

# Using Hackathons to reveal new Genomic Research Techniques

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20250424 Festival of Biologics

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# Agenda

- \*Motivation
- Tumor boards provide personalized advice.
- Hackathons formalize, scale and tune the tumor board process
- Why did the p1RCC hackathon winner win?
- Summary
- Acknowledgements

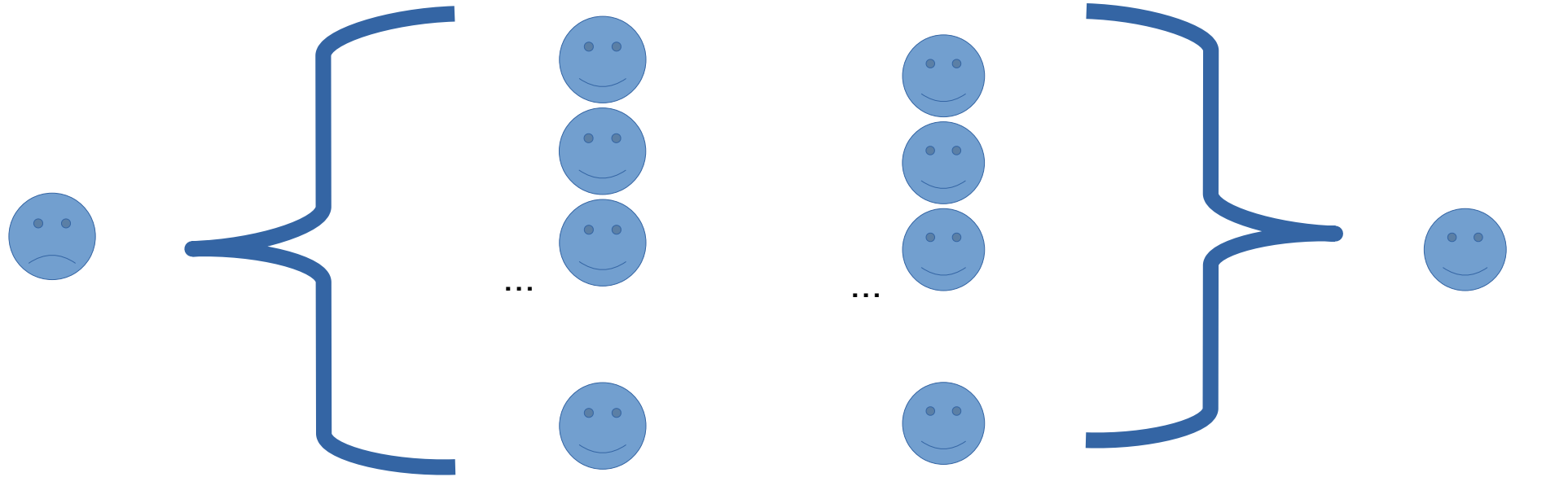
# My Motivation: p1RCC Diagnosis

- 1) Standard of Care – Small Market for rare diseases (eg p1RCC)
  - 2017 - So far, NO improvement in outcome over the last decade. - Laurence Albigres
- 2) Clinical Trials – Only add single digit months – rarekidneycancer.org
  - 2017 - "Recommendations for the Management of Rare Kidney Cancers" - Median PFS in rare RCC patients
    - for sunitinib and Everolimus groups was **6.1 versus 4.1 mo**
    - for ESPN, **8.3 versus 5.6 mo** for ASPEN,
    - and **7.2 versus 5.1 mo** for RECORD-3.
  - 2023 - Cabozantinib, which is a multikinase inhibitor targeting VEGF, MET, and AXL, demonstrated a superior median PFS of
    - **9.0 months, compared to sunitinib with 5.6 months**
- 3) So, given these stats and absent a SOC, how do I answer key questions?
  - E.g. Should I enroll in clinical trials?
  - What do I take if I progress?

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# Clinical Trials vs. Tumor Boards (Portfolios)



1 Researcher

N Patients

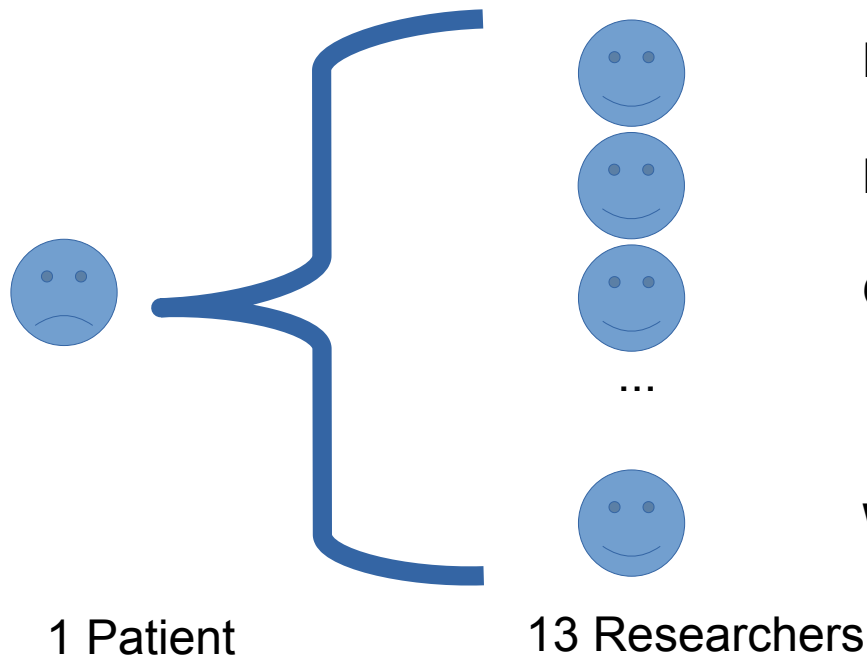
N Researchers

1 Patient

**Clinical Trial:** one Researcher many Patients

**Tumor Board:** many Researchers one Patient  
In essence, each member has a “2<sup>nd</sup> Opinion”

# Tumor Boards: Which is better Proton or Photon?



## Proton/Photon

Proton

Photon

Operate

...

