Real World Data is the Future of Medical Evidence

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Challenges of our Current Sources of Medical Evidence:

Efficacy vs. Effectiveness

High Cost Burden

Inadequacy

Dissemination

Complexity

Efficacy ≠ Effectiveness

	Efficacy study	**Effectiveness study**
Question	Does the intervention work under ideal circumstance?	Does the intervention work in real-world practice?
Setting	Resource-intensive 'ideal setting'	Real-world everyday clinical setting
Study population	Highly selected, homogenous population Several exclusion criteria	Heterogeneous population Few to no exclusion criteria
Providers	Highly experienced and trained	Representative usual providers
Intervention	Strictly enforced and standardized No concurrent interventions	Applied with flexibility Concurrent interventions and cross-over permitted

Singal AG, et al. Clinical and Translational Gastroenterology, 2014

Acknowledgement of a GAP in Real World Effectiveness

Efficacy to Effectiveness Gap

"A disconnect between outcomes from clinical trials and information needed for clinical practice has been identified in the process of standardization of drugs assessment (Schwartz, 1967),

evidence-based medicine (Feinstein, 1997),

and knowledge dissemination (Lehman, 1995),

and called the Efficacy to Effectiveness Gap

[casued by] …the weak generalizability of clinical trials due to their design.

The need for a more systematic assessment of effectiveness is now widely acknowledged. "

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C. Nordon, H. Karcher, Value in Health, Nov 2014

Real World Safety of Ibrutinib

Table 2. Adverse Events.*

Adverse Event	Grade 1–2	Grade 3–4	Total†
	number of patients (percent)		
Diarrhea	40 (47)	2 (2)	42 (49)
Upper respiratory tract infection	28 (33)	0	28 (33)
Fatigue	24 (28)	3 (4)	27 (32)
Cough	26 (31)	0	26 (31)
Arthralgia	23 (27)	0	23 (27)
Rash	23 (27)	0	23 (27)
Pyrexia	19 (22)	4 (5)	23 (27)
Edema, peripheral	18 (21)	0	18 (21)
Muscle spasms	16 (19)	1 (1)	17 (20)
Constipation	14 (16)	1 (1)	
Dizziness	14 (16)	1 (1)	
Headache	14 (16)	1 (1)	
Hypertension	11 (13)	4 (5)	
Nausea	14 (16)	1 (1)	
Sinusitis	11 (13)	4 (5)	
Contusion	14 (16)	0	
Vomiting	13 (15)	1 (1)	
Neutropenia‡	0	13 (15)	
Oropharyngeal pain	13 (15)	0	

Ibrutinib (N=73)

- Atrial fibrillation 20%
- Infection 12%
- Hematologic 9%
- Bleeding 9%
- Pneumonitis 8%

Table S4: Serious Adverse Events

	≤Grade 3	≥Grade 4 N (%)	Total
Pneumonia	9 (10)	1 (1)	10 (12)
Bacteremia	3 (4)	1 (1)	4 (5)
Cellulitis	4 (5)	0 (0)	4 (5)
Sinusitis	4 (5)	0 (0)	4 (5)
Atrial fibrillation	3 (4)	0 (0)	3 (4)
Febrile neutropenia	2 (2)	1 (1)	3 (4)
Abdominal pain	2 (2)	0 (0)	2 (2)
Clostridial infection	2 (2)	0 (0)	2 (2)
Dehydration	2 (2)	0 (0)	2 (2)
Sepsis	0 (0)	2 (2)	2 (2)
Subdural hematoma	2 (2)	0 (0)	2 (2)
Asthenia	1 (1)	0 (0)	1 (1)
Back pain	1 (1)	0 (0)	1 (1)
Bone lesion	1 (1)	0 (0)	1 (1)
Bronchitis viral	0 (0)	1 (1)	1 (1)
[illegible]	1 (1)	0 (0)	1 (1)
	1 (1)	0 (0)	1 (1)
ytic leukemia	0 (0)	1 (1)	1 (1)
	1 (1)	0 (0)	1 (1)
te	1 (1)	0 (0)	1 (1)
	1 (1)	0 (0)	1 (1)
	1 (1)	0 (0)	1 (1)
	1 (1)	0 (0)	1 (1)
seminated	1 (1)	0 (0)	1 (1)
	0 (0)	1 (1)	1 (1)
	0 (0)	1 (1)	1 (1)
	1 (1)	0 (0)	1 (1)
	1 (1)	0 (0)	1 (1)
	1 (1)	0 (0)	1 (1)

