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.

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

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.

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

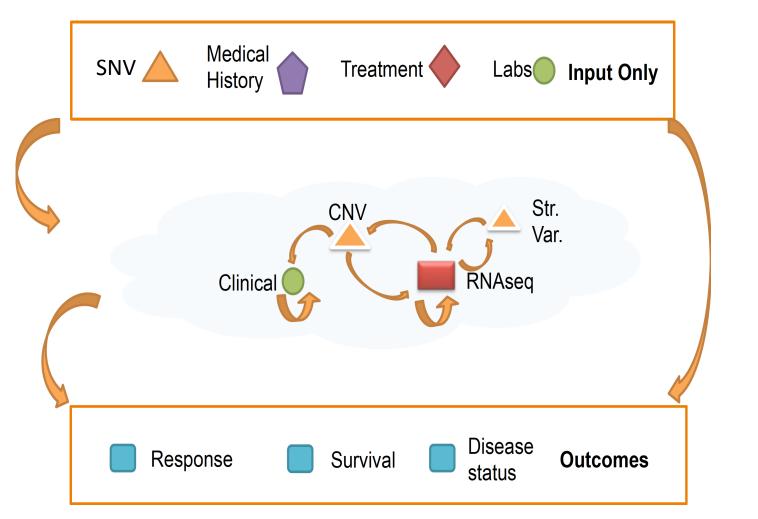
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Upstream	Downstream	Baseline Mean	Relative Change	P-value	Upstream Description	Downstream Description	Novelty
RN7SK PDXP	D_PT_dresp D_PT_dresp	0.64 0.66	-0.22 -0.20	0.0594 0.0715	RN7SK RNA, 7SK small nuclear PDXP pyridoxal (pyridoxine, vitamin B6) phosphatase	Derived response assessment Derived response assessment	Known Partial
MIR3648-1	D_PT_dresp	0.68	-0.37	0.0007	MIR3648-1 microRNA 3648-1	Derived response assessment	New
RP11-1029M2	o.responseno.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_WASABONE	MARRO D_PT_mmstatus_N o.responseno.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_N o.responseno.PD		-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_WASABONE	MARRO D_PT_mmstatus_S ustained.response	057	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_Complet e.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_WASABONE	WARRO bestresp_Partial.R esponse	0.36	-0.48	0.0094	Was a bone marrow transplant performed?	Best overall response. indicator for response_bestresp=Partial Response	Known
BMT_WASABONE		0.58 0.73	0.40 0.34	0.0005 0.0000	Was a bone marrow transplant performed? Was a bone marrow transplant performed?	Best response. vgpr or better is coded as 1. Any other with 0. Censor flag: first response	Known Known
snp_uc031rxg	g.1 censfrsp2	0.74	-0.40	0.0000	SNP in Region located in chr22, position 22385572-23265082 strand +	Censor flag: first response	New
BMT_WASABONE	MARRO censrdur2	0.33	-0.61	0.0013	Was a bone marrow transplant performed?	Censor flag: response duration	Known
D_LAB_M.PROT	TEIN fresp_Partial.Resp onse	0.53	0.30	0.0280	Lab measurement: M-PROTEIN (g/dL)	First response. indicator for response_fresp=Partial Response	Known
D_LAB_lgG_log10	Otrans fresp_Partial.Resp onse	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_TOTPR	OT fresp_Partial.Resp onse	0.53	0.32	0.0201	Lab measurement: TOTPROT (g/dL)	First response. indicator for response_fresp=Partial Response	Known
snp_FAT1	fresp_Partial.Resp onse	0.60	-0.50	0.0000	SNP at FAT atypical cadherin 1	First response. indicator for response_fresp=Partial Response	Partial
D_LAB_M.PROT	TEIN fresp_Very.Good.P artial.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_lgG_log10	Otrans fresp_Very.Good.P artial.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_TOTPR	OT fresp_Very.Good.P artial.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.PROT	•	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_lgG_log10	Otrans fresp_vgpr	0.59	-0.56	0.0000	Lab measurement: lgG (g/L) transformed using log10trans.	Best first response. vgpr or better is coded as 1. Any other with 0.	Known
D_LAB_TOTPR		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-Ka		0.90	-0.35	0.0000	Light Chain by Flow(coded) Kappa	Derived response assessment	Known
D_IM_lightc-Lan	'	0.90	-0.36	0.0000	Light Chain by Flow(coded) Lambda	Derived response assessment	Known
BMT_WASABONE		37.20	0.59	0.0777	Was a bone marrow transplant performed?	Time to OS event (censored) (wk)	Known
BMT_WASABONE	MARRO ttcpfsw	29.75	0.92	0.0609	Was a bone marrow transplant performed?	Time to PFS event (censored) (wk)	Known
ENSG00000234	.639 ttcfrspw	12.01	0.29	0.04381	protein phosphatase 2, regulatory subunit B', gamma isoform (PPP2RSC) 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		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

