Precision Oncology: The Optimism and Pessimism from Keyboard to Bedside

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Disclosures

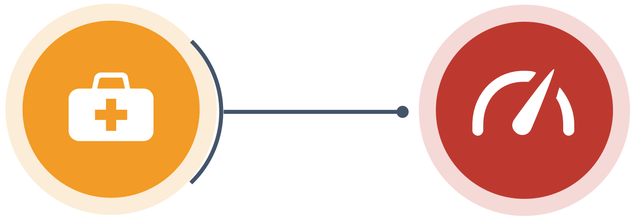
- I will discuss the off-label use of the following drugs:
  - Ruxolitinib
  - Imatinib
  - Bortezomib
  - Vorasidenib
- Member, Scientific Steering Committee, Celegene Connect MDS/AML Registry Study
- Founder, CancerPOP

Case Presentation

- 76 year-old white woman with profound fatigue. No recent infections.
- **CBC**: pancytopenia, requiring red blood cell transfusion
- **Chemistry, Iron, B12, folate**: normal
- **Bone marrow**: dysplastic hematopoiesis, 15% myeloblasts
- **Cytogenetics**: 46, X, del(X)(q23) → deletion of at least 42 known genes
- **NGS**: mutations in *EZH2*, *IDH1*, *CUX1* and *SRSF2*
- **Whole Exome Sequencing**: hundreds of gene SNPs and gene copy number variations

- **Treatment choices**:
  - ❑ Low intensity chemotherapy: Azacitidine or Decitabine
  - ❑ High intensity chemotherapy: Cytarabine ± Anthracycline
  - ❑ Allogeneic Hematopoietic Cell Transplant
  - ❑ Palliative Care → Hospice

Elements of Precision Oncology



Elements of Precision Oncology

Mapping Disease Biology

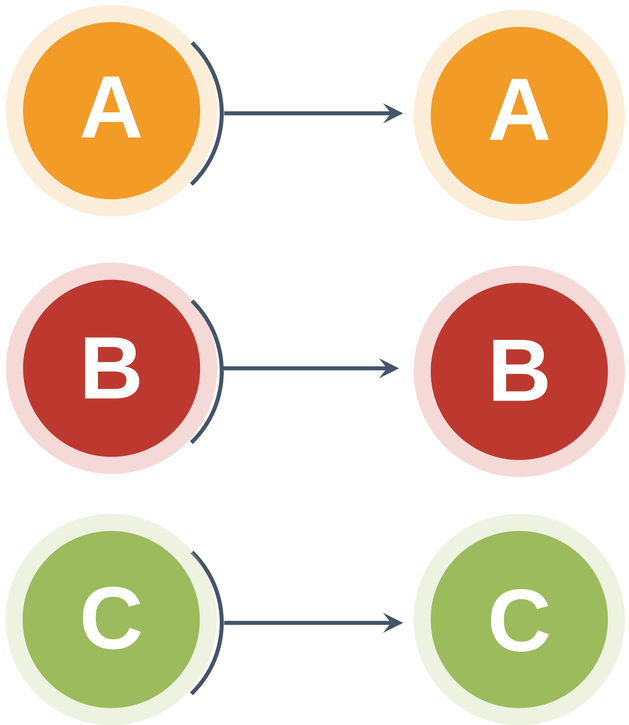
Predicting Responses

Personalizing Treatment

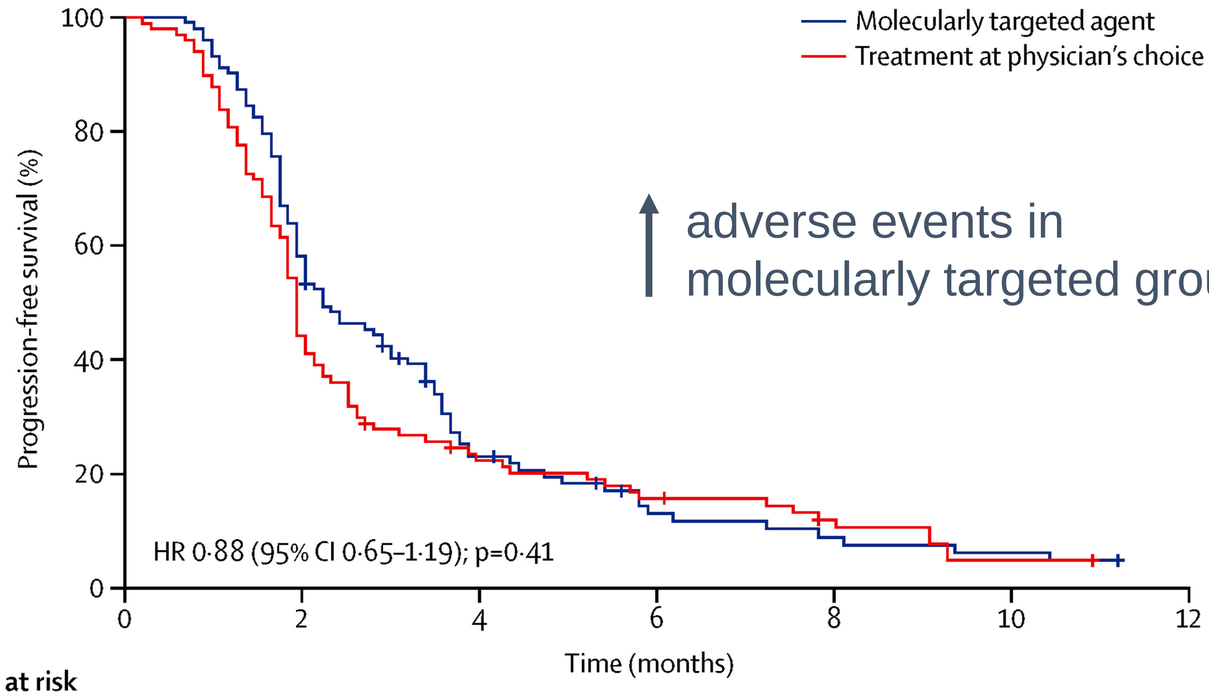
Monitoring Response

Adapting Treatment

Single Gene, Single Drug Matching



SHIVA Clinical Trial, *Lancet Oncology* 2015
refractory metastatic solid tumor, 10 gene-drug pairs



