Beyond The Ache: Aspirin's Journey as the Repurposed Wonder Drug across the Therapeutic Domains

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Abstract: Acetylsalicylic acid, also known as aspirin, is a cheap medication that has been around for a century and has a strong pharmacology and safety record. Aspirin's repurposing, especially in the prevention of colorectal cancer and as an adjuvant across various tumors, is supported by growing mechanistic, epidemiologic, and clinical evidence beyond its use in analgesia and antiplatelet indications. It also suggests roles in immunomodulation, metastasis suppression, and metabolic/inflammatory disorders. The main clinical findings (prevention, adjuvant use, biomarker-guided benefit), translational strategies (computational screens, phenotypic assays, real-world data, and randomized trials), safety and regulatory issues, evidence, ongoing trials, safety and regulatory considerations, and practical future directions for aspirin repurposing across clinical domains are all summarized in this review. Even if the evidence is encouraging, before new indications are routinely used, thorough biomarker-guided randomized trials and consideration of bleeding risk, dosage, and patient selection are crucial.

Keywords: Aspirin, Acetylsalicylic acid, Antiplatelet therapy, Cyclooxygenase inhibition, Cancer chemoprevention, cardiovascular disease prevention, Clinical trials and Real-world evidence, Drug repurposing, Drug repositioning, Dose optimization, Metastasis suppression, NSAIDS, Nanoparticle drug delivery, Neurodegenerative disorders, PIK3CA biomarker, Precision medicine.

I. INTRODUCTION

Drug repurposing (also called repositioning) uses existing drugs for indications other than their original authorization. This approach reduces time, cost, and early-stage safety uncertainty relative to de novo drug discovery and is particularly attractive for inexpensive generics such as aspirin. Aspirin's irreversible acetylation of cyclo-oxygenase enzymes and broad downstream effects on inflammation, platelets, and immune signaling provide mechanistic plausibility for diverse new uses. The literature includes major randomized trials, landmark epidemiologic analyses, molecular epidemiology identifying predictive biomarkers, and ongoing adjuvant trials, making aspirin an excellent case study in clinical repurposing[1].

II. HISTORICAL & PHARMACOLOGIC BACKGROUND

Acetylsalicylic acid, or aspirin, was initially created in the late 1800s and was quickly used to treat fever and pain. The crucial finding that aspirin and other NSAIDs prevent prostaglandin synthesis through cyclo-oxygenase (COX) enzymes defined the molecular mechanism of the medication and clarified its anti-inflammatory and antipyretic properties. Later analysis of COX-1 and COX-2 isoforms revealed their tissue-specific functions and the molecular underpinnings of their antiplatelet activity (platelet COX-1 acetylation permanently inhibits the formation of thromboxane A_2) [1,2,3,4].

III. PHARMACOLOGY AND MECHANISTIC RATIONALE

3.1 COX-dependent actions

Aspirin inhibits prostaglandin and thromboxane production by irreversibly acetylating COX-1 and COX-2; its antithrombotic actions are due to platelet

COX-1 acetylation [1, 2, 5]. Decreases in PGE_2 and TXA_2 have an effect on inflammation, platelet activation, and tumor-promoting prostanoid signaling, which makes them directly plausible for cardiovascular and cancer prevention purposes[1, 6, 7].

3.2 COX-independent, network effects

Aspirin and salicylate affect NF-κB signaling, STAT3/IL-6 pathways, Wnt/β-catenin activity, DNA repair and apoptosis/autophagy networks, and epigenetic markers, which can impact tumor genesis, development, and the tumor microenvironment[8-15]. Aspirin's inhibition of platelet activation also lowers platelet-tumor cell interactions, which protect circulating tumor cells and promote metastasis, implying a mechanism for metastasis prevention[16,17,18].

IV. WHY REPURPOSE ASPIRIN?

4.1 Well-established safety and pharmacokinetics. Decades of clinical use have yielded an abundance of safety data, allowing for informed risk-benefit evaluations[10,19].

4.2 Pleiotropic mechanisms. Aspirin has both COX-dependent (prostaglandin/thromboxane decrease) and COX-independent activities (NF-κB, Wnt/β-catenin, STAT3, epigenetic modification, platelet-tumor interactions), making it useful for treating conditions other than cardiovascular disease [8,9,15,20,21].

4.3 Public health and economic benefits. Aspirin, as a low-cost generic, is especially appealing for global health and diseases with few financially viable markets (for example, many malignancies and uncommon ailments) [11,22,23].

V. APPROACHES & METHODS USED TO STUDY REPURPOSING

5.1 Computational & Omics-driven strategies

Transcriptomic signature matching (e.g., Connectivity Map), network pharmacology, and machine learning on multi-omics datasets are utilized to identify aspirin-disease connections and medication combinations [24,25,26].