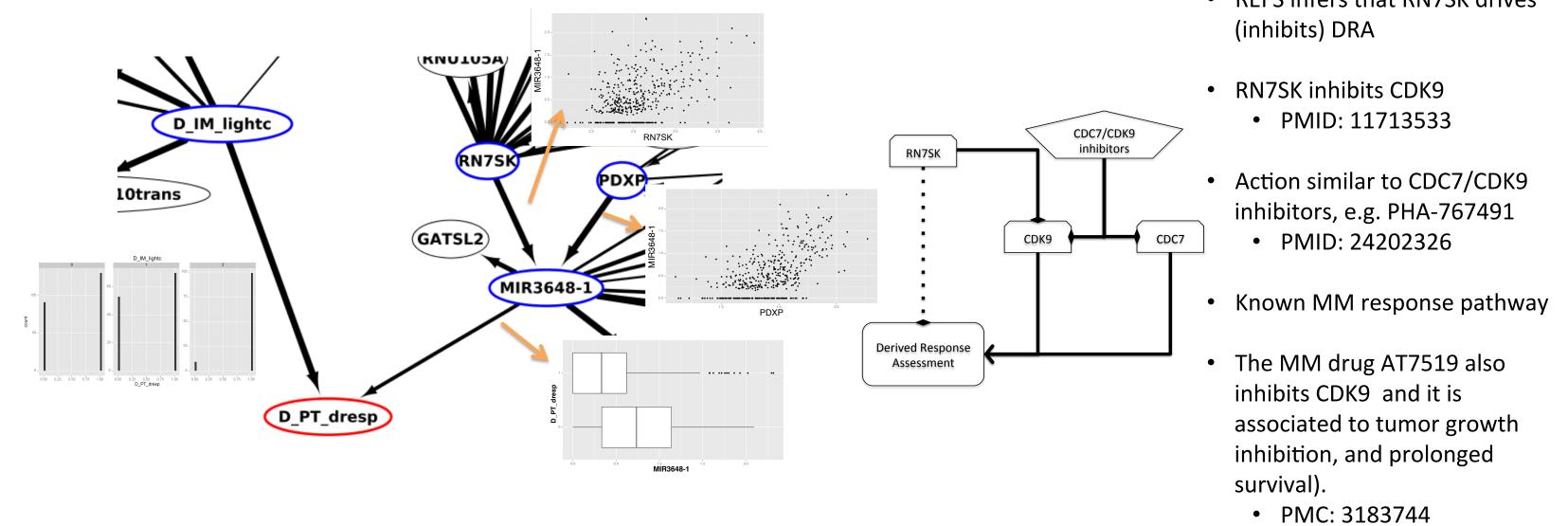
Methodology

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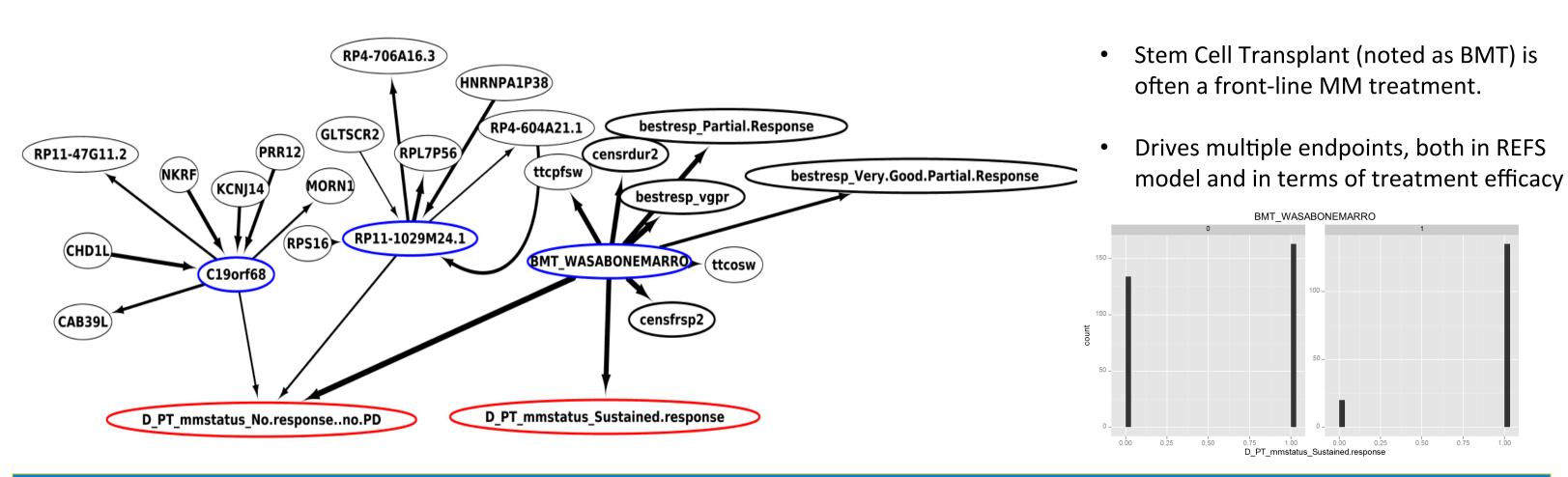
The GNS Healthcare REFS™ (Reverse Engineering, Forward Simulation) machine learning platform uses well documented mathematical techniques to infer causal relationships [2] in high dimensional datasets constrained by a minimal set of biological considerations but otherwise entirely *de novo*.



