



# Multi-Analyte Data Analysis Reduces False Positives in Cystic Fibrosis

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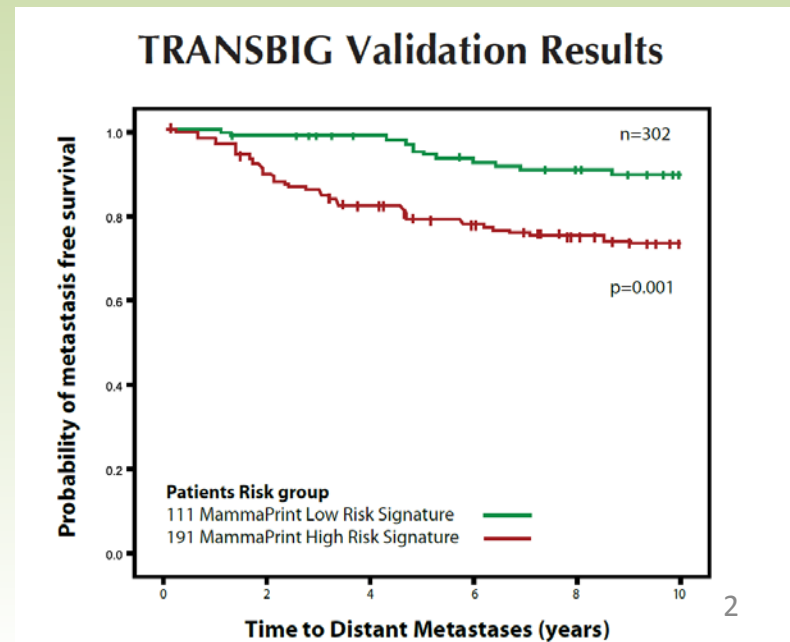
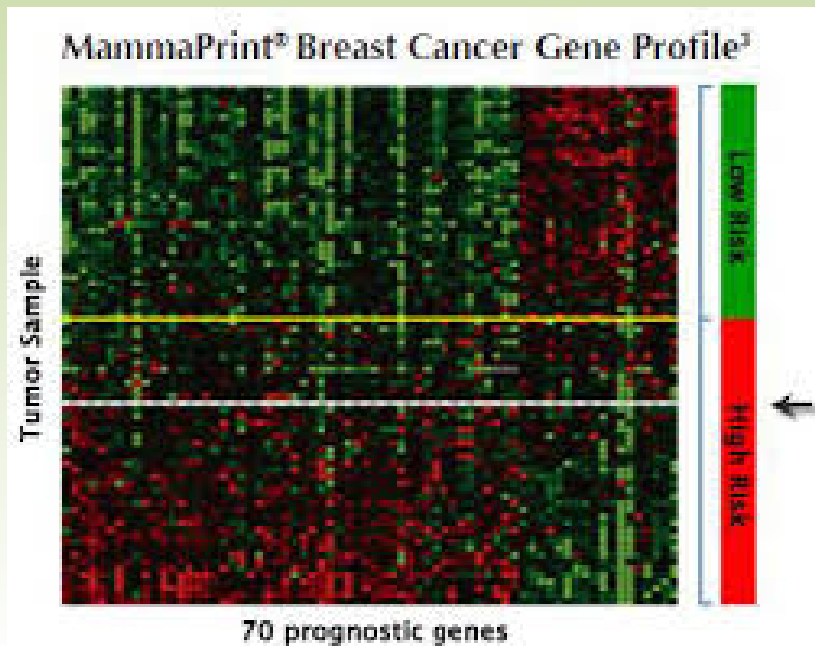
Iowa Newborn Screening Program

