Commercialization Principles and Consumer Considerations

As a quarter century follower of personalized medicine, the recent progress and pronouncements on precision medicine are greatly appreciated. Despite extraordinary complexities new ‘omics technologies are delivering solidly on precision and prediction in research and clinical applications. And with CRISPR/Cas9 pacing the last miles, whole genome sequencing (WGS) is now actively partnering in other ‘omics technologies to help expand adoption of true molecular profiling. Successful targeting and monitoring in certain cancers is not only game-changing for an increasing number of patients, it also stands to help shape other new clinical applications.

Two keys to full realization are biomarkers for precision medicine and systems biology for personalized patient care. Yet while significant expectations rest on both of these, each has extreme challenges rooted in the need for practical standards. This article recaps various sources of relevant standard-setting experience and suggests drivers to watch, for signs of progress.

For example, proteomics applications are leveraging mass spec-based platforms and MRMs methods across both research and clinical biomarkers. The in vitro and in silico research universe has evolved over the past 20 years into a global market surpassing the ~$50 B in vitro CRO services industry, and is developing key technologies, practices, and resources essential for precision medicine. The 3D cell model revolution (30% CAGR) is bringing credible promise of more realistic and reproducible research, plus leadership in cancer efficacy and liver. And the systems biology landscape of pathways, networks and targets is raising the predictive bar while also coupling valuable workflow, content, and even some decision-enabling tools. That’s the exciting view from 50,000 feet.

The ground-level challenge of building sustainable commercial demand is essentially about expanding beyond the ~$50B research market into a clinical market of ~$500 B. This includes the ~$50 B market for so-called ROO (research-use-only) applications, as well as more mature commercial LDTs (lab developed tests) and even a few maturing into full-fledged IVD (in vitro diagnostic) kits that many envision as a fundamental pillar of clinical market of ~$80 B. This includes the ~$30 B market for so-called RUO (research-use-only) applications, as well as more mature commercial.

This article deals mainly with these challenges and the progress being made. It seems unfair or negative to add more challenges to the list. And yet we see great commercial opportunity in understanding the ultimate demand of the patient as consumer. Could research tools help bridge the gap to creating full patient data clouds? How long can we continue to assume this someone else’s role? Thus the article concludes with some overview remarks on looking at the ultimate demand of the patient as consumer. See Figure 1.

9 Essential Models to Predict the Future of Precision Medicine

Challenge: Robust Biomarkers

Much of the promise of future precision medicine rests on robust biomarkers, and market forecasts continue to reflect big expectations, but actual clinical biomarker performance and use for treatment decisions has been questionable and new approvals slow. Interestingly, the challenges begin with a large gap in awareness of what is practical. While most drug developers and physicians believe that most, if not all, biomarker assays can be standardized to produce consistent results, the clinical laboratory community recognizes that even among decades-old tests only a few qualify as standardized in vitro diagnostics — total cholesterol, creatinine and glycosylated hemoglobin. They know widely variant results are possible if tests are performed in different labs, using different methodologies or platforms, or even within the same labs using the same but using different reagents. And that beyond LDTs (lab developed tests) significant variability is expected in in vitro diagnostic (IVD) kits utilized across different labs. They understand that even in the best cases such as HER2 biomarker, the odds of identifying HER2-positive patient candidates can vary significantly. And this remains despite substantial improvements in quality systems, oversight via certifications like CLIA (Clinical Laboratory Improvement Amendments), and via accreditation and proficiency testing provided by organizations like CAP (College of American Pathologists).

Proteomics is now being used to monitor cancer therapies and transplant immunosuppression, to analyze amino acids panels for newborn screening, to detect infectious disease, and for various wellness measurements. This ability to use the same analytical platform from discovery all the way to commercialization is certainly one key for validation and standardization. Other innovators are creating standards around their data methods. Based on 20 years of innovation performance has increased while costs have declined, enabling new applications not only in clinical biomarkers but also in home-based care for example dried blood samples collected by patients themselves. This enables a key facilitator of...
precision medicine - the ability to compare each individual's test results with his or her own normal range, something that up to now has been impractical because of cost and inconvenience. These innovations are expected to continue and to enable personal patient big data clouds over the next few years. The benefit of proteomics complexity is being proven, but still huge challenges loom.

Since the late 1960s the market for measuring proteins has grown to about $5 to $10 billion per year, including about 500 different FDA-approved IVD tests for proteins found in blood (for example diagnostic heart protein, TnI) and also about 100 laboratory-developed tests offered by big reference laboratories like Quest or Labcorp. Experts believe that there are thousands of additional proteins that may be diagnostically important, yet none of these have been adequately studied (using many markers in hundreds or preferably thousands of people) to find what is reproducibly different.

