. 2025;21:204-13. doi:10.30574/wjbphs.2025.21.1.1088
73. Shen J, Bu F, Ye Z, Zhang M, Ma Q, Yan J, et al. Management of drug supply chain information based on "artificial intelligence + vendor managed inventory" in China: perspective based on a case study. Front Pharmacol. 2024;15:1373642. doi:10.3389/fphar.2024.1373642 PMid:39081951 PMCid:PMC11286579
74. Grossman GM, Helpman E, Lhuillier H. Supply Chain Resilience: Should Policy Promote International Diversification or Reshoring? J Polit Econ. 2023;131(12):3462-96. doi:10.1086/725173
75. Badejo O, Ierapetritou M. Enhancing pharmaceutical supply chain resilience: A multi-objective study with disruption management. Comput Chem Eng. 2024;188:108769. doi:10.1016/j.compchemeng.2024.108769
76. Hosseini Shekarabi SA, Kiani Mavi R, Romero Macau F. Supply Chain Resilience: A Critical Review of Risk Mitigation, Robust Optimisation, and Technological Solutions and Future Research Directions. Glob J Flex Syst Manag. 2025;26(3):681-735. doi:10.1007/s40171-025-00458-8
77. Li Y, Omain S, Tan K. Supply Chain Resilience: A Review and Research Direction. Int J Acad Res Bus Soc Sci. 2021;11. doi:10.6007/IJARBSS/v11-i12/11985
78. Hernandez I, Sullivan SD, Hansen RN, Fendrick AM. Cheaper is not always better: Drug shortages in the United States and a value-based solution to alleviate them. J Manag Care Spec Pharm. 2024;30 (7): 719-27. doi:10.18553/jmcp.2024.30.7.719 PMid:38950157 PMCid:PMC11217858
79. Guo Y, Liu F, Song J-S, Wang S. Supply chain resilience: A review from the inventory management perspective. Fundam Res. 2025;5(2):450-63. doi:10.1016/j.fmre.2024.08.002 PMid:40242541 PMCid:PMC11997565
80. Marmolejo-Saucedo JA. Design and Development of Digital Twins: a Case Study in Supply Chains. Mob Netw Appl. 2020;25(6):2141-60. doi:10.1007/s11036-020-01557-9 PMid:40476942 PMCid:PMC7275123
81. Al-Hourani S, Weraikat D. A Systematic Review of Artificial Intelligence (AI) and Machine Learning (ML) in Pharmaceutical Supply Chain (PSC) Resilience: Current Trends and Future Directions. Sustainability. 2025;17(14). doi:10.3390/su17146591
82. Nuta S, Mattam AS, Marri NR, Polenwar S. Artificial Intelligence in Pharmaceutical Supply Chain Management. IJSAT-Int J Sci Technol. 2025;16(3). doi:10.71097/IJSAT.v16.i3.7919

83. Jones J. AI-Driven Demand Forecasting in Supply Chains: A Qualitative Analysis of Adoption and Impact. Preprints. 2025. doi:10.20944/preprints202501.1349.v1
84. Meknassi Salime G, Bhirich N, Cherif Chefchaouni A, El Hamdaoui O, El Baraka S, Elalaoui Y. Assessment of Automation Models in Hospital Pharmacy: Systematic Review of Technologies, Practices, and Clinical Impacts. Hosp Pharm. 2025. doi:10.1177/00185787251315622 PMid:40026489 PMCid:PMC11869230
85. Joshi SV, Patil SB, Patil SN, Bhosle S, Karhadkar NP, Rathore YK. Machine Learning Applications in Hospital Pharmacy for Predicting Drug Shortages and Supply Chain Optimization. Res J Pharm Technol. 2025;18(6):2939-45. doi:10.52711/0974-360X.2025.00393
86. Kaur A, Prakash G. Intelligent inventory management: AI-driven solution for the pharmaceutical supply chain. Societal Impacts. 2025;5:100109. doi:10.1016/j.socimp.2025.100109
