

Journal Pre-proof

Endophenotyping Oxaliplatin Hypersensitivity: Personalizing Desensitization to the Atypical Platin

Jared Silver, MD PhD, Marlene Garcia-Neuer, MS, Donna-Marie Lynch, NP, Gülden Pasaoglu, MD, David E. Sloane, MD EdM, Marianna Castells, MD PhD



PII: S2213-2198(20)30172-0

DOI: <https://doi.org/10.1016/j.jaip.2020.02.013>

Reference: JAIP 2705

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 13 June 2019

Revised Date: 2 February 2020

Accepted Date: 4 February 2020

Please cite this article as: Silver J, Garcia-Neuer M, Lynch DM, Pasaoglu G, Sloane DE, Castells M, Endophenotyping Oxaliplatin Hypersensitivity: Personalizing Desensitization to the Atypical Platin, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: <https://doi.org/10.1016/j.jaip.2020.02.013>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

Original Article**Title:**

Endophenotyping Oxaliplatin Hypersensitivity: Personalizing Desensitization to the Atypical
Platin

Authors:

Jared Silver, MD PhD^{1*}, Marlene Garcia-Neuer^{2*}, MS, Donna-Marie Lynch, NP¹, Gülden
Pasaoglu, MD³, David E. Sloane, MD EdM¹, Marianna Castells, MD PhD¹

¹ Division of Allergy and Immunology, Brigham and Women's Hospital, Harvard Medical
School Boston, Massachusetts, USA.

² The Ohio State University College of Medicine, Columbus, Ohio, USA.

³ Florence Nightingale Hospitals, Kadikoy Medicine Center, Department of Adult Immunology-
Allergy, Istanbul, Turkey

* These authors contributed equally to this work.

Corresponding Author:

David Sloane, MD, EdM
Division of Allergy and Immunology
Brigham and Women's Hospital
Hale Building for Transformative Medicine
60 Fenwood Rd.
Boston, MA 02115
USA
Phone: 617-732-5325
Fax: 617-732-5766
Email: dsloane@bwh.harvard.edu

28 **Funding Statement:** this study had no funding support

29

30 **Disclosure statement:** the authors declare they have no conflicts of interest related to this study.

31

Abstract:

Background: Oxaliplatin causes a wider variety of immediate hypersensitivity reactions than other platin-based chemotherapeutics. Some resemble Type I reactions that respond to desensitization. Others are atypical, possibly mast cell-independent Cytokine Release Reactions refractory to desensitization. Given this variability, clinicians need an evidence-based strategy to personalize therapy for oxaliplatin hypersensitive patients.

Objective: We developed a data-driven algorithm to optimize treatment of oxaliplatin hypersensitive patients.

Methods: We retrospectively analyzed the baseline clinical characteristics, biomarkers, and reactions of 48 oxaliplatin hypersensitive patients who received a total of 266 oxaliplatin desensitizations.

Results: We characterized four endophenotypes: Type I, Cytokine Release, Mixed, and Either. A mean 40-fold increase in serum concentration of Interleukin 6 helped define the Cytokine Release endophenotype. Younger patients were more likely to have a Cytokine Release endophenotype, while older patients were more likely to have a Type I reaction. Skin testing was not informative for determining endophenotype or risk of reaction during desensitization, and did not associate with initial or desensitization grade of reaction. Patients with a history of atopy and an initial Type I reaction responded to desensitization with antihistamine premedications, while nonatopic patients with the same initial reaction phenotype were more likely to convert to a Cytokine Release or Mixed reaction during desensitization. We combined these reaction patterns with biomarker data and desensitization outcomes to construct an algorithm that helps tailor desensitization protocol design to meet individual patient needs.

Conclusion: Endophenotyping oxaliplatin hypersensitivity reactions may help forecast desensitization outcomes and personalize treatment plans.

Highlights Box:

What is already known about this topic? Oxaliplatin is known to cause a variety of hypersensitivity reactions (HSRs).

What does this article add to our knowledge? Endophenotyping of oxaliplatin induced HSRs may help predict response to rapid drug desensitization (RDD).

How does this study impact current management guidelines? The article's endophenotype-based management algorithm may allow for improved personalized treatment for oxaliplatin allergic patients undergoing RDD.

Key Words:

Oxaliplatin, colorectal cancer, endophenotype, desensitization, hypersensitivity

Abbreviations used:

ADR – Adverse drug reaction

AGEP – Acute generalized exanthematous pustulosis

CRR – Cytokine release reaction

DRESS – Drug eruption with eosinophilia and systemic symptoms

HSR – Hypersensitivity reaction

IL-6 – Interleukin 6

RDD – Rapid drug desensitization

SJS – Stevens-Johnson syndrome

ST – Skin test

80 *TEN – Toxic epidermal necrolysis*

81

Drug hypersensitivity reactions (HSRs) prevent patients from receiving life-saving therapies. While rapid drug desensitization (RDD) can circumvent some reactions, allowing patients to remain on first line therapy, it is not always successful. Allergists caring for patients with drug-induced HSRs need to determine the appropriateness of RDD by estimating pretest probabilities that the procedure will succeed, forecast various desensitization reactions, and strategize how to modify premedication regimens or other aspects of an RDD protocol on an individual patient basis should that patient experience a reaction during or shortly after RDD ¹⁻⁵.

Endophenotyping is a classification system that describes disease variants in terms of their molecular mechanisms, distinct clinical features, and treatment responses.^{6,7} Endophenotyping promotes better understanding of complex, heterogenous diseases such as asthma, idiopathic pulmonary fibrosis, chronic recurrent sinusitis, and colorectal cancer, allowing for personalized disease diagnosis, prognosis, and management⁷⁻¹². To our knowledge, research about drug hypersensitivity has used endophenotyping in only a limited capacity for monoclonal antibodies but not for other chemotherapeutic agents such as platins ⁵. Endophenotyping can provide valuable new insights into drug HSRs, potentially predicting the likelihood of reacting during RDD and allowing for personalization of RDD protocols.

Patients allergic to chemotherapeutic drugs typically need repeated desensitizations over the long term because of the intermittent dosing schedules of these agents.^{1,3-5,13-16} Although RDD is safe and effective,^{1,3} varying HSRs may occur during desensitization and necessitate modifications in real-time and thoughtful tailoring of subsequent protocols to circumvent reactions ^{5,16} We hypothesized that endophenotyping would help characterize and mitigate desensitization reactivity.

Oxaliplatin ($C_8H_{14}N_2O_4Pt$) is a diaminocyclohexane, third generation platinum agent indicated for first-line and adjuvant treatment of metastatic colorectal cancer¹⁷. Oxaliplatin treated patients have a rate of HSRs varying from 10% to 19%, with severe (grade 3–4) reactions occurring in 0.5–2 % of cases^{1,3,18–22}. Oxaliplatin HSRs are heterogenous, and RDD is generally effective^{1,16,23}. We used oxaliplatin HSRs in patients with colorectal cancer as a model of endophenotyping.

Here we propose a framework for endophenotyping oxaliplatin HSRs using clinical, skin test, and laboratory data. We followed a two-step process to develop HSR endophenotypes: first, we classified initial and desensitization-associated HSRs into three proposed *symptomatic* endophenotypes; second, we used patient characteristics and biomarker data (serum tryptase and IL-6 concentrations) to further develop the proposed categories. Guided by our observations, data, and clinical experience, we developed an algorithmic approach toward personalized management of oxaliplatin HSRs.

METHODS

Patient selection

Patients received RDD as part of standard of care at the Drug Hypersensitivity and Desensitization Center at Brigham and Women's Hospital and Dana Farber Cancer Institute. All patients who received desensitization to oxaliplatin from January 2014 to July 2017 were included. The study was approved by the Brigham and Women's Hospital institutional review board (protocol number 2016P001276).

Patients with severe skin reactions consistent with Drug Eruption with Eosinophilia and Systemic Symptoms (DRESS), Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome (SJS), or Toxic Epidermal Necrolysis (TEN) were excluded, due to the high risk of recurrence of a severe reaction which could be fatal upon re-exposure^{24,25,26}.

Classification of type and severity of HSRs

Initial reaction and desensitization *symptoms* were classified as most consistent with a classic mast cell mediated Type 1 reaction (Type I), Cytokine Release reaction (CRR), or Either (a symptom consistent with either a Type I or a CRR). Initial and desensitization *reactions* were classified as Type 1 if they involved only Type I symptoms or (Type I + Either) symptoms; CRR if they involved only CRR symptoms or (CRR + Either) symptoms; Mixed if they involved any combination of at least one Type I symptom and one CRR symptom, regardless of whether there were also Either symptoms; and Either if they involved only Either symptoms. We thus had three symptom categories (Type I, CRR, and Either) and four reaction categories (i.e., Endophenotypes, namely Type I, CRR, Mixed, and Either). Symptoms classification was based upon literature review^{5,27,28}, independent review from allergist-immunologists at outside institutions and expert opinion from the Brigham and Women's Hospital drug allergy and desensitization team (Figure 1). We classified symptoms phenotypically. To limit institutional bias, we submitted the list of reaction symptoms to HSR experts at several academic medical centers and asked them to classify each symptom as most consistent with a Type I, CRR, or an Either HSR (Table E1). The symptom classification shown in Figure 1A reflects the consensus of the data-blinded experts as well our own and current literature²⁷. To create the clearest phenotypes, we used only those symptoms that we and the outside experts considered the most

salient and classic for a given reaction, while we assigned other symptoms to the Either category. Thus, for example, urticaria and wheezing are Type I symptoms, fever and rigors are CRR symptoms, and dyspnea and chest tightness are Either symptoms. This left more symptoms classified as Either than in previously published endophenotyping studies⁵. HSR severity was classified per Brown's HSR grading system²⁹.

Skin testing

All but one patient underwent skin testing to oxaliplatin with prick testing at 5mg/mL, and intradermal tests at 0.5mg/mL and 5mg/mL. Skin tests were performed at least 2 weeks after the initial HSR to minimize false negative results. A positive reaction was defined as a wheal with a diameter at least 3 mm larger than that produced by a negative control (normal saline). Histamine skin prick testing (10 mg/mL) was used as a positive control.