Biomarker qualification and clinical implementation have generally involved the development of an antibody-based protocol, typically ELISA assays which are often low throughput, very costly, and time-consuming. Also, protein-protein interactions and antibody interference problems have limited the ability to multiplex on and validate the individual components of these traditional platforms. In the past each clinical lab marker test was done separately from a different sample of blood, resulting in additional cost for additional tests. Up until the last couple of years, this kind of testing was so slow and expensive that only a dozen or two people at a time were evaluated, making it hard to find reproducible differences.

Yet now MS-based targeted protein quantitation technologies with multiplexing can measure panels of up to 50 proteins in one sample at a fraction of the cost, enabling greater predictivity.

It’s instructive to know that getting to this point has been tough. For several years it has been recognized that human plasma contains a very wide range of concentrations of proteins many at or below the nanogram/milliliter range and traditionally inaccessible by standard MS-based methods. Multiple reaction monitoring (MRM) based mass spectrometry has been used for several years to identify and quantify low abundance peptides in a complex mixture with very high sensitivity and speed. And now based on the unmet need of validating new clinical biomarkers, innovations like SISCAPA can extend the quantitative capability of MS-MRM to even lower abundance proteins by enriching specific signature peptides derived from the test proteins, thus avoiding autoantibody interferences. It also incorporates internal standards to correct for many sample processing and assay problems. This approach provides up to a 1,000-fold improvement in analysis of proteins in plasma. All of which has enabled a new “dried blood spot” technology where a patient as consumer can collect a couple of drops of blood on a filter paper, enabling far more medical information than from many vials of blood in the past.

Source 2

Predictive Drug Safety Testing and Research

Although the field of predictive safety and toxicology is becoming better understood, it’s still easy to forget the level of rigor that has been accomplished since the 1980s and 1990s, including full validation to enable decisions by environmental regulatory authorities. And in addition to these fully standardized (validated) regulatory uses, a host of drug research niches are using these same technologies for screening, safety assessments, and prioritization of new compounds. These encompass a wide range of technologies and market segments including stem cells and primary cells, omics, imaging, liquid handling and automation, cell-based assays, reagents and other consumables and bioinformatics (see Figure 2). Here important standards of practice are being developed.

Along with a strong growth market recently estimated as growing to $10 B by 2023 (57% CAGR).

The commercial landscape consists of large multinational companies like Agilent, PerkinElmer, and Thermofisher, plus a myriad of smaller companies and startups. Stem cell innovators are building businesses in the sector, on the way to developing stem cell therapeutic products, for example Cellular Dynamics, Inc. which recently announced an acquisition by regenerative medicine-oriented Fuji Film. Some themes have become key niches quite quickly, for example 3D cell culture. Overall the field has demonstrated strong collaborations and standard-setting. Several unifying principles have been proven, including integrated testing strategies, weight-of-evidence assessment frameworks, and primary/secondary compound screening strategies.

And yet there are plenty of challenges ahead to fuel innovation and growth, for example FDA’s intention stated last year to focus more attention on women’s unique health and toxicity concerns going forward, which experts believe could grow into a large field by itself. There are also compelling examples of companies using their predictive safety insights and technologies to develop clinical biomarkers, e.g. Stemina leveraging their expertise in neuronal stem cells, developmental and reproductive toxicology (DART) and metabolomics, to forge clinical collaborations and to develop a blood-based biomarker for autism.

![Figure 2- Predictive In Vitro and In Silico Technologies](image)

**Figure 2:** Predictive In Vitro and In Silico Technologies

![Figure 3- Example: Cell-Based Assays Landscape](image)

**Figure 3:** Example: Cell-Based Assays Landscape
3D Cell Culture Revolution

Another example of how emerging in vitro standards are poised to revolutionize life sciences research is being demonstrated in the 3D Cell Culture market. By now there is little doubt that long-term passage of cells as 2D monolayers can result in loss of their ability to respond to external signals, casting doubts on their relevancy to human physiology. 3D cell culture using primary and stem cells is enabling more rational assay responses across the discovery-development-testing chain and may ultimately help improve reproducibility across labs.

3D Adoption and Drivers

3D cell culture has evolved from being messy, laborious and expensive several decades ago into a much more organized offering of commercial tools, and has already enabled greater reusability of knowledge of tissue and cancer behavior. And as a positive indicator of future adoption and growth rates, there are beginning signs of delineation of common (not yet best) practices where specific supplier technologies are mapped to specific applications, offering hope of a coordinated landscape with less market friction than the free-for-all of yesterday. This includes 3D continuing to co-exist with 2D in most research application areas. In addition to change dynamics, this is also partly due to researchers’ perception of value in comparing 3D and 2D results for basic insights.

