
KNOWN
MEDICINE

Introduction to Known Medicine

At Known Medicine, our vision is to determine the best drug for every cancer patient and to create the best drug for every cancer. To do this we are building the world's largest custom designed, patient specific 3D cell culture dataset. This data will power a broad-spectrum drug effectiveness prediction engine with which we will:

- maximize the utility of existing cancer drugs,
- optimize clinical study design for drugs in development, and
- ultimately design truly personalized pharmacotherapeutic interventions.

The Promise of Technology

Almost a decade into the marriage of data science and biology, the appetite to find data solutions to life science problems remains largely unsated. Those who are familiar with the space are well acquainted with the tens of billions of dollars that have been spent to fund hundreds of new companies - each with its own distinct approach to biological and chemical inquiry. Notwithstanding the massive influx of capital and interest in the AI for drug discovery space, there remain several structural problems.

You're Going to Need a Bigger (Data) Boat

Above all, the sparse data problem remains the most intractable and will not be solved except by the continued expenditure of significant time, effort and capital. Poorly labeled or unlabeled data sets abound. Scraping publicly available data in the scientific literature, patent databases and from sources such as CheMBL, ProtDB and the like is not moving the needle. Many highly innovative minds are designing ML architecture to solve for the lack of good data but that is a poor substitute for actually generating the data and establishing ground truth - and lots of it.

Many companies are endeavoring to use technology broadly, and artificial intelligence in particular, to solve life science problems. We at Known Medicine believe that those investing in generating high quality, specifically designed training data sets to power machine learning approaches are going to be the most successful.

Hence, our overarching mission is to build the world's largest purpose-built 3D cell culture data set.

Time is Not on the Patient's Side

Additionally, AI companies working on discovering drugs are required to abide by traditional discovery and development timelines. The stasis in the regulatory framework governing drug

development means that while we can build high performance discovery engines, they are inherently limited by long standing regulatory constraints.

We are now a decade into what many describe as the golden age of AI in drug discovery. Only recently have we seen the first fruits of those efforts even reach the clinical development stage, with no evidence yet to suggest that these AI-derived drug candidates are any better than their traditionally discovered forebears. Many years remain before they may help any patient.

While Known Medicine will always maintain a data-first approach we are building our data set with two important additional drivers:

- We must offer immediate benefit to patients
- We believe that using functional data derived from actual patients is substantially superior to further upstream data inputs (e.g., genomics) that are more remote from clinical reality

As a company, we have a bias to action and require of ourselves that we make a real difference in patients' lives sooner. Our product roadmap allows us to realize both our long-term data build aspirations and short-term impact in equal measure.

Im-precision Medicine

Despite the herculean efforts of oncology researchers and physicians over several decades, the treatment of advanced cancer remains largely a sophisticated guessing game. The rapid rise in the availability of molecular information about cancer and the increasing array of targeted oncology therapeutics are, perversely, not making it any easier for physicians to make treatment decisions. Less than 50% of late-stage cancer patients respond to their first treatment regimen. The National Comprehensive Cancer Network estimates that 50% to 75% of cancer therapies in the United States are used off label, meaning that physicians prescribe therapies for clinical indications in manners different from those approved by FDA. Off-label usage of traditional cytotoxic therapies is often driven by physicians struggling to treat a patient's disease after it fails to respond to initial treatment regimens. Targeted therapies are used off label by oncologists who have expertise in genomics or access to diagnostic tools that allow them to make more informed decisions about off-label use of targeted therapies.

While the continued investment in biomarkers to predict patient response has yielded some gains, the promise of precision medicine has largely not been realized. Most currently available molecular diagnostic tests capture only a limited number of the most common and known genomic alterations and even when there is a genomics-based test available, such genomics-only based approaches benefit only a small percentage of that already small

patient pool. Many patients do not have the mutations these drugs target, and even when they do have the mutations often do not benefit from the targeted treatment offered.

One study found that the percentage of US patients with metastatic cancer estimated to benefit from genome-targeted therapy was a paltry 0.70% in 2006 and by 2018 it had increased only to 4.90%. (1)

A second has only a slightly more promising estimate. "[O]nly 7% of the successfully screened patients benefited from this [genomics based] approach." (2)

The oncology community clearly needs a solution that can (i) assess the functional impact of cancer drugs without subjecting patients to the damaging side effects and co-morbidities associated with all such treatments; (ii) distill complex, high dimensional biological information into a concise and actionable format and (iii) identify better quality drugs to fill biopharma pipelines.

