

A Multimodal Approach to Discover Biomarkers for Taxane-Induced Peripheral Neuropathy (TIPN): A Study Protocol

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Abstract

Introduction: Taxanes are a class of chemotherapeutics commonly used to treat various solid tumors, including breast and ovarian cancers. Taxane-induced peripheral neuropathy (TIPN) occurs in up to 70% of patients, impacting quality of life both during and after treatment. TIPN typically manifests as tingling and numbness in the hands and feet and can cause irreversible loss of function of peripheral nerves. TIPN can be dose-limiting, potentially impacting clinical outcomes. The mechanisms underlying TIPN are poorly understood. As such, there are limited treatment options and no tools to provide early detection of those who will develop TIPN. Although some patients may have a genetic predisposition, genetic biomarkers have been inconsistent in predicting chemotherapy-induced peripheral neuropathy (CIPN). Moreover, other molecular markers (eg, metabolites, mRNA, miRNA, proteins) may be informative for predicting CIPN, but remain largely unexplored. We anticipate that combinations of multiple biomarkers will be required to consistently predict those who will develop TIPN. **Methods:** To address this clinical gap of identifying patients at risk of TIPN, we initiated the Genetics and Inflammatory Markers for CIPN (GENIE) study. This longitudinal multicenter observational study uses a novel, multimodal approach to evaluate genomic variation, metabolites, DNA methylation, gene expression, and circulating cytokines/chemokines prior to, during, and after taxane treatment in 400 patients with breast cancer. Molecular and patient reported data will be collected prior to, during, and after taxane therapy. Multi-modal data will be used to develop a set of comprehensive predictive biomarker signatures of TIPN. **Conclusion:** The goal of this study is to enable early detection of patients at risk of

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developing TIPN, provide a tool to modify taxane treatment to minimize morbidity from TIPN, and improved patient quality of life. Here we provide a brief review of the current state of research into CIPN and TIPN and introduce the GENIE study design.

Keywords

chemotherapy-induced peripheral neuropathy, multi-omics, mRNA, miRNA, metabolites

Introduction

The basis for the proposed research is that chemotherapy-induced peripheral neuropathy (CIPN) is a common, and sometimes debilitating, toxicity of some cancer treatments, such as taxanes.¹ CIPN typically manifests as tingling, numbness, and pain in the hands and feet, but can also include motor and other sensory symptoms, and can have enormous impact on quality of life.¹ Taxanes are among the most efficacious chemotherapeutic agents for solid tumors and are frequently used in the treatment of early stage and metastatic breast cancer. However, taxanes are known to produce severe neuropathic pain (TIPN) which is also one of the primary dose-limiting toxicities.^{2,4} A meta-analysis reported that the TIPN prevalence with paclitaxel was 70.8% (95% CI 43.5-98.1).⁵ A high incidence of CIPN has been noted even two years after treatment and was associated with intense pain and long-term opioid use.^{3,6,7}

Since the pathophysiology of TIPN is complex and not yet completely understood, its clinical management remains a challenge. There is currently no standard treatment for preventing or mitigating TIPN, and no clinical tools exist to predict which patients will develop TIPN. Development of CIPN can necessitate treatment delays or discontinuation, which may lead to increased rates of cancer recurrence.^{8,9} To address this clinical challenge of identifying patients at risk of TIPN, we launched the Genetics and Inflammatory Markers for CIPN Study (GENIE) study, a multimodal assessment of genetic, transcriptional, DNA-methylation-based, metabolic, and inflammatory markers of CIPN, as part of the National Institutes of Health (NIH) Helping to End Addiction Long-term (HEAL) initiative (<https://heal.nih.gov/>).

Genetic Associations with TIPN

Numerous genetic association studies, and some genome-wide association studies (GWAS), have evaluated single-nucleotide polymorphisms (SNPs) and a wide variety of genes have been linked to CIPN (Table 1, Table 2).^{10,36} Using a cohort of 3431 patients from a phase III adjuvant breast cancer trial (ECOG-5103), investigators identified *rs3125923*, a SNP in a gene desert on Chromosome 1, associated with grade 3-4 paclitaxel-induced peripheral neuropathy.³⁵ In a follow-up study, rare variants in SET binding factor 2 (*SBF2*) were associated with increased risk of paclitaxel-induced peripheral neuropathy in African American patients ($n = 213$).³⁶ SNPs in *FGD4*,³⁷ *EPHA4*, *EPHA5*, & *EPHA6*,^{38,40} *ABCBI*, and *CYP1B1* have all been associated with paclitaxel-induced neuropathy.^{12,13} In

addition, SNPs in *VAC14*, a gene related to cellular structure, were found to be associated with docetaxel-associated neuropathy.⁴¹ Of note, most genes identified from these genetic association studies have been previously implicated in regulating nerve damage, nerve repair, apoptosis, and inflammation, but findings remain inconsistent across studies.⁴² While, these studies have led to the discovery of variants associated with TIPN, inconsistencies in GWAS are common for many complex traits, where replication is difficult due to—1) lack of standardized TIPN phenotype definitions, 2) limited cohort sizes, 3) inconsistent adjustments for potential confounding from clinical, behavioral, or environmental factors (eg, treatment regimen), which can all impact inter-study variability. Thus, it is timely to address these issues and design longitudinal studies with significant sample size that also use multiple instruments for reporting TIPN phenotypes in order to identify universal biomarkers.

