Investigation of Mechanisms of Response in Multiple Myeloma via Bayesian Causal Inference: An Early Analysis of the CoMMpass Study Data

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Introduction

Multiple myeloma (MM) is an incurable disease with a rapidly shifting treatment landscape that highlights the importance of a deeper understanding of drug response pathways to guide drug development and enable better drug targeting.

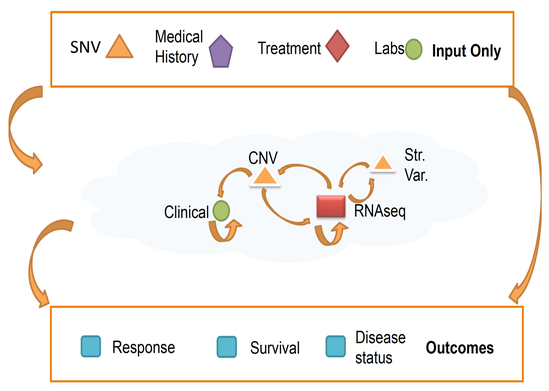
CoMMpass (NCT0145429) [1], a study by the Multiple Myeloma Research Foundation (MMRF), collects longitudinal data of newly diagnosed patients' responses to treatment. The CoMMpass Interim Analysis 7 (IA7) dataset provides extensive clinical and molecular data on a population of almost 800 enrolled patients.

Objectives

- Build MM disease models to characterize the probabilistic network connections among variables from the multiple data modalities generated in the CoMMpass study.
- Run *in silico* simulations of the MM disease models to identify novel intervention targets for modulating MM clinical endpoints.
- Build a software interface for data analysis and simulation for the MMRF and CoMMpass trial collaborators.

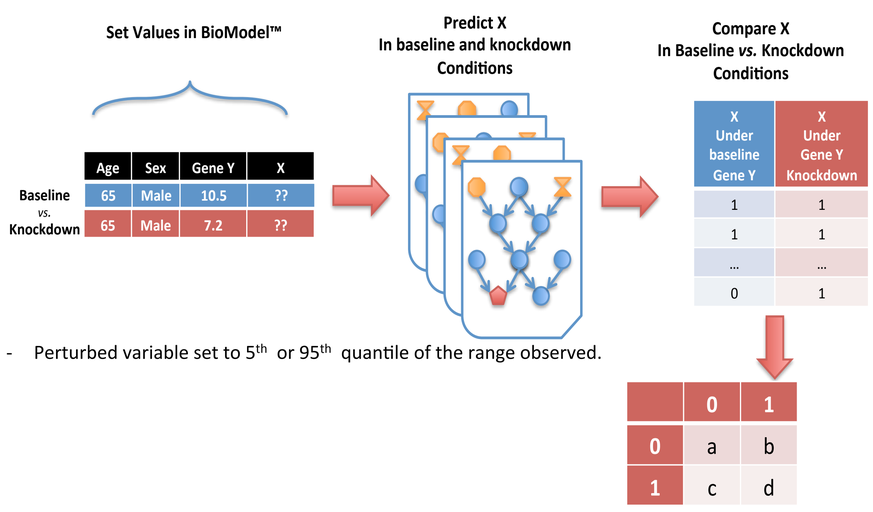
Methodology

The GNS Healthcare REFS™ (Reverse Engineering, Forward Simulation) machine learning platform uses well documented mathematical techniques to infer causal relationships [2] in high dimensional datasets constrained by a minimal set of biological considerations but otherwise entirely *de novo*.



To capture variability in data and inference and to distinguish confident predictions from incidental ones, REFS™ returns an ensemble of models that are all consistent with the observed disease biology.

Simulations on this ensemble are then developed to find which variables are potential drivers of the outcomes.



- Perturbed variable set to 5th or 95th quantile of the range observed.

Data

IA7 dataset includes clinical measurements (demographics, labs, treatment information, survival, etc), somatic single nucleotide variants (SNV), structural variants, somatic copy numbers (SCNV), and RNAseq gene expression.