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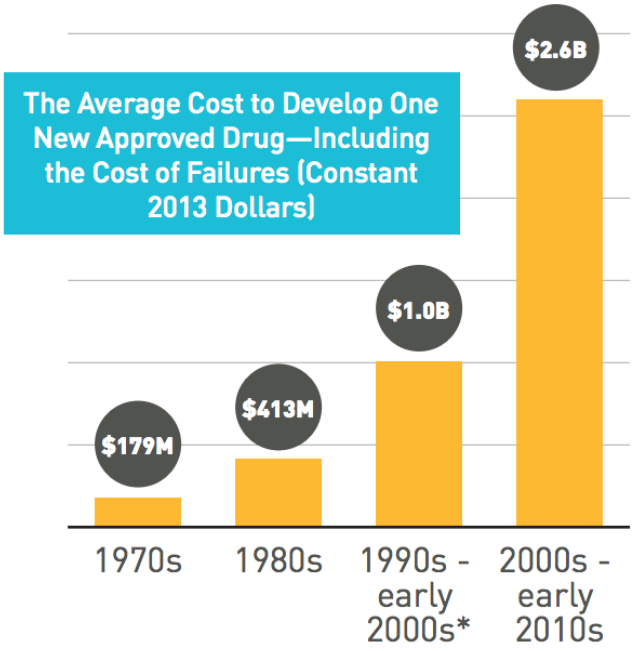
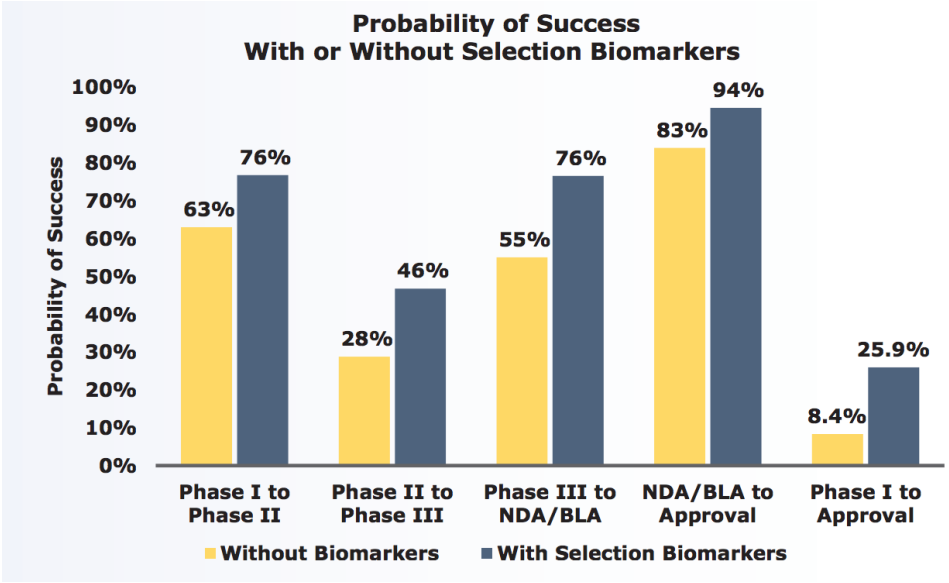
Byrd JC, et al. N Engl J Med. 2013;369:32-42

Anthony R. Mato, et al. Blood, 2016

Generation and Cost





Clinical Development Success Rates, 2006-2015, BIO

2015 Pharma Profile, PhRMA

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Inadequate Application

Trastuzumab approve by FDA in September 1998 for HER2+ breast cancer.

- 20%-30% of HER2+ positive patients experience high efficacy.
- *"About 5,000 patients in the US receive trastuzumab without any clinical benefit, and about 7,000 patients who could derive benefit are not being treated because of a false-negative test result."* – Genentech, 2007

Phillips J, 2010, JAMA

Nass SJ, Moses HL, editors. Cancer Biomarkers: The Promises and Challenges of Improving Detection and Treatment. Washington D.C.: The National Academies Press; 2007. Mar 27

Unreliable Reporting of Eligibility Criteria

Study compared reporting of eligibility criteria from 52 trial protocols within 78 subsequent publications produced at a German medical faculty.

Select Results:

- Mean number of EC was 25 (7-43)
- 100% of trials failed to report EC in a subsequent publication.
- 44% reported modified EC
- 21% reported newly added criteria
- Out of 1248 eligibility criteria in the protocols, 606 (49%) matched the subsequent publication, 479 (38%) were missing, and 163 (13%) were modified.

BMJ

RESEARCH

Reporting of eligibility criteria of randomised trials: cohort study comparing trial protocols with subsequent articles

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Cite this as: BMJ 2011;342:d1828
doi:10.1136/bmj.d1828

ABSTRACT

Objective To determine whether and how eligibility criteria of participants prespecified in protocols of randomised trials are reported in subsequent articles.

Design Cohort study.

Setting Protocols submitted to the ethics committee of a German medical faculty.

Data sources 52 trial protocols and 78 subsequent publications published between 2000 and 2006.

Main outcome measure Proportion of matching, missing, modified, or newly added eligibility criteria between trial protocols and subsequent publications.