Desensitization protocols and treatment of reactions

The sensitivity of skin testing to oxaliplatin is not known and therefore desensitization was offered to patients with or without positive skin testing, regardless of the severity of the initial HSR. Protocols consisted of 3 bag/12 step or 4 bag/16 step regimens, with a 2-2.5-fold drug dose increase between consecutive steps, delivered in 15 minute increments, except for the last step, which was prolonged to achieve the target dose at a rate of 80 mL/h - 125 ml/h until the infusion was completed^{1,3,16,23,30}.

Cetirizine (10 mg orally) and famotidine (20 to 40 mg orally or intravenously) were administered to all patients as RDD standard of care premedications. Aspirin and montelukast were used as prophylaxis if patients had experienced flushing or bronchospasm. COX-1

inhibitors, acetaminophen, corticosteroids, and opioids were used to prevent chills, rigors, fever, and pain^{1,3,5}. Patients were asked to hold beta-adrenergic antagonist medications for 24 hours before desensitization. Premedication was administered 30 minutes prior to the initiation of RDD and between steps if breakthrough reactions had occurred during previous RDDs. If a reaction occurred during desensitization, the infusion was paused and medications were administered according to symptoms. Once the reaction resolved, the infusion was resumed at the step where it was suspended.^{1,3} As noted in the results (see Figure 2), two patients experienced grade 3 reactions with features of Type I HSR but because they also had hypertension, epinephrine was not administered.

Biomarker measurement

Both concentrations of peripheral blood IL-6 and serum tryptase were available for some patients at baseline and during RDD reactions. Due to patient care and timing limitations, we were unable to obtain biomarkers for all initial or RDD reactions.

Statistical analysis

A primary goal of the study was to identify variables associated with successful RDD and reactivity to RDD, including: patient age, sex, atopy, previous lifetime exposures to oxaliplatin at time of initial reaction, results of skin testing, type of protocol, HSR phenotype, and laboratory biomarkers. To test statistical differences between the two groups, a two-sided Welch T-test with a 95% confidence interval was used for the continuous variables and a chi-squared test was used for the categorical variables. The mean and standard deviation for each variable and the number

and the percent for each categorical variable were calculated and reported. All statistical analysis was performed in R (statistical software, available at <https://www.r-project.org/>).

RESULTS

Demographic, patient characteristic, and desensitization data showed a patient population with advanced colorectal cancer, distributed evenly for gender, and generally tolerant of RDD. As shown in Table 1, patient age ranged from the 3rd through the 7th decade of life. Sixteen percent of patients were atopic and 35% reported a history of HSR to any drug other than oxaliplatin. It is important to note that we relied on documentation of other drug hypersensitivities in the medical record and did not independently confirm that those reports were accurate. The average number of oxaliplatin lifetime exposures prior to the initial HSR was 7.3. Of 273 total desensitizations, 266 (97.1%) were completed. We observed RDD reactions in 27 of the 48 patients (56.25%) (Table 1). A total of 73 reactions occurred, generally one per RDD.

We classified reaction symptoms according to what we and others considered their most likely pathophysiology (See Methods above, Figure 1A, and Discussion below). We identified four reaction endophenotypes: 1) Type I, 2) CRR, 3) Mixed (symptoms of at least one Type I symptom and at least one CRR symptom), and 4) Either (symptoms not clearly belonging to either Type I or CRRs). Two patients (ID's 4 and 32) developed thrombocytopenia, but this was not included in the endophenotype classification scheme and is believed to have a distinct pathobiology involving drug-specific antiplatelet antibodies (see Curtis BR, *et al.* Blood 2018;131(13):1486). Initial reaction type (Figure 1, grey) did not predict RDD reaction type

(Figure 1, black). The most frequent initial reactions were consistent Type I. However, the most frequent reactions during RDD were CRRs.

Figure 2 displays the initial reactions and desensitization outcomes of 48 individual patients as a heat map. Twenty-one (43.75%) patients had no reactions during any desensitization, including all four patients who had an initial Mixed HSR and all but one patient with an initial Either reaction. We term such patients “responders,” in contrast to patients who continued to have the same type of reaction during RDD as they did initially, whom we term “persisters.” Of the 23 patients with an initial Type I HSR, 10 were responders, while only two patients were persisters. Of the 14 patients with an initial CRR, 12 (86%) were persisters. We term those patients who had RDD reactions different than their initial reaction “converters.” One (7%) patient of the 14 with an initial CRR converted to having either a Type I or an Either HSR during a total of 12 desensitizations. Conversion from one initial reaction endophenotype to another during RDD was observed most frequently for patients with an initial Type I HSR (9 of 23, 39%), with 8 patients experiencing at least one CRR or a Mixed reaction during RDD and 1 patient having only a Mixed reaction during RDD.

With repeated desensitizations, patients reacted less often, likely due in part to modifications made to their protocols (see Figure E1-C). For this analysis, the grouping of patients with numbers of previous exposures (1-3, 4-6, 7-14, and >14) is based on our clinical experience and that of our oncology colleagues that patients often receive chemo in cycles of 6 exposures, though we acknowledge that this is an arbitrary division. Reactions were more frequent during desensitizations #1-3 and declined thereafter until desensitization #14 (5

patients) when desensitization reactions increased. Figure E1-D illustrates the percentages of patients who reacted during desensitization for the first time during desensitizations #1-4. Of the patients who did not react during their first desensitization, 22% reacted during their second. Of the patients who did not react during their first or second desensitizations, 24% reacted during their third. Patients who completed three desensitizations without a reaction were not observed to react thereafter even if they received up to 15 additional desensitizations.

As shown in Figure 3, selected aspects of patient clinical history were associated with subtypes of oxaliplatin reactivity. A history of atopy associated with an increased likelihood of a patient having an initial Type I HSRs (75% of 8 initial reactions) and RDD reactions (11% of 27 desensitizations), and having an 85% chance of undergoing desensitization without a reaction (85% of 27 desensitizations). Compared to atopic patients, non-atopic patients were less likely to have an Type I initial reaction (Type I HSR 41.5%, CRR 34.1%, Either 19.5%, and Mixed 4.9% among 41 initial reactions), and RDD reaction (of all their desensitizations, there were Type I HSRs in 4.1%, CRR HSRs in 17.1%, Either HSRs in 6.9%, and no reaction in 71.4% of 245 desensitizations). Comparing atopic and non-atopic patients, the latter had significantly more frequent CRR and Either reactions during RDD. Skin testing did not correlate significantly with initial reaction endophenotypes or reaction grade (Figure 3B, Table E1), and, counterintuitively, patients with a negative skin test had Type I reactions during RDD significantly more frequently ($p < 0.05$) (Figure 3 B).

The number of lifetime oxaliplatin exposures before the initial reaction correlated with desensitization endophenotype: 90% of patients with ≤ 2 oxaliplatin exposures before their initial

reaction did not react during RDD, while only 25% of patients with ≥ 15 exposures before their initial reaction did not react during RDD. Ten or fewer exposures correlated with a greater likelihood of Type-I HSRs during RDD and greater than 10 lifetime exposures correlated with CRR reactions during RDD. The average lifetime exposure number for a patient with an initial Type -1 HSR endophenotype was 6.5 and for an initial CRR endophenotype was 10.2 ($p < 0.001$). Responders had an average lifetime exposure of 7.2 ($p\text{-value} < 0.005$) (Figure 3C).

Age trended with the grade of reaction during both initial and desensitization reactions, with younger patients having more severe reactions than older patients (Figure 4A), though this was not statistically significant. Younger patients were more likely to have a CRR during RDD and older patients tended to have fewer desensitization reactions (i.e., they were more likely to be responders) and more Type I reactions during RDD. The average age for a patient with a Type I HSR during RDD was 57.4 years whereas that of a patient with a CRR during RDD was 49.8 years ($p < 0.005$) (Figure 4B). In all age groups, between 55.1% and 82.3% of patients were responders.

Peripheral blood IL-6 concentrations were significantly elevated in patients experiencing CRRs during RDD but not among those with Type 1 RDD reactions (Figure 5). By contrast, tryptase was not significantly elevated (i.e., > 11.4 ng/mL) for any reaction endophenotype during RDD. For those patients who had both a baseline and a reaction tryptase drawn, we also calculated the change in tryptase concentration using the $[(1.2 \times \text{baseline tryptase}) + 2]$ threshold, but this again showed no significant tryptase elevation.

Discussion

To provide individualized care for patients with drug-induced HSRs, allergists must a) answer the question “Should this patient be desensitized based on the likelihood that it will be successful?”, b) estimate the risk of various reactions during RDD, and c) know what to do in the long term as well as in the acute setting should the patient experience a reaction during or shortly after RDD. RDD is a critical tool for repeated administration of oxaliplatin for patients with colorectal malignancy and oxaliplatin hypersensitivity who are otherwise unable to receive this first line, life-saving therapy^{3,31,32}. Here, we expand oxaliplatin HSR classification beyond the classic Type I of the Coombs and Gell system based on clinical endophenotyping. This more detailed description of oxaliplatin HSRs allows allergists to start to address the three issues above and thus helps guide personalized management of patients. Based on our findings, we propose an algorithm to guide oxaliplatin desensitization protocol design and premedication selection (Figure 6).

We found that symptoms that clustered together during initial reactions often remained associated during desensitization reactions. Patients whose initial reactions were Type I responded well to desensitization, consistent with previous experience, as did those who had initial Either or Mixed reactions. However, the majority of patients with initial CRR continued to have CRRs during RDD. Importantly, nearly 40% of patients with initial Type I HSR converted to another endophenotype (most commonly CRR or a Mixed reactions) during RDD. Our data suggest that desensitization is most effective for Type I, Either, and Mixed reactions, and is less efficacious for CRR symptoms/reactions. Importantly, however, even patients who reacted

during RDD, regardless of their reaction endophenotype, were able to complete their infusions and thus receive the entire dose of oxaliplatin.

