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Predictors of Chemotherapy-Induced Peripheral Neuropathy in Colorectal Cancer Patients

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Abstract

Oxaliplatin-based chemotherapy remains central to curative and palliative treatment of colorectal cancer, but its use is limited by peripheral neuropathy, a biphasic toxicity comprising an acute, cold-triggered channelopathy and a separate, cumulative, dose-dependent chronic sensory neuropathy. This article synthesizes the published literature on who develops clinically significant chemotherapy-induced peripheral neuropathy (CIPN) in colorectal cancer specifically, and why. We trace the mechanistic basis of oxaliplatin neurotoxicity, the instruments used to grade it, and the three predictor categories the literature has converged on: demographic and clinical factors (older age, diabetes, elevated body mass index, smoking, and hypomagnesemia), treatment-related and dose-dependent factors (cumulative oxaliplatin dose and cold exposure), and genetic and biological markers, where the best-studied candidate, the GSTP1 polymorphism, has failed to show a reliable association across pooled analyses. Read together, the evidence supports a reasonably specific predictive picture built from routinely available clinical variables, while genetic and biomarker prediction, and validated prophylactic interventions for identified high-risk patients, remain considerably less mature and represent the clearest open directions for future research.

Keywords: chemotherapy-induced peripheral neuropathy; oxaliplatin; colorectal cancer; risk factors; neurotoxicity

1. Introduction

Oxaliplatin has been a backbone of curative-intent chemotherapy for colorectal cancer since the MOSAIC trial established FOLFOX4 (fluorouracil, leucovorin, and oxaliplatin) as standard adjuvant treatment for resected stage II and III colon cancer, and the drug remains equally central to first-line therapy for metastatic disease [1]. Its efficacy, however, comes bundled with a dose-limiting and often durable side effect: peripheral neuropathy. Unlike the alopecia or nausea that patients associate with chemotherapy in general, oxaliplatin-induced peripheral neuropathy (OIPN) has a biphasic character that surprises many newly diagnosed patients — an acute, cold-triggered dysesthesia that appears within hours of an infusion and typically resolves within days, and a separate, cumulative, dose-dependent sensory neuropathy that builds silently across cycles and, in a substantial minority of patients, persists for months or years after treatment ends [2,3].

This article synthesizes what the literature on colorectal cancer patients specifically — as opposed to the broader chemotherapy-induced peripheral neuropathy (CIPN) literature spanning taxanes, vinca alkaloids, and proteasome inhibitors — has established about who develops clinically significant OIPN and why. The question matters for a very practical reason: neuropathy, not disease progression, is the single most common reason oxaliplatin is dose-reduced, delayed, or stopped altogether in both the adjuvant and metastatic settings, and a reliable predictive picture would let clinicians front-load protective strategies, counsel patients accurately, and design stop-and-go or dose-modification schedules around individual risk rather than a population average [3]. We organize the discussion around the mechanisms that produce OIPN, the tools used to measure it, and then the three broad predictor categories the literature has converged on: patient-level demographic and clinical characteristics, treatment-related and cumulative-dose factors, and genetic or biological markers. We close with a discussion of what remains genuinely unsettled — chiefly, that individual predictors identified in single cohorts often have wide confidence intervals and modest effect sizes, that promising genetic candidates have not reliably replicated, and that no validated multivariable risk score has yet reached routine clinical use.

It is worth being explicit about scope from the outset.

This is a literature synthesis, not a new analysis of patient data; every number reported below is drawn directly from a published study or meta-analysis and is cited to its source. Where the evidence is genuinely mixed or a plausible candidate predictor has failed to replicate, we say so rather than smoothing the picture into false consistency, because an accurate account of an inconsistent literature is more useful to clinicians and future investigators than a tidier one that overstates what is actually known.