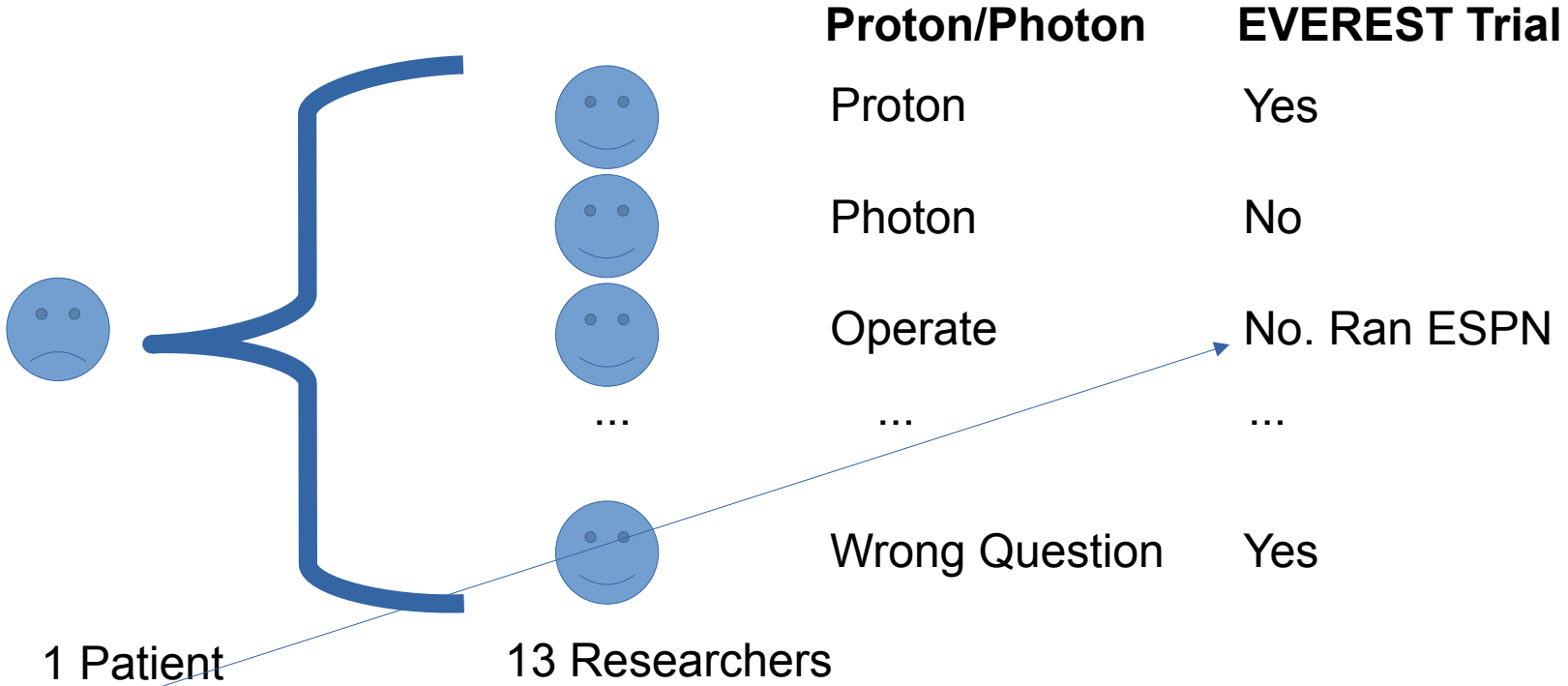
Wrong Question

- Like Mercedes vs. BMW Dealerships
  - Proton facilities recommend Proton
  - Photon facilities recommend Photon
- Facility with both: looking at the size and location, photons are most likely to be superior and would probably take only one fraction compared to a 5-6 weeks treatment with protons.
- Facility with Proton: “You’re asking the wrong question. Instead of asking what tool the mechanic uses, ask which garage has the best car repair rate.”
- #14 Varian Proton Engineer: Check the tech version and cross check the radiation plan.
- UCSF - photon

## ● Ensemble Reasoning

- “The best way to have a good idea is to have lots of ideas.” - Linus Pauling

# Tumor Boards: Should I participate in EVEREST



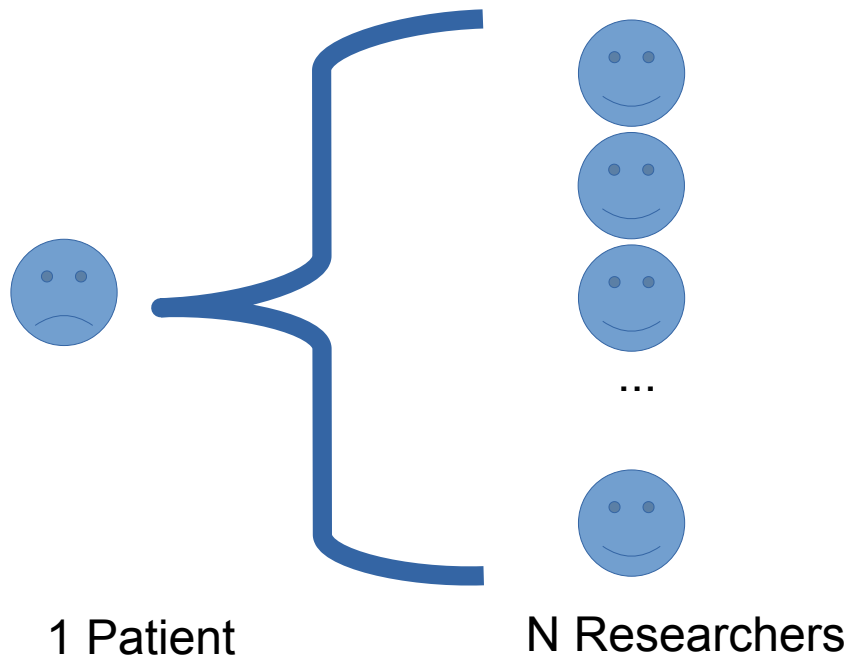
- "I do not recommend any adjuvant trial w/ mTOR inhibitors or VEGF targeted agents for papillary RCC. There will be trials w/ **immune checkpoint agents** in the near future but not soon enough to enroll on."
- Note: My EVEREST Clinical Trial Enrollment likely would not have increased overall success rate!!!