As has been previously shown for monoclonal antibodies, the most common initial HSR was Type I, though during desensitization CRR and Mixed symptoms were frequent^{5,31,32}. Network diagrams revealed global shifts in symptom type and frequency from predominantly Type I HSRs during initial reactions to predominantly CRRs during desensitization. Our data indicate that RDD effectively addresses Type I HSRs but is not as effective for CRRs. The conversion to CRR during desensitization was unexpected. We anticipated that patients with initial Type I reactions would be responders. In addition, we expected patients with an initial Mixed reaction to convert to the CRR endophenotype, as desensitization was anticipated to address their Type I symptoms but not their CRR symptoms, unmasking the latter. Instead, while the number of patients with an initial Mixed reaction was small ($n = 4$), all were responders. In our experience, oxaliplatin differs sharply from cisplatin and carboplatin in this regard, as CRR symptoms and reactions occur much less frequently after exposure to those latter two agents. Whether desensitization promotes CRRs in individuals predisposed to this form of hypersensitivity by allowing patients with initial Type I reactions to continue to receive oxaliplatin is currently unknown. The same is true of the cellular source(s) and basic mechanisms of CRRs.

We found selected clinical variables useful in determining oxaliplatin HSR endophenotypes and associated with RDD outcomes, including patient age, history of atopy, and serum IL-6 measured during or shortly after an RDD reaction. Patients with a Type I RDD reaction were significantly older than patients with a CRR RDD reaction. Patients with a history

of atopy were more likely to have a Type I reaction initially and during RDD. A limitation of these findings is that our analysis was univariate and not multivariate, as the effect size or the confidence level of multivariate analysis could be limited by small subgroup sizes. We continue to collect information on oxaliplatin hypersensitive patients and future studies with a larger data set will be subjected to multivariable analysis.

Like others, we found that elevation of serum IL-6 is a marker of oxaliplatin CRRs during RDD^{5,33,34}. Increased serum concentrations of IL-6 and TNF alpha are associated with advanced colorectal cancer and decreased survival, and may play roles in both oxaliplatin allergic reactions and in tumor responses³⁵⁻³⁷. Our patient population has an elevated IL-6 at baseline (Figure 5). Whether IL-6 elevations are relevant for CRRs occurring in the setting of other platin- or of taxane-based chemotherapies, monoclonal antibodies, and antibiotics is an area of active interest. Oxaliplatin is currently used predominantly in the treatment of colorectal cancer and we do not know its HSR profile in other malignancies. Other platins, such as carboplatin and cisplatin, are used in the treatment of a variety of ovarian and gynecologic malignancies without commonly causing significant CRRs, which may support the hypothesis that a CRR endophenotype is platin-colorectal cancer specific^{1,3,22,23,30-32,38,39}. As has been found among patients with CRRs in the context of CAR T cell therapy, inhibition of IL-6 with tocilizumab suggests itself as a possible treatment²⁸.

A number of other variables did not contribute significantly to oxaliplatin HSR endophenotyping. Although serum tryptase is considered a reliable marker of anaphylaxis, values were not significantly elevated in patients with oxaliplatin HSRs of any endophenotype

and were not useful in predicting RDD reaction type. However, our data are limited and this issue requires further investigation, especially for detection of small but potentially significant differences between an individual patient's baseline value and the value observed during a reaction (Figure 5). Given its longstanding use, we would consider an elevated serum tryptase in a patient with an HSR to be helpful in characterizing the reaction as Type I.

Interestingly, oxaliplatin skin testing was also not helpful in endophenotyping or in predicting responses to RDD except for the counterintuitive finding that skin test negative patients were more likely to have a Type I RDD reaction compared to skin test positive patients. Previous studies have found an increased frequency of reaction with positive skin test during desensitization¹⁶. Among our patients, there was no statistically significant association between skin testing and factors such as desensitization reaction grade or frequency (Table E1). In this context, it is important to note that a previous study that included a subgroup of 74 oxaliplatin-reactive patients who underwent skin testing, measurement of oxaliplatin-specific serum IgE, and drug provocation testing determined that skin testing sensitivity was 57.5%, specificity was 91.7%, positive predictive value was 92%, and negative predictive value was 56.4 (see Alvarez-Cuesta E *et al.* Allergy 2015; 70: 784-794). That study documented the clinical features and severity of reactions, but did not endophenotype the oxaliplatin reactions or further analyze this subgroup with respect to the value of oxaliplatin skin testing.

Long-term tolerization through repeat desensitizations has been described for monoclonal antibodies and other platins^{1,5,31,32,40}. Herein, we found a steady decline in the percentage of patients reacting on repeated oxaliplatin desensitizations, possibly indicating tolerance (Figure

1E-C). Relative to reported tolerization to other chemotherapeutics, the percentage of reactions to oxaliplatin is higher but tolerance may be transient^{1,5}, as we observed a rise in the rate of RDD reactions for those patients who completed 14 desensitizations (albeit with limited patient number). This, along with CRR symptoms during HSRs, is another manifestation of the atypicality of oxaliplatin. Our data indicate that a given patient's RDD reaction endophenotype is generally cemented after approximately three desensitizations; if they react during RDD, patients tend to do so within the first three oxaliplatin desensitizations and are otherwise unlikely to react during subsequent desensitizations (Figure E1-D). Nevertheless, while specialists can reassure patients with this trend ("three [desensitizations without reaction] and you're free"), they must remain vigilant even with patients who have tolerated multiple desensitizations.

We also observed oxaliplatin induced reactions that do not fall under the endophenotyping scheme used for this study. These reactions were consistent with previously reported data^{16,22,41}. Three patients had Coombs and Gell Type II hypersensitivity, two had thrombocytopenia, one had hemolytic anemia, one patient had a seizure, while others reported numbness, weakness, and paresthesias. A single patient only displayed a delayed Coombs and Gell Type IV HSR in the form of a rash.

Reaction endophenotype directly impacts personalized protocol design and premedication regimens (Figure 6). As indicated in Figure 6, the decision to use either a 3 bag/12 step or a 4 bag/16 step protocol largely depends upon initial reaction grade, patient clinical status (acuity and severity of comorbidities), and adverse response to a prior 3 bag/12 step protocol, as

opposed to a particular endophenotype. While desensitization is primarily meant to ameliorate Type I HSRs, it is also effective for Either and Mixed reactions (Figure 2).

Patients with initial CRRs tend to continue to experience CRRs during desensitization and benefit from blockade of cytokine effects with the empiric addition of NSAIDs and intravenous fluids to their premedication regimens (or just prior to protocol steps known from previous RDDs to trigger intense symptoms). Patients under 50 years of age and those with many prior exposures to oxaliplatin (>14) may also benefit from cytokine blockade measures (Figure 3C, 4B) Non-atopic patients with an initial Type 1 endophenotype have a high chance of converting to a CRR and may also benefit from preemptive inclusion of NSAIDs and intravenous fluids in their premedication regimens. Patients with atopy and those >50 years old are predisposed to Type 1 reactions (Figure 3A, 4B) and may benefit from H1 and H2 blockade, but not from medications intended to antagonize cytokine effects. In patients with persistent CRR reactions despite the use of NSAIDs and aggressive IV fluids, steroid premedication should be considered, taking into account the patient's reaction grade, variety and severity of clinical comorbidities, acuity, and oxaliplatin exposure history.

In conclusion, the diversity and atypicality of oxaliplatin HSRs compared to other platins offer fertile ground for clinical endophenotyping. While in its infancy, endophenotyping of drug HSRs may offer specialists a tool to forecast likely responses to RDD and the development of tolerance. Just as diagnostic endophenotyping has benefited fields such as cancer and asthma, an analogous approach toward chemotherapeutic hypersensitivity may limit reaction risk during RDD while optimizing administration of first line therapy for metastatic colorectal cancer.

423 Future investigations will determine whether similar endophenotyping can address HSRs to
424 monoclonal antibodies, taxanes, and other platin- based chemotherapies.

425

426

Journal Pre-proof

References:

1. Sloane D, Govindarajulu U, Harrow-Mortelliti J, Barry W, Hsu FI, Hong D, et al. Safety, Costs, and Efficacy of Rapid Drug Desensitizations to Chemotherapy and Monoclonal Antibodies. *J allergy Clin Immunol Pract* [Internet]. 2016 [cited 2018 Jul 30];4:497–504. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S2213219816000118>
2. Legere HJ, Palis RI, Rodriguez Bouza T, Uluer AZ, Castells MC, Castells MC. A safe protocol for rapid desensitization in patients with cystic fibrosis and antibiotic hypersensitivity. *J Cyst Fibros* [Internet]. 2009 [cited 2016 Sep 29];8:418–24. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19740711>
3. Castells MC, Tennant NM, Sloane DE, Ida Hsu F, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* [Internet]. 2008 [cited 2016 Sep 29];122:574–80. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0091674908007628>
4. Picard M, Pur L, Caiado J, Giavina-Bianchi P, Galvão VR, Berlin ST, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. *J Allergy Clin Immunol* [Internet]. 2016 [cited 2016 Aug 23];137:1154-64.e1-12. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26725998>
5. Isabwe GAC, Garcia Neuer M, de las Vecillas Sanchez L, Lynch D-M, Marquis K, Castells M. Hypersensitivity reactions to therapeutic monoclonal antibodies: Phenotypes and endotypes. *J Allergy Clin Immunol* [Internet]. 2018 [cited 2018 Jul 30];142:159–170.e2. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0091674918303063>

6. Hamilos DL. Chronic Rhinosinusitis in Patients with Cystic Fibrosis. *J Allergy Clin Immunol Pract* [Internet]. 2016 [cited 2018 Jul 30];4:605–12. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S2213219816301234>
7. Papi A, Saetta M, Fabbri L. Severe asthma: Phenotyping to endotyping or vice versa? *Eur Respir J* [Internet]. 2017;49:1–3. Available from: <http://dx.doi.org/10.1183/13993003.00053-2017>
8. Lötvall J, Akdis CA, Bacharier LB, Bjerner L, Casale TB, Custovic A, et al. Asthma endotypes: A new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* [Internet]. 2011 [cited 2018 Jul 30];127:355–60. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0091674910018580>
9. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet (London, England)* [Internet]. 2008 [cited 2018 Jul 30];372:1107–19. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S014067360861452X>
10. Goodwin AT, Jenkins G. Molecular Endotyping of Pulmonary Fibrosis. *Chest* [Internet]. 2016 [cited 2018 Jul 30];149:228–37. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26356594>
11. Sepulveda AR, Hamilton SR, Allegra CJ, Grody W, Cushman-Vokoun AM, Funkhouser WK, et al. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline Summary From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical

Oncology. J Oncol Pract [Internet]. 2017 [cited 2018 Jul 30];13:333–7. Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/28350513>

12. Tomassen P, Vandeplas G, Van Zele T, Cardell L-O, Arebro J, Olze H, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol [Internet]. 2016 [cited 2018 Jul 30];137:1449–1456.e4. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0091674916001846>

13. Brennan PJ, Rodriguez Bouza T, Hsu FI, Sloane DE, Castells MC. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. J Allergy Clin Immunol [Internet]. 2009 [cited 2016 Sep 29];124:1259–66. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19910036>

14. Patil SU, Long AA, Ling M, Wilson MT, Hesterberg P, Wong JT, et al. A protocol for risk stratification of patients with carboplatin-induced hypersensitivity reactions. J Allergy Clin Immunol [Internet]. 2012 [cited 2016 Sep 29];129:443–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22099941>

15. Liu VC, Wong LY, Jang T, Shah AH, Park I, Yang X, et al. Tumor evasion of the immune system by converting CD4⁺CD25⁻ T cells into CD4⁺CD25⁺ T regulatory cells: role of tumor-derived TGF-beta. J Immunol. 2007;178:2883–92.