DNA Methylation Associations with TIPN

We found a paucity of studies exploring epigenetic DNA-methylation processes that contribute to TIPN. In a study of cancer survivors with chronic paclitaxel-induced peripheral neuropathy, researchers identified evidence that the expression of *HISP* genes in peripheral blood, which is associated with chronic paclitaxel-induced peripheral neuropathy, may be regulated by DNA methylation.⁷² Another study demonstrated that DNA hypomethylation in the *PAX6* gene lead to the upregulation of the *PAX6* pathway contributing to the mechanical allodynia following oxaliplatin, paclitaxel, or bortezomib treatment.⁷⁵ Given the role that DNA methylation may play in the development and maintenance of neuropathy, there is an opportunity to investigate the DNA methylome in TIPN that can potentially lead to new predictors or therapeutic targets for TIPN.

mRNA and miRNA Associations with TIPN

While the pathophysiological mechanisms that lead to CIPN have been studied extensively and appear to involve neuronal dysfunction and inflammatory processes, comparative gene expression studies are still limited. Recent transcriptomic studies of the dorsal root ganglion (DRG) have shown that oxaliplatin treatment led to altered expression of genes associated with neuronal damage while vincristine- and cisplatin-induced gene expression changes were primarily associated with inflammatory responses.⁸² One study investigating mRNA expression in the spinal cord of a rodent model of paclitaxel-induced

Table 1. Snapshot of Studies (2010-2021) Conducted in the Field of Taxane-Induced Peripheral Neuropathy Across Different -Omics Platforms

Studies	Gene variants	mRNA	DNA methylation	Metabolomics	miRNA
GENIE	✓	✓	✓	✓	✓
Parker et al, 2010 ⁴³				✓	
Sucheston et al, 2011 ²⁰	✓				
Schneider et al, 2011 ⁴⁴	✓				
Baldwin et al, 2012 ¹³	✓				
Naguib et al, 2012 ⁴⁵		✓			
Wheeler et al, 2013 ⁴⁶	✓				
Hertz et al, 2013 ¹⁸	✓				
McWhinney et al, 2013 ²¹	✓				
Bergmann et al, 2013 ⁴⁷	✓				
Leandro-Garcia et al, 2013 ⁴⁸	✓				
Saura et al., 2013 ⁴⁹		✓			
Ochi-ishi. <i>Et al</i> 2014 ¹⁷		✓			
Beutler et al, 2014 ¹⁴	✓				
Hertz et al, 2014 ¹⁶	✓				
Chhibber et al, 2014 ²³	✓				
Park et al, 2014 ⁵⁰	✓				
Zhang et al, 2014 ²⁴		✓			
Boora et al, 2015 ¹⁵	✓				
Kulkarni et al, 2015 ²²	✓				
Johnson et al, 2015 ²⁸	✓				
Reyes-Gibby et al, 2015 ¹¹	✓				
Schneider et al, 2015 ³⁵	✓				
Wheeler et al, 2015 ²⁵		✓			
Komatsu et al, 2015 ⁵¹	✓				
Schneider et al, 2016 ³⁶	✓				
Boora et al, 2016 ¹²	✓				
Hertz et al, 2016 ²⁶	✓				
Lam et al, 2016 ⁵²	✓				
Sundar et al, 2016 ⁵³		✓			
Sisignano et al, 2016 ⁵⁴				✓	
Yamashita et al, 2017 ⁵⁵		✓			
Van Rossum et al, 2017 ⁵⁶	✓				
Kober et al, 2018 ⁵⁷		✓			
Wu et al, 2018 ⁵⁸				✓	
Mahmoudpour et al, 2018 ⁵⁹	✓				
Sucheston-Campbell et al, 2018 ⁶⁰	✓				
Sun et al, 2018 ⁶¹	✓			✓	
Leibovici et al, 2018 ⁶²					
Li et al, 2018 ⁶³		✓			
Mao et al, 2019 ⁶⁴		✓			
Peng et al, 2019 ⁶⁵					✓
Wu et al, 2019 ⁶⁶			✓		
Kober et al, 2019 ⁶⁷		✓			
Singh et al, 2019 ⁶⁸		✓			
Ha et al, 2019 ⁶⁹		✓			
Chen et al, 2019 ⁷⁰		✓			
Chen et al, 2020 ³⁷	✓				
Noda-Narita et al, 2020 ⁷¹					✓
Kober et al, 2020 ⁷²		✓	✓		
Meade et al, 2020 ⁷³		✓			
Tanabe et al, 2020 ⁷⁴	✓				
Zhang et al, 2020 ⁷⁵			✓		
Kim et al, 2020 ⁷⁶		✓			
Kim et al, 2020 ⁷⁷		✓			
Chua et al, 2020 ⁷⁸	✓				
Li et al, 2021 ⁷⁹		✓			
Caillaud et al, 2021 ⁸⁰		✓			
Adjei et al, 2021 ⁸¹	✓				

Table 2. Genes Containing Genetic Variants That Have Been Reported to be Significantly Associated with Taxane-Induced Neuropathy