March 3, 2016



# Multi-analyte data analysis

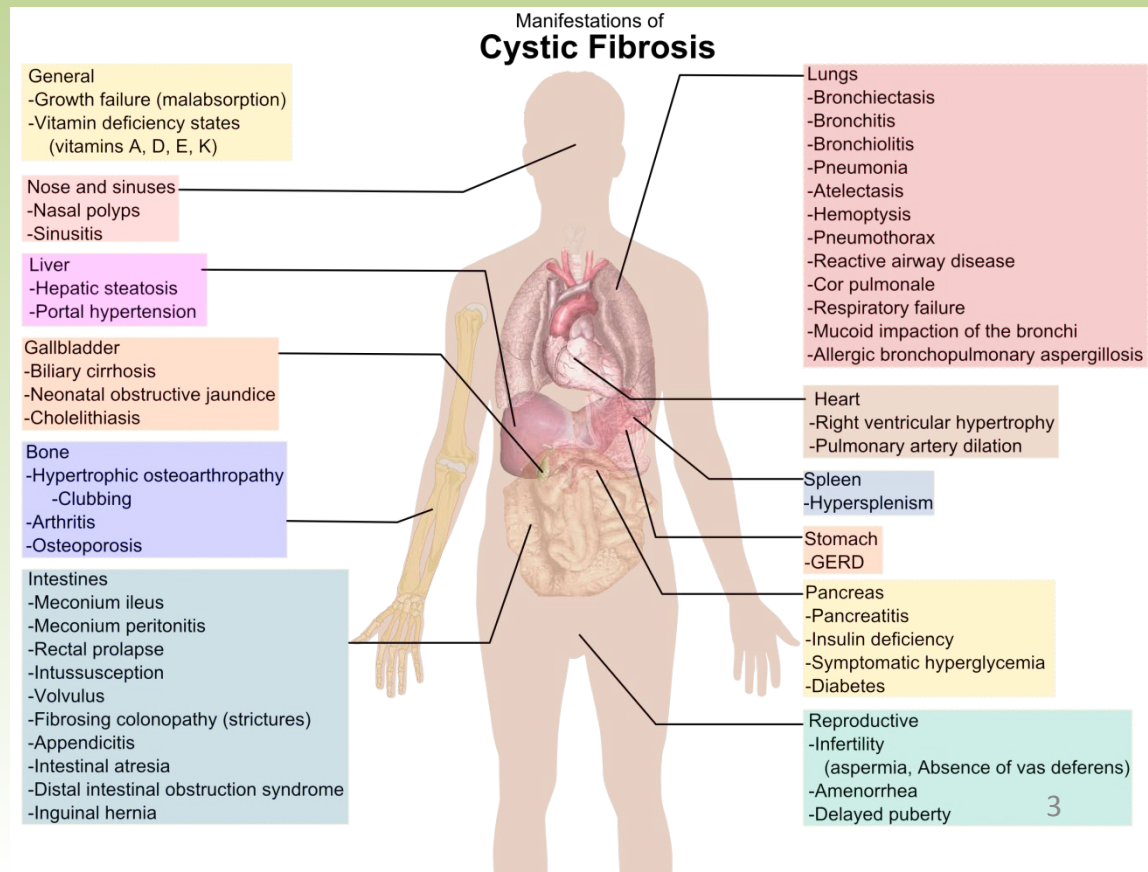
- Cancer genomics
  - MammaPrint breast cancer recurrence assay
  - Predicts risk for breast cancer recurrence based on gene expression data from 70 target genes
  - Developed using unbiased gene selection based on patient outcomes



# Multi-analyte analysis: Cystic Fibrosis

- Why can't NBS steal a page from the cancer book?
- Many NBS disorders are multi-system disorders
  - CF: respiratory, pancreatic, hepatobiliary, reproductive, etc.

- Perhaps additional biomarkers can be found that improve discrimination of disease states





# Multi-analyte analysis: Cystic Fibrosis

- Number of specimens: 27,961 (approx. 9 mos)
- Confirmed CF Dx: 9
- CRMS: 7
- Carriers: 29
- Total clinical cases: 45
- Normals: 27, 916
- Data points per specimen: 76 (demographic, facility, analyte, etc)
- Total dataset: 2,125,036