87. Santos JAM, Lopes MR, Viegas JL, Vieira SM, Sousa JMC. Internal Supply Chain Digital Twin of a Pharmaceutical Company. IFAC-PapersOnLine. 2020;53(2):10797-802. doi:10.1016/j.ifacol.2020.12.2864
88. Suri GS, Kaur G, Shinde D. Beyond boundaries: exploring the transformative power of AI in pharmaceuticals. Discov Artif Intell. 2024;4(1):82. doi:10.1007/s44163-024-00192-7
89. Roman E-A, Stere A-S, Roșca E, Radu A-V, Codroiu D, Anamaria I. State of the Art of Digital Twins in Improving Supply Chain Resilience. Logistics. 2025;9(1). doi:10.3390/logistics9010022
90. Hupman AC, Zhang J, Li H. Predicting pharmaceutical supply chain disruptions before and during the COVID-19 pandemic. Risk Anal. 2024;44(12):2797-811. doi:10.1111/risa.17453 PMid:39212118
91. Jaberidoost M, Olfat L, Hosseini A, Kebriaeezadeh A, Abdollahi M, Alaeddini M, et al. Pharmaceutical supply chain risk assessment in Iran using analytic hierarchy process (AHP) and simple additive weighting (SAW) methods. J Pharm Policy Pract. 2015;8(1):9. doi:10.1186/s40545-015-0029-3 PMid:25838919 PMCid:PMC4354976
92. Chen Y, Yang O, Sampat C, Bhalode P, Ramachandran R, Ierapetritou M. Digital Twins in Pharmaceutical and Biopharmaceutical Manufacturing: A Literature Review. Processes. 2020;8(9). doi:10.3390/pr8091088
93. Elkefi S, Asan O. Digital Twins for Managing Health Care Systems: Rapid Literature Review. J Med Internet Res. 2022;24(8):e37641. doi:10.2196/37641 PMid:35972776 PMCid:PMC9428772
94. Da Silva LC. Artificial Intelligence as an Extension of Pharmaceutical Care. J Hosp Pharm Health Serv. 2025;16(3):e1420. doi:10.30968/jhphs.2025.163.1420
95. Mousazadeh M, Torabi SA, Zahiri B. A robust possibilistic programming approach for pharmaceutical supply chain network design. Comput Chem Eng. 2015;82:115-28. doi:10.1016/j.compchemeng.2015.06.008
96. Goswami A, Baveja A, Ding X, Melamed B, Roberts F. An integrated framework for modeling pharmaceutical supply chains with disruptions and risk mitigation. Ann Oper Res. 2024. doi:10.1007/s10479-024-06381-y
97. Kungwalsong K, Cheng C-Y, Yuangyai C, Janjarassuk U. Two-Stage Stochastic Program for Supply Chain Network Design under Facility Disruptions. Sustainability. 2021;13(5). doi:10.3390/su13052596
98. Nikzad E, Bashiri M, Oliveira F. Two-stage stochastic programming approach for the medical drug inventory routing problem under uncertainty. Comput Ind Eng. 2019;128:358-70. doi:10.1016/j.cie.2018.12.055
99. Russell HV, Bernhardt MB, Berg S. Using decision modeling to guide drug allocation during a shortage. Pediatr Blood Cancer. 2017;64(7). doi:10.1002/pbc.26331 PMid:27862980
100. Hantel A, McManus ML, Wadleigh M, Cotugno M, Abel GA. Impact of Allocation on Survival During Intermittent Chemotherapy Shortages: A Modeling Analysis. J Natl Compr Canc Netw. 2022;20(4):335-41.e17. doi:10.6004/jnccn.2021.7047 PMid:35390765 PMCid:PMC10983800
101. Hantel A, Peppercorn J, Abel GA. Model solutions for ethical allocation during cancer medicine shortages. Lancet Haematol. 2021;8(4):e246-e8. doi:10.1016/S2352-3026(21)00055-7 PMid:33770477
