Q&A

Unlocking Precision Neuroscience and R&D Innovation for Chronic Diseases

A Q&A with Steve Gardner, PhD, Founder, and CEO of PrecisionLife

THE ERA OF precision medicine is taking over drug discovery and development. This patient-centric approach has already transformed oncology and will inevitably transform much more prevalent and expensive chronic conditions, but to achieve this we will need a radically different view of these diseases and improved approach to R&D.

Common conditions such as diabetes, cardiovascular disease, dementia, immune disorders, and respiratory diseases are challenging areas for unmet medical need and require more personalized diagnosis and treatment than the standard of care can currently offer.

Because of their prevalence, these chronic diseases affect billions of people and account for more than 80% of healthcare spending. Unfortunately, these diseases have not benefited from advances in genomic medicine like cancer or rare diseases because they are caused by a more complex interplay of genes and biological factors. Multiple biological mechanisms can lead to the same clinical symptoms. Depending on which mechanism a drug targets, different treatments will be more successful in some patients than others. Such interplay makes chronic diseases difficult to diagnose; for example, patients with chronic diseases may share the same diagnosis, but have different causes, trajectories, and responses to treatment.

The global crisis of chronic diseases and failure of public health to stem the rise in highly preventable risk factors have left populations vulnerable to acute health emergencies. But the challenge for biopharma and healthcare is understanding which targets and drugs will work for which subgroups of patients.

The *Journal of Precision Medcine* carried an article by Simon Beaulah, PrecisionLife SVP Healthcare, in the June 2021 issue on precision medicine and chronic disease. We, now *Precision Medicine Quarterly*, connected connected with Steve Gardner, CEO and co-founder of PrecisionLife to follow up on the company's rapid development.

Q1. Why does PrecisionLife see itself as a techbio company (as opposed to a biotech company)? What capabilities does a techbio company offer to pharmaceutical and biotech companies?

PrecisionLife's business is built around its unique combinatorial analytics platform. This provides us with a highly scalable way of analyzing patient datasets to identify innovative novel drug targets, mechanistic patient stratification biomarkers, and other valuable insights into how to approach complex, chronic diseases, many of which have almost 100 percent unmet medical need.

This scalability and the additional sensitivity of our approach generates multiple novel targets, all of which have supporting genetic evidence, strong mechanism of action links, and detailed data packages from scientific literature. Coupled with patient stratification biomarkers associated with all of the novel targets, the prevalence of the target mechanism, the fit of a target to the pharma company's therapeutic product profile, and even the secondary indication potential of the targets can all be evaluated during our initial target selection.

This incorporates and extends methodologies such as AstraZeneca's 5Rs framework to enable selection of the very best disease biology early in the process. This is further supported by patient stratification biomarkers that can be used as inclusion criteria to design more targeted clinical trials, accelerating and de-risking the clinical development process.

Being able to do this at scale across multiple indications means that PrecisionLife has already created more compelling opportunities than we could ever develop ourselves. We therefore work in strategic R&D partnerships with biopharma and other organizations to combine our disease insights with their deep disease knowledge and world-class drug development infrastructure to bring innovative new medicines to market.

Q2. PrecisionLife's focus is on chronic diseases. What is the nature of chronic diseases that drug therapies often lack sufficient clinical efficacy resulting in clinical trial failures?

PrecisionLife was borne from the success and frustration that followed the groundbreaking work of the Human Genome Project. While precision approaches have become routine for monogenic diseases such as some cancers and rare genetic disease, these tools have had less impact on complex, chronic diseases. In large part that's because these diseases arise from interactions between multiple genes and other clinical and environmental factors. Current tools such as genome wide association studies (GWAS) cannot capture the non-linear effects of these interactions, and so uncover only a small portion of the relevant genes in more complex diseases.

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Because they work at a population level, tools like GWAS also implicitly assume that the disease population being studied shares a largely common molecular etiology. At PrecisionLife we do not believe that is true – in fact we routinely stratify patient populations into clinically relevant subgroups based on their distinct mechanistic etiologies.

This distinction (mechanistic etiology and molecular versus solely molecular etiology) is important in diseases such as Alzheimer's where there have been many extensive (and expensive) Phase III clinical trials that have failed due to an inability to demonstrate clinical efficacy. Our work shows six distinct mechanisms are disease drivers in Alzheimer's patients; lipoprotein metabolism (the target for most current Alzheimer's programs) is only relevant to about one-third of these patients from drugs targeting those mechanisms. As well as costing hundreds of millions of dollars of R&D investment, this has also meant that several drugs that did in fact work very well for some patients have not made it to the market.

