

Using Genai to assist Rare Cancer Care

RareKidneyCancer.org

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20250219 Cancer Patient Lab

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Agenda

- *Rare Cancers: I have one. There isn't much treatment guidance.
- (ad hoc) Personalized Tumor Boards help me make decisions
 - Pro/Photon: (13 member) "Should Bill use Proton or Photon on his Brain Tumor?"
 - EVEREST: (13 member) "Should Bill participate in the EVEREST Trial".
 - Hackathons: (80 member) "What Treatments should Bill use upon progression?"
- Statistical Implications
- LLMs can be board members.
- Aggregators: LLMs can aggregate Tumor Board results.
- (in progress) Caretaker "agents" can wrap Data (EHRs), tools, and LLMs
- Summary
- Acknowledgements
- Final Word - You can help!

Basic Terminology

Standard of Care → Onco Clinical Trails → Post Clinical Trials

“Normal” Conditions

Note: Doctor MUST use SOC
For Reimbursement
And Legal

Failed SOC Conditions

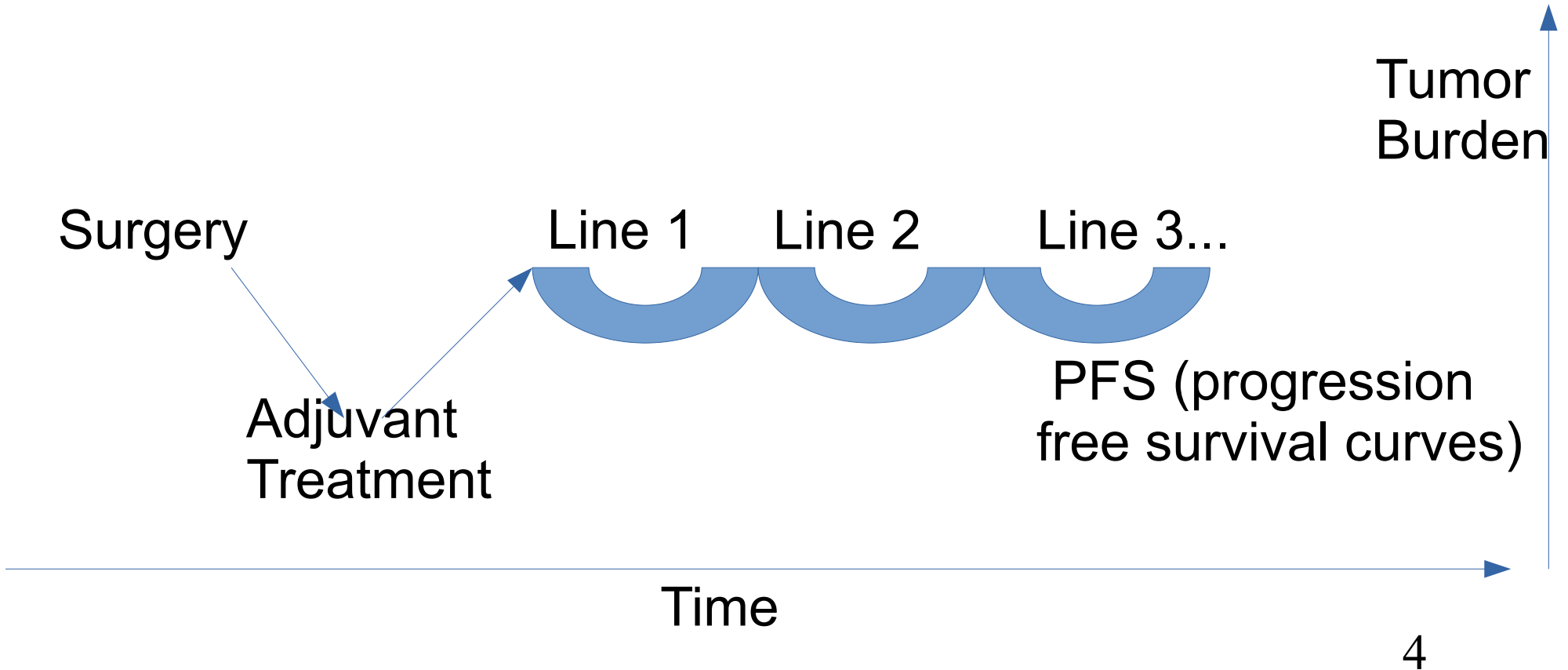
No Clinical Trails

Treatment Success Rate: 30-80% 3.5%** 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>

Basic Terminology



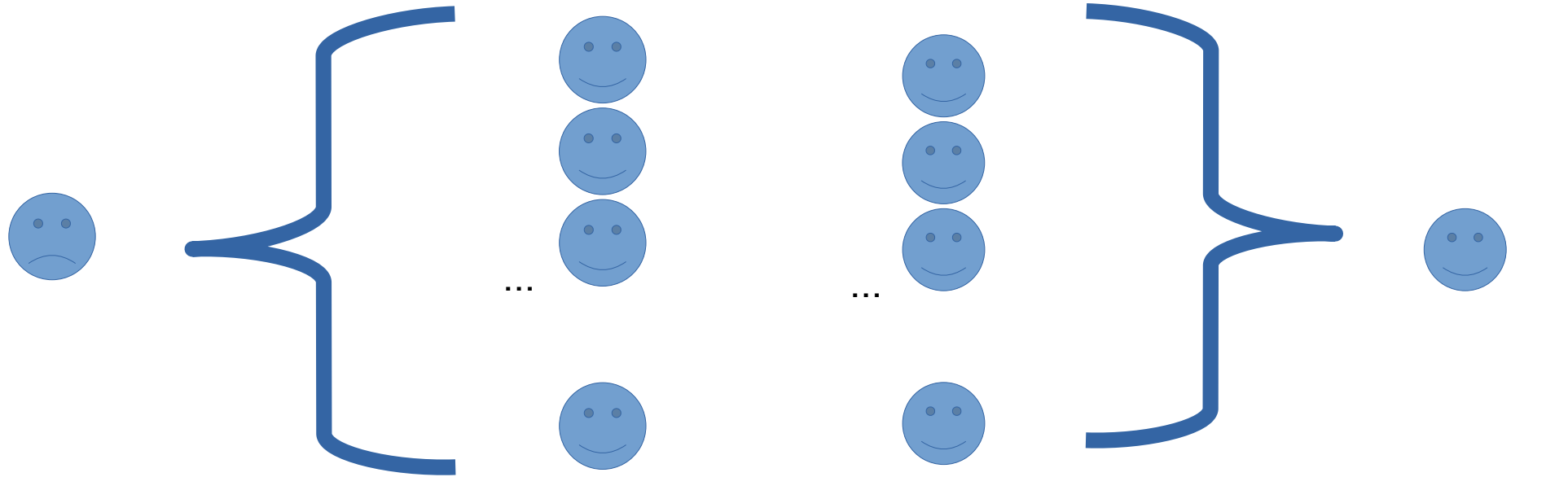
My Motivation: p1RCC Diagnosis

- 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? Should I get radiation?

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Clinical Trials vs. Tumor Boards (Portfolios)



1 Researcher

N Patients

N Researchers

1 Patient

Clinical Trial: one Researcher many Patients

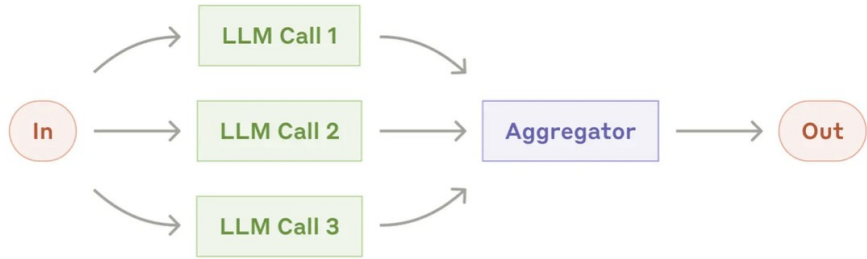
Tumor Board: many Researchers one Patient
In essence, each member has a “2nd Opinion”

What makes a good tumor Board?