Study	Gene	Taxane treatment
Sucheston et al, 2011 ²⁰	<i>FANCD2</i>	Paclitaxel
Schneider et al, 2011 ⁴⁴	<i>RWDD3,TECTA</i>	Paclitaxel
Baldwin et al, 2012 ¹³	<i>FGD4,EPHA5,FZD3</i>	Paclitaxel
Wheeler et al, 2013 ⁴⁶	<i>RFX2</i>	Paclitaxel
*Bergmann et al, 2013 ⁴⁷	<i>RWDD3,TECTA</i>	Paclitaxel
Hertz et al, 2013 ¹⁸	<i>CYP2C8</i>	Paclitaxel
McWhinney et al, 2013 ²¹	<i>SOX10, BCL2, OPRM1, TRPV1</i>	Paclitaxel & Docetaxel
Leandro-Garcia et al, 2013 ⁴⁸	<i>EPHA4, EPHA5, EPHA6, XKR4, LIMK2</i>	Paclitaxel
Beutler et al, 2014 ¹⁴	<i>PRX, ARHGEF10</i>	Paclitaxel
Hertz et al, 2014 ¹⁶	<i>CYP2C8, ABCG1</i>	Paclitaxel
Chhibber et al, 2014 ²³	<i>MAP1B, NGF, TRPV2, FXN, MT3, CCR5, CXCL12, RYK, SLIT1, NTRK3, NDELI</i>	Paclitaxel
Park et al, 2014 ⁵⁰	<i>MAPT, GSK3B</i>	Paclitaxel
Boora et al, 2015 ¹⁵	<i>ARHGEF10</i>	Paclitaxel
**Kulkarni et al, 2015 ²²	<i>RWDD3,TECTA</i>	Paclitaxel
Johnson et al, 2015 ²⁸	<i>GPX7, ABCC4, MGMT, GST</i>	Paclitaxel
Reyes-Gibby et al, 2015 ¹¹	<i>TP53, MYC, PARP1, P38 MAPK, TNF, BCL2</i>	Paclitaxel
Schneider et al, 2015 ³⁵	<i>FCAMR</i>	Paclitaxel
Schneider et al, 2016 ³⁶	<i>SBF2</i>	Paclitaxel
Komatsu et al, 2016 ⁵¹	<i>AIPL1, BCR</i>	Paclitaxel
Boora et al, 2016 ¹²	<i>EPHA5, ABCB1, CYP2C8, CYP1B1</i>	Paclitaxel
Hertz et al, 2016 ²⁶	<i>VAC-14</i>	Docetaxel
Lam et al, 2016 ⁵²	<i>FGD4, CYP2C8</i>	Docetaxel
van Rossum et al, 2017 ⁵⁶	<i>TECTA, GSTP1</i>	Docetaxel
Mahmoudpour et al, 2018 ⁵⁹	<i>FBXO33, INTU, BCL6, IL17RB</i>	Paclitaxel and Docetaxel
Sucheston-Campbell et al, 2018 ⁶⁰	<i>GNGT1, NXN, MIR5684, FGD2</i>	Paclitaxel
Leibovici et al, 2018 ⁶²	<i>BDNF</i>	Paclitaxel
Chen et al, 2020 ³⁷	<i>FZD3</i>	Paclitaxel
Tanabe et al, 2020 ⁷⁴	<i>SCN9A, SCN10A</i>	Paclitaxel and Docetaxel
Chua et al, 2020 ⁷⁸	<i>SIPRI</i>	Paclitaxel
Adjei et al, 2021 ⁸¹	<i>PDE6C, N08Cx, TMEM150C</i>	Paclitaxel

*In this study, the authors tested whether the two gene variants previously reported by Schneider et al, 2011 demonstrated a significant association with CIPN in their Scandinavian ovarian cancer cohort. However, Bergmann et al, didn't find any significant association.

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peripheral neuropathy identified 814 differentially expressed genes in treated rats exhibiting paclitaxel-induced peripheral neuropathy versus untreated controls.⁷⁹ These genes mapped to immune/inflammatory response, central sensitization, chronic

pain, and neurotrophin signaling pathways known to regulate neuroinflammation.⁷⁹ Paclitaxel has also been shown to modify gene expression in the DRGs while also over-expressing proteins, C-C motif chemokine ligand-2 (CCL2), tumor necrosis factor-alpha (TNF α) and interleukin-6 (IL-6), which may lead to PIPN.⁸³ It has also been shown that paclitaxel exposure resulted in expression of NLRP3 and activated fragments of caspase-1 and interleukin-1 β in L4-6 DRG and sciatic nerve indicating activation of Nod-like receptor proteins (NLRP3) inflammasome, which may result in peripheral neuropathic pain.⁸⁴ Peroxisome Proliferator-Activated Receptor (PPAR)- α expression is also known to regulate inflammatory responses leading to paclitaxel-induced peripheral neuropathy.⁸⁰ While, in the past, transcriptomic analyses have greatly extended our understanding of pain mechanisms,⁸⁵ comparative gene expression analyses to understand TIPN development is still lacking.

Available evidence regarding the role of miRNAs in TIPN is limited. Previously published work has established that selected miRNAs such as miR-155 and miR-124 play a role in inflammatory processes, neurodegeneration, neurodevelopment, and synapse morphology.^{86,87} Recently, miR-155 was shown to modify bortezomib (BTZ)-induced neuropathic pain through TNFR1-TRPA1 pathway, suggesting that miR-155 is a potential target in preventing CIPN development during BTZ treatment.⁸⁶ In another study, it was demonstrated that miR-451a, which regulates the expression of the drug-transporter protein P-glycoprotein, potentially promoted paclitaxel resistance.⁷¹ In summary, prior work exploring miRNAs in TIPN should be considered promising yet preliminary. Additional studies are needed to confirm findings and determine the clinical utility of measuring miRNAs as a tool to identify TIPN risk.