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# The First Hackathon: Kaggle

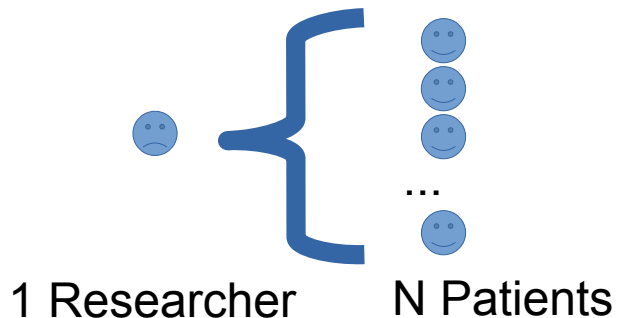


- Ensemble Reasoning
  - “The best way to have a good idea is to have lots of ideas.” - Linus Pauling
- [Kaggle](#):—Data Science Competition Platform founded 2010
  - “Set up to meet a mismatch between people collecting data and those with the skills to analyze it.”
  - Random Forests became dominant around 2012
  - “[Random Forests](#) or random decision forests is an ensemble learning method for classification, regression and other tasks that operates by constructing a multitude of decision trees at training time. For classification tasks, the output of the random forest is the class selected by most trees. For regression tasks, the mean or average prediction of the individual trees is returned. Random decision forests correct for decision trees' habit of overfitting to their training set.”
  - Note: Each tree is usually pretty Simple (Stupid).

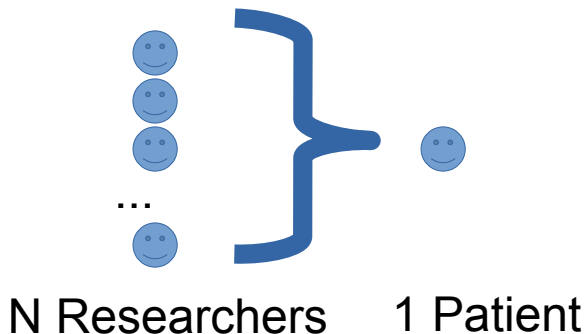
<https://www.science.org/doi/full/10.1126/science.331.6018.698>

# Hackathon (Game) Structure

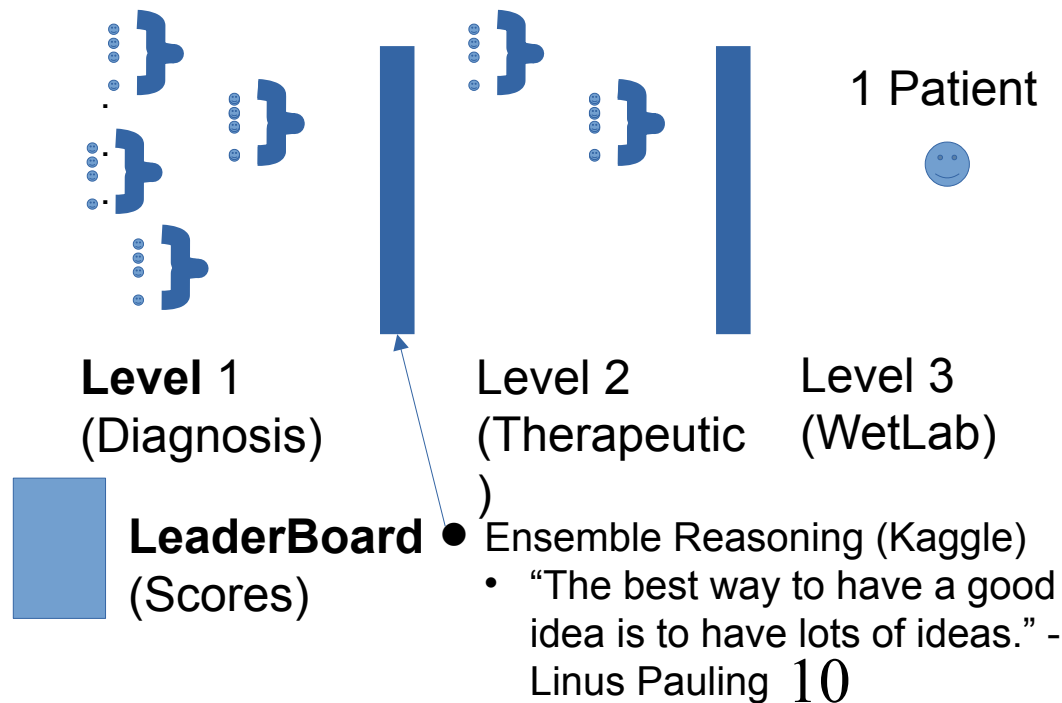
**Clinical Trial:** one Researcher many Patients