2. Pathophysiology of Oxaliplatin-Induced Peripheral Neuropathy

Understanding why some patients develop severe, persistent OIPN while others tolerate the same cumulative dose with minimal symptoms starts with the biology of how oxaliplatin damages peripheral nerves in the first place. Starobova and Vetter's widely cited review of CIPN pathophysiology lays out a multifactorial mechanistic picture that differs meaningfully by drug class, but for platinum compounds specifically converges on several interacting pathways: platinum-DNA adduct formation in the dorsal root ganglia, where neurons lack the protective blood-nerve barrier that shields most of the peripheral nervous system, and this exposure drives mitochondrial dysfunction, elevated reactive oxygen species, and ultimately axonal degeneration in the sensory neurons whose cell bodies reside there [4]. Oxaliplatin's oxalate metabolite additionally chelates calcium ions near voltage-gated sodium channels at the nodes of Ranvier, altering channel kinetics in a way that is thought to underlie the drug's most distinctive clinical signature — acute, cold-triggered paresthesias and dysesthesias that can appear within hours of infusion, well before any cumulative axonal injury could plausibly have occurred [4].

This acute syndrome and the chronic, cumulative neuropathy that follows it are increasingly understood as mechanistically distinct, even though both are labeled "oxaliplatin-induced peripheral neuropathy" in clinic notes and case report forms. The acute syndrome is thought to be a largely reversible channelopathy; the chronic syndrome reflects genuine structural axonal loss that DNA-adduct accumulation and mitochondrial injury produce over repeated cycles, and it does not necessarily track with the severity of a patient's acute symptoms in early cycles [4,5]. Meregalli and colleagues'

review of candidate blood biomarkers for CIPN underscores how much of this mechanistic picture remains inferential rather than directly verified in patients: markers of neurofilament light chain, oxidative stress, and neuroinflammation have all shown associations with CIPN severity in various cohorts, but none has yet been validated prospectively as a predictive biomarker that clinicians could order before or during treatment to flag a patient at elevated risk [5]. This gap between a reasonably well-characterized cellular mechanism and the absence of a clinically actionable biomarker is a recurring theme throughout the predictor literature discussed in this article.

Acute Versus Chronic Neuropathy as Distinct Clinical Entities

The distinction matters practically because a patient's acute cold-sensitivity phenotype and their eventual chronic neuropathy grade are reported by different studies to be only partially correlated, which complicates any effort to use early acute symptoms as a simple early-warning predictor of eventual chronic disability. Gonjobe and colleagues' cohort of colorectal cancer patients in Tanzania illustrates this directly: 71% of their cohort reported acute OIPN symptoms during treatment, while a somewhat smaller 59.7% went on to develop chronic OIPN symptoms, and the severity distributions of the two syndromes did not overlap cleanly — most acute symptoms were graded 2 (69.4% of acute cases), while chronic symptoms skewed toward the milder grade 1 (62.2% of chronic cases) [6]. That asymmetry is a useful empirical anchor for the broader claim that acute and chronic OIPN, while causally linked, are not simply the same process observed at two time points.

3. Colorectal Cancer Chemotherapy Regimens and Neurotoxic Exposure

Cumulative dose is, almost by construction, one of the most consistently identified predictors of OIPN severity across the literature, precisely because oxaliplatin's neurotoxic mechanism is dose-dependent in a way that most of its other toxicities are not. The MOSAIC trial that established FOLFOX4 as adjuvant standard of care for colon cancer administered oxaliplatin at 85 mg/m² every two weeks for twelve cycles, and peripheral sensory neuropathy was the principal toxicity that limited how many of the planned cycles patients could actually complete, a pattern that has been reproduced in

essentially every subsequent oxaliplatin-containing regimen studied in colorectal cancer [1,3]. This dose-toxicity relationship is precisely why "stop-and-go" and dose-modification strategies exist at all in colorectal cancer chemotherapy: rather than treating cumulative neurotoxicity as an unavoidable cost of a fixed protocol, oncologists routinely interrupt or reduce oxaliplatin dosing once neuropathy reaches a threshold severity, resume once symptoms improve, or substitute a non-platinum regimen for maintenance, all explicitly to manage the tradeoff between disease control and cumulative nerve injury [3].