Metabolomics

There are few studies describing metabolic changes from taxanes and their role in the pathogenesis of neuropathic pain, and to our knowledge, only a single study specific to paclitaxel.⁸⁸ A cell-based metabolomics survey performed in neuroblastoma cells suggested a potential role of altered fatty acid oxidation in different neurotoxicity patterns observed such as neuropathic pain induced by paclitaxel treatment.⁸⁸ However, the role of metabolites deriving from other drugs, such as oxaliplatin, have been implicated to be involved in the etiology of CIPN. For instance, oxalate (derived from oxaliplatin) alters calcium signaling leading to damage in intracellular structures in neuronal and glial cells.⁸⁹ Recently, a metabolomics approach was employed to develop a user-friendly tool that can predict vincristine-induced peripheral neuropathy susceptibility at different stages of a patient's chemotherapy treatment.⁹⁰ While there is a paucity of such data, especially for taxanes, we anticipate that metabolic biomarkers may improve model predictions of TIPN.

In summary, current literature includes numerous studies that have explored potential relationships between genomic variants and TIPN. Several genetic biomarkers show promise yet remain inconsistent in predicting TIPN. By contrast, there are fewer studies exploring relationships between the miRNome,

DNA methylome, and metabolome with TIPN. A few potential epigenetic or metabolomic biomarkers have emerged, but to date have limited ability to predict TIPN.

This proposal seeks to enhance this knowledge based on the premise that a single biomarker from one modality (i.e., genetic) will be insufficient to consistently predict TIPN. We anticipate that multiple biomarkers from several modalities (e.g., genetic, epigenetic, and metabolomic) together will be required to consistently predict those who develop TIPN. We also anticipate heterogeneous presentations of TIPN and that one biomarker signature will not work for all patients, but rather a set of signatures will be needed to capture all those who are at risk for developing TIPN.

The primary objective of this study is to build predictive biomarker signatures of peripheral neuropathy in patients undergoing taxane therapy to treat breast cancer. We will use pre-treatment, on-treatment, and post-treatment blood samples from patients treated with taxanes for breast cancer. We will investigate genetic (SNPs), mRNA, miRNA, DNA-methylation, inflammatory, and metabolic associations with validated self-reported pain questionnaires that measure sensory, motor, and autonomic symptoms, and functional limitations related to TIPN.^{10,16} From this data, machine learning techniques will be used to construct predictive biomarker signatures. In addition to the molecular markers, we will also use baseline demographic variables (e.g., race, age, ethnicity, insurance status) and other clinical variables from medical history such as pre-existing comorbidities, other therapies, surgery, prescription medications, and baseline clinical labs to investigate associations with TIPN.

We hypothesize that patients that develop TIPN will 1) have differences in baseline clinical and molecular characteristics and 2) develop detectable differences in molecular biomarkers over time. As an initial step towards conducting a GWAS, we will first investigate gene candidates which are already established to be associated with TIPN in previous GWAS studies (Table 2). We anticipate that patients who develop TIPN will overrepresent gene variants in pain, metabolic, and neuroinflammatory pathways, and anticipate that pain-associated genes such as *CNR2*, *SCN9A*, *COMT*, *CDKL5*, *TRPA1*, and *OPRM1*, will develop detectable differences in mRNA expression over time. We also hypothesize that molecular biomarker signatures exist that (i) identify patients with high probability of developing TIPN and (ii) will change in the presence of taxanes and serve as a leading indicator for TIPN development. We envision that the results from this study will provide a means of identifying susceptible patients early in their development of TIPN, enabling personalized dose adjustments to minimize adverse symptoms, optimize therapeutic outcomes, and improve quality of life.

Methods

Focused Literature Review

To form the scientific foundation for conducting this study, we performed an initial survey of the literature to establish a benchmark of the published genomic, transcriptomic, metabolomic,

inflammatory, and DNA-methylation-based biomarkers of TIPN. We conducted an electronic search in PubMed using the following terms: “paclitaxel”, “taxanes”, “chemotherapy-induced peripheral neuropathy”, “gene variants”, “SNP”, “GWAS”, “gene expression”, “messenger RNA”, “mRNA”, “microRNA”, “DNA methylation”, “metabolite”, and “biomarker” in published work from 2004 to 2021. For our focused review, we included papers that investigated associations between each of the different molecular data types above or multi-modal analyses for TIPN associated outcomes. In this review, we restricted our criteria to only include papers that investigated more than one biomarker candidate in GWAS and mRNA-based studies, therefore excluding single candidate gene studies. However, due to paucity of studies for metabolomics, DNA methylation, and miRNA surveys, we included papers that investigated single biomarker candidates and also expanded beyond only taxanes to include other treatment regimens such as cisplatin, oxaliplatin and vincristine (ie, CIPN). At the time of this analysis, we identified 145 published papers between 2004 and 2021 discussing genetics, miRNA, mRNA, DNA-methylation or metabolomics related to CIPN. Of those, 17 were clinical trials, two were meta-analyses, 14 were narrative reviews and one was a systematic review. By domain, 120 described genetic findings, of which 30 were genetic association studies, two DNA-methylation based, 20 mRNA-based, two miRNA-based and four described metabolite findings associated with CIPN. Within this body of literature, we explored the following questions—1) What genes and gene variants have been associated with CIPN? 2) Which DNA-methylation mechanisms and RNA (mRNA and miRNA)-based processes have been associated with CIPN? 3) What metabolic processes are associated with CIPN? The knowledge and associated gaps identified from these studies are discussed below.