Wisdom of Crowds - https://en.wikipedia.org/wiki/The_Wisdom_of_Crowds

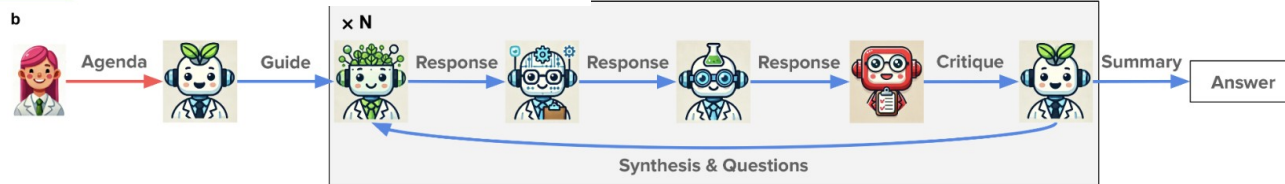
- Diversity of opinion
 - Each person should have private information even if it is just an eccentric interpretation of the known facts. (Chapter 2)
- Independence
 - People's opinions are not determined by the opinions of those around them. (Chapter 3)
- Decentralization
 - People are able to specialize and draw on local knowledge. (Chapter 4)
- Aggregation
 - Some mechanism exists for turning private judgements into a collective decision. (Chapter 5)

This->



Not this->

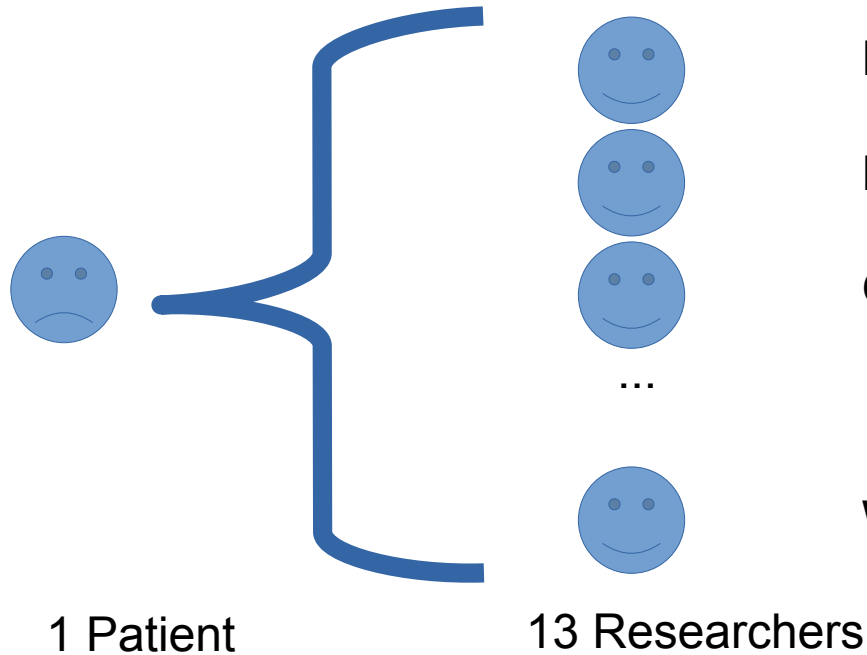
(Information Cascade)



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Tumor Boards: Which is better Proton or Photon?



Proton/Photon

Proton

Photon

Operate

...

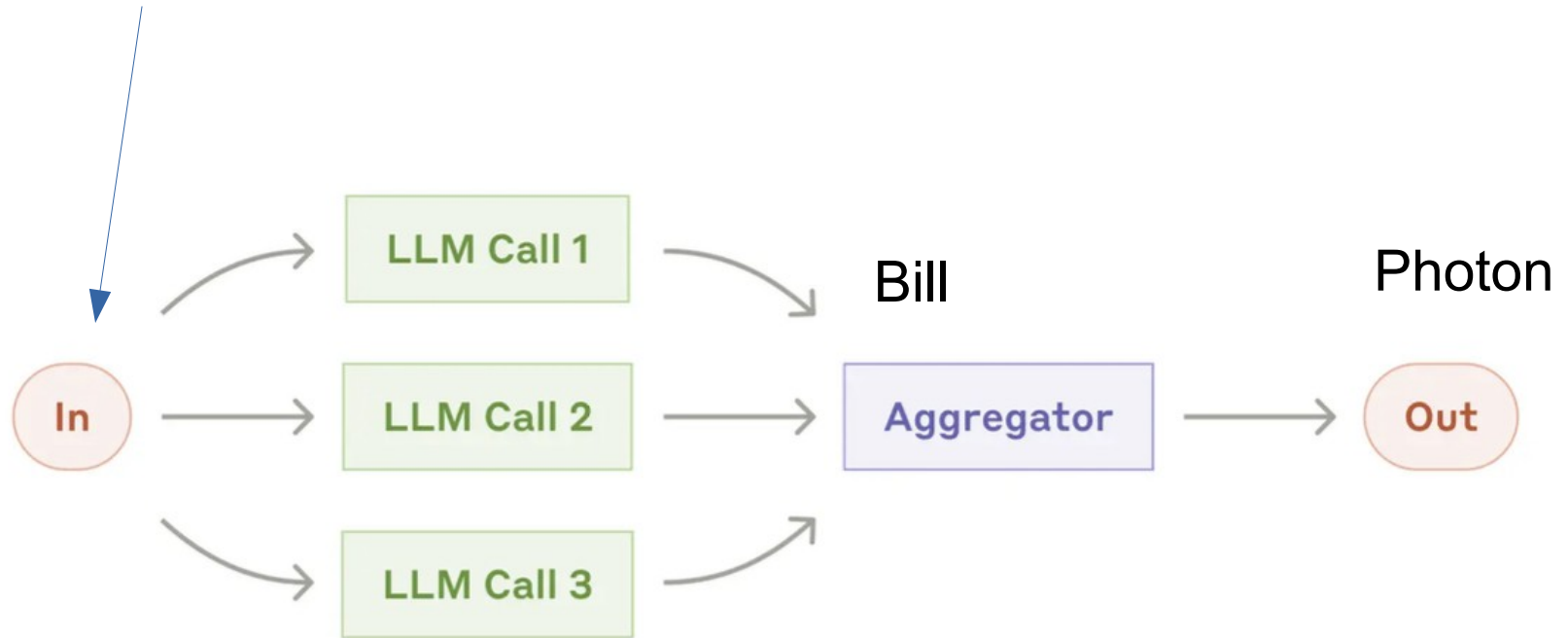
Wrong Question

- Ensemble Reasoning

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

- 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

Tumor Boards: Which is better Proton or Photon?