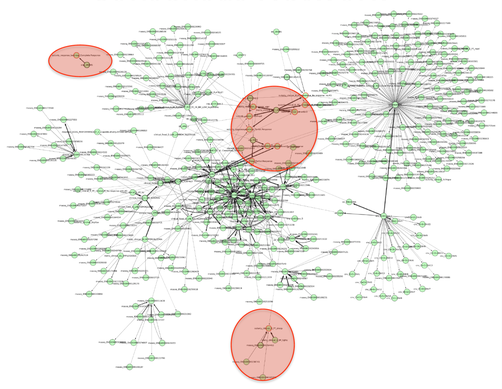
The final dataset after preprocessing had 452 patients, and 28,200 variables.

Preprocessing:

- SNVs were first filtered with Strelka, MuTect, and Seurat and then aggregated into gene region burden scores.
- mRNA variables with zero expression in majority of samples were removed.
- SCNVs were segmented with the CBS algorithm.

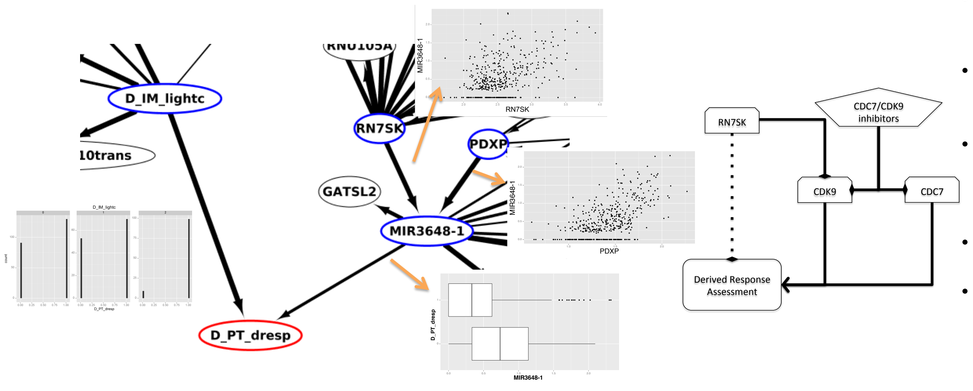
Selected Results

Consensus Network



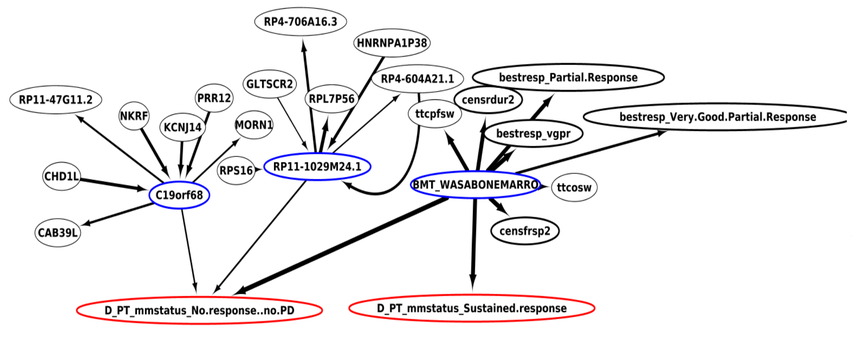
Upstream	Downstream	Baseline Mean	Relative Change	P-value	Upstream Description	Downstream Description	Novelty
RN7SK	D_PT_dresp	0.64	-0.22	0.0594	RN7SK RNA, 7SK small nuclear	Derived response assessment	Known
PDXP	D_PT_dresp	0.66	-0.20	0.0715	PDXP pyridoxal (pyridoxine, vitamin B6) phosphatase	Derived response assessment	Partial
MIR3648-1	D_PT_dresp	0.68	-0.37	0.0007	MIR3648-1 microRNA 3648-1	Derived response assessment	New
RP11-1029M24.1	D_PT_mmstatus_No.response..no.PD	0.36	-0.50	0.0059	RP11-1029M24.1	MM status(derived). indicator for clinical_D_PT_mmstatus=No response/ no PD	Partial
BMT_WASABONEMARRO	D_PT_mmstatus_No.response..no.PD	0.26	-0.93	0.0000	Was a bone marrow transplant performed?	MM status(derived). indicator for clinical_D_PT_mmstatus=No response/ no PD	Known
C19orf68	D_PT_mmstatus_No.response..no.PD	0.35	-0.48	0.0114	C19orf68 chromosome 19 open reading frame 68	MM status(derived). indicator for clinical_D_PT_mmstatus=No response/ no PD	New
BMT_WASABONEMARRO	D_PT_mmstatus_Sustained.response	0.57	0.53	0.0000	Was a bone marrow transplant performed?	MM status(derived). indicator for clinical_D_PT_mmstatus=Sustained response	Known
snp_DNAH5	bestresp_Complete.Response	0.15	1.15	0.0069	SNP at dynein, axonemal, heavy chain 5	Best overall response. indicator for response_bestresp=Complete Response	Partial
BMT_WASABONEMARRO	bestresp_Partial.Response	0.36	-0.48	0.0094	Was a bone marrow transplant performed?	Best overall response. indicator for response_bestresp=Partial Response	Known
BMT_WASABONEMARRO	bestresp_vgpr	0.58	0.40	0.0005	Was a bone marrow transplant performed?	Best response. vgpr or better is coded as 1. Any other with 0.	Known
BMT_WASABONEMARRO	censfrsp2	0.73	0.34	0.0000	Was a bone marrow transplant performed?	Censor flag: first response	Known
snp_uc031rxg.1	censfrsp2	0.74	-0.40	0.0000	SNP in Region located in chr22, position 22385572-23265082 strand +	Censor flag: first response	New
BMT_WASABONEMARRO	censrdur2	0.33	-0.61	0.0013	Was a bone marrow transplant performed?	Censor flag: response duration	Known
D_LAB_M.PROTEIN	fresp_Partial.Response	0.53	0.30	0.0280	Lab measurement: M-PROTEIN (g/dL)	First response. indicator for response_fresp=Partial Response	Known