Regimen choice within the oxaliplatin-containing family also appears to modulate neurotoxic exposure, though the evidence here is less uniformly consistent than for cumulative dose alone. Douillard's review comparing XELOX (capecitabine plus oxaliplatin) with infusional 5-fluorouracil-based FOLFOX regimens in metastatic colorectal cancer found broadly comparable efficacy between the two backbones, but noted that the toxicity profiles differ somewhat by regimen and administration schedule, a distinction relevant to clinicians weighing which platinum-containing combination to select for a given patient's risk profile [7]. Because XELOX and FOLFOX deliver oxaliplatin on different dosing schedules (typically every three weeks versus every two), the cumulative dose delivered over a fixed number of treatment months, and therefore the pace at which cumulative neurotoxicity accrues, is not identical between the two regimens even when total planned exposure is similar — a subtlety that matters for interpreting cross-study comparisons of neuropathy incidence.

4. Measuring and Grading CIPN in Clinical Studies

Any synthesis of predictors has to reckon with the fact that different studies measure "peripheral neuropathy" in meaningfully different ways, which complicates direct comparison of reported incidence and effect sizes. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) clinician-graded scale is the most widely used instrument in oncology trials and is what most of the predictor studies discussed in this article use to define their outcome, but clinician grading is known to systematically underestimate the severity and functional impact of sensory symptoms relative to what patients themselves report [8]. This

observation motivated the development of the EORTC QLQ-CIPN20, a 20-item patient-reported outcome measure covering sensory, motor, and autonomic symptom domains that Postma and colleagues developed specifically because existing clinician-rated toxicity scales were not capturing the patient experience of CIPN with adequate granularity [8]. Kieffer and colleagues' subsequent psychometric evaluation of the QLQ-CIPN20 across a large international sample confirmed its reliability and validity for measuring the sensory and motor subscales specifically, while noting that the autonomic subscale performed less consistently, a caveat that later validation and cross-cultural adaptation studies have generally reproduced [9].

Objective, examiner-independent measures provide a third axis of assessment alongside clinician grading and patient-reported outcomes. Argyriou and colleagues demonstrated that nerve conduction studies can objectively quantify oxaliplatin-induced sensory axonal loss and track its progression across cycles in a way that is less susceptible to the subjective grading variability that affects both clinician CTCAE assessments and patient self-report, though the added time, cost, and specialist equipment nerve conduction studies require have limited their routine use outside dedicated research cohorts [10]. Smith and colleagues' validation of the Modified Total Neuropathy Score-Reduced instrument, developed and tested specifically in patients receiving taxane and platinum chemotherapy, offered a middle path — a brief, clinician-administered composite that combines limited objective testing (reflexes, vibration sense) with symptom report and performed with good reliability and validity relative to more elaborate instruments [11]. The practical consequence of this instrument heterogeneity for the predictor literature synthesized in the remainder of this article is that a reported odds ratio for a given risk factor is always, implicitly, an odds ratio for that risk factor's association with neuropathy as defined by whichever instrument a given study used, and cross-study comparisons should be read with that caveat in mind.

The practical stakes of this measurement heterogeneity extend beyond methodology into quality of life. Kieffer and colleagues' validation work found that the QLQ-CIPN20 sensory subscale correlated meaningfully with broader quality-of-life domains captured on the

companion EORTC QLQ-C30 core instrument, reinforcing that CIPN is not a side toxicity to be tracked separately from a patient's overall wellbeing during and after treatment, but a symptom cluster that measurably erodes function, sleep, and daily activity in ways patients themselves rate as important even when a clinician's CTCAE grade records only a modest severity [9]. This is part of why the field has gradually shifted toward including patient-reported instruments alongside clinician grading in newer predictor studies, even though, as noted above, the older clinician-graded literature that still makes up much of the evidence base synthesized in this article was not designed with that dual-measurement approach in mind.