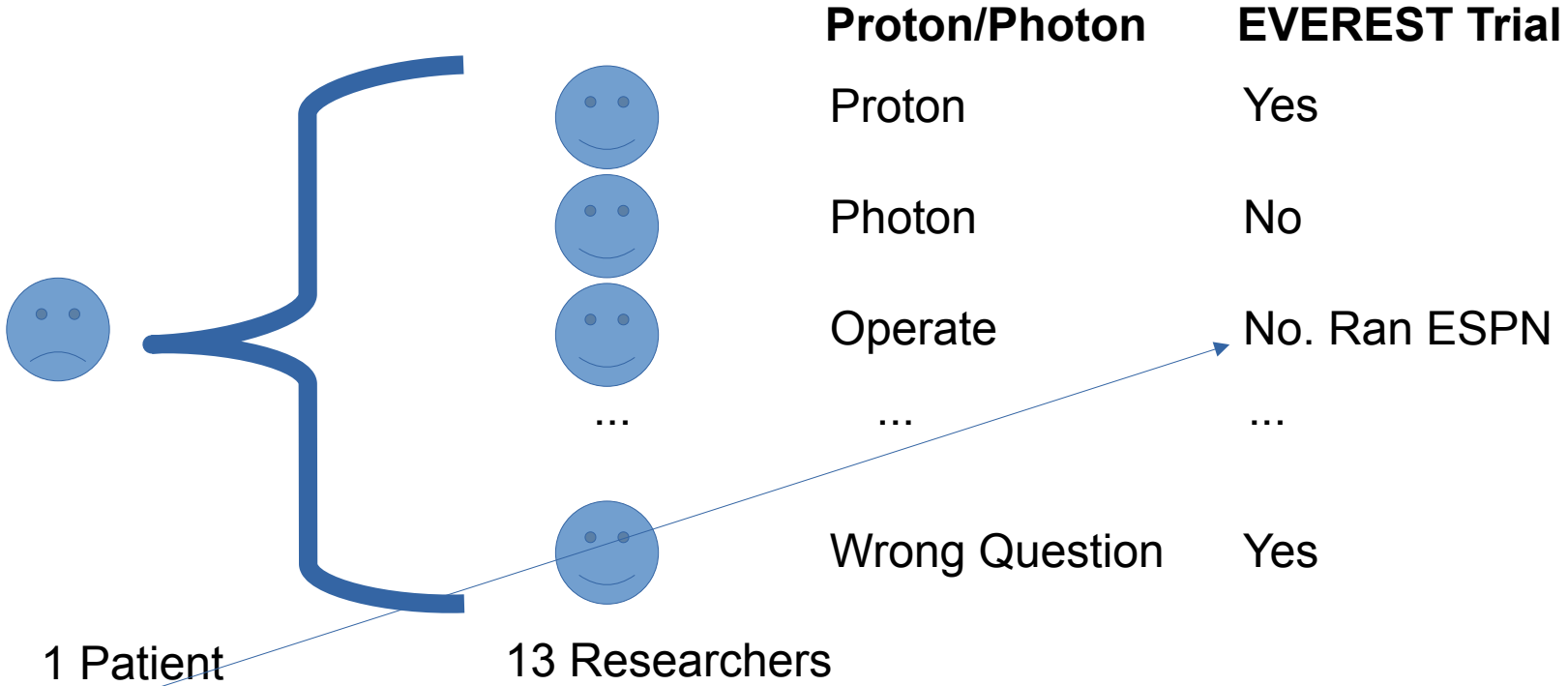


13 Hospitals with
Proton/Photon Machines

Agenda

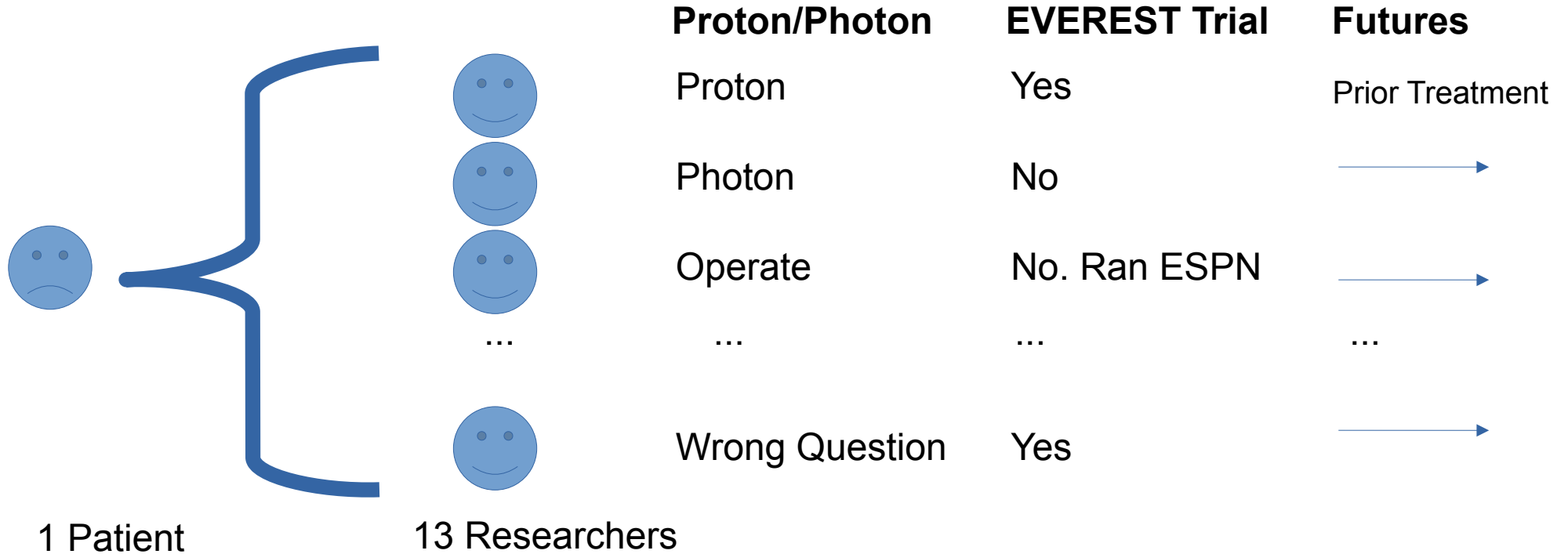
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Tumor Boards: Should I participate in EVEREST



- "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

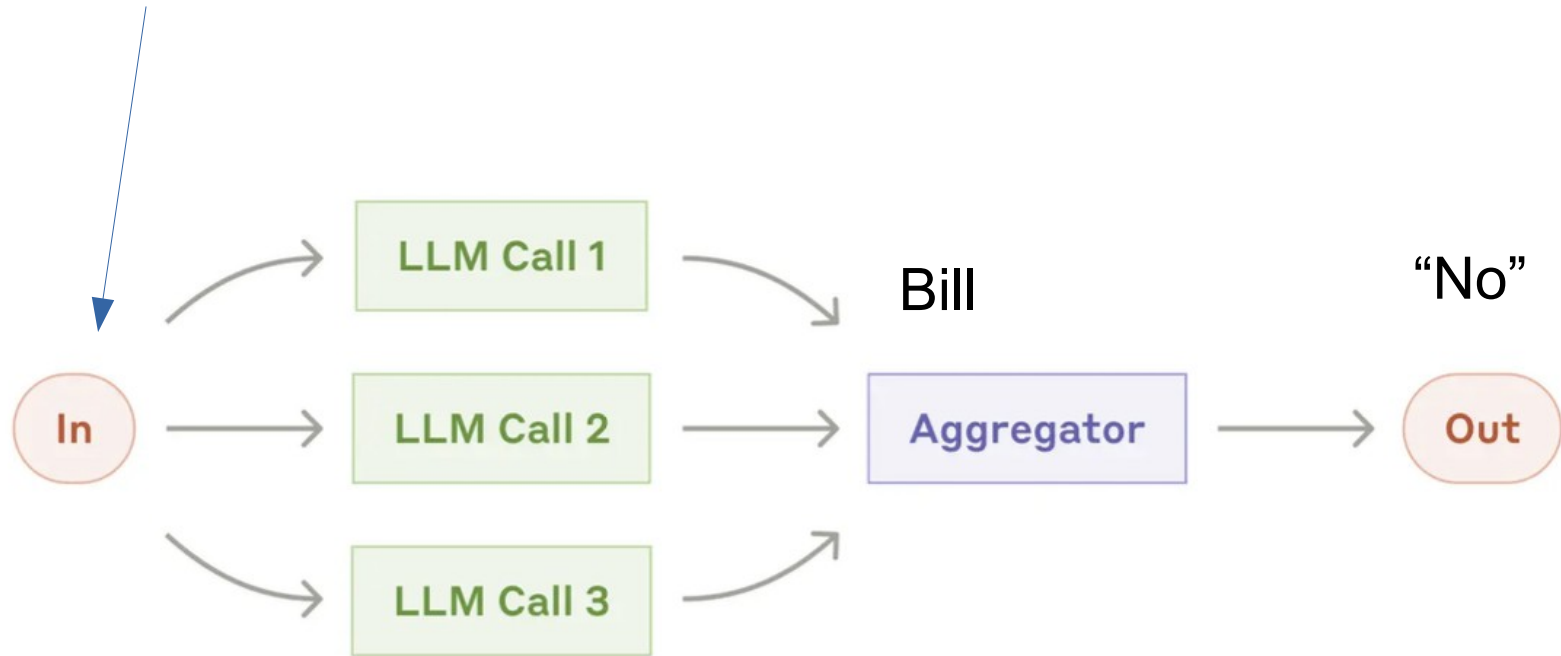


- Ensemble Reasoning

- “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!!!

Tumor Boards: Should I participate in EVEREST?