Q3. PrecisionLife's combinatorial analytics platform sits at the core of the company and is designed to generate disease biology insights from patient datasets. Can you describe the basic concepts behind creating the PrecisionLife chronic disease database and its platform to overcome possible failures in clinical trials?

We realized that we had to fundamentally reimagine how to analyze multi-modal patient datasets more effectively in complex, chronic diseases to identify and understand the full range of the drivers of disease biology as they affect different patient subgroups.

We believe that chronic diseases don't arise simply from mutations in single genes. They're caused by a complex interplay of multiple genes and other factors – technically they're polygenic and heterogenous. Looking at the effect of one thing at a time cannot capture this non-linear signal, which is much more prevalent and important in chronic diseases.

Rather than looking for more and more ultra-rare variants in single genes to explain disease, we analyze how interactions between multiple relatively common variants and other external factors come together to trigger disease processes. Finding the SNPs and other features whose non-linear interactions have measurable impact on a clinical phenotype allows us to perform high-resolution patient stratification. Clustering disease associated combinations of SNPs by the patients in which those combinations co-occur. From this, we can explain how the various aspects of disease biology affect different subgroups of patients and identify novel drug targets relevant to those patients.

This initial patient stratification by mechanistic etiology is something we do for every disease we study – uncovering in a hypothesis-free manner all the combinations of disease associated features, which could be not only genomic, but also clinical, epidemiological or environmental.

Of course, finding and validating these disease-associated combinations is difficult to do, which is why our unique mathematical approach is central to our ability to do this discovery work at scale for the most challenging and heterogenous diseases.

Q4. Can you compare the combinatorial analytics platform with other approaches? What are the advantages offered by this approach versus other approaches?

The combinatorial approach is considerably more sensitive than GWAS and requires much smaller patient populations. It enables identification of novel genetic associations and mechanisms that may only be relevant to a subgroup of patients, leading to more novel associations than GWAS when analyzing the same datasets.

This approach has been validated in multiple disease studies both us and our collaborators, in some cases using *in vitro* and *in vivo* disease assays to demonstrate novel target genes' disease modification potential, and in others by the presence in pharmaceutical companies' R&D pipelines of drug programs targeting mechanisms that were identified by combinatorial analysis, but which could not be found using GWAS on available patient datasets.

We have data from direct head-to-head comparisons. For example, by using combinatorial analysis in the study of risk factors for severe COVID-19, we were first to report the association of 156 loci and 68 genes with the risk of developing severe COVID-19. This analysis was run in May 2020 on the first UK Biobank dataset of just 725 patients and 1450 controls, and contrasts with the 11 and 13 loci discovered using a GWAS approach, respectively, by 23andMe (16,500 patients/controls) and the COVID-19 HGI consortium (over 2,000,000 patient/controls) in similar studies.

The genes that we identified cover the range of features and symptoms observed in COVID-19 patients – viral binding and replication, immune system and cytokine responses, plasma cell membrane changes, endothelial cell function associated with leaky vasculature and micro-coagulation, senescence and genes that we have associated with multiple neurodegenerative diseases (thought to account for 'Covid fog'). Of the 68 genes that we reported, 48 have subsequently been associated with the disease by other groups using methods such as single-cell analysis and transcriptomic profiling. We validated our findings in a US clinical population with UnitedHealth Group where we showed that key clinical attributes could predict severe disease and the need for oxygen support.

This study was also the first to predict dutasteride as a drug repurposing candidate to reduce symptom severity, identify those who need intensive care, and cut remission times in a subset of COVID-19 patients; findings which have been borne out by subsequent double blind randomized controlled clinical trials.

Q5. Can you cite an example of an insight into a disease or drug mechanism of action through PrecisionLife's platform that could not be gained otherwise? How is this insight being used to advance a drug or diagnostic to the clinical stage (either a trial or in practice)?

We have several examples of such validation and development work for novel targets and patient stratification biomarkers across diseases such as COVID-19 (as we already described), ALS, non-T2 asthma, schizophrenia, and others.

Most recently, we published a study in ME/CFS*, a massively debilitating chronic disease affecting 17 million patients that presents with diverse symptoms and currently lacks known pathogenesis, diagnostic criteria, and treatment options. Patients' lives are devastated and often cannot even get a definitive diagnosis, let alone any effective disease modifying therapies.