D_LAB_IgG_log10trans	fresp_Partial.Response	0.42	0.79	0.0000	Lab measurement: IgG (g/L) transformed using log10trans.	First response. indicator for response_fresp=Partial Response	Known
D_LAB_TOTPROT	fresp_Partial.Response	0.53	0.32	0.0201	Lab measurement: TOTPROT (g/dL)	First response. indicator for response_fresp=Partial Response	Known
snp_FAT1	fresp_Partial.Response	0.60	-0.50	0.0000	SNP at FAT atypical cadherin 1	First response. indicator for response_fresp=Partial Response	Partial
D_LAB_M.PROTEIN	fresp_Very.Good.Partial.Response	0.45	-0.27	0.0957	Lab measurement: M-PROTEIN (g/dL)	First response. indicator for response_fresp=Very Good Partial Response	Known
D_LAB_IgG_log10trans	fresp_Very.Good.Partial.Response	0.53	-0.46	0.0006	Lab measurement: IgG (g/L) transformed using log10trans.	First response. indicator for response_fresp=Very Good Partial Response	Known
D_LAB_TOTPROT	fresp_Very.Good.Partial.Response	0.45	-0.27	0.0926	Lab measurement: TOTPROT (g/dL)	First response. indicator for response_fresp=Very Good Partial Response	Known
D_LAB_M.PROTEIN	fresp_vgpr	0.48	-0.34	0.0242	Lab measurement: M-PROTEIN (g/dL)	Best first response. vgpr or better is coded as 1. Any other with 0.	Known
D_LAB_IgG_log10trans	fresp_vgpr	0.59	-0.56	0.0000	Lab measurement: IgG (g/L) transformed using log10trans.	Best first response. vgpr or better is coded as 1. Any other with 0.	Known
D_LAB_TOTPROT	fresp_vgpr	0.49	-0.34	0.0225	Lab measurement: TOTPROT (g/dL)	Best first response. vgpr or better is coded as 1. Any other with 0.	Known
snp_FAT1	fresp_vgpr	0.42	0.64	0.0002	SNP at FAT atypical cadherin 1	Best first response. vgpr or better is coded as 1. Any other with 0.	Partial
D_IM_lightc-Kappa	D_PT_dresp	0.90	-0.35	0.0000	Light Chain by Flow(coded) Kappa	Derived response assessment	Known
D_IM_lightc-Lambda	D_PT_dresp	0.90	-0.36	0.0000	Light Chain by Flow(coded) Lambda	Derived response assessment	Known
BMT_WASABONEMARRO	ttcosw	37.20	0.59	0.0777	Was a bone marrow transplant performed?	Time to OS event (censored) (wk)	Known
BMT_WASABONEMARRO	ttcpfsw	29.75	0.92	0.0609	Was a bone marrow transplant performed?	Time to PFS event (censored) (wk)	Known
ENSG00000234639	ttcfrspw	12.01	0.29	0.04381	protein phosphatase 2, regulatory subunit B', gamma isoform (PPP2R5C) pseudogene	Time to first response	New
RP11-108P20.1	ttcfrspw	15.1	-0.22	0.06333	Novel lincRNA. Chromosome 18: 58,752,148-58,754,477 forward strand	Time to first response	New
RP11-108P20.2	ttcfrspw	16.10	-0.28	0.0122	RP11-108P20.2: Chromosome 18: 58,754,859-58,757,842 reverse strand	Time to first response	New
CXCR6	ttcfrspw	11.56	0.3	0.05501	CXCR6 chemokine (C-X-C motif) receptor 6	Time to first response	Partial