5. Demographic and Clinical Predictors

The most consistent and best-replicated predictors of OIPN in colorectal cancer patients are demographic and clinical characteristics that are already routinely recorded at treatment initiation, which is part of what makes them attractive candidates for a bedside risk-stratification tool. Zeng and colleagues' 2026 systematic review and meta-analysis pooled ten studies comprising 2,008 colorectal cancer patients and identified six statistically significant predictors of CIPN development: age 60 years or older (odds ratio 1.47, 95% CI 1.02-2.13), a history of smoking (OR 1.55, 95% CI 1.06-2.27), diabetes mellitus (OR 2.18, 95% CI 1.01-4.07), hypomagnesemia (OR 4.17, 95% CI 2.00-8.33, the strongest single association identified in the pooled analysis), cumulative oxaliplatin dose of 500 mg/m² or greater (OR 1.79, 95% CI 1.20-2.63), and cold exposure during or shortly after infusion (OR 1.54, 95% CI 1.03-2.30) [12]. Reported CIPN prevalence in the studies contributing to this pooled analysis ranged from roughly 39% in prospective cohort designs to 55% in case-control designs, a spread that itself reflects both genuine population heterogeneity and the instrument-dependence problem noted above [12].

Diabetes mellitus deserves particular attention as a predictor because it has an independently plausible mechanism, not merely a statistical association: diabetic patients frequently already carry subclinical peripheral nerve damage from chronic hyperglycemia before oxaliplatin exposure even begins, so oxaliplatin's neurotoxic insult is added to a nerve substrate with reduced baseline reserve rather than a healthy one. Uwah and colleagues' dedicated study of diabetic

colorectal cancer patients receiving oxaliplatin found that pre-existing diabetes was associated with a meaningfully elevated risk of clinically significant OIPN relative to non-diabetic patients receiving comparable cumulative doses, a finding directionally consistent with the pooled effect Zeng and colleagues later reported across a larger combined sample [13,12]. Obesity and elevated body mass index show a similarly consistent, if variably sized, association across independent cohorts. Gonjobe and colleagues' Tanzanian cohort found a markedly elevated risk among obese patients (OR 21.66, 95% CI 2.574-182.244), while Kanbayashi and colleagues' larger Japanese retrospective cohort of 322 oxaliplatin-treated patients found a more modest but still statistically significant per-unit association between BMI and neuropathy severity (OR 1.06 per kg/m², 95% CI 1.00-1.12, $p=0.043$), with receiver-operating-characteristic analysis identifying a BMI threshold near 20.5 kg/m² above which grade 2 or worse neuropathy became substantially more likely [6,14]. The very wide confidence interval around the Tanzanian cohort's obesity estimate, driven by its comparatively small sample of 62 patients, is a useful illustration of how much single-cohort effect sizes can vary even when the underlying direction of association (higher BMI, higher risk) replicates.

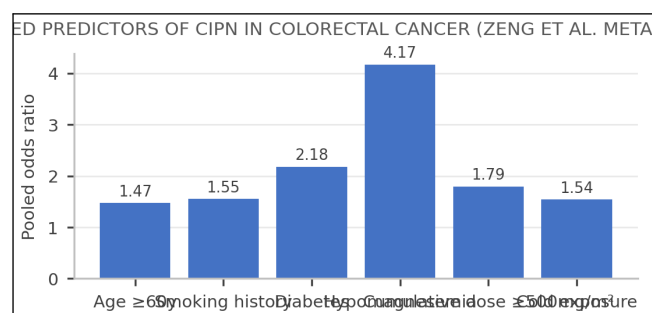


Figure 1: Pooled odds ratios for six statistically significant predictors of chemotherapy-induced peripheral neuropathy in colorectal cancer patients, from a meta-analysis of 10 studies and 2,008 patients. Bars show the point estimate odds ratio for each predictor; an odds ratio of 1.0 (dashed reference) indicates no association [12].