Known Medicine's Solution – Finding the Best Drug for Every Cancer Patient

We have designed our Oncology Diagnostics Inference Network - ODIN™ platform to address each of these issues. From patient tumor samples we generate hundreds of micro-tumors, our M3DUSA™ models, and treat them with an extensive panel of drugs or drug combinations. Each model made on our autonomous platform is representative of the patient's tumor *in vivo* and is made of cancer, stromal, and immune cells as well as extracellular matrix components. Through our proprietary IRIS™ analysis, a bespoke machine learning-based image analysis pipeline, we determine drug sensitivity. Data can be provided to oncologists in essentially real time for use as a decision support tool – our rapid turnaround time being particularly vital for late-stage patients, where every day counts.

Our ODIN™ platform offers distinct and unique advantages over other approaches:

- It uniquely models the tumor environment and captures how the cells are actually responding to treatment, not predicting how they may respond
- It relies upon imaging data to derive clinical, biological, and analytical insight. Images are extraordinarily data rich and inexpensive to generate, which makes it perfect for rapid scaling, platform expansion, and cost containment
- It utilizes scalable, high-throughput processes for 3D culture manufacturing and data acquisition
- It provides clinically relevant, actionable data to treating oncologists and patients in a matter of days, facilitating better treatment decisions for even the sickest cancer patients

Our data set grows by tens of thousands of images with each patient sample allowing us to derive increasingly sophisticated biological, computational, and clinical insights with every patient we help.

Known Medicine's Solution – Creating the Best Drug for Every Cancer

As well as patient facing solutions that maximize the utility of currently marketed drugs, we can deploy the ODIN™ platform earlier and earlier in the discovery and development process to improve each stage.

Clinical Trials Optimization & Companion Diagnostics

Biomarker driven development is widespread now with >900 immuno-oncology programs and >300 targeted therapy programs currently active. This represents an annual clinical study patient population of >130,000 patients. The ODIN™ platform can be used to determine which patients are most likely to respond to a drug candidate and thus can enrich for the most appropriate to include in clinical studies.

Recent studies have described striking intra-patient, intra-tumor heterogeneity and how clonal evolution under treatment pressure represents a major obstacle in relying solely on genetics to profile patients. As well as the uncertainty around prescribing initial treatment regimens, sustained clinical response is also at ever-present risk of the development of drug resistance.

Our ODIN™ platform can provide insight into the current state of drug sensitivity of any given tumor at any given time. Instead of only relying on an upstream, remote genetic readout, which is a poor predictor of clinical success and is only relevant for a tiny fraction of the oncology patient population in any event, Known Medicine takes the experiment out of the patient, takes the guesswork out of study design and patient selection, and provides a rapid functional readout of whether this patient is right for your investigational drug trial.

At the end of 2010, just 9 companion diagnostic (CDx) assays had been approved by the FDA. Ten years later that number had nearly quintupled, with 44 CDx assays on the market. As cancer treatment becomes ever more personalized, the ODIN™ platform will offer a wide variety of functionally driven companion diagnostics products that we expect will outperform the existing genetics-based approaches.

Novel Combination Therapies

The past decade has witnessed the rapid development of drug cocktails for improved therapeutic outcomes in a variety of oncology indications. Combination therapy has been a successful strategy to enhance efficacy, increase response, reverse resistance and reduce

toxicity as well as address tumor heterogeneity through using drugs that display varied pharmacodynamics and interact with varied molecular targets. However, much of the success of combination therapies has been serendipitous and largely the result of trial and error.

At Known Medicine we can replace that serendipity with data driven systematization of combination therapy selection and development.

Improved Discovery Programs

As our data set grows and our platform performance continues to improve, we will open the door to data driven decision making at the earliest stages of drug development. Our platform and analysis pipeline will enable target identification and mechanism deconvolution at the earliest stages of discovery and facilitate the generation of highly nuanced biomarker profiles to support increasingly effective development programs.

The Take Home

We are always on the lookout for curious, audacious and creative people to collaborate with, brainstorm with, and partner with to build the world's most powerful 3D cell culture dataset. We would love to connect with you and share our journey as we:

- maximize the utility of existing cancer drugs,
- optimize clinical study design for drugs in development, and
- ultimately design truly personalized medicines for a truly individual disease

1. Marquart J, Chen EY, Prasad V. Estimation of the percentage of US patients with cancer who benefit from genome-driven oncology. JAMA Oncol. 2017;7:586-595.
2. Massard et al. High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers: Results of the MOSCATO 01 Trial. Cancer Discov. 2017 Jun;7(6):586-595. PMID: 28365644