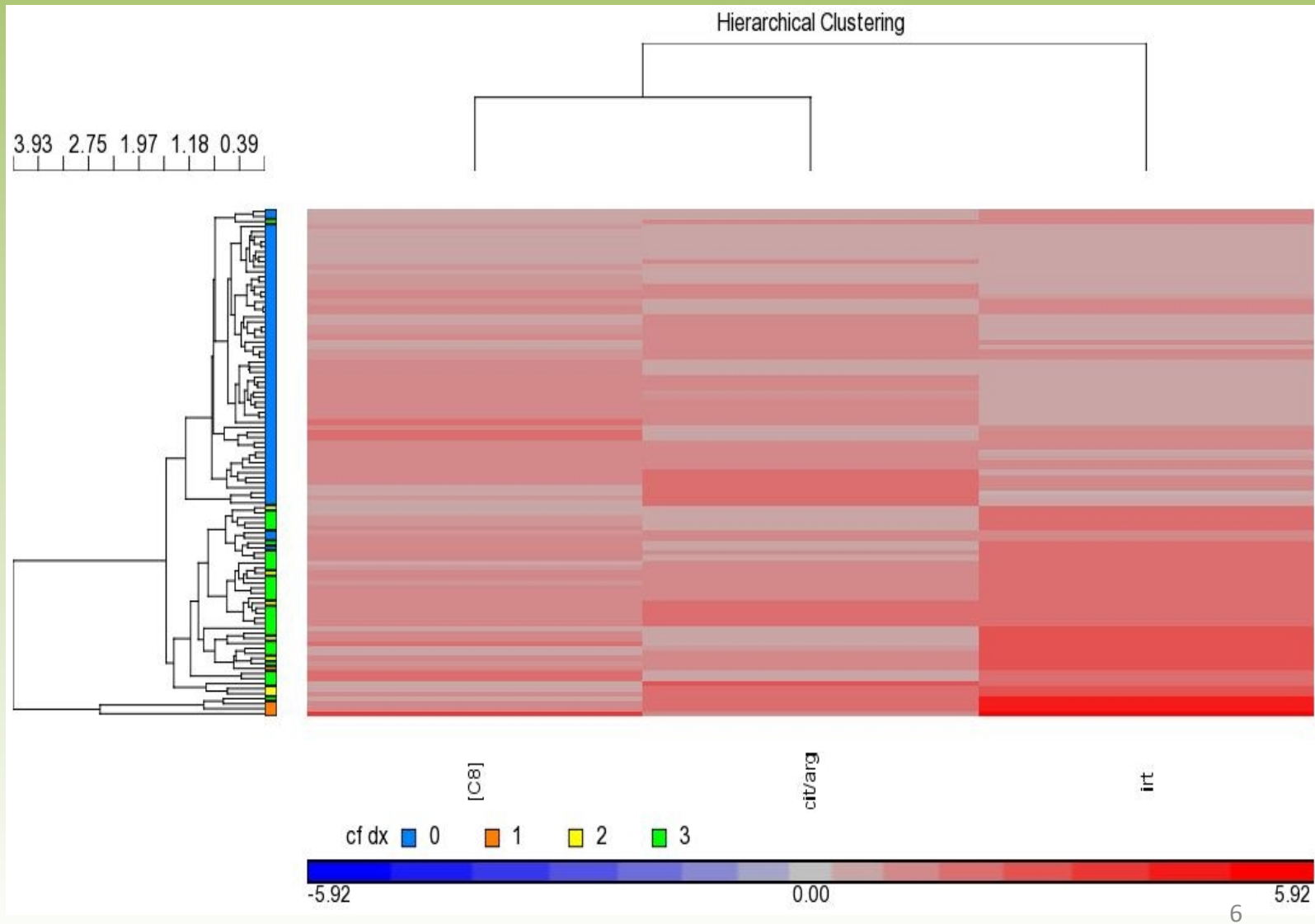


# Multi-analyte analysis: Cystic Fibrosis

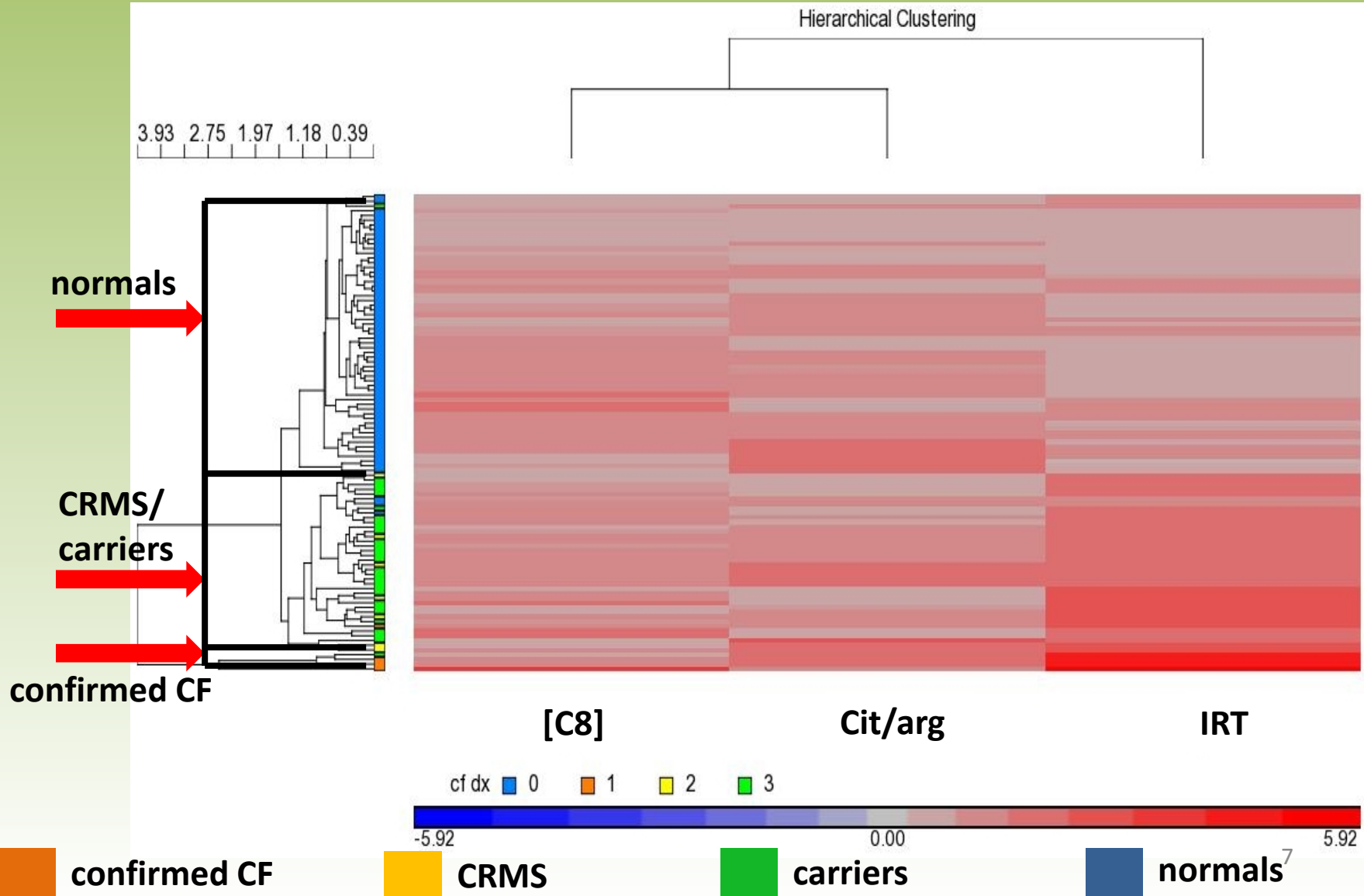
- Analysis performed using Partek Genomic Suite
- Data median normalized
- ANOVA performed across all analytes using CF diagnosis as the comparator groups (confirmed CF versus CRMS/carriers)
- Analytes with a greater than 2-fold change and false discovery rate of  $p < 0.05$  used for unsupervised hierarchical clustering



# Multi-analyte analysis: Cystic Fibrosis



# Multi-analyte analysis: Cystic Fibrosis



# Multi-analyte analysis: Cystic Fibrosis

- IRT + cit/arg + [C8] (dataset n=27,961):
  - Accurately stratified 8 of 9 confirmed CF cases (1 false negative) from CRMS/carriers
  - Accurately stratified 7 of 7 CRMS from confirmed CF cases
  - Accurately stratified 28 of 29 CF carriers from confirmed CF cases
  - Misclassified 4 normals into CRMS/carrier group
- IRT/DNA: potentially less reflexed for DNA mutation, less for sweat testing (1 or 2 mutations forwarded)