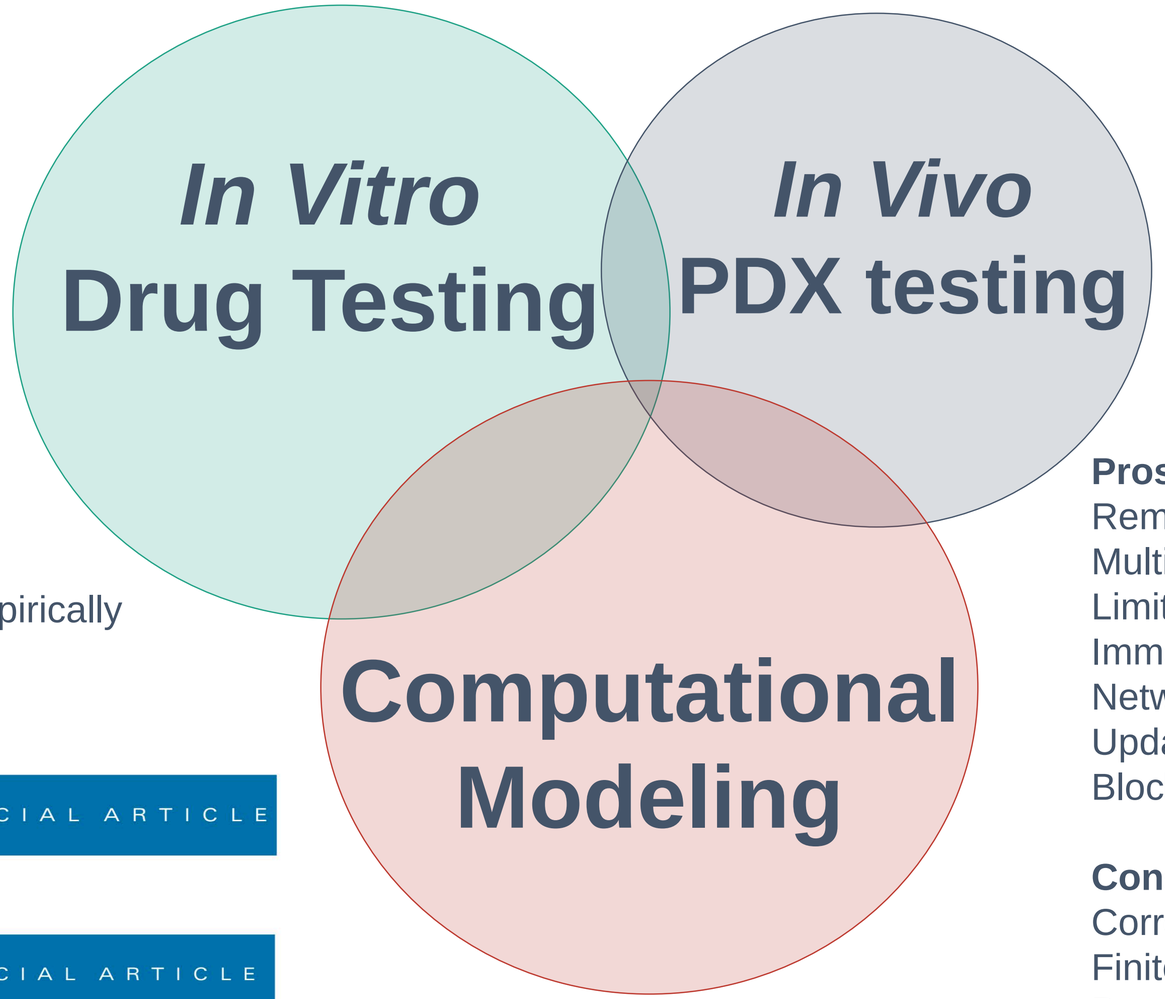
adverse events in molecularly targeted group

Number at risk							
Molecularly targeted agent	99	62	20	10	5	2	0
Treatment at physician's choice	95*	50	19	12	8	1	0

Varieties of Precision Oncology

Pros:
Compact assay
Complete intracellular programming
Number of drug & combos
Variety of read-outs possible
Normal cell referencing
Automation, high throughput
Reproducible

Cons:
Technical failure rate (historical)
Correlates with clinical?
Limited number of drugs
Recommends same drugs given empirically
Currently lacks cancer environment



Pros:
Includes environment

Cons:
Correlates with clinical?
Limited number of drugs
Labor-intensive
Technically challenging

Pros:
Remotely accessible assay: mobile, cloud
Multi-gene, multi-drug / high-dimensional
Limitless number of drugs
Immortalized model
Network/pathway identification
Updates with advancing knowledge
Block-chain permissable

Cons:
Correlates with clinical?
Finite elements due to software coding
Depends on data completeness
Currently lacks cancer environment

