Academic Entrepreneurship 101: How to be an entrepreneur without starting a company.

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“Corporate” Disclosure

- Fibrogen, Inc., Co-Founder, but cut out due to COI (FGEN) Cap=$1.8B
  - Initially anti-fibrotics, but just declined on Phase 3 safety profile of HIF anemia drug
- Helix Therapeutics, Inc.
  - Oral anti-fibrotic agents based on prolyl-hydroxylase inhibitors.
- Capgen Biosciences, Inc.
  - Co-Founder, RNA based diagnosis of in-stent restenosis
- SeqLL, Inc. (Formerly Helicos Biosciences)
  - Scientific Advisory Board.
- True Bearing Diagnostics, Inc.
  - Co-Founder and Shareholder
  - RNA-based diagnosis of coronary artery disease and internal infections

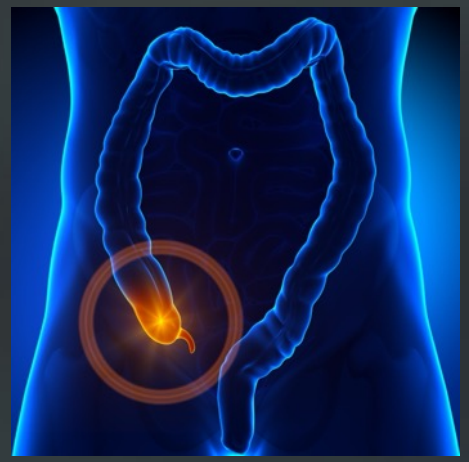
True Bearing Diagnostics, Inc.

Navigation for Precision Healthcare

*A fundamental problem in medicine is the inability to distinguish **INFECTION** from sterile inflammation such as allergy, injury, autoimmunity, or toxic exposure.*

The True Bearing Solution:
TruNAV

The TruNAV Diagnostic:



- RNA Biomarkers of Internal Infection
  - Massive market of abdominal pain cases (>16M/yr @ ER)
  - Six RNA biomarkers measured in stabilized whole blood
  - Highly accurate and reliable droplet digital PCR detection (ddPCR)
  - ddPCR platform has FDA clearance w/ Dx instrument distributed
  - Detects bacterial, viral, and biofilm infections by host response
  - Discovery/Validation trial published, 2nd validation published
  - COVID19 host response detection published
  - Three patents w/ claims allowed
  - Finalizing sites for FDA Clearance Trial

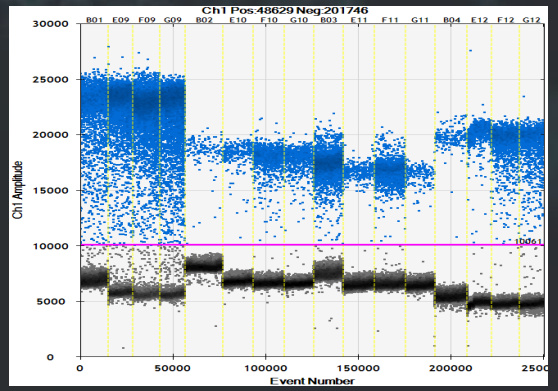
TruNAV Clinical Studies

- *Discovery/Validation Trial: Gut Troponin (GT)*
  - ER recruitment of 270 patients yielding 40 patients with abdominal pain
  - Accuracy: Discovery = 100%, Validation = 88.9%
  - *Chawla et al. BMC Medical Genomics 9:40, 2016*
- *More Accurate Diagnosis of Abdominal Infections by RNA (MADAIR)*
  - ER screening of 427 patients to yield 100 patients
  - Negative predictive value: High likelihood of Infection = 94%, Admission = 90%
  - *Scientific Reports (Nature Journal): Meltzer et al, 13: 2297, 2023.*
- *COVID19 Host Immune Detection by TruNAV (CoNAV)*
  - ICU patients (n>38) with various degrees of COVID19 Severity
  - Sensitivity for SARS-CoV2 RNAemia: 95.5%
  - *Wargodsky et al. PLOS One 17(1), Jan 2022.*

TruNAV on the BioRad ddPCR Dx Platform

- Blood Draw (2.5 ml)
- RNA Isolation (30 min)
- cDNA Synthesis (30 min)
- ddPCR (2 hours)
- Analysis for TruNAV markers (seconds)
- Report issued to prescribing physician

FDA 510K Cleared



TruNAV Report *(draft prototype)*

TRUE BEARING DIAGNOSTICS, INC.