# Multi-analyte analysis: Cystic Fibrosis

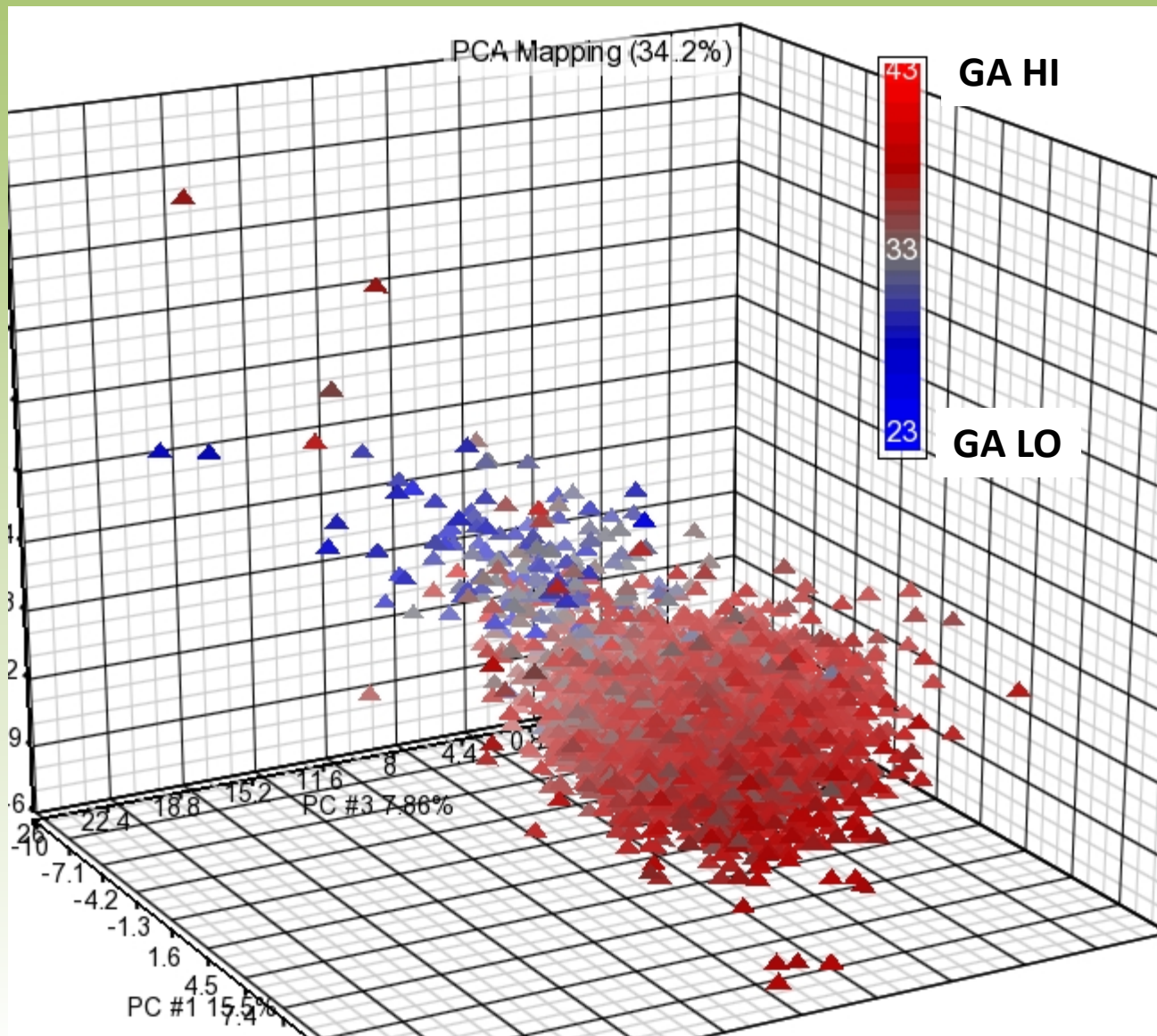
- What's next:
  - Additional data being added to refine/improve CF model training set
  - Pilot project with multi-analyte model run in parallel with current CF screening algorithm
- Multi-analyte analysis is challenging but provides opportunities for discovery



