Development of a Multivariate Digital Biomarker of Vaccine-Induced Inflammation and its Relationship to Immunogenicity

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CellCarta

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Development of a Multivariate Digital Biomarker of Vaccine-Induced Inflammation and its Relationship to Immunogenicity

- Reactogenicity - relationship to safety and efficacy
- Inflammation and immunogenicity
- Wearable sensors – tracking individual physiologic changes
- Personalized physiologic analytics (PPA) & Inflammatory Multivariate Change Index (iMCI)
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- iMCI response after vaccine & relationship to reported symptoms
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Reactogenicity

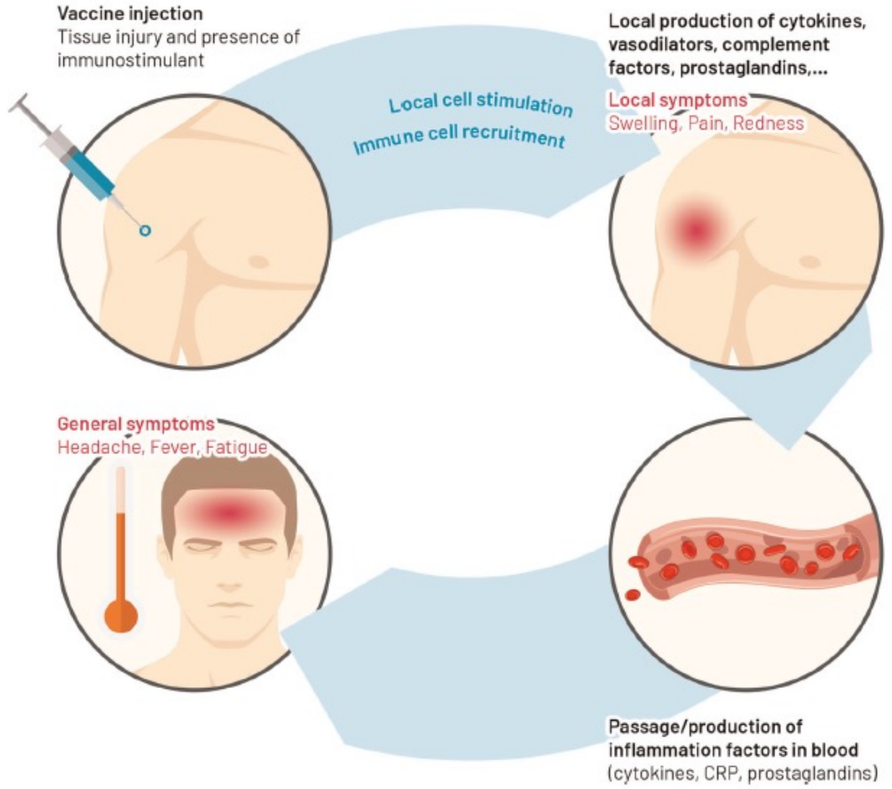
A subset of “expected” reactions that occur soon after vaccination that are a physical manifestation of the inflammatory response to vaccination.

Local Reaction

- Activation of pattern-recognition receptors on local immune cells.
- Releasing proinflammatory cytokines, chemokines, and vasodilators, promoting cell recruitment.

Systemic Reaction

- Pyrogenic factors enter the systemic circulation, communicate with CNS via receptors on the vagus nerve.
- Intracerebral levels of PGE2 increase, activating neuronal circuits which adjust autonomic and behavioral responses.



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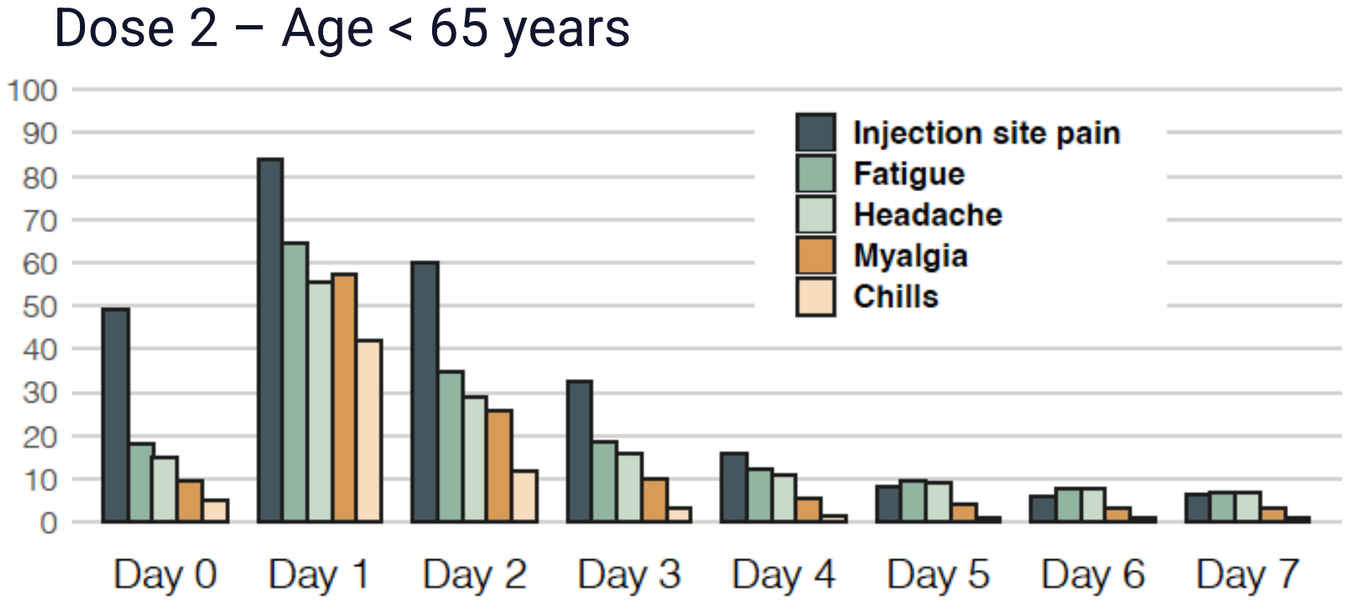
Hervé C. npj Vaccines 2019;4:39

Symptoms of Reactogenicity following COVID-19 vaccination

V-safe Active Surveillance System

- mRNA vaccine-related subjective symptoms in >3.6 million individuals.
- Any injection site reaction occurred in:
  - First dose - 70.0%
  - Second Dose – 75.2%
- Any systemic reaction occurred in:
  - First Dose – 50.0%
  - Second Dose – 69.4%

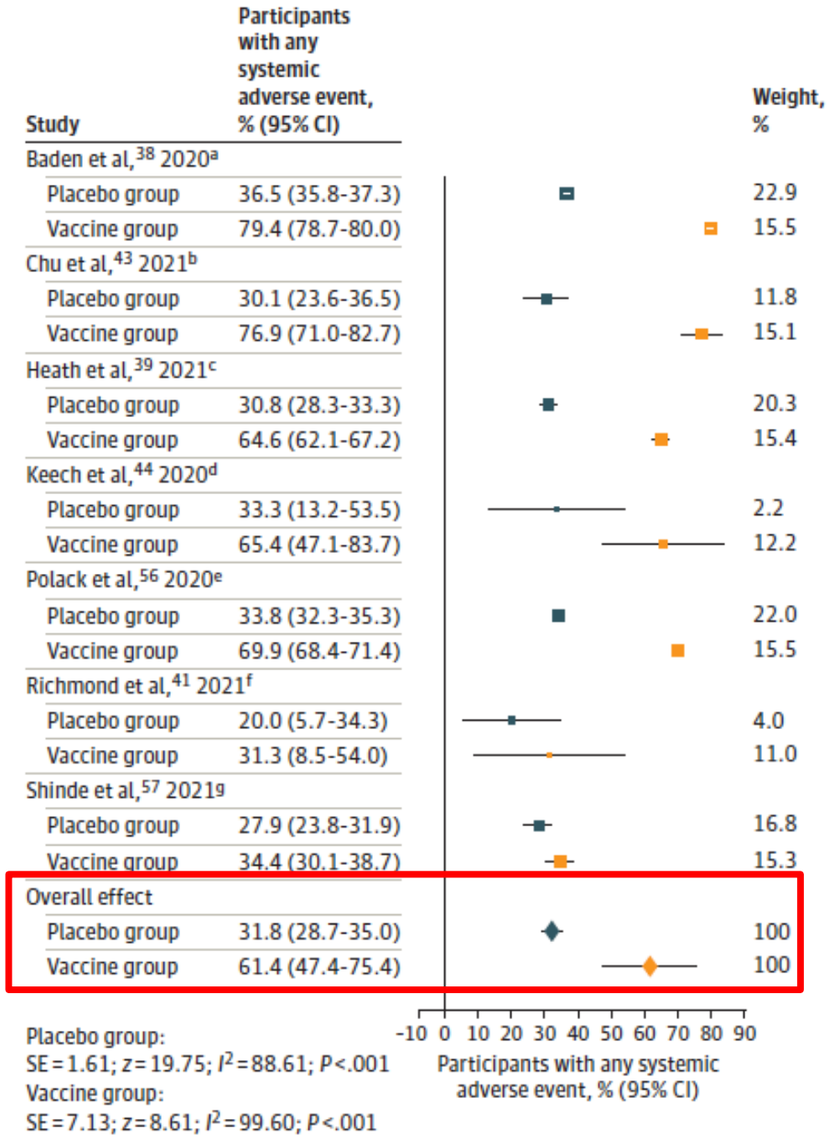


Chapin-Bardales J. JAMA 2021;325:2201-2

Nocebo Effect & Reported Reactogenicity

- Meta-analysis of placebo-controlled trials of COVID-19 vaccine trials
- >45,000 participants
  - ~22,600 placebo recipients
  - ~22,800 active vaccine recipients
- Incidence of systemic reactions in placebo arm:
  - 35.2% after first dose
  - 31.8% after second dose
- Nocebo response accounted for ~51.8% of reported systemic reactions to the COVID-19 vaccine

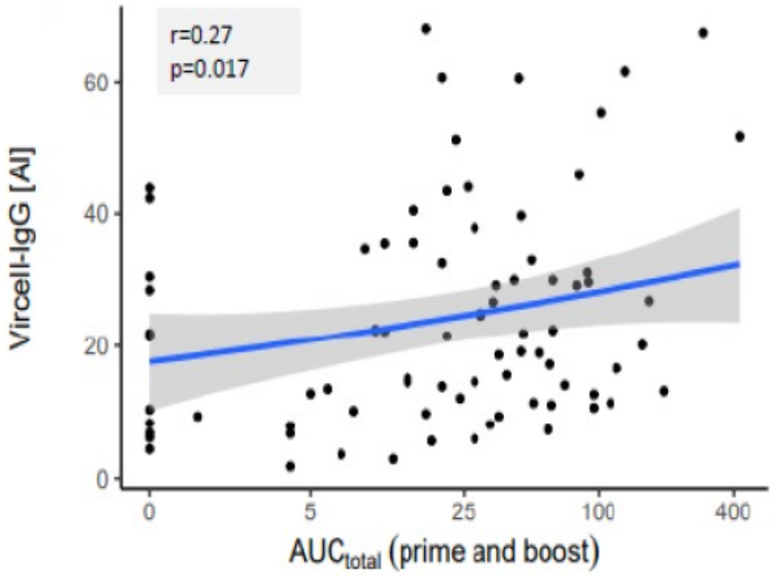
Systemic Reaction After Second Dose



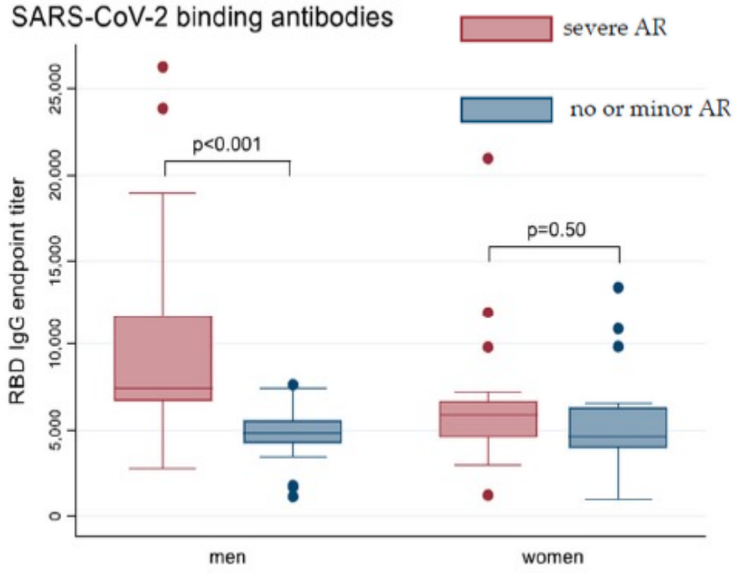
Haas JW. JAMA Network Open. 2022;5(1):e2143955.