We were the first group to identify reproducible genetic associations with ME/CFS after 30 years of study into the disease. While GWAS on two UK Biobank datasets found no hits, our combinatorial analysis found 14 genes that were significantly associated with 91 percent of the cases. We replicated some of these associations in another separate CFS cohort.

These genes map to distinct patient subgroups via previously suspected cellular mechanisms, covering energy production, response to stress/infection, autoimmunity, sleep disturbance and disruption of circadian rhythms. We have also observed several of these ME/CFS genes in long Covid, other post-viral syndromes, multiple sclerosis, and fibromyalgia, which share aspects of symptomology.

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These types of insights enable the development of more accurate diagnostic tools and selection of more effective, personalized treatment options for patients. In the case of dutasteride, for example, our patient stratification biomarkers predict a specific severe Covid population of males as responders with very high selectivity (the biomarkers identified 71 cases or 71 likely responders). This finding was confirmed by the double blind randomized controlled trial where remission times and the need for intensive care units were reduced by over 40% and viral shedding, inflammation and blood clotting markers were all significantly lowered.

We also routinely identify development candidates and drugs modulating the novel targets that we identify using our stratification-led precision drug repositioning approaches. These are validated via analysis of real-world data collections with longitudinal prescription/disease incidence information, and pharmacologically in new assay systems using known active drugs and development candidates as tool compounds. Given a good safety profile and biomarkers for potential responders, these may provide opportunities for secondary indications, benefitting both patients and the biopharma inventors.

Q6. How does PrecisionLife arrange and manage partnerships with pharma and biotechs? What does partnering with PrecisionLife look like in terms of, say, building a relationship, agreeing on terms and conditions, and settling on deliverables?

We have a variety of strategic R&D partnerships, ranging from novel target and discovery projects, identification of patient stratification biomarkers for clinical trials design around existing target programs, retrospective analysis of Phase III data to identify biomarkers of drug response, through to the identification of secondary indication potential for development programs. In some cases, many of these outputs will be generated in a single collaboration.

In cases where a product profile has not yet been fully evaluated, we start by working closely with the partner to establish and inform the specific target product profile (TPP) that they wish to focus on and identify patient datasets that can provide suitable insight into the disease. We have several data access agreements with research consortia and disease non-profit organizations specific to disease studies that we are conducting. We will then run the study, extensively validate data (in silico), annotate the findings, and disclose detailed supporting data packages around targets, mechanisms, and biomarkers to the partner to enable them to choose the targets on which they want to focus validation and development efforts.

Our commercial partnerships usually have a similar structure – there is an up-front fee, followed by licensing and development milestones and, in some cases, sales royalties. We very much view our first projects as opportunities to demonstrate the benefits of the precision approach and our platforms with a view to incorporating these into all the future programs of our partners.

Q7. Matching biomarkers and targets is key to precision medicine. Since PrecisionLife generates patient stratification biomarkers from its platform, how do these biomarkers add potential value to biopharma companies in clinical development programs (e.g., trial enrichment / trial rescue)? Can you describe the advantages of your approach for matching biomarkers with targets for therapies?

A good example is our work in ALS, a terrible disease that is highly heterogenous with almost no effective therapy options. Starting with patient genotype data we identified 33 novel genetic associations with ALS. With our partners, we then validated the disease modification potential across multiple mechanisms of 11 of the druggable targets in this set using known modulators in patient derived cellular assays. Several showed the potential to improve motor neuron survival. We now have over 10 novel ALS targets that are the subject of R&D partnerships – all of which are supported by patient stratification biomarkers.

One of the patient subgroups contains the most rapid disease progression; in fact, they share a common, novel target. For this subgroup, we can use the patient stratification biomarkers as inclusion criteria for subsequent clinical trials. These biomarkers are exquisitely selective combinations of a few dozens of SNPs that can be delivered via a simple, low-cost genotype test or low-pass sequencing. This enables more targeted (smaller and therefore cheaper and faster to read out) clinical trials to be designed. We are also using a similar approach to develop biomarkers to support our partners' existing programs where they do not have such tools to aid clinical development.

The other application of this capability is trial rescue. As we have seen especially in neurodegeneration, many trials struggle to demonstrate clinical efficacy – not because the drugs do not bind their targets well or even have a good safety profile but simply because the disease has multiple mechanistic etiologies and not enough potential responders can be recruited for the Phase III trial population.

We are working with top 5 pharma companies to use the level of drug response observed in Phase III and retrospectively identify drug response biomarkers that can more accurately predict responders. These markers can be used as part of a refined regulatory and trial design strategy to enrich likely responders and increase the efficacy signal, and as a cost-effective companion diagnostic tool to support the launch of the drug into the clinic.