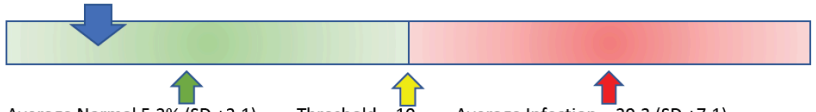
TruNAV© Report

Patient Name: John Do
Patient Id: XYZ-456-IN319
Patient Gender (reported): Male
Patient Age: 56

Physician Name: John Smith, M.D.
Physician Organization: MyDocs, LLC
Date Received: 10/4/2021
Date Reported: 10/7/2021

TruNAV results: Abnormal

TruNAV Accessible Infection Score: 2.1% DEFA is LOW NORMAL



Average Normal 5.2% (SD ±2.1) Threshold = 10 Average Infection = 29.3 (SD ±7.1)

TruNAV Biofilm Score: 39.9% Biofilm score is ELEVATED

Average Normal = 13.8 (SD ±3.2) Threshold = 20 Average Infection = 34.3 (SD ±6.8)

TruNAV Viral Score: 0.9% Viral score is NORMAL

Average Normal = 1% (SD ±0.2) Threshold = 5 Average Viral Infection = 15.3 (SD ±3.1)

Interpretation: Patients with this pattern of an Accessible Infection score that is low normal, and a Biofilm Score that is elevated are commonly found to have Biofilm-type infections in abdominal organs. The most common form is appendicitis, followed by diverticulitis, urogenital infections, or bowel obstructions. Biofilm infections are rarely of viral origin.
Conclusion: ***Further testing should be considered.***

----------see reverse for Quality Control results and Caveats for Usage----------

Caveats:

1 – While TruNAV is very sensitive to detecting that the person's immune system is detecting an infection, it is quite non-specific (agnostic) about the location of the infection. Clinical signs that locate the infection, and further imaging tests such as ultrasound or CT imaging are an important part of the overall diagnosis.

2 - The present results should ***only*** be used in the context of a broader clinical evaluation of all potential indicators of the presence of an internal infection. Other signs that may be useful would be the presence of fever, an elevated white cell count, and an elevated neutrophil-to-lymphocyte ratio (NLR). TruNAV partially incorporates an elevated white cell count, although the absolute white cell count is largely minimized in TruNAV by using a standard amount of RNA, and expressing the DEFA and Biofilm scores as a % of Actin RNA. Thus, TruNAV is designed to measure the ***ACTIVITY*** of immune cells, with a lesser impact of their numbers.

QC Metrics:

All procedural QC checks were within parameters:

Blood volume collected:
Tube weight empty: 16.47 g
Tube weight full: 19.57 g Blood volume = 3.1 g

Total RNA yield (from Tempus spin w/on column DNAse): 6.1 ug per 3.1 g blood (mild high)

RNA quality metrics: RNA Integrity Number (RIN) = 8.4 is acceptable (range 0-10, low-perfect)

ddPCR droplet numbers: 14,738 droplets for ACTB/IL8RB, 13,698 droplets for DEFA/ALPL (OK)

ACTB Copy numbers: 235,678 copies per 20 ul
DEFA1 Copy numbers: 12,255 copies per 20 ul = 5.2% of ACTB copies
ALPL Copy numbers: 46,899 copies per 20 ul = 19.8% of ACTB copies
IL8RB Copy numbers: 47,135 copies per 20 ul = 20.1% of ACTB copies

Biofilm Score is %ALPL + %IL8RB = 39.9%

Comparison to CareDx, Inc.

	CareDx, Inc.		**True Bearing Diagnostics, Inc.**	
Indication	Transplant Rejection		Infection	
Market Size	Kidney	30K Total	Abdominal	16M/yr
	Heart	20K Total	Dental implants	5M/yr
	Lung	20K Total	Hip implants	300K/yr
Multiple Tests/patient?	Yes	Average 5/pt	Yes	Likely >2/pt
Market Penetrance	~90% of transplant centers		Unknown	
Technology	RNA Biomarkers	20 transcripts	RNA Biomarkers	6 transcripts
Format of Test	Draw blood, mail to Company		Draw blood, mail to Company	
Assay method	Conventional qPCR		Droplet digital PCR	
Accuracy				
Negative Predictive Value	Strong	98%	Likely comparable	
Positive Predictive Value	Low	not stated	Likely much higher	
First Product Launch	2005		2023 expected	
Revenue (2020)	>$200 M		n/a	
Growth rate (Yr over Yr)	>64%		n/a	
Growth Margin (Non-GAAP)	70%		n/a	
EBITDA Margin (Adjusted)	8%		n/a	
Market Capitalization	$2.22B		n/a	