Reactogenicity and Immunogenicity in COVID-19 Vaccine

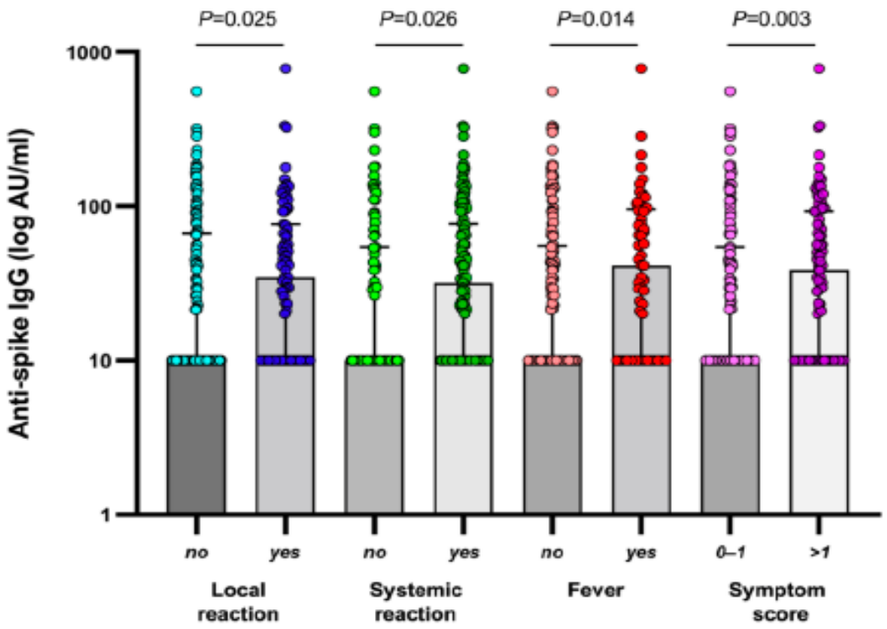
Adverse effect burden and Ab levels in 80 people



Severity of symptoms and Ab levels in 76 people



Adverse effects and Ab levels in 206 HD patients



Bauernfeind S. Vaccines 2021;9:1089

Held J. Vaccines 2021;9:1063

Lin T-Y. Vaccines 2022;10:1366

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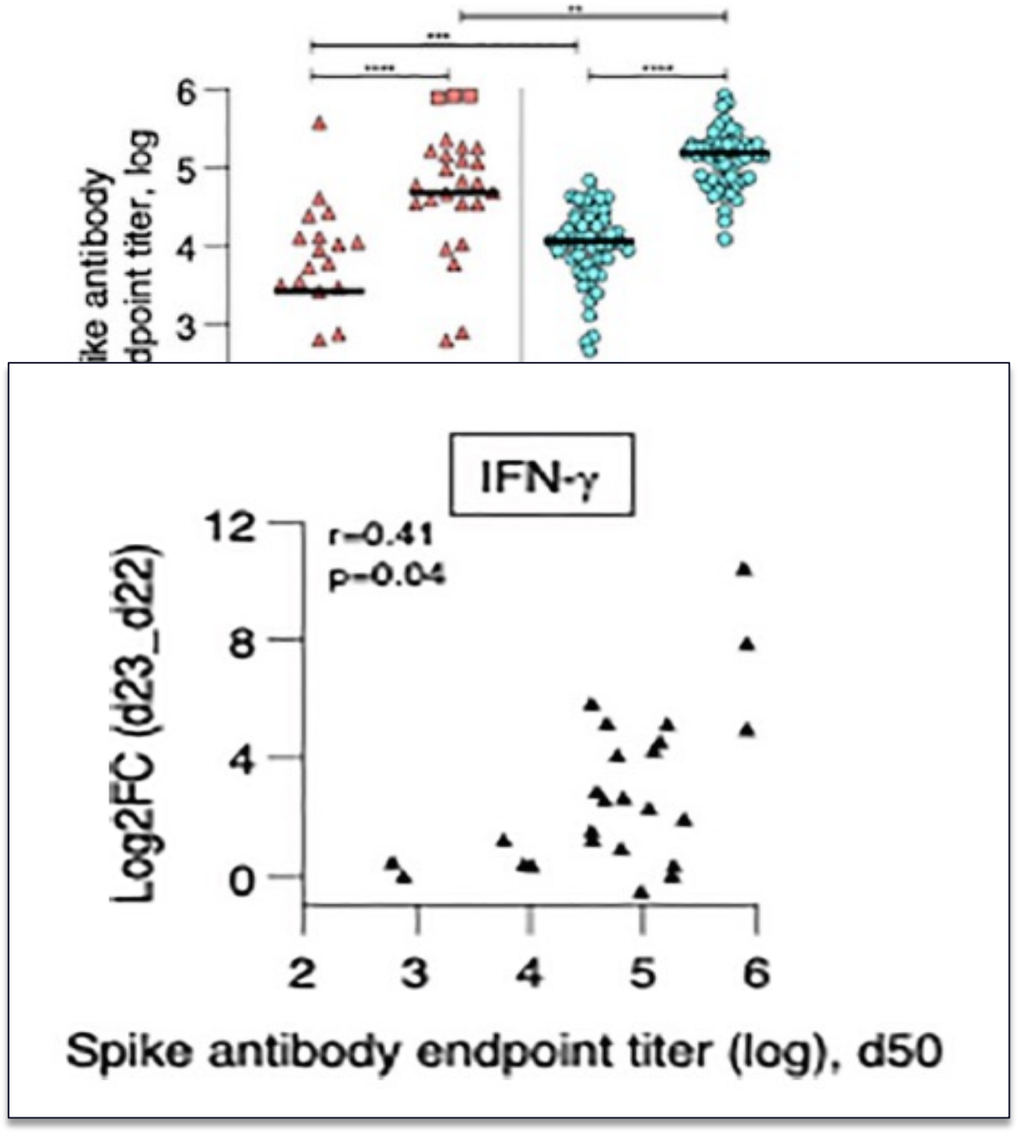
Inflammation & Immunogenicity After mRNA COVID Vaccines

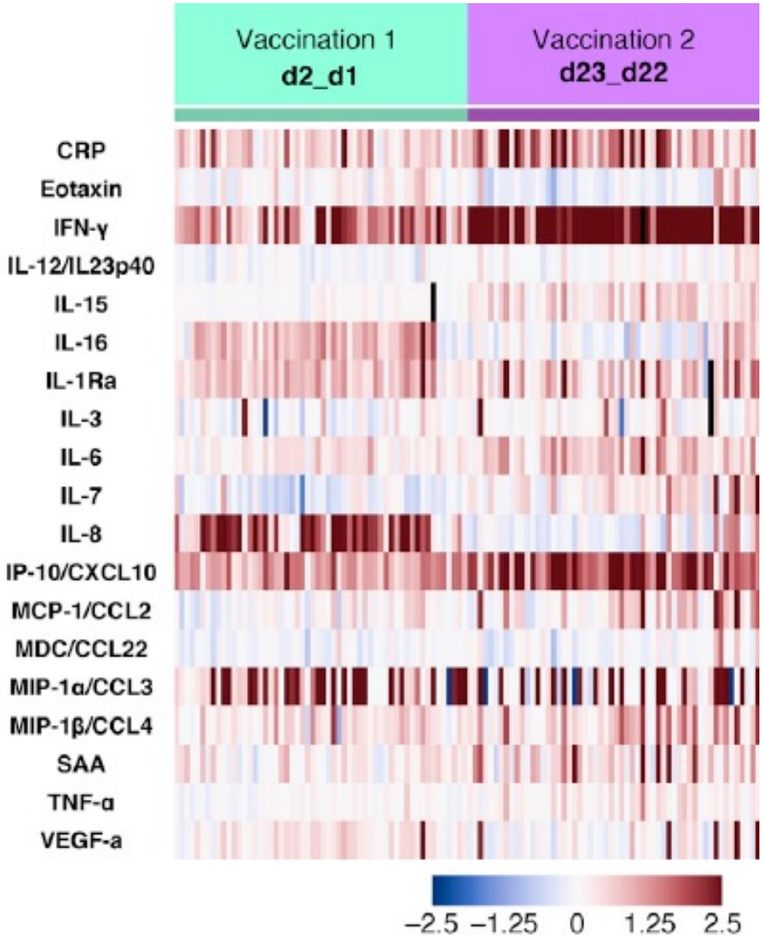
- 29 people with history of hematologic malignancies & 57 healthy controls.
- Anti-Spike Ab determined 22 days after 1st dose and ~30 days after 2nd dose of BNT162b2 mRNA
- Wide range of response – median of 4.7 log with a range of undetected to ~6 log - after 2nd dose.
- 47 inflammatory analytes analyzed day of and day after each vaccine dose, with 29 above threshold of detection.
- IFN-γ as the most significantly upregulated cytokine after 2nd vaccination (~6-fold) and positively correlated with Ab response at day 22 and 50. (r=0.41, p=0.04)

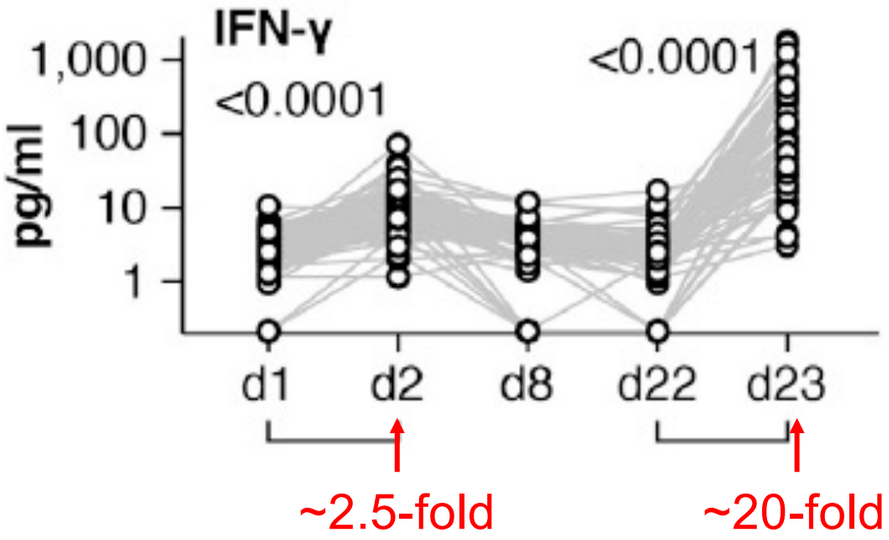


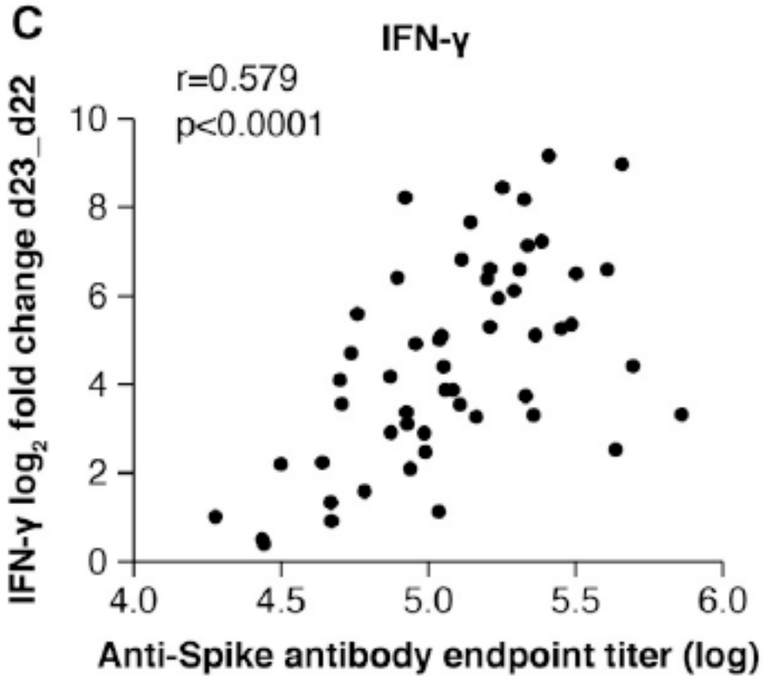
Bergamaschi C. Front. Immunol. 13:899972. doi: 10.3389/fimmu.2022.899972

Inflammation & Immunogenicity for mRNA COVID Vaccines

58 individuals, 2-dose mRNA vaccine, with analysis of 41 different cytokine/chemokine before and after each dose + association with antibody response







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Bergamaschi C. Cell Reports 2021;36: https://doi.org/10.1016/j.celrep.2021.109504