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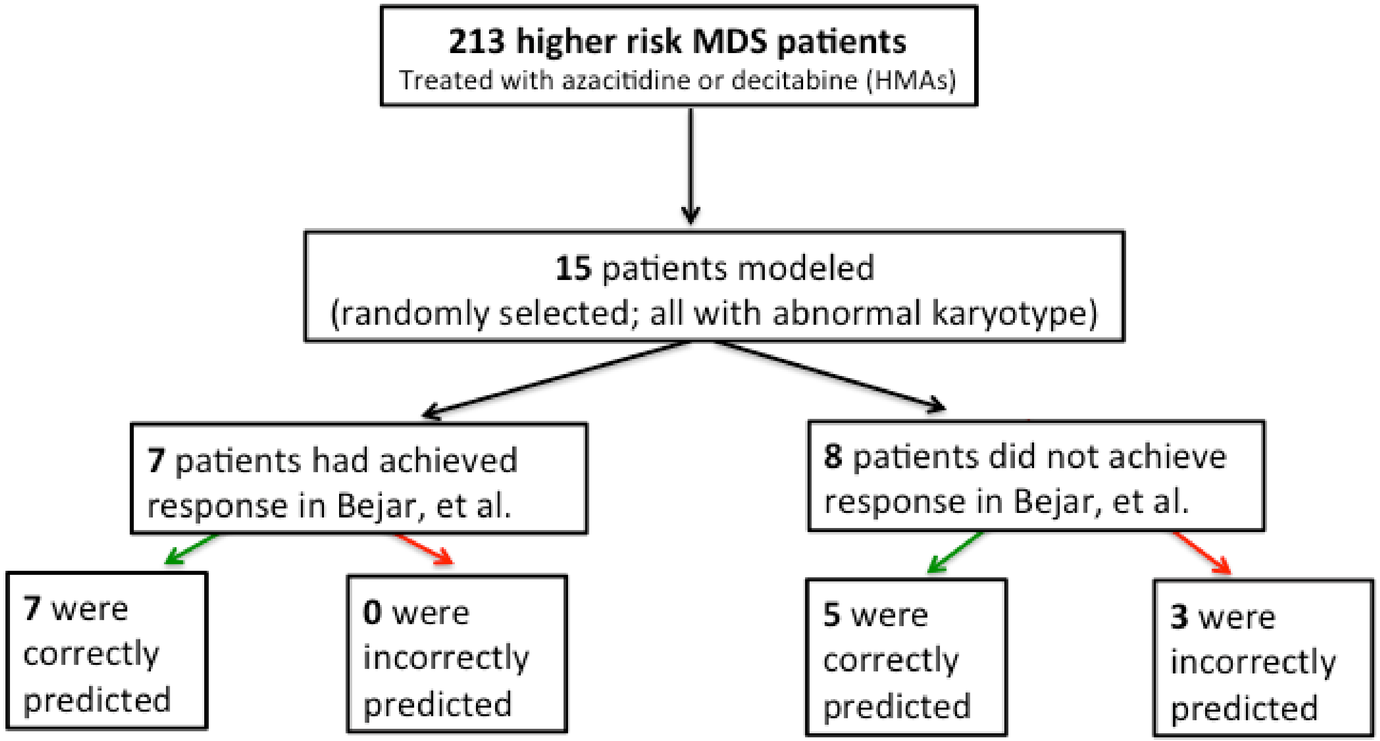
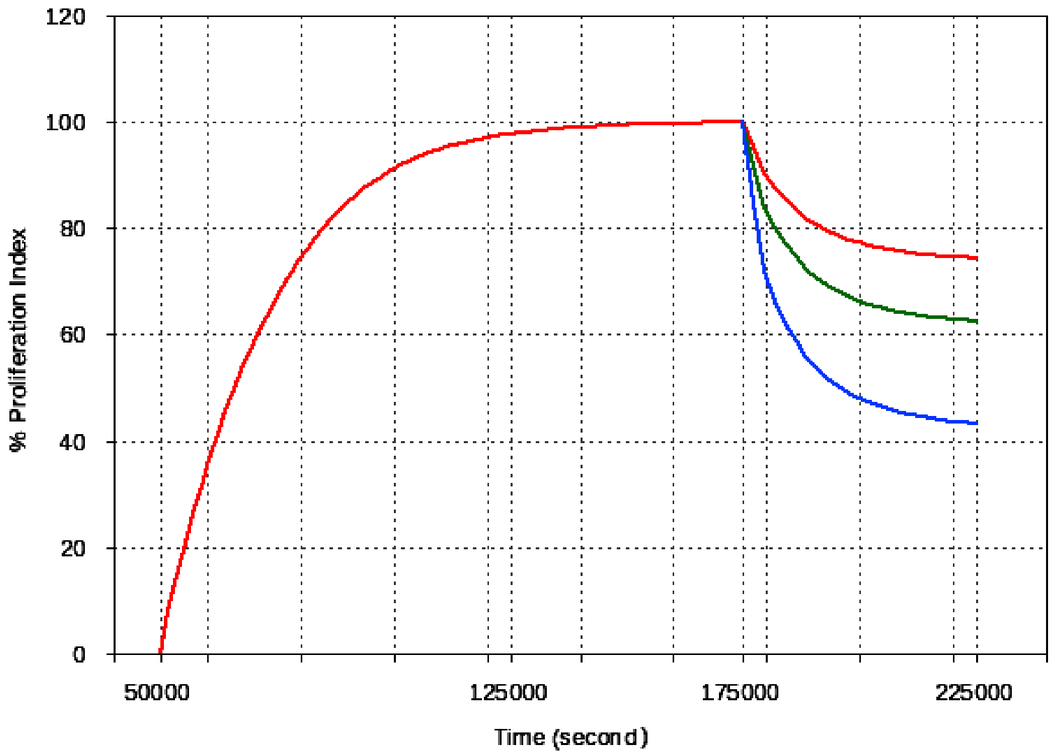
JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

VOLUME 29 · NUMBER 24 · AUGUST 20 2011
JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Computational Biology Modeling & Digital Drug Simulation in MDS and AML

