Informatics to enable routine personalized cancer therapy [U01 CA180964]

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UT School of Biomedical Informatics

Funda Meric-Bernstam, MD
UT MD Anderson Cancer Center

Problem

From: Xiong,Wen
Sent: Thursday, June 12, 2014 10:13 AM
To: Meric-Bernstam,Funda
Cc: Piha-Paul,Sarina Anne
Subject: mutation report [redacted]

Dr. Meric:

Please review the patient for BKM120. She has PIK3CA mutation.

Name: [redacted]
MRN: [redacted]
Protocol: 2013-0682
Diagnostics: Fallopian tube/Ovarian CA

Thanks,

Wendy Xiong.
Clinical Studies Coordinator.
Investigational Cancer Threrapeutics.
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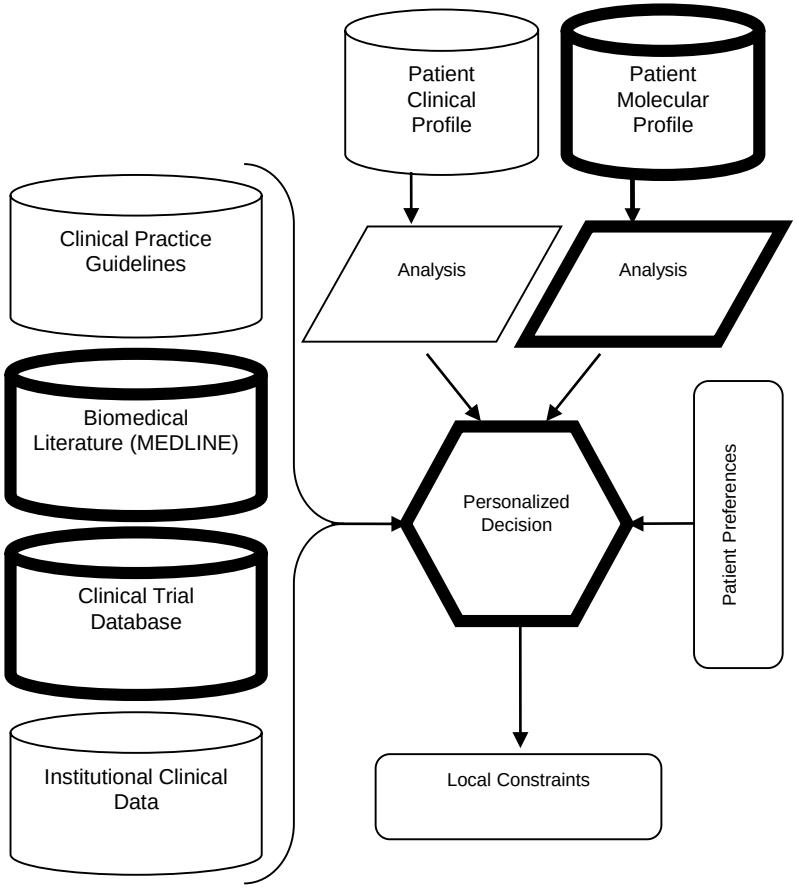
5 page report attached

Overview


Patient Clinical Profile
Patient Molecular Profile
Clinical Practice Guidelines
Analysis
Analysis
Biomedical Literature (MEDLINE)
Personalized Decision
Patient Preferences
Clinical Trial Database
Institutional Clinical Data
Local Constraints

Real and immediate problem

- Clinical application at MD Anderson
  - The Khalifa Institute for Personalized Cancer Therapy (IPCT)
    - "Clearinghouse" protocol
      - >4000 patients with molecular profiles
    - Human-curated "gene sheets"
      - Gold standards for evaluation of automated methods
  - Department of Investigational Cancer Therapeutics
    - Phase I program
    - Primarily "trial-driven"
      - Problem is: given patient → assign to appropriate clinical trial
      - ~800 ongoing therapeutic trials at MD Anderson alone
- Plans discussed for UT System clinical trial recruitment