Patents related to blood RNA biomarkers:

- Patents that are fully or partially allowed:
- US 7,550,300 B1. Prediction of bare metal stent restenosis. Jun 23, 2009 (Lundergan, Burke, McCaffrey)
- US 2021/0062266 A1. Blood biomarkers for respiratory infections. Mar 4, 2021 (McCaffrey & Chawla)
- US 11,066,706 Blood Biomarkers for Appendicitis and diagnostic methods using biomarkers. May 17, 2018. (Chawla & McCaffrey)
- US 2017/0356908 Blood Biomarkers for Appendicitis and diagnostic methods using biomarkers. April 21, 2017 (Chawla, McCaffrey, and Astute)

Your Competitive Edge:

- Patient Access
  - Form a consortium so that you can rapidly test therapies or diagnostics. (N Matters)
  - Patients & physicians will be your best advocate, teacher, and connectors to funding
- Clinical Market Understanding
  - You have intimate knowledge of exactly where a drug/diagnostic fits
- Breadth of University Faculty Expertise
  - You can access engineers, data scientists, chemists, etc. at no cost
- Access to supportive services
  - GW/CN has great clinical research, incubator, IP, PR, funding, workforce resources…use them.
- Availability of 'non-dilutive' funding
  - Federal, Foundation, Philanthropic sources do not take part of your company.

NONE OF THIS REQUIRES YOU TO FORM A COMPANY

Forming a company…

- **WHY:** To make money? To insulate from risk? To raise money?
- **WHY NOT:**
  - You will likely not make money
  - You may insulate from clinical risks, but you exposure yourself to securities risk
  - VC/Investor funds are not easy to gain and require VERY substantial time/money
  - Most advisors want cash upfront and equity on back end
  - Potential Conflict of Interest (you now have 2 employers)
  - Tendency to be protective rather than interactive
  - Forming too early creates impression of low progress, ie years of no funding
  - VC/Investors want major input on organizational and capital structure

→Act like an ENTREPRENEUR
long before you form A COMPANY!!

Keys to success:

- Intellectual Property (IP):
  - Engage with Tech Office to do patent searches
  - “Non-obvious” is a high hurdle, record what doesn’t work as well as what does
  - Examiners like ‘unexpected’ findings as ‘non-obvious’
- A strong TEAM with a successful history
  - Recruit colleagues at prestigious sites such as NIH, Mayo, etc.
  - Apply and win NIH, DOD, BARDA, SBIR, etc funding
  - Publish in peer-reviewed journals
- A favorable Risk/Reward Ratio:
  - Use Federal, Philanthropic, and Foundation funds to get through FDA (de-risk)
  - Demonstrate the Reward/Market value with comparables, not calculations
  - Be prepared to put your money/family/friends into the project

What no one is telling you:

- Intellectual Property (IP):
  - You are going to write the patent, and then pay someone to put in ‘legalese’
  - It is easy to file a provisional ($150), but hard to achieve allowed claims
  - It is expensive: think $20K to $100K for US or worldwide patent issuance
  - Even allowed patents are not necessarily ‘valuable’ if they can be easily skirted
  - Defending against patent infringement is very expensive and time consuming
- Prestige matters:
  - VC firms want a big name to show investors
  - Absent a big name, the bar for risk/reward goes way up

What no one is telling you: (*continued*)

- No matter how strong your idea and results, it's 'too early':
  - They always want to see more patients (N matters)
  - Any drug/device/test is very risky until it is FDA cleared
  - Even FDA cleared products have a long road to clinical uptake, ***but at 'low' risk***
  - VC want a 3-10X return on investment in a 3-5 year time frame, ***because 70% fail***
- Funding is different than networking:
  - Everyone will listen, advise, encourage, but almost no one writes a check
  - Be prepared to put your money/family/friends into the project
- Focus versus agility and new opportunities
  - Everyone has another idea for your invention: Listen, but stay on course
  - But, 'never be so focused on what you are chasing that you ignore what you found.'

