

Using AI methods to enable clinical trial success

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20240910 – Clinical Trials in Rare Diseases

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Agenda

- *Increasing Clinical Trial success rate by better patient pre qualification
- Tumor boards provide personalized advice and pre-qualify patients.
- Hackathons formalize, scale and tune the tumor board process
- Hackathons can be automated
- Summary
- Final Word

My Motivation as of 2018

- Diagnosed with Papillary Kidney Cancer (pRCC) and a (Brain) Meningioma.
- Standard of Care – pRCC's primary treatment is surgery ("cut and pray")
- Clinical Trials - pRCC has no dedicated trials
 - (pRCC "piggybacked" on clear cell RCC trials.)
- Research - "So far, NO improvement in outcome over the last decade."
 - Slide 5 of Albirges' 2017 papillary RCC presentation

Such is the predicament of most rare disease patients

Quiz Question

- I'd like to do a poll.
- Out of 100 patients in an oncologic clinical trial, how many typically benefit?
 - 5?
 - 10?
 - 20?
 - 40?
 - 80?
 - 90?

Quiz Answer

- I'd like to do a poll.
- Out of 100 patients in an oncologic clinical trial, how many typically benefit?
 - 5?
 - 10?
 - 20?
 - 40?
 - 80?
 - 90?

3.5

3.5% is bad for everybody

- Patients
- Doctors
- Pharma
- I want to increase this is via better patient pre-qualification
- Let's start with the question

What alternatives exist to the clinical trial collaboration structure?

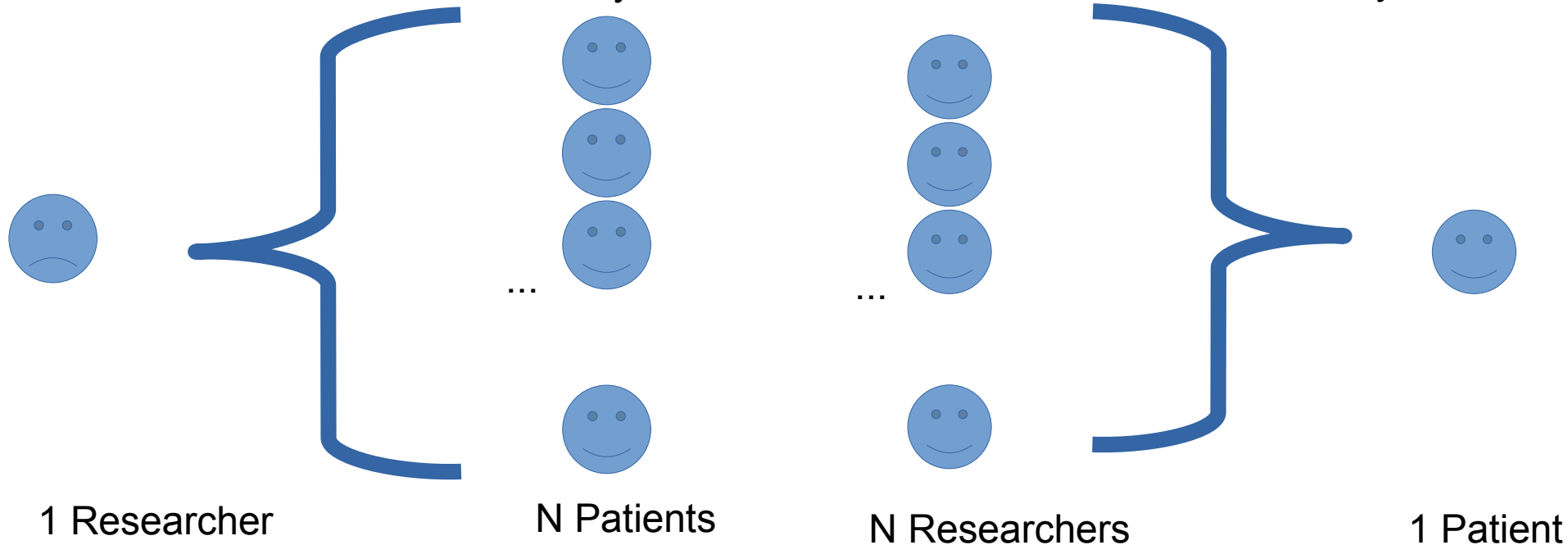
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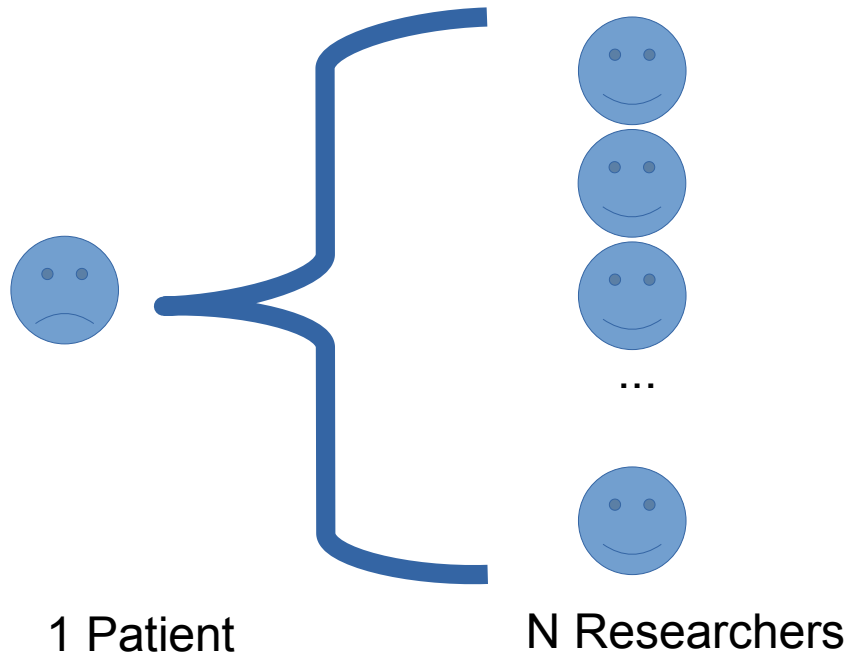
Clinical Trials vs. Tumor Boards