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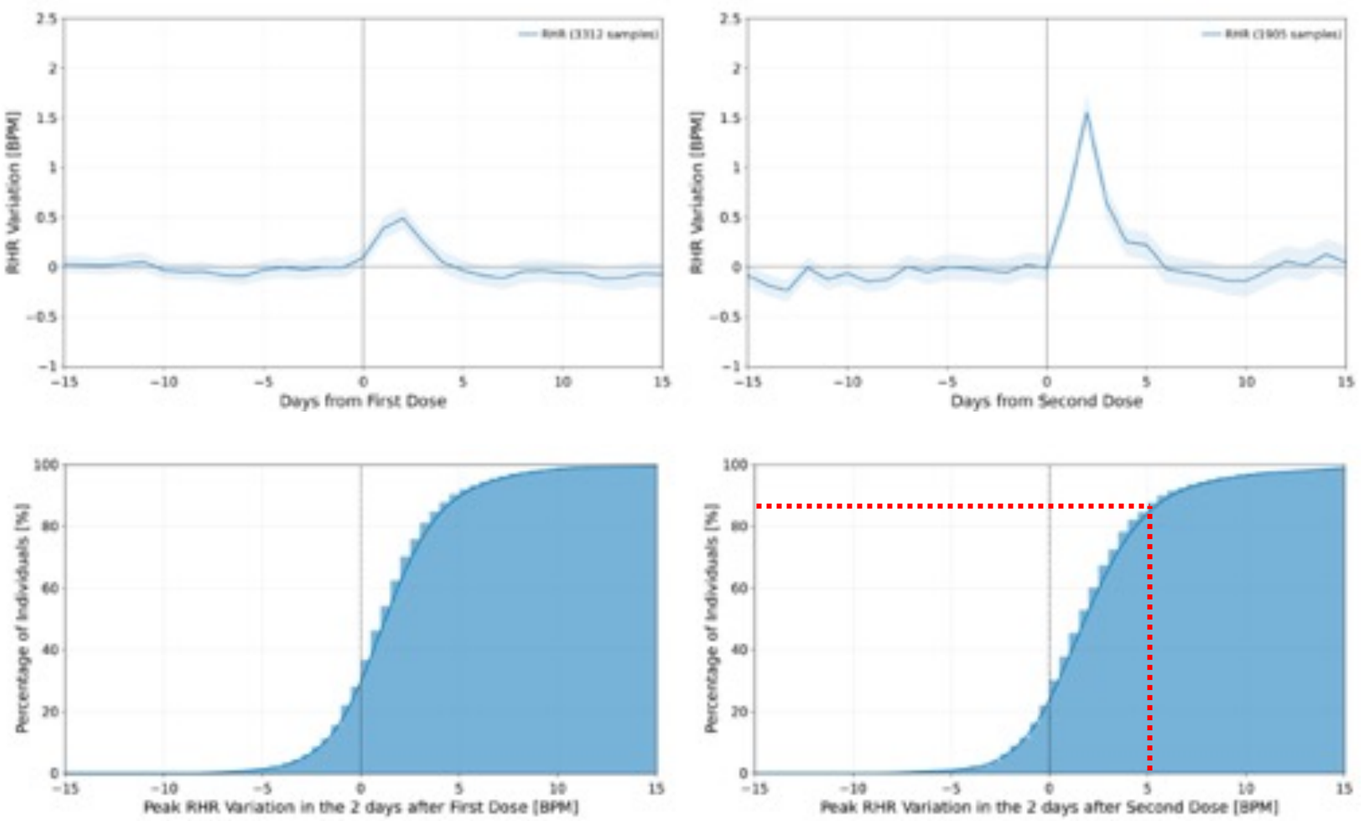
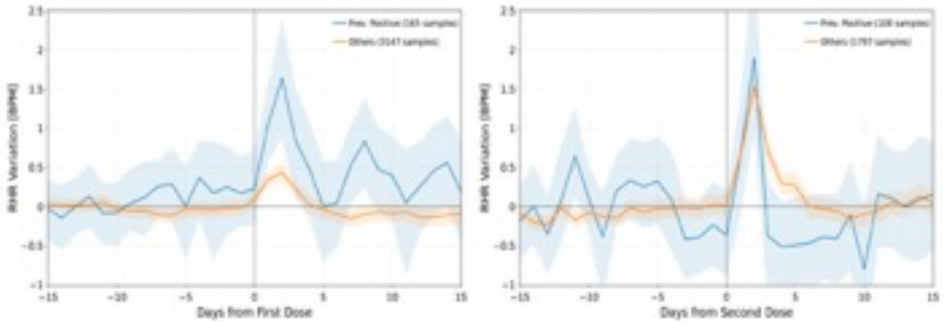
Detection of Vaccination-Induced Inflammation via Wearables

~3,300 individuals Pfizer or Moderna vaccines



- Significantly greater response to first dose in those with prior infection.
- Significantly greater response, after both doses with Moderna vs Pfizer-BioNTech



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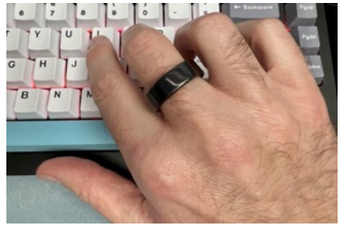
Quer G. npj Digital Medicine (2022) 5:49 ; https://doi.org/10.1038/s41746-022-00591-z

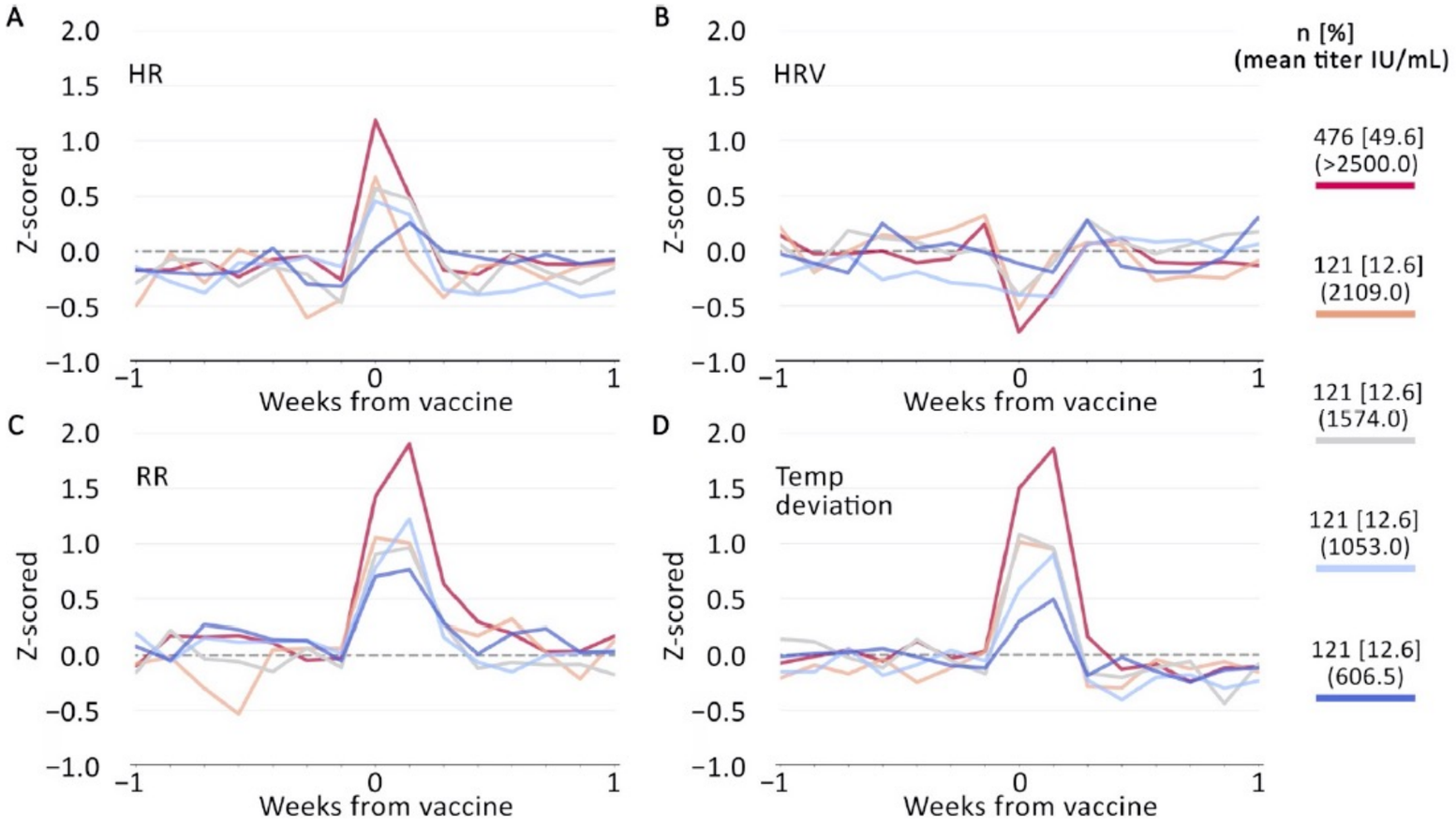
Wearables-Detected Inflammation & Immunogenicity



1179 individuals wearing an Oura ring pre/post vaccine with antibody testing and average of ~38 days after

All measured changes were significantly associated with antibody response.

Only temperature change was significant by multivariate analysis

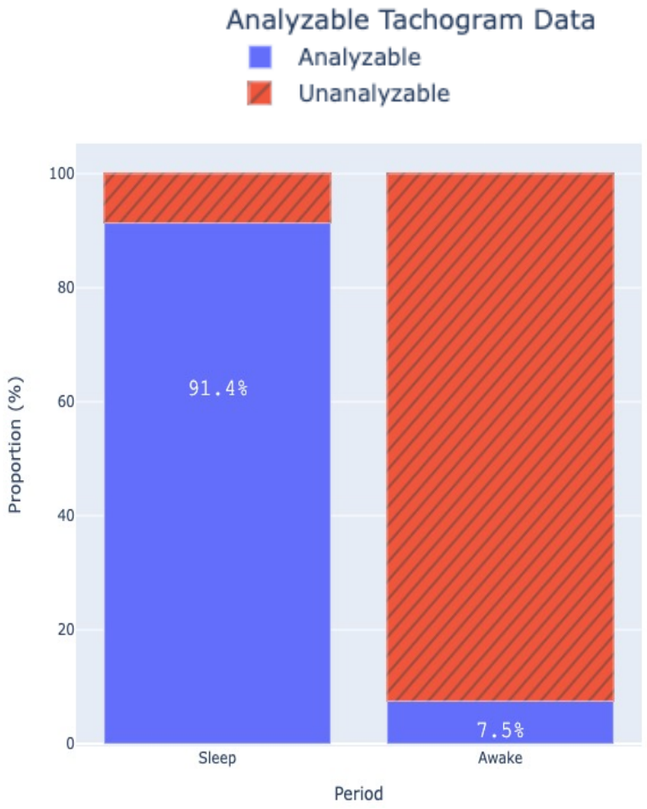


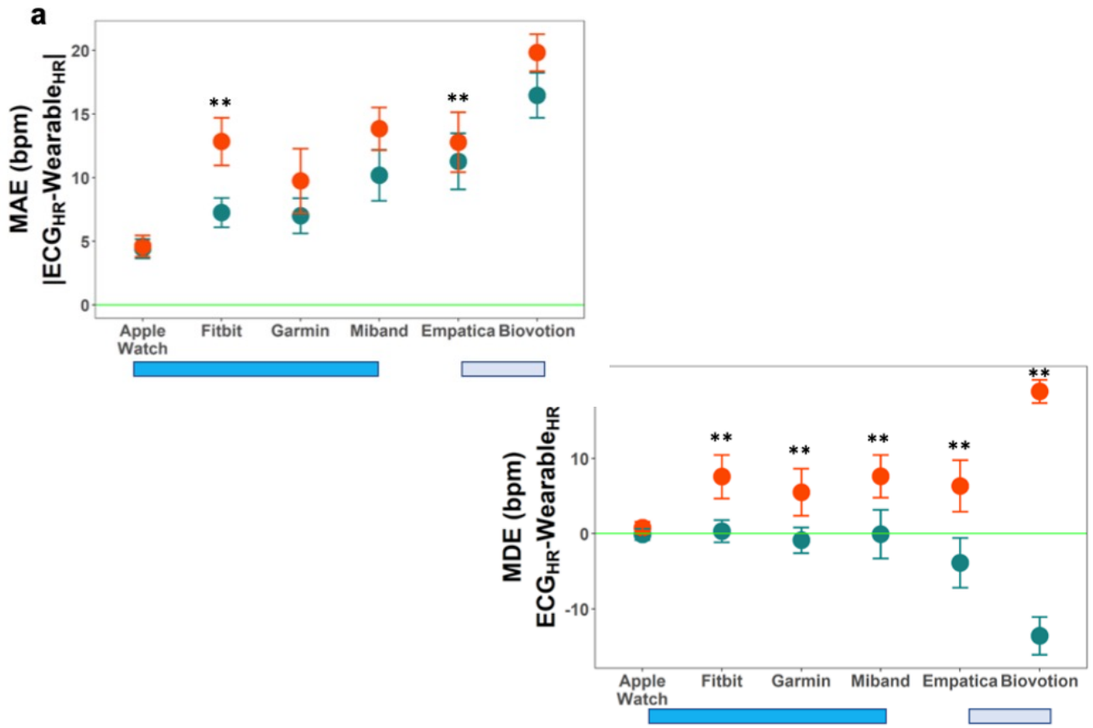
Differences in Physiologic Data Availability & Quality

For extremity-based PPG sensors, physiologic data can be extracted primarily only during sleep

Fitbit Heart Study

- Tachogram data was analyzable a median of 8 hours per day – primarily during sleep.
- During a median of 7 days of simultaneous ECG patch monitoring in 1040 individuals:
  - Tachogram data was analyzable <8% of non-sleep time





- During rest, the MAE of consumer wearables was 7.2 ± 5.4 bpm and for research-grade wearables 13.9±7.8 bpm.
- During physical activity, results were 10.2 ± 7.5 bpm and 15.9±8.1 bpm, respectively.