16. Wong JT, Ling M, Patil S, Banerji A, Long A. Oxaliplatin Hypersensitivity: Evaluation, Implications of Skin Testing, and Desensitization. J Allergy Clin Immunol Pract [Internet]. 2014 [cited 2018 Jul 30];2:40–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24565767>

17. André T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to *BRAF* Mutation and Mismatch Repair Status of the MOSAIC Study. *J Clin Oncol* [Internet]. 2015 [cited 2018 Jul 30];33:4176–87. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26527776>
18. Syrigou E, Syrigos K, Saif MW. Hypersensitivity reactions to oxaliplatin and other antineoplastic agents. *Curr Allergy Asthma Rep* [Internet]. 2008 [cited 2018 Jul 30];8:56–62. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18377776>
19. Lee C, Gianos M, Klaustermeyer WB. Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents. *Ann Allergy, Asthma Immunol* [Internet]. 2009 [cited 2018 Jul 30];102:179–87. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19354063>
20. Maindrault-Goebel F, André T, Tournigand C, Louvet C, Perez-Staub N, Zeghib N, et al. Allergic-type reactions to oxaliplatin: retrospective analysis of 42 patients. *Eur J Cancer* [Internet]. 2005 [cited 2018 Jul 30];41:2262–7. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S095980490500612X>
21. Kang SP, Saif MW. Infusion-related and hypersensitivity reactions of monoclonal antibodies used to treat colorectal cancer--identification, prevention, and management. *J Support Oncol* [Internet]. 2007 [cited 2018 Jul 30];5:451–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18019853>
22. Polyzos A, Tsavaris N, Gogas H, Souglakos J, Vambakas L, Vardakas N, et al. Clinical

features of hypersensitivity reactions to oxaliplatin: a 10-year experience. *Oncology* [Internet]. 2009 [cited 2018 Jul 30];76:36–41. Available from: <https://www.karger.com/Article/FullText/178163>

23. Wang AL, Patil SU, Long AA, Banerji A. Risk-stratification protocol for carboplatin and oxaliplatin hypersensitivity: repeat skin testing to identify drug allergy. *Ann Allergy Asthma Immunol* [Internet]. 2015 [cited 2018 Jul 30];115:422–8. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S108112061500486X>

24. Phillips EJ, Chung W-H, Mockenhaupt M, Roujeau J-C, Mallal SA. Drug hypersensitivity: Pharmacogenetics and clinical syndromes. *J Allergy Clin Immunol* [Internet]. 2011 [cited 2018 Jul 30];127:S60–6. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0091674910019433>

25. Bachot N, Roujeau J-C. Differential diagnosis of severe cutaneous drug eruptions. *Am J Clin Dermatol* [Internet]. 2003 [cited 2018 Jul 30];4:561–72. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12862499>

26. Pirmohamed M, Friedmann PS, Molokhia M, Loke YK, Smith C, Phillips E, et al. Phenotype Standardization for Immune-Mediated Drug-Induced Skin Injury. *Clin Pharmacol Ther* [Internet]. 2011 [cited 2018 Jul 30];89:896–901. Available from: <http://doi.wiley.com/10.1038/clpt.2011.79>

27. Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy, Asthma Immunol* [Internet]. 2015 [cited 2018 Aug 12];115:341–84. Available from:

<http://linkinghub.elsevier.com/retrieve/pii/S1081120615005153>

28. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* [Internet]. 2014 [cited 2018 Aug 12];124:188–95. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24876563>
29. Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* [Internet]. 2004 [cited 2018 Jul 30];114:371–6. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0091674904013983>
30. Caiado J, Venemalm L, Pereira-Santos MC, Costa L, Barbosa MP, Castells M, et al. Carboplatin-, Oxaliplatin-, and Cisplatin-specific IgE: Cross-reactivity and Value in the Diagnosis of Carboplatin and Oxaliplatin Allergy. *J Allergy Clin Immunol Pract* [Internet]. 2013 [cited 2016 Sep 29];1:494–500. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S2213219813002808>
31. Jimenez-Rodriguez T, Garcia-Neuer M, Alenazy LA, Castells M. Anaphylaxis in the 21st century: phenotypes, endotypes, and biomarkers. *J Asthma Allergy* [Internet]. 2018 [cited 2018 Jul 30];Volume 11:121–42. Available from: <https://www.dovepress.com/anaphylaxis-in-the-21st-century-phenotypes-endotypes-and-biomarkers-peer-reviewed-article-JAA>
32. Labella M, Garcia-Neuer M, Castells M. Application of precision medicine to the treatment of anaphylaxis. *Curr Opin Allergy Clin Immunol* [Internet]. 2018 [cited 2018 Jul 30];18:190–7. Available from: <http://insights.ovid.com/crossref?an=00130832->

900000000-99254

33. Luheshi GN. Cytokines and fever. Mechanisms and sites of action. *Ann N Y Acad Sci* [Internet]. 1998 [cited 2018 Jul 30];856:83–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9917868>
34. Tonini G, Santini D, Vincenzi B, Borzomati D, Dicuonzo G, La Cesa A, et al. Oxaliplatin may induce cytokine-release syndrome in colorectal cancer patients. *J Biol Regul Homeost Agents* [Internet]. [cited 2018 Jul 30];16:105–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12144121>
35. Chen M-F, Chen P-T, Lu MS, Lin PY, Chen W-C, Lee K-D. IL-6 expression predicts treatment response and outcome in squamous cell carcinoma of the esophagus. *Mol Cancer* [Internet]. 2013 [cited 2018 Jul 30];12:26. Available from: <http://molecular-cancer.biomedcentral.com/articles/10.1186/1476-4598-12-26>
36. Waldner MJ, Neurath MF. Master regulator of intestinal disease: IL-6 in chronic inflammation and cancer development. *Semin Immunol* [Internet]. 2014 [cited 2018 Jul 30];26:75–9. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S1044532313001589>
37. Liu Y, Starr MD, Bulusu A, Pang H, Wong NS, Honeycutt W, et al. Correlation of angiogenic biomarker signatures with clinical outcomes in metastatic colorectal cancer patients receiving capecitabine, oxaliplatin, and bevacizumab. *Cancer Med* [Internet]. 2013 [cited 2018 Jul 30];2:234–42. Available from: <http://doi.wiley.com/10.1002/cam4.71>
38. Hesterberg PE, Banerji A, Oren E, Penson RT, Krasner CN, Seiden M V, et al. Risk

stratification for desensitization of patients with carboplatin hypersensitivity: clinical presentation and management. *J Allergy Clin Immunol* [Internet]. 2009 [cited 2016 Sep 29];123:1262–7.e1. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19501233>

39. Picard M, Matulonis UA, Castells M. Chemotherapy hypersensitivity reactions in ovarian cancer. *J Natl Compr Canc Netw* [Internet]. 2014 [cited 2018 Jul 30];12:389–402. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24616544>

40. Galvão VR, Castells MC, Li GN, Wang SP, Xue X, Qu XJ, et al. Hypersensitivity to biological agents-updated diagnosis, management, and treatment. *J allergy Clin Immunol Pract* [Internet]. 2013 [cited 2016 Sep 29];3:175–85; quiz 186. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25754718>

41. Tuttle KL, Garcia-Neuer M, Connell NT, Hong DI, Castells MC, Wickner PG. Oxaliplatin Induced Immune Thrombocytopenia in Patients with Oxaliplatin Hypersensitivity: Implications for Desensitization. *J Allergy Clin Immunol* [Internet]. 2017 [cited 2018 Jul 30];139:AB41. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0091674916317092>

FIGURE LEGENDS:

Figure 1: Symptom Classification and Frequency. (A) percent of reaction by symptom for

initial and desensitization reaction, (B) initial reaction symptoms network map (n=49), (C) desensitization reaction symptoms network map (n= 73), Network map: radius of node (circle) is directly proportional to the number of occurrences of that symptom, thickness of edge (line) connecting two nodes is directly proportional to the frequency of co-occurrence of the two corresponding symptoms.