Clinical Trial: one Researcher many Patients

Tumor Board: one Patient many Researchers



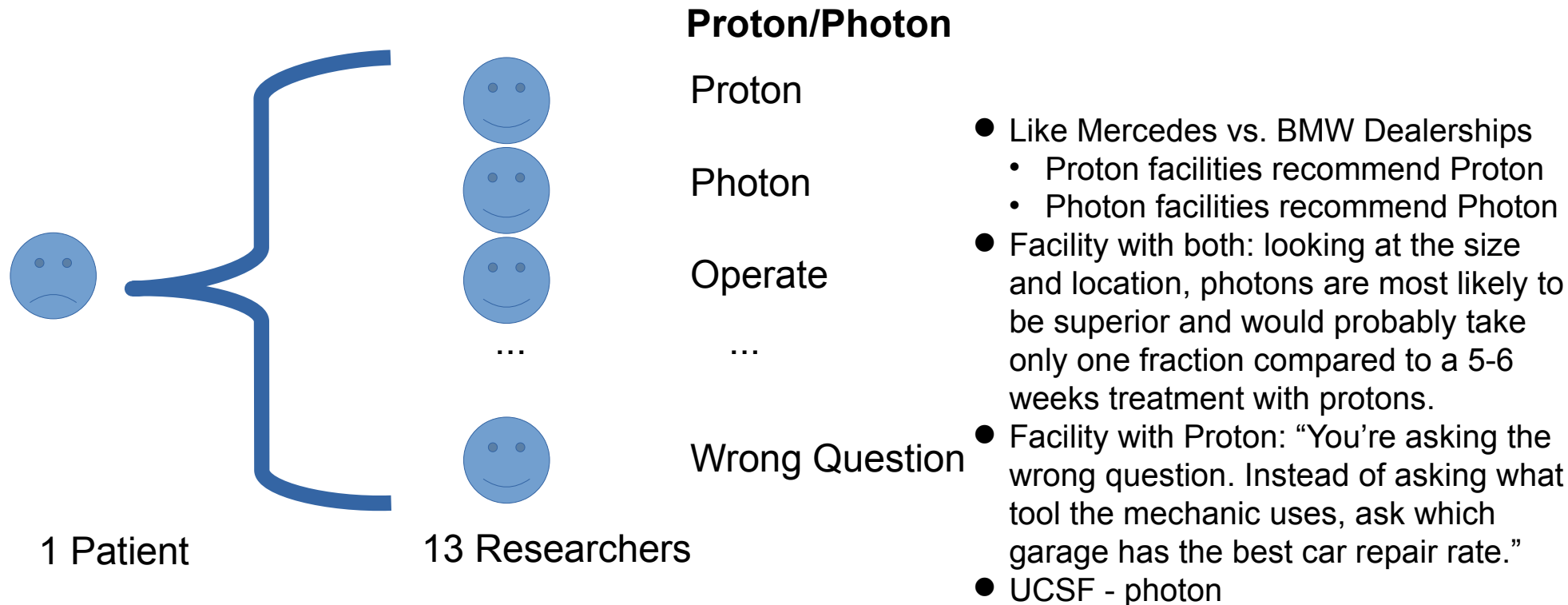
Tumor Boards and Ensemble Reasoning



- 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.331.6018.69>

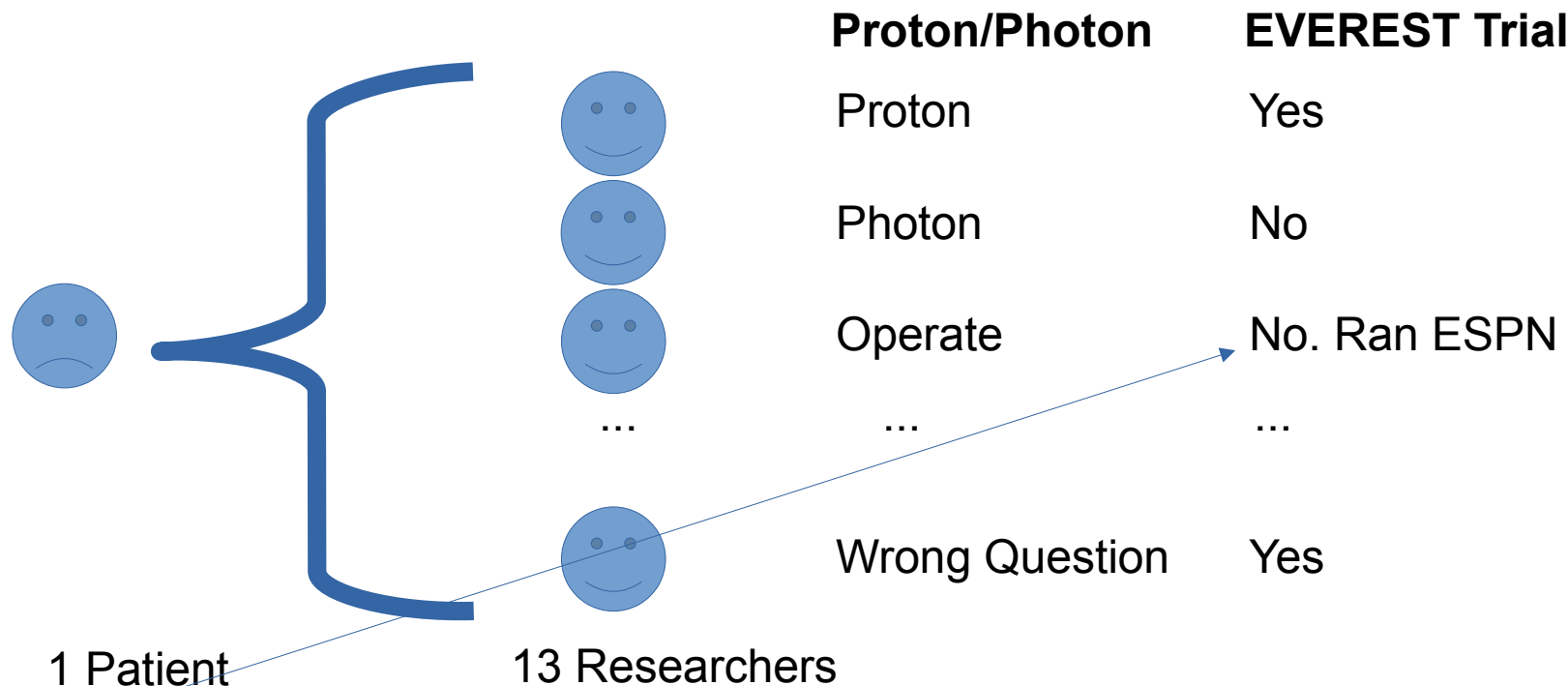
Tumor Boards: Which is better Proton or Photon?



- Ensemble Reasoning

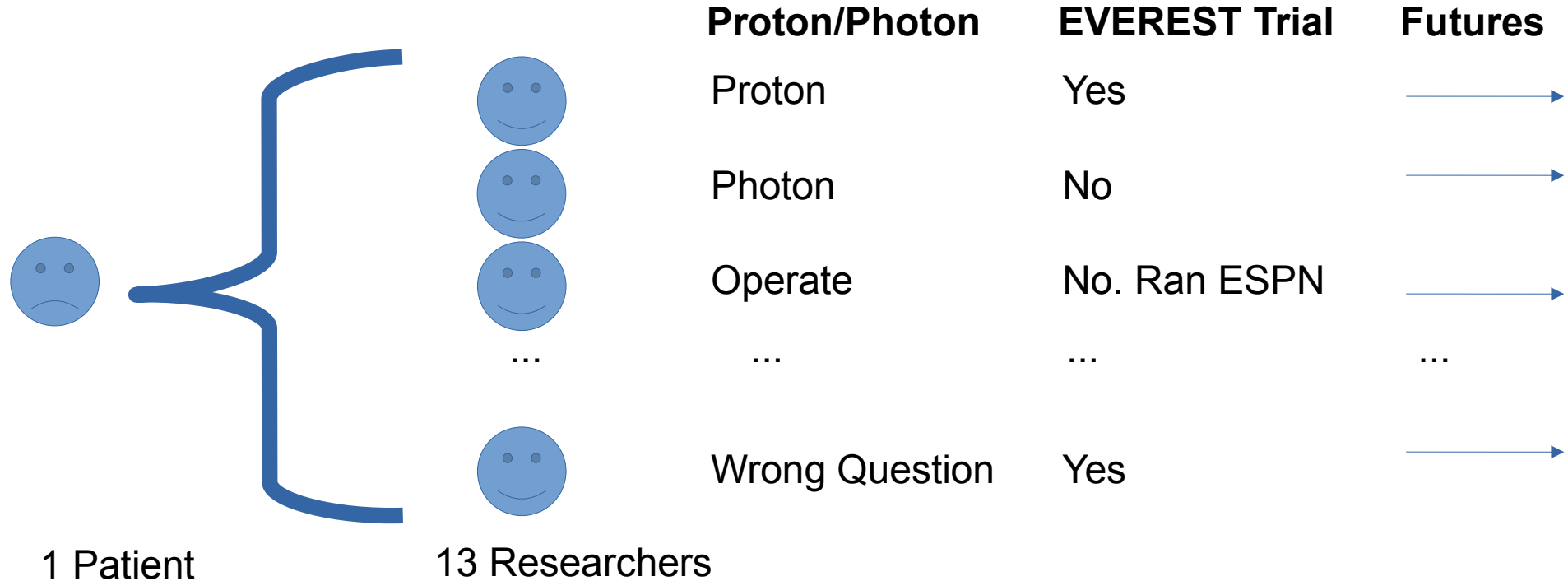
- “The best way to have a good idea is to have lots of ideas.” - Linus Pauling

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!!!