- Retrospective Studies



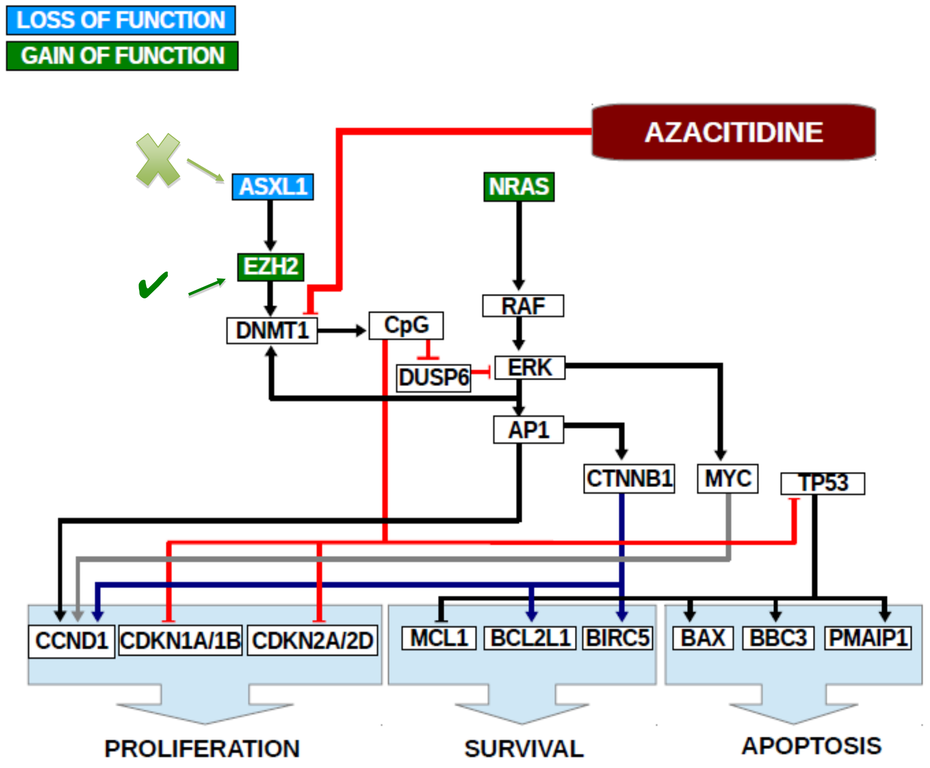


Drusbosky, et al. *Leukemia Research* 2016

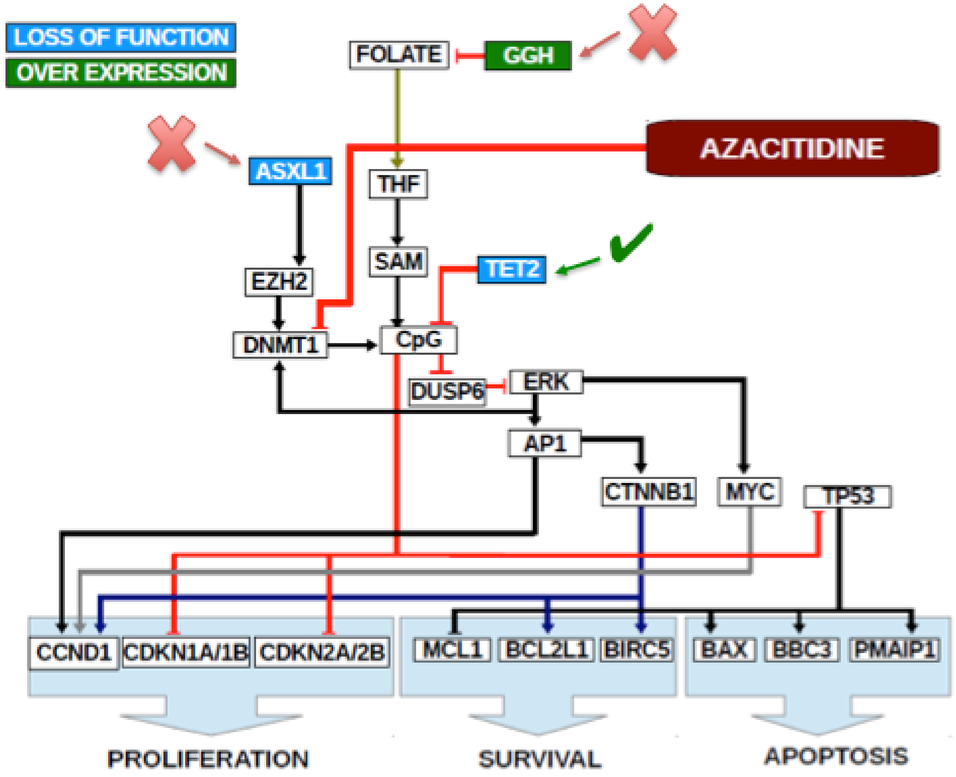
Computational Biology Modeling & Digital Drug Simulation in MDS and AML