Q8. Many in the pharmaceutical R&D industry foresee a potential neuroscience renaissance in the latter half of this decade. In follow up to Q6 and Q7, PrecisionLife recently partnered with Ono Pharmaceutical on a multi-target CNS drug discovery collaboration. How might PrecisionLife support this effort in chronic neuroscience diseases through precision medicine solutions? What can you tell us about that partnership and what makes the targets you hope to discover unique?

In general, our multi-indication precision neuroscience partnerships such as the Ono Pharmaceutical collaboration are based on understanding the specific TPP and indications that a partner wishes to address. We can then identify novel targets which have the potential to meet this TPP, have good clinical prevalence, druggability and ideally also multiple indication potential.

Aside from our patient data analysis pipeline, we have an extensive and detailed knowledge graph, druggability pipeline, and sets of bioinformatics and literature analysis tools to provide a detailed data package to evaluate the relative merits of these targets in collaboration with our partners.

Because PrecisionLife has now analyzed multiple CNS disorders, including a range of neurological, psychiatric, and neurodegenerative diseases, we can look across those at the genes/mechanisms that are common to different indications. We have identified over 35 novel targets that play a clinically relevant role in the pathology of multiple neurological diseases. We also have patient stratification biomarkers for these targets/mechanisms in each of the CNS disorders in which they are implicated, enabling rapid validation of their effect in these disease populations.

Q9. Would you have any closing comments on the utility of combinatorial analytics and your patient stratification biomarkers in chronic disease?

We believe that to better address unmet medical need in chronic disease it is essential to perform high-resolution mechanistic patient stratification to generate deeper insights of the mapping of disease biology to specific patient subgroups.

These diseases are multi-factorial – polygenic, heterogenous, and influenced by multiple clinical and environmental factors. This combination of factors is far too complex for existing tools such as GWAS alone as it simply does not return a significant portion of the disease association signal in complex, chronic diseases. This insufficiency means that the polygenic risk scores, causal inference tools, and machine learning models built on GWAS results alone are always going to be missing key analytical data.

We posit that only by observing the non-linear impacts that combinations of features have on patients' phenotypes and then mapping these mechanisms back to patient subgroups can we hope to uncover all the key drivers of complex disease biology in these conditions. By so doing, we can improve the likelihood of success of biopharma innovation and enable precision medicine for chronic diseases. PMQ

About PrecisionLife

PrecisionLife is changing the way the world looks at predicting, preventing, and treating chronic diseases – extending the reach of precision medicine beyond cancer and rare disease.

PrecisionLife developed a combinatorial analytics platform specifically to generate deeper insights into the complex biology of chronic diseases, enabling its researchers to identify and understand more deeply the biological mechanisms that are driving disease within subgroups of patients.

Partnering with biopharma, these insights inform and derisk every stage of drug discovery and clinical development to find better treatment options for patients with unmet medical needs.

The techbio company stratifies patient populations at an unprecedented level of resolution and has now discovered new biomarkers that identify all the clinically relevant patient subgroups who share a disease mechanism and found novel drug targets and indication extension opportunities for treating those subgroups in over 40 complex chronic diseases.

In doing so, PrecisionLife has generated the largest IP portfolio outside of major pharma. Perhaps most impressively, all the company's assets are protected by unique and highly specific patient stratification biomarkers, with an understanding of disease prevalence, efficacy and secondary indication potential, to maximize the probability of success from concept to clinic.

This has led to major pharmaceutical companies taking note, with multi-target multi-indication R&D partnerships signed with Ono Pharma, Sosei Heptares, and an undisclosed top 5 pharma company in Q4 2022.

Steve Gardner, PhD

Steve Gardner is a serial technology entrepreneur with over 30 years' experience developing and commercializing ground-breaking data science and informatics in the healthcare, life sciences and agri-food sectors. He is a former Global Director of Research Informatics for Astra A/B and has consulted with drug discovery and safety teams in over 20 biopharma companies. Steve is currently Chair of the Genomics Advisory Committee for the UK's Bioindustry Association. PrecisionLife is headquartered near Oxford, UK, and has operations in Aalborg and Copenhagen, Denmark; Warsaw, Poland; and Cambridge, MA, USA.

Footnote

* Das, S., Taylor, K., Kozubek, J. et al. Genetic risk factors for ME/CFS identified using combinatorial analysis. J Transl Med 20, 598 (2022). https://doi.org/10.1186/s12967-022-03815-8