**Tumor Board:** one Patient many Researchers



**Hackathon:** one Patient many TumorBoards (Teams)

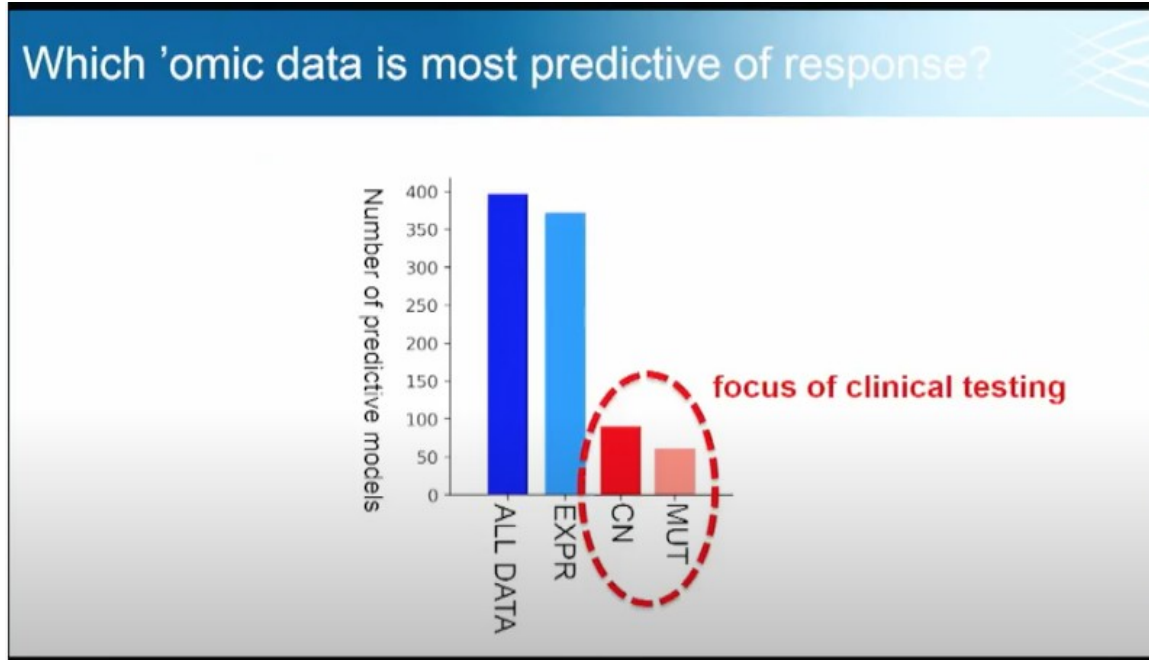


# 2018 p1RCC Hackathon Teams



80 People (some Remote) formed 17 Teams (50 pictured)<sup>11</sup>

# Input: (Lots of) Research Data



James Watson: targeting metabolism is a more promising avenue in current cancer research than gene-centered approaches. [20160515 NYT](#)

- Genetics- brother has thyroid cancer
- Genomics - TCGA Thyroid cancer clusters close to p1RCC
- Metabolomics - High Uric Acid - “Thyroid hormones influence kidney function and thereby might alter serum urate levels, a major risk factor for gouty arthritis.”
- Co-morbidities - Bradycardia (Slow Heart Rate): “hypothyroidism results in an insufficient amount of thyroid hormone which leads to a slower heart rate
- MicroBiome from Dental Records

<https://www.scientificamerican.com/article/colon-cancer-linked-to-mouth-bacteria/> 12

# Goal: One Question, One Answer\*

- Given this medical data, what is the Therapeutic Recommendation?
- (Scoring) Cross Check: What are the Genes of Interest?

# 2018 p1RCC DNA Hackathon Process

TCGA Data

Bill Data (DNA)

Ensemble of 17 weak classifiers

## 119 Recommended Genes

cancer-genome-workbench								
causalnucleotidenetwork								
RecausalNucleotideNetworks								
Aizheng	AKR1B10	BASP1P1	CLEC2B	CYP4F11	LINC00621	PLEKHO1	PLEKHO2	...
BioMarkers.ai	DMRT2	FHL1	KNG1	PTGER3	UMOD			
DamTheRiver	AC139425.3	ACSM2A	ANO9	AQP12B	GRIN3B	HEXB	HIVEP3	...
GEViz	NRF2-ARE							
HelloKidney	ITGAM	TNFSF4						
KidneyBean	TUBB8							
studentec	AMPD2	DPP6	FLG2	FTMT	ST6GALNAC5			
trimericQGs	AGBL4	ARIDA1	CUL-2	HPSE2	LAMC-1	SK3	TRABD2B	...
DeeperDrugs	<b>BARD1</b>	APOB	CDK9	TTRAP				
GNOME	<b>BARD1</b>	<b>PDE4DIP</b>	AHNAK	ANAPC1	BCLAF1	DNAJ27	PABPC1	...
HelloKidney2		<b>PDE4DIP</b>	FOLH1	GDNF	MTHFR	PFKP	PSMA	...
codeomics						<b>MTOR</b>	<b>PIK3CA</b>	...
HSIEH	<b>SETD2</b>	<b>NF2</b>	<b>BAP1</b>	<b>KDM6A</b>	<b>PBRM1</b>	<b>MTOR</b>	<b>PIK3CA</b>	...
ExpressForce	<b>SETD2</b>	<b>NF2</b>	<b>BAP1</b>	<b>KDM6A</b>	<b>PBRM1</b>	<b>FGFR1</b>	ARID1A	...
HIF1AIsNotAnOncogene						<b>FGFR1</b>	CDK4	...

10 Up Weighted Classifications ( Genes)

- BARD1
- PDE4DP
- SETD2
- NF2
- BAP1
- KDM6A
- PBRM1
- MTOR
- PIK3CA
- FGFR1

- What is the best way to reconcile (judge) results?
  - Independent Teams discover the same Gene?
  - Independent Teams discover “Industry Standard” Genes?

# Merging 2018 and 2020 Results

Team - 2018	Gene	BP-Tumor -2020
studentec	FLG2	-0.569807
BioMarkers.ai	FHL1	-0.370446
HelloKidney2	TAS2R19	-0.363179
ExpressForce	TERT	-0.358329
HelloKidney2	TYMS	-0.287382
...	...	...
trimericOGs	HPSE2	0.567236
BioMarkers.ai	PTGER3	0.59603
BioMarkers.ai	DMRT2	0.621588
BioMarkers.ai	UMOD	0.657959
BioMarkers.ai	KNG1	0.668831

Join & sort

- 2018 p1RCC
  - 119 recommended Genes
- 2020 p1RCC
  - 6 Normalized
  - p1RCC patient's RNA genes

What is the best way to reconcile (judge) results?