Tumor Boards project alternate Futures



- Ensemble Reasoning

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

- Note: My EVEREST Clinical Trial Enrollment likely would not have increased Success Rate!!! 12

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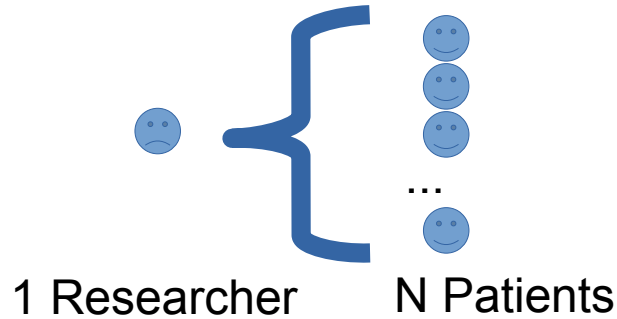
2018 p1RCC Hackathon Teams



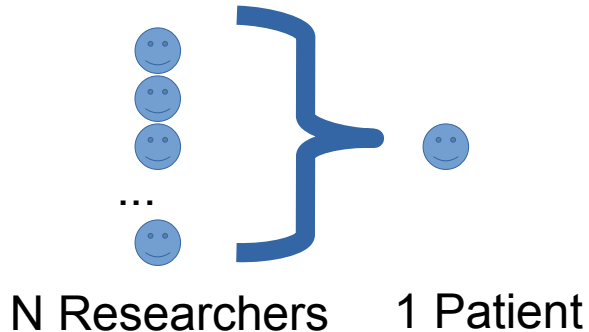
80 People (some Remote) formed 17 Teams (50 pictured)¹⁴

Clinical Trials, Tumor Boards and Hackathons

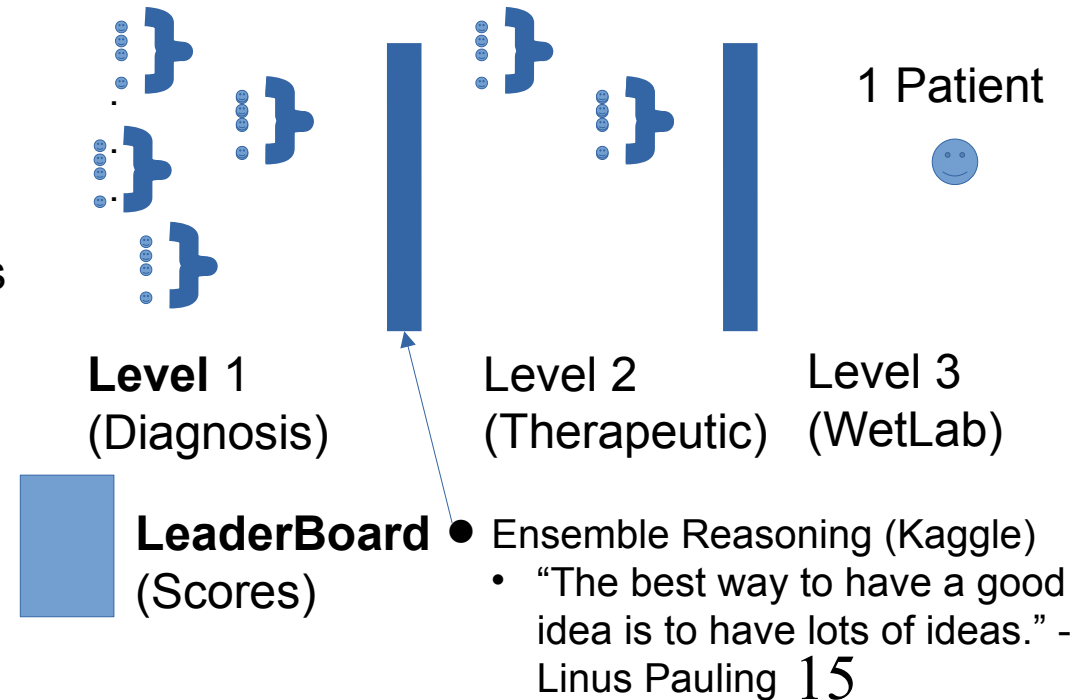
Clinical Trial: one Researcher many Patients



Tumor Board: one Patient many Researchers

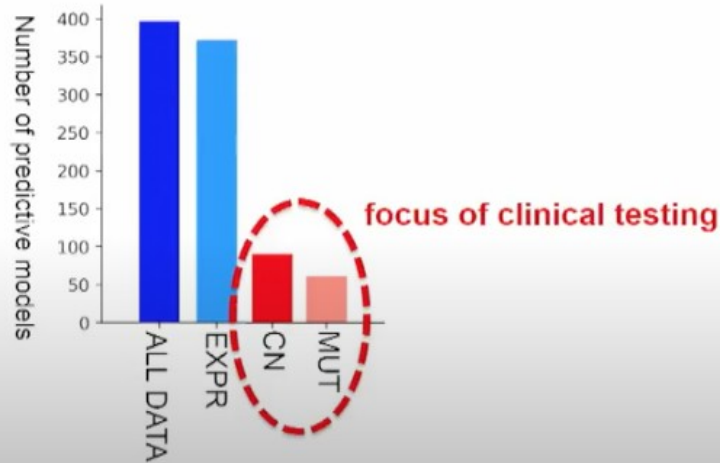


Hackathon: one Patient many TumorBoards (Teams)



Clinical vs. Research Data

Which 'omic data is most predictive of response?



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
- Dental Records

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

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			
trimericOGs	AGBL4	ARIDA1	CUL-2	HPSE2	LAMC-1	SK3	TRABD2B	...
DeeperDrugs	BARD1	APOB	CDK9	TTRAP				
GNOME	BARD1	PDE4DIP	AHNAK	ANAPC1	BCLAF1	DNAJ27	PABPC1	...
HelloKidney2		PDE4DIP	FOLH1	GDNF	MTHFR	PFKP	PSMA	...
codeomics						MTOR	PIK3CA	...
HSIEH	SETD2	NF2	BAP1	KDM6A	PBRM1	MTOR	PIK3CA	...
ExpressForce	SETD2	NF2	BAP1	KDM6A	PBRM1	FGFR1	ARID1A	...
HIF1AIsNotAnOncogene						FGFR1	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?