Study Design

We intend to conduct a prospective, observational, repeated measures, multicenter study to collect data across several domains. This study will be conducted at (i) Cleveland Clinic Foundation (8 regional sites in Ohio and 1 in Florida); (ii) Huntsman Cancer Institute, University of Utah. The study population will consist of patients scheduled to receive taxane chemotherapy for breast cancer at two tertiary medical centers. Eligible participants will be: a) female > 18 years of age; b) have no history of pre-existing neuropathy or chronic pain; c) presenting for their initial course of taxane-based chemotherapy for breast cancer, d) scheduled to receive intravenous standard-dose taxane (paclitaxel, docetaxel) and e) able to provide informed consent (Supplementary Table 1). Patient will be invited to participate at their initial visit with a medical oncologist. Exclusion criteria focus on the use of other chemotherapeutic agents known to cause CIPN, chronic opioid use, pre-existing neuropathies, and chronic steroid use. Detailed inclusion and exclusion criteria are presented in Supplementary Table 1. The total enrollment goal is 400 patients. Subjects will be active in the study for approximately 13 months (screening, 8-12 weeks of therapy and 9 months follow-up). The study is planned to enroll

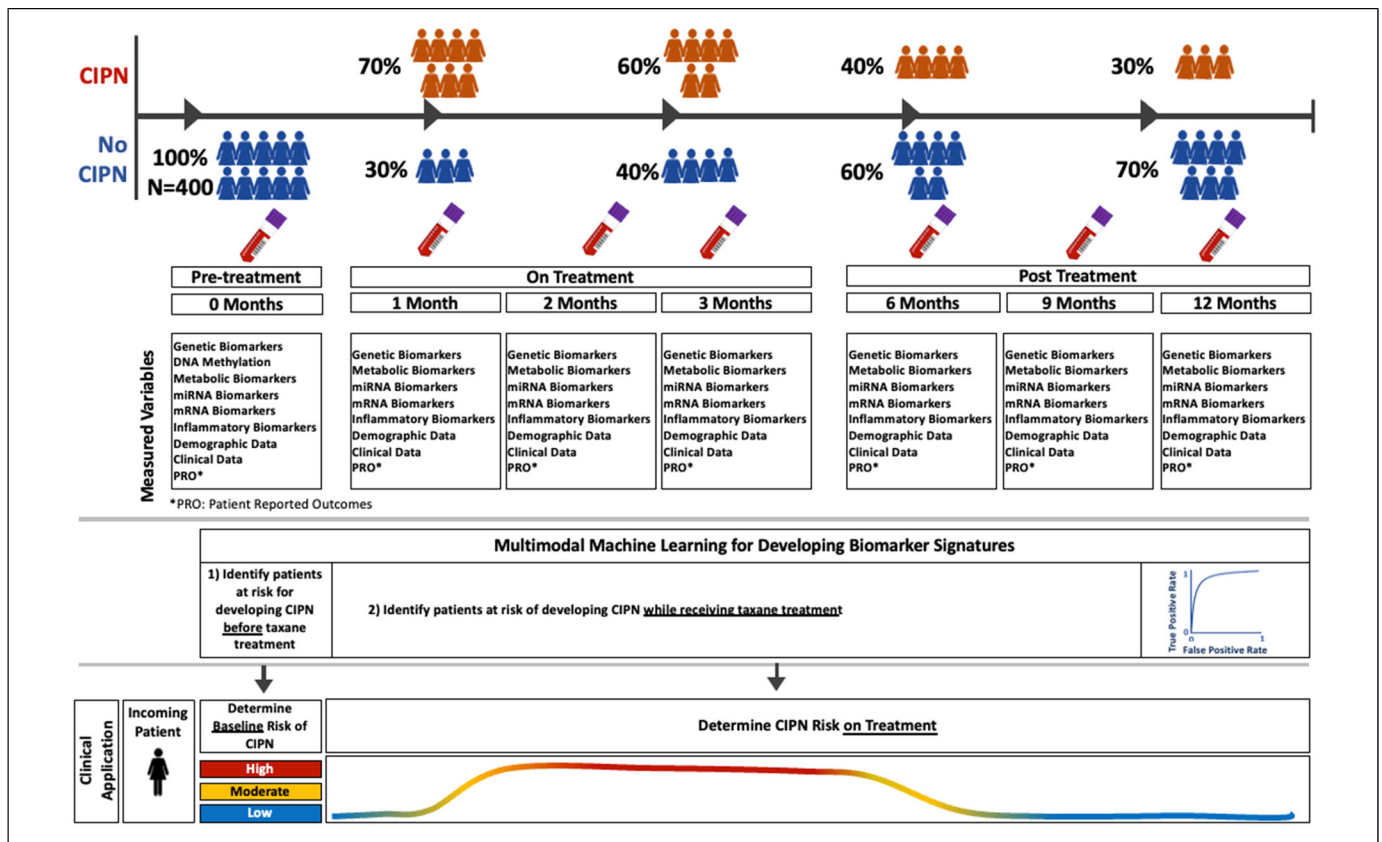


Figure 1. Schematic representation of the study design and future clinical utility. A total of 400 patients with breast cancer will be enrolled prior to initiation of taxane-based chemotherapy. Based on previous studies, we anticipate approximately 70% of patients enrolled will experience at least mild chemotherapy induced peripheral neuropathy (CIPN), and many will experience persistent CIPN post-treatment. Detailed questionnaires will be completed at each study visit (Table 2) and blood samples will be collected to investigate multiple -omics platforms. Machine learning will be utilized to develop (1) a biomarker signature to predict risk of CIPN pre-treatment, and (2) an on-treatment biomarker to serve as a leading indicator of CIPN onset.

for 42 months, and the total duration from opening enrollment to last patient visit should be 48–54 months.