Results Differences were found between protocols and subsequent publications for all 52 trials. Information on eligibility criteria was missing in the publications for all 52 trials (100%, 95% confidence interval 93% to 100%), modified for 44 (85%, 72% to 93%), and newly added for 21 (41%, 27% to 55%). The mean number of eligibility criteria for each trial was 25 (range 7-43) and the mean proportion of matching eligibility criteria per trial was 50% (95% confidence interval 44% to 55%, range 13-93). Of 1248 eligibility criteria prespecified in the protocols, 606 (49%, 46% to 51%) were matching in subsequent publications, 479 (38%, 36% to 41%) were missing, and 163 (13%, 11% to 15%) were modified. 51 eligibility criteria were added to publications. Most prespecified eligibility criteria were about comorbidity (42%, 39% to 45%), treatment (20%, 18% to 22%), or type or severity of illness (17%, 15% to 19%). Most of the missing eligibility criteria (96%, 94% to 97%) and modified eligibility criteria (54%, 46% to 62%) suggested broader study populations and most of the added eligibility criteria (86%, 74% to 94%) suggested narrower study populations.

Conclusions Many users of trial information rely on published journal articles. These articles generally do not reflect the exact definition of the study population as prespecified in the protocol. Incomplete or inadequate reporting of eligibility criteria hampers a proper assessment of the applicability of trial results.

INTRODUCTION

Published information about clinical trials is often incomplete.[1] If the reporting is selective the available information misrepresents the scientific evidence. It has long been recognised that only part of the results of trials are published in peer reviewed journals. For instance, "positive" results confirming the effect of new treatments are more likely to be published.[2] Evidence is now accumulating that not only entire studies but also individual study outcomes are reported selectively, leading to outcome reporting bias.[3-6] The reporting of trial results and related biases has been studied extensively, but less is known about how the design of trials and methods is reported. Definitions of medical interventions have been shown to be reported incompletely.[7] Incomplete reporting of trials also occurs for other key information, such as the calculation of sample size and methods of statistical analysis. For example, only 18% of trials approved by a scientific ethics committee in Denmark in 1994-5 described a priori sample size calculations adequately in both the protocol and the publications.[8] Differences between protocols and publications were also found for the reporting of allocation concealment and adverse events.[7,9]

Little is known about the reporting of the eligibility criteria used for selection of trial participants. A precise definition of a trial's study population is important to assess whether results can be applied to other patients with the same condition.[9] Trial participants often do not represent the patient population that clinicians see in their daily practice.[10-12] If, for example, it is unclear whether patients with particular comorbidities were excluded from a trial, practitioners using the trial report for medical decision making cannot know whether the results can apply to their patients with one of these comorbidities. Unreported exclusion criteria falsely let the reader assume that the results of a trial are more widely applicable. A patient with several health problems may, however, be at increased risk of severe side effects of the intervention.

We characterised the eligibility criteria defined in trial protocols to investigate whether they are reported in subsequent articles and described trial characteristics potentially associated with differences in the reporting of eligibility criteria.