Lubitz S. Circulation 2022;146: DOI: 10.1161/CIRCULATIONAHA.122.060291
Bent B. npj Dig Med 2020;3:18 doi: 10.1038/s41746-020-0226-6

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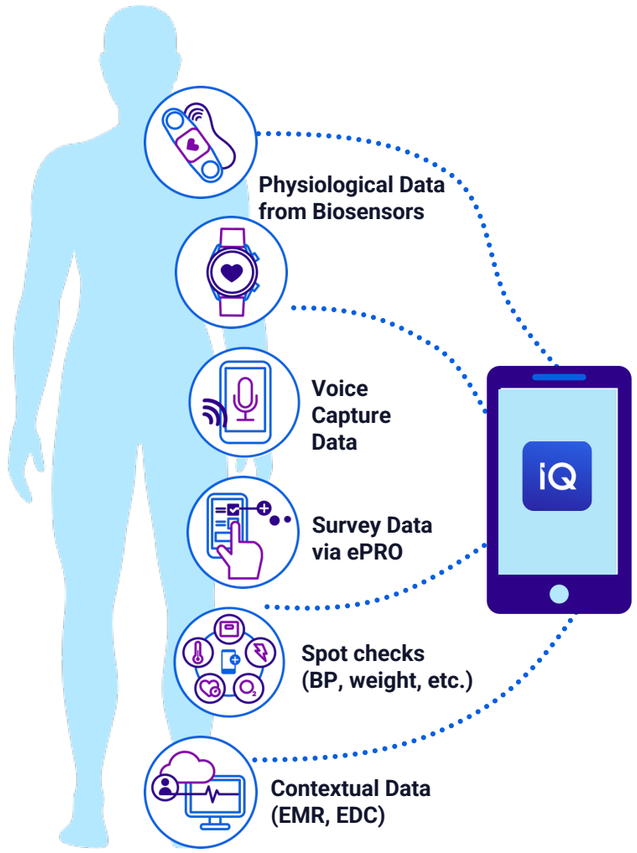
Personalized Physiology Analytics (PPA) → Digital Twin

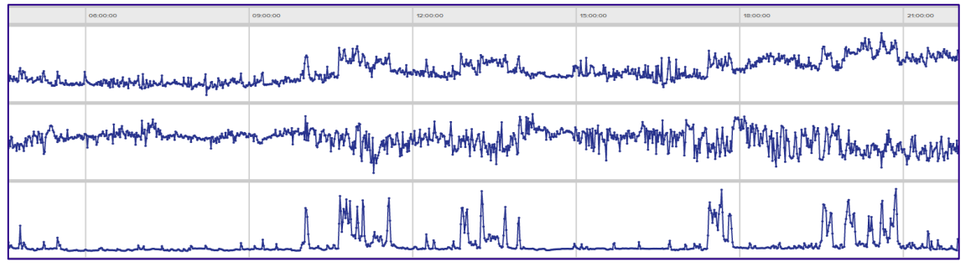
Real-time, Continuous Physiological Data Streamed via 'any' Wearable Biosensors

- Heart Rate
- Respiratory Rate
- Temperature
- Activity

17 Unique features per minute

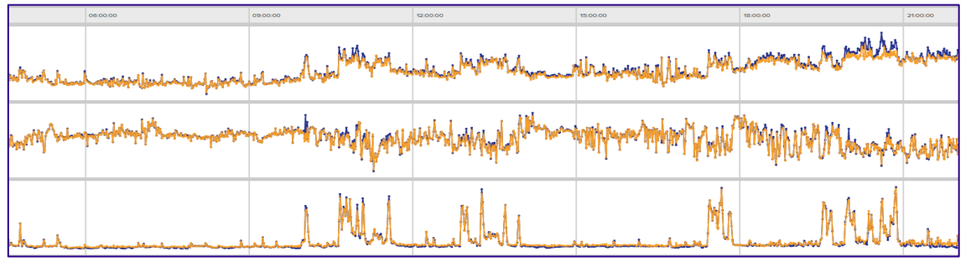
350 Additional Derived Source Signals





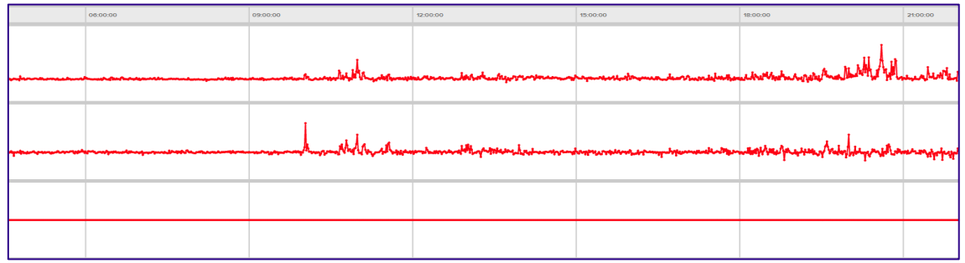
Personalized Baseline

Learns & simulates patient normal physiological dynamics to create a patient 'Digital Twin'



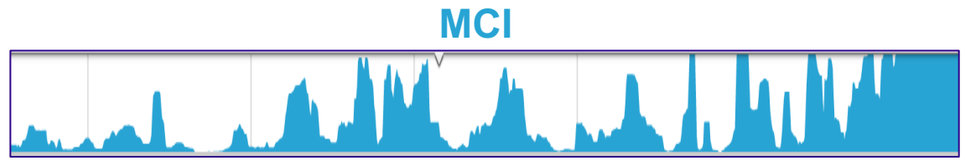
Actual To Digital Twin

Compares patient current physiological dynamics to the patient's 'Digital Twin'



Residual Calculation

Calculates the difference between patient current physiological dynamics and the patient's 'Digital Twin'



Multivariant Change Index

Transforms the residual calculation into a scaled index representing positive & negative change from the 'Digital Twin'

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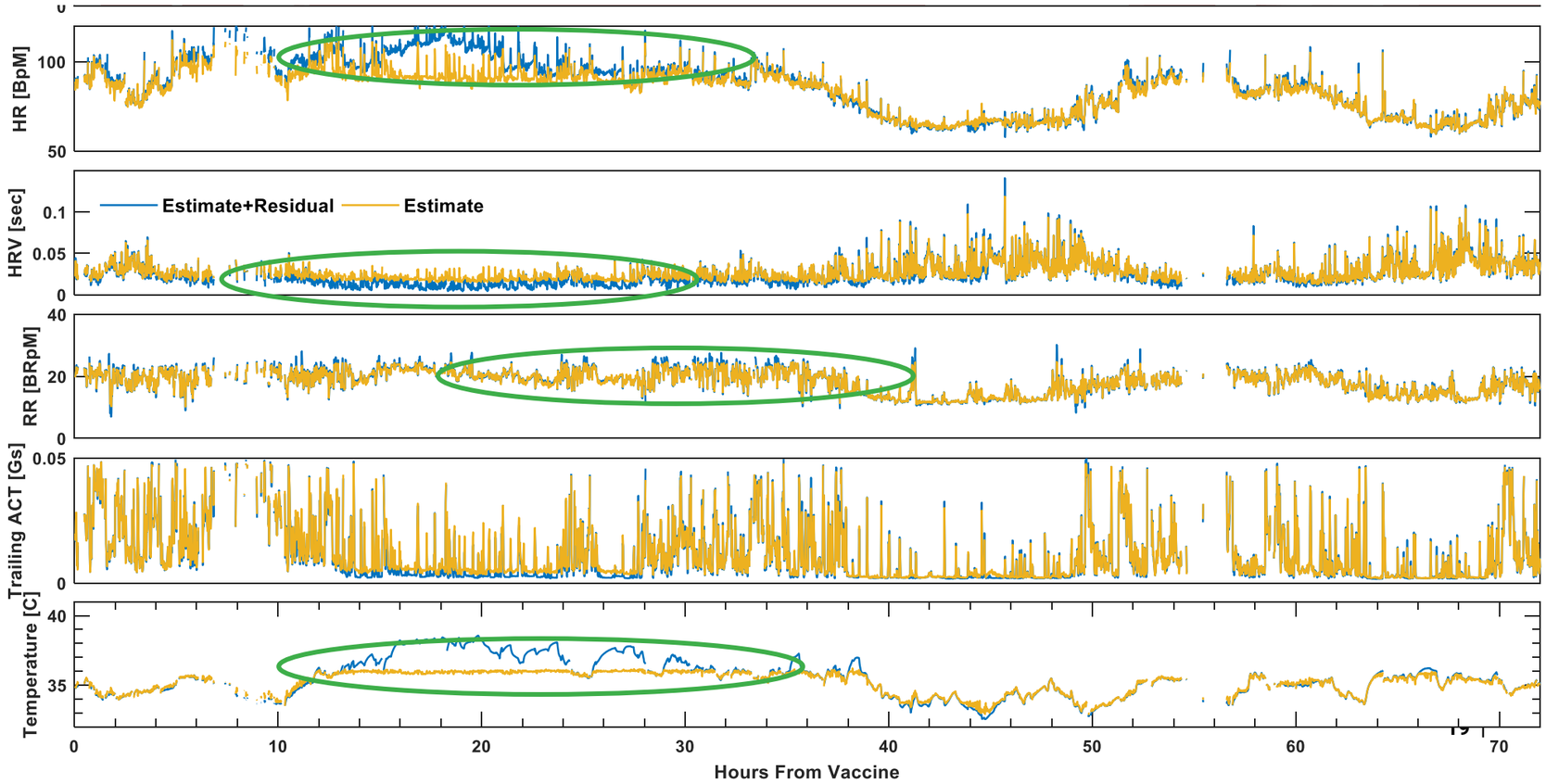
Individualized, Continuous Vaccine-Induce Inflammatory Response

- Torso Patch Sensor worn 5 days before and 7 days after vaccination.
- Machine learning method of similarity-based modeling (SBM) to create a “digital twin” through personalized physiologic analytics.

- Digital twin estimated biometrics in orange.
- Real-time biometrics in blue.
- Subtle, but unexpected deviations from that individual’s expected “normal” detected.
- Summation of these deviations (and multiple others not shown) combine into the **iMCI**.



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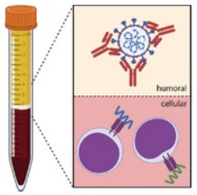
VACCINE-INDUCED INFLAMMATION INVESTIGATION (VIII) Study Design – Primary and Substudy - 118 total dose-responses



Vaccine * Dose 1

Vaccine * Dose 2 or 3

~21 -28 days

5 days prior | 7 days after

5 days prior | 7 days after

5 days prior | 7 days after

5 days prior | 7 days after

5 days prior | 7 days after

5 days prior | 7 days after

Baseline -5 days prior V1

~14 +/- 2 for T-cells

~14 +/- 2 for T-cells

Long-term, ~60 days antibodies

Minute-level Continuous Multiparametric Biometrics

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All VIII Study Participant Characteristics

Total number participants	97
Total number of vaccine doses	118
Age (mean±SD)	38.1 ± 14.0
Female (%)	49.5%
BMI (mean±SD)	24.8 ± 3.8
Self-reported prior COVID-19 (% of participants)	11.34%
mRNA Vaccine (% of participants)	99.0%
# of first dose of mRNA	17
# second or booster dose mRNA	101
Moderna vaccine (% of all doses)	46.2
BioNTech/Pfizer vaccine (% of all doses)	52.9

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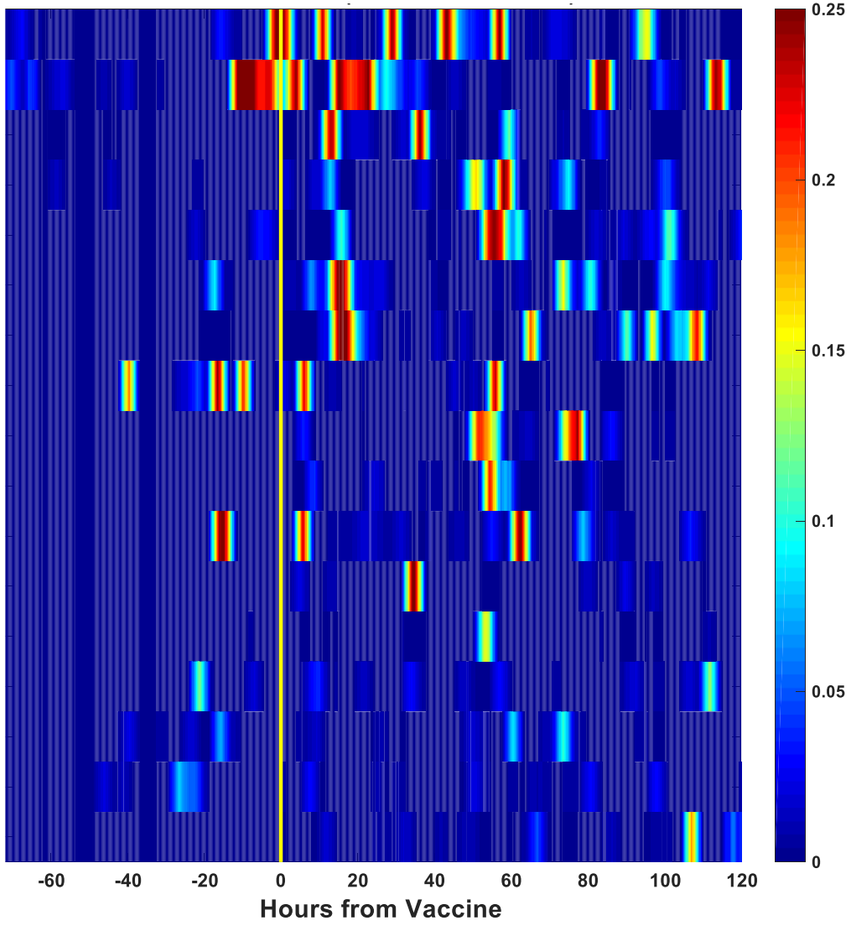
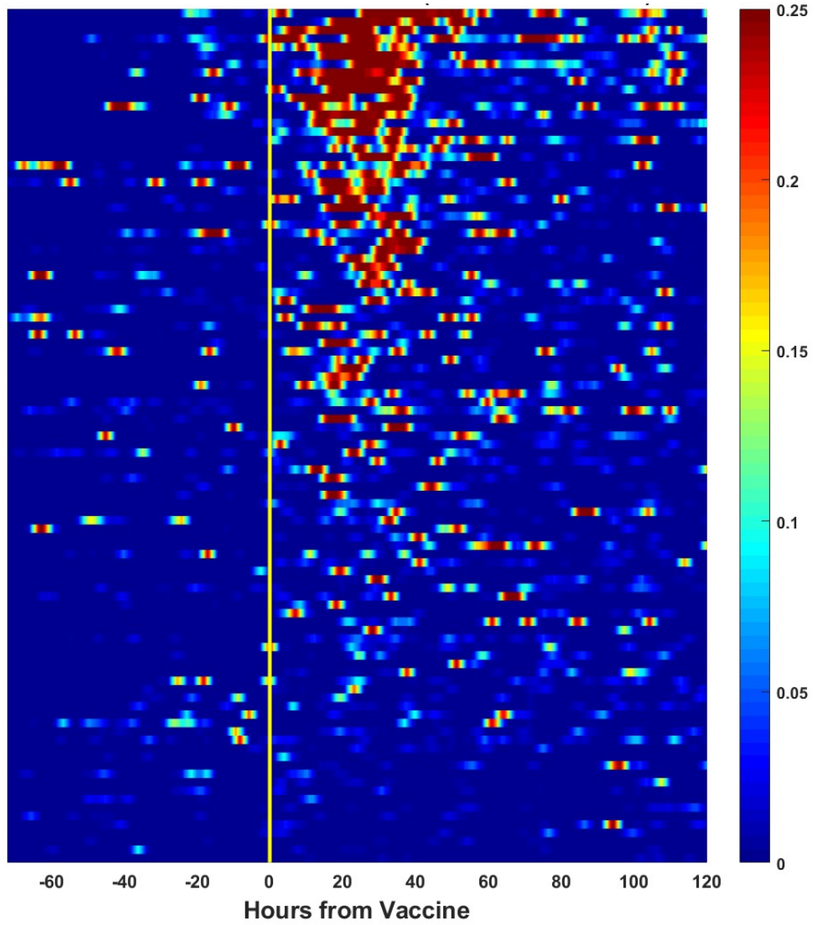
Vaccine-Induced Inflammatory Response