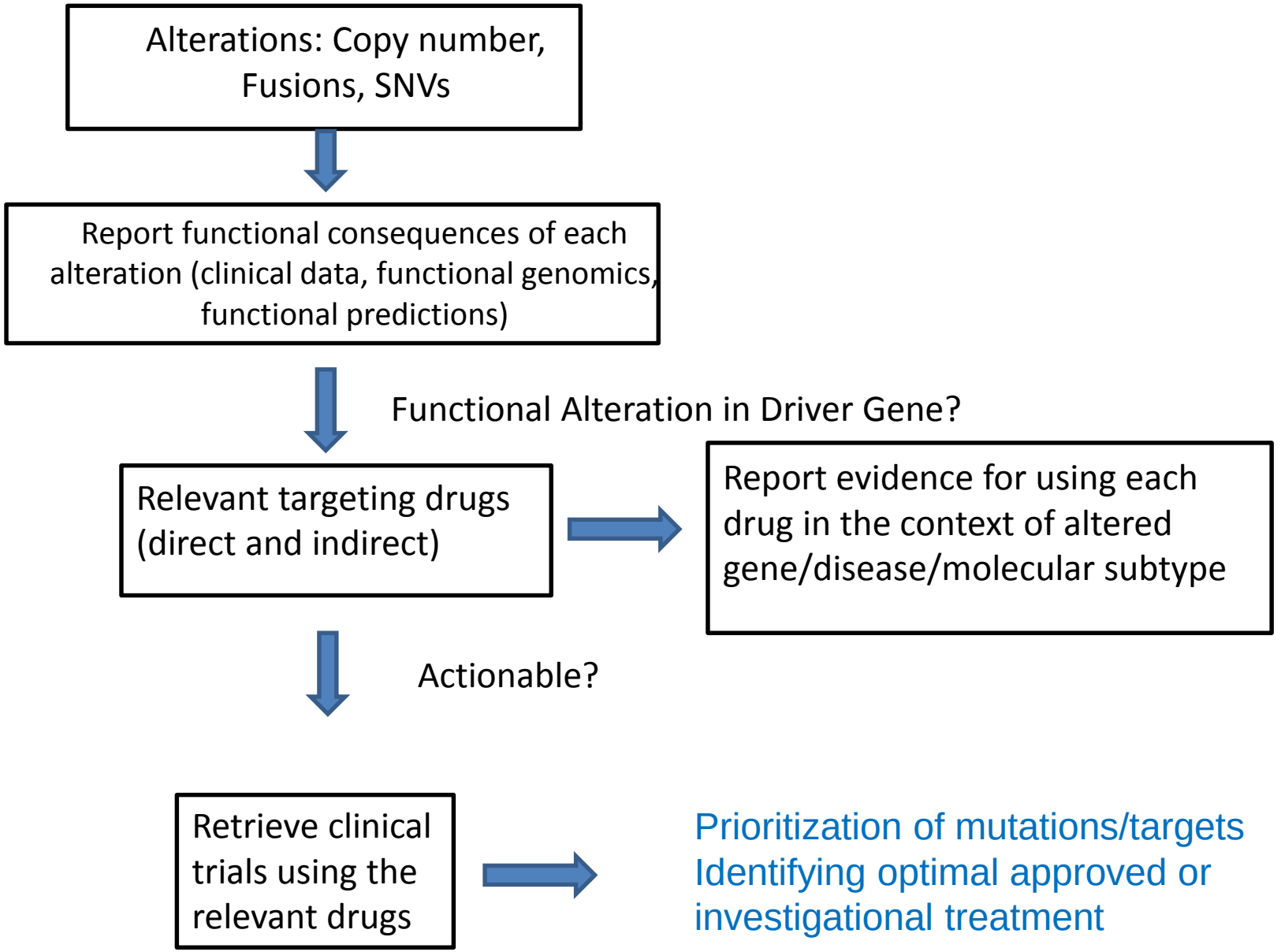
Approach

- Adapt and apply existing informatics techniques (SBMI)
- Evaluate against human-curated gold standards (IPCT/ICT)
- Apply to clinical trial matching
  - Outcome = recruitment