5.2 Experimental / Preclinical testing

Phenotypic screenings, cell line panels, organoids, and animal models are used to evaluate the antiproliferative, pro-apoptotic, anti-metastatic, and immunomodulatory properties of aspirin and salicylate derivatives; certain nanoparticle and prodrug techniques aim to increase delivery and tumor selectivity [27,28,29].

5.3 Clinical / Epidemiologic evidence & trials

The human evidence base includes observational cohorts, case-control studies, meta-analyses, and randomized trials (both primary preventive and adjuvant contexts). Notable randomized primary-prevention trials (ASCEND, ARRIVE, and ASPREE) have defined the balance of benefit vs. bleeding risk in various populations, whereas adjuvant trials (e.g., Add-Aspirin) assess oncologic objectives [21].

VI. CLINICAL EVIDENCE — PREVENTION, ADJUVANT USE, AND BIOMARKERS

6.1 Oncology: prevention, adjuvant use and metastasis suppression

Epidemiologic signals and pooled randomized trial studies show that using low-dose aspirin on a daily basis for several years reduces the incidence and long-term mortality of some malignancies, particularly colon cancer [1,30,31]. Observational molecular epidemiology revealed that post-diagnosis aspirin use was associated with increased survival in CRC patients whose tumors contained PIK3CA mutations, a possible predictive biomarker that has fueled precision repurposing efforts [18,20].

Landmark genetic prevention research in Lynch syndrome (CAPP2) found that carriers randomized to aspirin had lower CRC incidence, indicating chemoprevention in high-risk populations [32,33]. Ongoing randomized adjuvant trials, most notably the Add-Aspirin platform, are investigating whether aspirin after curative therapy lowers recurrence and

improves survival across common solid tumors; the findings will be critical for formal indications [8,34].

Mechanistic and preclinical studies demonstrate that aspirin decreases platelet-mediated immune suppression and metastatic seeding; a high-impact 2025. According to a Nature report, aspirin decreases platelet TXA_2-mediated T-cell suppression and lowers metastases in experimental models. This strengthens the immunologic justification for oncology repurposing and combination with checkpoint inhibitors. [16,35] Meta-analyses and systematic reviews provide an overall picture of possible benefit, but also show heterogeneity between studies and cancer types, emphasizing the importance of randomized, biomarker-stratified trials. [30,31,36]

6.2 cardiovascular disease: prevention and the modern risk–benefit balance

The role of aspirin in secondary prevention of atherothrombotic events (antiplatelet treatment) is well recognized. [5,70] However, recent large primary-prevention randomized trials — ASCEND (diabetes), ARRIVE (moderate risk), and ASPREE (older adults) — found modest or no net benefit for primary prevention in many contemporary populations, as well as an increased bleeding risk, prompting guideline shifts toward individualized rather than routine primary prevention. [14,15,17,37]

6.3 Obstetrics: prevention of preeclampsia and adverse pregnancy outcomes

Low-dose aspirin (generally 60-162 mg daily; commonly 81 mg in the US) started in the late first or early second trimester lowers the risk of preeclampsia and related adverse outcomes in high-risk women, and it is recommended by major bodies such as ACOG and the USPSTF for high-risk pregnant people [38-41]. Emerging data has addressed the ideal dose and timing (initiation before 16 weeks may be most effective), with subsequent studies questioning whether 162 mg is preferable in some high-risk individuals. [42-44]

6.4 Metabolic disease and inflammation (salicylates, salsalate)

In short-term experiments, high-dose salicylates (salsalate and aspirin) demonstrated glucose-lowering and insulin-sensitivity effects, lending support to the idea that anti-inflammatory salicylates may improve metabolic disorders [7,45,46]. However, bigger definitive trials are needed to determine the safety, long-term efficacy, and cardiovascular effects [7,45,46].

6.5 Neurodegeneration and cognitive disorders

Epidemiologic research and molecular rationales for aspirin in Alzheimer's disease and other neurodegenerative disorders are equivocal; some observational data imply a decreased prevalence with chronic NSAID usage, but randomized evidence is either nonexistent or neutra [47,48,49]. Although neuroinflammation remains an appealing target, no clear clinical recommendations can be given at this time.

6.6 Infectious and inflammatory conditions, and acute settings

Aspirin and salicylates have been studied in a variety of inflammatory and infectious settings (e.g., sepsis, COVID-19 thrombosis management, influenza complications), with mixed results and a focus on thorough bleeding risk stratification [50,51,52]. Aspirin's antiplatelet and anti-inflammatory effects remain mechanistically relevant in hypercoagulable infectious conditions, but its routine usage outside of clinical trials has not been demonstrated.

VII. REPRESENTATIVE USE-CASES & TRANSLATIONAL EXAMPLES

7.1 Observational and trial data suggest that multiyear aspirin can reduce the incidence and death of colorectal cancer. Adjuvant aspirin is now being tested in molecularly-selected subgroups, such as PIK3CA mutants [20,53,55,56].

7.2 Preclinical studies suggest that aspirin can diminish platelet-tumor interactions and improve T-cell anti-tumor responses. Combining aspirin with immune checkpoint drugs is a promising field of research [33,35,57].