(3 days pre vaccine through 5 days after)

Response to First Dose (n=17)

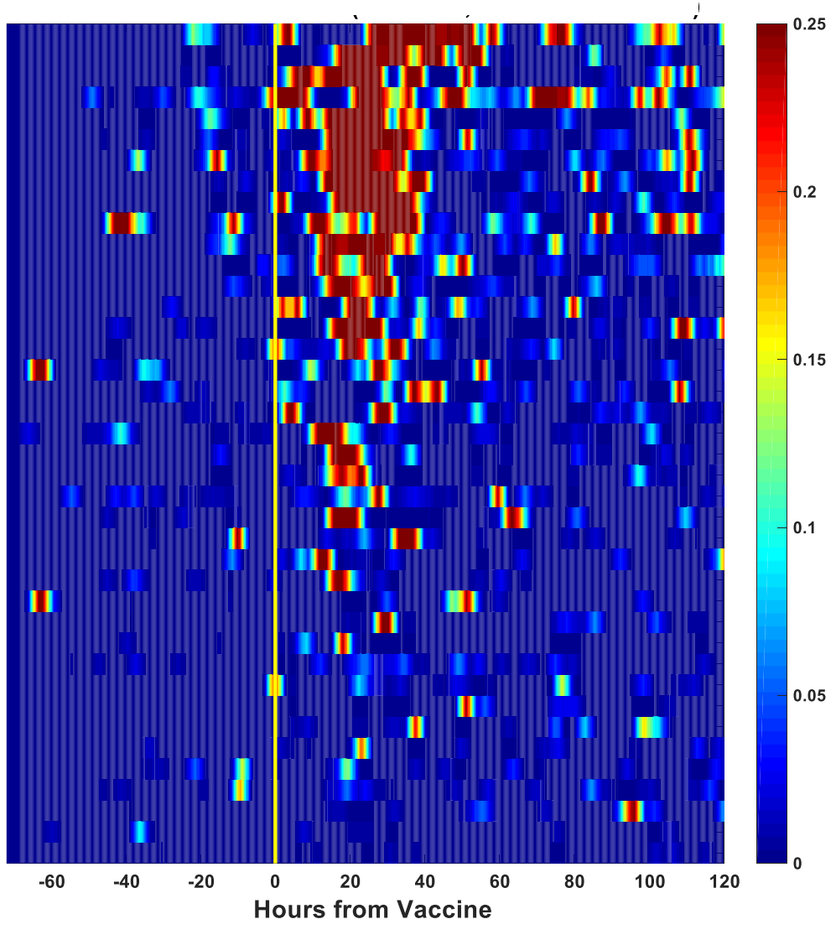


Response to 2nd or Booster Dose (n=101)

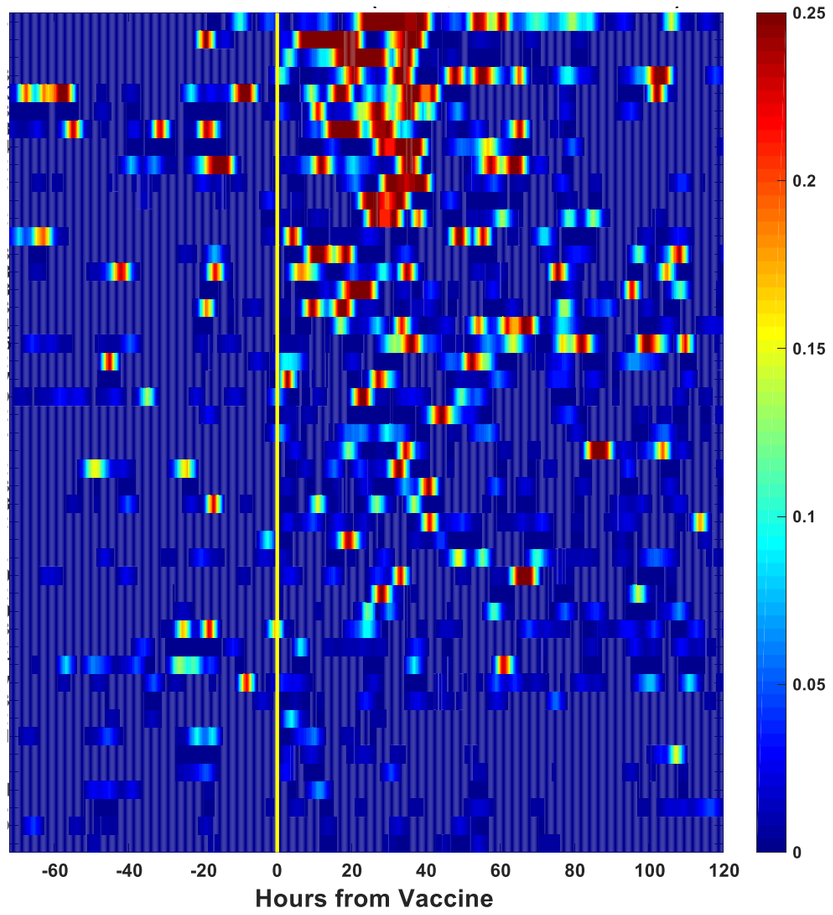


mRNA Vaccine Type and Inflammation (2nd & Booster Dose Only)

Moderna

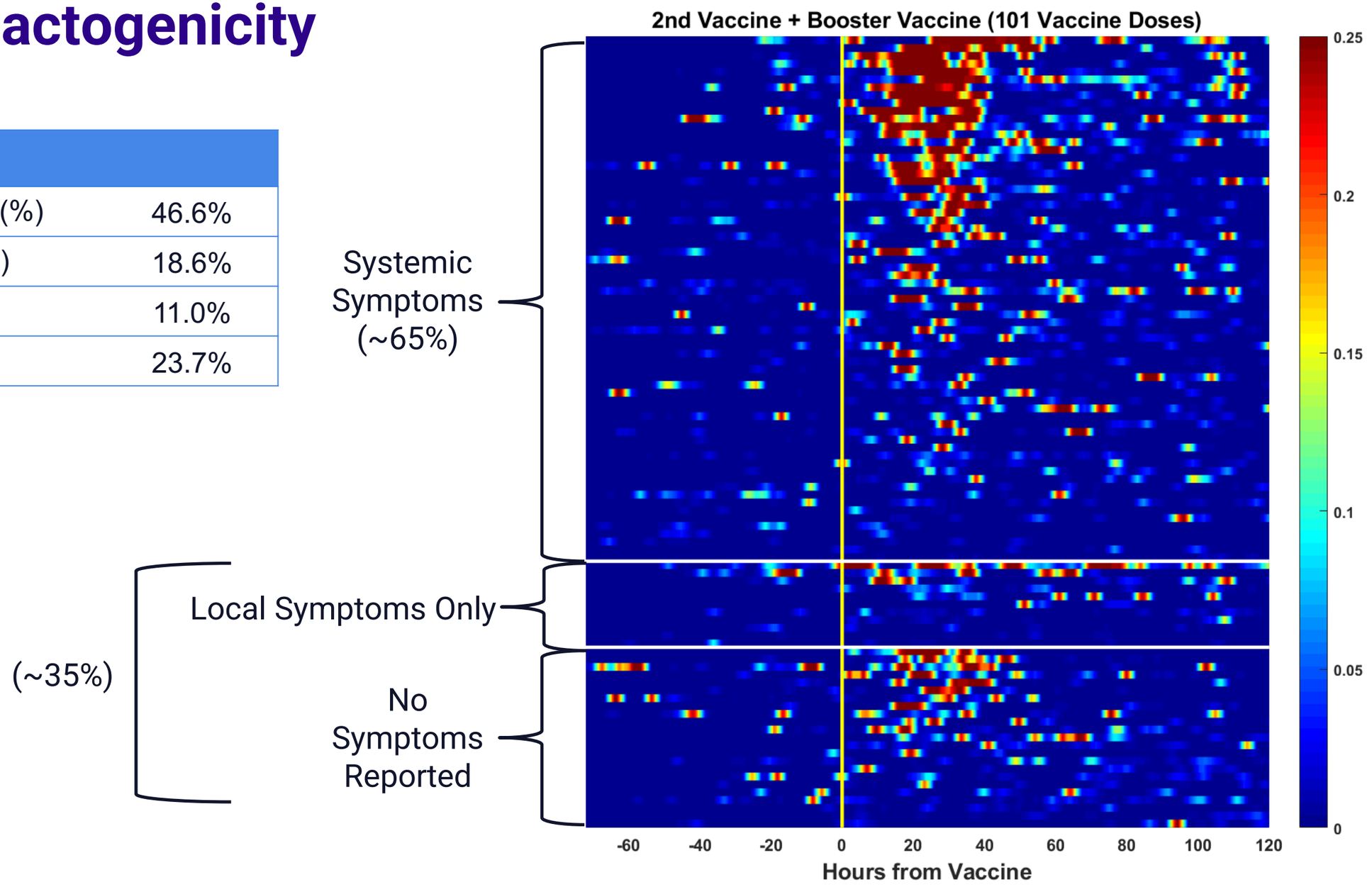


BioNTech/Pfizer



Subjective Reactogenicity

Systemic + Local Symptoms (%)	46.6%
Systemic Symptoms Only (%)	18.6%
Local Symptoms Only (%)	11.0%
No Symptoms Reported (%)	23.7%



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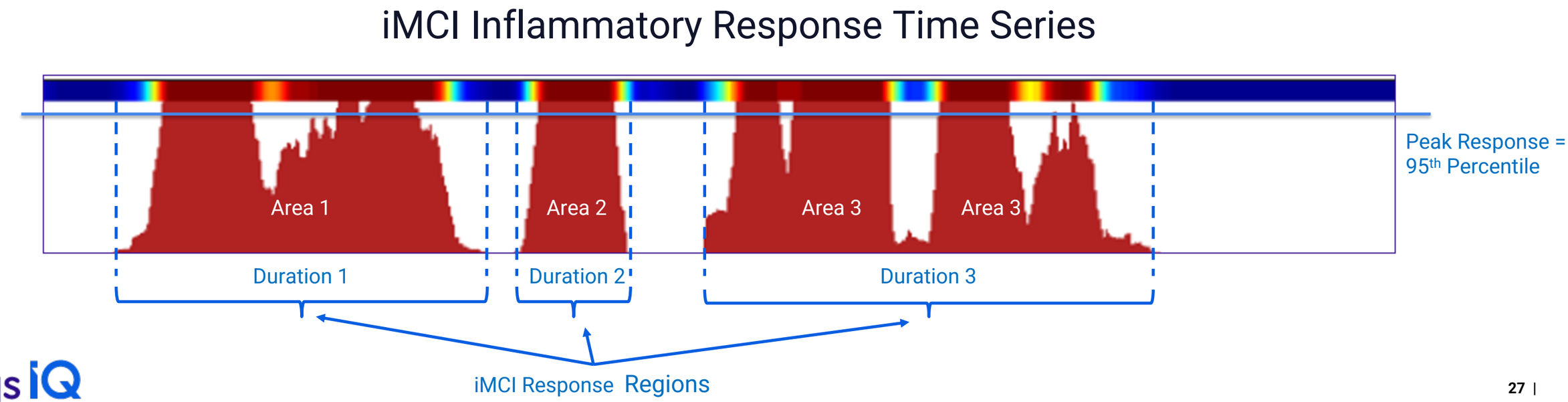
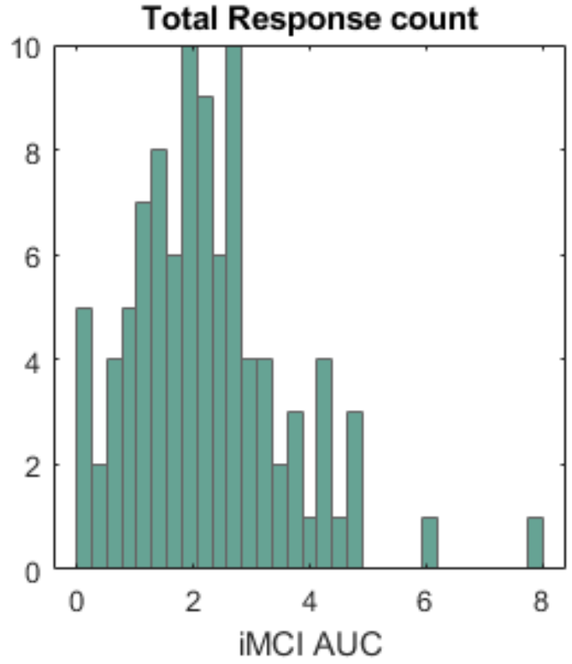
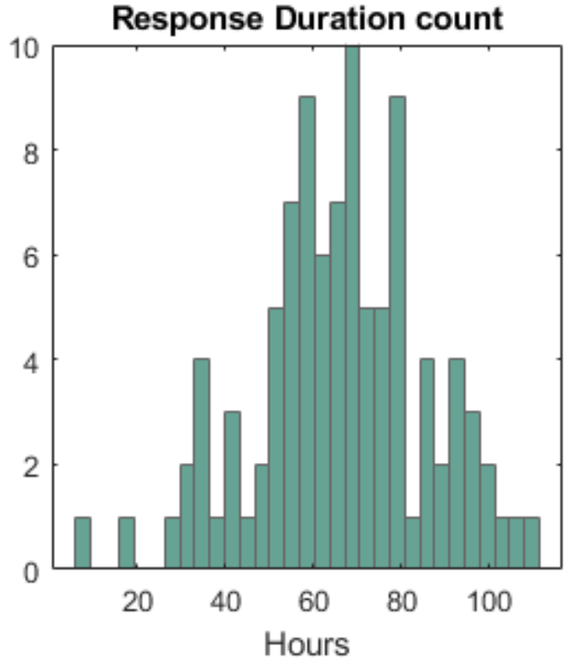
iMCI-Based Inflammation Response Metrics