Figure 2: Endophenotype Heat Map. Heatmap of patient demographics, risk stratification

markers and desensitization course for 266 completed desensitization protocols in 49 patients. X-axis: F = IV fluids were administered either initially or in the indicated desensitization (boxes above) and once started were administered with every subsequent desensitization, Initial Reaction = endophenotype of the initial reaction, Age = patient age in years at first desensitization, Exposure = number of exposures to oxaliplatin at the time of the initial HSR (N = not recorded), Atopy = history of atopy (+ = yes, – = no), ADR = history of previous adverse drug reaction (+ = yes, – = no), ST = oxaliplatin skin test result (+ = positive, – = negative, np = not performed), Initial grade = initial reaction severity. Y-axis: D1 = desensitization #1, *et cetera*.). Gray boxes indicate desensitizations without a reaction. Colored boxes indicate desensitizations with reactions, with the color indicating the endophenotype and the number indicating the reaction severity. Initial reaction grades were as follows: grade 1 n = 14, grade 2 n= 24, and grade 3 n= 10. Desensitization reactions were as follows grade 0 n= 201, grade 1 n= 31, grade 2 n= 36, and grade 3 n= 6

Figure 3: Endophenotypic Correlations with Patient Clinical Characteristics. (A) History of Atopy corresponding to initial and desensitization reaction endophenotype. (B) Correlation between positive and negative skin test results and initial/desensitization reaction endophenotypes. (C) Relationship between oxaliplatin exposure and initial/desensitization reaction endophenotypes. Red = Type 1, Purple = Mixed, Blue = CRR, Yellow = Either, Green = no reaction. P value significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 4: Age Correlations with Phenotype and Grade of Reaction. (A) Grade of initial and desensitization reaction correlated with age. ns = not significant. (B) reaction endophenotypes correlated with age. Red = Type 1, Purple = Mixed, Blue = Cytokine, Yellow = Either, Green = no reaction. n = number of patients. P value significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 5: Biomarkers for endophenotypes. Baseline IL-6 and tryptase levels were obtained for 6 and 5 patients, respectively, before the first desensitization. IL-6 and tryptase values for Type-1 and cytokine HSRs during desensitization. P value significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. NL = normal value.

Figure 6: Oxaliplatin Protocol and Premedication Algorithm

Journal Pre-proof

634 **TABLE LEGENDS:**

635 Table 1: Demographic and Patient Characteristics. ADR History was based on documentation in
636 the patient's electronic medical record. Exposure = lifetime exposures to oxaliplatin at the
637 time of the initial oxaliplatin HSR. ST = oxaliplatin skin test result.

638

A

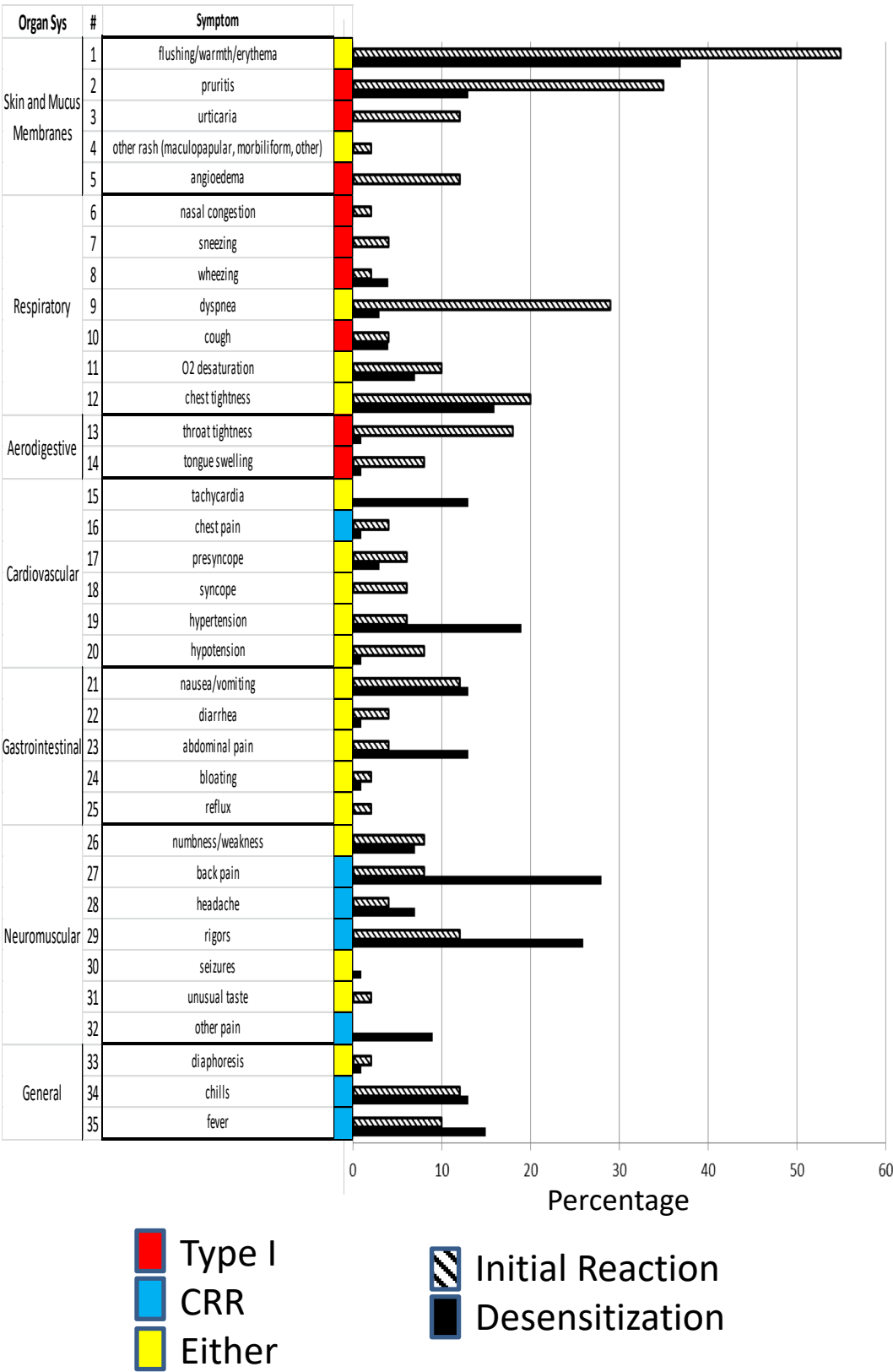
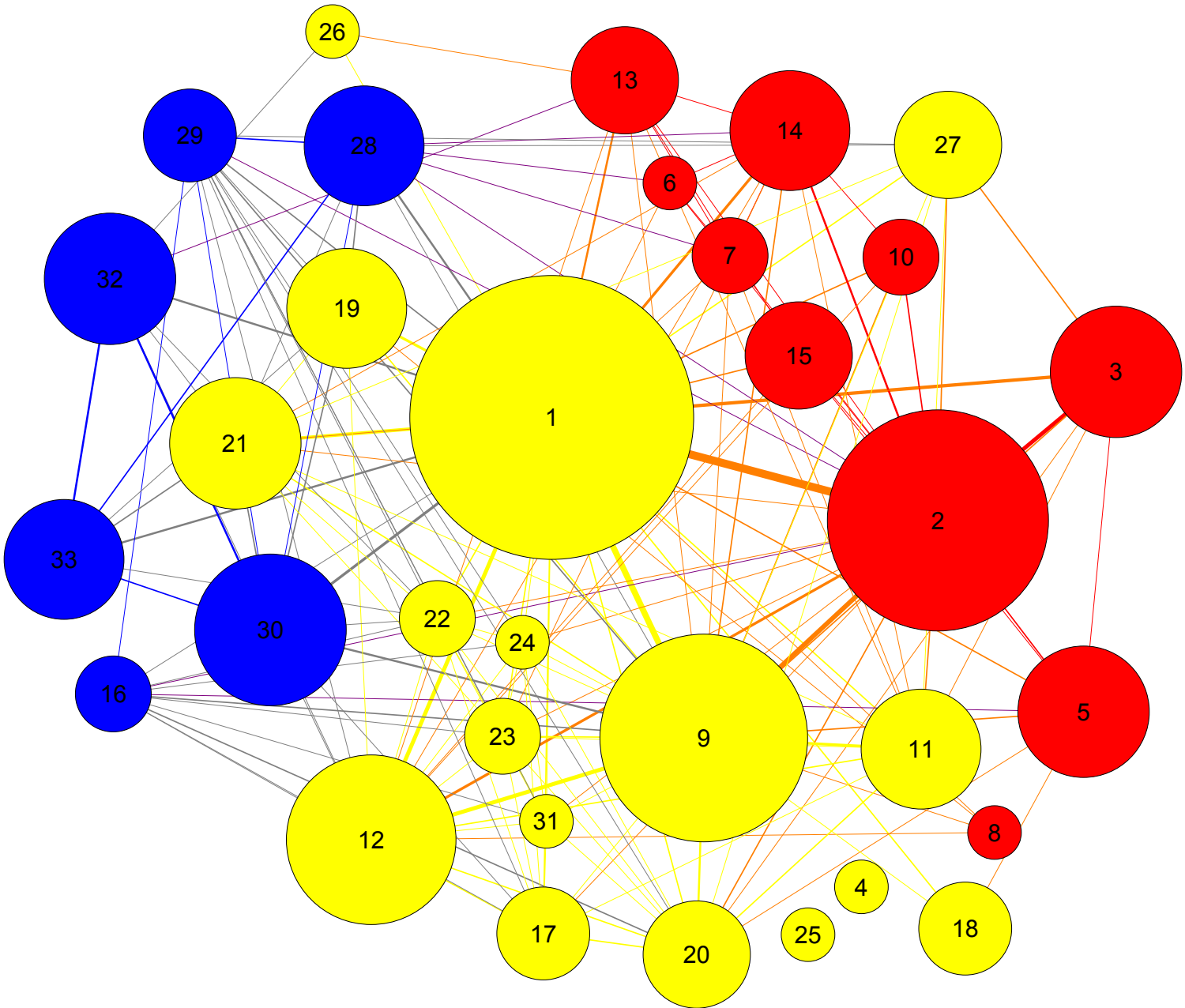