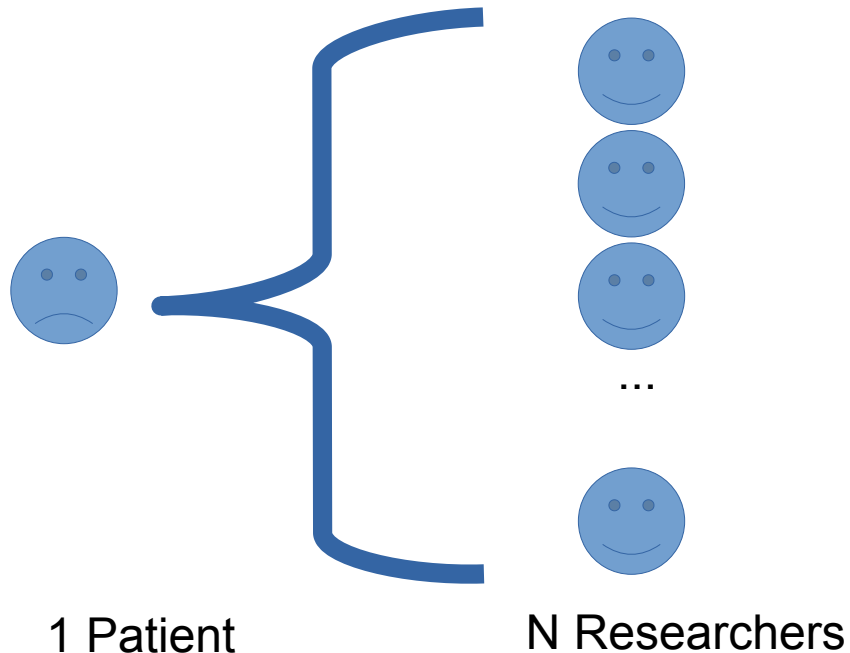


13 Doctors with Clinical
Trial Experience

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The First Hackathon: Kaggle

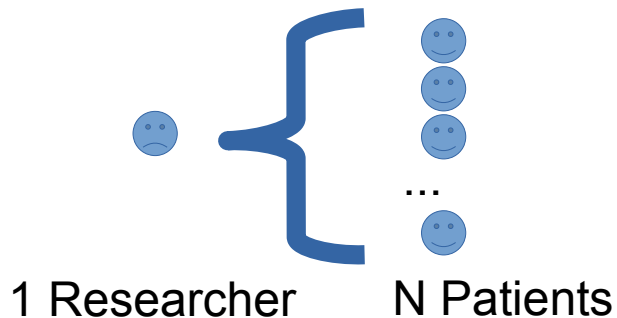


- Ensemble Reasoning
 - “The best way to have a good idea is to have lots of ideas.” - Linus Pauling
- [Kaggle](#): –Data Science Competition Platform founded 2010
 - “Set up to meet a mismatch between people collecting data and those with the skills to analyze it.”
 - Random Forests became dominant 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).

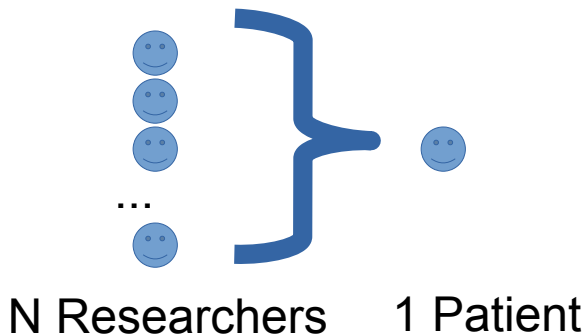
<https://www.science.org/doi/full/10.1126/science.331.6018.698>

Hackathon (Game) Structure

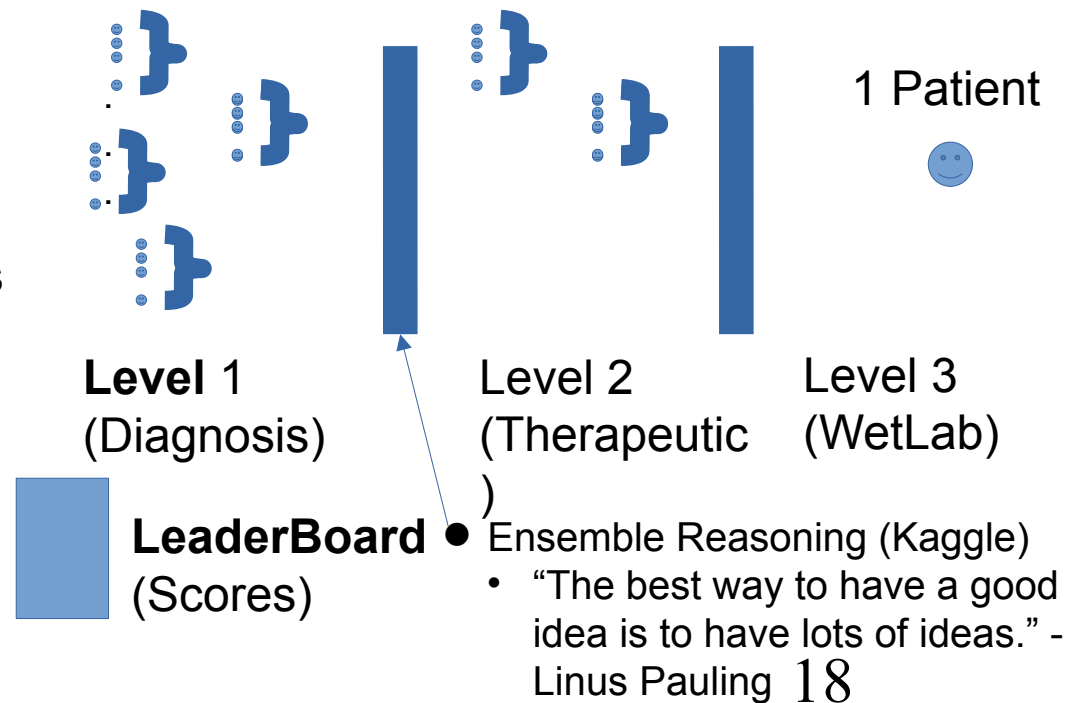
Clinical Trial: one Researcher many Patients



Tumor Board: one Patient many Researchers



Hackathon: one Patient many TumorBoards (Teams)