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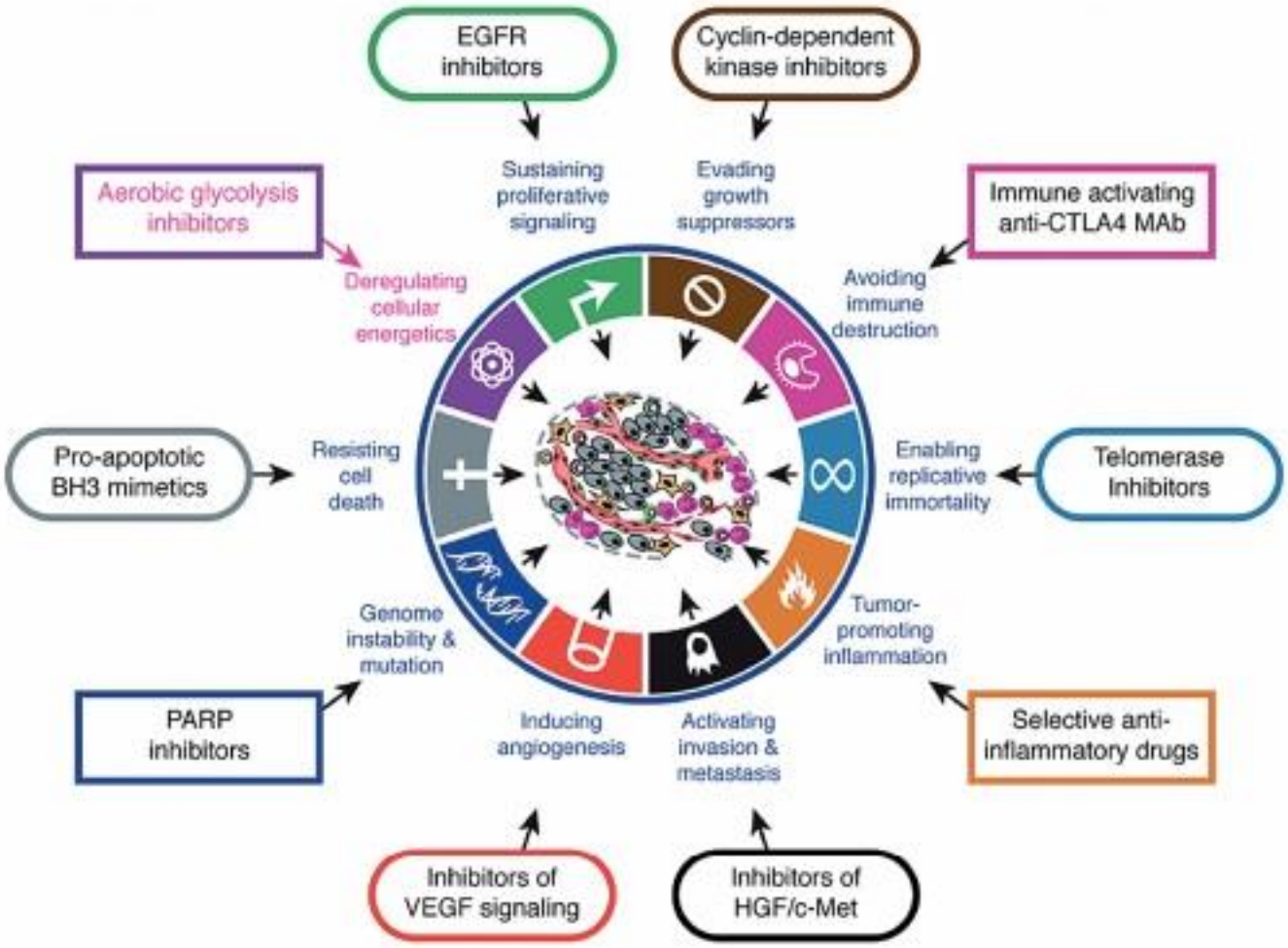
Blümle, A. et al. BMJ 2011

Oncology therapeutics development has provided an increasingly complete and targeted set of interventions…



Knowledge of the pharmacopeia:

- Labelled Indications
- Dosing / Cycles
- Toxicities
- Generics/Biosimilars
- Contraindications
- Co-morbidities
- Supportive Care
- Adherence