Response Assessment: first treatment response that lasts at least 1 year before a progressive disease.



- REFS infers that RN7SK drives (inhibits) DRA
- RN7SK inhibits CDK9
  - PMID: 11713533
- Action similar to CDC7/CDK9 inhibitors, e.g. PHA-767491
  - PMID: 24202326
- Known MM response pathway
- The MM drug AT7519 also inhibits CDK9 and it is associated to tumor growth inhibition, and prolonged survival).
  - PMC: 3183744

MM status: No response or sustained response



- Stem Cell Transplant (noted as BMT) is often a front-line MM treatment.
- Drives multiple endpoints, both in REFS model and in terms of treatment efficacy

References

[1] Lonial, Sagar, Venkata D Yellapantula, Winnie Liang, Ahmet Kurdoglu, Jessica Aldrich, Christophe M Legendre, Kristi Stephenson, et al. "Interim Analysis of the Mmrf Commpass Trial: Identification of Novel Rearrangements Potentially Associated with Disease Initiation and Progression." Blood 124, no. 21 (2014): 722–722.

[2] N. Friedman, "Inferring Cellular Networks Using Probabilistic Graphical Models," Science, vol. 303, no. 5659, pp. 799–805, Feb. 2004.

[3] G. Lazennec and A. Richmond, "Chemokines and chemokine receptors: new insights into cancer-related inflammation," Trends Mol. Med., vol. 16, no. 3, pp. 133–144, Mar. 2010.

[4] B. Homey, A. Müller, and A. Zlotnik, "Chemokines: agents for the immunotherapy of cancer?," Nat. Rev. Immunol., vol. 2, no. 3, pp. 175–184, Mar. 2002.

[5] K. Flanagan and H. L. Kaufman, "Chemokines in tumor immunotherapy," Front. Biosci. J. Virtual Libr., vol. 11, pp. 1024–1030, 2006.

Conflict of Interest

There are no relevant conflicts of interest to disclose.