Sex is a less consistently reported predictor but appears with some regularity in individual cohorts. Kanbayashi and colleagues' ordered logistic regression analysis found female sex independently associated with higher-grade OIPN (OR 1.67, 95% CI 1.06-2.61, $p=0.026$) after adjustment for cumulative dose and BMI, a finding the authors note is broadly consistent with sex-based differences reported for other neurotoxic and pain-related chemotherapy side effects, though the

mechanism specific to oxaliplatin neuropathy is not established [14]. Mizrahi and colleagues' analysis of risk factors across both paclitaxel- and oxaliplatin-treated patients similarly identified older age and body composition measures, alongside baseline hemoglobin concentration, as independently associated with CIPN risk, adding anemia to the list of readily available laboratory values worth considering in a bedside risk assessment, though the authors are careful to frame this as an association requiring further mechanistic and prospective validation rather than an established causal predictor [15].

6. Treatment-Related and Dose-Dependent Predictors

Cumulative oxaliplatin dose is the single best-replicated treatment-related predictor across the literature synthesized here, which is unsurprising given the dose-dependent mechanism described earlier, but the specific dose thresholds at which risk accelerates differ somewhat between studies, likely reflecting differences in patient population, regimen, and how neuropathy was graded. Zeng and colleagues' pooled threshold of 500 mg/m² sits within the range reported by individual cohort studies: Kanbayashi and colleagues' ROC-derived thresholds of 680 mg total dose for grade 2 or worse neuropathy and 1,040 mg for grade 3 or worse neuropathy imply a substantially higher absolute cutoff, though total-dose and dose-per-body-surface-area metrics are not directly comparable across studies without normalizing for patient body size, which limits how precisely these numbers can be reconciled [12,14]. Gonjobe and colleagues' Tanzanian cohort, working with a smaller and comparatively lower-dose-exposed population, found that patients who received seven or fewer treatment cycles, and separately those whose cumulative dose stayed at or below 780 mg/m², had substantially lower odds of developing OIPN (OR 0.227, 95% CI 0.053-0.971 for fewer cycles; OR 0.104, 95% CI 0.022-0.502 for lower cumulative dose), framing the same underlying dose-response relationship from the protective rather than the risk-elevating direction [6].

Hypomagnesemia's status as the strongest single predictor identified in Zeng and colleagues' pooled analysis is worth dwelling on because it sits at an interesting intersection of patient characteristic and treatment-related factor: serum magnesium can be depleted by the chemotherapy regimen itself (through

renal wasting associated with platinum compounds, and through gastrointestinal losses from treatment-related diarrhea), which means hypomagnesemia is not purely a pre-existing patient trait in the way age or diabetes status is, but can develop over the course of treatment and interact with cumulative oxaliplatin exposure [12]. This mechanistic plausibility — magnesium's established role in stabilizing voltage-gated calcium and sodium channel function at the node of Ranvier, the very channels oxaliplatin's oxalate metabolite is thought to disrupt — is one reason intravenous calcium and magnesium infusion was, for a period, widely adopted as a prophylactic strategy against OIPN before the evidence supporting it became more contested, a development discussed in the section on prevention below [4,16].

Table 1: Representative predictors of chemotherapy-induced peripheral neuropathy in colorectal cancer patients receiving oxaliplatin, by category, with the effect estimate each cited study reports. [12,14,6,13,15,17].

Predictor	Category	Source	Reported Effect
Hypomagnesemia	Treatment-related / metabolic	Zeng et al. [12]	OR 4.17 (95% CI 2.00-8.33), pooled meta-analysis
Cumulative oxaliplatin dose ≥ 500 mg/m	Treatment-related, dose-dependent	Zeng et al. [12]	OR 1.79 (95% CI 1.20-2.63), pooled meta-analysis
Diabetes mellitus	Clinical comorbidity	Zeng et al. [12]; Uwah et al. [13]	OR 2.18 (95% CI 1.01-4.07), pooled; independently elevated risk in diabetic cohort
Higher body mass index / obesity	Demographic / clinical	Kanbayashi et al. [14]; Gonjobe et al. [6]	OR 1.06 per kg/m (95% CI 1.00-1.12); OR 21.66 (95% CI 2.574-182.244) for obesity
Age ≥ 60 years	Demographic	Zeng et al. [12]	OR 1.47 (95% CI 1.02-2.13), pooled meta-analysis
Lower baseline hemoglobin	Clinical / laboratory	Mizrahi et al. [15]	Independently associated with elevated CIPN risk
GSTP1 Ile105Val polymorphism	Genetic	Peng et al. [17]	No significant association, OR 1.08 (95% CI 0.67-1.74), pooled meta-analysis