Current projects and progress

- Information curation for decision support
  - Gene knowledge sheets
  - Trials and drugs
  - Patient reports
  - Actionable gene panels
- Automated identification of molecular effects of drugs (AIMED)
  - Done, published
  - Working on improvements (e.g., ranking, statistical NLP)
- Creating a pipeline for literature curation
  - Ongoing

Decision Support via Knowledgebase Development and Molecular Tumor Board



Current Genomic Selection Strategies for Targeted Trials

97 unique trials with 53 unique genomic alterations and 62 drugs

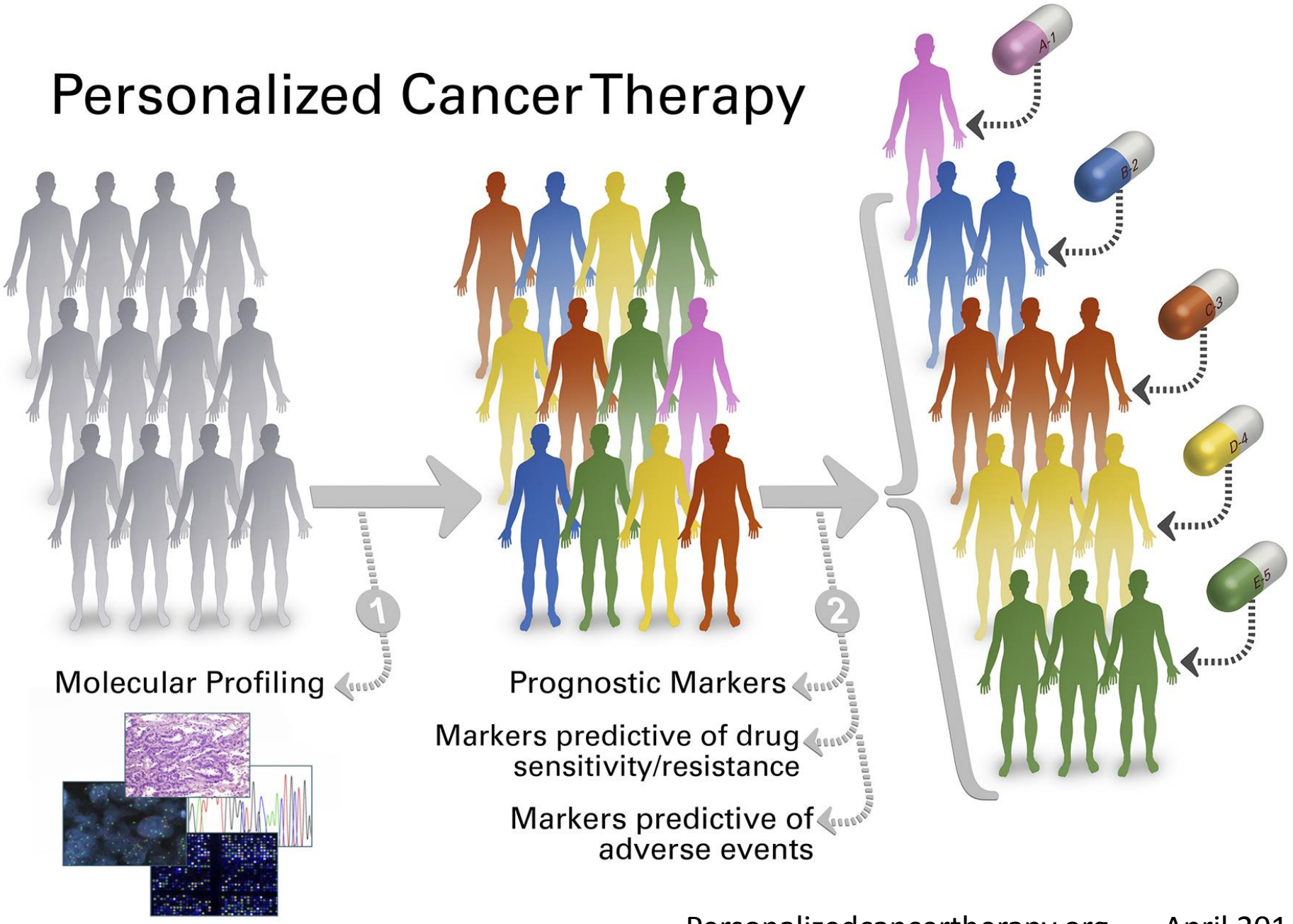
Gene Knowledge Sheets

- Created “knowledge sheets” on 27 relevant genes
  - E.g., PIK3CA = 11 pages
- For each gene, detailed mutations
  - found to disrupt the protein structure
  - their therapeutic implications