- **BioMarkers.ai sorted to either end of the chart.**
  - Perhaps diagnostic
  - Likely not therapeutic

# Leaderboard (Open)

Team - 2018	Gene	BP-Tumor -2020	Approach
studentec	FLG2	-0.569807	<a href="https://github.com/SVAI/studentec">https://github.com/SVAI/studentec</a>
BioMarkers.ai	FHL1	-0.370446	<a href="https://github.com/SVAI/Biomarkers.AI">https://github.com/SVAI/Biomarkers.AI</a>
HelloKidney2	TAS2R19	-0.363179	<a href="https://github.com/SVAI/HelloKidney2">https://github.com/SVAI/HelloKidney2</a>
ExpressForce	TERT	-0.358329	<a href="https://github.com/SVAI/ExpressForce">https://github.com/SVAI/ExpressForce</a>
HelloKidney2	TYMS	-0.287382	<a href="https://github.com/SVAI/HelloKidney2">https://github.com/SVAI/HelloKidney2</a>
...	...		
trimericOGs	HPSE2	0.567236	<a href="https://github.com/SVAI/trimericOGs">https://github.com/SVAI/trimericOGs</a>
BioMarkers.ai	PTGER3	0.59603	<a href="https://github.com/SVAI/Biomarkers.AI">https://github.com/SVAI/Biomarkers.AI</a>
BioMarkers.ai	DMRT2	0.621588	<a href="https://github.com/SVAI/Biomarkers.AI">https://github.com/SVAI/Biomarkers.AI</a>
BioMarkers.ai	UMOD	0.657959	<a href="https://github.com/SVAI/Biomarkers.AI">https://github.com/SVAI/Biomarkers.AI</a>
BioMarkers.ai	KNG1	0.668831	<a href="https://github.com/SVAI/Biomarkers.AI">https://github.com/SVAI/Biomarkers.AI</a>



# Level 2: Therapeutic Options



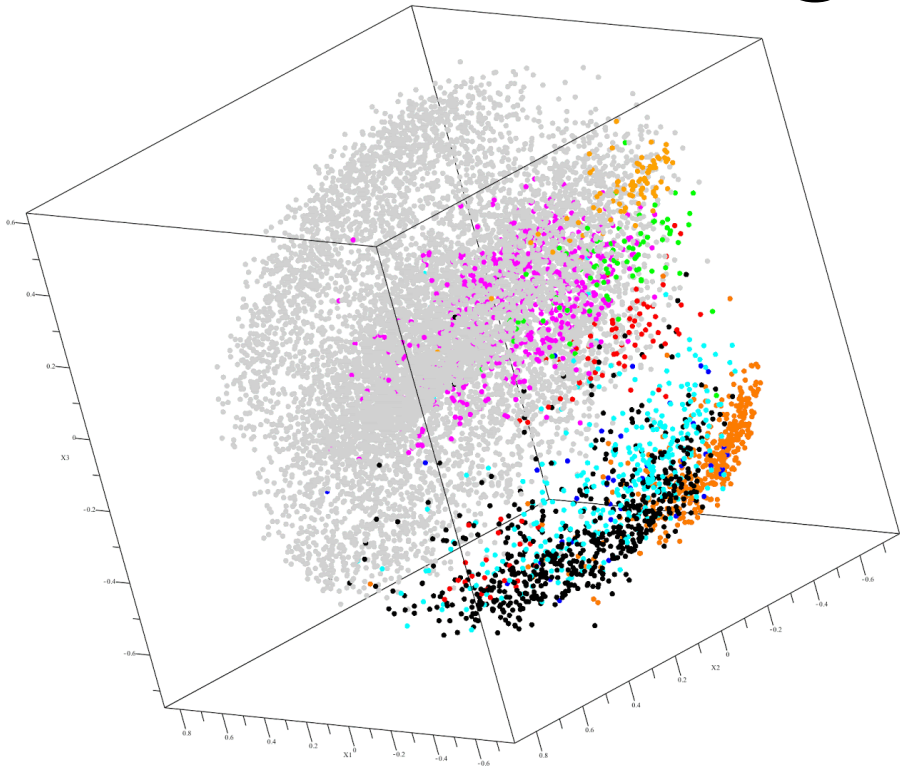
# Level 3: Lab in the Loop

- Travera
  - 20 wells on a tray
  - Each with fresh tumor
  - And a different Treatment in each well
- Rare Cancer Research Foundation
- <https://www.arctoris.com/>
  - Cell Line Labs

# Results

- ✓ Therapeutic Recommendation
  - 2018
  - 2020
- Scoring Metrics
  - Independent Teams discover the same Gene?
  - Independent Teams discover “Industry Standard” Genes?
  - “Genes of Interest” sorted by RNA-seq expression level
- Papers
  - Linking Binary Gene Relationships to Drivers of Renal Cell Carcinoma Reveals Convergent Function in Alternate Tumor Progression Paths
  - Cellular State Transformations Using Deep Learning for Precision Medicine Applications (**GANS – Synthetic Data**)
- General Insights
  - p1RCC Clusters close to Thyroid Cancer
- Analysis Approaches
  - Why did Biomarkers.ai (Bioada) do so much better than the other 16 teams? 19

# Parents, Siblings, Cohort Genetics



<b>KIRP</b>	Cyan
<b>KIRC</b>	Black
<b>KICH</b>	Red
<b>LIHC</b>	Coral
<b>THCA</b>	Magenta
<b>CHOL</b>	Blue
<b>UVM</b>	Orange
<b>ACC</b>	Lime
<b>Others</b>	Light Gray

- Papillary Kidney Cancer and Thyroid Cancer cluster closest together
- Unbeknownst to Quantum Insights, my brother was diagnosed with thyroid cancer a month earlier

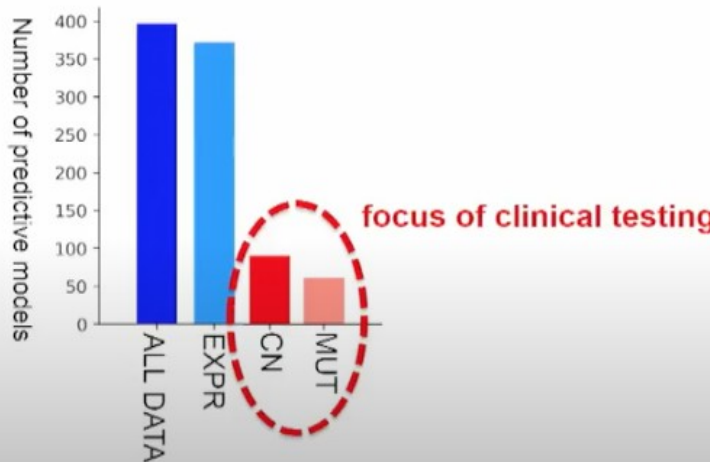
2018 QuantumInsights.io DQC  
20

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- Tumor boards provide personalized advice and pre-qualify patients.
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# Why did BIOada.com do better?