- Retrospective Studies

SENSITIVITY



RESISTANCE

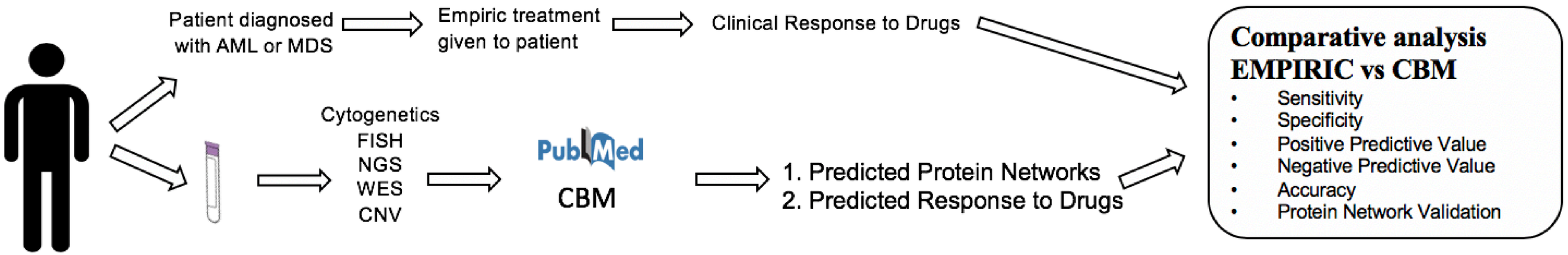


Drusbosky, et al. *Leukemia Research* 2016

Patient Cohort	1	2	3
Patients Modeled	46	15	10
Patients Excluded	6	98	26
MDS Risk Category	Low: 48% Int-1: 50% Int-2: 2% High: 0%	Low: 13% Int-1: 27% Int-2: 40% High: 20%	Low: 0% Int-1: 10% Int-2: 50% High: 40%
Cytogenetic Abnormalities	del(5q)+/- other abnormalities	Variety	Variety
Treatment	Lenalidomide 10 mg PO QD D1-21 every 28-day cycle	Azacitidine 75 mg/m2 SC QD D1-7 of each 28-day cycle or Decitabine 20mg/m^2, IV QD D1-5 of each 28 day cycle	Azacitidine 75 mg/m2 SC QD D1-5 and Lenalidomide 10mg PO QD D1-21 of each 28-day cycle
Patients who Achieved Response (N, %)	37 (80%)	7 (46%)	8 (80%)
Patients Who Did Not Achieve Response (N, %)	9 (19%)	8 (53%)	2 (20%)
Correctly Predicted Responders (N)	33 (89%)	7 (100%)	8 (100%)
Correctly Predicted Non-Responders (N)	4 (44%)	5 (63%)	2 (100%)
Positive Predictive Value (%)	89%	100%	100%
Negative Predictive Value (%)	44%	63%	100%

Computational Biology Modeling & Digital Drug Simulation in MDS and AML

- Prospective Pilot Study



Drusbosky, et al. *In review.*

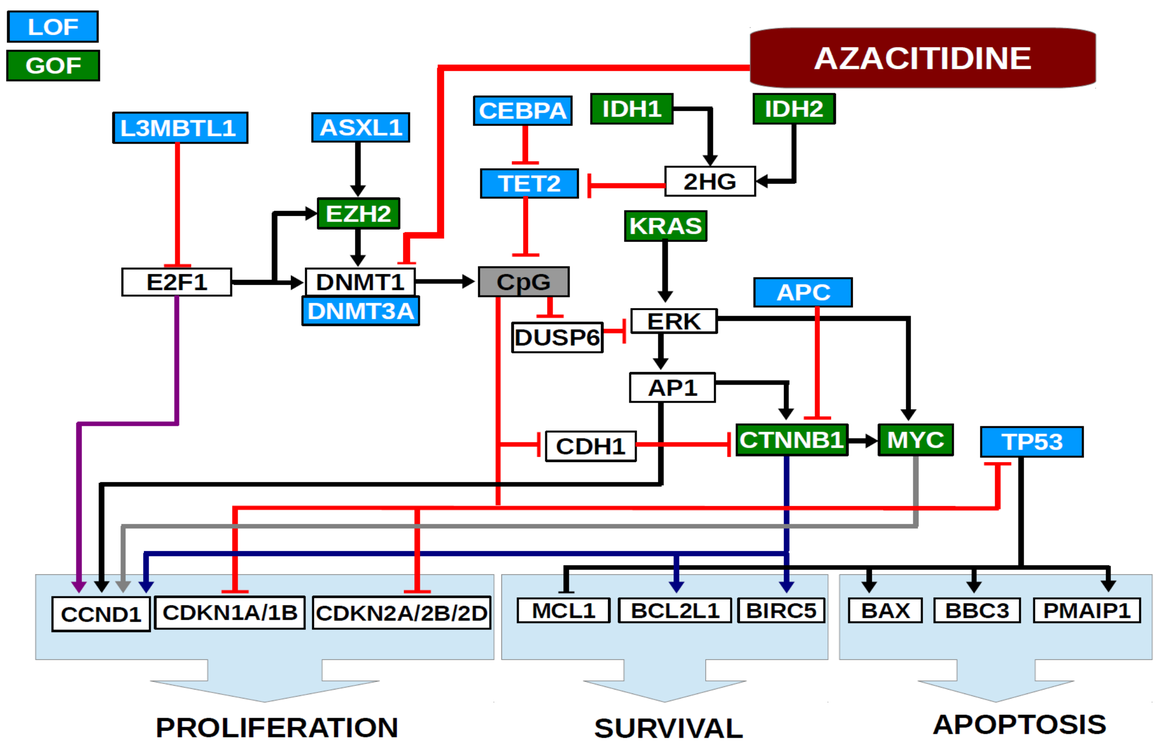
Computational Biology Modeling & Digital Drug Simulation in MDS and AML

Characteristic	Participants Evaluable for Clinical Response, N = 50 (% pateints)
Median age (range)	66.5 (42–90)
Sex, n (%)	
Female	25 (50)
Male	25 (50)
Disease and origin, n (%)	
MDS	15 (30)
AML	33 (66)
De novo	21 (64)
Secondary	12 (36)
CMML-2	1 (2)
Myelofibrosis	1 (2)
Diagnosis, n (%)	
Newly diagnosed	34 (68)
Relapsed/refractory	16 (32)
Prior therapy, n (%)	
No	20 (40)
Yes	30 (60)
Cytogenetics, n (%)	
Uninformative	17 (34)
Complex	31 (62)
Other	2 (4)