Environmental cold exposure, identified as a significant predictor in the pooled Zeng analysis (OR 1.54), is mechanistically the most directly traceable to the acute channelopathy described earlier: because oxaliplatin's

acute neurotoxicity is a cold-triggered phenomenon at the level of individual sodium channel kinetics, patients whose occupational or environmental circumstances expose them more frequently to cold temperatures, cold water, or cold objects during the acute post-infusion window would be expected, on purely mechanistic grounds, to experience more frequent or severe acute symptoms, and the epidemiological association reported in the pooled analysis is broadly consistent with that expectation [12,4].

7. Genetic and Biological Predictors

The genetic predictor literature for OIPN presents a genuinely more mixed and, in places, disappointing picture relative to the demographic and treatment-related predictors discussed above, and it is important not to paper over that inconsistency. GSTP1 (glutathione S-transferase pi 1), an enzyme involved in cellular detoxification of platinum compounds, was for some years one of the most actively investigated candidate genes for OIPN susceptibility on the reasonable mechanistic hypothesis that reduced detoxification capacity conferred by the Ile105Val polymorphism might increase intracellular platinum accumulation and therefore neurotoxic injury. Peng and colleagues' systematic review and meta-analysis, pooling fourteen studies and 2,191 patients, found no statistically significant association between the GSTP1 Ile105Val polymorphism and oxaliplatin-induced neuropathy under any of the genetic models tested (dominant model odds ratio 1.08, 95% CI 0.67-1.74, $p=0.754$; recessive model odds ratio 1.67, 95% CI 0.56-4.93, $p=0.357$; allelic model odds ratio 1.22, 95% CI 0.67-2.24, $p=0.513$) [17]. This null result across a reasonably large pooled sample is a useful corrective against treating every mechanistically plausible candidate gene as an established predictor before the aggregate evidence has actually accumulated, and it stands as one of the clearer examples in this literature of a biologically reasonable hypothesis that did not survive rigorous meta-analytic scrutiny.

The broader search for validated blood-based biomarkers of OIPN risk or severity remains, at the time of this synthesis, an active but not yet clinically mature research area. Meregalli and colleagues' review of candidate molecular biomarkers for CIPN more broadly — spanning neurofilament light chain, markers of oxidative stress, and inflammatory cytokines —

describes a field with numerous biologically plausible candidates supported by preclinical and small clinical studies, but concludes that none has yet undergone the kind of large-scale prospective validation that would justify routine clinical use as a pretreatment risk-stratification tool [5]. Kanbayashi and colleagues' earlier methodological paper, which established ordered logistic regression as a statistically appropriate approach for modeling neuropathy as a graded rather than binary outcome across several distinct neurotoxic chemotherapy classes (bortezomib, taxanes, oxaliplatin, and vincristine), is itself a useful reminder that much of what the field currently has confidence in is clinical and demographic rather than molecular — the statistical machinery for building a multivariable predictive model is mature, but the genetic and biomarker inputs that would make such a model meaningfully more precise than a clinical-variables-only model are still, for the most part, not there yet [18].

Age, Comorbidity Burden, and the Limits of Single-Predictor Interpretation

It is worth noting explicitly that none of the demographic or clinical predictors discussed above operates in isolation in an actual patient, and most of the studies reviewed here used multivariable regression specifically to adjust each reported association for the others. Kanbayashi and colleagues' model, for instance, adjusted the BMI, sex, and cumulative dose associations for one another simultaneously, which is part of why those particular estimates are more directly comparable across the three predictors than, say, a bivariate association reported without adjustment would be [14]. Age and diabetes, in particular, tend to co-occur in an older colorectal cancer population, and disentangling how much of an elevated risk attributed to age reflects age itself versus the higher prevalence of diabetes, reduced renal magnesium handling, and other comorbidities that accumulate with age is a genuine interpretive challenge that individual cohort studies, even well-adjusted ones, cannot fully resolve without much larger sample sizes than most of the studies synthesized here achieved.