Data Collection

Molecular data, demographic, clinical, and patient reported outcomes will be collected prior to receiving taxane therapy, the fourth, eighth, and 12th week of chemotherapy, and at 3, 6, and 9 months after completion of therapy (Figure 1, Supplementary Table 2). Data on the demographics of the patients, their chemotherapy, concomitant drug use, and symptoms reported on validated questionnaires will also be obtained. The following clinical variables will be assessed via medical record review: date of diagnosis, stage, date of the on-study chemotherapy infusion, chemotherapy regimen, changes in the treatment regimen, and prescribed medications including antibiotics (up to six months prior) and opioids. Clinical data including adverse events (AEs), concomitant medications, clinical outcomes and laboratory data will be recorded in a secure database. The database will be subjected to internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate. All study documents will be retained for a

minimum of 3 years following study termination and will subsequently move to long term storage at primary study site.

Molecular data will include genetic, epigenetic, metabolic, and inflammatory biomarkers. A list of variables is presented in Supplement Table 2. The objective of this study is to acquire blood samples over 12 months starting from the first initiation of chemotherapy. The blood samples will be used to identify biomarkers from a series of genetic, epigenetic, and metabolomic changes to determine their prognostic and diagnostic utility. As with any study where multiple sites are generating data or multiple assay runs are used to generate data, it is important to take measures to minimize and address any observed batch effects. To minimize batch effects between sites, all sites will be trained jointly on the blood processing protocol to ensure consistent processing. In addition, we will also evaluate the sample quality (e.g., mRNA) between sites. To address any batch effects that are observed, due to repeated assay runs, we will include a set of pooled QC samples in each run to allow for adjustments to be made to address any observed batch effects. These measures will 1) minimize the development of batch effects, and 2) correct for any observed batch effects at the analysis stage.

There is no universally accepted CIPN phenotype, which adds to the challenge of comparing results from multiple studies. The use of multiple pain assessment tools has been recommended as a strategy to improve detection and quantification of pain in CIPN.⁹¹ We will collect the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) reporting for peripheral sensory and motor neuropathy. In addition, we will use a set of four patient-reported outcomes instruments to assess pain and other neuropathic symptoms. They include: 1) The European Organization for Research and Treatment of Cancer's CIPN20, a 20-item questionnaire, is a measure of pain, sensory, motor, autonomic symptoms, and functional limitations related to CIPN.⁹² 2) The short form (9-item) and pain severity versions (4-item) of the Brief Pain Inventory (BPI), which is a measure of the severity and functional impact of pain.^{93,94} 3) The pain catastrophizing scale (PCS)^{95,96} which is a 13-item instrument is a 13-item measure of how patients ruminate about their pain, magnify their pain, and feel helpless to manage their pain.^{97,99} 4) The Patient Reported Outcome Measurement System (PROMIS) which is a measure of anxiety, depression, and pain interference developed by the NIH to characterize pain, function, and other domains in cancer patients.^{100,101} These assessments are part of the NIH common data element (CDE) repository (<https://cde.nlm.nih.gov/home>)¹⁰² and are being used across the NIH HEAL initiative (<https://heal.nih.gov/>)¹⁰³ to improve opportunities for data sharing and integration across studies.

To further characterize a CIPN phenotype, we will explore relationships between CIPN20 scores over time with the other patient-reported outcomes instruments. We anticipate that selected profiles of CIPN20 responses in combination with measures of pain, anxiety, depression, catastrophizing, and pain interference will create reproducible profiles of clinically significant TIPN and can be used to create a tool to discriminate those that have and don't have TIPN.

The study protocol adheres to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with the National Cancer Institute (NCI) guidelines. Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial follows the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). Data collected for this study will be analyzed and stored at the Cleveland Clinic. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Cleveland Clinic and any NIH required repositories (e.g., DBGaP) for use by other researchers including those outside of the study. Permission to transmit data will be included in the informed consent.

The Genetics and Inflammatory Markers for CIPN Study (GENIE) Approach. In the field of precision oncology, genomics with analyses from other modalities has revealed key mechanisms

in cancer development, treatment resistance, and recurrence risk. This approach has been successfully utilized to predict risk of recurrence in breast cancer by several clinically validated, and widely used platforms, such as Oncotype DX and the The Prosigna Breast Cancer Prognostic Gene Signature Assay (PAM50).⁹⁴ These systems use signatures derived from multiple genes to develop a predictive score that has been widely used to guide clinical practice.^{94,95} In one study, it was found that use of the Oncotype DX recurrence score altered the treatment of 44% of patients.⁹⁶

Using, the multimodal data, we expect to assemble an effective and practicable panel of biomarkers that can be used to evaluate the severity and progression of TIPN in breast cancer patients. As described below, we will leverage recent advancements in interpretable machine learning to ensure that the models provide clear information about why they are making certain predictions in order to increase trust and subsequent clinical adoption. We will begin by characterizing the association of biomarkers in each modality with the presence or absence of TIPN. Machine learning will be used to build candidate biomarker signatures to predict TIPN before and during taxane treatment. The following are methodologic gaps that we hope to address: 1) identify a single, optimal self-reported questionnaire for TIPN in patients with a heterogenous presentation of TIPN; 2) identify modeling approaches that best utilize the data that will be obtained from each -omic modality.