- Alternative interventions including radiation and surgery

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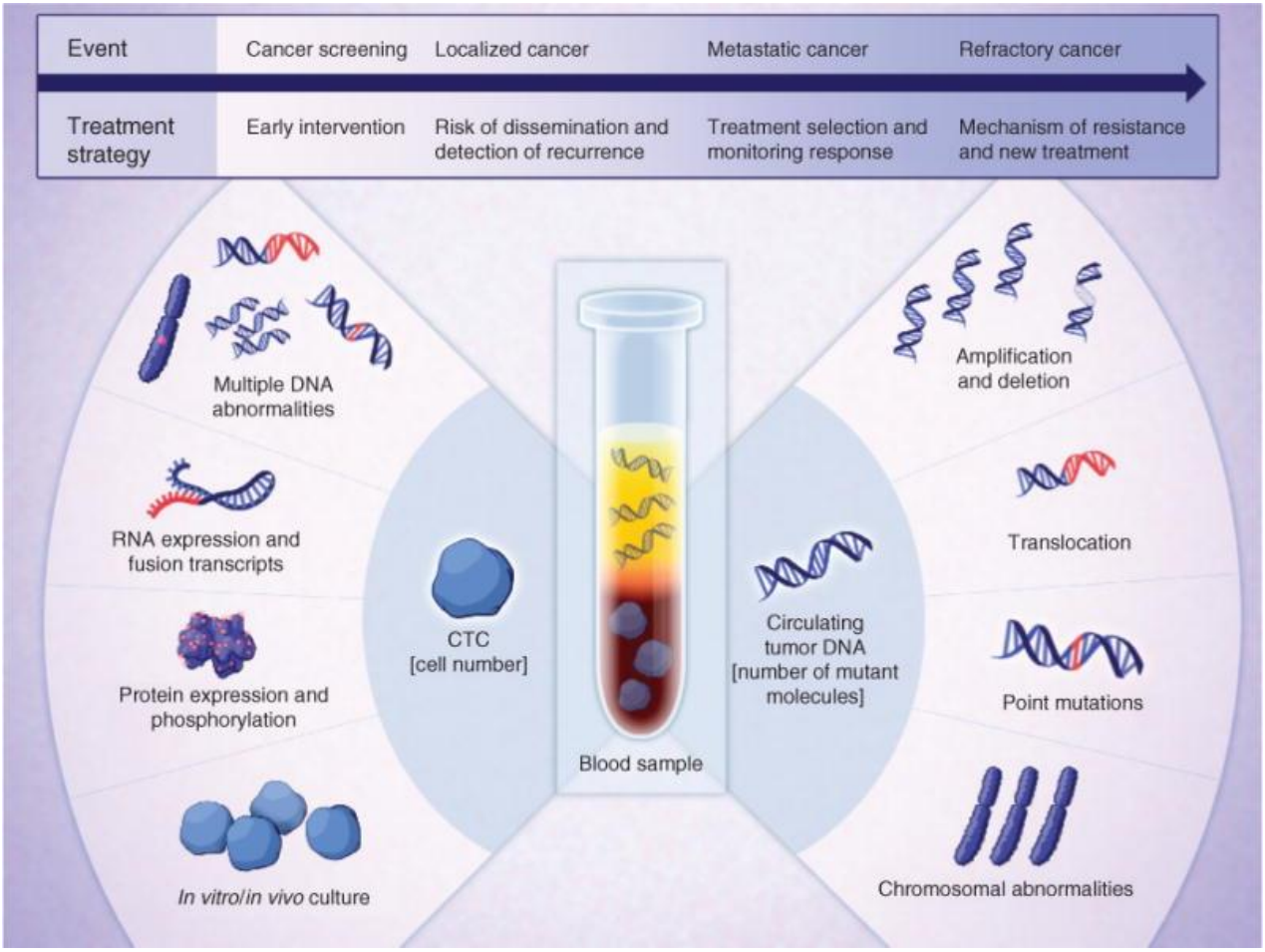
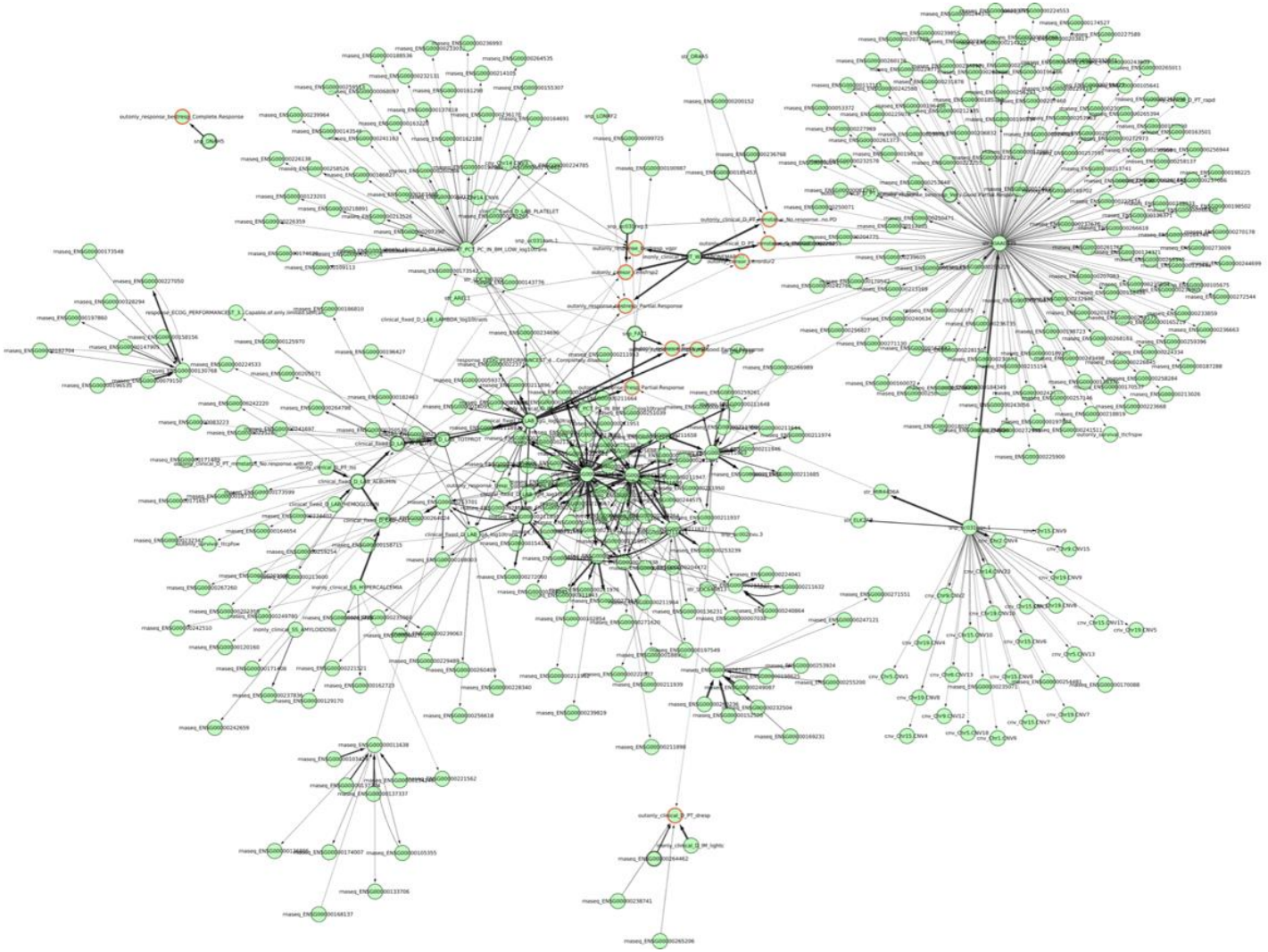
Marc Beishon: Targeting the supply lines: metabolic approaches to killing cancer cells, Cancer World, June 2015

… and characterizing and monitoring tumors has made great advances.