  - targeted therapies
  - Trials
    - That select patients with this aberration
    - Of therapies targeting this aberration
- Open access (with registration) at http://personalizedcancertherapy.org
  - 95,469 page views during 41,562 visits by 22,728 unique users in the first year
  - Dropped after registration required

Trials and Drugs

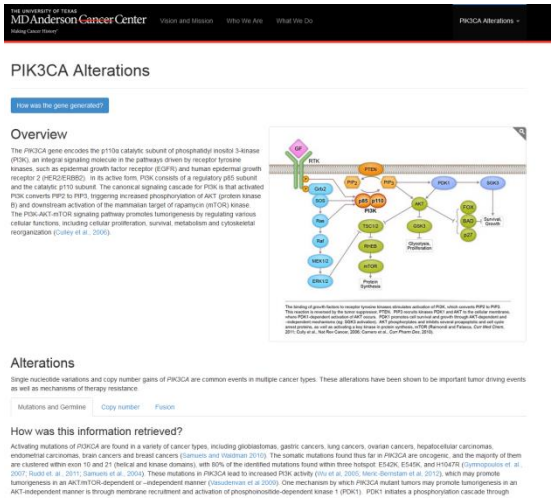
- Curated over 1500 clinical trials
  - all MD Anderson trials + others
  - details of selection criteria in context of molecular evidence
- Curated over 600 drugs
  - all drugs used in MD Anderson clinical trials + others
  - providing genes targeted by drugs

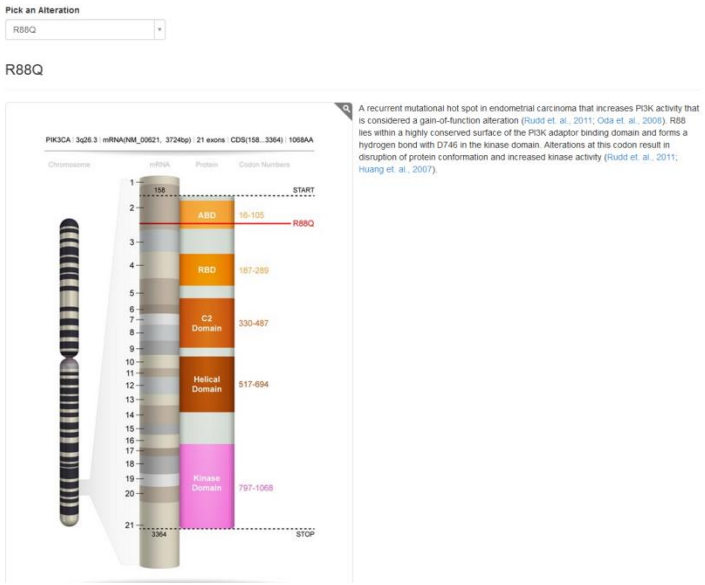
Personalized Cancer Therapy



Personalizedcancertherapy.org --- April 2014
@kennamshaw on twitter for announcement