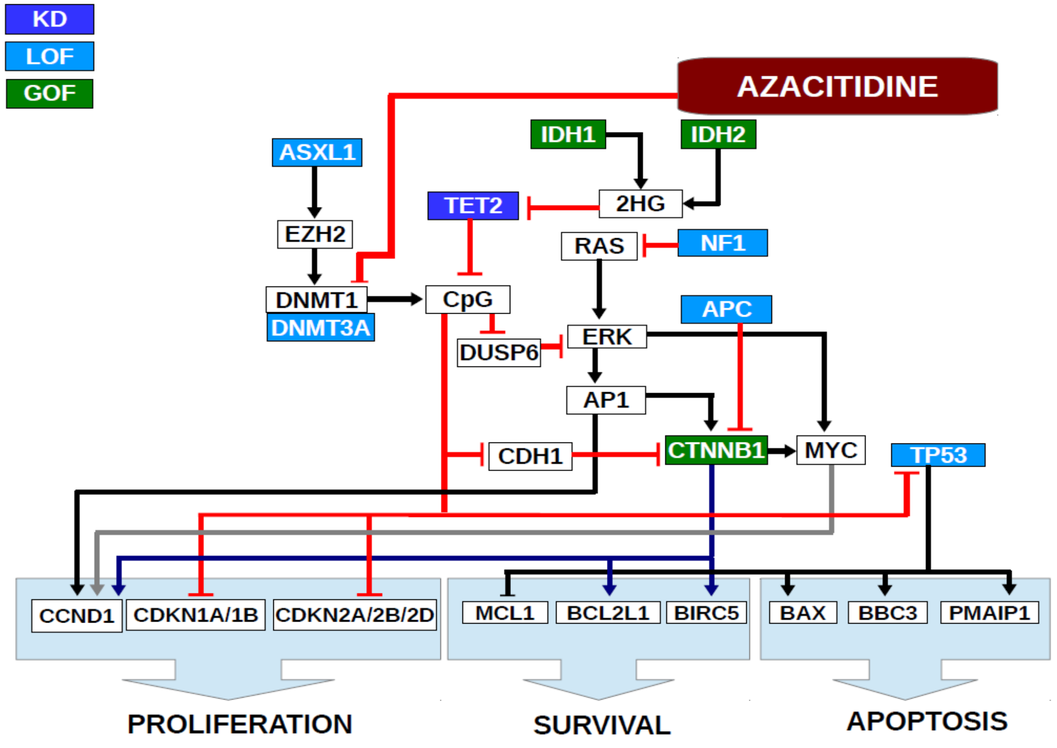
Drusbosky, et al. *In review.*

Computational Biology Modeling & Digital Drug Simulation in MDS and AML

SENSITIVE



RESISTANT

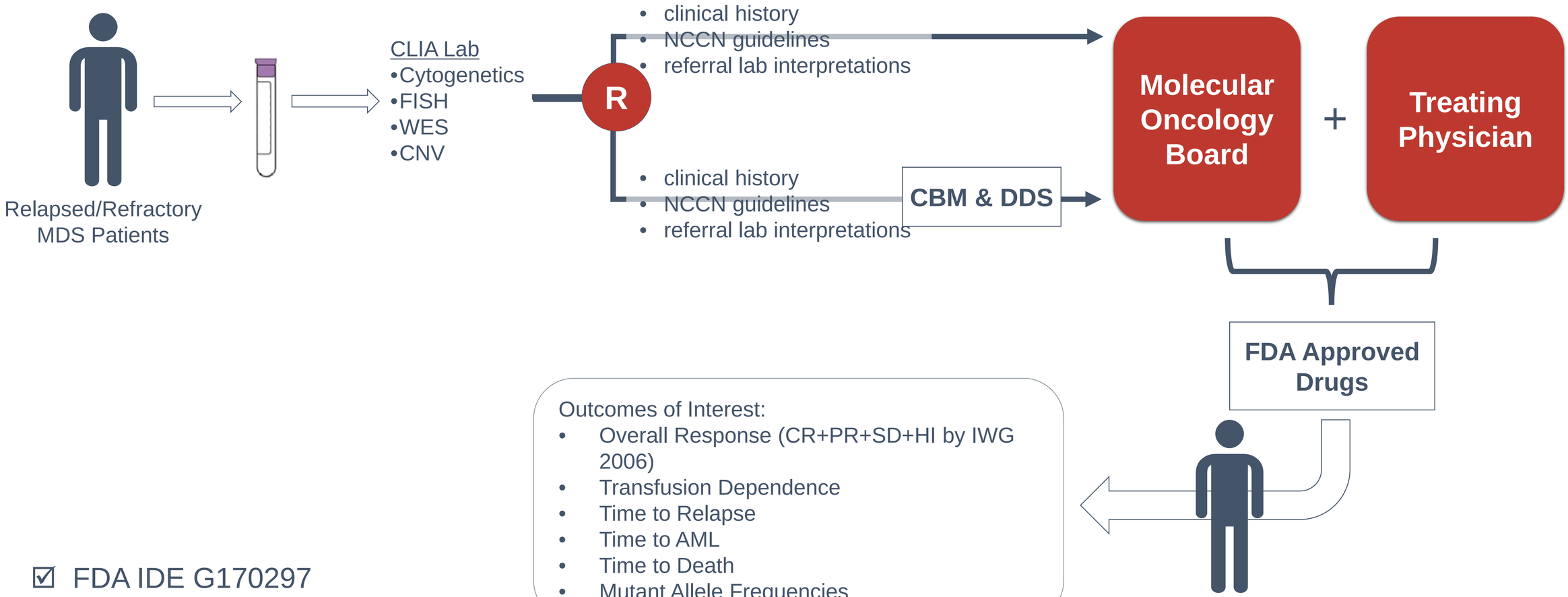


Drusbosky, et al. *In review.*

Drug	N [a]	Correct prediction, n/N	Positive response prediction		Negative response prediction		Sensitivity	Specificity	PPV	NPV	Accuracy	P value
			True	False	True	False						
HMA [b]	18	16/18	4		12	2	67%	100%	100%	86%	89%	6.060E-02
Lenalidomide	2	2/2			2			100%		100%	100%	5.000E-01
Ruxolitinib	2	2/2	2				100%		100%		100%	5.000E-01
Imatinib	1	1/1	1				100%		100%		100%	1.000E-00
HiDAC [c]	17	17/17	14		3		100%	100%	100%	100%	100%	3.615E-03
Bortezomib	1	1/1			1			100%		100%	100%	1.000E-00
Cytarabine + fludarabine	1	1/1			1			100%		100%	100%	1.000E-00
Vorasidenib (AG-881)	1	1/1			1			100%		100%	100%	1.000E-00
7+3 [d]	18	14/18	12	3	2	1	92%	40%	80%	67%	78%	2.353E-01
Overall	61	55/61	33	3	22	3	94%	88%	94%	88%	90%	6.416E-05