Haber DA, Velculescu VE. *Cancer Discov.* 2014;4(6):650-661.

Putative Causal Molecular Mechanisms Underlying Multiple Myeloma and Clinical Outcomes



And now we need to ***personalize*** It?

The Path to A New Medical Evidence Paradigm

- Advance real-world registry analysis to become a gold standard Medical Evidence
  - Precompetitive registries by national or international consortia or disease-focused organizations
  - Establish best practice analytical methods and gold-standards
  - Enable a fabric of freely-accessible, registry-based data commons.
- Enhance the structures and capabilities of transferring real-world clinical data from EMRs into registries for future analysis.
- Continue to build-out and deploy Clinical Decision Support systems to navigate the increasingly complex medical evidence

Efficacy vs. Effectiveness

High Cost Burden

Inadequacy

Dissemination

Complexity

Progress

FLATIRON

COTA | CANCER OUTCOMES TRACKING & ANALYSIS

ORIEN ONCOLOGY RESEARCH INFORMATION EXCHANGE NETWORK

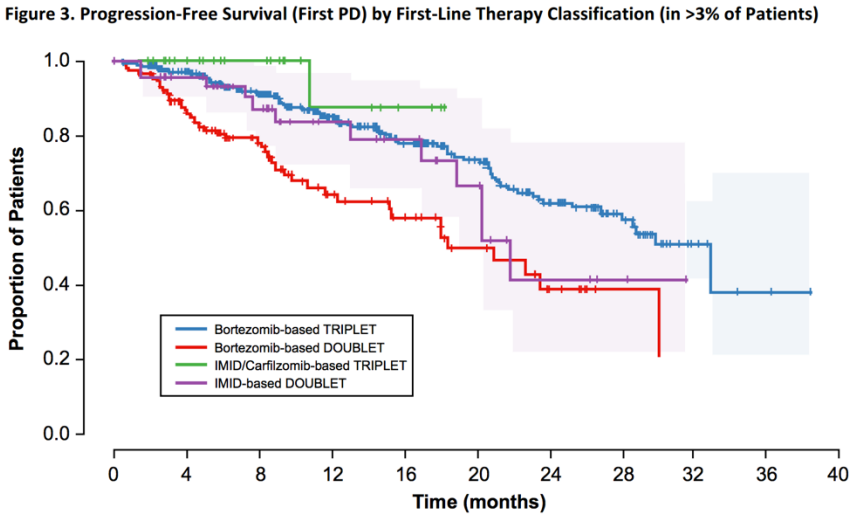
ROPR | REGISTRY of PATIENT REGISTRIES

Registry-Drived Personalized Care Pathways Demonstration

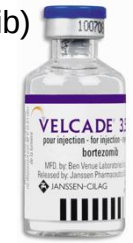
Demonstrate opportunity to differentiate anticipated treatment responses for Multiple Myeloma patients who receive either:

- Velcade alone
- Velcade in with immunomodulatory drugs (IMiDs)

Study based on a primarily population of 465 eligible patients.



Velcade (Bortizumib)



Revlimid (Lenalidomide)