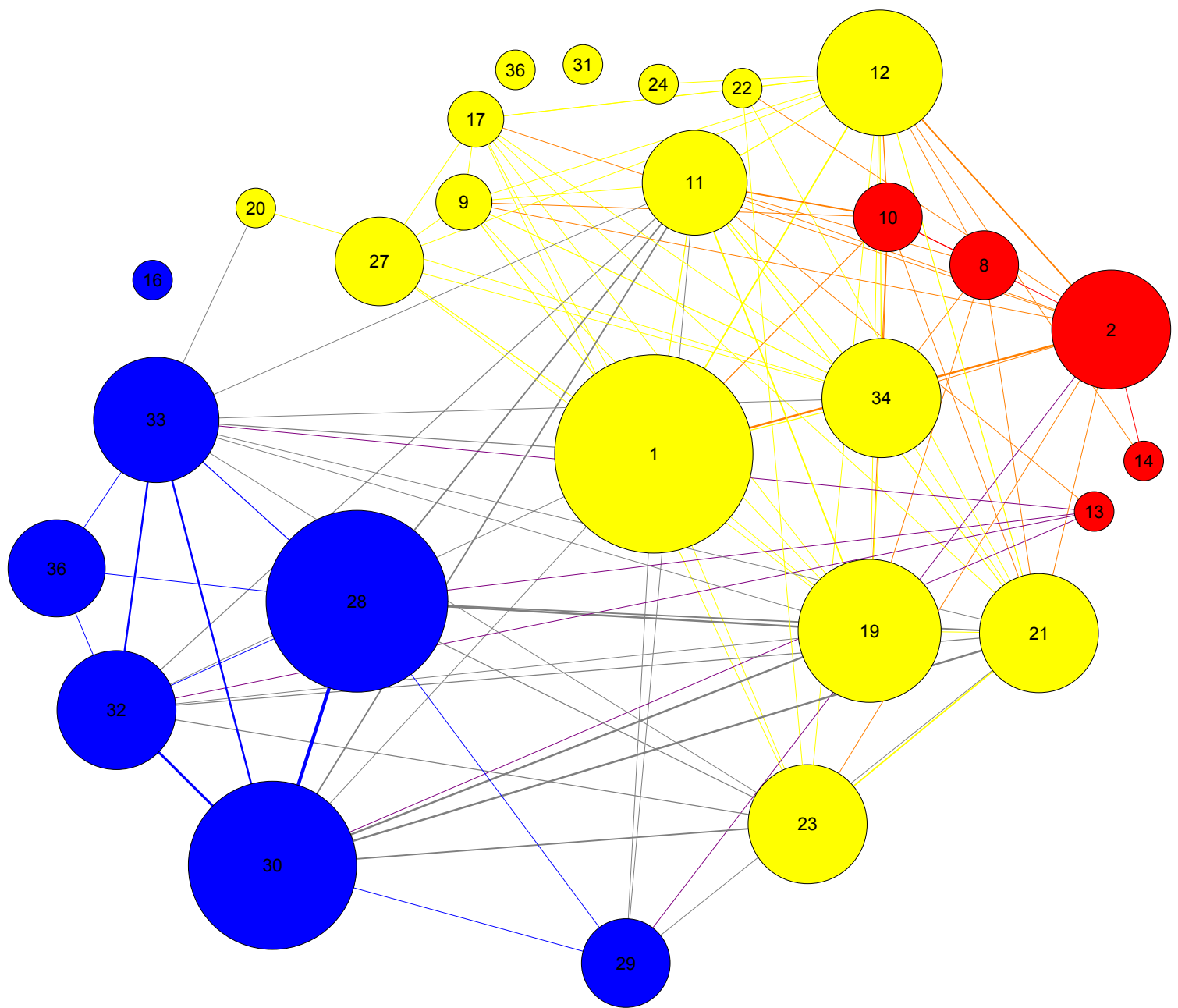
Figure 1: Classification and Frequency of Symptoms

Figure 1B



1	flushing/warmth/erythema	10	cough	19	hypertension	28	back pain
2	Pruritis	11	O2 desat	20	hypotension	29	headache
3	Urticaria	12	chest tightness	21	nausea/vomiting	30	rigors
4	Other rash	13	Throat tightness/swelling	22	diarrhea	31	diaphoresis
5	Angioedema	14	Throat itching	23	abdominal pain	32	chills/cold
6	nasal congestion	15	tongue swelling	24	bloating	33	Fever
7	Sneezing	16	chest pain	25	reflux/difficulty swallowing	34	Tachycardia
8	wheezing	17	presyncope	26	unusual taste	35	Seizures
9	dyspnea, SOB	18	syncope	27	numbness /weakness/tigling	36	Other Pain

Figure 1C



1	flushing/warmth/erythema	10	cough	19	hypertension	28	back pain
2	Pruritis	11	O2 desat	20	hypotension	29	headache
3	Urticaria	12	chest tightness	21	nausea/vomiting	30	rigors
4	Other rash	13	Throat tightness/swelling	22	diarrhea	31	diaphoresis
5	Angioedema	14	Throat itching	23	abdominal pain	32	chills/cold
6	nasal congestion	15	tongue swelling	24	bloating	33	Fever
7	Sneezing	16	chest pain	25	reflux/difficulty swallowing	34	Tachycardia
8	wheezing	17	presyncope	26	unusual taste	35	Seizures
9	dyspnea, SOB	18	syncope	27	numbness /weakness/tiglnig	36	Other Pain

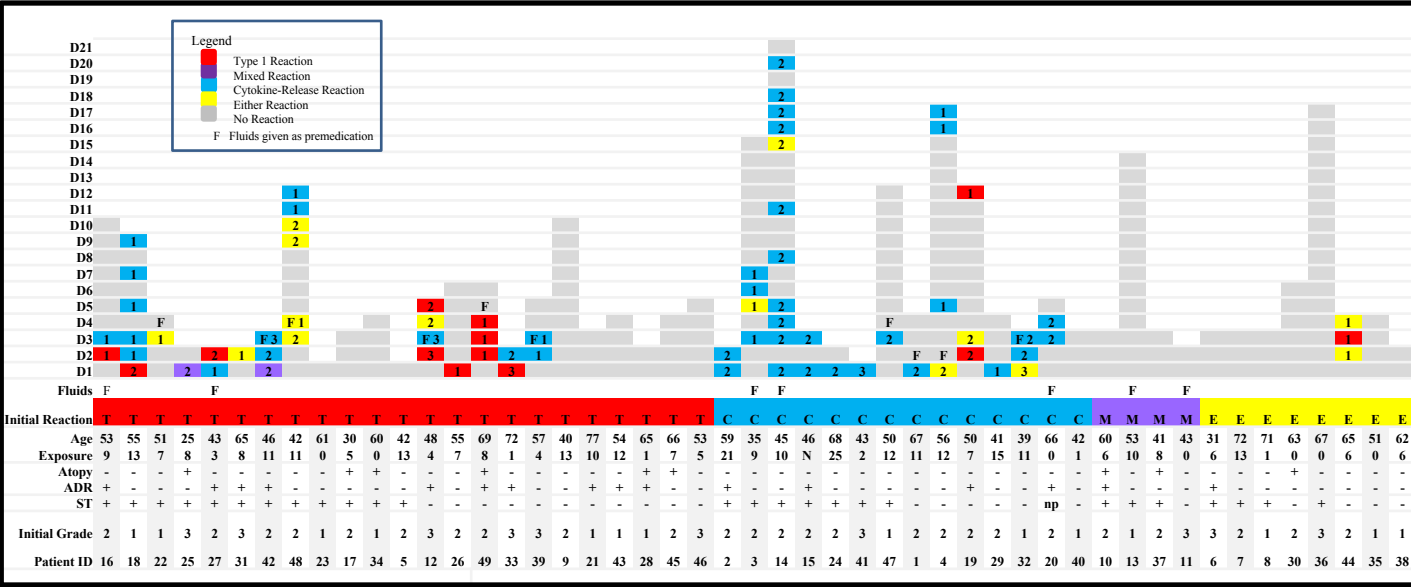
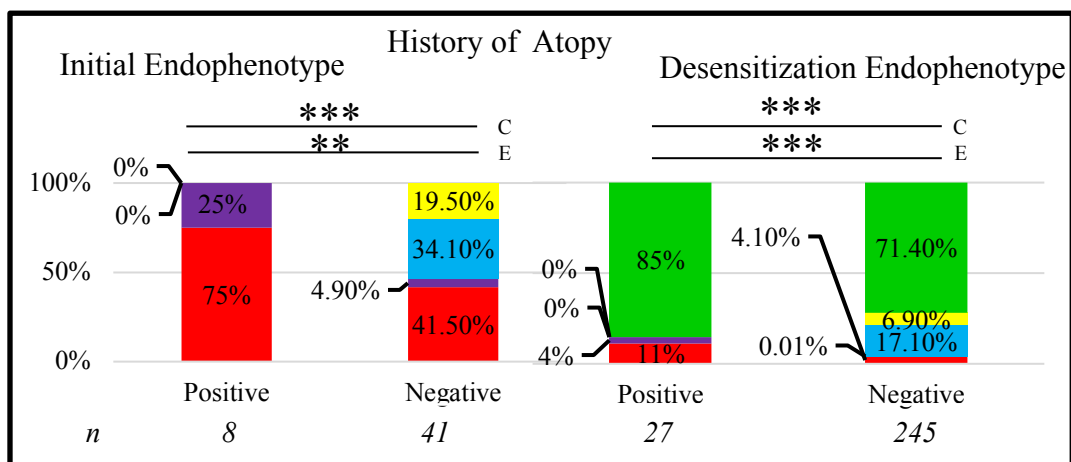