OPEN

Linking Binary Gene Relationships to Drivers of Renal Cell Carcinoma Reveals Convergent Function in Alternate Tumor Progression Paths

William L. Poehlman¹, James J. Hsieh^{1,2}  & F. Alex Feltus¹

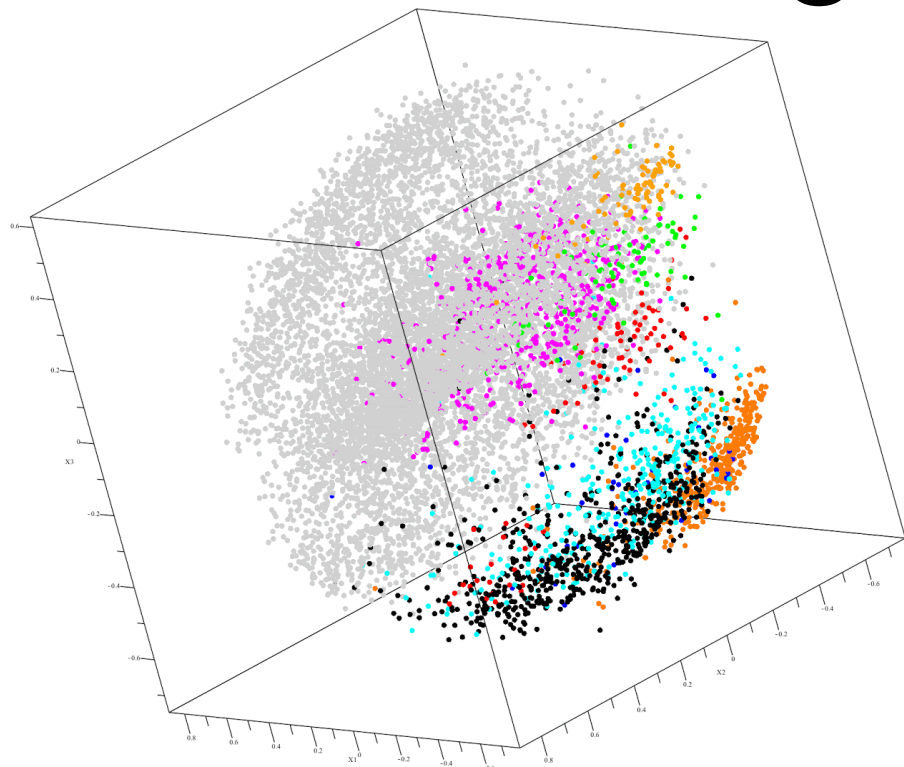
Received: 25 October 2018

Accepted: 28 January 2019

Published online: 27 February 2019

Renal cell carcinoma (RCC) subtypes are characterized by distinct molecular profiles. Using RNA expression profiles from 1,009 RCC samples, we constructed a condition-annotated gene coexpression network (GCN). The RCC GCN contains binary gene coexpression relationships (edges) specific to conditions including RCC subtype and tumor stage. As an application of this resource, we discovered RCC GCN edges and modules that were associated with genetic lesions in known RCC driver genes, including VHL, a common initiating clear cell RCC (ccRCC) genetic lesion, and PBRM1 and BAP1 which are early genetic lesions in the Braided Cancer River Model (BCRM). Since ccRCC tumors with PBRM1 mutations respond to targeted therapy differently than tumors with BAP1 mutations, we focused on ccRCC-specific edges associated with tumors that exhibit alternate mutation profiles: VHL-PBRM1 or VHL-BAP1. We found specific blends molecular functions associated with these two mutation paths. Despite these mutation-associated edges having unique genes, they were enriched for the same immunological functions suggesting a convergent functional role for alternate gene sets consistent with the BCRM. The condition annotated RCC GCN described herein is a novel data mining resource for the assignment of polygenic biomarkers and their relationships to RCC tumors with specific molecular and mutational profiles.

Parents, Siblings, Cohort Genetics

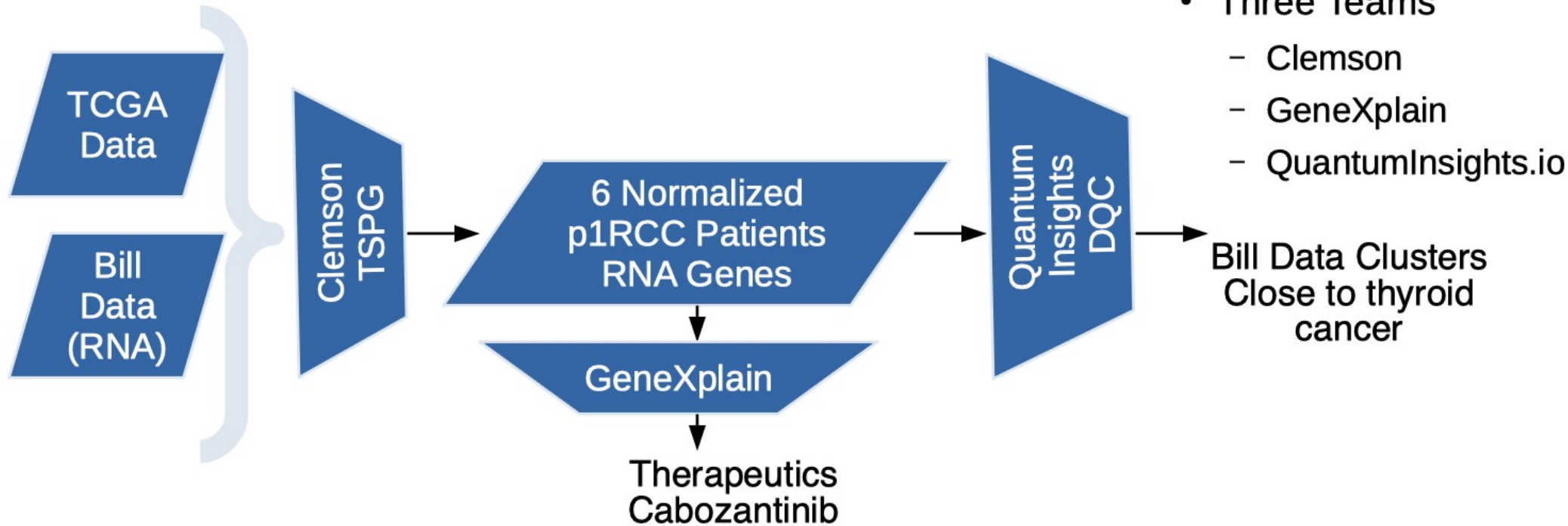


KIRP	Cyan
KIRC	Black
KICH	Red
LIHC	Coral
THCA	Magenta
CHOL	Blue
UVM	Orange
ACC	Lime
Others	Light Gray