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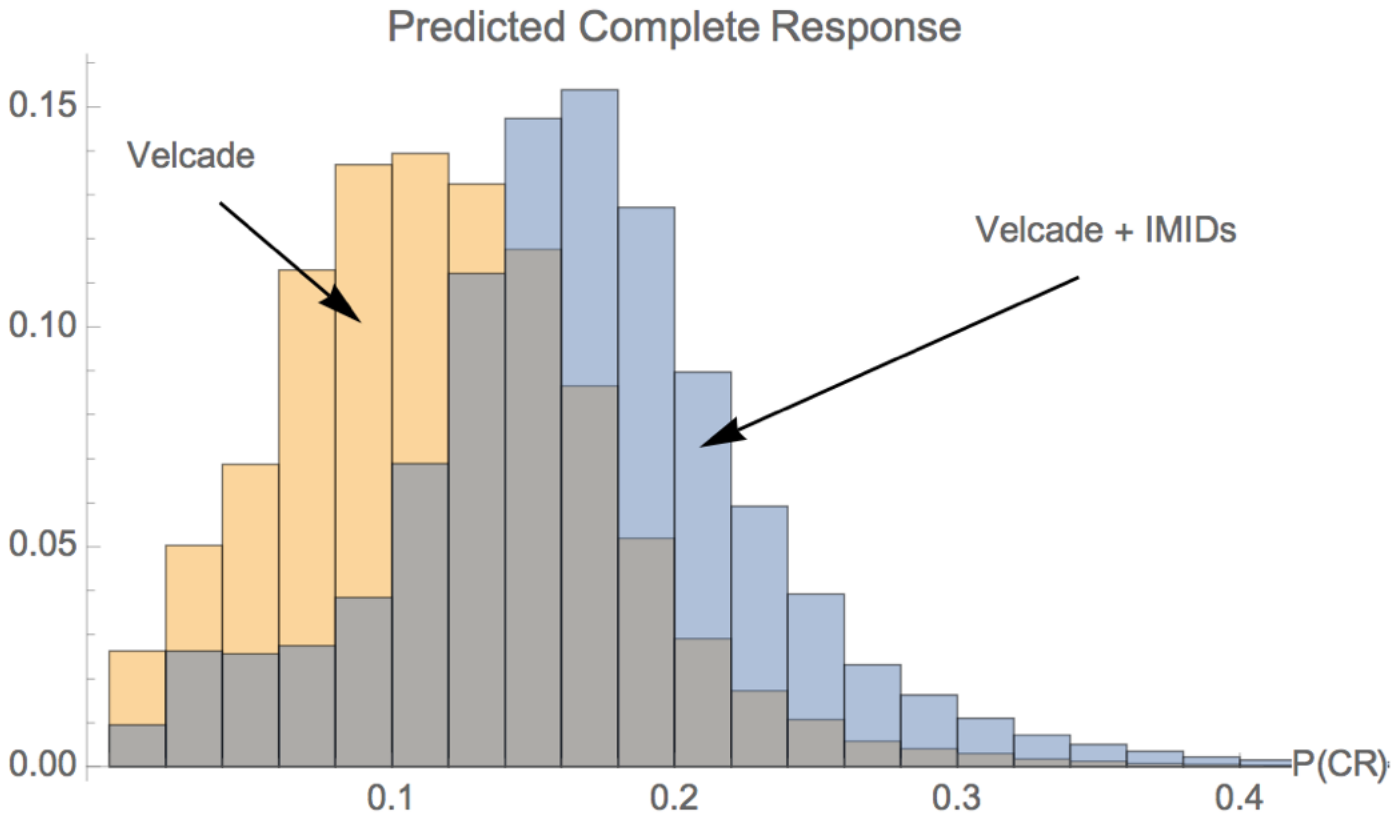
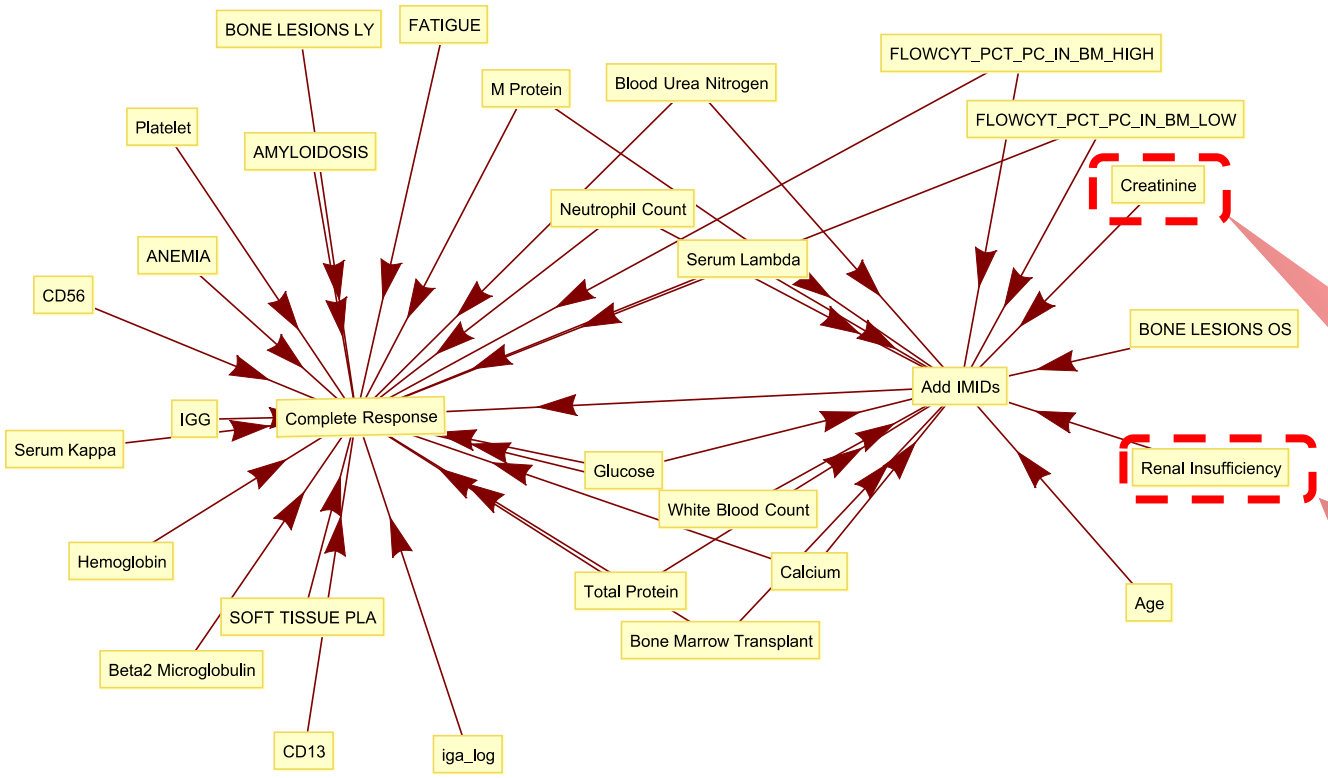
Study based on MMRF's CoMMpass registry IA8 dataset