# Multi-analyte: special populations

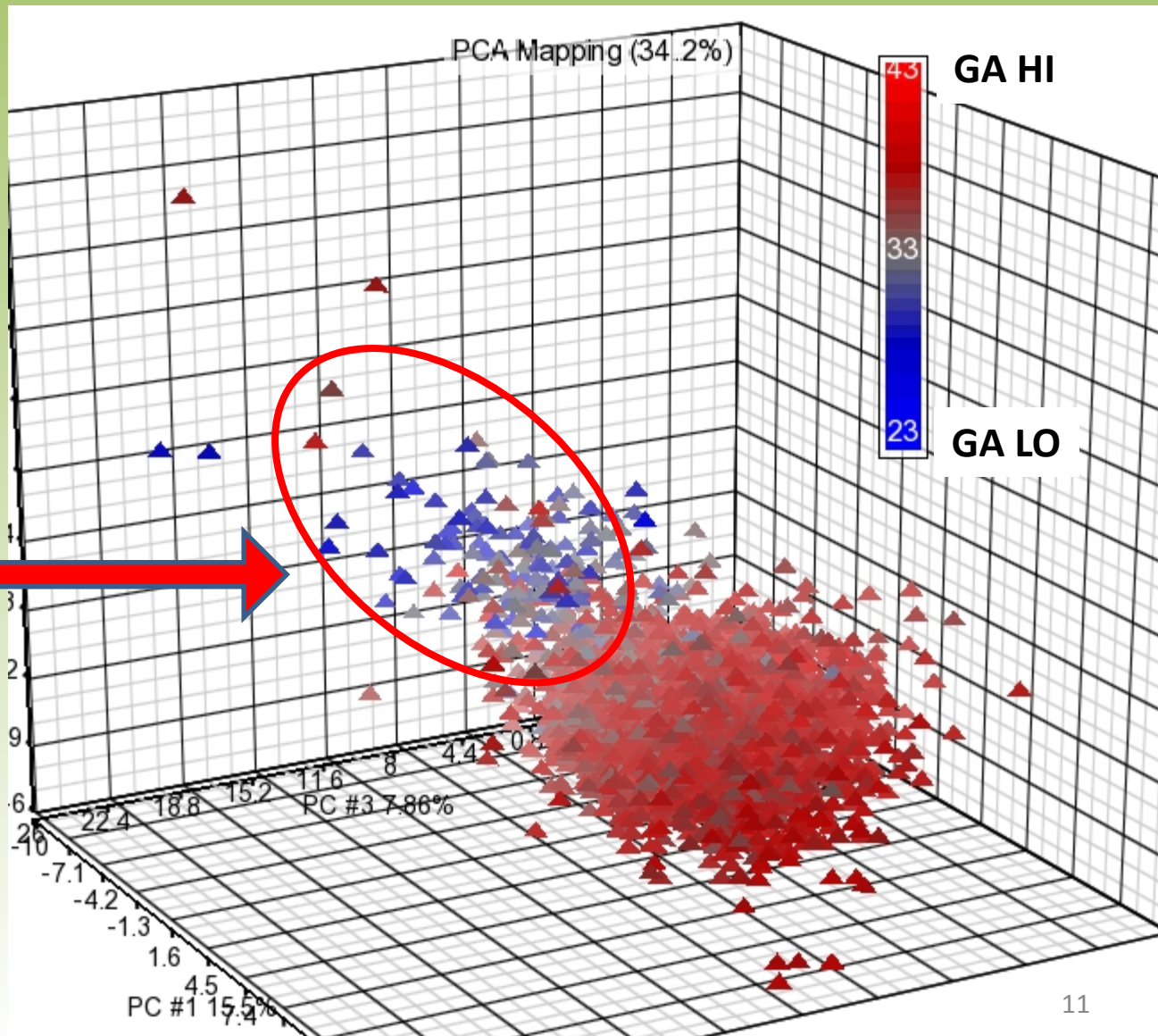
- Preterm, LBW, NICU

GA, weight, and gender variance scatterplot