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

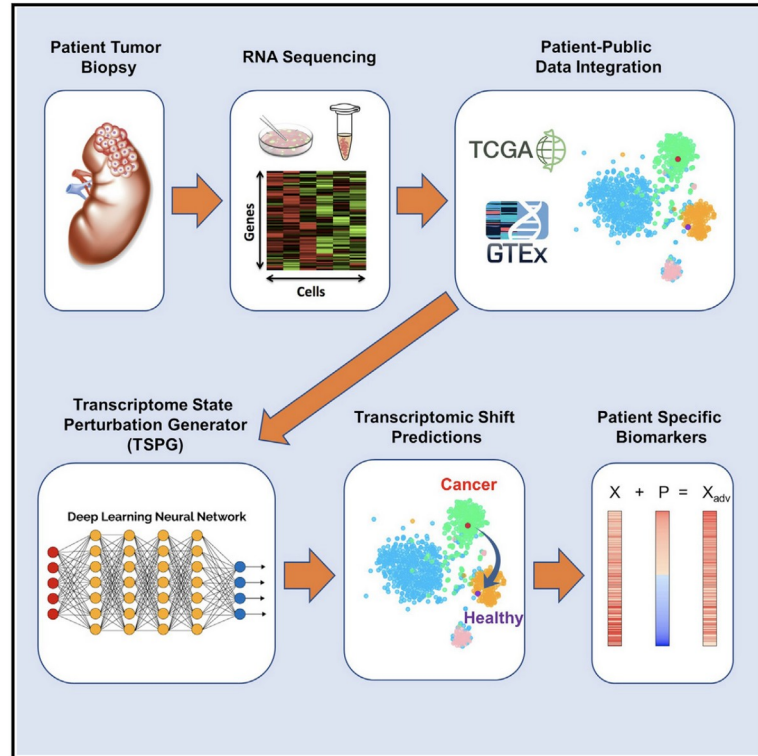
2018 QuantumInsights.io DQC
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2020 p1RCC RNA Hackathon Process



Cellular State Transformations Using Deep Learning for Precision Medicine Applications

Graphical Abstract



Highlights

- We present the Transcriptome State Perturbation Generator (TSPG) algorithm.

Authors

Colin Targonski, M. Reed Bender, Benjamin T. Shealy, Benafsh Husain, Bill Paseman, Melissa C. Smith, F. Alex Feltus

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In Brief

Cells express genes in unique combinations that enable distinct functions. Using machine learning, we present an algorithm that takes a source gene expression snapshot and learns how to change it to mimic a target snapshot. We applied the Transcriptome State Perturbation Generator algorithm to learn which genes have changed in a single patient's tumor relative to a normal tissue sample. By knowing which gene expression changes are required to leave a normal state in a single person, it is possible to design therapeutic strategies tailored for that patient.

GAN
Generation

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

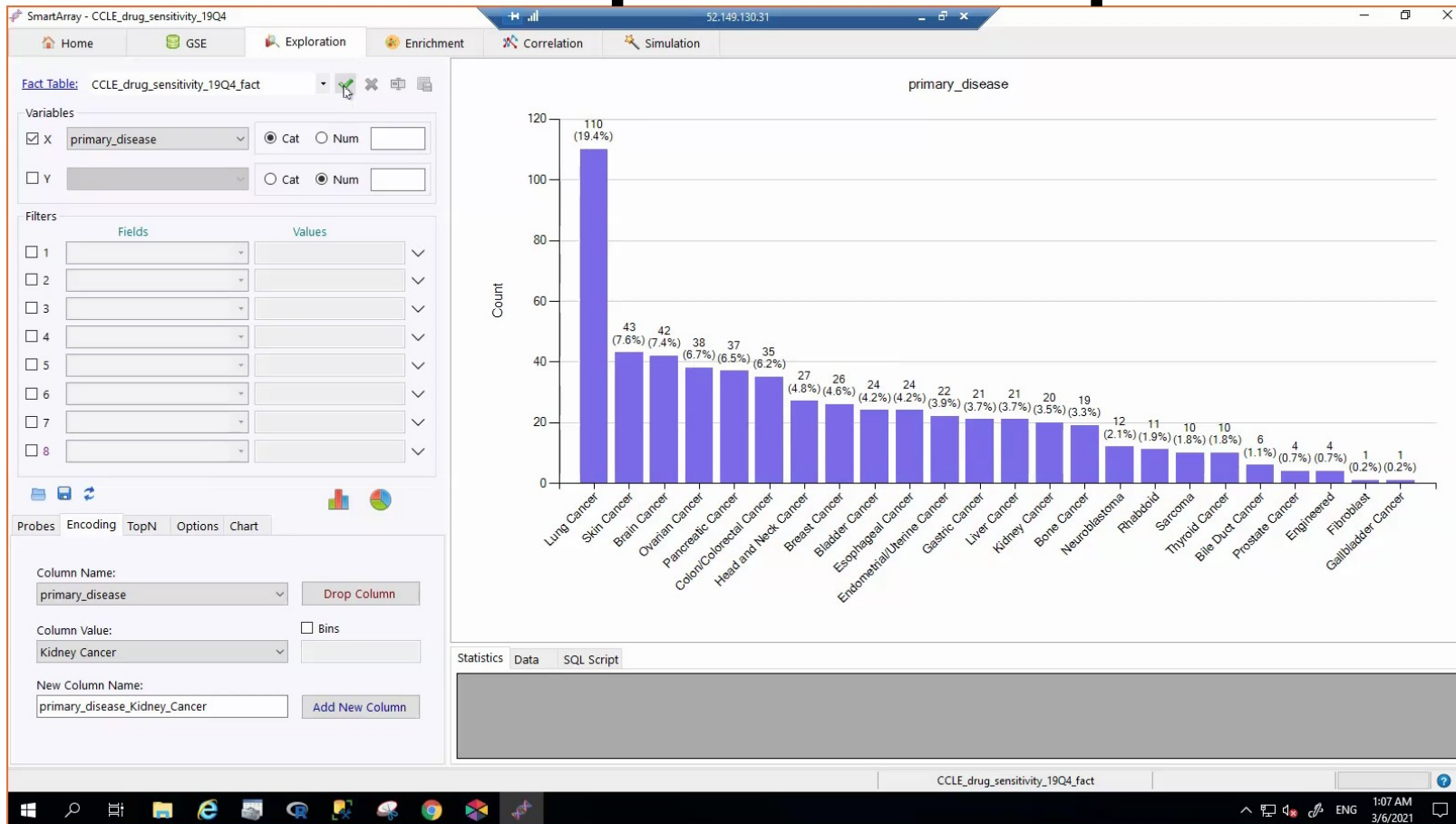
What is the best way to reconcile (judge) results?

- **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	https://github.com/SVAI/studentec
BioMarkers.ai	FHL1	-0.370446	https://github.com/SVAI/Biomarkers.AI
HelloKidney2	TAS2R19	-0.363179	https://github.com/SVAI/HelloKidney2
ExpressForce	TERT	-0.358329	https://github.com/SVAI/ExpressForce
HelloKidney2	TYMS	-0.287382	https://github.com/SVAI/HelloKidney2
...	...		
trimericOGs	HPSE2	0.567236	https://github.com/SVAI/trimericOGs
BioMarkers.ai	PTGER3	0.59603	https://github.com/SVAI/Biomarkers.AI
BioMarkers.ai	DMRT2	0.621588	https://github.com/SVAI/Biomarkers.AI
BioMarkers.ai	UMOD	0.657959	https://github.com/SVAI/Biomarkers.AI
BioMarkers.ai	KNG1	0.668831	https://github.com/SVAI/Biomarkers.AI

Level 2: Therapeutic Options



Level 3: Wetlab (TBD)

- 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

Biomarkers.ai - 2018

- 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

Why did BIOada.com do better?

- Saed Sayad came to the hackathon with a set of favorite tools already in place (BIOada.com) which saved analysis time.
- 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.
- His team was small and focused. Note that a 2019 article entitled “[Can Big Science Be Too Big?](#)” posited that papers with few authors tended to report more breakthrough research and papers with many authors tended to confirm existing findings.
- His outsized results are supported by 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.
- 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.

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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.