7.3 Nanotechnology and targeted delivery: Folate-decorated nanoparticles and other delivery systems have been developed to promote tumor targeting of aspirin, potentially lowering systemic bleeding risk and boosting local anticancer effectiveness [27,58].

7.4 Exploratory data exists for non-oncologic repurposing, including neuroprotection, metabolic regulation, and infectious/inflammatory diseases, although clinical evidence remains preliminary [28,42,59,60].

VIII. ONGOING TRIALS AND PRIORITY RESEARCH DIRECTIONS

Biomarker-driven precision repurposing (e.g., PIK3CA and other pathway changes) to select responders.

Combination tactics with immunotherapy or targeted agents;

Advanced formulations to lower systemic toxicity and improve tumor delivery and reduce hemorrhage (e.g. nanoparticles, local release, prodrugs).

Use adaptive trial designs and master protocols to efficiently evaluate aspirin in diverse environments.

Support generic trials through collaborative funding methods[25,27,33,44,61].

IX. PRACTICAL CLINICAL IMPLICATIONS (CURRENT)

Currently, aspirin's accepted repurposed uses include:

Secondary prevention of cardiovascular events (established antiplatelet treatment) [5].

Low-dose aspirin prophylaxis for pregnant people at high risk of preeclampsia, according to ACOG and USPSTF [38-41].

Using CAPP2 data, consider chemoprevention in specific high-risk genetic disorders such as Lynch syndrome [32,33].

Outside of these situations, regular aspirin for primary prevention or adjuvant cancer therapy is not widely recommended in the absence of definitive randomized data and rigorous customized evaluation of bleeding risk [14,15,32,34].

X. SAFETY, DOSE, AND REGULATORY CONSIDERATIONS

The biggest safety concern with repurposing is the possibility of bleeding (GI and intracranial), particularly for older persons or those using anticoagulants. RCTs inform absolute risk increases and help guide population selection[14].

Dose optimization remains an unresolved issue. While low-dose regimens (75-100 mg) have shown cancer-prevention benefits, other preclinical effects may require greater concentrations, potentially posing long-term safety risks[1,6,62].

Aspirin's generic status limits commercial incentives for costly adjuvant trials, necessitating governmental funding, cooperative partnerships, and charitable methods[31,63]. Regulatory pathways: Formal approval for new indications requires RCT data confirming net benefit, while off-label use continues but does not replace regulatory support[32].

XI. CHALLENGES & LIMITATIONS

Heterogeneity of effect: Genetic subtypes (e.g., PIK3CA) and tumor microenvironments influence benefit, underscoring the importance of biomarker-driven trials[64,65] .

Nephrotoxic Effect: Acute kidney injury, particularly in the elderly, volume-depleted patients, and chronic patients. The most common method is COX 1/COX 2 inhibition, which reduces renal prostaglandin (PGE_2/PGI_2) synthesis, reducing afferent arteriolar vasodilation and decreasing GFR and renal perfusion[66] .

Translational gaps: Some intriguing preclinical processes have yet to provide consistent human benefits beyond colorectal cancer signals[67].

Funding and Commercial viability: Large biomarker-stratified RCTs are expensive and necessitate non-commercial funding for generic drugs[13].

XII. FUTURE DIRECTIONS & RECOMMENDATIONS

To identify responders, conduct biomarker-driven precision trials (e.g., PIK3CA and other pathway changes)[3,53].

Combination strategies: Combine aspirin with targeted therapy, chemotherapy, radiation, and immunotherapy in reasonable, mechanism-based ways [33,68].

Novel formulations that improve tumor delivery and decrease bleeding (nanoparticles, local release, prodrugs) [27,58].
Platform/adaptive trial approaches, as well as the utilization of real-world data, will help to speed testing across tumor types and biomarker subgroups [2,9,69].

To counter generics' low economic incentives, shared funding approaches (academic consortia, public funding) are being used[31,32,63].

XIII. CONCLUSION

Aspirin illustrates the potential and complexities of medication repurposing: it is widely available, well-characterized, pleiotropic, and inexpensive, yet it is hampered by safety trade-offs, dose uncertainty, and a lack of economic incentives for rigorous research. Aspirin is an archetypal repurposing candidate: it is widely available, affordable, mechanistically adaptable, and has a large body of data supporting its advantages in cancer preventative and adjuvant situations. The outcomes of current adjuvant trials, biomarker-directed investigations, new delivery methods, and AI-driven patient classification in the future years could shed light on the circumstances in which aspirin's repurposed benefits surpass its risks. The balance of benefit vs. bleeding risk, as well as the impact of biomarkers like PIK3CA and the necessity for high-quality RCT evidence, are critical to bringing aspirin's promise into normal treatment for novel purposes. Well-designed biomarker-stratified trials and better delivery mechanisms,and collaborative funding strategies will be critical in realizing aspirin's repurposing potential.

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