8. Prevention and Pharmacologic Management

Given how consistently cumulative dose predicts OIPN severity, a natural clinical response has been to seek pharmacologic interventions that could either prevent neuropathy from developing in the first place or treat it

once established, so that the dose-neurotoxicity tradeoff described earlier becomes less binding. Intravenous calcium and magnesium infusion around the time of oxaliplatin administration was, for roughly a decade, the most widely adopted prophylactic strategy, motivated by the same channel-stabilization mechanism discussed in the context of hypomagnesemia above. The NCCTG N04C7 trial, a randomized, placebo-controlled, double-blind study led by Grothey and colleagues in the adjuvant colon cancer setting, however, found no statistically significant benefit of calcium and magnesium infusion over placebo in reducing sensory neurotoxicity, a result that led to substantial reconsideration of the practice in clinical guidelines [16]. Wu and colleagues' subsequent systematic review and meta-analysis pooling multiple calcium-magnesium trials found a more mixed overall picture, with some pooled analyses suggesting a modest protective signal on certain neuropathy endpoints even as the largest individual trial (N04C7) reported a null result, illustrating how a single well-powered negative trial and a broader, more heterogeneous meta-analytic pooling can leave a genuinely unsettled clinical question even after a decade of accumulated study [19,16].

Pharmacologic treatment of established, symptomatic CIPN has a firmer evidence base, even though it addresses symptoms rather than the underlying predictors this article is chiefly concerned with. Smith and colleagues' randomized, placebo-controlled trial of duloxetine, a serotonin-norepinephrine reuptake inhibitor, in patients with established painful CIPN (the majority of whom had received oxaliplatin or paclitaxel) found a statistically and clinically meaningful reduction in average pain relative to placebo, and duloxetine subsequently became the only agent with a strong evidence-based recommendation for treating painful CIPN once it has developed [20]. Non-pharmacologic approaches have also shown promise specifically for functional rehabilitation rather than pain reduction: Ikio and colleagues' pilot randomized controlled trial of a combined hand exercise intervention in patients with established CIPN found measurable improvements in hand function and patient-reported symptom burden relative to a control condition, suggesting that structured rehabilitation may have a role in managing CIPN's functional consequences even where the underlying nerve injury itself cannot be reversed [21].

The practical upshot for risk-based clinical decision-making is that prevention remains considerably less well-supported than treatment of established symptoms. A clinician equipped with a patient's age, diabetes status, BMI, baseline magnesium, and expected cumulative dose can make a reasonably well-evidenced estimate of that patient's relative risk using the predictors reviewed in the preceding sections, but currently has no pharmacologic intervention with strong trial support to offer that patient prophylactically on the basis of that elevated risk — a genuine and clinically consequential gap between prediction and prevention that the following section discusses further.

9. Open Challenges

Several limitations recur across the predictor literature synthesized here and deserve to be stated plainly. First, effect sizes for even the best-replicated predictors are frequently modest and carry wide confidence intervals, particularly in the smaller single-center cohorts that make up a substantial share of the published evidence; Gonjobe and colleagues' 62-patient Tanzanian cohort, with its obesity odds ratio spanning from just above 2.5 to well over 180, is an illustrative extreme, but even Zeng and colleagues' larger ten-study pooled analysis reports several confidence intervals that only narrowly exclude the null [6,12]. This should temper how confidently any single predictor is communicated to an individual patient as a quantitative risk estimate, even when the direction of the association is well-established.