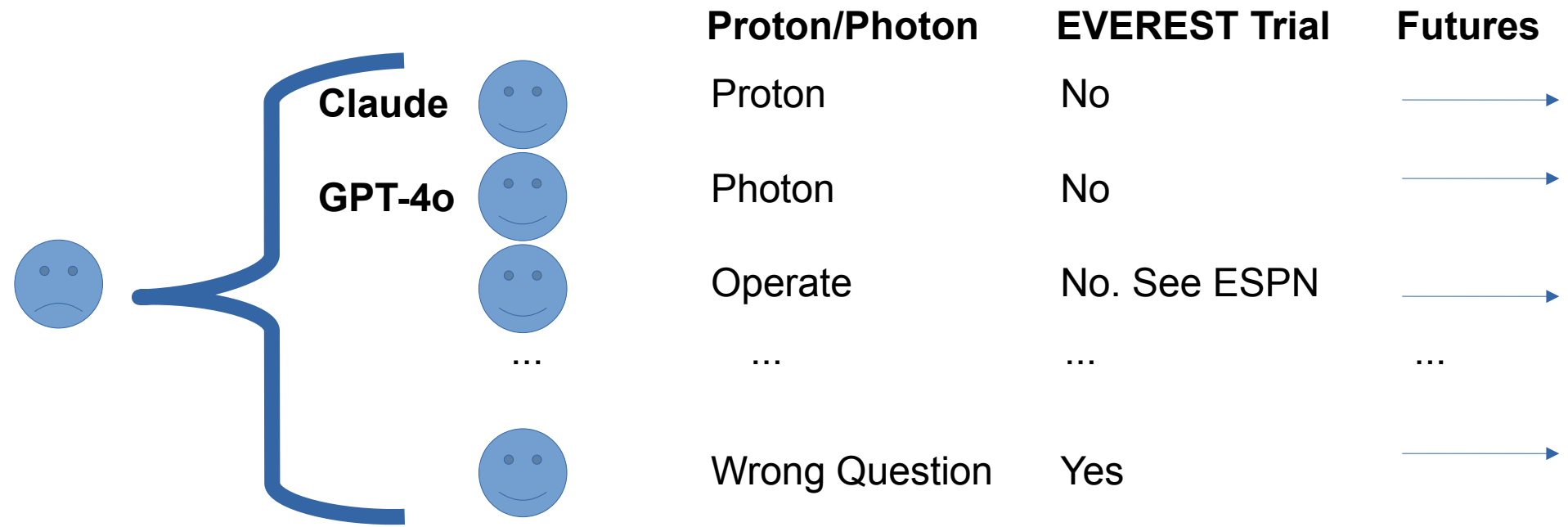
“Treat Research Teams as formal computational objects”

- 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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Since 20240423 - Tumor Board Augmentation!!!!



1 Patient

13->15 Researchers – Welcome Claude and GPT-4o to the Team!

- Ensemble Reasoning
 - “The best way to have a good idea is to have lots of ideas.” - Linus Pauling
- Note: My Clinical Trial Enrollment in EVEREST likely would not have increased success rate!!!

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ChatGPT on p1RCC

- Question: What adjuvant clinical trial is more promising for papillary RCC and why?
- Answer: The most promising adjuvant clinical trials for papillary renal cell carcinoma (pRCC) are those **involving immune checkpoint inhibitors**, particularly given the success of these agents in renal cell carcinoma (RCC) overall, including ongoing research in non-clear cell subtypes like pRCC. Here's why:

- 1. Mechanism of Action:

- **Immune checkpoint inhibitors** (e.g., pembrolizumab, nivolumab) work by unleashing the immune system to attack cancer cells. This approach has shown robust efficacy in various cancers, including RCC, by targeting the PD-1/PD-L1 pathway, which tumors use to evade immune detection.

- 2. Clinical Trial Success in RCC:

- **KEYNOTE-564 Trial:** This trial focused on pembrolizumab in high-risk RCC after surgery. The trial demonstrated a significant improvement in disease-free survival compared to placebo. While this trial predominantly involved clear cell RCC, the success of immune checkpoint inhibitors in RCC provides a strong rationale for their use in other subtypes like pRCC.
- **CHECKMATE Trials:** Trials involving nivolumab (with or without ipilimumab) in RCC have shown impressive results, particularly in the metastatic setting, leading to interest in their potential as adjuvant therapies.

• 2014 advice: "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." 31

ChatGPT on p1RCC (continued)

- 3. Emerging Evidence in Non-Clear Cell RCC:
 - Although most of the robust data comes from trials focused on clear cell RCC, there is growing evidence and ongoing trials assessing the efficacy of immune checkpoint inhibitors in non-clear cell RCC, including pRCC. This is particularly promising given the challenges of treating non-clear cell subtypes with traditional therapies.
- 4. Limited Efficacy of Alternatives:
 - **VEGF-Targeted Therapies:** Trials like ASSURE and S-TRAC showed limited benefits and significant toxicity with VEGF-targeted agents like sunitinib in the adjuvant setting, particularly in non-clear cell RCC.
 - **mTOR Inhibitors:** Evidence from trials like ESPN suggests that mTOR inhibitors like everolimus may be less effective, especially in the first-line setting for metastatic RCC, raising concerns about their utility in the adjuvant setting.

Conclusion:

- Adjuvant trials incorporating immune checkpoint inhibitors are currently the most promising for papillary RCC. This is due to the strong evidence of efficacy in RCC overall, the mechanism of action that is effective across different tumor types, and the emerging interest in applying these agents to non-clear cell RCC subtypes. As research progresses, these trials may offer the best chance of reducing recurrence and improving outcomes in patients with papillary RCC.
- 2014 advice: "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." 32

Claude on p1RCC

- Question: What adjuvant clinical trial is more promising for papillary RCC and why?
- When considering adjuvant clinical trials for papillary renal cell carcinoma (pRCC), it's important to note that research in this area is ongoing, and the landscape can change rapidly. However, I can provide some insight into promising directions based on recent research and trials.
- One of the more promising adjuvant clinical trials for papillary RCC is the KEYNOTE-564 trial, which, while not specifically designed for papillary RCC, has shown promising results that may be applicable to this subtype. Here's why it's considered promising:
 - 1. Immunotherapy approach: KEYNOTE-564 uses pembrolizumab, an immune checkpoint inhibitor. Immunotherapy has shown promise in various RCC subtypes, including papillary RCC.
 - 2. Broad inclusion: While primarily focused on clear cell RCC, the trial included a subset of non-clear cell RCC patients, which encompasses papillary RCC.
 - 3. Positive results: The trial showed significant improvement in disease-free survival in the overall population, which is encouraging for potential application to papillary RCC.
- 2014 advice: "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."

Claude on p1RCC (continued)

- 4. Targeted therapy limitations: Traditional targeted therapies like everolimus (used in the EVEREST trial) have shown limited efficacy in papillary RCC, making immunotherapy a potentially more promising approach.
- 5. Molecular basis: Papillary RCC, especially type 2, often has genomic alterations that might make it more responsive to immunotherapy.
- 6. Unmet need: Papillary RCC has historically had fewer treatment options, making any potentially effective adjuvant therapy particularly valuable.
- However, it's crucial to note that while KEYNOTE-564 shows promise, trials specifically designed for papillary RCC are needed. The PAPMET trial, though not an adjuvant trial, has provided valuable insights into treating metastatic papillary RCC, which could inform future adjuvant approaches.
- Other ongoing trials, such as those exploring combinations of immunotherapies or targeted therapies specifically in non-clear cell RCC populations, may also yield promising results for papillary RCC in the adjuvant setting.
- In conclusion, while KEYNOTE-564 shows promise that could extend to papillary RCC, the field is rapidly evolving. The most promising approach may emerge from trials specifically designed for papillary RCC or from further subgroup analyses of broader RCC trials. It's always best to consult with oncologists and keep an eye on the latest clinical trial results for the most up-to-date information.
- 2014 advice: "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."