Statistical Analyses

Sample Size Determination and Power Analyses. Our sample size was developed with the goal of identifying combinations of biomarkers that will discriminate patients with TIPN. The proposed analyses will have sufficient statistical power to detect very reasonable prediction accuracies for classifying patients based on their likelihood of developing TIPN. We will recruit 400 patients undergoing taxane treatment for breast cancer. Based on a 1/3 sample size for the withheld test set ($n = 132$), and with a conservative estimate of 20% developing TIPN, we will have >80% power at the 0.05 significance level to detect an AUC >0.67 between those with TIPN and those without, indicating that the study is well powered to achieve the stated objectives.¹⁰²

Model Development Overview. To determine an optimal set of biomarkers to include in the multimodal TIPN biomarker signature, we will implement multiple approaches to analyzing data from a repeated measures study. With this approach, we anticipate a large, high-dimensional data set consisting of numerous genetic, epigenetic, transcriptomic, and metabolic measurements from hundreds of patients over time. Selected approaches will include:

1. The questionnaire scores described in the previous section will be evaluated either as dichotomized variables (i.e., having TIPN or not at any point during the study) or as continuous variables. CIPN20 score will

be used as the primary endpoint. Associations between baseline biomarkers across all domains and the presence or absence of TIPN will be explored using appropriate regression models.

2. Models predicting TIPN from data collected at baseline, on treatment, and after treatment will be built using the *lmms* framework.¹⁰³ This framework is a serial modeling approach to reduce time course data to only that which is needed and includes a clustering analysis to identify data profile groups correlated over time.
3. We will explore potential sources of bias that may influence biomarker associations with TIPN, (e.g., treatment regimen, comorbidities, patient demographics). We will determine whether these data can be incorporated as predictors or if statistical adjustments are needed to address the bias.

Each approach holds potential to elucidate biomarkers predictive of TIPN and may also provide new insight into the etiology of this disorder.

Multimodal Biomarker Signatures Using top Signals. We will use two randomly allocated sets of patient data: a discovery cohort for cross-validation, and a test cohort to evaluate model performance and overfitting. We will build two models, one that offers predictions of TIPN from pre-treatment data and a second one that offers predictions of TIPN based on 1-2 month changes post-treatment and prior to the onset of TIPN. We anticipate that not all biomarkers from each domain will be needed, but that a parsimonious set of biomarkers from multiple modalities may improve predictive accuracy. The overall result will be a predictive risk score for TIPN that can be used to classify patients as low, moderate, or high risk to guide clinical management,^{104,106} based on extent of impacts on physical functioning and likelihood of treatment discontinuation.

Due to the high dimensionality of the data that will be generated, we will first need to reduce the feature space. We will do this by performing statistical analyses on each individual modality to identify the top signals. We will then evaluate a variety of modeling approaches using these top signals including simple regression to more complex machine learning approaches, such as Random Forest Ensemble Classification, Support Vector Machine Classification/Regression, and Neural Networks. We will also employ Ensemble Learning approaches, which construct a single learning algorithm from multiple models. In addition, new developments in wide-and-deep neural networks allow for flexible model structures that can jointly train data from multiple input modalities.¹⁰⁷

Machine learning algorithms are notoriously difficult to interpret, making clinical implementation a challenge. To address this, we will focus on approaches that best enable clinical adoption. One example is the use of Random Forest for variable selection, and then modeling these variables using Classification and Regression Trees (CART) to produce an easily understood decision tree.¹⁰⁸ This approach has the

advantage of capturing complex interactions while having excellent interpretability.¹⁰⁹ In addition, advancements in interpretable machine-learning have enabled insight into model decisions that were previously black-boxes. For example, Shapley Additive exPlanations (SHAP) method no longer require one to trade model interpretability with model performance.¹¹⁰ Approaches like SHAP allow for one to see the weights associated with specific predictive features with the subsequent model prediction, enabling trust in the model predictions and ultimately improved clinical adoption. We are committed to identifying parsimonious and interpretable models since the goal of this study is to develop clinically actionable biomarker signatures for TIPN.

Promising predictive biomarker models will be constructed using cross-validation to prevent model over-fitting. Model predictive performance will be measured by receiver operating characteristic curve analysis, and predictive performance metrics such as sensitivity and specificity will be ascertained. There is limited literature demonstrating implementation of machine-learning models to develop biomarker signatures using SNP, DNA methylation, mRNA, miRNA, or cytokine data for TIPN. A metabolomics study recently identified an approach for early prediction of vincristine-induced peripheral neuropathy (AUC >0.9).⁹⁰ Other studies have investigated the various potential biomarkers using association tests, but did not evaluate them in a withheld test, so predictive accuracy cannot be ascertained.¹¹¹ We hope to achieve an AUC >0.8 for our models using multimodal data in order to have a clinically actionable model.