# Multi-analyte: special populations

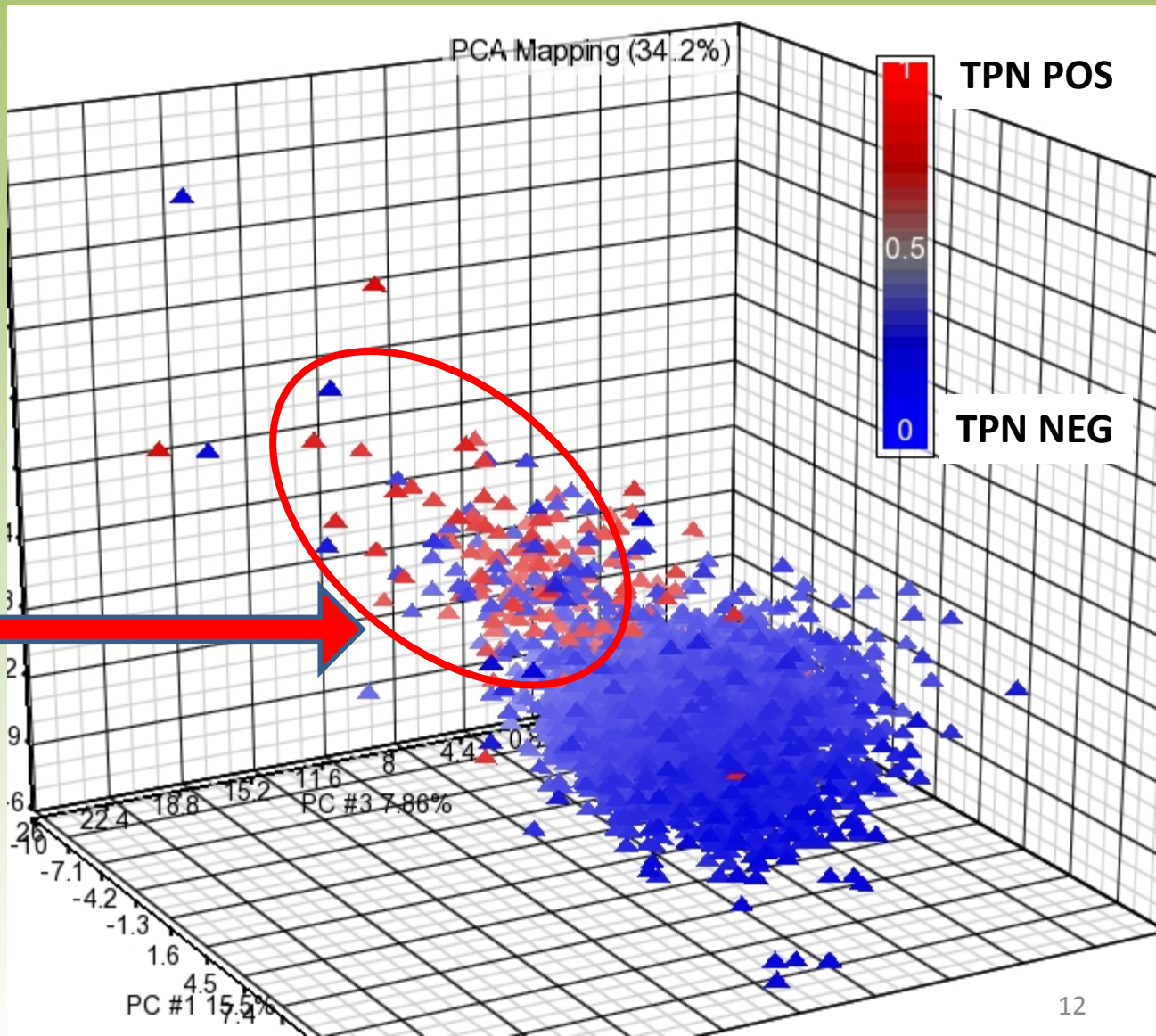
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# Multi-analyte: special populations