Response Assessment: first treatment response that lasts at least 1 year before a progressive disease. • REFS infers that RN7SK drives

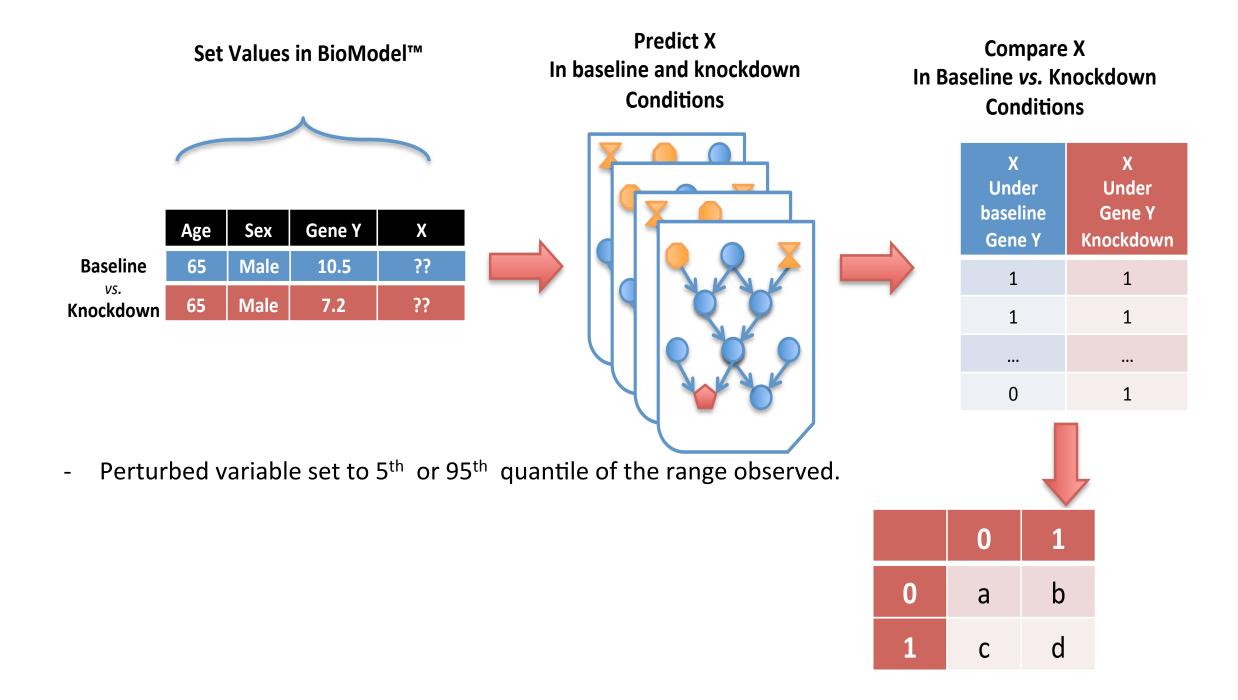


MM status: No response or sustained response



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.





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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.