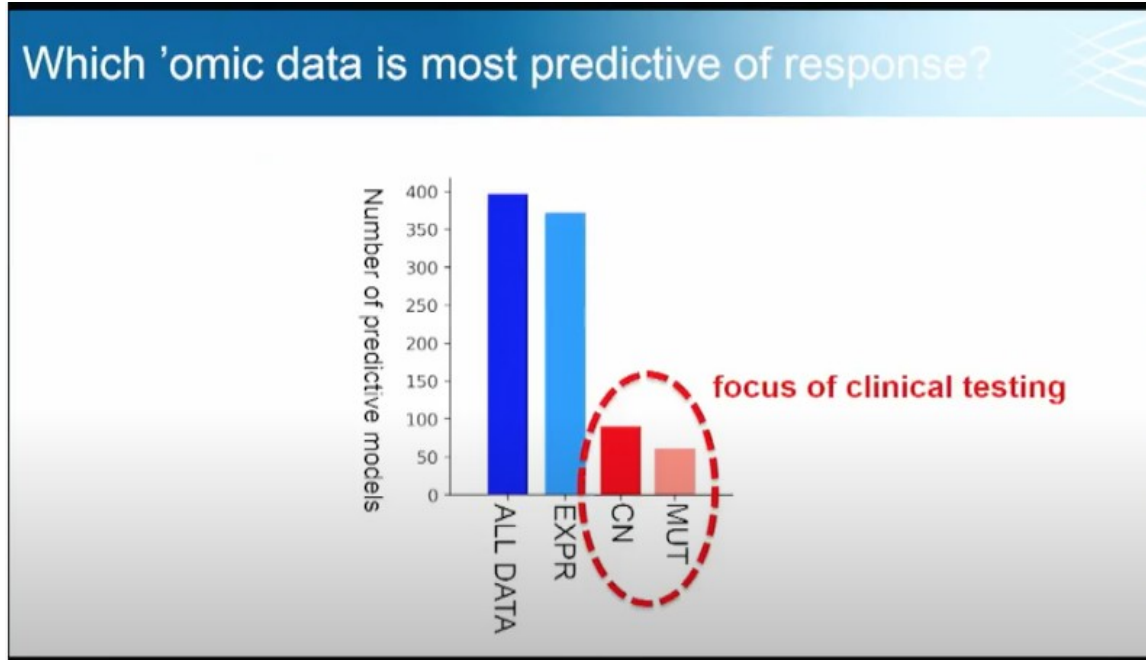


2018 p1RCC Hackathon Teams



80 People (some Remote) formed 17 Teams (50 pictured)¹⁹

Input: (Lots of) Research Data



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

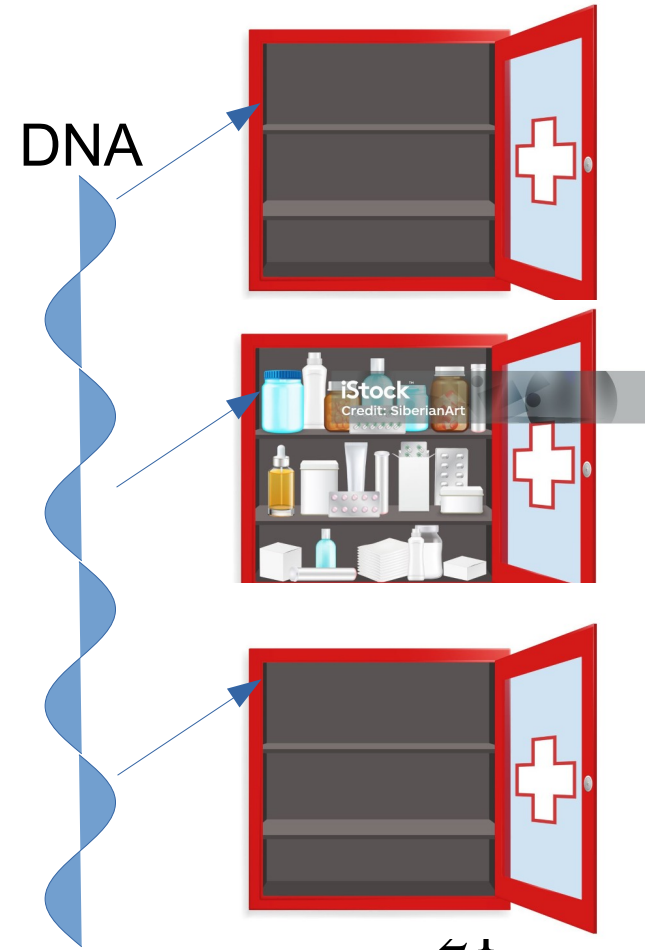
- Genetics- brother has thyroid cancer
- Genomics - TCGA Thyroid cancer clusters close to p1RCC
- Metabolomics - High Uric Acid - “Thyroid hormones influence kidney function and thereby might alter serum urate levels, a major risk factor for gouty arthritis.”
- Co-morbidities - Bradycardia (Slow Heart 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/on-cancer-linked-to-mouth-bacteria/> 20

Goal: One Question, One Answer*

- Given this medical data
 - 1 What are the Genes of Interest?
 - 2 What is the Therapeutic Recommendation?

Note: If each gene pointed to a drug in a medicine cabinet, most of the shelves would be empty.



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 | 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 moderate (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

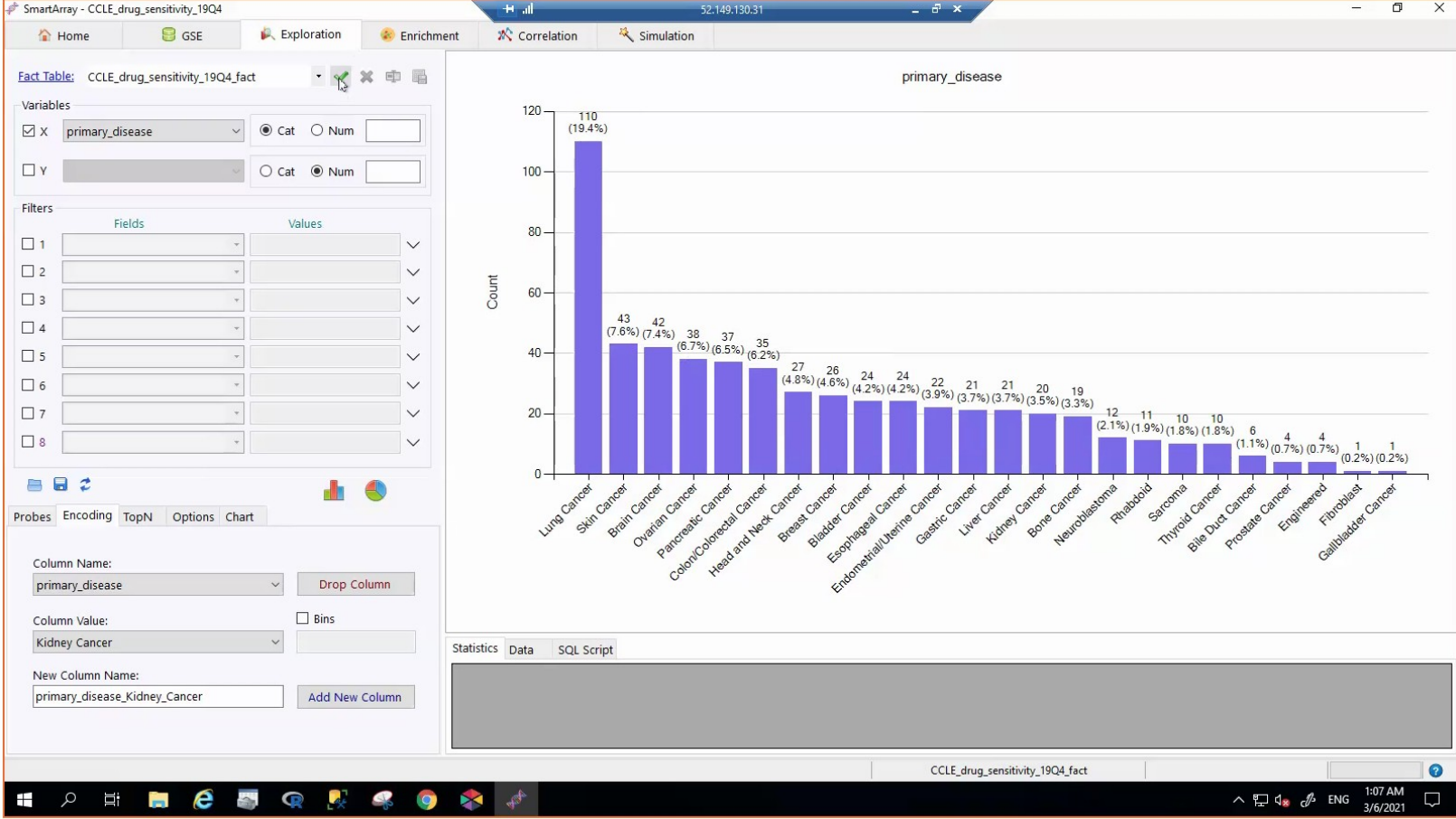
What is the best way to moderate (judge) results?

- **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



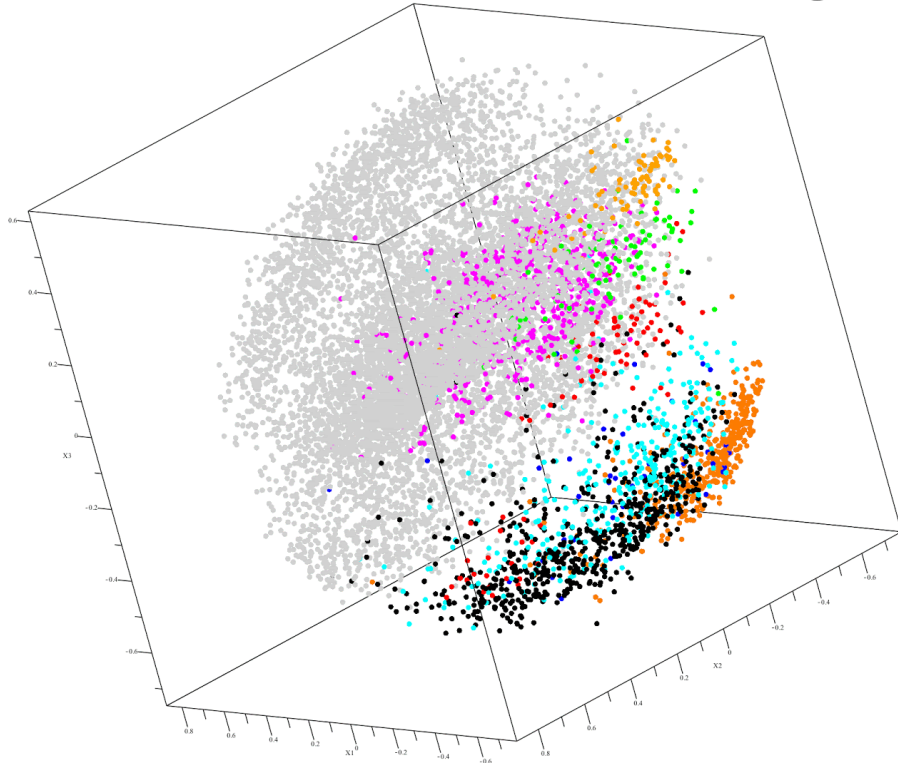
Level 3: Wetlab (TBD)

- 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

Results

- ✓ Therapeutic Recommendation
 - 2018
 - 2020
- Scoring (Aggregation) 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 – Expand Cohort, Future Mutations?
- General Insights
 - p1RCC Clusters close to Thyroid Cancer
- Analysis Approaches
 - Why did Biomarkers.ai (Bioada) do so much better than the other 16 teams? 27

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
28

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 construction³⁰

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.