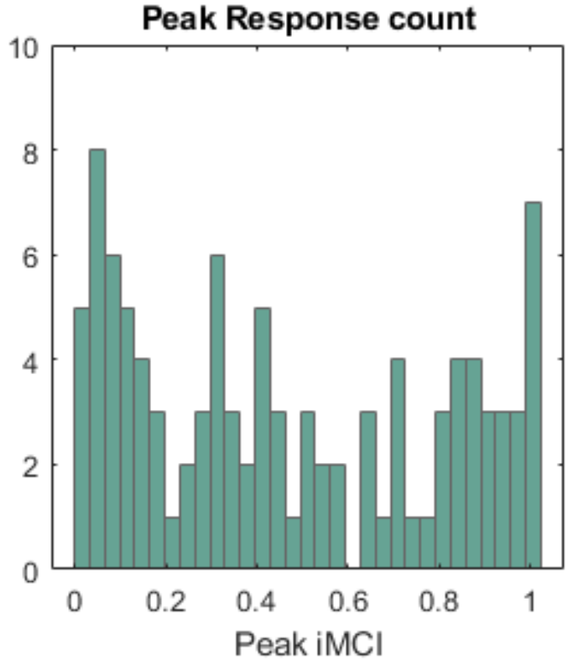
- **Total Response (iMCI AUC)**: Sum of the Area Under the Curves (AUCs) of the non-zero regions (Area **) of iMCI response time series normalized by the duration (Duration **) of each non-zero response region
- **Response Duration**: Total duration in hours of non-zeros iMCI regions
- **Peak Response**: The 95th Percentile of all non-zero regions of iMCI



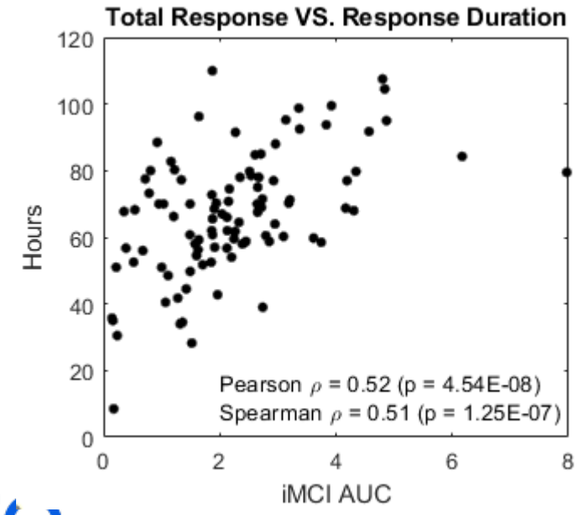
Distribution of Measured Inflammatory Response

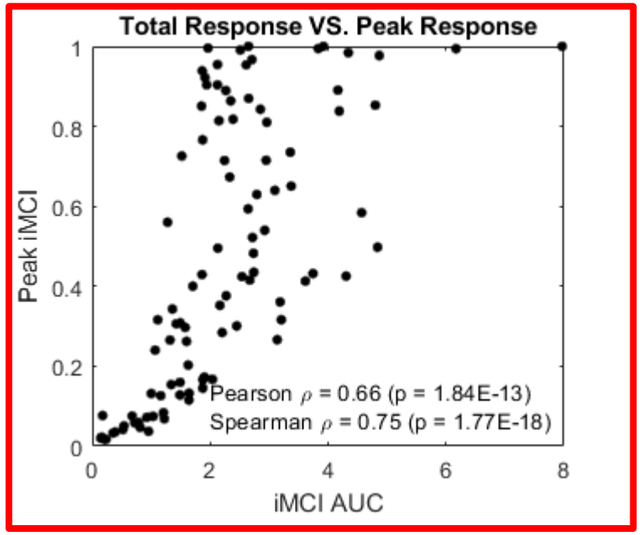


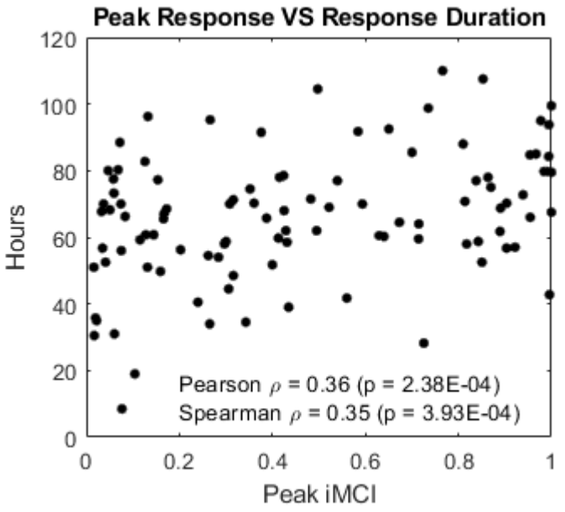




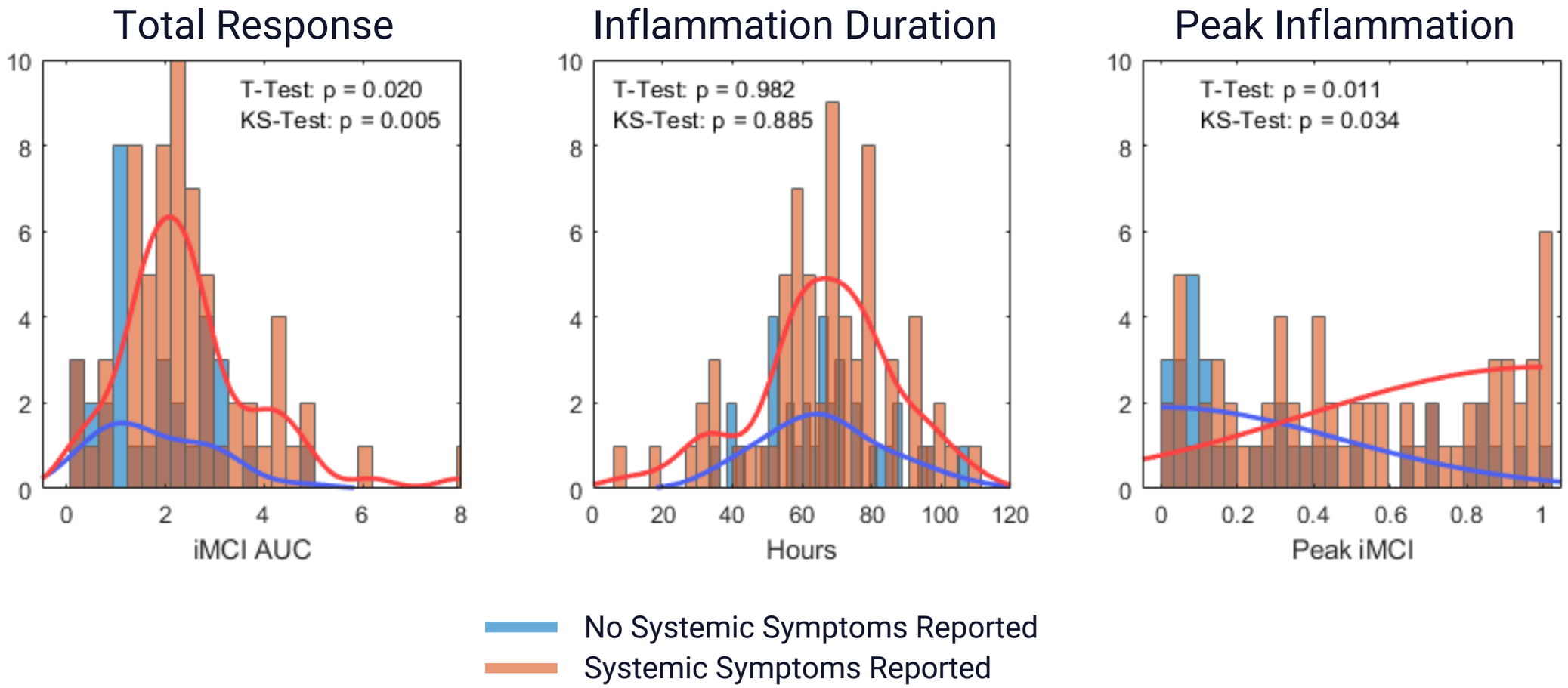
~95% experienced a measurable response







Relationship Between Measured Inflammation and Symptoms



☆ Both total and peak inflammation (but not total duration of inflammation) were significantly associated with systemic symptoms.

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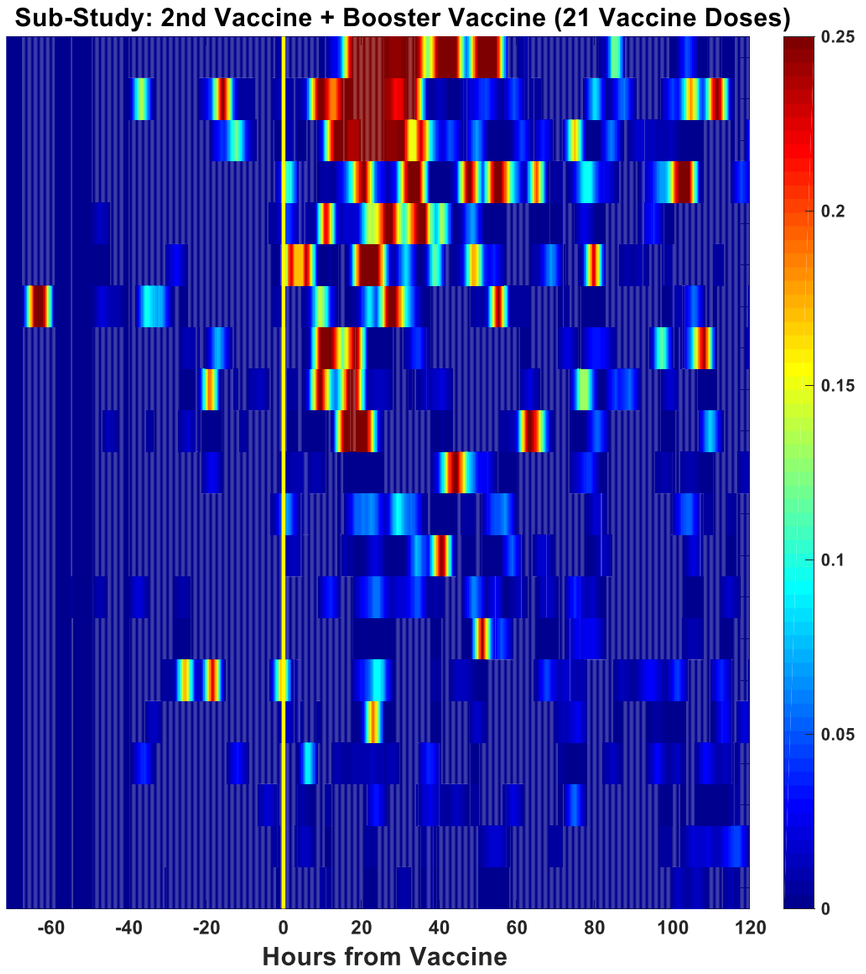
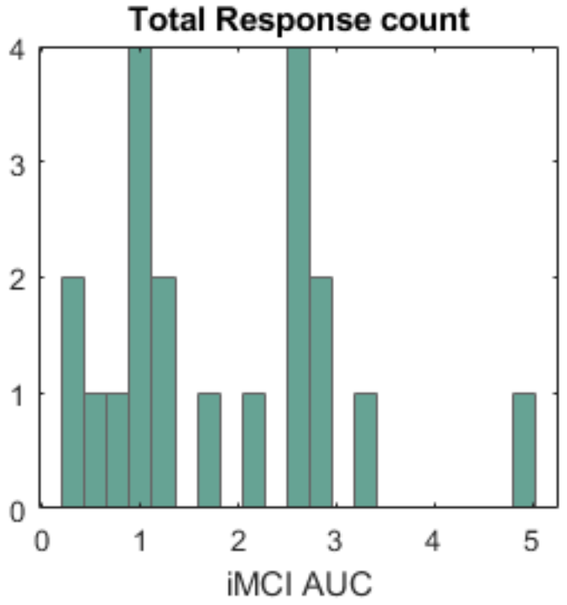
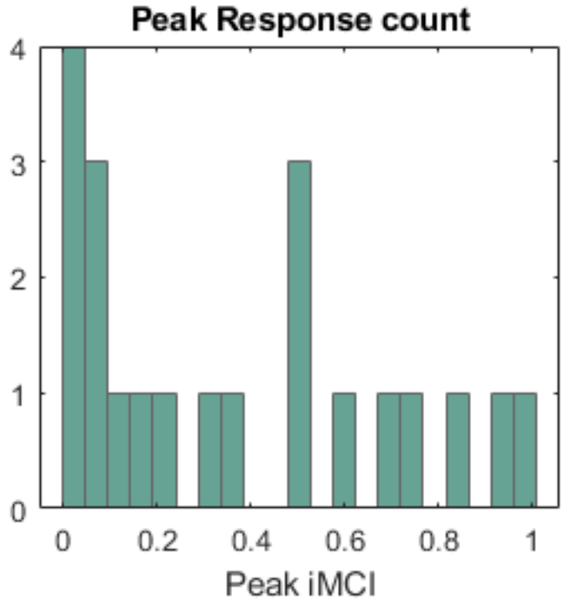
Inflammation in Immunogenicity Sub-Study Participants