Second, no multivariable predictive model combining the demographic, clinical, and treatment-related predictors reviewed here has, to our knowledge, been externally validated across multiple independent colorectal cancer cohorts and translated into a clinical decision tool in routine use. Kanbayashi and colleagues' ordered logistic regression models are methodologically the most sophisticated approach used in the studies synthesized here, appropriately treating neuropathy grade as an ordinal rather than binary outcome, but even these remain single-cohort, internally validated models rather than externally validated risk-prediction tools ready for bedside deployment [18,14]. Third, and related, the genetic and biomarker literature has, with GSTP1 as the clearest example, produced more null and non-replicating results than confirmed predictors, which means the field currently lacks a molecular complement to the demographic and clinical risk factors

that would meaningfully sharpen prediction beyond what routinely collected clinical variables already provide [17,5].

Fourth, the acute-chronic distinction discussed early in this article is not consistently handled across studies: some report a single "any-grade CIPN" outcome that conflates transient acute cold-sensitivity with persistent chronic sensory loss, while others, like Gonjobe and colleagues, explicitly separate the two [6]. Because the predictors of acute and chronic OIPN are not necessarily identical, and because chronic neuropathy is the syndrome with the greater long-term functional and quality-of-life impact, future predictor studies would benefit from consistently reporting acute and chronic outcomes separately rather than as a combined endpoint. Fifth, the prevention literature's mixed results for calcium and magnesium infusion, discussed above, mean that even a patient correctly identified as high-risk by the predictors this article reviews currently has limited prophylactic options beyond dose modification and schedule adjustment, which is itself a form of accepting reduced treatment intensity to manage neurotoxicity risk [16,19].

Finally, much of the predictor literature synthesized here, including several of the larger and more methodologically rigorous studies, was conducted in specific national or regional populations — Japanese, Tanzanian, and UK cohorts feature prominently among the individual studies discussed — and the degree to which reported effect sizes generalize across the broader international population of colorectal cancer patients receiving oxaliplatin, who differ substantially in baseline nutritional status, comorbidity prevalence, and genetic background, is not yet well characterized [14,6,22].

10. Conclusion

The literature synthesized here supports a reasonably specific and clinically useful, if incomplete, picture: chemotherapy-induced peripheral neuropathy in colorectal cancer patients receiving oxaliplatin is predicted most consistently and with the largest, best-replicated effect sizes by cumulative oxaliplatin dose, hypomagnesemia, older age, diabetes mellitus, elevated body mass index, and, to a lesser but still statistically supported degree, smoking history and cold exposure during treatment [12,14,6,13,15]. Secondary analysis of the large multicenter SCOT trial provides further independent confirmation that clinical and

patient-level factors, assessed prospectively across a substantial trial population rather than retrospectively in a single center, meaningfully associate with CIPN development and severity in colorectal cancer specifically, lending additional external support to the predictor categories this article has organized its discussion around [22]. By contrast, the genetic and molecular biomarker literature has, at least for the most extensively studied candidate, GSTP1, failed to confirm a clinically useful predictive signal, leaving prediction in this domain currently grounded in readily available clinical and demographic variables rather than genotype or blood biomarkers [17,5].

Translating these predictors into practice will require two things the field does not yet fully have: a validated multivariable risk model built and externally tested across diverse colorectal cancer populations, and prophylactic interventions with trial evidence strong enough to justify acting on a patient's elevated predicted risk before neuropathy develops, rather than only treating pain once it is established, as duloxetine currently allows [20,16]. None of the gaps identified in this synthesis are reasons to discount the predictors that have been identified; a patient's age, diabetes status, baseline magnesium, body mass index, and expected cumulative dose already give an oncology team a meaningfully better basis for individualized counseling and treatment-schedule planning than a one-size-fits-all protocol does. But converting that predictive picture into genuine prevention, validated across the populations who actually receive oxaliplatin worldwide, remains the honest state of the evidence and the clearest direction for future research in this area.

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Conflict of Interest

The authors declare that they have no competing interests relevant to this work.

Data Availability Statement

No new clinical or experimental data were generated for this article, as it is a literature synthesis. All findings discussed are drawn from the cited published sources, and readers should consult those original publications for their underlying data availability statements.

Ethical Approval

Not applicable. This article is a literature synthesis and did not involve the recruitment of human participants, animal subjects, or the collection of primary clinical data.

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