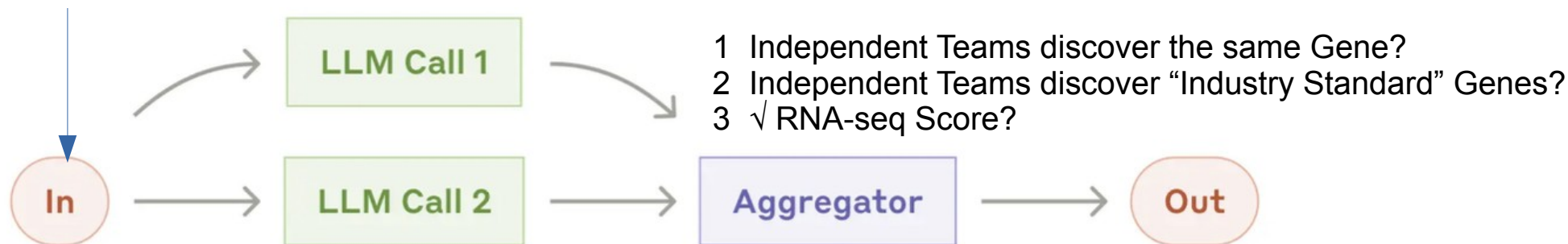
“Game Elements”

- 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.

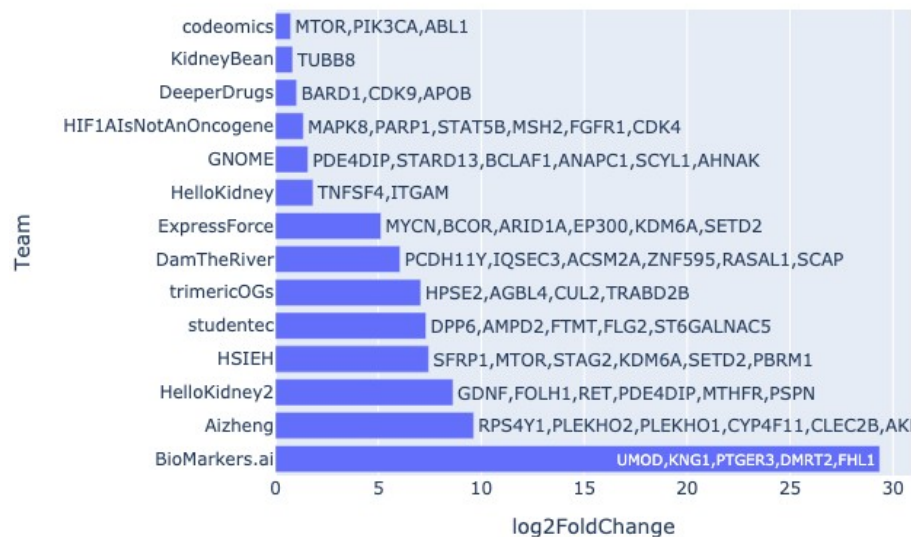
“Treat Research Teams as formal computational objects”

- 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

Tumor Boards: What are Bill's Genes of Interest?



17 Teams with Genomics/Medical Experience



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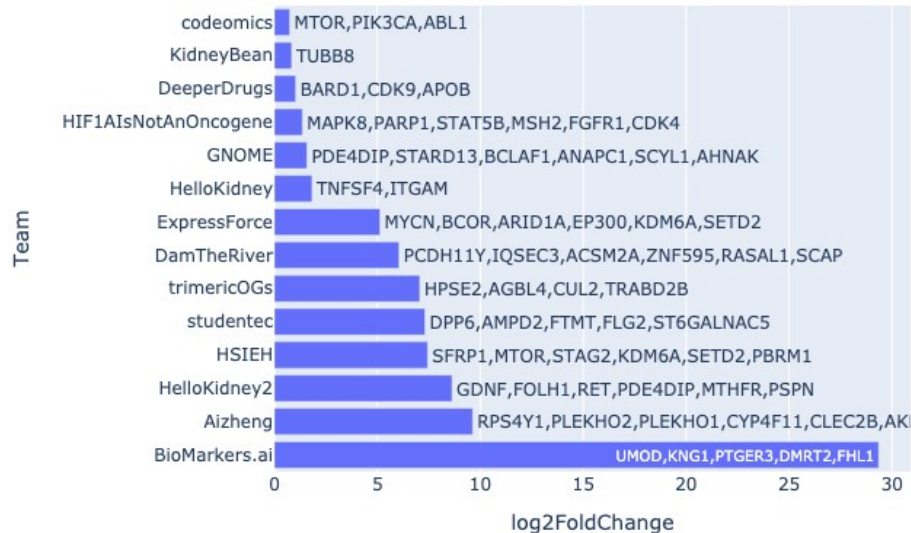
Statistics – How much data do we need?

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
 - Sales
 - City Populations
 - Pandemics
 - Death in Wars/Terrorist Attacks
 - Word Occurrences in Text
 - Academic Citations
 - Company Sizes

2nd 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/>

Since 20240122: Statistics

Standard of Care

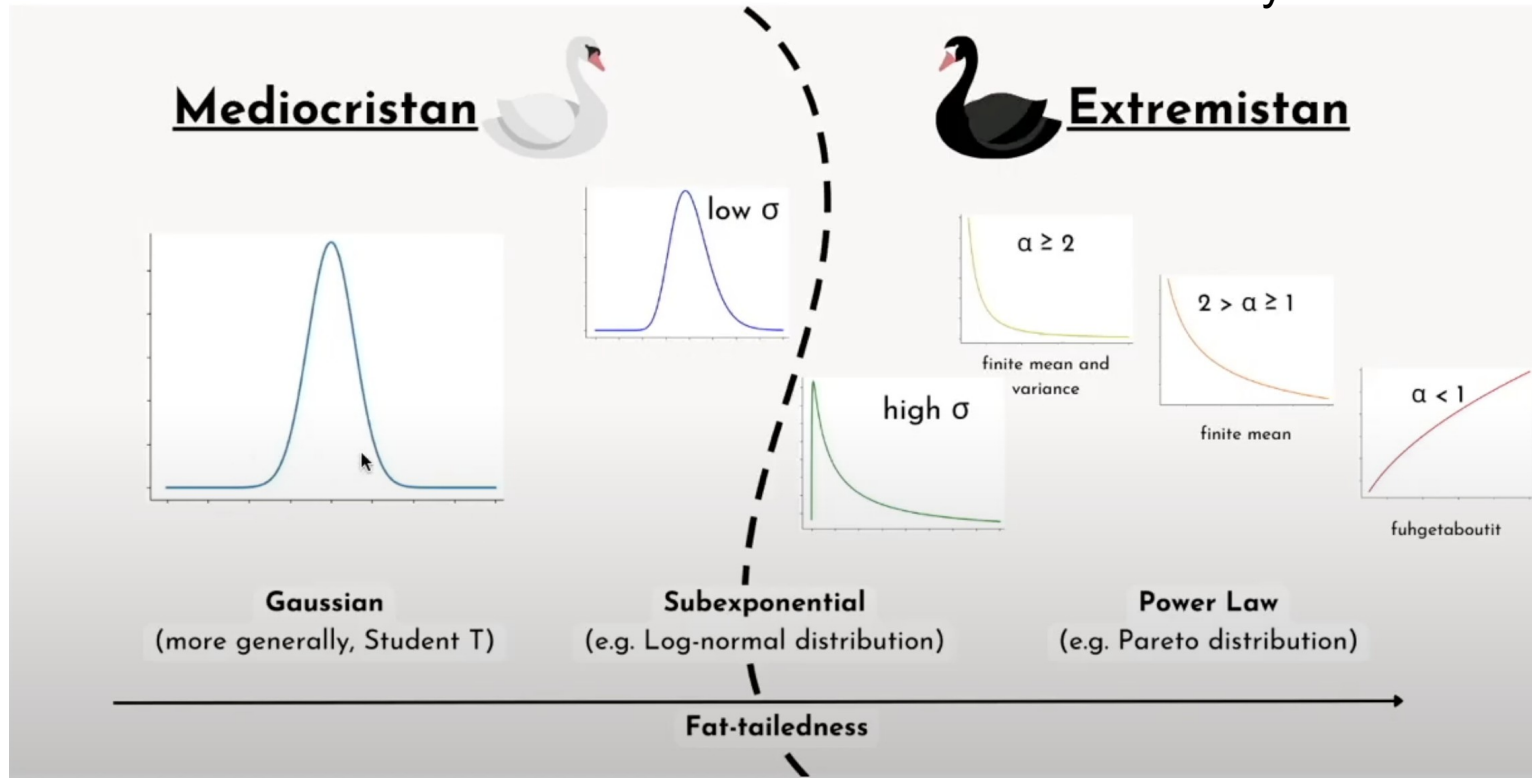
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Post Clinical Trials

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>

How many opinions do we need to evaluate treatments for rare conditions?