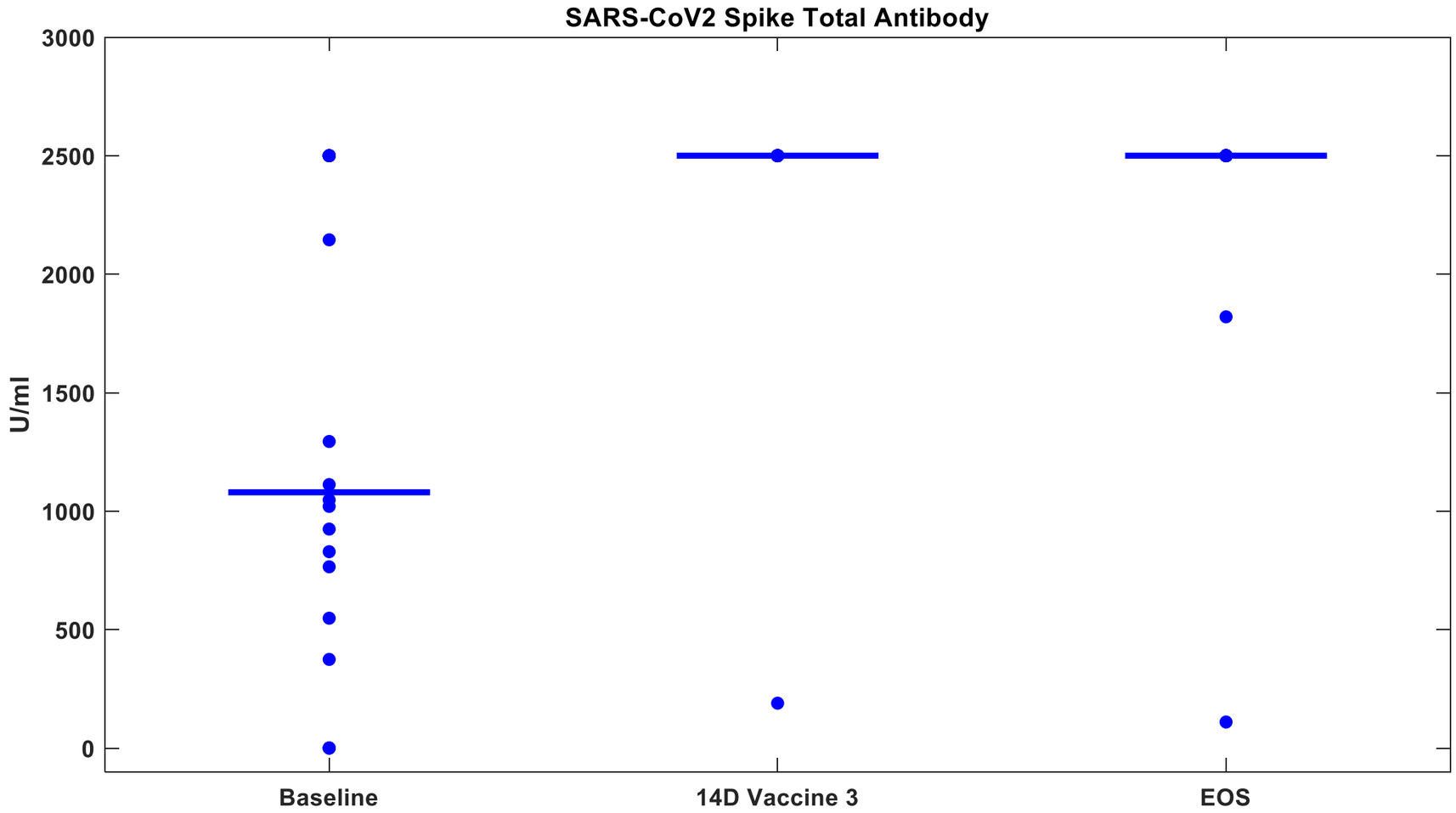






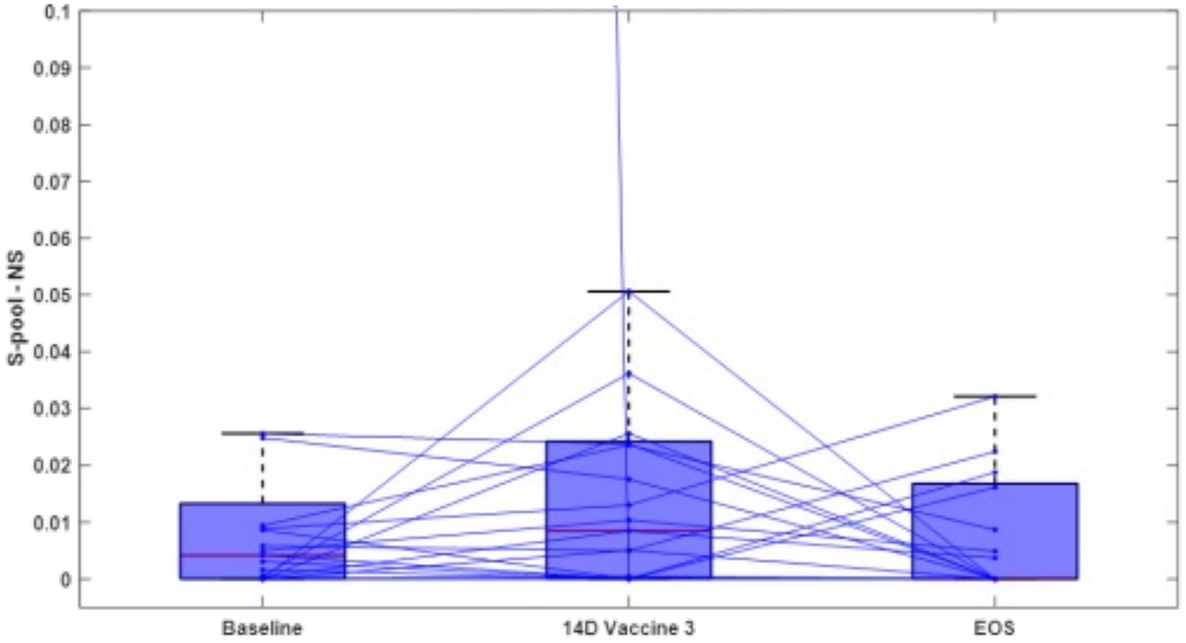
Humoral Immunogenicity
Anti-Spike Antibody Response

(As only a semi-quantitative assay has been run so far, we have not yet been able to explore the association between individual inflammation and humoral immunogenicity)

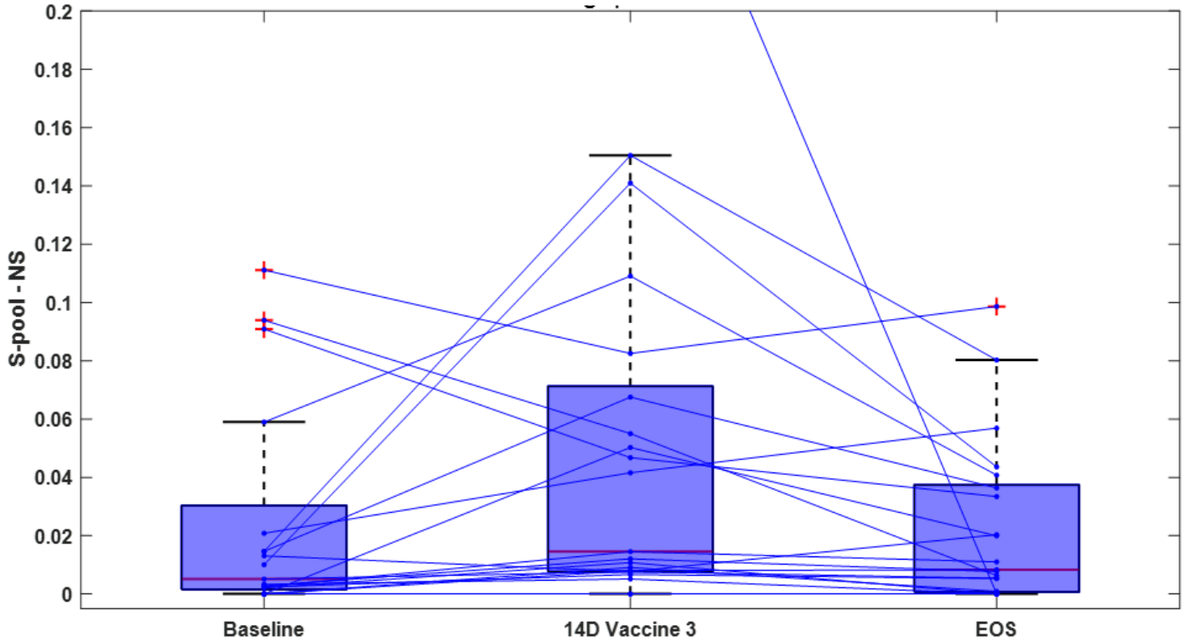


Cellular Immunogenicity
Change in Frequency of CD4+ and CD8+ Distribution from Baseline

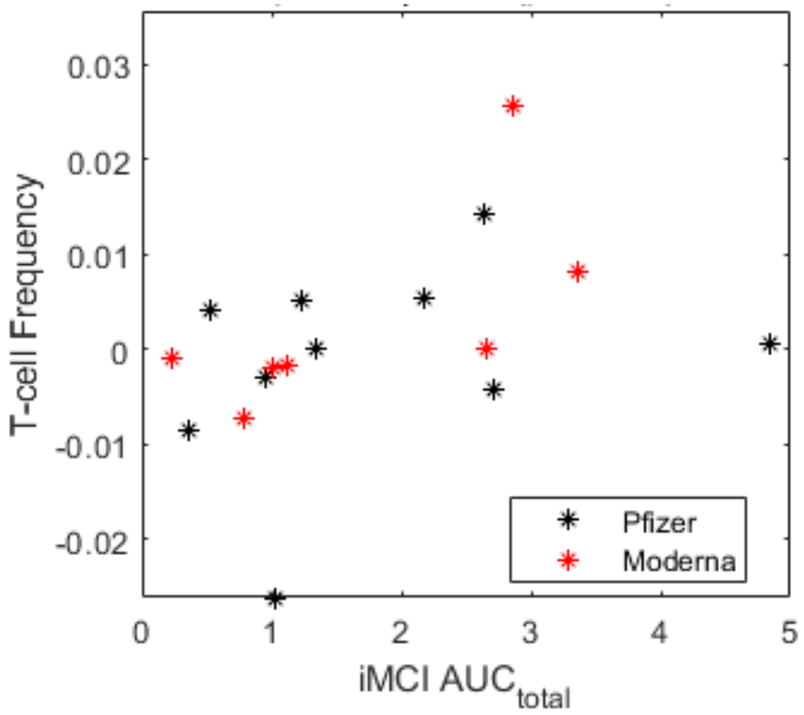
CD4+ (IL21 +) as a Percent of Total CD4+