Which 'omic data is most predictive of response?



- **Preparation**
  - Saed Sayad came to the hackathon with a set of favorite tools already in place (BIOada.com) which saved analysis time.
- **Clever way to turn DNA into RNA-seq data**
  - He created a normalized cohort by looking up RNA data on NCBI [GEO](#) (Gene Expression) data) using my DNA data as a key. RNA provided a stronger signal than my DNA data, and ultimately matched my RNA-seq data when it became available.
  - This stronger signal allowed him to use a simpler data analysis technique (LDA- Linear Discriminant analysis) to get clean data separation and so make better predictions.

# Why did BIOada.com do better?

- **Small and focused Team.**
  - “[Can Big Science Be Too Big?](#)” (2019) - papers with few authors tended to report more breakthrough research and papers with many authors tended to confirm existing findings.
- **Finance: Portfolio theory.**
  - Dr. Sayad took on a lot of risk (Using one tool, BIOada.com. Abandoning DNA data, using GEO instead. Using one method, LDA. Using a small team, generating fewer new ideas) and so was likely to either get a big win, or go bust.
    - INTC, CSCO, PYPL, EBAY, **MSFT – BIOada is MSFT**
    - 47%, 103%, 128%, 209%, **2105%** ← Change since 1997
- **Finance: Hackathons are portfolios of Real Options**
  - In that sense, a hackathon can be viewed as a portfolio of [real options](#), and a hackathon “portfolio” has similar risk/return math to that used in financial portfolio construction.
- **Difference from Finance**
  - Patient holds the portfolio! And only one entry needs to win!

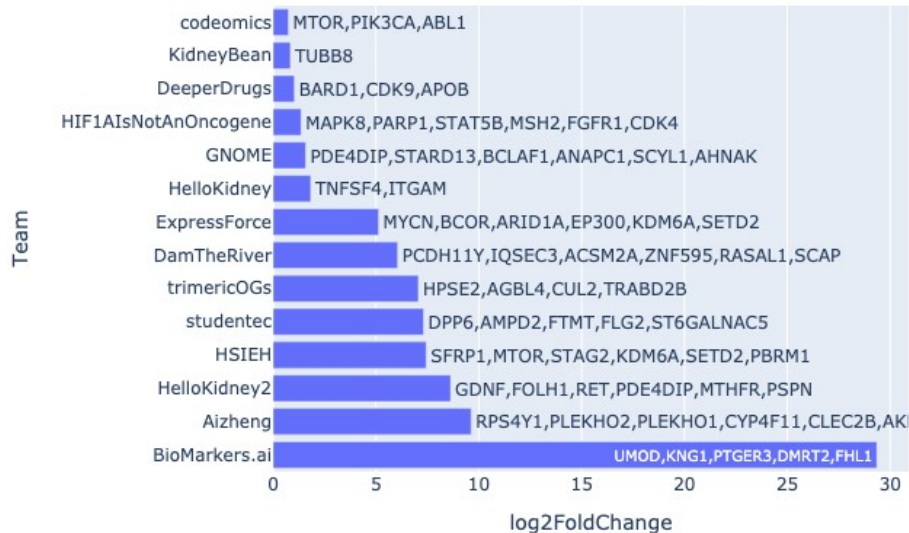
# Statistics – How many teams do we need?

Everest: 1/13

Pro/Photon: 2/13

Hackthon: 1/17

Top 6 Genes



How the data is distributed will tell use how much data we need to decide.

- Normal – Finite mean and variance
  - IQ
  - Weight Height
  - Calorie Consumption
  - Test Scores
  - Car Accidents
  - Mortality Rates
  - Blood Pressure
- Long Tail – Finite mean if you are lucky
  - Wealth – Amazon Employee Party
  - Sales
  - City Populations
  - Pandemics
  - Death in Wars/Terrorist Attacks
  - Word Occurrences in Text
  - Academic Citations
  - Company Sizes



# 2<sup>nd</sup> Opinions, Portfolios & Power Laws

- Cleveland Clinic(\*) - second opinions lead to a diagnosis change in 28% of cases. .. initial diagnosis was either incorrect or incomplete for almost one-third of patients. 72% of treatment plans are modified after a second opinion. (So) even if the initial diagnosis is correct, there may be room for improvement in the recommended course of action.
- Linus Pauling: “The best way to have a good idea is to have lots of ideas.”
- Personal Finance – Here is a Portfolio I created in 1997 for my son and left untouched
  - INTC, CSCO, PYPL, EBAY, MSFT
  - 47%, 103%, 128%, 209%, 2105% ← Change since 1997
- Venture Capital Portfolios - <https://pitchbook.com/profiles/fund/11170-18F#investments>
  - Kleiner IX (formed 1999) – 38 investments: 37 OK, #38 was named GOOGLE
    - “Zero to One” (Peter Thiel)
      - “The biggest secret in venture capital is that the best investment in a successful fund equals or outperforms the entire rest of the fund combined.”
- Power-law distributions - the largest entity is typically bigger, more valuable, or more powerful than all others combined.
- **Do “Second Opinions” have a Power Law Distribution?**

\* <https://www.clinicbyclevelandclinic.com/blog/how-often-are-second-opinions-different/>