Whatever the answer is, it is most likely >1

<https://thesecondopinion.org/about/>

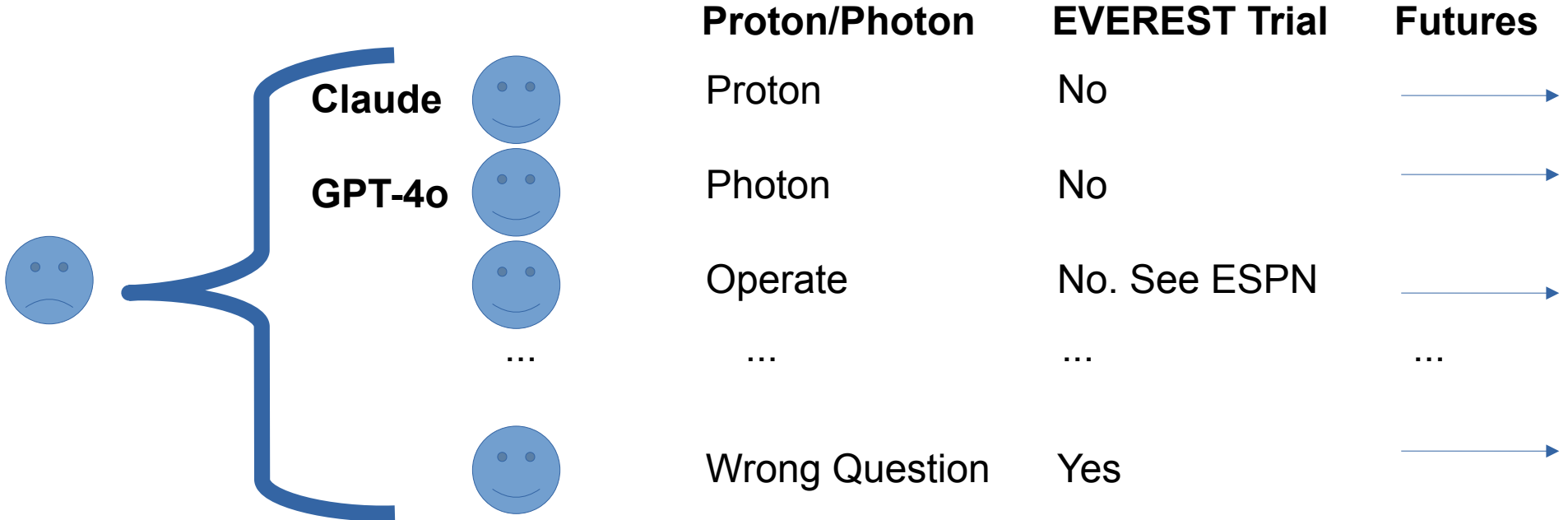
CONSIDER GETTING A SECOND OPINION IF YOU:

- Have questions about your current course of treatment or diagnosis.
- Need confirmation of your diagnosis and extent of disease.
- Desire a fuller understanding of test results and their significance.
- Seeking suggestions for additional treatment alternatives or additional diagnostic procedures.
- Want information about relevant clinical trials.
- Are delaying treatment.

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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!!!

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.

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." 41

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.

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." 43

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.**

Agenda

- Rare Cancers: I have one. There isn't much treatment guidance.
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 - Hackathons: (80 member) "What Treatments should Bill use upon progression?"
- *Statistical Implications
- LLMs can be board members.
- *Aggregators: LLMs can aggregate Tumor Board results.
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Aggregator: Unstructured

- Human tumor board members spend a lot of time explaining their positions to each other
- Can I get an LLM to aggregate (Moderate) the tumor Board?
 - Human Packages: [Assistants API](#) , [Swarm](#) , [Playoff Prompt](#)
- Asking LLM(s) for the Best Approach gives weasel words. E.g.

Prompt:

I am considering participation in the EVEREST clinical trial after a full left nephrectomy for a papillary kidney cancer.

I created a “tumor board” of 13 physicians to determine if this is a good idea. Their (numbered) responses are below.

The number is a physician id. This is followed by a “yes” or “no” as to whether I ought participate. Next is the physician “label”. Finally, their rationale is included. Given this data, Please act as a tumor board moderator and tell me if I ought participate in the trial. Please include your rationale.

Response:....

Recommendations: **I encourage you to have a detailed discussion with your primary oncologist or a specialist familiar with your case.** They can provide personalized guidance taking into account your medical history, current health status, and treatment goals. This conversation will help you make an informed decision that aligns with your values and preferences.

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20241015 Aggregator: "Playoff"

- Prompt: Create a playoff with physicians 1-5 and 7. Pair one of the 3 "yes" physicians with one of 3 "no" physicians into 3 matchups (pairs). Compare each yes/no pair and choose a winner based on how convincing their argument is. If result is unanimous (3 "yes" or 3 "no"), report it. If it is not, create two more playoffs between the minority opinion and each of the majority opinions. Report the results from each step.
- Playoff Results
 - **All three matchups were won by the "No" physicians.**
 - **Unanimous Outcome: The "No" position prevails based on the strength and persuasiveness of the arguments.**
- Conclusion: Based on this playoff analysis:
 - Recommendation: The arguments against participating in the EVEREST clinical trial are more compelling among these physicians.
 - Key Factors Influencing the Outcome:
 - Lack of Efficacy Evidence: Past trials like the ESPN trial suggest Everolimus may not be effective for papillary kidney cancer.
 - Safety Concerns: Significant potential side effects, including kidney failure, pose substantial risks.
 - Alternative Options: Waiting for future trials with more promising treatments (e.g., immune checkpoint inhibitors) may be advisable.
- Next Steps:
 - Consult Your Oncologist: Discuss these findings with your primary oncologist to consider how they align with your personal health situation.
 -

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Agents

- Workflows are systems where LLMs and tools are orchestrated through predefined code paths.
- Agents, on the other hand, are systems where LLMs dynamically direct their own processes and tool usage, maintaining control over how they accomplish tasks.

Caregiver: Dee's Tips (EHR and Research)

1) Create a spreadsheet of analyses, including tissue (or blood) source, date, summary of findings.

2) Keep analyses and reports in Google Drive in a "Medical Folder" for easy access and sharing with clinicians, researchers and advocates like you. If she finds it difficult to find or download reports from the various institution portals, contact the clinician to email directly to her (sometimes they will, HIPAA be damned), try copy/paste from the portal, or even a screenshot then place in Folder. It's key to be able to forward the information with ease and with speed.

3) When finding any article, clinical trial or research paper that is compelling, find the leading researcher (often has their email or contact info) and email them with a brief clinical summary, asking if willing to share a 10 minutes to chat. I've also just called directly toward end of day (their time) and I don't hesitate to leave a message, always very mindful, respectful and appreciative of her/his time.