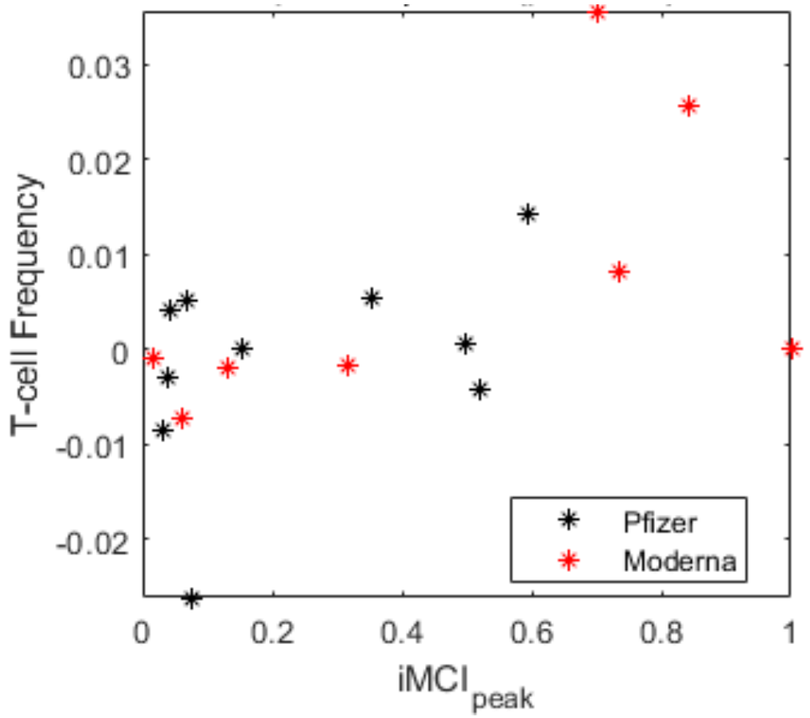


CD8+ (Interferon γ +) as a Percent of Total CD8+



CD4+ (IL21 +) as a Percent of Total CD4+

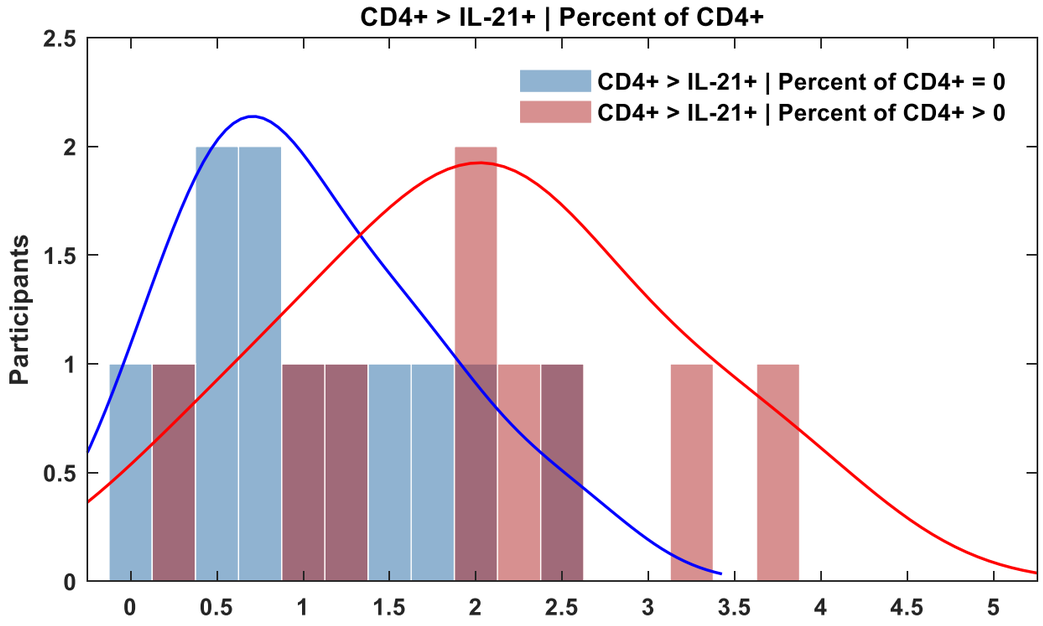




Total Response
Pearson ρ = 0.42 (p=0.1)
Spearman ρ = 0.56 (p=0.02)

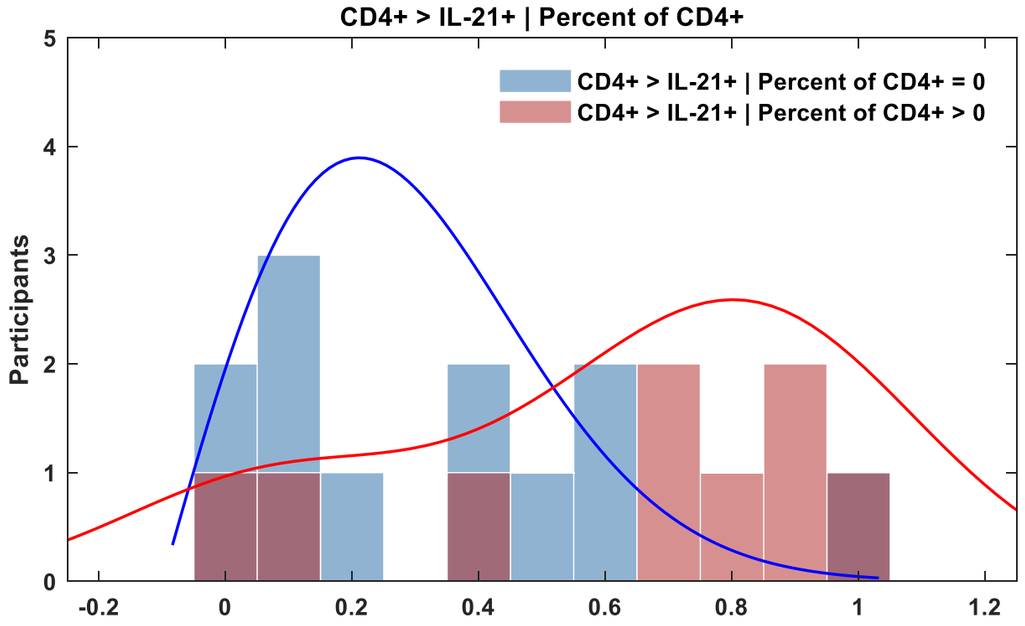
Peak Response
Pearson ρ = 0.58 (p=0.01)
Spearman ρ = 0.59 (p=0.001)

CD4+ Population – Dichotomous Response



Total Inflammation Response

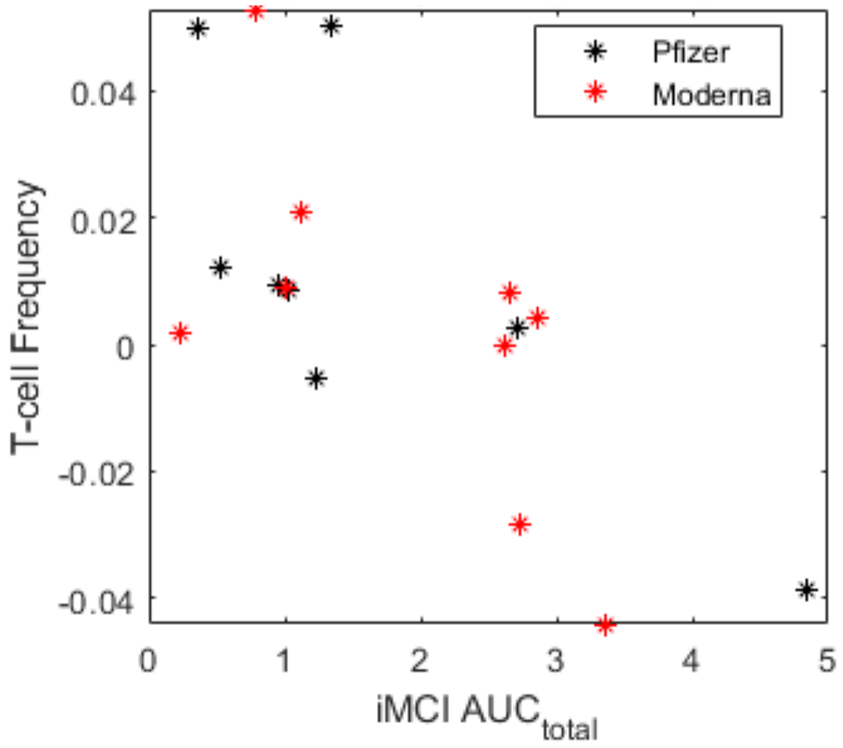
t-test p-value: 0.0203
KS-test p-value: 0.0352

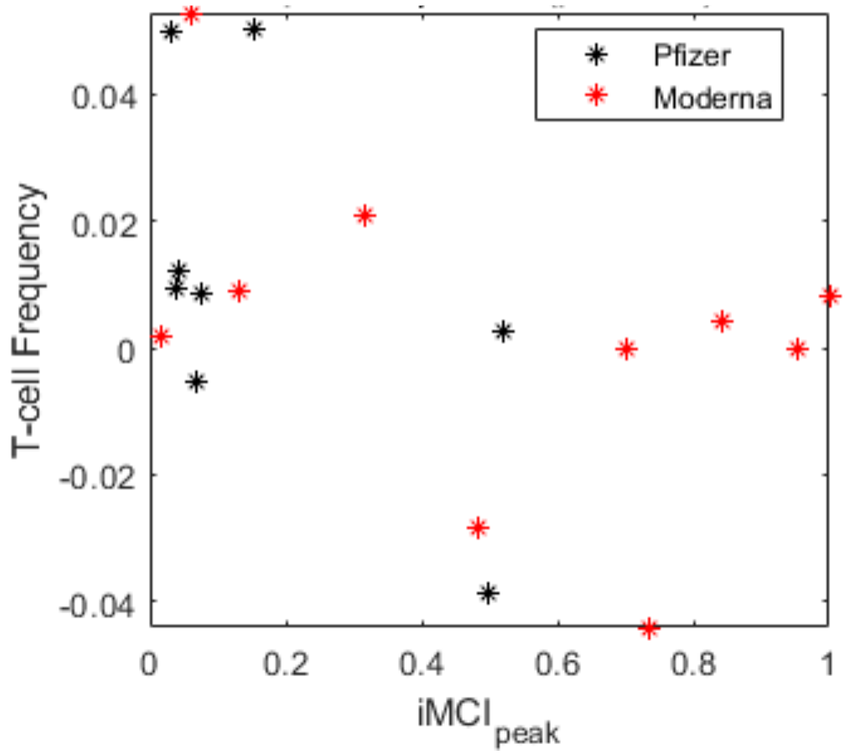


Peak Inflammation Response

t-test p-value: 0.0621
KS-test p-value: 0.0352

CD8+ (Interferon γ +) as a Percent of Total CD8+

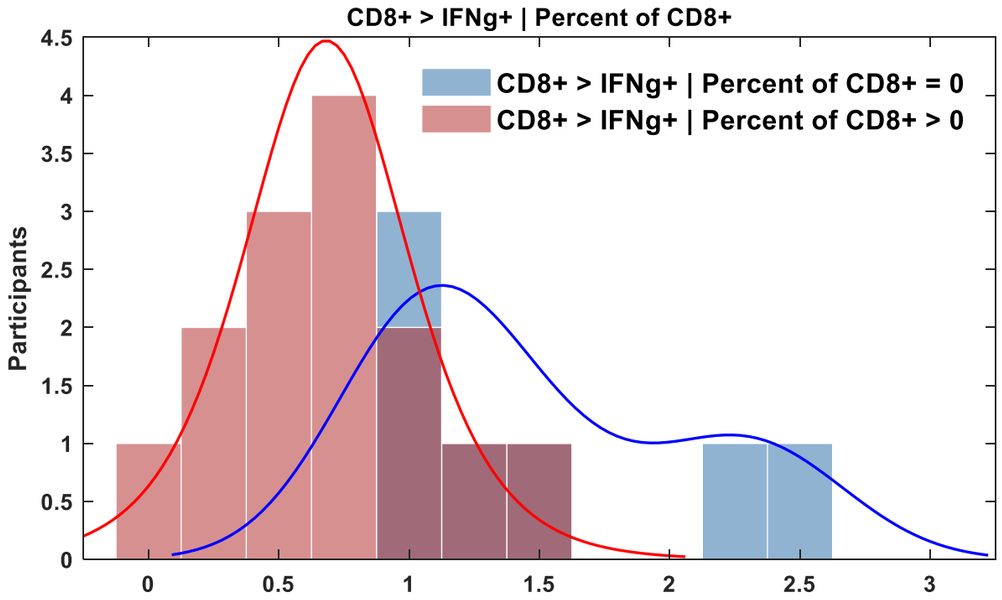




Total Response
Pearson ρ = -0.70 (p<0.01)
Spearman ρ = -0.65 (p=0.01)

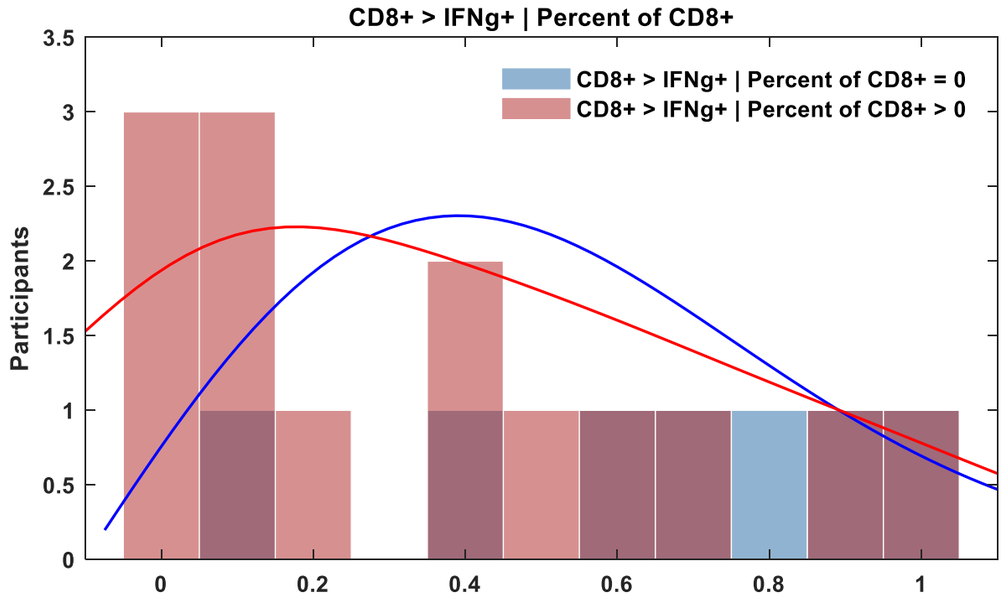
Peak Response
Pearson ρ = -0.45 (p=0.06)
Spearman ρ = -0.47 (p=0.05)

CD8+ Population – Dichotomous Response



Total Inflammation Response

t-test p-value: 0.0015
KS-test p-value: 0.0078



Peak Inflammation Response

t-test p-value: 0.0911
KS-test p-value: 0.2710

Development of a Multivariate Digital Biomarker of Vaccine-Induced Inflammation and its Relationship to Immunogenicity - ***Conclusions***

- A multivariate digital biomarker for inflammation can capture objective evidence of the entirety of an individual's physiologic response to mRNA vaccination in the vast majority of individuals.
- The degree of the measured inflammatory response after vaccination correlates with the subjective symptoms experienced.
- The measured CD4+ T-cell immunogenicity was moderately directly correlated with the inflammatory response, whereas CD8+ response was strongly negatively correlated.
- Ongoing work is further exploring the relationship to humoral immunity, the broader T-cell response, and in non-vaccine inflammatory settings.