One area where 3D has the potential to grow into a significantly bigger role than 2D is in liver safety and even basic liver biology. And yet signs of delineation of common (not yet best) practices are being investigated at the cellular level these days occur over very brief time windows, which can easily be missed. This integration will require continued innovation by the 3D community.

Cancer

Cancer research has long used 3D systems, not only for safety but also for efficacy testing and basic research. Following are a few key areas which will likely lead in the continued growth of the efficacy role, and which may leverage this experience into leading precision medicine applications of the future:

- Co-Culture
- Metastases
- Tumor Recurrence
- Patient-Derived Cells

Liver

3D cell culture plays a very important role in understanding liver function as well as dysfunction due to toxins or drug induced liver injury. The benefit of 3D versus 2D in liver is dramatic, and adoption is anticipated to ramp sharply in the next 3-7 years, based on the increasing possibility for regulatory support to coalesce around a specific role for 3D in drug safety testing for liver toxicity and drug induced liver injury (DILI). This is most likely in sub-segments such as so-called slow release (metabolism of compounds) indications. For this role to be defined and made mandatory, substantial progress is required on development of key standards and best practices in many aspects. One example of the type collaboration needed with regulators is being demonstrated by the CiPA initiative in cardiac safety testing.

One exciting possibility is that this strong unmet need, in the face of the liver’s extreme complexity, will help drive increased integration of various ‘omics approaches together with cell culture and analysis. For example in pharmacos, lab directors have pointed to difficulties with cell extraction from scaffold or gel, for example it often ends up being the denatured supernate which is analyzed. And this removal of proteins from the scaffold is known to have a significant change on protein structure. Also, many of the biochemical changes that are being investigated at the cellular level these days occur over very brief time windows, which can easily be missed. This integration will require continued innovation by the 3D community.

Cancer Research and Development

Cancer stem cell applications include the safety testing and research of new drug candidates, along with potential direct clinical application as cell therapies and regenerative medicine. Basic technical and operating standards for stem cell production are now being developed with 3D cell culture having played a key role since the mid 1980’s.

The most important and challenging aspects of stem cells are their ability to self-renew and to differentiate into many different kinds of cells. Furthermore, many applications require a large number of high quality cells, requiring quick cell expansion.

3D culture can significantly improve stem cell viability and function and thus offer a higher degree of efficiency, consistency, and predictability which is important for preclinical research and certainly for regenerative medicine. In addition to these key benefits for minimizing differentiation, microenvironments, and high throughput screening markers, 3D is also demonstrating advantages for fundamental applications like more efficient validation of new cell line pluripotency.

3D Cell Culture Commercializes Across a Complex “3D” Landscape

‘2D’ Cell Culture

- Roller bottles, vaccines, plates and cubes
- Suspension-based (bioreactors)
- Continuous (perfusion)

3D Cell Culture Technologies and Global Markets

The level of innovation is expected to remain high. Technology requirements will likely approach the sophistication of the organotypic level, which may create tension with requirements in reproducibility, pricing, and throughput. In fact, some expect unit price declines across the applications landscape, unlike in organotypic skin applications which have held level prices for many years. However the volume increases to support the substantial growth envisioned will come from an increasing array of applications, as detailed in the BCC Research report 3D Cell Culture Technologies and Global Markets.

Liver

Liver is a difficult organ to model in vitro due to the complexity of its structure. Also, many of the biochemical changes that are being investigated at the cellular level these days occur over very brief time windows, which can easily be missed. This integration will require continued innovation by the 3D community.

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In Vitro Platforms

- Microplates
- Cell-based assays
- Detection and imaging
- Organotypic models
- Cells and tissues
- Reagents, media, and sera
- Stem cells
- Microfluidics

3D Cell Culture Tech Tools and Consumables

- Extra cellular matrix (ECM)
- Gels and other scaffolds
- Spheroids
- Magnetic
- Organ-on-a-chip
- Printing

Research Fields

- Cancer safety and efficacy
- Tissue engineering
- Developmental biology
- Stem cells
- ADNEX
- Liver

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Metabolomics raw data processing is considered the most challenging and time-consuming step and involves including noise reduction, data integration and alignment, and compound identification and quantification. Once metabolic composition is determined, data reduction techniques can be used to elucidate patterns and relationships among metabolite profiles. These approaches have historically been based on statistics, but are evolving to knowledge-based pathway and network models.

Commercial Landscape

The metabolomics, bioinformatics and systems biology landscape is innovative and dynamic. There are a wide variety of freely available databases and tools that help to analyze and organize metabolomic information. Most of these are created by academics and nonprofit research groups. Typically these links to each other and together constitute a substantial foundation of free bioinformatics tools.

Building on this public base are a number of commercial market participants of different types, including equipment manufacturers like Agilent that also develop appropriate software compatible with their instrumentation. Also some bioinformatics companies have a specific focus on metabolomics research including prediction models and an overall understanding of complex biological pathways. Furthermore there are companies like Metabolon focused on clinical biomarkers like inborn errors of metabolism (IEM).