Model Identifies Variability in Response to MM Therapy



Velcade vs Velcade with IMiDs



Example Confirmatory Finding:
Known link between IMIDs and Kidney Function

Takeaway: Analysis reveals strong signal and affirms known elements of clinical practice

Model identifies patient subset who will benefit least from IMiDs


Resistance to Lenalidomide in Multiple Myeloma Is Associated with a Switch in Gene Expression Profile

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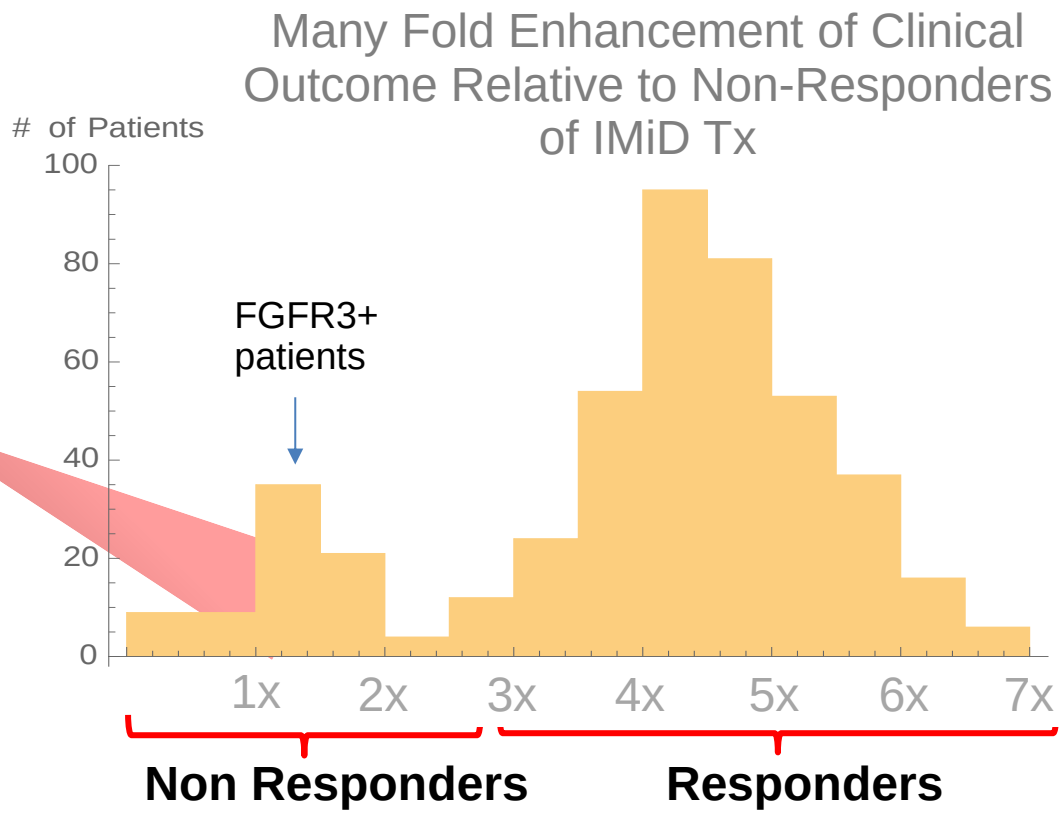

Patients identified as responders are expected to achieve a ~5x higher likelihood of achieving a clinical outcome as compared to the non-responders

1. M. Amatangelo, P. Neri et. Al Resistance to Lenalidomide in Multiple Myeloma Is Associated with a Switch in Gene Expression Profile, Blood Dec 3, 2015: 126 (23)

THANK YOU

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