Genomics Knowledgebase





- Gene and variant level information
- Mutations/copy number changes
- Frequency of alterations
  - in TCGA
  - In Cosmic
  - In MD Anderson IPCT experience
- Therapeutic Implications
- Drugs targeting alterations
- Clinical Trials
  - Genotype-specific Trials
  - Genotype-relevant trials

Other Progress

- Hot spot testing on over 6000 pts
- Targeted exome sequencing /annotated almost 2000 samples
  - Unusual responder program
  - Clearinghouse testing
- Optimizing annotation
  - Functional? Driver? CANDriver
  - COSMIC and TCGA frequencies
  - Therapeutic Implications>
  - Level 1 or 2 of evidence– clinical data
  - Preclinical data
    - Functional genomics
- Germline calls/return of incidental results
  - First large scale return of incidental results initiative (Meric-Bernstam et al Ann Onc 2015)
- Tools for point care annotation of variants
- JAMIA special issue on precision medicine informatics
  - Near record submissions (within 2-3 for any special issue)
  - 17 papers accepted, coming out in print July 2016
  - Cancer was a common application area

Personalized Results Reporting

- Leveraging in-house knowledge base → annotations for single patients
- Report that includes
  - Targetable aberrations
  - Targeted therapies
  - Summary context information (narrative)
  - Related genomic alterations
  - FDA approved therapy options
  - MD Anderson clinical trials
  - Clinical trials at other institutions

Actionable Gene Panel

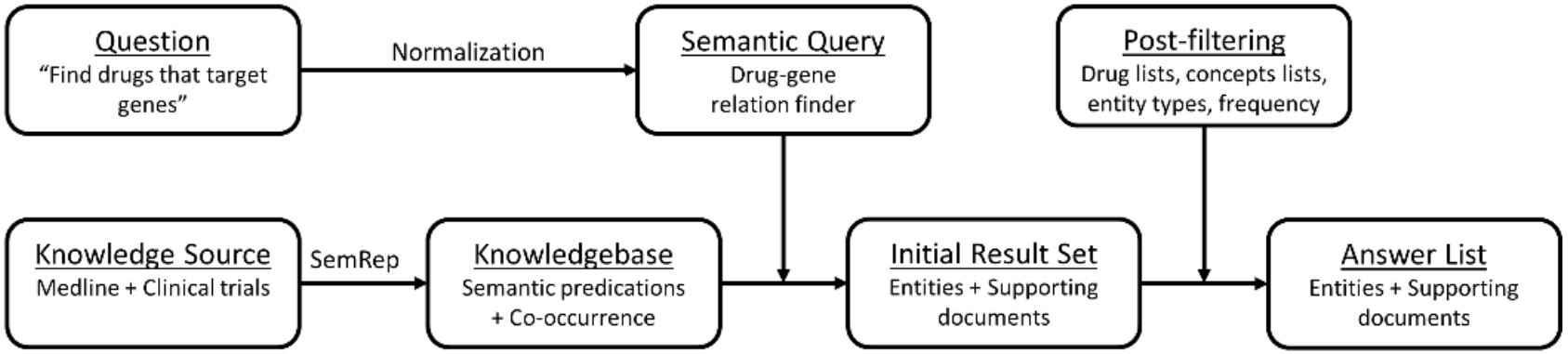
- Gene recognition tool
- Clinical trial pipeline
- In-house drug database
  - Clinical “actionability” of genes in CLIA-certified gene panels- panel agnostic
    - 3-tier system
- Help clinicians identify mutations with available therapeutic options
  - Future design of panels with only actionable genes

Leveraging the literature to identify drugs and targets

Trevor Cohen MBBS, PhD (Co-I)