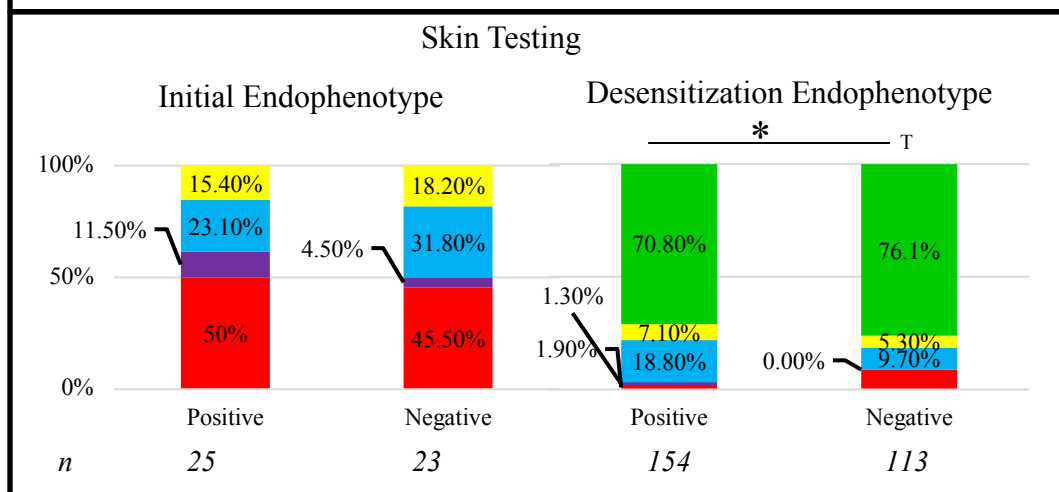
Figure 2: Endophenotype Heat Map

Figure 3: Endophenotypic Correlations

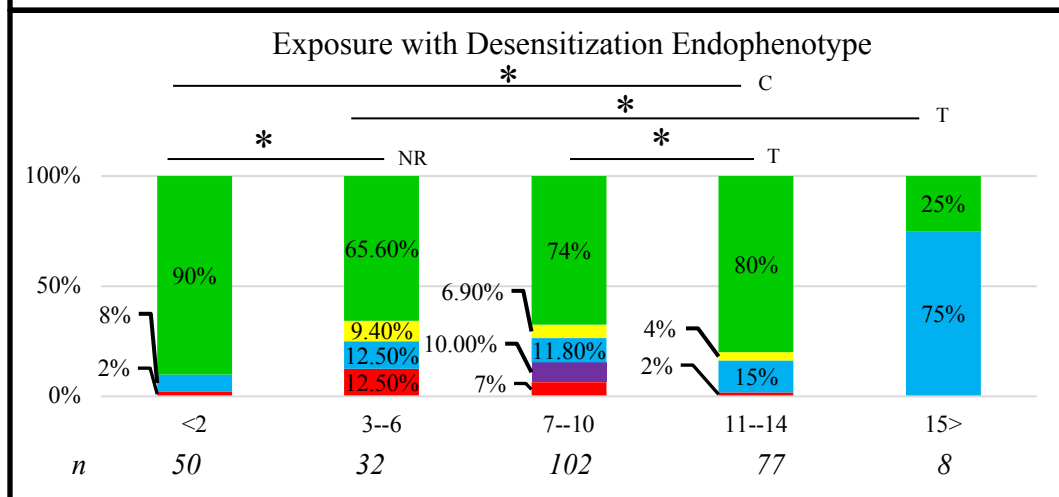
A



B



C



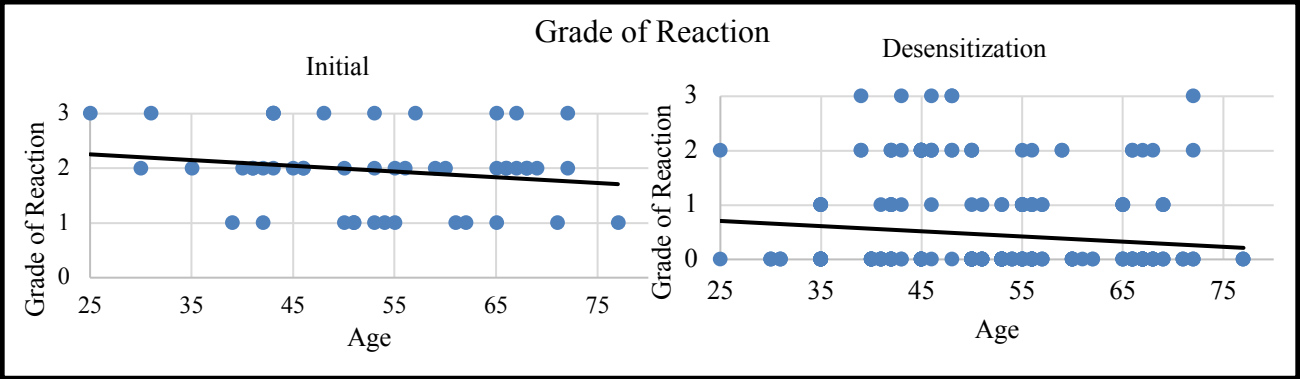
Endophenotype	T (Type I)	M (mixed)	C (CRR)	E (either)	NR (no rxn)
Average	6.5*	9.5	10.2*	9.1	7.4*

- Type 1 and Cytokine endophenotype and Cytokine and Non Reactions endophenotype are significantly different with a p value less than 0.01

■ T ■ M ■ C ■ E ■ NR

Figure 4: Age Correlations

A



Age	Correlation	Slope	
Frequency of Reactions Desensitization	-0.12	-4.27	ns
Reaction Grade Desensitization	-0.13	-2.44	ns
Initial Reaction Grade	-0.17	-3.089	ns

B

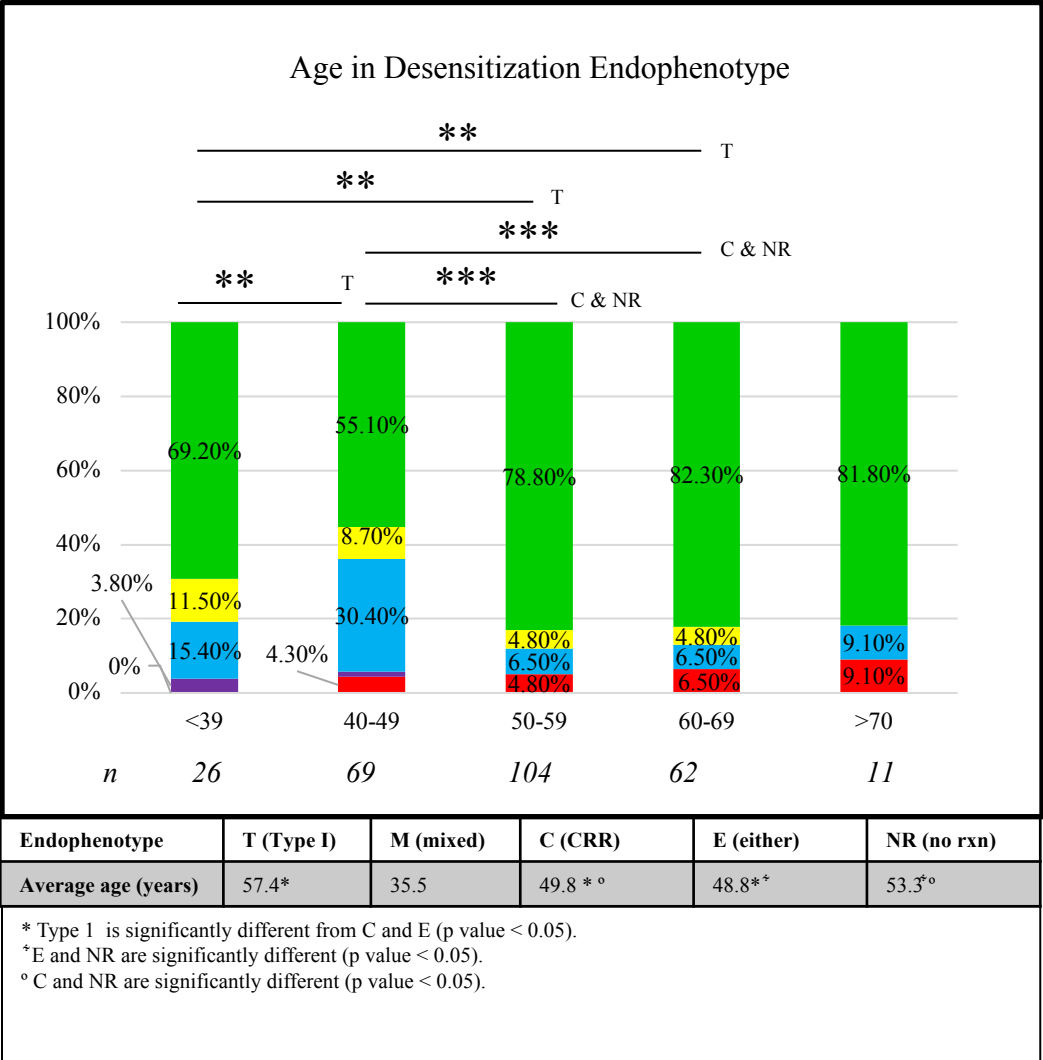


Figure 5: Biomarkers

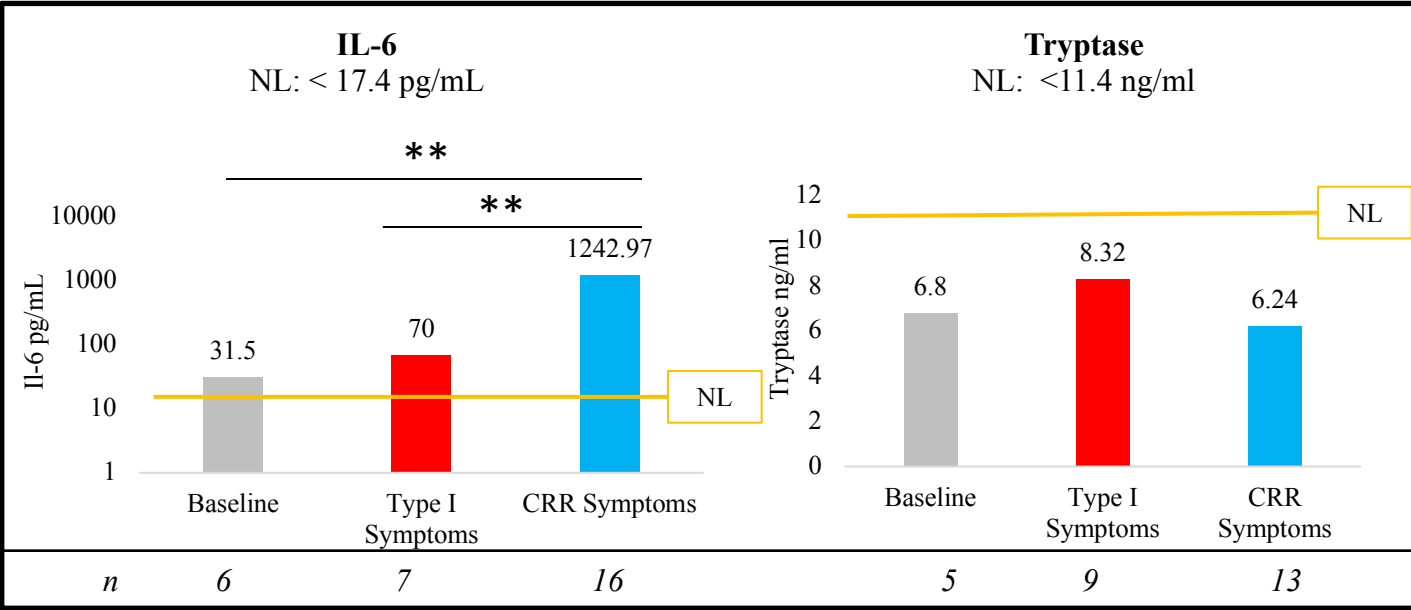
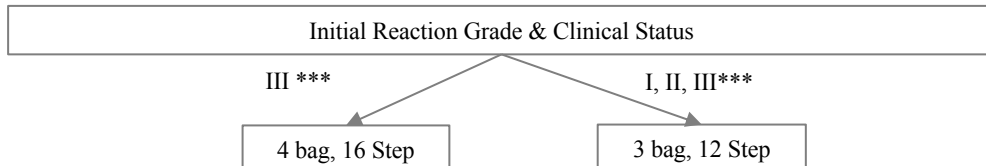