Data Standards and other Unmet Needs

To maximize the value of data sets, it is important that data is made publicly available in formats and with metadata that are widely accepted as standard. This is essential to facilitate experimental replication and comparison across multiple investigators and laboratories. Standards for data reporting have been attempted, but unfortunately are still not widely used. In this sense, the field of metabolomics lags behind genomics and proteomics. Some of the reasons for this slow adoption of standards include the proliferation of analytical platforms and vendors, and the complexity of sample processing which remains the focus of significant attention.

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A patient taking statins may experience muscle aches, commonly termed myalgia, and some patients have a small chance of developing a serious, life-threatening adverse drug reaction called statin-induced myopathy.

Other important PGx applications include chronic pain medications, mental health medications, and polypharmacy situations. Pharmacogenomics also includes testing to support cancer therapies and a subset of prenatal testing (period). There non-invasive prenatal testing or NIPT is poised to become a $1 billion market particularly for inborn errors of metabolism (IM) which are relatively rare but extremely serious conditions such as lysosomal storage disorders. MS-based screening for IM in neonates is now routinely done in most industrialized countries. Otherwise, while major medical centers are beginning to implement pharmacogenomic tests in patients undergoing certain procedures or taking certain medications, most physicians do not receive pharmacogenetics training and a big gap in awareness and know-how remains.

**Source 7**

**Wellness Monitoring**

It is interesting to note that some leaders of Precision Medicine like the proteomics example cited earlier are focusing on wellness monitoring as an attractive market application. Furthermore, Leroy Hood's Institute for Systems Biology has made progress with their 100k Wellness Vision, reporting initial results from their first pilot of 300 individuals, and planning to scale to 1000 people this year, to 10,000 in 2016 and eventually 50,000 well individuals and follow them for 25 years to see who develops disease and how. They also report striking response from many leaders at research institutions, medical centers and integrative health systems in the U.S. and abroad who have already initiated strategic partnership discussions with them. Internationally, they envision a franchise-like model with rigorous scientific and security standards and an agreement to aggregate and share data. The 100k study harnesses IBIS's systems approach and expertise in the integrated analysis of biological data. From genomic sequences to collect blood, saliva, stool and urine samples every three months to measure microbiome diversity in the gut; clinical chemistries that are focused on nutrition; 1,600 blood metabolites; epigenetic (methylated) status of white blood cell DNA; blood organ specific fingerprints from the brain, heart and liver; selected hormones; ongoing clinical histories, psychological tests, and data from “quantified-self” devices including heart rate, activity, sleep quality, blood pressure, weight, etc. They plan to study the molecular basis of health and the initiation and progression of disease. Along with “actionable outcomes” in conjunction with health coaching and medical oversight. So far after analyzing just a few types of data for the 300 Pioneers they find that 100% have multiple actionable potential areas to improve their wellness and/or avoid disease. Thus their audience appear to be healthy individuals concerned with only their own wellness but also to the cause of integrating big data, systems biology and “omics.” This sounds great for long term, but what about trying to help people who desperately need it?

**Source 8**

**Functional Medicine**

That’s exactly what the field of integrative or functional medicine has been doing off the radar for many years. According to PwC, estimates the annual expenditures on complementary and alternative medicine (CAM) are worth $34.8 billion. The majority are cash-paying customers, since CAM services are mostly not covered by insurance. Think about this. Data from this population is available on their behaviors, their effectiveness, their lifestyle, their family history, their present and past health concerns, what will hold their interest long enough to guide them to breakthroughs in longevity? And what about older individuals, will they want to stay in debilitation or will they turn over all stones, or will some act proactively to predict and create their optimal health? How do we model this type consumer behavior, as the quantified-self/HTTRT, hard-core fitness demographic? And more to our context, what can we do with the precision medicine field possibly do about it?

We see a future driver of Precision Medicine being patient as consumer adoption, with an opportunity for life science innovators to contribute essential content to education and awareness. FDA has started the conversation with their ‘Blue Button’ vision of patients data access and consent, but admires there are many details to be worked out in basics like understanding the potential motivations and goals of individuals and organizations for interacting with the data. We are launching a new initiative to research consumer awareness of precision medicine, along with adoption drivers and needs for education and support, and look forward to sharing these insights in the future.

**Conclusion**

Viewing precision medicine as a collection of technology applications and market segments, and studying commercialization, standardization and adoption of these individually and collectively, can inform the nature and rate of change in this highly complex environment. The 9 Sources profiled (Figure 4) constitute a broad array of models, and purposefully include some in areas that are not traditionally associated with life sciences in order to highlight new drivers such as patient-consumer engagement.