# Statistics

Standard of Care

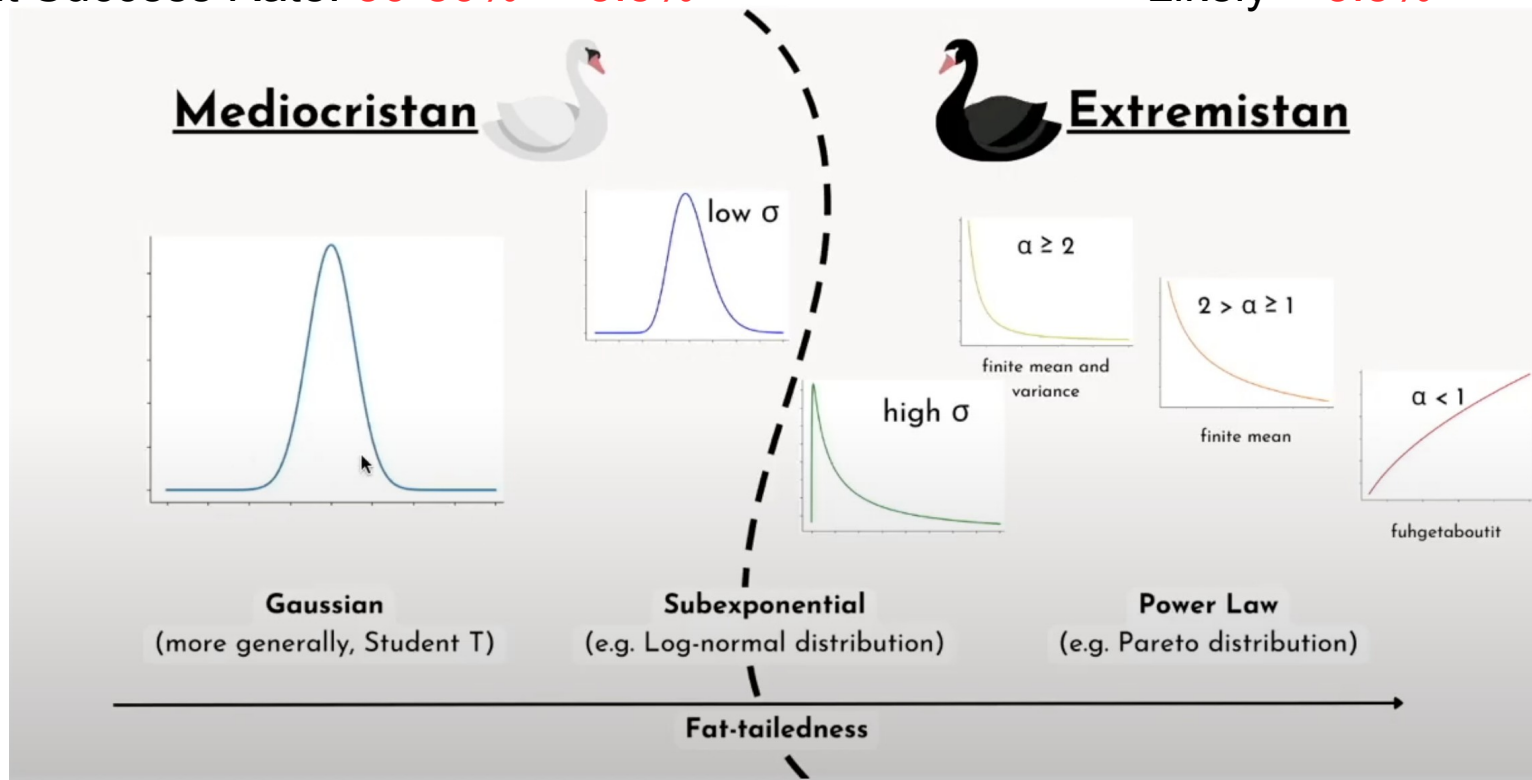
Treatment Success Rate: 30-80%

Onco Clinical Trails

3.5%\*\*

Post Clinical Trials (Hackathons)

Likely < 3.5%



\*\*American Council on Science and Health

<https://www.acsh.org/news/2020/06/11/clinical-trial-success-rates-phase-and-therapeutic-area-14845>

Shaw Talebi - Pareto Power Laws and Fat Tails

# Biomarkers.ai–Genes of Interest

- KNG1 uses alternative splicing to generate two different proteins: High MWt kininogen (HMWK) and MWt kininogen (LMWK). HMWK is essential for blood coagulation and assembly of the kallikrein-kinin system. This might explain my medical history.
  - Got warfarin/coumadin for diagnosis of deep vein thrombosis
  - DVT Symptoms returned. Went back and found: 7 cm mass left kidney, cerebral meningioma and spots in lung.
- Uromodulin (encoded by UMOD; also known as Tamm-Horsfall protein) is the most abundant protein in mammalian urine under normal physiological conditions.
  - UMOD can distinguish Normal Tissue from p1RCC with 100% accuracy.
  - Is UMOD also a good urine-based biomarker for p1RCC?
- FHL1 was an indicator for petrochemical exposure. For a time I worked in chemical refineries and on oil rigs. This might be the source of my somatic mutation.
  - Exposure to benzopyrene and several other agents enhances FHL1 expression

# Patient Centered, Game Elements, Ensemble Learning

## “Patient Centered”

- Patients view themselves as having a “rare disease” that is not served well by cohort analysis. We hope to use sibling and parent genetic data as a "control" in future events.
- Patients themselves host and maintain control of the event and are responsible for providing their own data.
- Data Control allows patients to create a current, longitudinal record over time for each subsequent hackathon as their disease develops.

## “Game Elements”

- Hackathon participants are divided up into teams.
- The Game has “levels” which include diagnosis and therapeutic recommendations.
- Team’s results are “scored” which helps the Patient prioritize future research approaches.
- Scores can be posted on a LeaderBoard, which allows sharing of Research Approaches.

## “Treat Research Teams as formal computational objects”

- Apply an “Ensemble Learning” technique called "bucket of models".
- For each model  $m$  in the bucket:
  - Do  $c$  times: (where ' $c$ ' is some constant)
    - Randomly divide the training dataset into two datasets: A, and B.
    - Train  $m$  with A; Test  $m$  with B
- Select the model that obtains the highest average score

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# Summary

- Rare Cancers: I have one. They aren't researched much. How I deal with it.
- Portfolios, Juries, Parole and Tumor Boards: I do this using Personalized Tumor Boards.
  - Tumor Boards: "A meeting of healthcare professionals that discuss complex cancer cases to determine the best treatment plan for a patient."
  - Insights from two 13 member Tumor Boards I created.
    - EVEREST: "Should Bill participate in the EVEREST Trial".
    - Pro/Photon: "Should Bill use Proton or Photon radiation to treat his Brain Tumor."
- Hackathons: 80 person (genomic) competition between 17 "gamified" Tumor Boards
  - "Result ranking" functions are used to determine who won the game.
- You can help!.