Potentially ‘fatal’ mistakes:

- Incomplete literature and patent searches
  - You can wake up years in to find out ‘it’s been done’
- ‘Nurturing’ your idea
  - Don’t protect your idea from challenge, try to break it early and often
- Secrecy
  - If I hear ‘***don’t tell anyone, they might steal it***’ one more time…
  - Learn what ‘***an enabling disclosure’*** means
- Commercializing too early
  - Investors want to see a product, not an idea, or a plan for a product
  - Most investors want to see working prototypes or sales as evidence

A Modest Proposal…

Hindsight is 20/20…

- Create a consortium of key clinical sites and patient groups in your area
- Identify and access ***existing data sets*** to move toward your vision
- Devise a system for brute force screening of promising approaches
- Apply to NIH, DOD, NSF, etc. for support to innovate/iterate in an agile space
- Record failures/successes with equal detail to build IP case for an unexpected finding
- Critical step: ***Fail EARLY and Fail often.***
- →Actually: You ***never*** fail, you either succeed or you learn.
- Potentially partner with pharma/biotech leaders in the space to advance your plan
- Only form a company when you are fully told ‘no’ by government and non-profits.
- Even when you are ‘too advanced’ for NIH, the ‘Valley of Death’ is real
- Traversing the valley requires risk-friendly Angels, Foundations, Incubators/Accelerators

Partnerships with Industry: Lessons Learned Along the Way

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Disclosures – Over my career, I have:

- Consulted, been on advisory boards or given educational lectures for:
  - Novo Nordisk
  - BioMarin
  - Pfizer
  - Sandoz
  - Ipsen
  - Ascendis
  - OPKO
  - QED Therapeutics
  - A few investment firms whose names I don't remember
- Received grant or clinical trial revenue support from:
  - BioMarin
  - Novo Nordisk
  - Pfizer
  - Genentech
  - Ipsen
  - NICHD
  - Lumos
  - Neurocrine

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Types of interactions with industry

- Industry Initiated Clinical Trial Site PI
- Industry Initiated Clinical Trial/Study Overall PI
- Investigator Initiated Grant
  - Just drug
  - Drug and money
- Advisory Boards/Consultants
- Speaker's Bureau

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INDUSTRY ≠ THE DEVIL

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Industry Initiated Trials/Studies

- Pros
  - Access to new medications for you and your patients
  - Helps foster drug development
  - Can learn a lot about GCP and how to conduct a trial
  - It can be a fun change of pace
  - Travel to investigator meeting
  - Publication credit
  - Can build relationships
  - Occasional presentation opportunity
- Cons
  - It's a lot of work for very little financial gain (to your institution) and perhaps even a loss
  - Publication credit?
  - Not a great way to advance your academic career as compared to doing your own research
  - Need to have a very strong support team for study coordination and regulatory submissions

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Investigator Initiated Studies

- Big pharma and biotech companies have online portals for submissions
- It is very easy to get free drug, much harder to get money.
  - Stories of PAPP-A2 and GHR mutation
  - However, if your trial dovetails with the company's interests, it can be a win-win situation.
    - Story of growth hormone for Aggrecan Trial
- It helps to know someone at the company to help shepherd it through the process.

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Vosoritide for Selected Genetic Causes of Short Stature – AKA "What the heck did I get myself into?"

- Fellowship sequencing research finds a patient with NPR2 mutation
- Learn about novel CNP therapies being developed – super cool.
- I call and email BioMarin and get 100% ignored.
- Fast forward ~5 years
- Ron Rosenfeld introduces me to Jonathan Day in a hotel lobby in Lisbon
- I fly to San Francisco for a day and am the only person in all of Marin County wearing a suit.
- Kim Boucher and I write an IND by reading the FDA online guidance.
- The two of us have a meeting with the FDA review team (more than 2 of them ☺) and negotiate the terms of the trial.
- We are now the only site in the world running a trial like this.

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Advisory Boards, Consultancy, and Speaker's Bureaus

- I have never been on a speaker's bureau and never will be. I will leave it at that.
- I have consulted and been on numerous advisory boards.
  - Pros – You make money. You make contacts. You gain important insights into the field.
  - Cons – Need to avoid conflict of interest, becoming a marketing mouthpiece, distracting from your other work.

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Conflicts of Interest and How to Avoid Them

- BioMarin
  - Divest yourself from personal financial gain
  - Disclose everything and work with your COI officer
  - Downside – you don't make money from this approach (but were you really going to anyway?)
- Lumos Investor Conference
  - Be honest about your opinions
  - Divest yourself so you can be honest
  - You are not a mouthpiece
  - Make your own slides

Remember Open Payments

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WARNING – There are very real non-financial gains that could influence decision making.

- Opportunities to present at meetings
- Authorship opportunities
- Being liked by people
- Getting a positive result from your research

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Bottom Line:

- Working with industry can be very productive and collaborative.
- Excellent potential alternative source of funding.
- Think about conflicts of interest and be honest with yourself.
- Disclose everything.
- Sponsors are key to opening doors. Pay it forward.
- Go for it.

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