Figure 6: Oxaliplatin Protocol and Premedication Algorithm

- A. Premedications:** H₁ and H₂ antagonists for all patients
- If flushing/wheezing, add montelukast ± ASA
 - If pain, add gabapentin
 - If mixed or cytokine reaction, add COX-1 inhibitor and IVFs

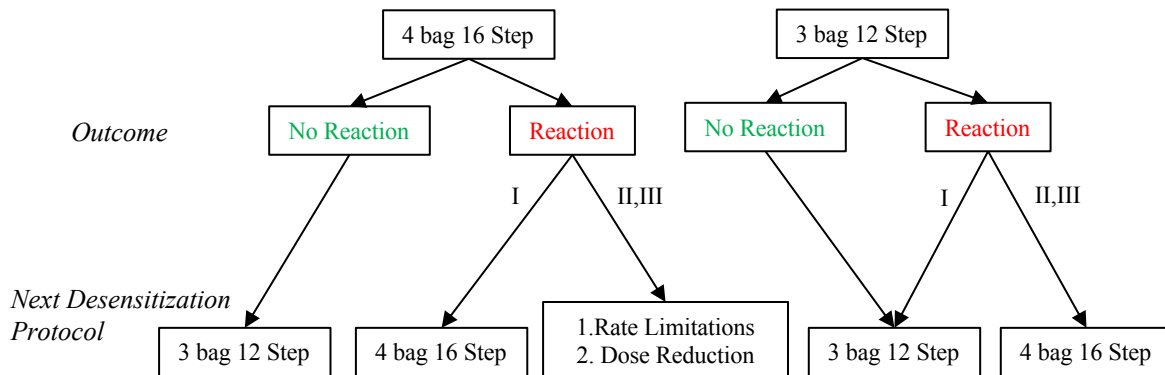
B. Desensitization Protocol



*** For Grade III reactions, provider discretion based on clinical comorbidities decides between protocols

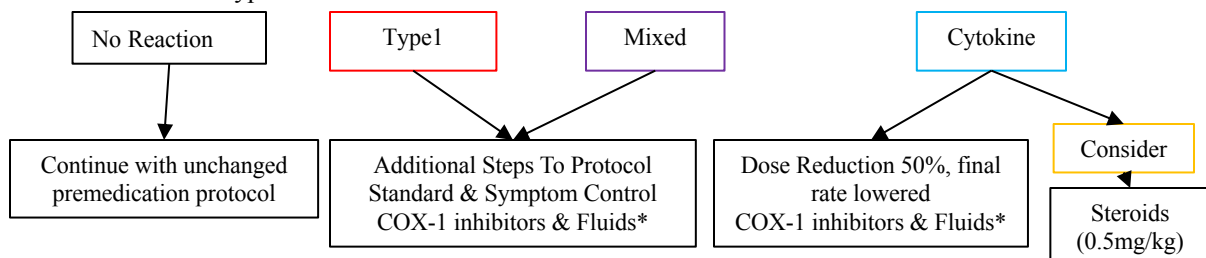
C. Post Desensitization Assessment

I. Initial Desensitization Protocol Outcomes



II. Premedication modification for next desensitization

Phenotype Reaction:



Premedication

Standard (H1/H2 blockers) cetirizine 10 mg PO and famotidine 20-40 mg IV

Symptom Control: montelukast, 10 mg PO, aspirin 325 mg PO, gabapentin 100-300 mg PO

COX-1 Inhibitors: ibuprofen 600-800 mg PO, ketorolac 15-30 mg IM

Fluids: CRR reactions: 100 cc/hr until step 12/16 w/increase to 250cc/hr - 500cc/hr during reaction.

Dose Reduction: 75%, 50% or 25% of target dose.

Slow Final Rate: 60 or 40 cc/hr

**Tryptase and IL-6 should be drawn at 30 min – 4 hours post reaction

FIGURE E1 LEGEND:

Endophenotypic Correlations with Patient Clinical Characteristics: A) History of previous adverse drug reaction (ADR) corresponding to initial and desensitization reaction endophenotype, B) Correlations between initial reactions endophenotype and reactivity during desensitization. C) Relationship between reaction frequency with number of exposures during desensitization, D) Relationship between reaction frequency with number of exposures during desensitization without previous reaction. Red- Type 1, Purple Mixed, Blue- CRR, Yellow- Either, Green- no reaction. . P value significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

TABLE E1 LEGEND:

Initial Grade of reaction and Skin Test results correlated with demographic characteristics. ADR = adverse drug reaction.

Table 1

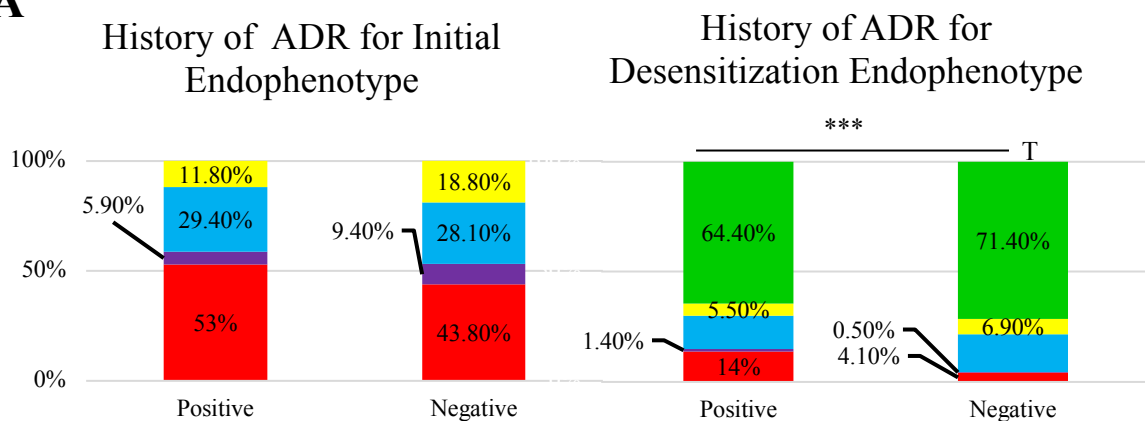
Demographics and Patient Characteristics (n = 49)											
Sex		Age	Atopy	ADR History	Diagnosis	Exposure	Desensitization n = 274			ST n = 48	
Female	Male	53.5 (range 25- 77)	8 (16%)	17 (35%)	GI Malignancy 38 (78%)	7.3 (range 0-25)	Number of Reactions	Patients Reacted	Successfully Completed	Pos	Neg
26 (53%)	23 (47%)				Stage IV 32 (65%)		68 (25%)	28 (57%)	266 (98%)	26 (54%)	22 (46%)

Table E1

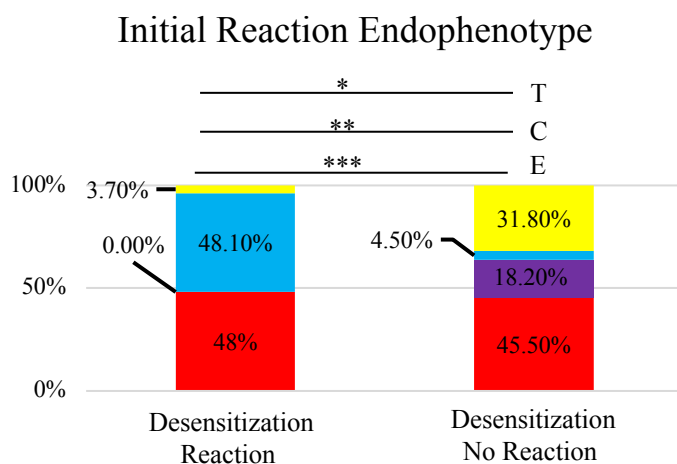
Initial Grade	Grade 1	Grade 2	Grade 3	
Desensitization				
Reaction Frequency	17.2%	33.0%	26.2%	p = 0.01
Reaction Grade	1.54	1.66	2.09	ns
Skin Testing	Positive	Negative		
Average Reaction Frequency	0.35	0.28	ns	
Average Reaction Grade	0.61	0.45	ns	
If reaction, Grade	1.67	1.57	ns	
Age	50.5	56.36	ns	
Exposure	8.4	6.4	ns	
Atopy	0.19	0.13	ns	
ADR	0.31	0.36	ns	
Initial Grade	1.9	1.9	ns	

Figure E1

A

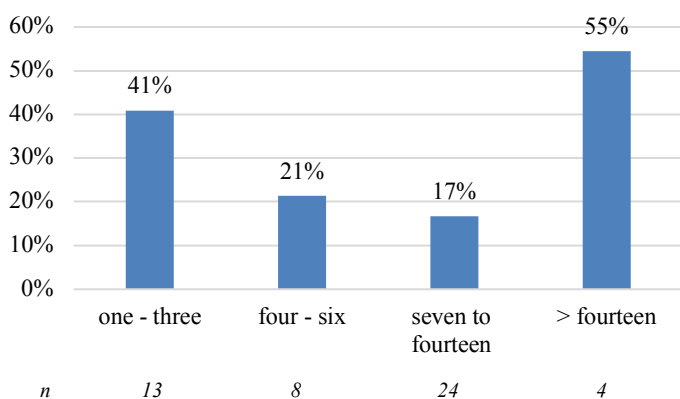


B



C

Percent Reaction with number of exposures



D

Percent Reaction w/o previous reaction