# Where are we headed?

	<b>Before</b>	<b>Now</b>	<b>Future</b>
Actors	Pharma, Research Hospitals	Hackathons (Kaggle)	<b>Automated Tumor Boards</b>
Market	Common Diseases (\$\$\$)	Rare Diseases	Rare Diseases
Tech	Proprietary	Open Source	Open Source
Data	Ring Fenced (HIPAA)	TCGA+Patient Data +GANS	TCGA+Patient Data + GANS+ <b>Open Data</b>
Data	Lab in the Loop	Lab in the Loop	<b>Synthetic Data</b>
Funding	Government+Pharma	Volunteers+Private	Volunteers + <b>AI (“Free”)</b>

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# Acknowledgements

- Tissue: UCSF's Dr. Max Meng and Tasha Lea
- Sequencing: Yale's Dr. Kaya Bilguvar and Christopher Castaldi and UCLA's Dr. Brian Shuch
- Sequencing Experiment Specification and Validation: Mike D'Amour for specifying the sequencing experiment parameters and fastq Validation Process
- 2018 Venue Donation: Salesforce's Steve Tamm and Lisa Ferrier
- 2018 Hackathon Teams
- 2018 Biomarker.ai Lead: Dr. Saed Sayad
- 2018 and 2020 Hackathon Master of Ceremonies: Ben Busby
- 2020 Hackathon: The TRI-con organizer: Kaitlyn Barago of healthtech
- 2020 Hackathon: Research to the People Organizer: Pete Kane
- 2020 Hackathon: "Clemson's 2020 normalized cohort" creators: Reed Bender, Ben Shealy and Benafsh Hussain from Dr. Alex Feltus' group
- 2020 Hackathon: Therapeutic Recommendations: GeneXplain's Dr. Jeannette Koschmann
- 2018 and 2020 Target Identification: QuantumInsights.io's Bernard Chen and Marvin Weinstein
- 2018 Hackathon: sv.ai volunteers: Ryan Leung, Clayton Melina, Lily Vittayarukkul, Hunter Dunbar, Pete Kane, Bill, Dom Jones, Marguerite, David Schachter, Anabelle Tang, Nina Sardesh, Sean Davis


# 2018 p1RCC Hackathon Teams

Team	Members	Summary
<a href="#">Alzheng</a>	Alex Feltus, Ben Shealy, Colin Targonski, Courtney Shearer, Eddie Weill, Ken Matusow, Sufeng Niu, William Poehlman	Model TCGA-RCC tumors as a “time series” across stage
<a href="#">BioMarkers.ai</a>	Peyman Mirtaheri, Saed Sayad, Usman Qazi	Candidate p1RCC Biomarkers and environmental factors influencing expression
cancer-genome-workbench	Betty, rene lopez, Rui, Sarah	Predict/classify a sample cancer type using genetic data with: Unsupervised clustering, Dimensionality reduction, Somatic SNPs, Data exploration
<a href="#">causalnucleotidenetwork</a>	Arkarachai Fungtammasan, Naina Thangaraj, Ola Zalcman, Steve Osazuwa	Variational Autoencoder and tSNE clustering
<a href="#">codeOmics</a>	Daniel Hornburg, Milena Duerrbaum	Biomarkers to precision drugs
<a href="#">DamTheRiver</a>	Andrew Wallace, Christian Clough, Felix Frayman, Matt Callahan, Nandita Damaraju, Pak Yu, Sebastian Nguyen, William Wright	Identification of neo-antigens present within patient P1RCC sequence data

# 2018 p1RCC Hackathon Teams

<a href="#">DeeperDrugs</a>	Andrew Mills, Biter Bilen, Jeff Lam, Lei Tian, Michael D'Amour, Monika Maleszewska, Prasun Mishra, Tahera Zabuawala, XIAOWEI ZHU	Rigorous variant filtering and target pruning
<a href="#">ExpressForce</a>	Amrit Virdee, Maricris Macabeo, Nikhil Balaji, Sofia Medina Ruiz, Yuri Bendana	Netflix for Genes
<a href="#">geviz</a>	Maytas Monsereenusorn, Natnicha Vanitchanant, Navi Tansaraviput, Thanapat Worasaran	Gene Expression Visualization
<a href="#">GNOME</a>	In-Hee Lee, Sek Won Kong	Prioritizing germline and somatic variants potentially associated with p1RCC
<a href="#">HelloKidney</a>	Terje Norderhaug	Autoimmune Clues to Kidney Cancer
<a href="#">HelloKidney2</a>	Clinton Mielke, Robert Van Spyk	Genetic Markers
<a href="#">HIF1AsNotAnOncogene</a>	Eric Danziger, Joshua Bloomstein, Stephanie Kinnunen, Wanlin Zheng	A preliminary case study in EGFR

# 2018 p1RCC Hackathon Teams

<a href="#">KidneyBean</a>	Bea Nguy, Eric Kalosa-Kenyon, James (3), Jay (3), Kallen Schwark, Kandy Nachimuthu, Mabel Furutsuki, Maninder Singh, Marcus Strauss, Rahim Hashim, Sam Rapp, Wessam Sonbol	Drug candidates towards personal medicine
<a href="#">RecausalNucleotideNetworks</a>	Andrew Carroll, Jason Chin, Pi-Chuan Chang, Samantha Zarate	How Effective Are Illumina Methods for BGI-SEQ? <a href="#">20180531 BLOG POST</a>
<a href="#">studentec</a>	Brian Hanley, Rush Tehrani	USING BIGQUERY FOR GENOMIC DATA ANALYSIS
<a href="#">trimericOGs</a>	Christine Kim, Lily Vittayaruskul, Phoebe So, Rohith Krishna, Samson Mataraso, senay yakut	Classifying Tumor Stages based on Structural Variants in Patient Data 

# Final Word

**“If you work on frequent cancers, do randomized trials! If you work on rare cancers—find friends!”**

Olson, TA, Schneider, DT, Brecht, IB, et al.

If you want to help improve rare disease treatment options, contact

Bill ([bill@rarekidneycancer.org](mailto:bill@rarekidneycancer.org))

Pete ([pete@researchtothepeople.org](mailto:pete@researchtothepeople.org))