ChatGPT on Proton/Photon

Question: What radiation treatment type, proton or photon, is better for treatment of a brain meningioma and why?

- Answer: ...
- Proton Therapy ... Best For:
 - Tumors Near Critical Structures: When a meningioma is located near critical structures like the optic nerves, brainstem, or other vital areas, proton therapy's precision in limiting radiation to surrounding healthy tissues can be highly beneficial.
 - Patients Requiring High Radiation Doses: Proton therapy may allow for higher doses to the tumor while minimizing the dose to adjacent tissues, potentially improving control of the tumor while reducing side effects.
- Photon Therapy ... Best For:
 - Widespread Use: For patients who do not have access to proton therapy or where cost is a significant concern, photon therapy remains an effective and well-established treatment.
 - Proven Track Record: Photon therapy, especially when using advanced techniques like IMRT, is effective for many patients with brain meningiomas, with well-documented outcomes
- Conclusion:
- **Proton therapy is often considered the better option** for treating brain meningiomas, particularly when the tumor is located near critical structures or when minimizing radiation exposure to healthy brain tissue is a priority. The precision of proton therapy in delivering radiation directly to the tumor while sparing nearby healthy tissue makes it an attractive option for these cases.
- However, photon therapy remains a highly effective treatment and is more widely available. If access to proton therapy is limited, or if the meningioma is not located near critical structures, photon therapy may still be a suitable option, especially when advanced techniques like IMRT are employed.

Claude on Proton/Photon

Question: What radiation treatment type, proton or photon, is better for treatment of a brain meningioma and why?

Answer: ...

When considering radiation treatment for brain meningiomas, both proton therapy and photon therapy (conventional radiation therapy) can be effective. However, proton therapy is often considered advantageous for treating brain meningiomas for several reasons:

1. Precision and dose distribution: Proton therapy offers superior dose distribution compared to photon therapy. Protons have a characteristic called the Bragg peak, which allows them to deposit most of their energy at a specific depth in the tissue. This means: Higher dose to the tumor and Less radiation to surrounding healthy brain tissue
2. Reduced side effects: Due to the more precise targeting, proton therapy typically results in fewer side effects. This is particularly important for brain tissue, which is highly sensitive to radiation damage.
3. Better for critical structures: Meningiomas are often located near critical brain structures. Proton therapy can better avoid these structures, potentially preserving function.
4. Long-term outcomes: Reduced radiation to healthy tissue may lead to better long-term cognitive outcomes and quality of life.
5. Retreatment possibility: If retreatment is needed in the future, the lower overall radiation exposure from initial proton therapy makes this safer and more feasible.
6. Large or irregularly shaped tumors: Proton therapy can be particularly beneficial for large or irregularly shaped meningiomas, as it can conform to the tumor shape more precisely.
7. Pediatric cases: For younger patients, reducing long-term radiation effects is crucial, making proton therapy particularly advantageous.

Claude on Proton/Photon (cont'd)

- However, it's important to note:
- Availability: Proton therapy is less widely available and often more expensive than photon therapy.
- Case-specific factors: The choice between proton and photon therapy should be made on a case-by-case basis, considering factors like tumor location, size, and patient-specific characteristics.
- Expertise: The effectiveness of either treatment also depends on the expertise of the treatment team.
- While proton therapy offers these advantages, photon therapy techniques like Intensity-Modulated Radiation Therapy (IMRT) have also advanced significantly and can be very effective for many meningioma cases.
- In conclusion, while **proton therapy often has advantages for treating brain meningiomas**, the best choice depends on individual circumstances and should be made in consultation with a radiation oncologist who can consider all relevant factors.

20220824 - maastro.nl - Dr Lambin, I have a meningioma (below) inaccessible by surgery. I glanced at your 2016 paper and was hoping that your current software recommends treatment type for cases like mine.

Dr. Philippe Lambin - we do not have a decision support for this specific question I suggest you ask the question to Dr Eekers she does both I suspect the answer will come from a treatment planning with protons compared to a planning with photons. If there is no significant difference I would go to photons (cheaper).

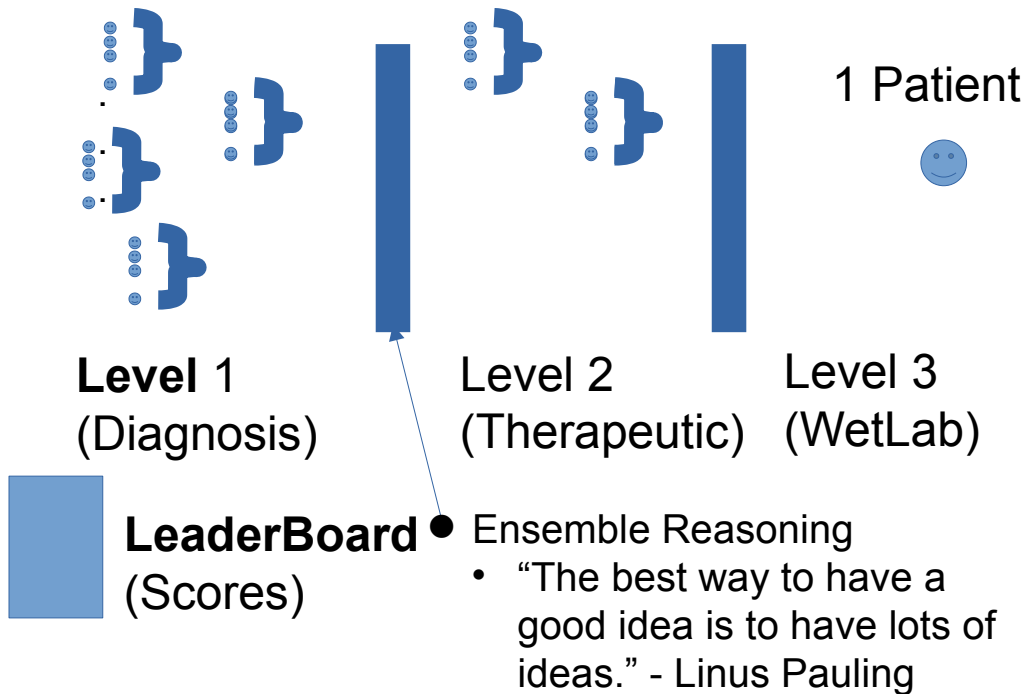
Dr. Danielle Eekers - I agree with dr Lambin that a plan comparison would answer this question. In the Netherlands reimbursement is only possible if there is a dosimetric reduction of $\geq 5\%$ to the supratentorial brain and/or hippocampi after a plan comparison. But looking at the size and location, **photons are most likely to be superior and would probably take only one fraction compared to a 5-6 weeks treatment with protons.**

Review and Next Steps

- 2014 EVEREST (NCT01120249) Clinical Trial
- (< 2018) Traditional
 - $R \rightarrow P+$ Clinical Trials - One Researcher, many Patients
 - $P \leftarrow R+$ Tumor Boards - One Patient, many Researchers
- (2018) Patient Directed manual Tumor Boards
 - $(P \leftarrow R+)+$ Gamified Hackathon (Kaggle) - Competing Human Tumor Boards
- (2024) Patient Directed semi-automated Tumor Boards
 - $P \leftarrow (R \mid \text{llm})+$ Tumor Boards - One Patient, many Researchers and LLMs
- Next
 - $(P \leftarrow (R \mid \text{llm})+)+$ Automated Hackathon - **Collaborating** LLM Agents
 - Apparently, human tumor boards spend a lot of time trying to understand one another.
- Other?
 - RareBench: Can LLMs Serve as Rare Diseases Specialists? - [pdf](#)
 - CORAL: Expert-Curated Oncology Reports to Advance Language Model Inference
 - RAFT: Adapting Language Model to Domain Specific RAG