Associate Professor, UT SBMI

AIMED pipeline



Performance

Marketed	Yes	Pred.	>4	INHIBITS, INTERACTS_ WITH, COEXISTS_ WITH	phsu, orch	2,251	80	0.69	0.3	0.42	0.55
3	Yes	Pred.	-	INHIBITS, INTERACTS_ WITH, COEXISTS_ WITH	-	299	61	0.35	0.3	0.32	0.34
2	Yes	CoOcc Sen	-	-	-	4,723	205	0.5	0.17	0.25	0.36
1 / 2	Yes	CoOcc Sen	-	-	-	3,875	40	0.29	0.18	0.22	0.26
1	Yes	CoOccDoc	-	-	-	1,609	129	0.25	0.19	0.22	0.24
All Phases						**12,757**	**515**	**0.39**	**0.21**	**0.27**	**0.33**

- "False positive" results
  - ~26% actually true positive (i.e., should be on gold standard)
  - ~61% "should be considered" (i.e., not gold standard, but should be reviewed)

Ongoing work

- Ranking
  - Heuristics
  - “Learning to rank”
- Develop annotation pipeline
  - Drugs → genes
    - Drugs
    - Papers
- Two tasks
  - New gene
  - Update gene
    - Avoid repeat review of papers/drugs

Lessons learned

- Hard task
  - No real “gold standard”
    - Constantly changing
    - Inter-observer variability
  - Her2 intracellular domain protein = drug
- 100% recall is not what users actually want
  - Ranking is important
- Have to get workflow right

Publications and products

1. Fathiamini S, Johnson AM, Zeng J, Araya A, Holla V, Bailey AM, Litzenburger BC, Sanchez NS, Khotskaya Y, Xu H, Meric-Bernstam F, Bernstam EV* , Cohen T* . Automated Identification of Molecular Effects of Drugs (AIMED). J Am Med Inf Assoc, in press. [* = co-senior/corresponding authors]
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3. Yu Z, Bernstam EV, Cohen T, Wallace BC, Johnson TR. Improving the Utility of MeSH terms Using the TopicalMeSH Representation. J Biomed Inform. 2016 Jun;61:77-86.
4. Rogith D, Yusuf RA, Hovick RS, Fellman BM, Peterson SK, Burton-Chase AM, Li Y, Bernstam EV, Meric-Bernstam F. Patient knowledge and information-seeking about personalized cancer therapy. Int J Med Inform. 2016 Apr;88:52-7. PMCID: PMC 4789765
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9. Rogith D, Yusuf RA, Hovick SR, Peterson SK, Burton-Chase AM, Meric-Bernstam F, Bernstam EV. Attitudes regarding privacy of genomic information in personalized cancer therapy. J Am Med Inform Assoc. 2014 Oct;21(e2):e320-5.
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11. Bailey AM, Mao Y, Zeng J, Holla V, Johnson A, Brusco L, Chen K, Mendelsohn J, Routbort MJ, Mills GB, Meric-Bernstam F. Implementation of biomarker-driven cancer therapy: existing tools and remaining gaps. Discov Med. 2014 Feb;17(92):101-14. PMCId: PMC 4160907
12. Zhou W, Chen T, Zhao H, Eterovic AK, Meric-Bernstam F, Mills GB, Chen K. Bias from removing read duplication in ultra-deep sequencing experiments. Bioinformatics. 2014 Jan 21. [Epub ahead of print] PMCID: PMC 3982159
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14. Meric-Bernstam F, Brusco L, Shaw K, Horombe C, Kopetz S, Davies MA, Routbort M, Piha-Paul SA, Janku F, Ueno N, Hong D, De Groot J, Ravi V, Li Y, Luthra R, Patel K, Broaddus R, Mendelsohn J, Mills GB. Feasibility of Large-Scale Genomic Testing to Facilitate Enrollment Onto Genomically Matched Clinical Trials. J Clin Oncol 2015; May 26 [Epub]. PMCID: PMC 4550690
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17. Chen, K., et al., Clinical actionability enhanced through deep targeted sequencing of solid tumors. Clin Chem, 2015. 61(3): p. 544-53. PMCID: PMC 4511273
18. Updated Semantic Predication file hosted by NLM: https://skr3.nlm.nih.gov/SemMedDB/index_uth.html

Thank you

Questions?