4) What not to do: Be passive, apologetic or hesitant to ever advocate for oneself. 52

Caregiver: Clinical Trial Finder

cubeomatic

Help Warranty Reset Click items to 'select' or 'deselect' (Last Updated: Fri Sep 17 15:18:14 2021)

Condition show all

- Birt-Hogg
- Chromophobe
- Clear Cell papillary
- Collecting Duct
- Leiomyomatosis
- Medullary
- Mucinous
- Non Clear Cell
- Papillary**
- Rhabdoid
- SDHB
- Sarcomatoid
- Translocation
- Unclassified
- Von Hippel-Lindau
- Wilms

Phase show all

-
- early phase 1
- n/a
- phase 1
- phase 1/phase 2
- phase 2
- phase 2/phase 3
- phase 3**
- phase 4

Overall status show all

- active; not recruiting
- completed
- enrolling by invitation
- not yet recruiting
- recruiting
- suspended
- terminated
- unknown status
- withdrawn

State show all

- california**

Country show all

- united states**

Zip show all

- 90027
- 90033
- 90034
- 90048
- 90057
- 90095
- 90095-1781

Official title show all

Search:

- 60. a phase 3; randomized; controlled; multi-center; open-label study to compare tivozanib (av-951) to sorafenib in subjects with advanced renal cell carcinoma (tivo-1)
- 61. a phase 3; randomized; controlled; multi-center; open-label study to compare tivozanib hydrochloride to sorafenib in subjects with refractory advanced renal cell carcinoma
- 160. a phase iii randomized study of bay43-9006 in patients with unresectable and/or metastatic renal cell cancer

Facility show all

Search:

- 81. ais cancer center at san joaquin community hospital
- 135. alta bates summit medical center - summit campus
- 136. alta bates summit medical center-herrick campus
- 203. arroyo grande community hospital
- 360. bay area breast surgeons inc
- 364. bay area tumor institute

NCT_id show all

- [link](#) nct00072046
- [link](#) nct00073307
- [link](#) nct01030783
- [link](#) nct01120249
- [link](#) nct01575548
- [link](#) nct02627963
- [link](#) nct03091192
- [link](#) nct04000000

Keyword show all

Search:

- 0.
- 15. accelerated phase chronic myelogenous leukemia
- 19. acute undifferentiated leukemia
- 38. adult acute lymphoblastic leukemia in remission
- 39. adult acute myeloid leukemia in remission
- 40. adult acute myeloid leukemia with 11q23 (mll) abnormalities
- 41. adult acute myeloid leukemia with inv(16)(p13;q22)

Intervention show all

Search:

- 46. atezolizumab
- 55. axitinib
- 64. bevacizumab
- 80. cabozantinib
- 85. carboplatin

Caregiver: Decision Support Tool (Prototype)

Question

Should I participate in the Everest Clinical Trial?

Moderators

4) Return Strong... x

Submit

Opinions

| | Moderator 4 | Answer | ID | Argument |
|---|-------------|--------|-------------|--|
| 0 | No | Yes | Sutter | "Minimal Downside" |
| 1 | No | Yes | Stanford | "If you are eligible always a good idea to partake on trials" |
| 2 | No | Yes | Davis | "No cons other than ending up in the placebo arm or having to deal w |
| 3 | No | No | Los Gatos | "Kidney cancer has had no successful treatment (e.g. radiation, chem |
| 4 | No | No | MD Anderson | Nizar Tannir: "I do not recommend any adjuvant trial w/ mTOR inhibit |

Answers

| | Moderator | Answer | IDs | Argument |
|---|-----------|--------|-------------|--|
| 0 | 4 | No | MD Anderson | Nizar Tannir: "I do not recommend any adjuvant trial w/ mTOR inhibitor |

Caregiver Agent

- Tools for Dee
 - Data - spreadsheet of analyses, including tissue (or blood) source, date, summary of findings; Move data across sharing interfaces; Search for any article, clinical trial or research paper that is compelling then find the leading researcher
 - Clinical Trial Finder
 - Decision Support Tool
- Caregiver Agent (An Electronic Dee)
 - Data - spreadsheet of analyses, including tissue (or blood) source, date, summary of findings; Move data across sharing interfaces; Search for any article, clinical trial or research paper that is compelling then find the leading researcher
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 - Decision Support Tool

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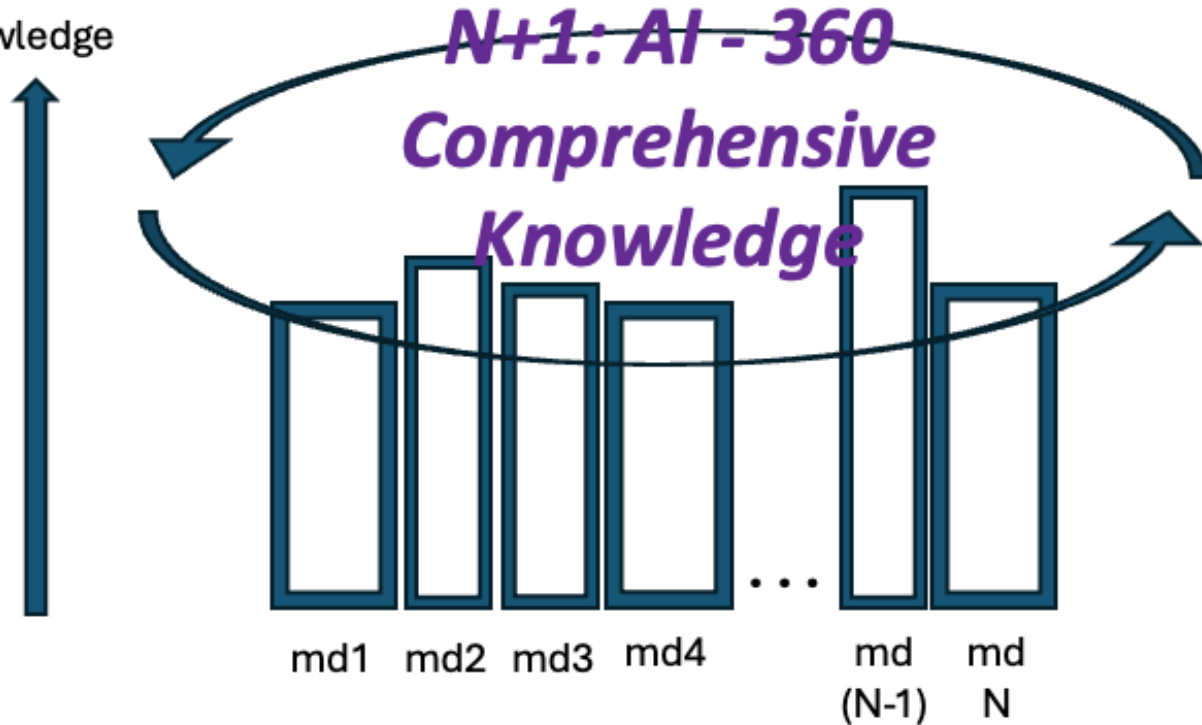
Takeaway 1: Crowdsourcing

We are getting more integrable knowledge sources.

Each one is different some wider some deeper.

Crowdsourcing them will get us to better answers faster.

depth of knowledge



different width of knowledge

- Dad's Rule: "Pay Attention and Do your best"
- Drilling Rig Rule: Your safety is your responsibility. Watch the oldest Drillers.
 - First Day, Helicopter (Remove the seatbelt, dump the vest), laying casing, paraplegic
- First DVT (Blood Clot) rule: If you are told "Everything is fine!" Pay double attention.
- Expert ("Best you can find") Recommendation
 - E.g. Asked Brother-in-law for Surgeon
- Work with the experts - rarekidneycancer.org
 - E.g. - 2017 - "Recommendations for the Management of Rare Kidney Cancers"
- Wisdom of Crowds - https://en.wikipedia.org/wiki/The_Wisdom_of_Crowds
 - Diversity of Opinion, Independence, Decentralization, Aggregation
- Caregiver Tools can help make decisions
 - Personal EHR, Clinical Trial Tool, Tumor Board Tool
- Go with the Tumor Board guy who makes the most sense
 - E.g. Everest: "Everolimus failed first line for your condition. So it's likely a poor adjuvant"
- Information changes through time
 - E.g. "Newer Models of Proton Machine" example.
- Ask a team, not just an individual
 - E.g, MD Anderson re proton/photon recommendation
- Secretary Problem - https://en.wikipedia.org/wiki/Secretary_problem
 - If you have a Small, Finite number of experts, visit at least $1/e$ (37%) of them
- Prompts have to be intelligent – LLMs give radically different answers based on "same" input

Takeaway 2-12

Agenda

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Acknowledgements

“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.

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 spec: Mike D'Amour
- 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
- 2025 Presentation Review: Zoran Kunic, Rami Rubin


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 |
| HIF1AsNotAnOncogene | 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  |

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Final Word

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

I can always use more friends.

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

Bill (bill@rarekidneycancer.org)