Computational Biology Modeling & Digital Drug Simulation in MDS and AML

- Randomized, Phase 2 Clinical Trial



Outcomes of Interest:

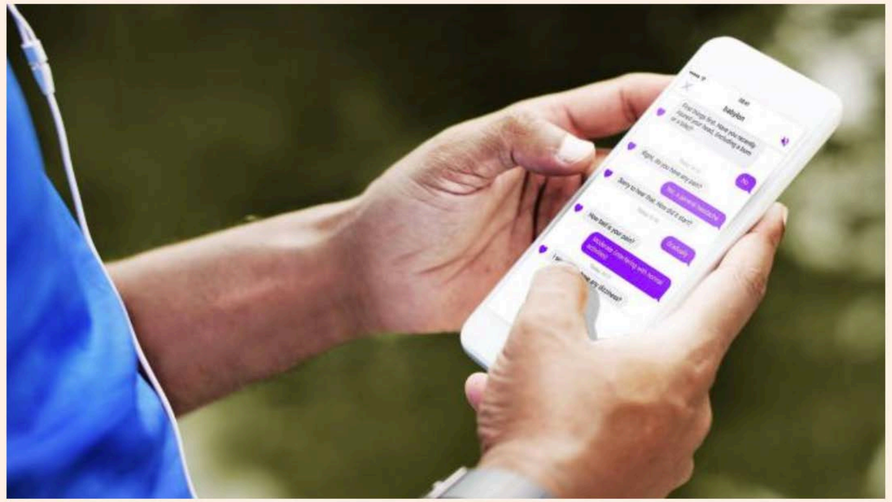
- Overall Response (CR+PR+SD+HI by IWG 2006)
- Transfusion Dependence
- Time to Relapse
- Time to AML
- Time to Death
- Mutant Allele Frequencies

☑ FDA IDE G170297

Financial Times

High-profile health app under scrutiny after doctors' complaints

Babylon advice service faces warnings it can miss symptoms of serious illness



Babylon is one of a number of new tech products being adopted by overburdened health services

Aliya Ram and **Sarah Neville** JULY 13, 2018 41

STAT News

EXCLUSIVE

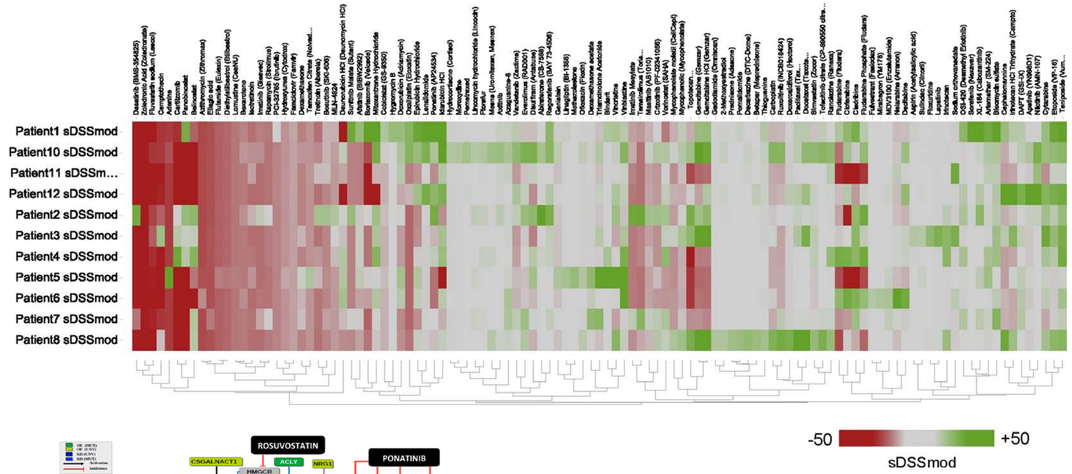
IBM's Watson supercomputer recommended 'unsafe and incorrect' cancer treatments, internal documents show

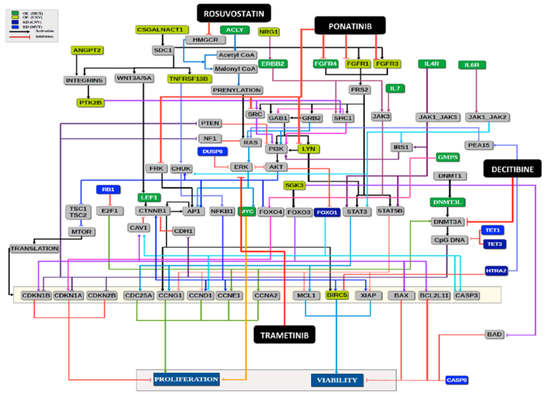
By CASEY ROSS @caseymross *and* IKE SWETLITZ @ikeswetlitz / JULY 25, 2018