Next Gen approaches to automate data sharing and research

Now: Competition (**Gamification**)



Next: Automation

- Process – Basically, Hackathons are multi-armed clinical trials for research processes.
 - Scale Hackathons up and make them faster.
 - Automate creation of Hackathon variants.
- Researcher(s) → LLM Agent team members
 - Chatbot → ResearchBot
- Patient(s) → LLM Agent Digital Twins
 - HIPAA – Not an issue for me
 - Need to do better later
 - EHR → DigitalTwin
 - Need to Represent Time Well
 - Integrate Genomics/Radiology later
 - Diagnosis vs hallucinations
- Data → Genomic GANS for rare diseases

Next Case: Prostate

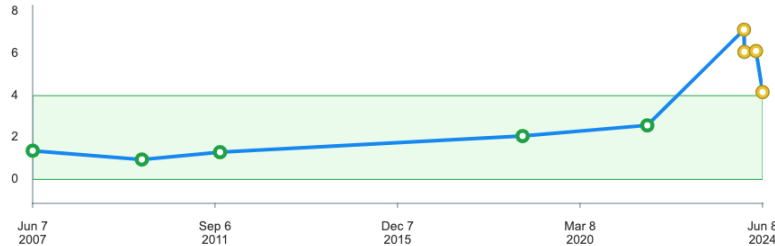
Chance of Cancer

PSA - ??%

MRI – 50%

ExoDX – 33.74%

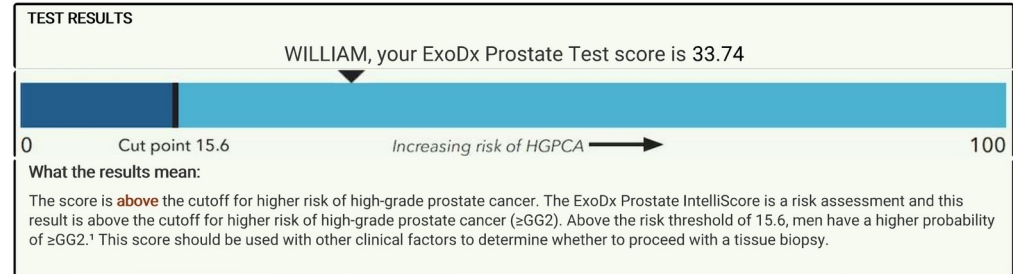
Prostatic Specific Antigen (PSA)
Normal range: 0.00 - 4.00 ng/mL



Data table ^

Date	Value	Normal Range
Jun 8, 2024	4.17 ng/mL High	0 - 4 ng/mL
Apr 13, 2024	6.13 ng/mL High	0 - 4 ng/mL
Jan 5, 2024	6.09 ng/mL High	0 - 4 ng/mL
Jan 2, 2024	7.15 ng/mL High	0 - 4 ng/mL
Oct 1, 2021	2.58 ng/mL	0 - 4 ng/mL

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Prostatitis, or inflammation of the prostate gland, can be caused by a number of factors, including: [🔗](#)

- Bacteria: Bacteria from the rectum or infected urine can spread to the prostate. Acute bacterial prostatitis is often caused by common bacteria strains, and can be spread from other parts of the urinary or reproductive systems. [🔗](#)

Agenda

- Increasing Clinical Trial success rate by better patient pre qualification
- Tumor boards provide personalized advice and pre-qualify patients.
- Hackathons formalize, scale and tune the tumor board process
- Hackathons can be automated
- *Summary
- Final Word

Summary

- I am not interested in cancer researchers' tools.
 - They can use their tools better than I.
- I am not interested developing new tools for cancer researchers.
 - There are better tool developers than I.
- I am interested in “Improving how Cancer Research Improves”
- I believe that Innovative use of Tumor Boards is one way to get faster improvement.

Agenda

- Increasing Clinical Trial success rate by better patient pre qualification
- Tumor boards provide personalized advice and pre-qualify patients.
- Hackathons formalize, scale and tune the tumor board process
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- Summary
- *Final Word

Final Word

An obvious point needs to be made explicitly here. Though I contributed data on the front end of the process and did a few SQL table joins and sorts on the back end of the process, NONE of the biology is my work. It is the work of the many volunteer researchers who spent many hours exploring my data on my behalf. Thank You.

“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. Rare tumors: a different perspective on oncology. In: Schneider, DT, Brecht, IB, Olson, TA, Ferrari, A, eds. Rare Tumors in Children and Adolescents. Berlin: Springer; 2012: 3–15.

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 Vittayarukskul, Hunter Dunbar, Pete Kane, Bill, Dom Jones, Marguerite, David Schachter, Anabelle Tang. Nipa Sardesh, Sean Davis


2018 p1RCC Hackathon Teams

Team	Members	Summary
Alzheng	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
BioMarkers.ai	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
causalnucleotidenetwork	Arkarachai Fungtammasan, Naina Thangaraj, Ola Zalcman, Steve Osazuwa	Variational Autoencoder and tSNE clustering
codeOmics	Daniel Hornburg, Milena Duerrbaum	Biomarkers to precision drugs
DamTheRiver	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

DeeperDrugs	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
ExpressForce	Amrit Virdee, Maricris Macabeo, Nikhil Balaji, Sofia Medina Ruiz, Yuri Bendana	Netflix for Genes
geviz	Maytas Monsereenusorn, Natnicha Vanitchanant, Navi Tansaraviput, Thanapat Worasaran	Gene Expression Visualization
GNOME	In-Hee Lee, Sek Won Kong	Prioritizing germline and somatic variants potentially associated with p1RCC
HelloKidney	Terje Norderhaug	Autoimmune Clues to Kidney Cancer
HelloKidney2	Clinton Mielke, Robert Van Spyk	Genetic Markers
HIF1AlsNotAnOncogene	Eric Danziger, Joshua Bloomstein, Stephanie Kinnunen, Wanlin Zheng	A preliminary case study in EGFR

2018 p1RCC Hackathon Teams

KidneyBean	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
RecausalNucleotideNetworks	Andrew Carroll, Jason Chin, Pi-Chuan Chang, Samantha Zarate	How Effective Are Illumina Methods for BGI-SEQ? 20180531 BLOG POST
studentec	Brian Hanley, Rush Tehrani	USING BIGQUERY FOR GENOMIC DATA ANALYSIS
trimericOGs	Christine Kim, Lily Vittayarukkul, Phoebe So, Rohith Krishna, Samson Mataraso, senay yakut	Classifying Tumor Stages based on Structural Variants in Patient Data 

Final Final Word

- Pete Kane of sv.ai (now researchtothepeople.org) was in charge of hackathon attendance. He built up a significant list of engineers, biologists, researchers etc by hosting monthly lectures.
- Part of the motivation for the hackathons came from the community wanting to engage sv.ai's open and collaborative data science projects.
- Bioinformaticians!!!!
- Contact Pete to help with current cases!
- or Bill you want to get involved in improving the hackathon process (LLMs are the current focus)
 - bill@rarekidneycancer.org
 - pete@researchtothepeople.org