Multimodal, Time-Course, Model Development. Integrating data across modalities by identifying similar expression changes over time could identify co-regulated molecules from a common underlying mechanism, leading to an on-treatment biomarker capable of serving as a leading indicator of TIPN onset. The DynOmics approach, developed by Straube et al, accommodates high-dimensional data with potential for lagged effects.¹¹² We anticipate that selected predictive biomarkers may have a delay in observed expression.¹¹² This innovative approach can identify timing differences in the expression for miRNA, metabolites, mRNA, and cytokines.¹¹² Additional approaches have also been developed which are capable of clustering time series data, which may elucidate subgroups that have modified CIPN risk based on similar expression profiles across biological modalities^{113,114}

Discussion

To address the clinical challenges with TIPN, approaches are needed that better capture the risk of TIPN at multiple biological levels (eg, molecular pathways, genetic, epigenetic, metabolic). While prior research efforts focused on individual molecules, pathways, or cells of interest, new -omics technologies including metabolomics, proteomics, and epigenetics allow characterization of complex biological systems across a wider scale. Our focused literature review indicated that there is a

substantial lack of research into many molecular processes related to CIPN. Although many studies have investigated the role of genetic variation in the development of CIPN, few studies have investigated biological processes that are dynamically impacted by both genetics and environment, such as miRNA, DNA methylation, metabolomics and others. This presents an opportunity to identify novel biomarkers that may be useful in predicting risk of CIPN. Furthermore, the lack of a single, accepted definition of CIPN has complicated the ability to compare findings across studies, highlighting the need to use common data elements for PRO collection. Additionally, given the complex pathophysiology of CIPN, there can be different sources of influence such as treatment regimens, underlying comorbidities, race, and sex, which also need to be investigated. Therefore, studies like GENIE that implement integrative new approaches leveraging advancements in multimodal analysis may provide substantial progress in our understanding of CIPN.

To address the identified gaps due to inconsistent CIPN assessments, our study will use four different assessment tools which are linked to NIH CDEs to standardize quantification and allow for future comparability. We will also investigate the use of a weighted cumulative score from all four instruments that could lead to a more multifaceted way to measure TIPN. The longitudinal nature of this study will allow for investigation of molecular changes associated with TIPN that occur over the course of treatment. The use of multimodal biomarkers over time and the ability for machine learning to identify non-linear relationships in data provides new opportunities for developing a clinically relevant biomarker signature.

In the event that we do not observe statistically significant biomarker associations with the development of TIPN using marker-by-marker approach, we will still be able to consider whether combinations of biomarkers, while not independently statistically significant, can collectively result in a clinically meaningful and robust biomarker signature for predicting which patients are at risk of TIPN. This is possible due to the ability of machine learning to account for non-linear relationships between many variables.

As with any study, there are important study limitations that should be considered. First, the time from when blood samples are obtained to when they are processed may influence biomarker measurements across modalities, and we have developed standard operating procedures in an effort to mitigate this risk. Second, although we plan to enroll a large study cohort for a study of this type, a sample size of 400 patients may be inadequate to detect biomarkers with smaller effect sizes. Should we discover meaningful relationships between selected gene variants or pronounced differences in gene expression among other findings, additional work would be warranted with larger sample sizes to confirm these relationships with TIPN. Third, we may find that certain biomarkers, although predictive, may be difficult to translate into clinical practice. A feasibility study will be required to evaluate the clinical utility of these models at the point of care in terms of cost

and the time required to gather the necessary sample. Importantly, this work is primarily exploratory in nature and will require a prospective study to confirm the effectiveness of using the developed predictive models to personalize taxane therapy management in a manner that minimizes the risk of developing TIPN.

Depending on the results of this study, a follow-up study will be planned to test the efficacy of our models in a randomized, prospective trial of risk-based cancer care delivery, at the Cleveland Clinic and Huntsman Cancer Hospital, University of Utah, in addition to other potential sites. In addition, the risk prediction model can be tested in a prospective-retrospective analysis using samples and data from other cohorts such as SWOG S1714 (<https://www.swog.org/clinical-trials/s1714>) and SWOG S0221 (<https://www.swog.org/clinical-trials/s0221>).

Conclusion

At the completion of this study, we intend to have developed a robust clinical risk prediction algorithm for peripheral neuropathy for patients treated with taxanes. The risk prediction model could: 1) inform the assessment and discussion of risks versus benefits of taxane-based treatment in individual patients, 2) provide functional insights which would allow development of mechanism-based prevention strategies for TIPN, and 3) allow identification of a population at risk in which to prospectively evaluate strategies to mitigate TIPN. The ability to predict who is at greatest risk for TIPN would improve treatment selection in the immediate term, and more importantly could inform drug development by providing a greater understanding of the pathophysiology of TIPN and allow interventional trials designed to prevent TIPN in patients at greatest risk of developing neuropathy. We are dedicated to making our research fully transparent so that other researchers may reproduce our results and extend our methods to advance the knowledge in this important and poorly understood area of medicine.

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Conflict of Interest Disclosures

D.M.R. has received research support from Novo Nordisk, consulting honoraria from Pharmazaam, has equity in Clarified Precision Medicine, LLC, is on the board of Bluem, and owns intellectual property related to the detection of liver cancer. K.B.J. has received research support from Medtronic, has equity in Applied Medical Visualizations, LLC, is on the advisory board of Senzime, is a board examiner for the American Board of Anesthesiology, the Section Editor of International Anesthesia Research Society–Anesthesia and Analgesia, and on the Editorial Board of the International Anesthesia Research Society. J.H. has received consulting honoraria from MCG Health.

Ethics and Dissemination Statement


The GENIE study has been approved by the Institutional Review Board (IRB) of the Cleveland Clinic (approval no. IRB#20-908). All patients provided informed consent prior to enrollment in the study.


The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject and the investigator-designated research professional obtaining the consent. Consent will be obtained by the study coordinator or investigator of the study at each site. Consent will be documented in the medical record.

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Supplemental Material

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