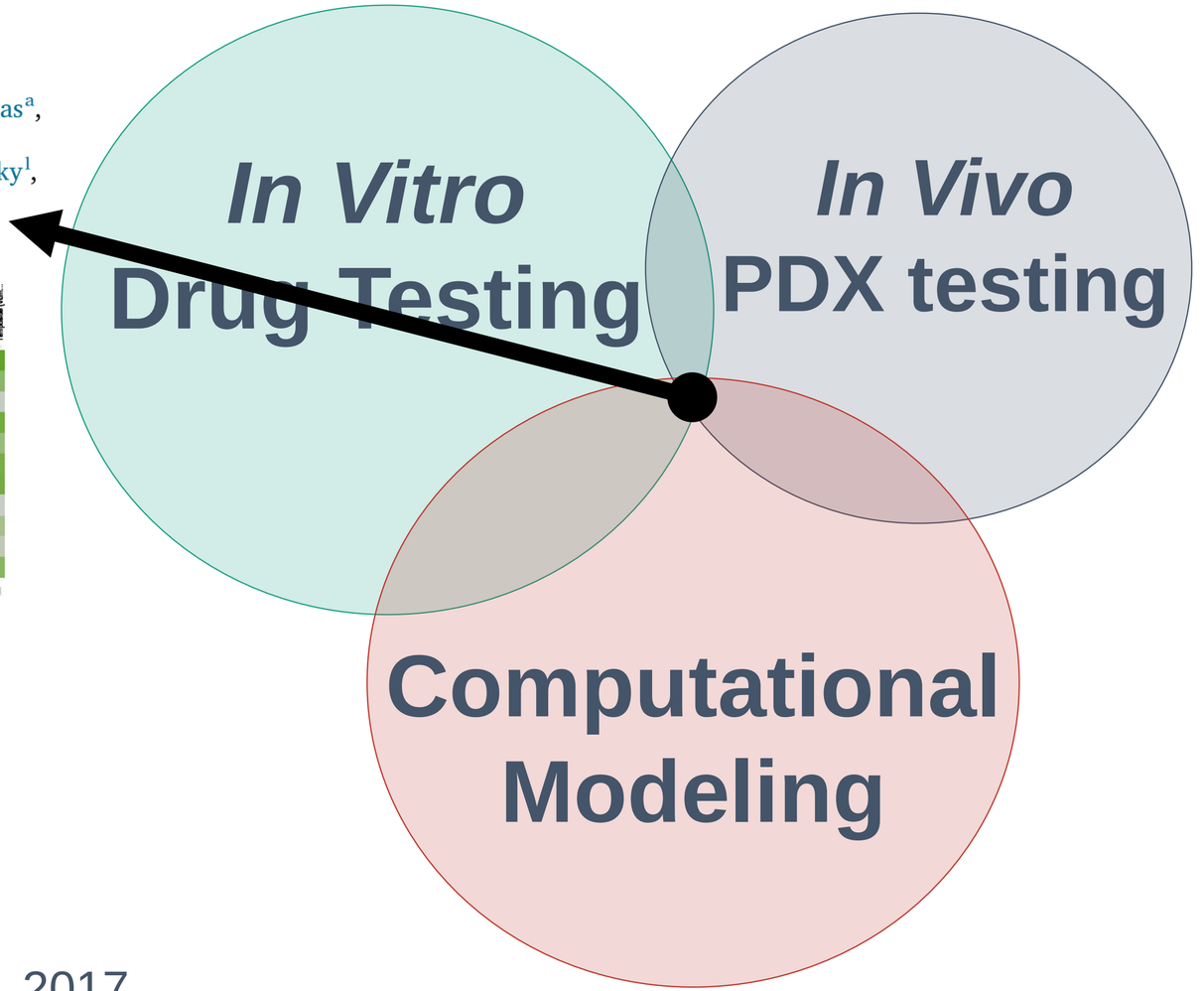
Synergy Among Precision Oncology

Ex-vivo sensitivity profiling to guide clinical decision making in acute myeloid leukemia: A pilot study

Ronan T. Swords[a,1], Diana Azzam[b,c,d,1], Hassan Al-Ali[d,e,f,g,1], Ines Lohse[b,c,d,1], Claude-Henry Volmar[b,c,d], Justin M. Watts[a], Aymee Perez[a], Ana Rodriguez[a], Fernando Vargas[a], Roy Elias[a], Francisco Vega[a], Arthur Zelent[a], Shaun P. Brothers[b,c,d], Taher Abbasi[h], Jonathan Trent[a], Shaukat Rangwala[i], Yehuda Deutsch[j], Eibhlin Conneally[k], Leylah Drusbosky[l], Christopher R. Cogle[l], Claes Wahlestedt[b,c,*]







Leukemia Research, 2017

Physician – Patient Data Relationship

Physician – Patient Data Relationship

Visual Thinking Strategies

Find the Vowel

jklwkdvktz

bmnqifsdlt

klwrxjbjdsr

qnxvrjklpc

tkxbrtmds

klasdzwptr

fgstnbpctn

- What’s going on in this picture?
- What do you see that makes you say that?
- What more can you find?

Physician – Patient Data Relationship

Visual Thinking Strategies

Case Presentation

- 76 year-old white woman with profound fatigue. No recent infections.
- **CBC**: pancytopenia, requiring red blood cell transfusion
- **Chemistry, Iron, B12, folate**: normal
- **Bone marrow**: dysplastic hematopoiesis, 15% myeloblasts
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- **Whole Exome Sequencing**: hundreds of gene SNPs and gene copy number variations

- **Treatment choices**:
  - ✓ **Low intensity chemotherapy: Azacitidine x 4 years**
  - ❑ High intensity chemotherapy: Cytarabine ± Anthracycline
  - ❑ Allogeneic Hematopoietic Cell Transplant
  - ❑ Palliative Care → Hospice

Physician – Patient Data Relationship

- Visual Training Exercises Among Radiologists
  - Adrian-Harris, *Radiography*, 1979
- Dolev, et al., *JAMA* 2001
- Bardes, et al., *Med Educ*, 2001
- Naghshineh, et al., *J Gen Int Med*, 2008
- Commentary on Visual Thinking Practice
  - Braverman, *Clin Dermatol*, 2011
- Teaching Dermatology Residents to Observe More Closely
  - Huang, et al., *British Journal of Dermatology*, 2016