- Preterm, LBW, NICU

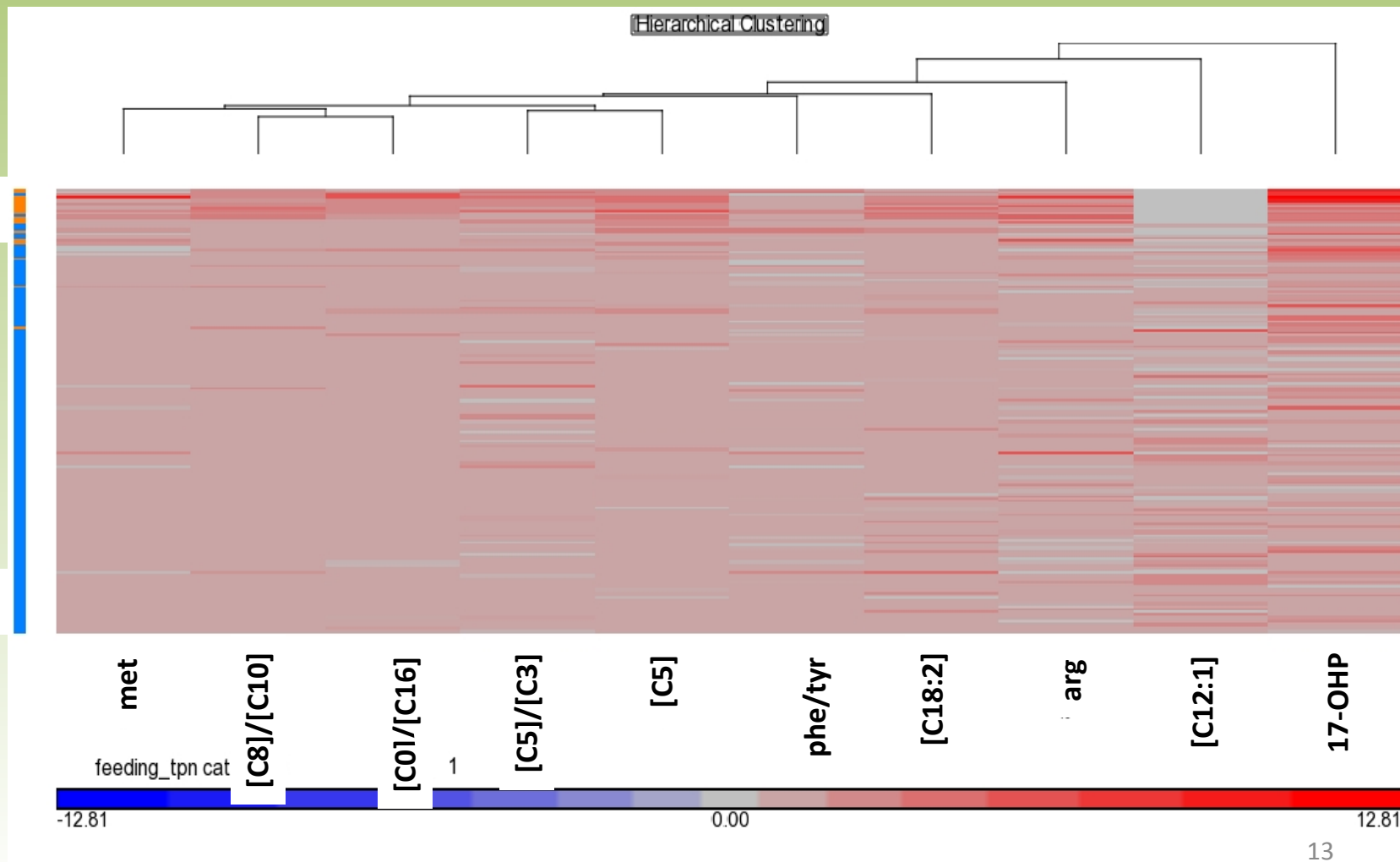
TPN





# Multi-analyte: special populations

- TPN signature (in progress)





# Conclusions

- Screening is for risk stratification
- Multi-analyte data analysis improves risk stratification for true CF cases and CRMS/carriers
- Algorithms can be embedded in the laboratory to reduce the number of cases forwarded to follow up
- Existing analyte data may be leveraged to provide improved screening risk stratification



# Acknowledgements

- Iowa Department of Public Health
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