102. Vicente JJ. Optimizing Supply Chain Inventory: A Mixed Integer Linear Programming Approach. Systems. 2025;13(1). doi:10.3390/systems13010033
103. Vázquez-Serrano JI, Peimbert-García RE, Cárdenas-Barrón LE. Discrete-Event Simulation Modeling in Healthcare: A Comprehensive Review. Int J Environ Res Public Health. 2021; 18 (22). doi:10.3390/ijerph182212262 PMid:34832016 PMCid:PMC8625660
104. Vecillas Martin D, Berruezo Fernández C, Gento Municio AM. Systematic Review of Discrete Event Simulation in Healthcare and Statistics Distributions. Appl Sci. 2025;15(4). doi:10.3390/app15041861
105. Gan Z, Fu Z, Dong P, Ju Y, Shen Y. Computational modeling and analysis of medical resource shortages in hospital alliance: A simulation-driven approach. PLoS One. 2025;20(8):e0330871. doi:10.1371/journal.pone.0330871 PMid:40857292 PMCid:PMC12380337
106. Bastani P, Sadeghkhani O, Ravangard R, Rezaei R, Bikine P, Mehralian G. Designing a resilience model for pharmaceutical supply chain during crises: a grounded theory approach. J Pharm Policy Pract. 2021;14(1):115. doi:10.1186/s40545-021-00399-4 PMid:34969402 PMCid:PMC8717826
107. Organisation for Economic Co-operation and Development. Securing Medical Supply Chains in a Post-Pandemic World. Paris: OECD Publishing; 2024.
108. Faiman B. Providing Care During Cancer Drug Shortages. J Adv Pract Oncol. 2023;14(5):356-7. doi:10.6004/jadpro.2023.14.5.1 PMid:37576367 PMCid:PMC10414530
109. Pathak N, Shrestha R, Shrestha S. Improving patient outcomes during cancer drug shortages: the role of patient education. Eur J Hosp Pharm. 2025;32(5):397-8. doi:10.1136/ejhpharm-2025-004548 PMid:40169182
110. Tisoskey SP, Ford DW, Locantore-Ford PA. Communicating the Crisis: Navigating the Challenges of Chemotherapeutic Drug Shortages with a Patient-Centered Ethical Dialogue Framework. Blood. 2023;142:5171. doi:10.1182/blood-2023-190243
111. Shickh S, Leventakos K, Lewis MA, Bombard Y, Montori VM. Shared Decision Making in the Care of Patients With Cancer. Am Soc Clin Oncol Educ Book. 2023;43:e389516. doi:10.1200/EDBK_389516 PMid:37339391
112. Toorajipour R, Sohrabpour V, Nazarpour A, Oghazi P, Fischl M. Artificial intelligence in supply chain management: A systematic literature review. J Bus Res. 2021;122:502-17. doi:10.1016/j.jbusres.2020.09.009
113. Abu-El-Ruz R, Hasan A, Hijazi D, Masoud O, Abdallah AM, Zughaier SM, et al. Artificial Intelligence in Biomedical Sciences: A Scoping Review. Br J Biomed Sci. 2025;82:14362. doi:10.3389/bjbs.2025.14362 PMid:40837680 PMCid:PMC12360964
114. Tucker EL, Cao Y, Fox ER, Sweet BV. The Drug Shortage Era: A Scoping Review of the Literature 2001-2019. Clin Pharmacol Ther. 2020;108(6):1150-5. doi:10.1002/cpt.1934 PMid:32521038
115. Elleuch H, Dafaoui E, Elmhamedi A, Chabchoub H. Resilience and Vulnerability in Supply Chain: Literature review. IFAC-PapersOnLine. 2016;49(12):1448-53. doi:10.1016/j.ifacol.2016.07.775
116. Katsoulakis E, Wang Q, Wu H, Shahriyari L, Fletcher R, Liu J, et al. Digital twins for health: a scoping review. NPJ Digit Med. 2024; 7 (1):77. doi:10.1038/s41746-024-01073-0 PMid:38519626 PMCid:PMC10960047



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